# Some studies in nitrogen heterocyclic chemistry using Reissert compounds

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# SOME STUDIES IN NITROGEN HETEROCYCLIC CHEMISTRY USING REISSERT COMPOUNDS

by

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A Doctoral Thesis

Submitted in partial fulfilment of the requirements

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of

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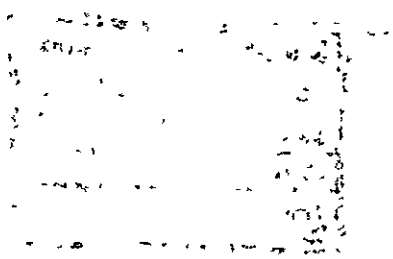
Supervisor: Dr. B.C. Uff, B.Sc., Ph.D., C.Chem., F.R.S.C.

Department of Chemistry

To: Mum and Dad,
Tony, Jeanette and Yee-Fun,
with love.



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Finally, I am most grateful to my parents, brother and sisters for their love, continual encouragement and moral support during the preparation of this work.

# SUMMARY

The thesis reports the first examples of Reissert compounds prepared from five-membered ring heterocycles. The method utilises trimethylsilyl cyanide as the key reagent in a single phase non-aqueous medium. Previous attempts to synthesise such compounds have failed because, under the conventional two phase conditions, the reaction either does not proceed or ring opening of the heterocycle occurs.

Reaction of benzothiazole with an acid chloride (aliphatic, aromatic or chloroformate) and trimethylsilyl cyanide in dichloromethane has been shown to give rise to 3-acyl-2-cyano-2,3-dihydrobenzothiazoles. Eight such five-membered ring Reissert compounds have been prepared, mostly in yields exceeding 70%. The mechanistic involvement of trimethylsilyl cyanide is discussed. The novel Reissert compounds have been shown to be versatile intermediates for the further modification of the starting heterocycles.

The Reissert compound conjugate bases were shown to be generated readily, using sodium hydride in dimethylformamide. Once formed, these anions could be used in various synthetic schemes. For example, intramolecular alkylation of the anion from 3-(4-chlorobutanoyl)-2-cyano-2,3-dihydrobenzothiazole led to the tricyclic system 4a-cyano-2,3,4,4a-tetrahydro-1-oxo-1H-pyrido [2,1-b]benzothiazole. In a similar manner, the tetracyclic benzo-analogue, 5a-cyano-5a,6-dihydro-11-oxo-11H-benzothiazolo [3,2-b]isoquinoline was synthesised from 3-(2-chloromethyl-benzoyl)-2-cyano-2,3-dihydrobenzothiazole.

Intermolecular alkylation of the conjugate bases of benzothiazole Reissert compounds followed by alkaline hydrolysis of the product provided a route to the synthesis of 2-alkyl-benzothiazoles. Similar hydrolysis of unsubstituted Reissert compounds yielded benzothiazole at room temperature but under reflux conditions, gave ring opening.

Treatment of substituted or unsubstituted chloroformate-derived benzothiazole Reissert compounds with hexanoic acid, cyclohexanecarboxylic or benzoic acid achieved a retro-Reissert reaction.

3-(4-Chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole was cleaved with phosphorus pentachloride to give 2-cyanobenzothiazole in 56% yield.

Reissert compound formation using solid-liquid phase transfer catalysis with potassium cyanide under non-aqueous conditions showed no advantages over alternative procedures in the cases studied.

A second series of the five-membered ring Reissert compounds was prepared using the indazole system. Such reactions were successful with indazole itself and 1-methylindazole, but failed with 5-nitroindazole. The use of 2-methylindazole in which the benzo-ring contains an o-quinonoid system, gave rise to the first examples of benzologous Reissert compounds.

From the corresponding conjugate bases from the indazole Reissert compounds including the benzologous example, alkylation followed by alkaline hydrolysis gave the 1,3- or 2,3-dialkylindazoles.

Condensation of a phthalazine Reissert anion with an aromatic aldehyde provided a route to the corresponding phthalazin-1-yl carbinol, which on treatment with phosgene, gave the 3H-oxazolo [4,3-a]phthalazin-3-one in modest yield.

The use of an alternative cyanating agent, i.e. tri-n-butyltin cyanide in the Reissert reactions was also investigated but shown to offer no clear improvement.

Attempts to convert pyrazole to a Reissert compound with ethyl chloroformate and trimethylsilyl cyanide gave only N-ethoxycarbonylpyrazole. Attempts to prepare Reissert compounds from 1-methylpyrazole returned only starting material.

# CONTENTS

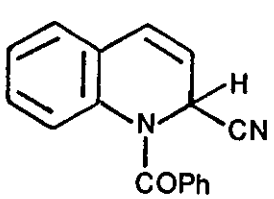
# INTRODUCTION

## A. General

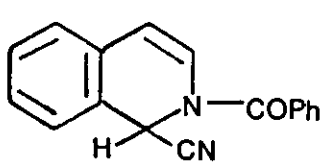
Studies with Reissert compounds have generated a valuable methodology for the modification of isoquinolines and related six-membered ring heterocycles: synthetic applications have yielded access to isoquinoline alkaloids and novel heterocycles, some with potential biological use.[1,2]

This research project sets out to further such studies, and with the advent of new synthetic reagents, to investigate potential new pathways for the synthesis of Reissert compounds and analogues, and hence their exploitation.

The original Reissert compounds were prepared in 1905 by the reaction of quinoline and isoquinoline with benzoyl chloride in the presence of aqueous potassium cyanide to give as crystalline compounds 1-benzoyl-2-cyano-1,2-dihydroquinoline (1)[3] and the corresponding isoquinoline analogue (2).



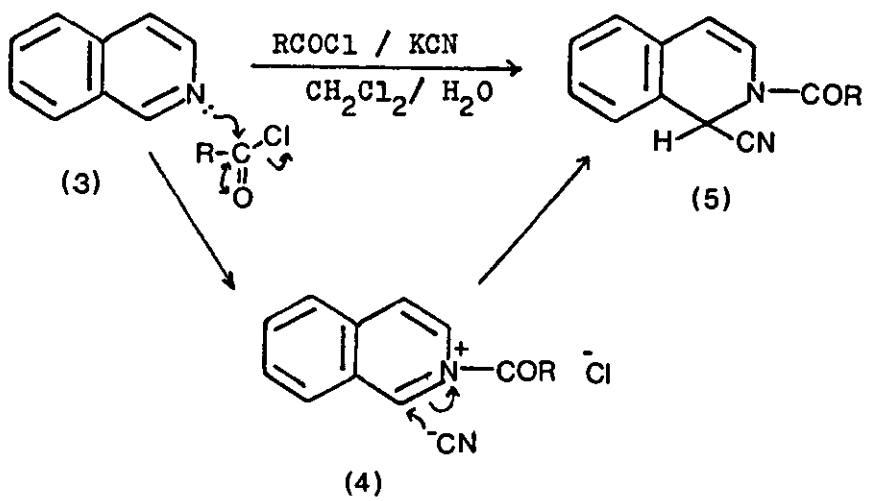

(1)



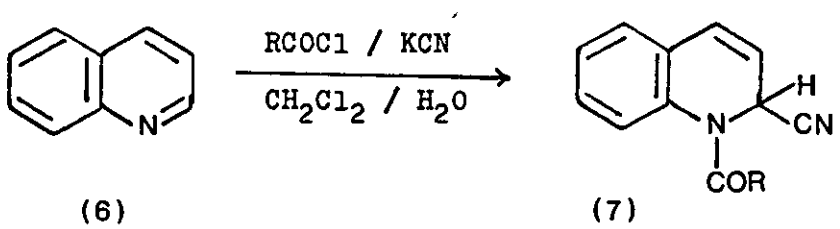

(2)

However, the now conventional and general method for the preparation of Reissert compounds, developed by F.D. Popp in 1961, is by the use of an acid chloride, inorganic cyanide and heterocycle in a two-phase medium of dichloromethane and water ($CH_2Cl_2/H_2O$)[4,5](Scheme 1), rather than the single aqueous phase system.

Scheme 1



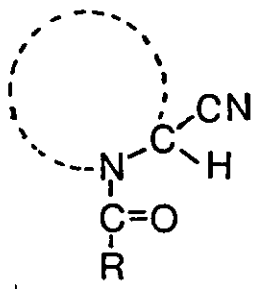

Similarly with quinoline (6)




Compounds of type (5) and (7) have been developed into useful intermediates for a variety of synthetic applications[1,2,6-10] in both heterocyclic and non-heterocyclic chemistry, but more so with the isoquinoline class of compounds.

As can be seen, the Reissert method allows modification at the C=N portion of the heterocycle when normally, the nitrogen-containing ring is the less reactive of the two rings.

Hence the characteristic features[1] of cyclic Reissert compounds are:-

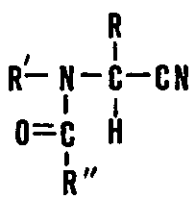



(8)

a) a tertiary amide group in which N is part of a heterocyclic ring.

b) a hydrogen atom and a cyano group bonded to a ring carbon atom adjacent to the ring nitrogen.

Compounds which are related to Reissert compounds have been prepared in which the acylated nitrogen is not part of a heterocyclic ring,[1,11] and such compounds have been termed open-chain Reissert analogues (9).



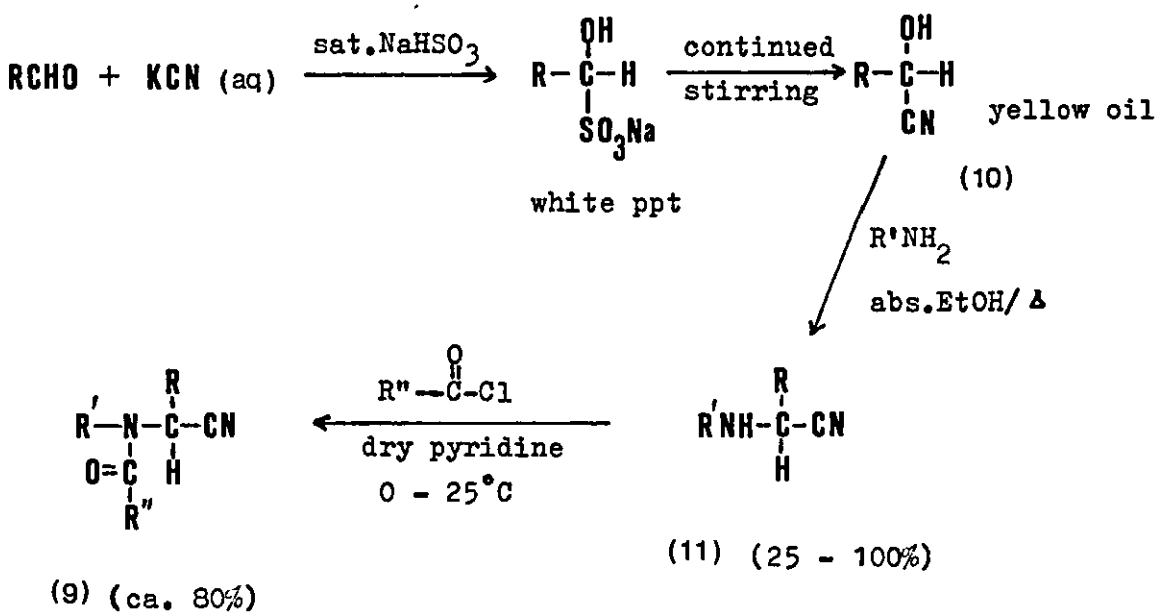

R=H, alkyl or aryl

R', R" = alkyl or aryl

(9)

A general procedure for the synthesis of this class of compounds is shown in Scheme 2.[11c]

Scheme 2




Open-chain Reissert analogues are generally stable, crystalline species which are easily purified by recrystallisation or column chromatography.

In general it is the Reissert compounds derived from heterocycles which have been used as intermediates for further synthetic studies.

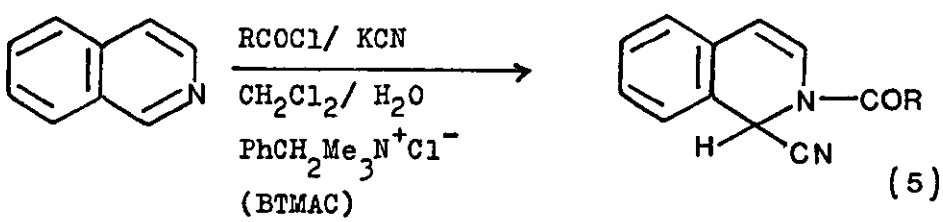
## B. Progressive Developments in the Preparation of Reissert Compounds

### 1. Preparation in mixed-solvent systems

As mentioned earlier, most Reissert compounds have been prepared in a two-phase reaction medium, usually dichloromethane and water as potassium cyanide is not adequately soluble in organic solvents.[4,5,7a]

The method was subsequently improved in 1977 following an

observation in this Department[12] and elsewhere[13] that a phase-transfer catalyst such as benzyltrimethylammonium chloride (BTMAC) facilitated the transfer of $^{-}CN$ from the aqueous phase to the organic phase, giving higher yields of Reissert compounds.




(5)

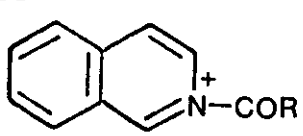
The role of the phase-transfer reagent can be represented as follows:-

Aqueous phase $[A^+X^-] + B^- \rightleftharpoons [A^+B^-] + X^-$

$\uparrow\downarrow$

Organic phase $[A^+X^-] + QB \rightleftharpoons [A^+B^-] + Q^+X^-$

where $A^+ = PhCH_2N^+Me_3$ ; $X^- = Cl^-$

$B^- = {}^-CN$ ; $Q^+ =$ 

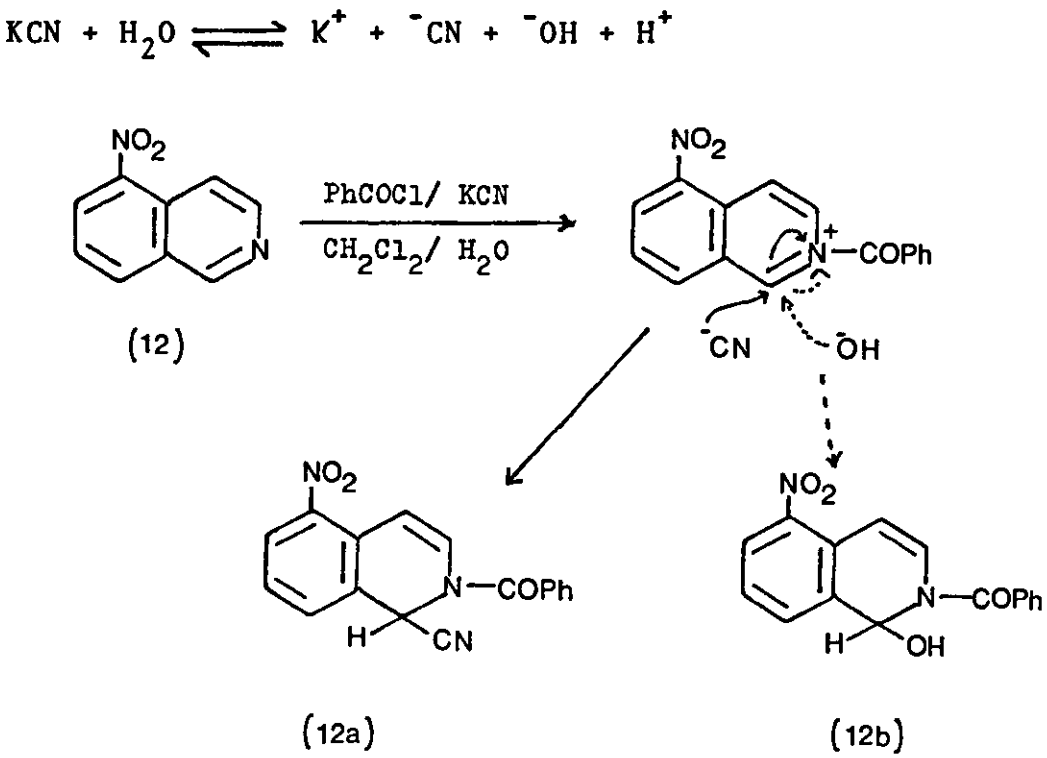

But the use of a two-phase medium has several shortcomings:-

i) both starting heterocycle and product Reissert compound are insoluble in water;

ii) the reactive acid halides can undergo hydrolysis;

iii) in the case of heterocycles such as 5-nitroisoquinoline (12)[14] the presence of water can lead to competitive formation of an N-acyl pseudo-base (12b) in addition to or instead of the required Reissert compound (12a) (Scheme 3).

Scheme 3

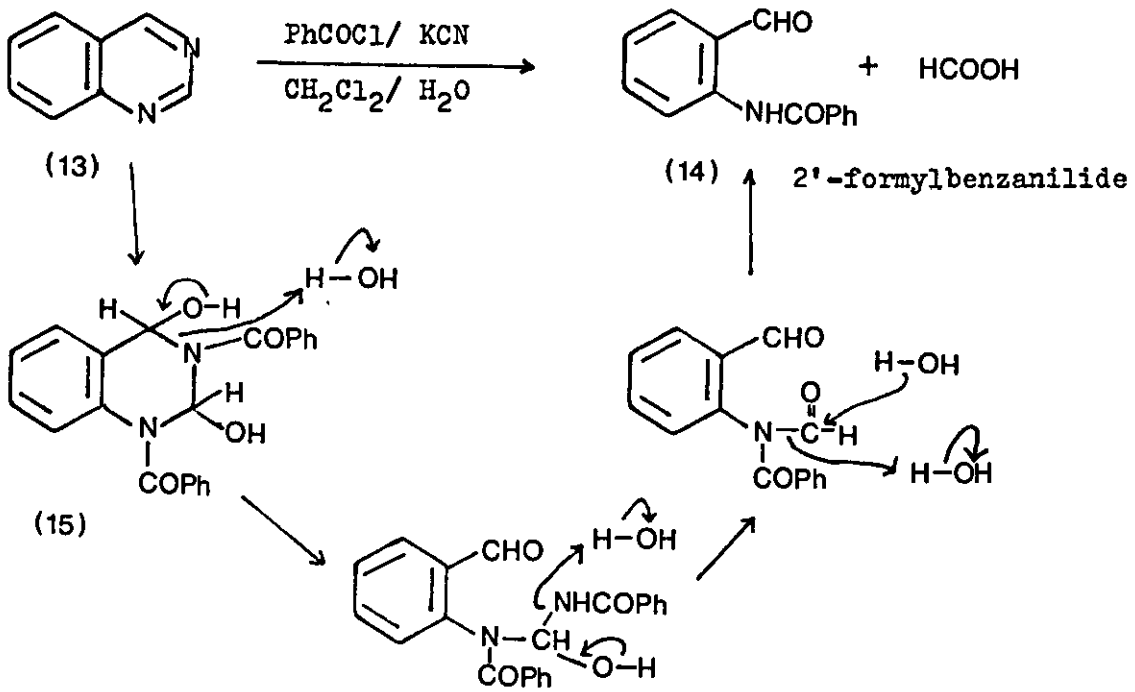



The reason for this change of pathway is that the presence of the electron-withdrawing group at position 5 makes C-1 more electrophilic i.e. a harder acid centre and therefore the harder base $^{-}OH$ from water, will attack C-1 preferentially since $^{-}CN$ is a softer base.[15]

This problem of N-acyl pseudo-base formation is further exemplified in the case of the six-membered ring diaza-heterocycle quinazoline (13) and with certain five-membered ring heterocycles. Under the two-phase conditions, ring opening occurs due to preferential attack by $^{-}OH$.

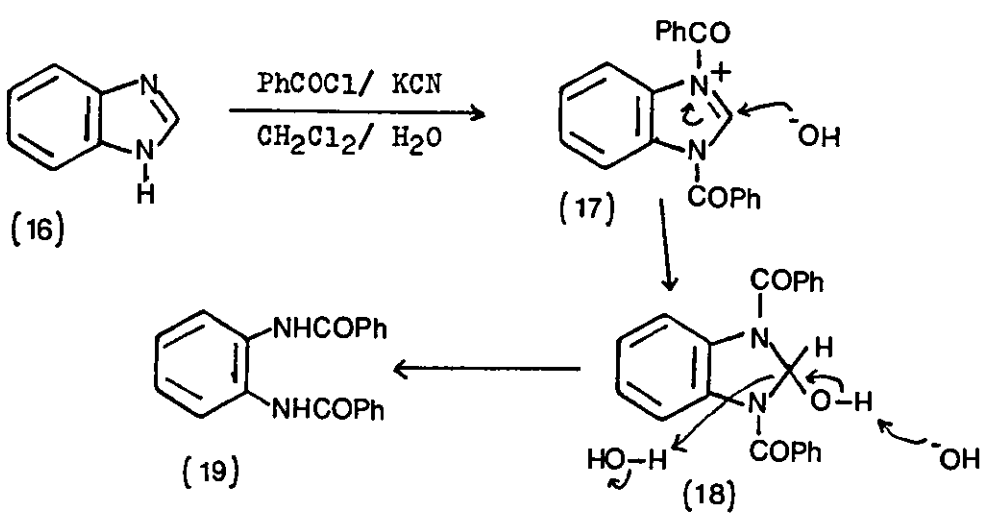
In the case of quinazoline, one mechanism proposed for its ring opening is described in Scheme 4, via the bis-N-acyl pseudo-base intermediate (15).[14a,16]

Scheme 4




Under similar reaction conditions, five-membered ring heterocycles such as benzimidazole (16) would undergo ring opening due to preferential attack by $^{-}OH$ and with probable involvement of the N-acyl pseudo-base (18)[14a] (Scheme 5).

Scheme 5




The idiosyncratic chemical reactivity of the more unconventional Reissert substrates therefore presented us with

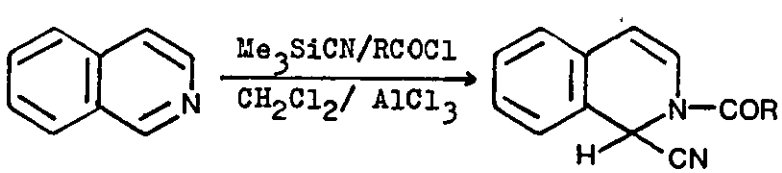
a challenge to the development of new procedures to achieve Reissert compound formation.

2. Preparation in non-aqueous media

Because of the problems observed with the use of the two-phase system, non-aqueous media have been investigated for the synthesis of Reissert compounds. Woodward[17] found that no reaction was observed when common solvents such as acetonitrile, acetone, benzonitrile, chloroform, dioxan or ether was substituted for water in the original procedure of Reissert.

One non-aqueous medium which was successful involved the use of anhydrous hydrogen cyanide[18], but this has obvious drawbacks.

More recently in 1977, Ruchirawat in Thailand[19a] reported the use of trimethylsilyl cyanide in anhydrous dichloromethane as a source of cyanide soluble in organic media, to form an isoquinoline Reissert compound (5), aluminium chloride being present as catalyst.[19]




(3) (5)

This suggested to us that trimethylsilyl cyanide under non-aqueous conditions might provide access to the formation of Reissert compounds from quinazoline and from appropriate five-membered ring heterocycles, where the reaction had failed

previously. Once prepared, such Reissert compounds would provide a new and potentially versatile means of extending the chemistry of the ring systems.

In view of our interest in the organosilicon reagent it would be appropriate to discuss briefly some distinctions between organosilicon compounds and carbon analogues.

Because silicon is just below carbon in the periodic table, a resemblance between the chemistry of the two classes of compounds is to be expected. But four important differences between carbon and silicon are as follows.[20]

i) Silicon, like carbon, is normally tetracovalent but silicon with its low-lying d orbitals can readily expand its octet to a coordination number of five or six. The electronic configuration C is $1s^2 2s^2 2p^2$ and that of Si is $1s^2 2s^2 2p^6 3s^2 3p^2$.

ii) The atomic radius and electron polarisibility of silicon are much greater than those of carbon.

iii) Silicon is electropositive compared with carbon and hydrogen whereas an H attached to C is positive relative to the carbon.

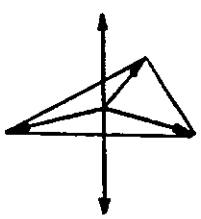
i.e. $Si^{\delta+}\!\!-\!\!C^{\delta-}$ ; $Si^{\delta+}\!\!-\!\!H^{\delta-}$ but $C^{\delta-}\!\!-\!\!H^{\delta+}$

iv) Silicon, like other second-row elements, is reluctant to participate in p-p$\pi$ bonds.

Certain bonds such as Si-O (ca. 531 $kJmol^{-1}$) are more stable than C-O bond (340 $kJmol^{-1}$). This is due mainly to the availability of empty 3d orbitals on silicon.[21] The silicones contain chains of Si-O-Si bonds and have a high thermal stability and are used as lubricants, hydraulic fluids

and synthetic rubbers.

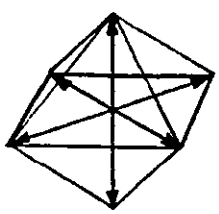
The nature of the d orbitals is such that hybridisation with s and p orbitals may lead to a number of alternative geometries. Of these, the most important in organic chemistry are the trigonal bipyramidal and octahedral geometries (Fig. 1).



$dsp^3$ trigonal bipyramidal

(s,px,py,pz,$dz^2$)

$90^o$ and $120^o$



$d^2sp^3$ octahedral

(s,px,py,pz,$dz^2$,$dx^2-y^2$)

$90^o$

Fig. 1 Hybridisation schemes involving d orbitals. Heavy arrows show the directions in which the lobes point. Bond angles are given.

Silicon compounds are much more susceptible to bimolecular nucleophilic substitution than are the corresponding carbon atoms.

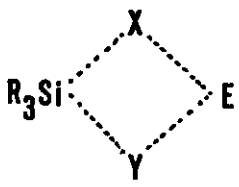
$$\geq Si\text{-}X + Z^- \longrightarrow Z\text{-}Si\leq + X^-$$

The reaction rather resembles an $S_N2$ reaction at carbon, with the possible difference that 3d-orbital participation may be involved in the stabilisation of transition states and/or unstable intermediates whose structures and free energy closely approximate the transition state. Such participation could make the silicon atom electron-rich in the transition state.

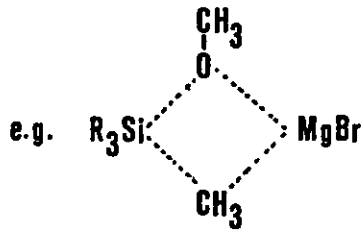
Bimolecular substitution reactions that occur with retention of configuration are often observed with acyclic compounds with poor leaving groups, especially in non-polar

solvents. In a large number of such reactions, the attacking reagent (E-Y) may give an electrophilic assistance to the leaving group (X).[20]

i.e.

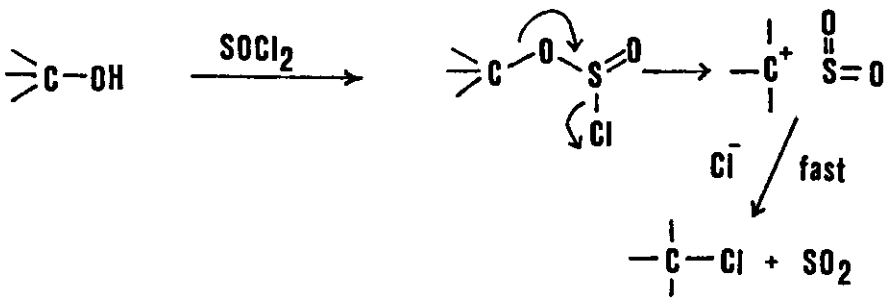


e.g.

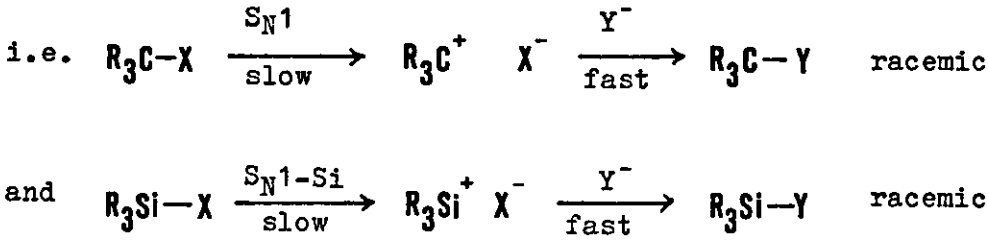


Nucleophilic substitution reactions with retention of configuration at carbon sometimes occur via ion-pair formation.[22]

e.g.



But such reactions occur at silicon atoms without the involvement of siliconium-ion pairs. It might, however, be predicted that siliconium ions would intervene in nucleophilic substitution reactions as readily as would carbonium ions, especially since silicon is more electropositive than carbon.



As yet, no unequivocal example of a reaction by this path

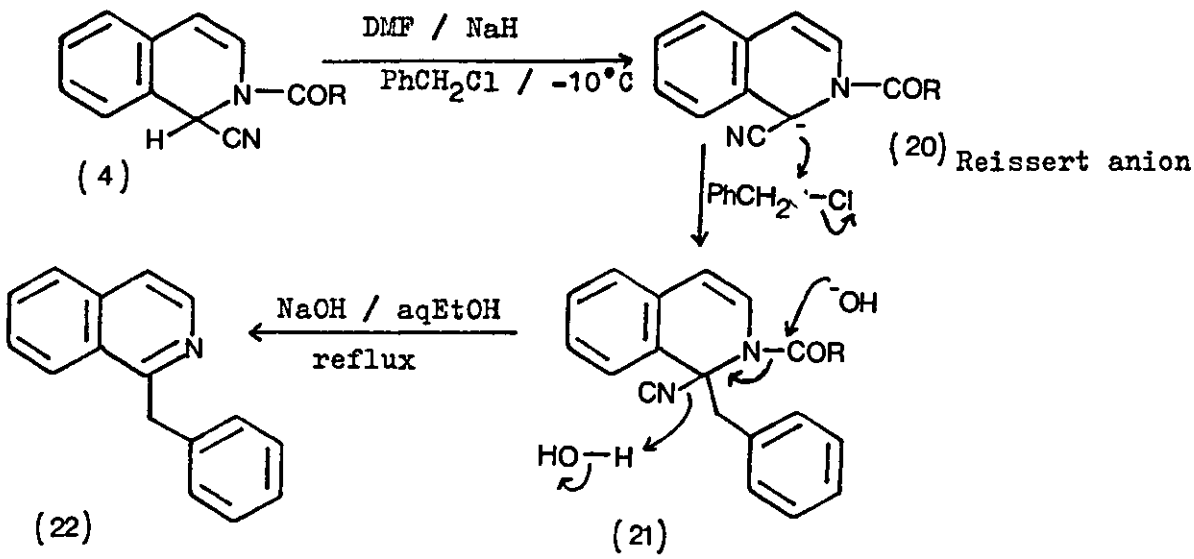
is known. When even poor nucleophiles are present, it appears that the $S_N1$-Si pathway is simply unable to compete with $S_N2$-Si reactions. This may be because siliconium ions are generally less stable than carbonium ions, but a more likely reason is that bimolecular substitution occurs so readily at the silicon atom that mechanisms involving siliconium ions have no chance to compete.

C. Some Chemistry and Reactions of Reissert Compounds

As mentioned earlier, Reissert compounds have been widely used as important intermediates for heterocyclic modification and in the synthesis of appropriate alkaloids and biologically useful compounds.[1]

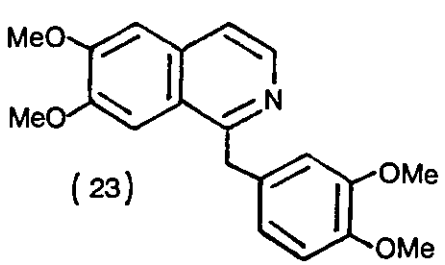
1. Isoquinoline Reissert compounds(4) in particular, have been used for synthesising 1-benzylisoquinoline alkaloids.[8a,23] The Reissert anion may be generated using sodium hydride in dimethylformamide at $0^{o}C$ (20). Once prepared the anion can take part in a variety of synthetic schemes. Alkylation with benzyl halide followed by hydrolysis gives 1-benzylisoquinoline (22) (Scheme 6).

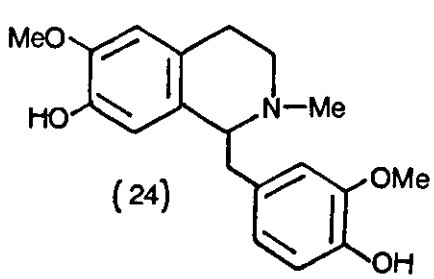
Scheme 6

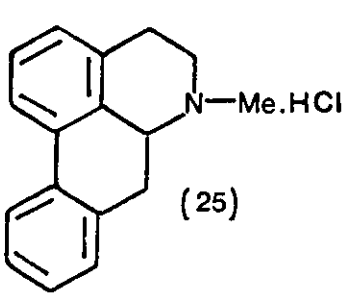


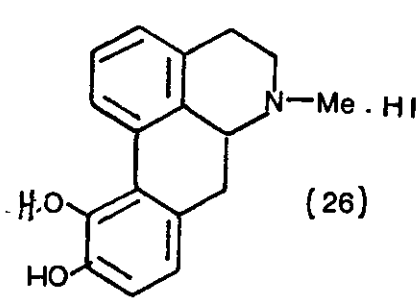

Alkaloids based on 1-benzylisoquinoline structures (22) are abundantly found in nature and have been the subject of extensive chemical and pharmacological investigations.[8a,23]

Examples of such alkaloids prepared via Reissert compounds are papaverine (23)[18a], reticuline (24)[1,24], aporphine hydrochloride (25)[25] and apomorphine hydroiodide (26).[26]



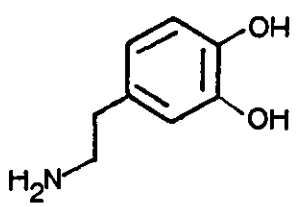



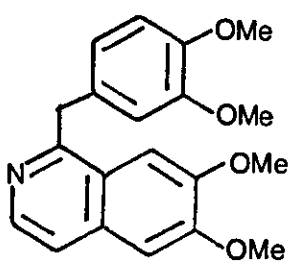




Papaverine (23) is one of the main benzylisoquinoline derivatives in opium (from the seeds of the Oriental poppy

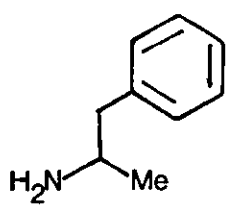
Papaver somniferum). Papaverine itself does not possess analgesic activity, but it is said to potentiate the analgesic action of morphine. It also has a stimulant action on the dopamine receptors in the central nervous system and its structure is chemically related to other drugs with this action, e.g. (27-30).[27]



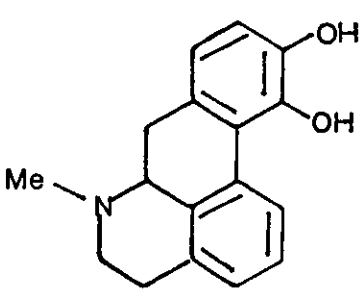

(27)
dopamine



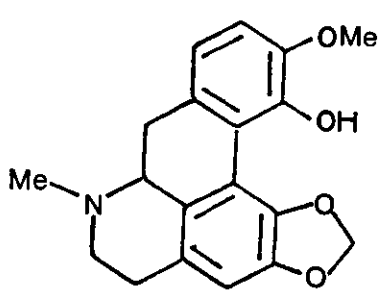

(23) papaverine




(28) amphetamine




(29) apo morphine



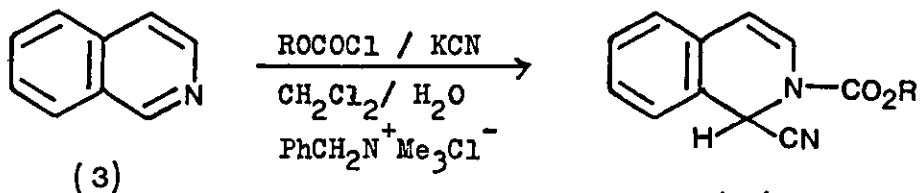

(30) bulbocapnine

The beneficial effect of drugs that stimulate central dopamine receptors led to attempts to synthesise drugs with a selective action in the hope that they would have value in the treatment of Parkinsonism, a disease characterised by muscular rigidity and tremors.

## 2. Reissert compounds derived from chloroformates

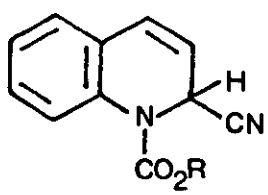
Reissert compounds have also been prepared by reacting, e.g. quinoline or isoquinoline with potassium cyanide and a variety of chloroformates[28] (Scheme 7).

Scheme 7



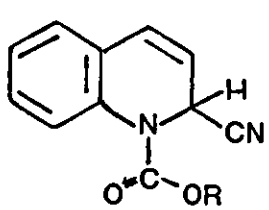

(3) (31)

and similarly,




(32)

Most of the first examples prepared by Popp et al[28] were submitted to the National Cancer Institute (NCI) for screening against L1210 lymphoid leukaemia in mice.[29] It was found that the isoquinoline series of compounds were inactive (T/C against L1210 leukaemia was less than 111, where T/C was the ratio of survival time of treated to control animals expressed as a percentage) as antineoplastic agents, but that the quinoline analogue, where R=methyl i.e. 2-cyano-1,2-dihydro-1-methoxycarbonylquinoline (32) was highly active, giving a T/C ratio of 209% with a dosage of 100 $mgkg^{-1}$.




(32, R = Me)

None of the other related analogues showed such appreciable activity, the next most active analogue which was where R = $C_6H_5$-, showing a T/C value against L1210 leukaemia of 113% at a dosage of 400 $mgkg^{-1}$.

3. Formation of Reissert compounds using heterocycles other than isoquinoline and quinoline

Strictly speaking, the term "Reissert compound" applies only to those compounds derived from quinoline or isoquinoline utilising an aroyl or acyl chloride and the term Reissert analogue should be given to other related compounds. The literature however, is not consistent and both terms are found applied to species derived from a variety of heterocyclic bases and of acid chlorides (e.g. RCOCl, $RSO_2Cl$, ROCOCl, $R_2NCOCl$).

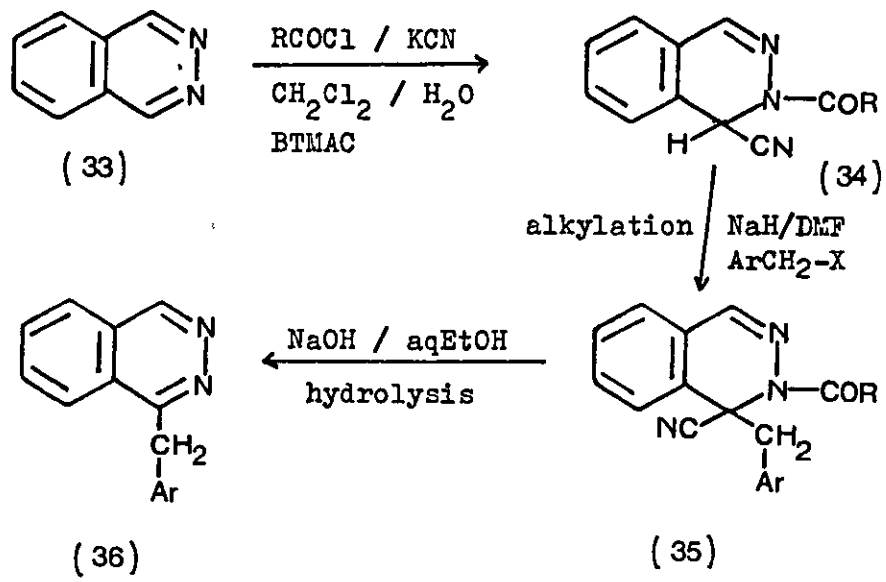
i) Reissert compound formation from some diazaheterocycles

a) From phthalazine (33)

A particularly active field of research recently has been the study of Reissert compounds from phthalazine, e.g. (34) compounds (Scheme 8) which are also of potential biological interest.[8b,12,13,30-36]

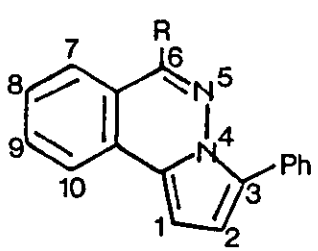
Treatment of the phthalazine Reissert compound (34) with benzyl halides and sodium hydride in dimethylformamide has given adduct of the type (35) via the anion, which can then be hydrolysed with sodium hydroxide to 1-benzylphthalazine (36) (Scheme 8).[30]

Scheme 8




Certain substituted phthalazines and fused ring phthalazines are of importance or potential importance as antihypertensive agents.

Previous research, in this Department,[37] into systems such as (37) has shown activity against hypertension.



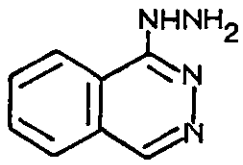
(37) pyrrolo[2,1a]phthalazine system

Antihypertensive activity was observed with compounds where

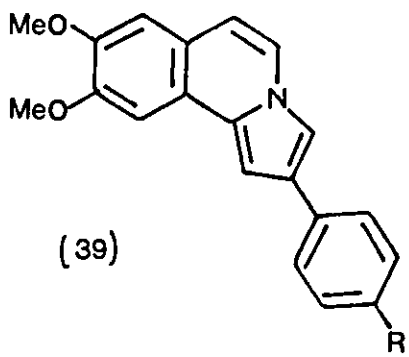
R = $NH\text{-}NH_2$ ; OEt ; $OCH_2CH = CH_2$ ; COMe

Interest in the synthesis of such tricyclic systems as (37) as potential antihypertensive agents was based in part, on the

known active phthalazine drug hydrallazine (38) and on the antihypertensive activity of the tricyclic systems[38] of the type (39).




(38)



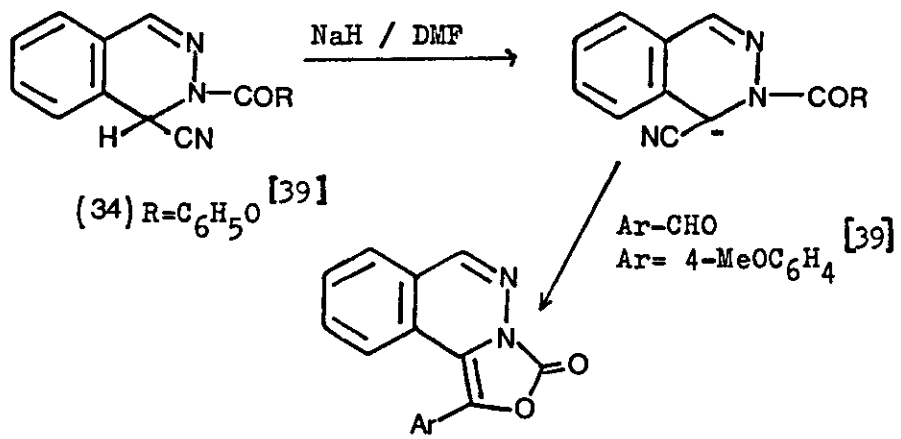

(39)

R=H; OMe; $OCH_2C_6H_5$; OH;
$(CH_2)_2NMe_2$; $CH_2$-$CH_2$-N

Hydrallazine (38) has a direct dilating action on blood vessels, relaxing vascular smooth muscle and hence reducing peripheral resistance significantly.

The synthesis of the novel 3H-oxazolo[4,3a]phthalazine system (40) has been achieved in low yield by F. Hussain in this Department.[39] This was formed from the generation of the anion from the phthalazine Reissert compound (34) using sodium hydride followed by condensation with an aromatic aldehyde (Scheme 9).

Scheme 9



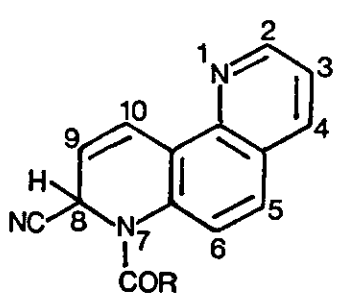

(34) R=$C_6H_5O$ [39]

(40) 1-aryl-3H-oxazolo[4,3a]phthalazin-3-one

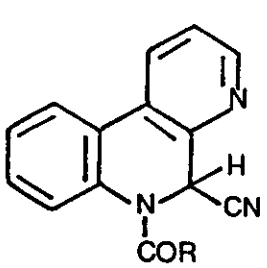
One of the objectives of this project was to examine further the synthesis of the system (40), to give a route with improved yields.

b) From phenanthrolines

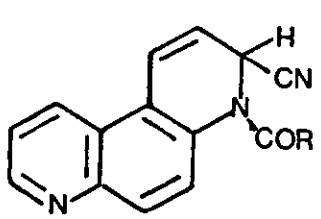
Reissert compounds have been formed from a variety of other heterocyclic nitrogen compounds including 1,7-phenanthroline (41) and 4,6-phenanthroline (42) and 4,7-phenanthroline (43).[40]




(41)




(42)

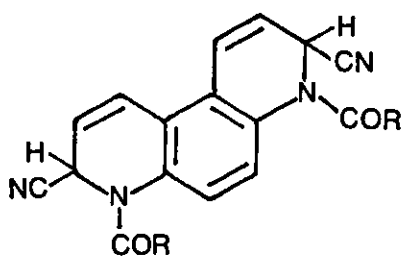



(43)

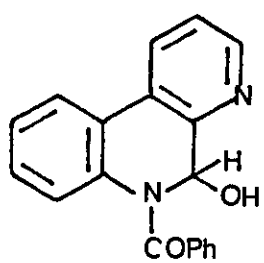
In the case of 1,7-phenanthroline, no bis-Reissert compound was formed, i.e. under no conditions could a bis-Reissert compound be isolated as a result from reaction at the N-1

position. This is in accord with the observation that 8-substituted quinolines do not usually form Reissert compounds,[6,41] due probably to steric inhibition.

Reaction of 4,7-phenanthroline with benzoyl chloride and potassium cyanide in $CH_2Cl_2/H_2O$ gave (43, R=$C_6H_5$), but treatment of 4,7-phenanthroline with benzoyl chloride and trimethylsilyl cyanide in the presence of a catalytic amount of aluminium chloride in $CH_2Cl_2$ afforded 3,8-dicyano-4, 7-dibenzoyl-3,4,7,8-tetrahydro-4,7-phenanthroline (44).[8b]




(44, R=Ph)




(45)

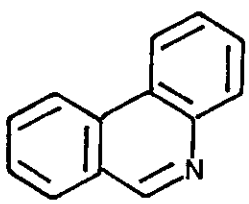
Compound (44) was the first preparation of a true bis-Reissert compound. An analogue of (44) where R=OEt was also prepared.[8b]

Reaction of 4,6-phenanthroline with benzoyl chloride and potassium cyanide in $CH_2Cl_2/H_2O$ gave the N-acyl pseudo-base (45), which could be reconverted to 4,6-phenanthroline on treatment with base.

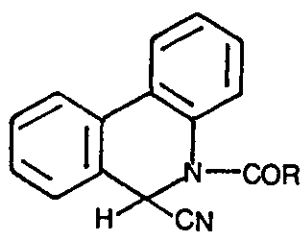
However, use of trimethylsilyl cyanide in a single phase medium gave rise to the mono-Reissert compound (42, R=Ph) which could also be obtained by the two-phase method on inclusion of a phase-transfer catalyst.[8b]

The Reissert compounds (42) are analogous to those from the monoaza system phenanthridine (46). Such Reissert compounds

(47) have been prepared in high yields by the slow addition of freshly distilled benzoyl chloride in $CH_2Cl_2$ to trimethylsilyl cyanide in $CH_2Cl_2$.[42] A series of Reissert compounds were prepared in a similar manner from appropriate acid chlorides, chloroformates and benzenesulphonyl chlorides. Other routes have also been recorded.[43,44]



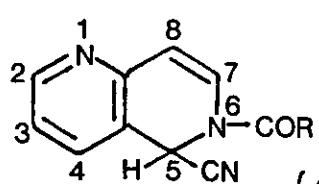

(46)



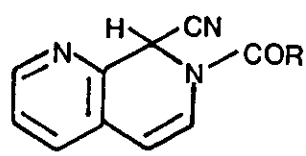

(47)

c) From naphthyridine

Reissert compounds have also been formed using 1,6-naphthyridine as the heterocycle (48) and from 1,7-naphthyridine (49).[45]




(48)

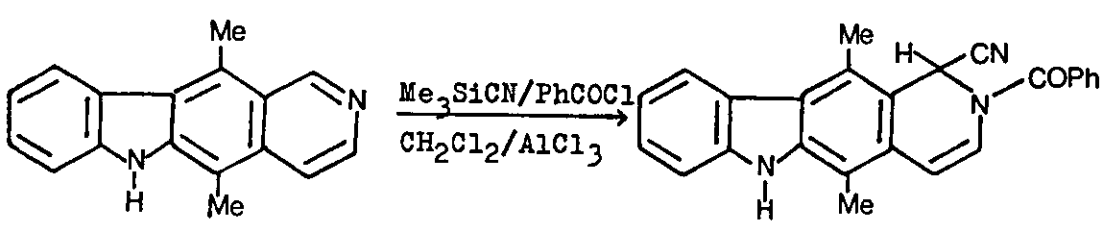



(49)

d) From ellipticine

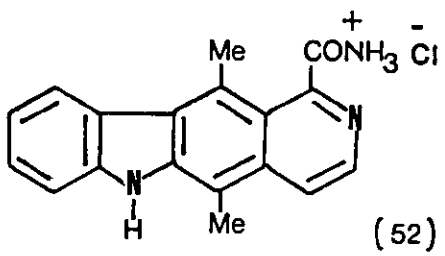
Reaction of ellipticine (50)[19c,46] with benzoyl chloride and trimethylsilyl cyanide afforded the Reissert compound 2-benzoyl-1-cyano-1,2-dihydroellipticine (51) (Scheme 10).

Scheme 10




(50) (51)

Interest in this series of Reissert compounds arose after the discovery of anti-tumour activity in ellipticine[47] and related compounds. It was thought that such Reissert compounds were potential antineoplastic agents. A series of ellipticine Reissert compounds were prepared and screened against P388 lymphocytic leukaemia in mice at the National Cancer Institute, but the only compound which gave appreciable activity was the hydrochloride of ellipticine-1-carboxamide (52) (T/C of 134% at dosage of 400 $mgkg^{-1}$ compared with ellipticine T/C of 190% at 100 $mgkg^{-1}$; T/C being the ratio of survival time of treated to control animals expressed as a percentage).

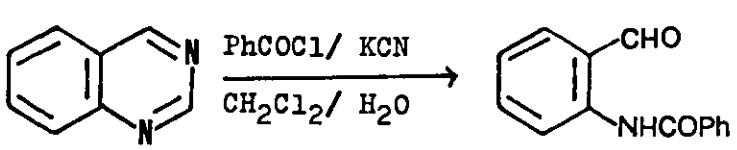



(52)

e) From quinazoline

As discussed earlier (p 7 ), quinazoline ring-opens under the conventional conditions for Reissert compound formation, i.e. with a two-phase medium $CH_2Cl_2/H_2O$, to give 2-formylbenzanilide (14).[14a]

Scheme 11

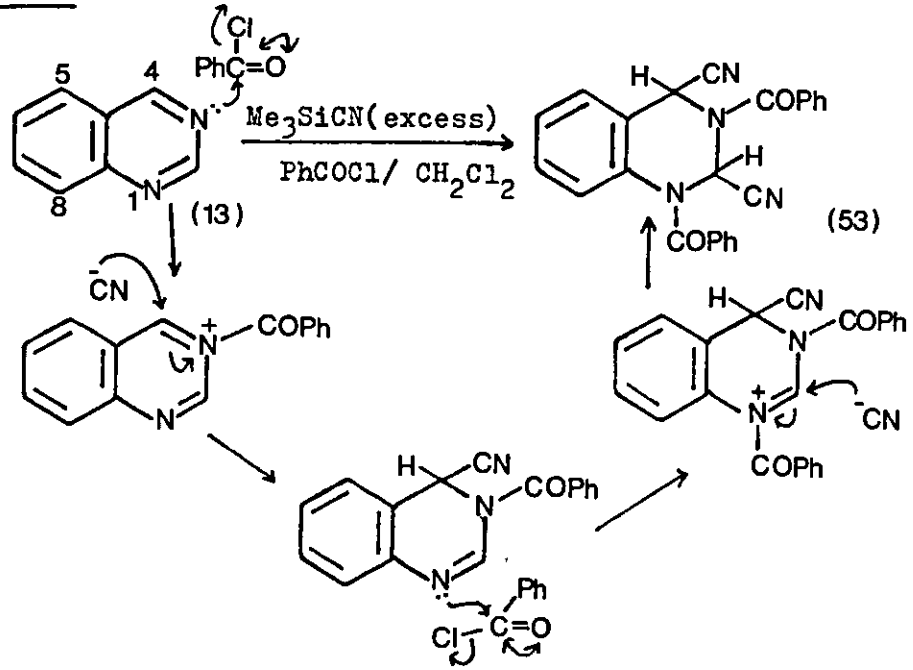



(13) (14)

But this problem has been overcome by the use of trimethylsilyl cyanide in a single non-aqueous medium,

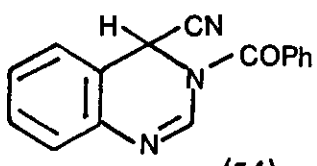
$CH_2Cl_2$. The reaction of quinazoline with an excess of trimethylsilyl cyanide and benzoyl chloride leads to the bis-Reissert compound (53)[48](Scheme 12).

Scheme 12




Mono-Reissert compound formation could in theory occur at either the more reactive 3,4 C=N or at the less reactive 1,2 C=N. Popp and Uff et al[49] and Higashino et al[50] in Japan showed that using equimolar ratios of reagent and substrates, mono-Reissert compound formation occurred across the 3,4 double bond.

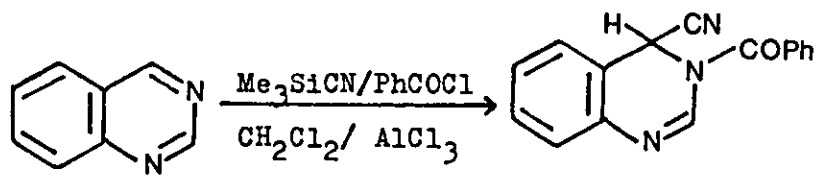
Higashino and co-workers[50] achieved the mono-Reissert compound formation via an indirect two-step procedure involving reaction of quinazoline with hydrogen cyanide to give 4-cyano-3,4-dihydroquinazoline which was then benzoylated to yield compound (54).



(54)

The Reissert compound (54) was prepared in 67% yield by Popp and Uff et al[49] using a more convenient one-step procedure utilising trimethylsilyl cyanide (Scheme 13).

Scheme 13



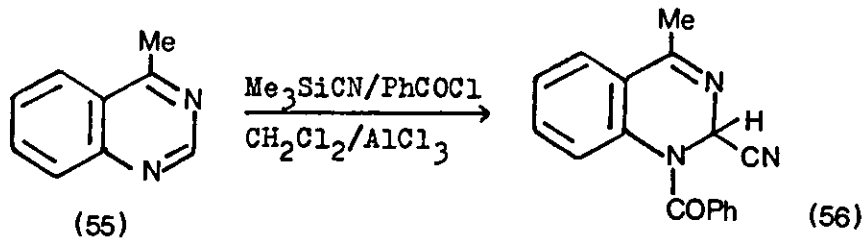

(13) (54)

In this Department, the problem of selectively functionalising the 1,2 C=N was approached[49a,b,d] and studies were concentrated on blocking position 4 of the quinazoline ring.

Miss B.L. Joshi[49a] initially carried out studies in Reissert compound formation using 4-methylquinazoline (55) as the starting heterocycle.

Reaction of the heterocycle (55) with trimethylsilyl cyanide and benzoyl chloride in dichloromethane gives the mono-Reissert compound (56) (Scheme 14).[49b,d]

Scheme 14

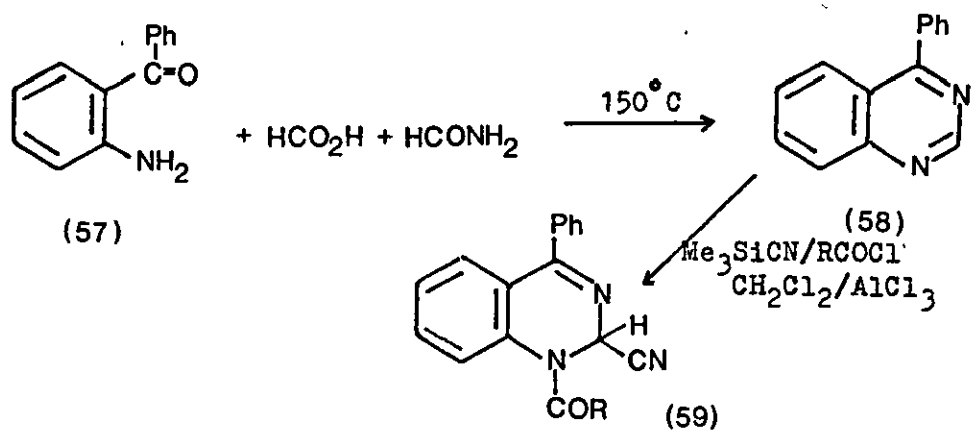



(55) (56)

But the use of the methyl group as a substituent at C-4 was not ideal because of the tendency of the products to form oils on exposure to moisture. However, a series of Reissert compounds (59) were prepared successfully and in generally good yields, using 4-phenylquinazoline (58) as the starting

heterocycle, the products showing no tendency to undergo covalent hydration (Scheme 15).[49d]

Scheme 15

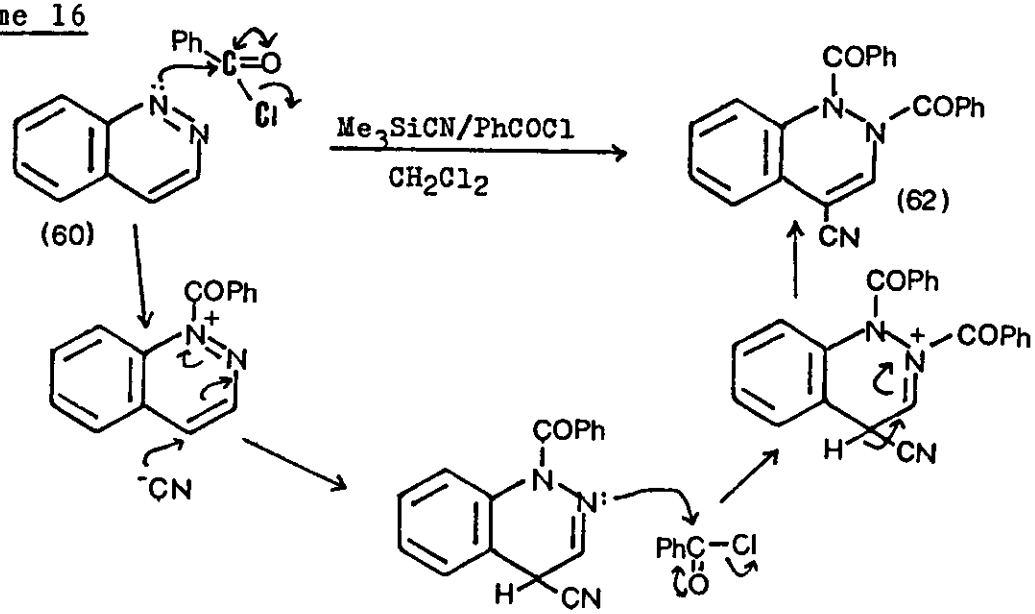



Reissert compounds from 4-phenylquinazoline (58) may lead to compounds of interest pharmacologically as derivatives of the quinazoline ring have found considerable application in medicine, providing examples of antihypertensive agents, diuretic agents, sedative and hypnotic agents, antihistamines and antitumour agents.[51]

f) From cinnoline (60) and quinoxaline (61)[48]

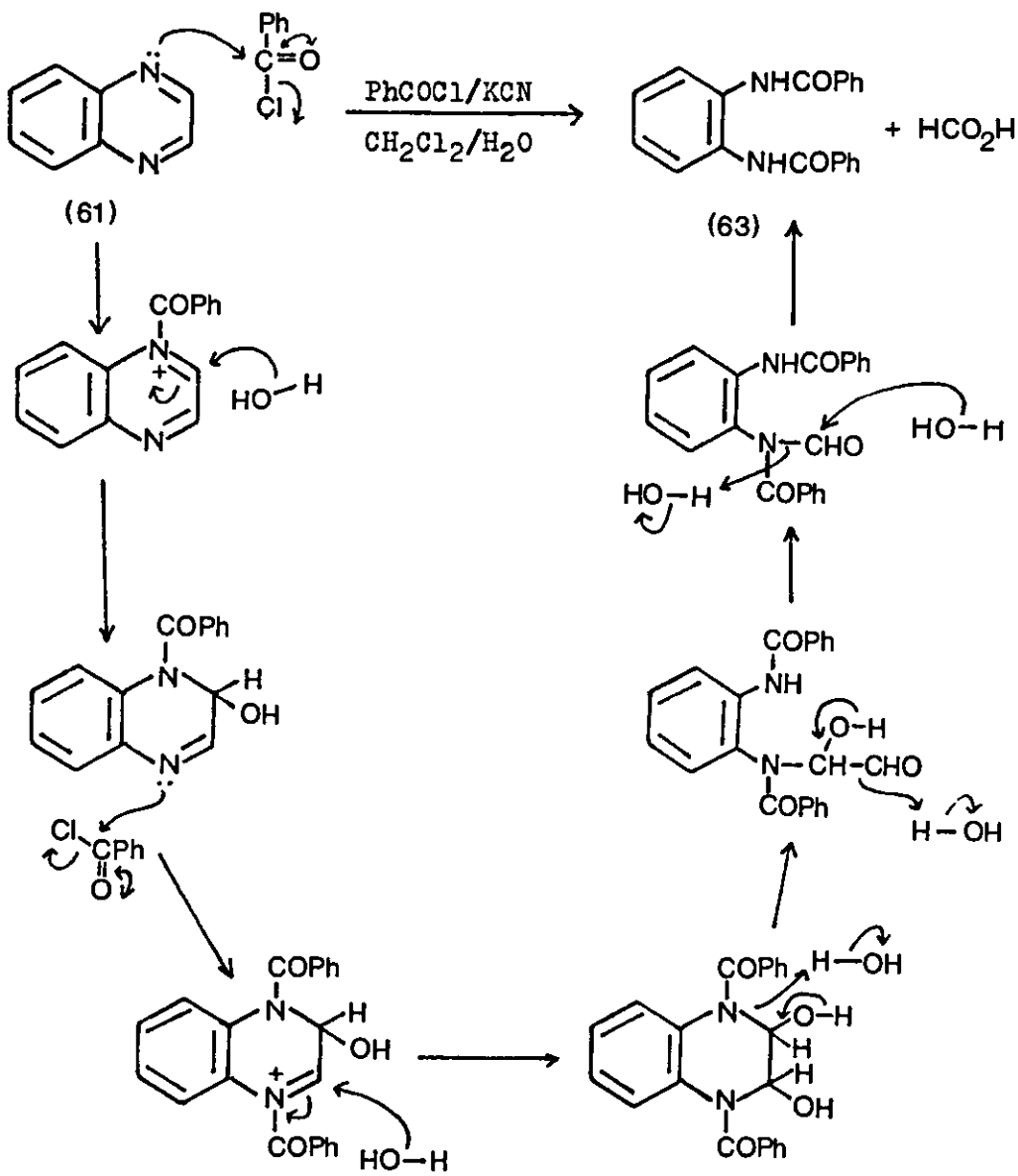
Treatment of cinnoline with benzoyl chloride and trimethylsilyl cyanide in dichloromethane gave structure (62). We present a possible mechanism (Scheme 16).

Scheme 16



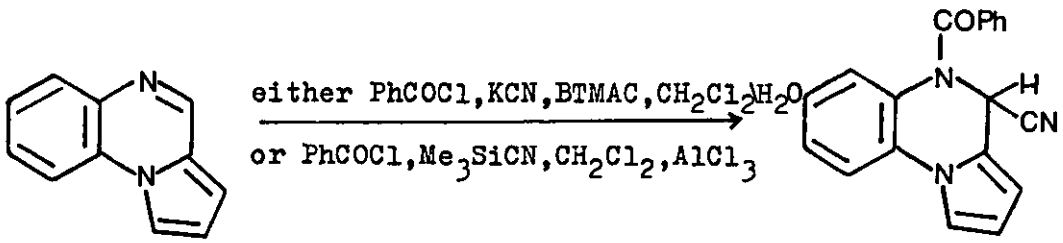
The isomer quinoxaline (61) has been reported[48] to undergo ring opening to o-phenylenediaminedibenzamide (63) when reacted with benzoyl chloride and potassium cyanide in $CH_2Cl_2/H_2O$. We show a possible mechanism (Scheme 17).

Scheme 17




Although quinoxaline itself undergoes ring opening, a tricyclic analogue pyrrolo[1,2-a]quinoxaline (64) does form a Reissert compound (65)[52] (Scheme 18).

Scheme 18



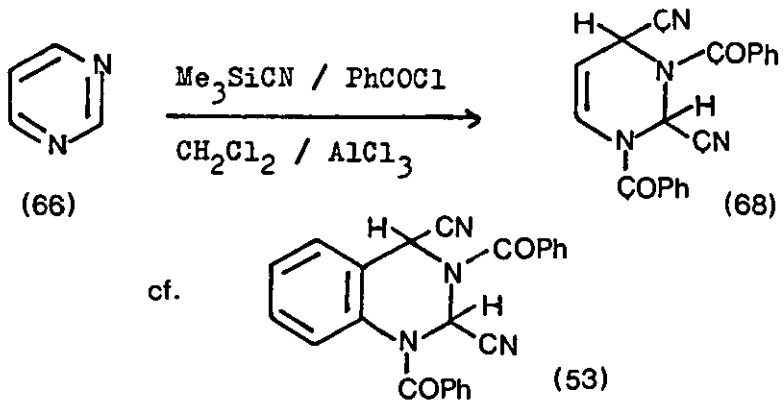

(64) (65)

ii) Monocyclic Reissert Compounds

The first two examples of monocyclic Reissert compounds were recently prepared by Popp and co-workers[19c] in 1981, using pyrimidine (66) and 3-methylpyridazine (67) as the starting heterocycles.

It was found that pyrimidine reacts at room temperature with trimethylsilyl cyanide, benzoyl chloride and a catalytic amount of $AlCl_3$ in $CH_2Cl_2$ to give the bis-Reissert compound (68) in 59% yield. The formation of 1,3-dibenzoyl-2,4-dicyano-1,2,3,4-tetrahydropyrimidine (68) from pyrimidine is analogous to the formation of the bis-Reissert compound (53) from quinazoline (Scheme 19).

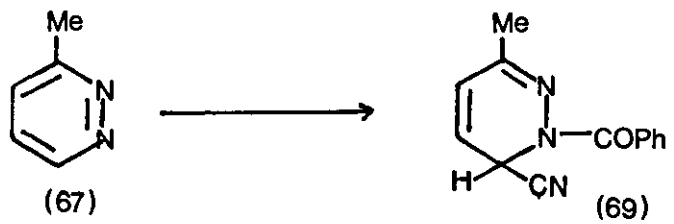
Scheme 19




(66) (68) (53)

A similar reaction carried out with 3-methylpyridazine gave

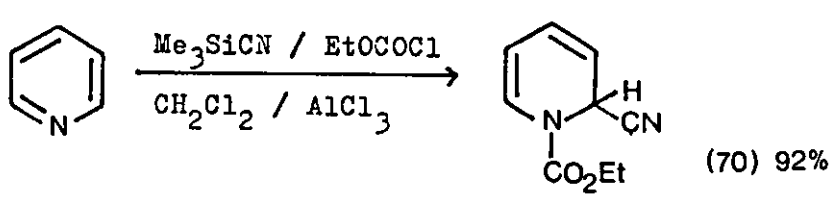
a 41% yield of the corresponding Reissert compound (69).




Some time ago, Reuss and Smith and Winters[53] reported the preparation of a pyridine Reissert compound (70) in 25% yield by treatment of pyridine and sodium cyanide with ethyl chloroformate using a two-phase $CH_2Cl_2/H_2O$ system.

Popp et al[54] more recently reported the preparation of the same compound (70) in 92% by stirring anhydrous pyridine in dry dichloromethane with trimethylsilyl cyanide and ethyl chloroformate with a catalytic amount of $AlCl_3$ at room temperature for four hours (Scheme 20).

Scheme 20




Popp also found that the use of benzyltrimethylammonium chloride (1%) as a phase transfer catalyst in the $CH_2Cl_2/H_2O$ method gave compound (70) in 75-85% yield.

iii) Reissert compound formation with five-membered ring heterocycles

As discussed earlier, previous attempts at forming five-membered ring Reissert compounds have failed because under normal two-phase conditions, ring opening occurs (p7 ).

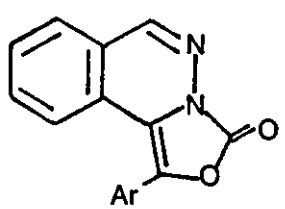
Therefore, this presented a major challenge, to investigate

the synthesis of such Reissert compounds, which once prepared, could provide a new and potentially versatile means of extending the chemistry of these five-membered ring systems as has been found with the six-membered ring Reissert compounds.

# DISCUSSION

## CHAPTER I The Use of Phthalazine Reissert Compounds in Heterocyclic Syntheses

As mentioned in the Introduction (p.19), the synthesis of the novel 3H-oxazolo[4,3-a]phthalazine system (40,Ar = p-$MeOC_6H_4$-) was achieved in low yield (14%) by F. Hussain in this Department,[39] but the product was only characterised by infrared and nmr spectral data.

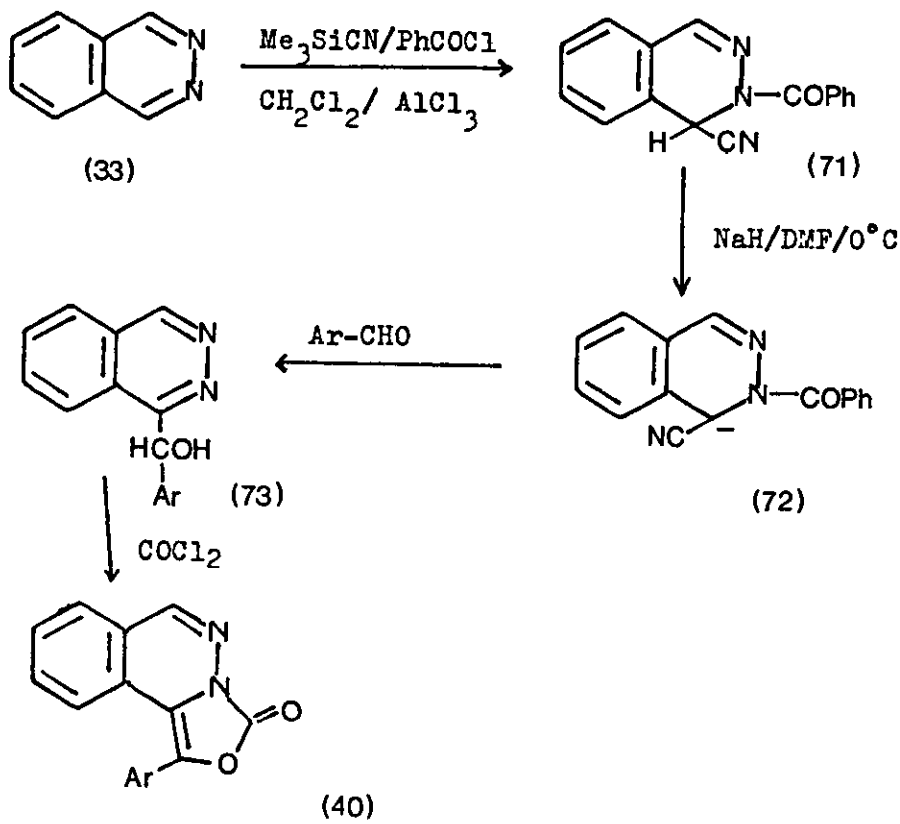



(40)

In view of the possible biological activity of the ring system, we considered it worthwhile to endeavour to improve the synthesis of (40) by a different route.

The general scheme that was examined is described below (Scheme 21).

Scheme 21

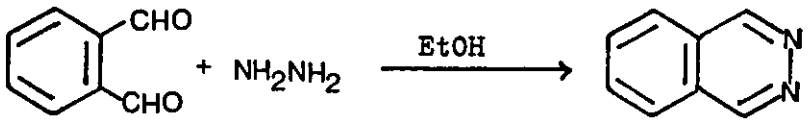



The sequence of reactions involved will now be considered individually.

i) Preparation of phthalazine

We used the method of Hirsch and Orphanos[55] to prepare phthalazine (33). Ring closure was achieved by reacting o-phthalic dicarboxaldehyde (74) with hydrazine hydrate in ethanol stirring at 0°C initially, and then at room temperature (Scheme 22). Phthalazine was obtained as cream-coloured needles in 91% yield, m.p. 88-90°C, lit[55] 90-91°C. The nmr spectrum showed the C-1 and C-4 protons at $\delta$9.30.

Scheme 22

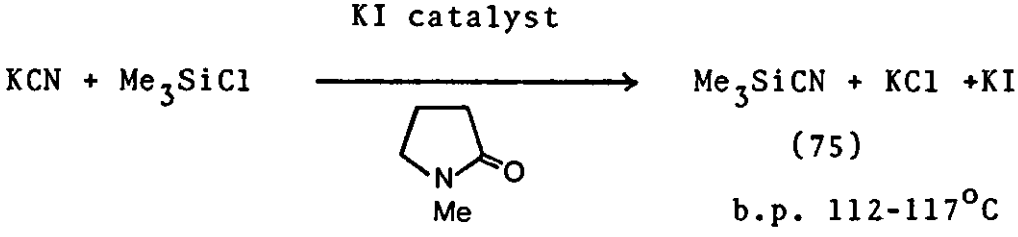



(74) (33)

ii) Preparation of trimethylsilyl cyanide (75)

For the preparation of Reissert compounds in a single, non-aqueous phase system, the reagent trimethylsilyl cyanide was adopted as the key source of cyanide. Commercial samples could be purchased (Aldrich Chemical Co.), but in view of the cost, we examined the various literature methods for its preparation.

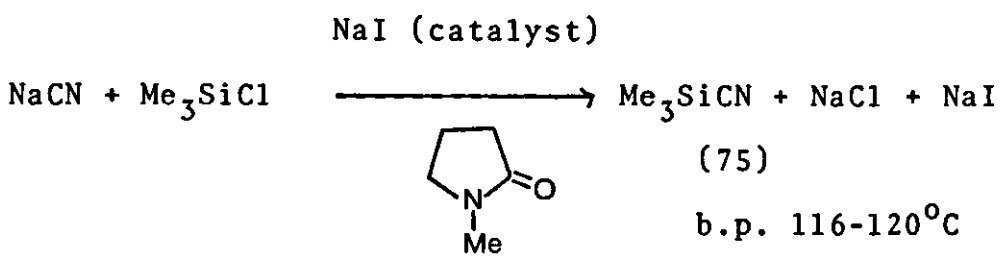
The method of Reetz and Chatziiosifidis[56] used potassium cyanide: trimethylsilyl chloride: N-methylpyrrolidinone in the mole ratio of 5:5:1 with potassium iodide (0.5 mole ratio) as a catalyst, stirred at room temperature for 12 hours. The product is distilled directly from the reaction flask.




A yield of 86-87% was claimed by the authors[56] using this procedure. Although we have carried out this preparation on many occasions, we have not managed to obtain the yield of $Me_3SiCN$ (75) beyond 30-35% even after varying the reaction conditions. We achieved a 35% yield of $Me_3SiCN$ by refluxing the reaction mixture for 3 hours and after cooling, allowed it

to stir at room temperature overnight before distilling directly from the reaction flask. However, some trimethylsilyl chloride was recovered and the yield of trimethylsilyl cyanide based on this recovery was 85%.

An alternative method by Hunig and co-workers[57] using sodium cyanide, trimethylsilyl chloride and a large excess of N-methylpyrrolidinone, claimed a yield of trimethylsilyl cyanide of 65-80%, but under these conditions, we obtained only 18% yield.




Reetz and Chatziiosifidis[56] also described what they regarded as a more straightforward method for the synthesis of trimethylsilyl cyanide. They claimed that a yield of 85% was obtained by stirring a suspension of sodium cyanide and sodium iodide in trimethylsilyl chloride at room temperature for 75 hours in the absence of the solvent N-methylpyrrolidinone. But on following this method, we obtained no trimethylsilyl cyanide but only recovered trimethylsilyl chloride.

The catalytic effect of potassium or sodium iodide may be rationalised by assuming trimethylsilyl iodide is formed as an intermediate, thus providing a better leaving group on attack by cyanide.

$$Me_3Si\text{-}Cl \xrightarrow{NaI} Me_3Si\text{—}I \longrightarrow Me_3SiCN + NaI$$
$$\qquad\qquad\quad \uparrow$$
$$\qquad\qquad\quad {}^{-}CN$$

In addition to the safe handling of cyanide (see Experimental) the following precautions were observed. The apparatus used in the preparations were carefully dried, the finely ground inorganic cyanide was kept in a vacuum desiccator overnight and N-methylpyrrolidinone was freshly distilled and stored over potassium hydroxide.

These precautions were taken so to minimise presence of moisture which would have an adverse effect on the preparation as trimethylsilyl cyanide is converted to hexamethyldisiloxane (76) (b.p. 100°C).[58]

$$2\ Me_3SiCl + H_2O \longrightarrow Me_3SiOSiMe_3 + 2\ HCl$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (76)$$

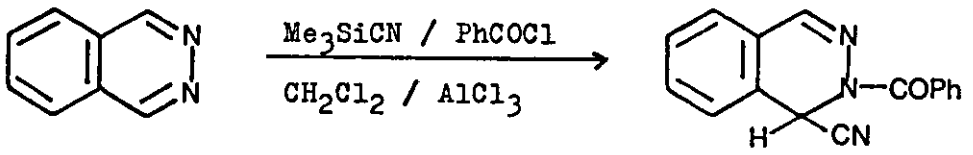
Other literature procedures for the preparation of (75) appeared to offer no further advantages over the above methods.[57,59]

To date, the mechanistic involvement of trimethylsilyl cyanide in the formation of Reissert compounds has not been discussed in the literature, and we comment on the topic later in the thesis (p.61 ).

iii) Preparation of a phthalazine Reissert compound

Use of phthalazine: benzoyl chloride: trimethylsilyl cyanide in the molar ratio of 1:1:1 gave 2-benzoyl-1-cyano-1, 2-dihydrophthalazine (71) in 80% yield, m.p. 165-166°C, lit[28] 163-164°C (Scheme 23).

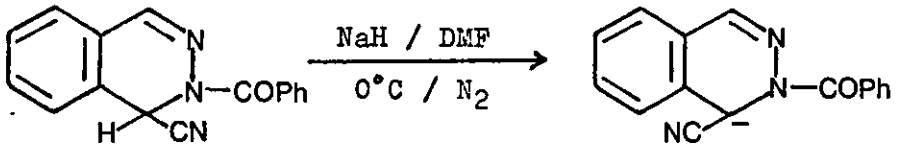
Scheme 23




(33) (71) 80%

The infrared of the Reissert compound (71) shows the amide carbonyl absorption frequency at 1650 $cm^{-1}$ and a weak absorption for the cyano grouping at 2250 $cm^{-1}$. The pmr included a sharp singlet at $\delta$6.75 which is likely to be the C-1H.

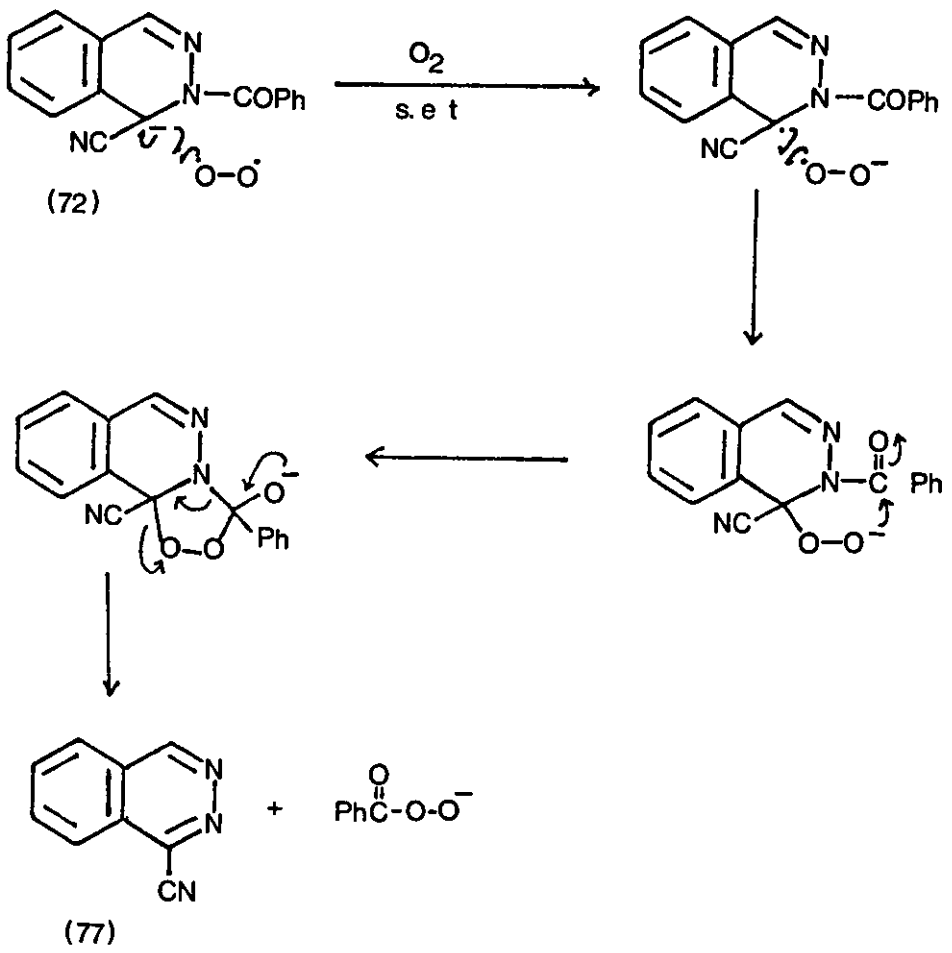
The conjugate base (72) of the Reissert compound (71) was readily generated by treating with sodium hydride and dimethylformamide at 0°C and under an atmosphere of nitrogen.[23] A deep red or purple colour was indicated of the generation of the anion (72).




(71) (72)

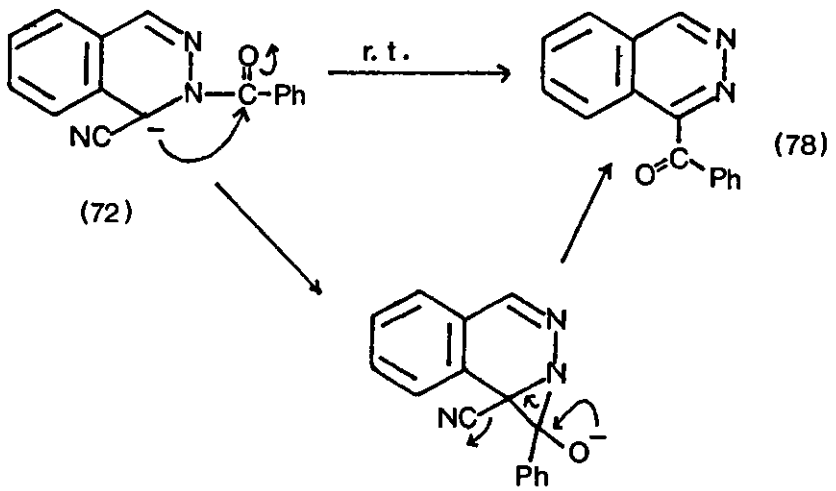
Reactions involving the conjugate base of a Reissert compound are usually carried out under a blanket of nitrogen in order to avoid a competing reaction between the Reissert anion and oxygen[60] giving rise to the by-product 1-cyanophthalazine (77) (Scheme 24). This reaction may proceed via a radical mechanism.[61]

Scheme 24




If the conjugate base (72) is left in the absence of a competing electrophile, it is likely to undergo a 1,2-rearrangement to give 1-benzoylphthalazine (78) (Scheme 25) as is observed with the isoquinoline analogue.[62]

Scheme 25




a fused aziridine intermediate

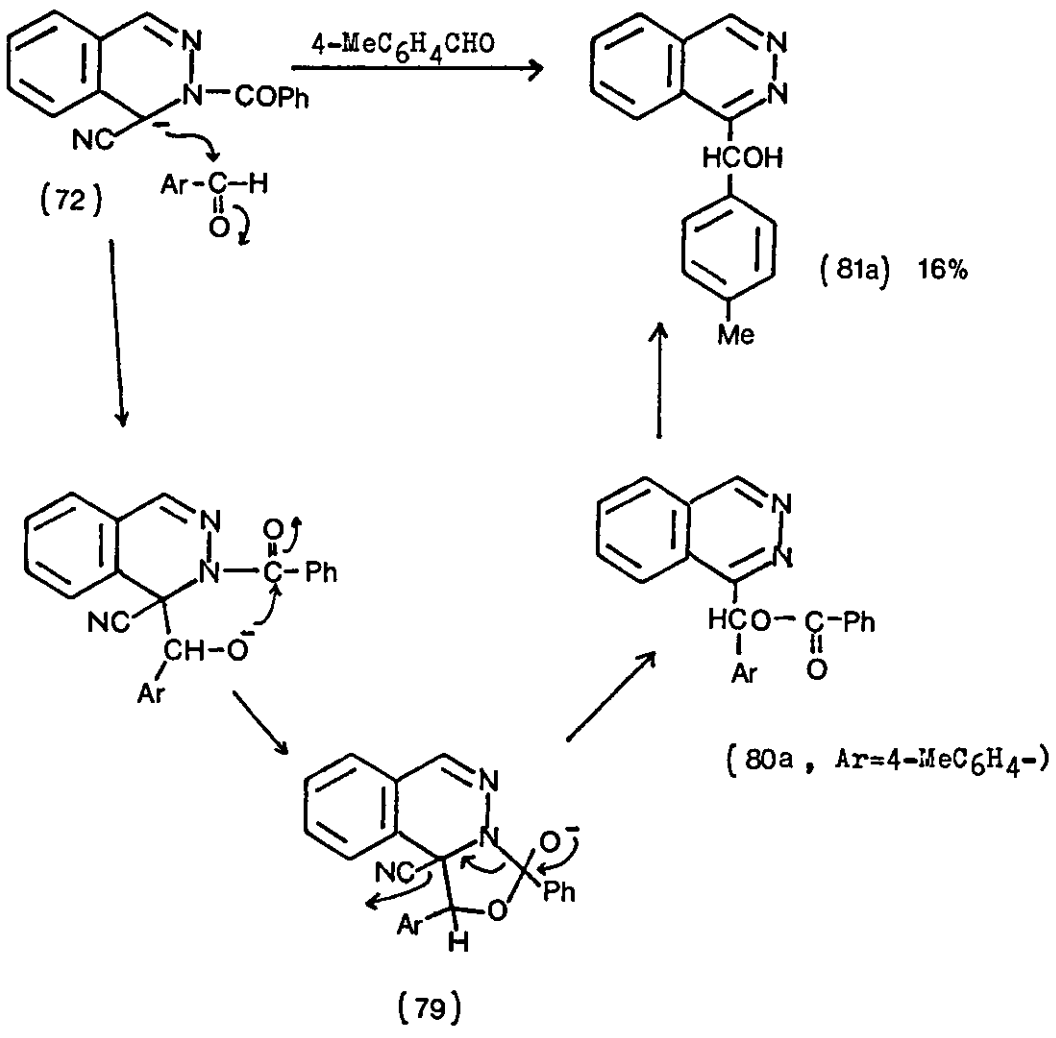
iv) Conjugate base condensation with aromatic aldehydes: aryl phthalazin-1-yl carbinol and ester formation

A mixture of the Reissert compound (71) and 4-methylbenzaldehyde was added to sodium hydride in dimethylformamide at 0°C. The reaction mixture was stirred at 0°C for one hour and at room temperature overnight. During addition, the reaction mixture became dark red but gradually changed to a brown colour. The reaction was carried out under an atmosphere of nitrogen so to exclude the presence of oxygen which can lead to a competing reaction (p.35) and the low temperature was to prevent a 1,2-rearrangement reaction (Scheme 25).

After work-up, the expected product 4-methylphenyl phthalazin-1-yl carbinol (81a) was obtained after recrystallisation from ethanol in 16% yield, m.p. 141-143°C. The

mechanism proposed for the reaction seems likely to proceed via the oxazolo[4,3-a]phthalazine intermediate (79) and the ester (80). The last step, hydrolysis of the ester, presumably occurs during the aqueous base conditions of the work-up (Scheme 26).

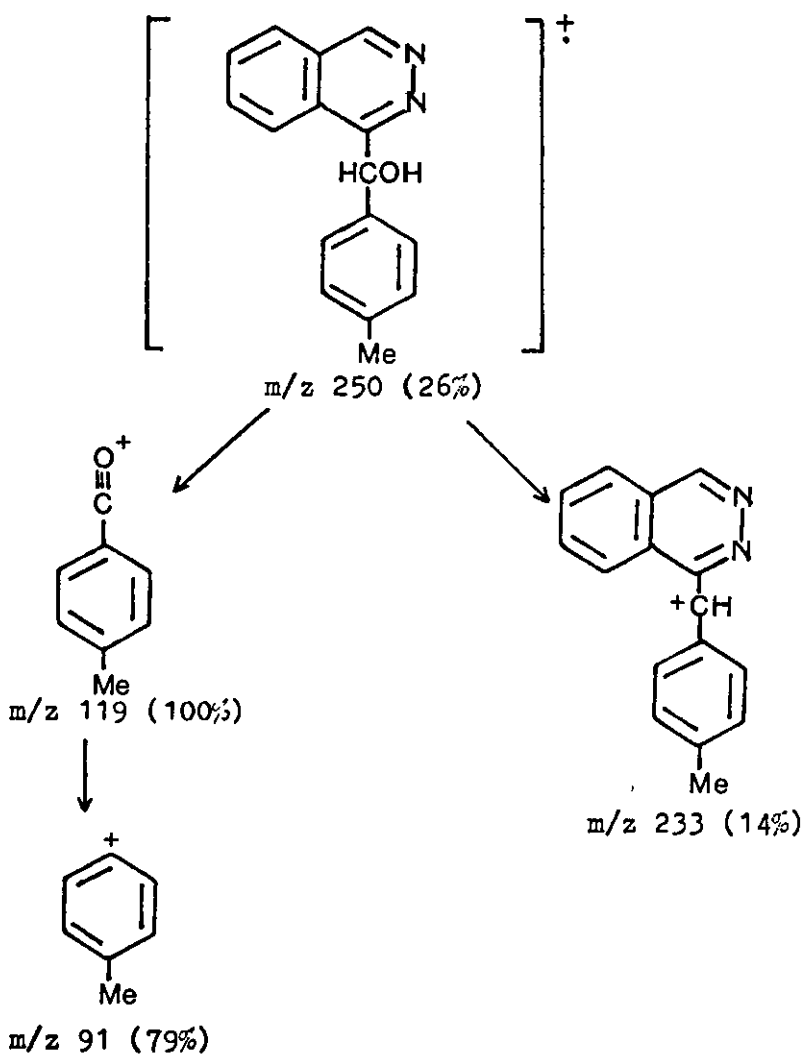
Scheme 26




The infrared of the product carbinol (81a) showed a broad hydroxyl absorption frequency at 3310 $cm^{-1}$ but absence of the amide carbonyl from the starting Reissert compound at 1650 $cm^{-1}$. In the pmr, the methine proton of CHOH appeared at $\delta$ 6.56, and a broad peak at $\delta$ 4.38 indicated the OH grouping.

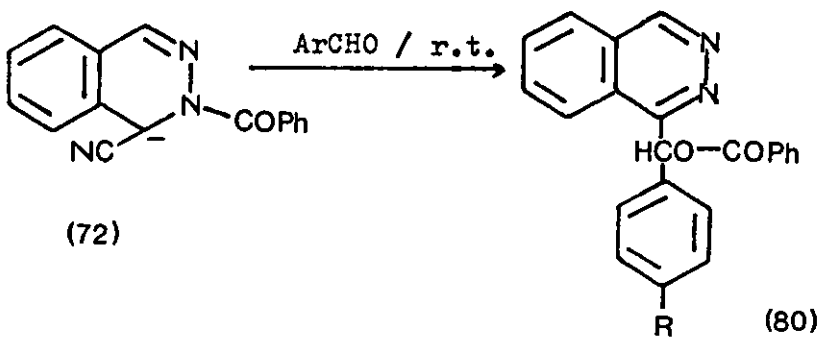
This latter peak collapsed on the addition of $D_2O$ to the pmr sample, hence reinforcing the assignment. In the mass spectrum of (81a) the molecular ion was observed at m/z 250 (26% relative intensity) and the base peak at m/z 119 (100%). Other ions detected were 91 (79%) and 233 (14%) (Scheme 27).

Scheme 27




But when we extended this approach to prepare similar carbinols from other aromatic aldehydes, we found that it was the esters of general structure (80) which were isolated after work-up. This suggests the esters (80b-d) were either more

resistant to the hydrolytic step, (80) to (81), or that work-up conditions were inadvertently different in the case of (80a). i.e.




(72) (80)

(80b) R = MeO-

(80c) R = H-

(80d) R - Cl-

In each case, the crude solid obtained showed the presence of two components on analytical tlc and so flash column chromatography[63,64] was used to carry out the separation. This involved the use of a column containing 6 inches of silica gel (0.040 - 0.063mm mesh) and ethyl acetate (80%) and petroleum ether (b.p. 40-60°C)(20%) as eluent.

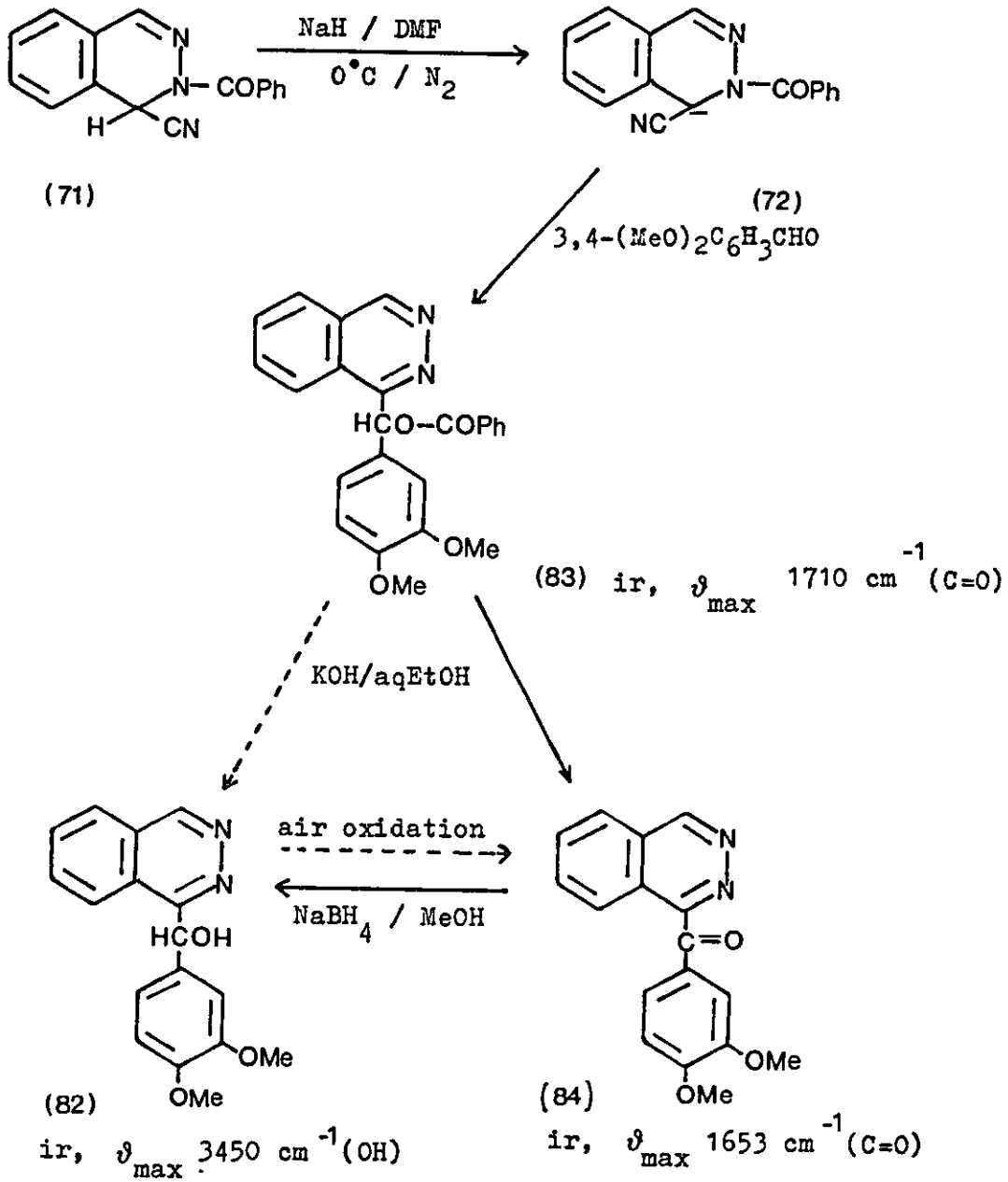
Flash column chromatography is an air pressure driven hybrid of medium pressure and short column chromatography which has been optimised for particularly rapid separations.[63] It was the second fraction which was the isolated ester in each case. The first fractions were of very low yield and were not characterised. The results from these findings are summarised in the table below.

Table 1

| Ester | m.p./°C | Yield/% | ir $\vartheta_{max}/cm^{-1}$(C=0) |
|---|---|---|---|
| 80b | 138-140 | 66 | 1694 |
| 80c | 168-170 | 72 | 1700 |
| 80d | 155-157 | 58 | 1695 |

The infrared absorption frequencies attributed to the carbonyl group of the esters were consistent with the observations made by Popp and Bhattacharjee[30] during the preparation of 3,4-dimethoxyphenyl phthalazin-1-yl carbinol (82). They found that a crude ester (83) ir, $\vartheta_{max}$ 1710$cm^{-1}$ (C=0), was isolated from the reaction of 2-benzoyl-1,2-dihydrophthalazine (71) and 3,4-dimethoxybenzaldehyde with sodium hydride in dimethylformamide (Scheme 28).

Scheme 28



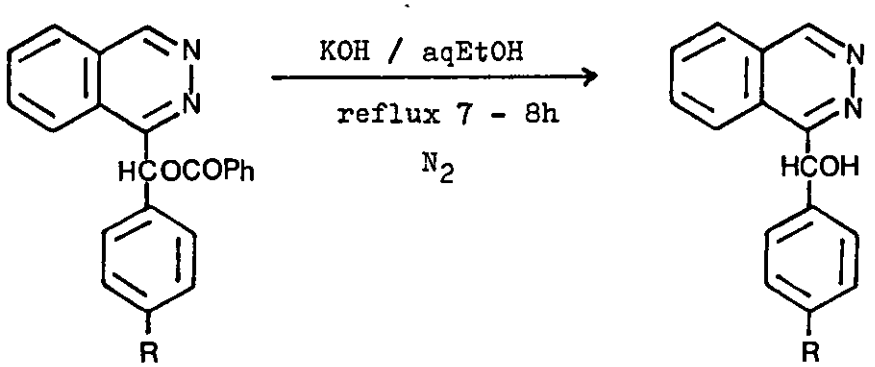

When the ester (83) was hydrolysed using aqueous alcoholic potassium hydroxide, the ketone 3,4-dimethoxyphenyl phthalazin-1-yl ketone (84) was the unexpected product obtained instead of the carbinol (82).[30]

The rationalisation for this anomaly was that hydrolysis of

the ester (83) to the carbinol (82) had occurred, but in the presence of air, air oxidation[18a] caused the conversion of the carbinol (82) to the ketone (84).

The carbinol (82) was eventually obtained by reduction of the ketone (84) using sodium borohydride in methanol (Scheme 28).[30] We confirmed these observations by repeating Scheme 28. Ketone (84), $\vartheta_{max}$ 1653cm$^{-1}$, showed a melting point some 13°C higher than the value previously recorded.[30]

So with the problem of air oxidation in mind, we carried out the hydrolysis of the esters (80b-d) with aqueous alcoholic potassium hydroxide under an atmosphere of nitrogen. The hydrolysis was successful and carbinols of type (81) were obtained.




(80b) R = MeO-
(80c) R = H-
(80d) R = Cl-

(81b) R = MeO-
(81c) R = H-
(81d) R = Cl-

The results from the preparations of the carbinols (81a-d) and (82) are summarised in Table 2.

Table 2

| Carbinol | Yield/% | m.p./°C | ir, $\vartheta_{max}/cm^{-1}$ (OH) | pmr, ∂/ppm (OH), exchangeable with $D_2O$ |
|---|---|---|---|---|
| 81 a | 16[a] | 141-143 | 3310 | 4.38 |
| 81 b | 84.5[b] | 166-168 | 3410 | 5.80 |
| 81 c | 56.5[b] | 173-175 | 3400 | 5.40 |
| 81 d | 32[b] | 172-174 | 3400 | 5.30 |
| 82 | 67[c] | 233-234[d] | 3450 | 5.45 |

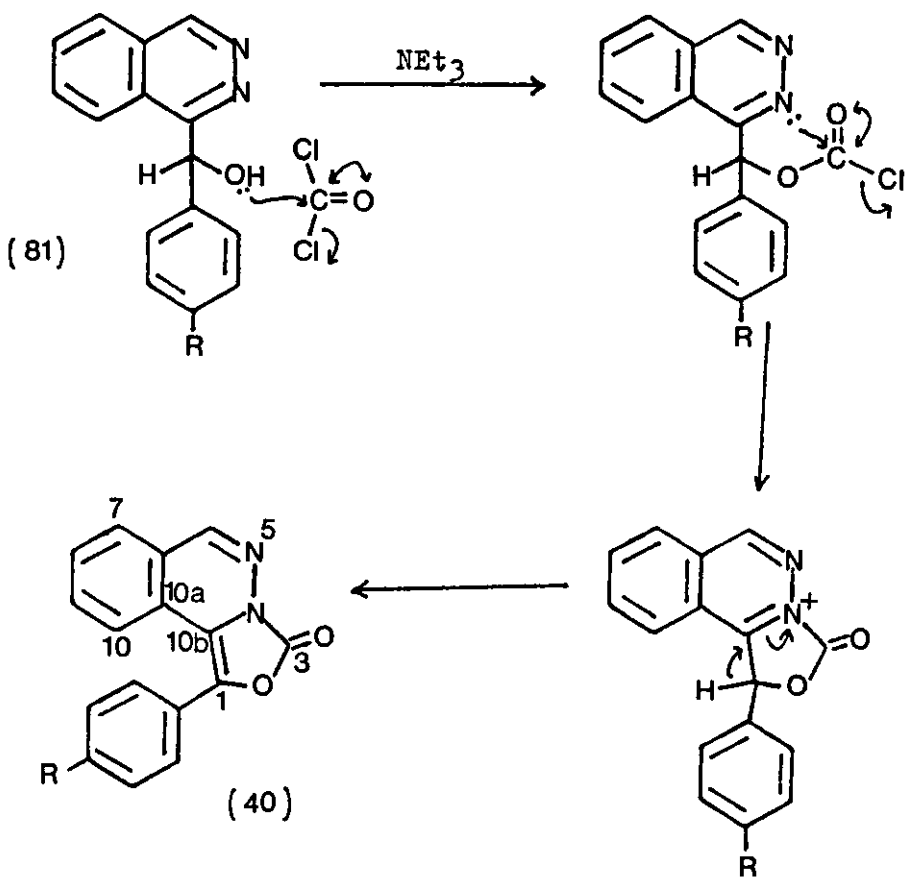
[a] from Reissert compound (71); [b] from hydrolysis of corresponding ester (80); [c] from reduction of ketone (84); [d] lit. m.p. 235-236 °C.[30]

The structures of the carbinols (81a-c) were confirmed by satisfactory microanalyses. Compound (81d), a single spot on tlc, gave a correct atomic composition for the molecular ion on accurate mass spectral determination.

v) Synthesis of the oxazolo[4,3-a]phthalazine system from aryl phthalazin-1-yl carbinols and phosgene

For this synthesis, we attempted to cyclise the aryl phthalazin-1-yl carbinols with phosgene to give the 3H-oxazolo[4,3-a]phthalazine ring system (40) first achieved by Hussain.[39] The method used by Hussain will be discussed later (p.47). The sequence of reaction which was our aim is described as follows (Scheme 29).

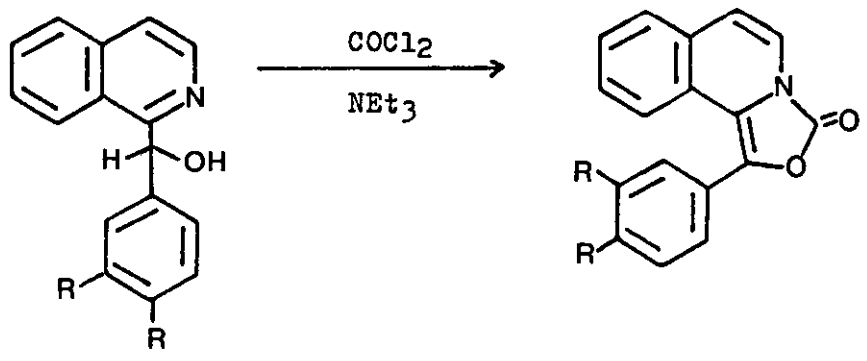
Scheme 29




Isoquinolyl carbinols (85) have been reported by Neumeyer and Boyce[65] in 1973 to undergo an analogous cyclisation. Three different procedures were described by the authors.

a) Phosgene gas was passed into a solution of carbinol in dichloromethane together with aqueous sodium bicarbonate and triethylamine. The completion of reaction was indicated by vigorous evolution of carbon dioxide. The fused isoquinoline (86a) was obtained in a reported yield of 91%.[65]

i.e.




(85)

(86a) R = H

(86b) R = $OCH_3$

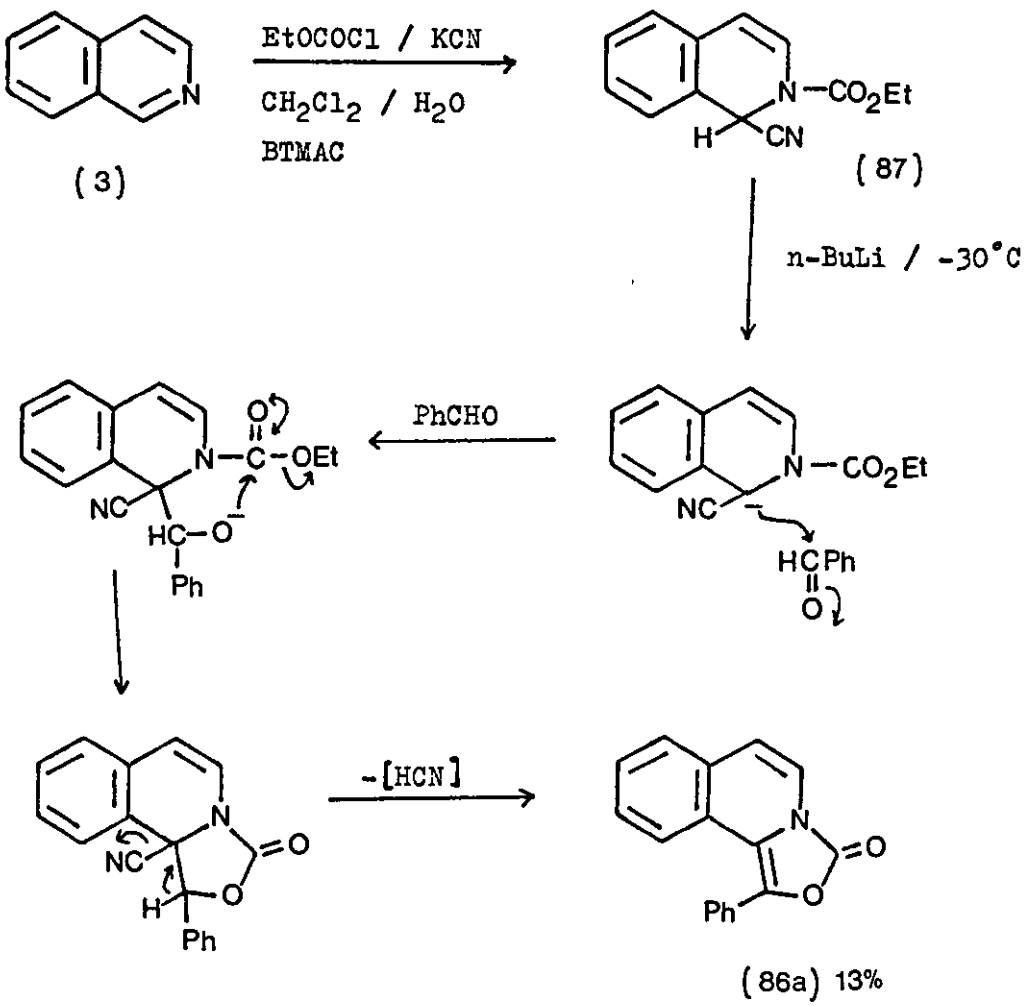
(86c) R = $OCH_2Ph$

b) Phosgene was dissolved in diethyl ether and added to a solution of carbinol and triethylamine also in ether and stirring the reaction mixture overnight. The yield of (86b) was reported as 79%.[65]

c) The third method was similar to the second, except in this case, the solvent used throughout was dichloromethane. The yield of (86c) was 41% after stirring the reaction mixture overnight.[65]

Previous to the work by Neumeyer and Boyce, Popp and co-workers[28] had reported in 1968, the formation of the oxazolone (86a) in 13% yield from the isoquinoline Reissert compound (87) derived from ethyl chloroformate and benzaldehyde (Scheme 30) in the presence of n-butyllithium at -30°C.

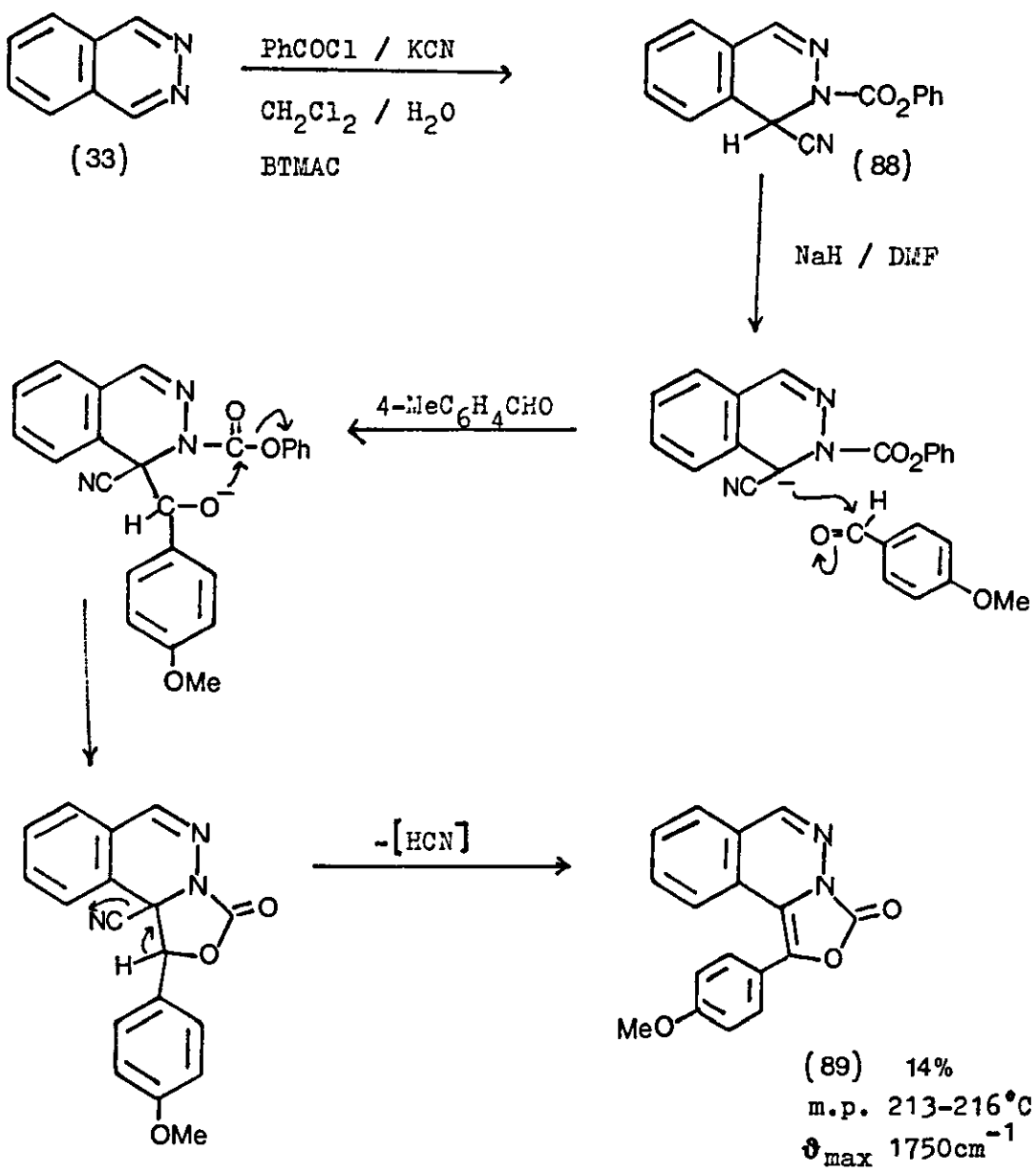
Scheme 30




The first synthesis of the analogous 3H-oxazolo[4,3a] phthalazine system (40) was achieved in this Department by Hussain.[39] He used a chloroformate derived Reissert compound (88), the anion was generated with sodium hydride and then condensed with 4-methoxybenzaldehyde to cyclise directly to (89) in a yield of 14%. The product was characterised only by its infrared spectrum and a whole number molecular ion from low resolution mass spectrometry.[39] A sample was subsequently submitted for accurate mass measurement and provided a fit for

the expected $C_{17}H_{12}N_2O_3$ to within 0.2mmu. The process involved $PhO^-$ as a leaving group and HCN was eliminated in situ (Scheme 31).

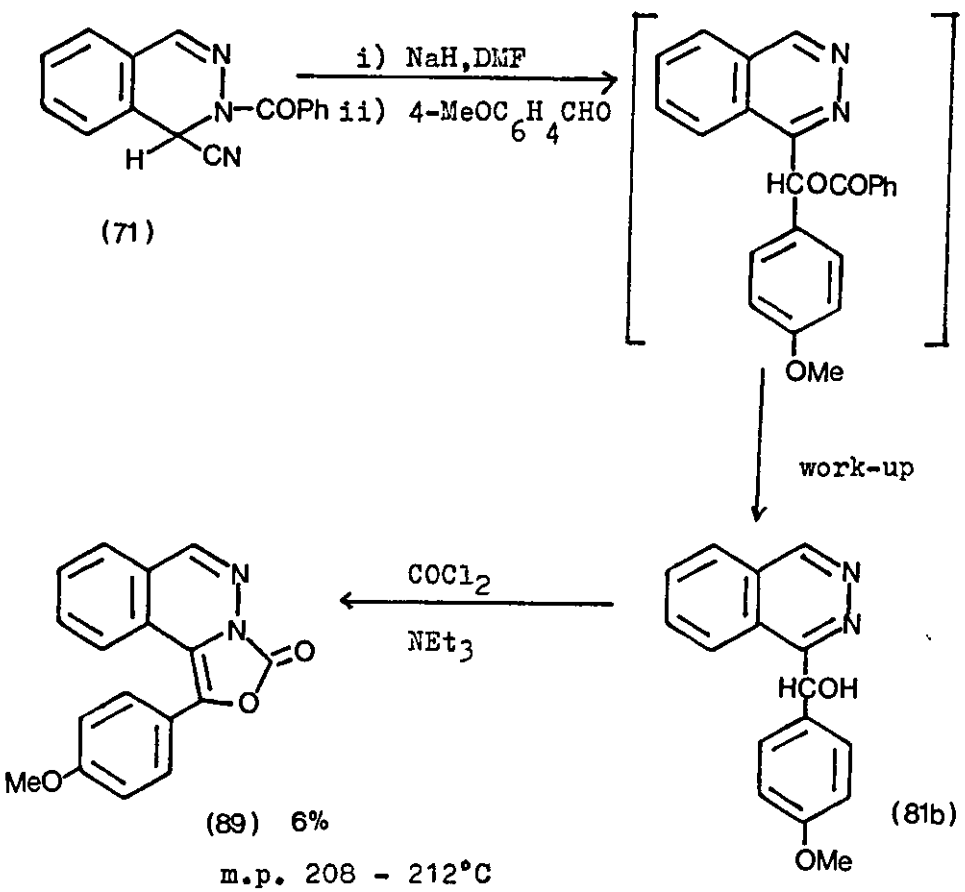
Scheme 31




Also in this Department, M.S. Haji[66] achieved the cyclisation product (89) in 6% yield by passing phosgene gas into a mixture of carbinol (81b) in dichloromethane in the

presence of aqueous sodium bicarbonate and triethylamine, (method (a) p.45) (Scheme 32). He characterised the product by low resolution mass spectrometry.

Scheme 32




Thus, we sought to investigate further the synthesis of (89) by following Neumeyer's approach and attempt to improve the yield of such tricyclic systems.

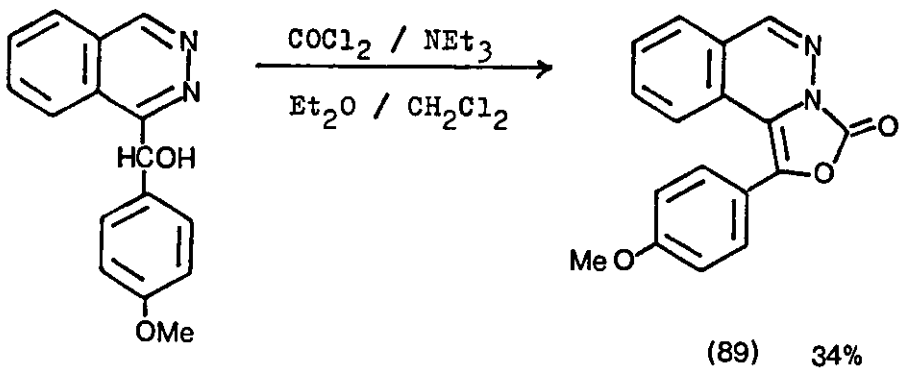
Firstly, we carried out the synthesis by the 2-phase system described by Neumeyer and Boyce[65] (method (a) p.45). Phosgene gas was passed into 4-methoxyphenyl phthalazin-1-yl carbinol (81b) in dichloromethane in the presence of aqueous sodium bicarbonate and triethylamine. The addition of phosgene

was stopped after about one hour and reaction mixture was stirred for 30 minutes. The layers were separated and the work-up involved washes with 8% aqueous sodium bicarbonate and water. The product obtained after work-up was found to be recovered starting material and no 1-(4-methoxyphenyl)3H-oxazolo[4,3-a]phthalazin-3-one (89) was isolated. The failure of the carbinol (81b) to cyclise was thought to be due to an insufficient amount of phosgene in the reaction mixture.

Starting material was also recovered when method (c) (p.46) was followed. That is, phosgene was dissolved in dichloromethane and added slowly to a solution of carbinol (81b) and triethylamine in dichloromethane. The reaction mixture was stirred overnight and after work-up, the residue obtained was recovered carbinol (81b).

Finally, the reaction was carried out by the addition of phosgene solution dissolved in diethyl ether to a mixture of carbinol (81b) and triethylamine in diethyl ether and dichloromethane; the latter solvent was added because the carbinol (81b) was insoluble in diethyl ether alone. During the addition of phosgene solution, a vigorous reaction was observed, in the form of thick white fumes and a cloudy suspension being formed. The dense white fumes may be due to the formation of triethylammonium chloride. The reaction mixture was stirred overnight and after work-up, orange crystals of the oxazolo[4,3-a]phthalazine (89) were obtained which had identical characteristics to the product (89) obtained by Hussain[39] and Haji.[66]

i.e.




(81b)

(89) 34%

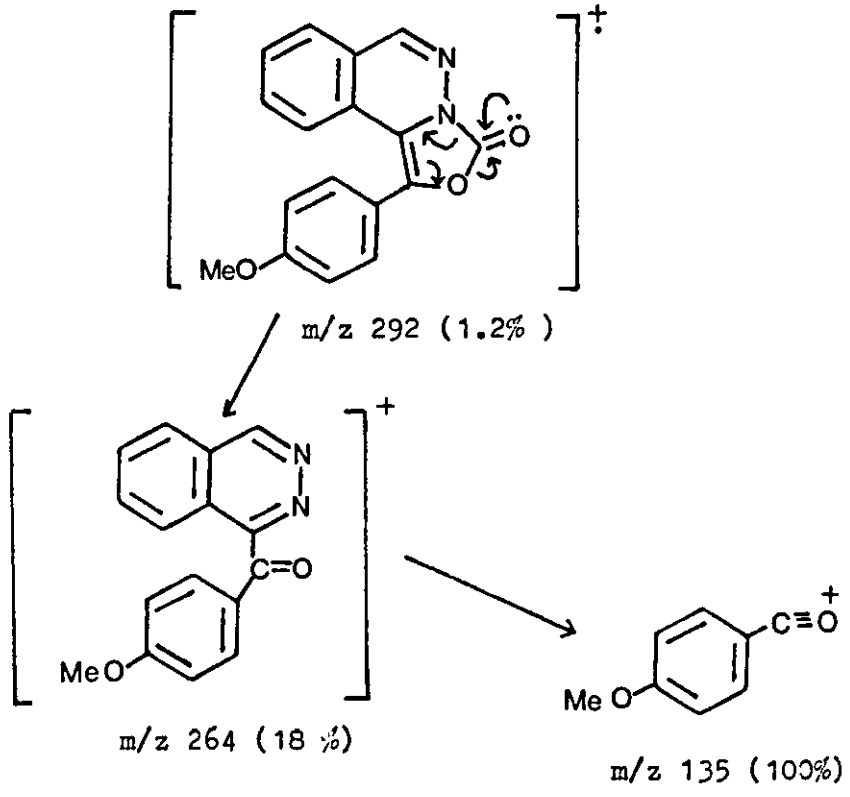
m.p. 210 - 214°C

$\vartheta_{max}$ 1745cm$^{-1}$ (C=O)

The mass spectrum of (89) showed the molecular ion $M^{+\cdot}$ at m/z 292 (with correct accurate mass) and the base peak at 135 corresponding to a methoxybenzoyl fragment. The fragmentation behaviour is similar to that described for product (89) prepared by Hussain[39] and Haji.[66]

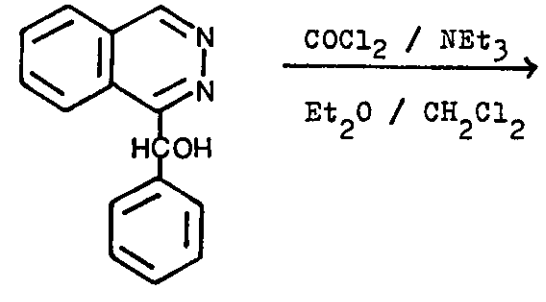
The fragmentation pattern is as follows (Scheme 33).

Scheme 33




The same approach was applied to phenyl phthalazin-1-yl carbinol (81c) which gave the cyclised system (90) in 48% yield.

i.e.




(81c)

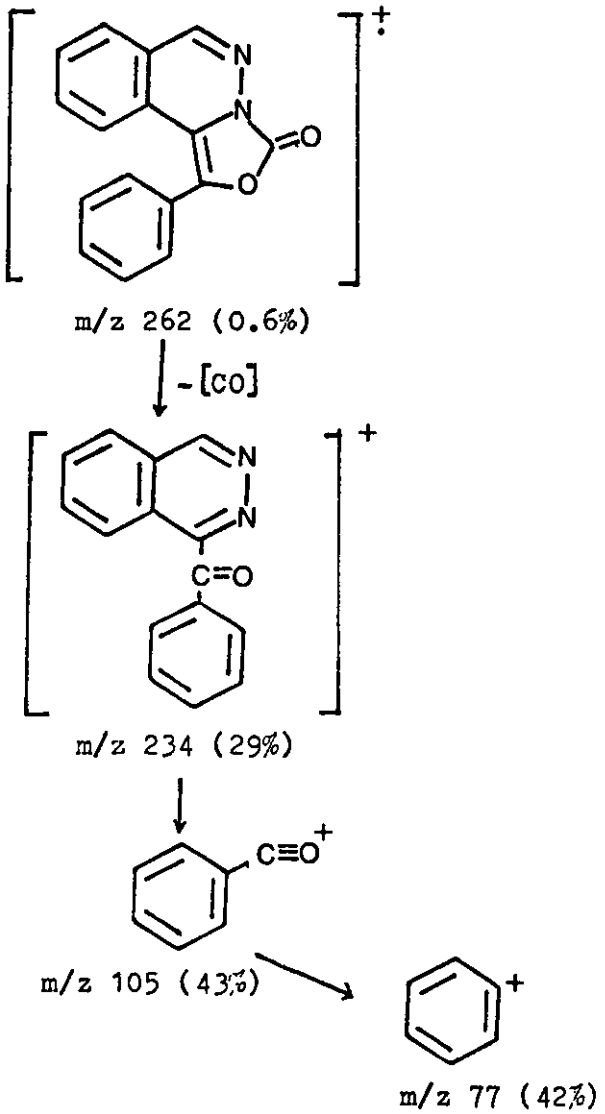
(90) 48%

m.p. 148 - 150°C

$\nu_{max}$ 1755cm$^{-1}$

Again, the fragmentation pattern from the mass spectrum of (90) was similar to that observed with the tricyclic system (89) (Scheme 34).

Scheme 34




When this experimental procedure was applied to carbinols (81a) and (81d), only recovered starting materials were obtained after work-up.

The oxazolo[4,3-a]phthalazines (89) and (90) each showed one spot by tlc and gave the correct atomic composition by accurate mass measurement. However, the compounds deteriorated on keeping and we were unable to obtain satisfactory microanalyses on either.

Thus, although we had improved the yield of the cyclisation

step to give (89), and obtained (90) in 48% yield, the failure of (81a) and (81d) to cyclise and the instability of the heterocycles (89) and (90) led us not to pursue the investigation further.

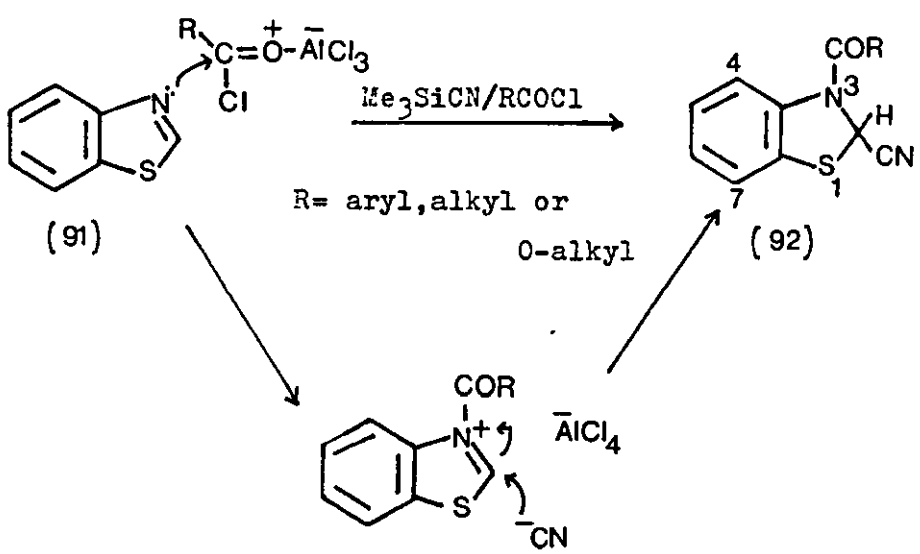
## CHAPTER II Benzothiazole Reissert Compounds

### Part I: The Synthesis of Benzothiazole Reissert Compounds

As discussed in the Introduction, previous attempts at formation of Reissert compounds from the five-membered ring heterocycle benzimidazole had failed because under the conventional two-phase reaction media conditions, ring opening of the heterocycle occurred.[14a]

We now report[67,68,69] that novel five-membered ring Reissert compounds can be formed by treatment of benzothiazole (91) with trimethylsilyl cyanide and an acid chloride in the presence of a Lewis acid catalyst $AlCl_3$, in dry dichloromethane to give 3-acyl-2-cyano-2,3-dihydrobenzothiazole (92) (Scheme 35).

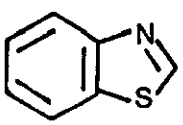
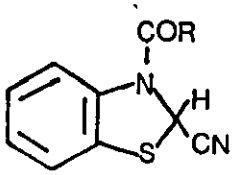
Scheme 35




This is the first example of such an application to five-membered ring heterocycles.

Preliminary work was undertaken by Miss Anne Chen, an

undergraduate in this Department, who carried out the synthesis of 2-cyano-2,3-dihydro-3-(4-methylbenzoyl)benzothiazole (92a).[70]

i.e.  $\xrightarrow[CH_2Cl_2 \,/\, AlCl_3]{Me_3SiCN/\ 4\text{-}MeC_6H_4COCl}$ 

(91)

(92a, R=4-$MeC_6H_4$)

48%

We repeated this reaction and improved the yield of (92a) to 87%, m.p. 158-160°C. The infrared of this product showed an amide carbonyl at 1663cm$^{-1}$ and a weak cyano group at 2225cm$^{-1}$. The pmr include a sharp singlet at $\delta$6.30 which is assigned to the C-2H. This compound (92a) gave a satisfactory microanalysis. The mass spectrum showed the molecular ion at m/z 280 with a relative intensity of 16%, and the base peak was at m/z 119 corresponding to 4-$MeC_6H_4CO$ which is a typical fragmentation observed in six-membered ring Reissert compounds.[71,72]

We showed the reaction to be general by the preparation of a series of derivatives (Table 3). The relative molar ratios of the reactants used were benzothiazole : acid chloride : trimethylsilyl cyanide, 1:1:1.1. The slight excess of trimethylsilyl cyanide would guard against any loss due to its extreme volatility e.g. during its transfer to the reaction flask. The best yields were obtained when the reaction mixtures were stirred at room temperature for 72 hours.

Table 3

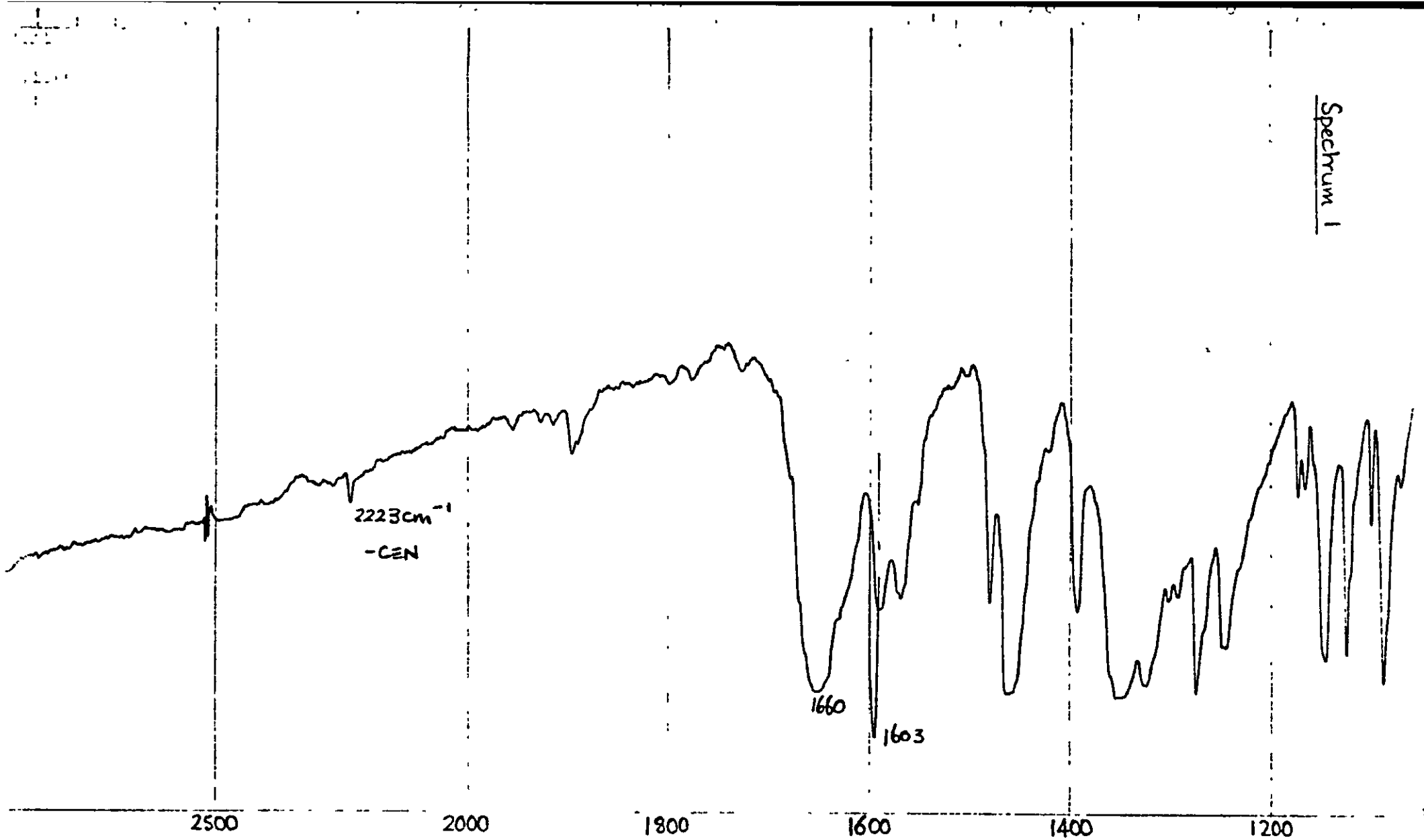
| 92 | R- | Yield/% | m.p./°C | ir(KBr) C=0 $\nu_{max}/cm^{-1}$ | C-2H $\partial$/ppm |
|---|---|---|---|---|---|
| a | $4\text{-}MeC_6H_4$- | 87 | 158-160 | 1663 | 6.30 |
| b | $4\text{-}ClC_6H_4$- | 85 | 115-118 | 1660 | 6.42 |
| c | $4\text{-}O_2NC_6H_4$- | 94 | 191-193 | 1675 | 6.30 |
| d | $4\text{-}Cl(CH_2)_3$- | 84 | 104-105 | 1670 | 6.42 |
| e | MeO- | 78 | 101-102 | 1735 | 6.43 |
| f | $2ClCH_2\text{-}C_6H_4$- | 73 | 188-190 | 1665 | 6.43 |
| g | $C_6H_5$- | 44 | 140-141 | 1655 | 6.40 |
| h | $4\text{-}CH_3OC_6H_4$- | 19 | 122-123.5 | 1675 | 6.41 |

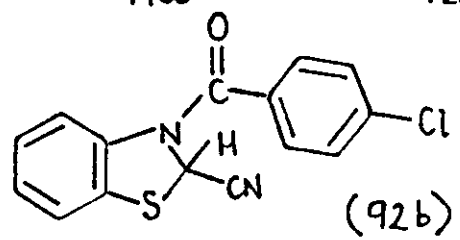
All the eight compounds (92) were recrystallised from ethyl acetate and gave satisfactory microanalytical data. The results indicate a major breakthrough in the synthesis of Reissert compounds from five-membered ring heterocycles. We have shown benzothiazole Reissert compounds can be prepared from aroyl chlorides, aliphatic acid chloride (92d) and from a chloroformate (92e).

It should also be noted that six (except 92c & g) of these novel Reissert compounds showed an absorption due to a cyano group in the infrared spectra, in the range 2220-2250$cm^{-1}$. These absorptions were of weak but clearly visible intensity. The infrared spectrum of 3-(4-chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92b) is reproduced (Spectrum 1)(p.57a).

With the six-membered ring Reissert compounds, the cyano absorption is usually not observable in the infrared. McEwen

Spectrum 1



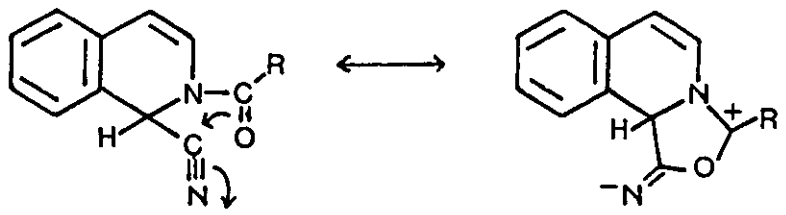




(92b)

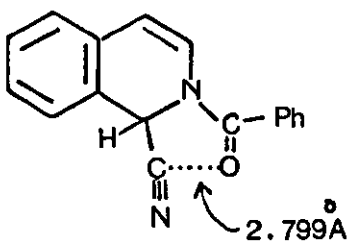
KBr disc

and Cobb's[6] reasoning for this was that there is an electronic association between the carbonyl oxygen atom and the carbon of the nitrile group. This may result in the modification of the triple bond characteristics of the nitrile and hence its absorption in the infrared.

i.e.



An X-ray crystallographic study of the isoquinoline Reissert compound 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (2) has been carried out by Tykarska et al.[144a] From the data given, we have calculated the interatomic distance between the carbonyl oxygen and the carbon atom of the nitrile: this was found to be 2.799Å .[144b]

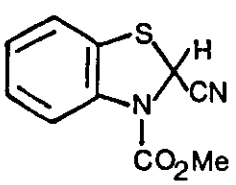



This distance of 2.799Å is less than the combined Van der Waals radii of 3.1Å for oxygen (1.4Å) and carbon (1.7Å )[145] and thus, implies that there is a marked interaction between carbonyl oxygen and the carbon atom of the nitrile group.

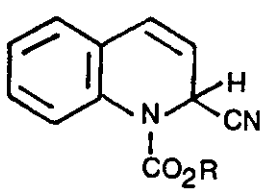
To date, there are no X-ray models to provide similar data in the benzothiazole series but intuitively, one might expect the O-C interatomic distance to be larger because of the smaller five-membered ring moving the adjacent substitutents further apart.

The reason why not all of the benzothiazole Reissert compounds show the nitrile absorption in the infrared is unclear and X-ray cyrstallographic studies would be necessary in order to clarify this.

Preparation of 2-cyano-2,3-dihydro-3-methoxycarbonyl-benzothiazole




(92e)




(32, R=Me)

There was a further purpose behind the preparation of the novel Reissert compound (92e) from benzothiazole and methylchloroformate. It is known that the analogous compound from quinoline (32, R = Me) has antineoplastic activity[29] against L1210 leukaemia in mice (as described on p.15).

Based on the fact that the divalent sulphur atom in (92e) is approximately isosteric with the vinylene grouping (-CH = CH-) in structure (32),[73,74] the novel Reissert compound (92e) has been sent to the Brussels Laboratory of the National Institutes of Health, National Cancer Institute,

Bethseda, Maryland, U.S.A. for screening for antineoplastic activity.

The concept of isosterism[73] is frequently used to describe groups of atoms which impart similar physical or chemical properties to a molecule due to similarities in size, electronegativity or stereochemistry. The concept has had considerable recognition in the design and synthesis of potentially active compounds. Indeed, benzene and thiophene have been termed "ring equivalents" in medicinal chemistry.[73]

Under the terms of a Nato award to promote International Collaboration in Science, Dr. B.C. Uff in this Department and Prof. F.D. Popp (University of Missouri - Kansas City, U.S.A.) have exchanged information on the Reissert chemistry proceeding in each Department.

By arrangement, J. Kant and F.D. Popp have studied the application of the five-membered ring heterocycle benzoxazole in the Reissert method with trimethylsilyl cyanide and an acid chloride under single phase reaction conditions.

The findings from the two laboratories have been reported in a joint publication.[67]

i) Mechanistic involvement of trimethylsilyl cyanide in the formation of Reissert compounds

At this point, it seems appropriate to consider possible mechanisms for the involvement of trimethylsilyl cyanide in the formation of Reissert compounds as, to date, this has not been discussed in literature.

Reetz and co-workers[75] have recently discussed the use of trimethylsilyl cyanide to cyanate tertiary alkyl chlorides in the presence of a Lewis acid ($SnCl_4$) in dichloromethane. i.e.

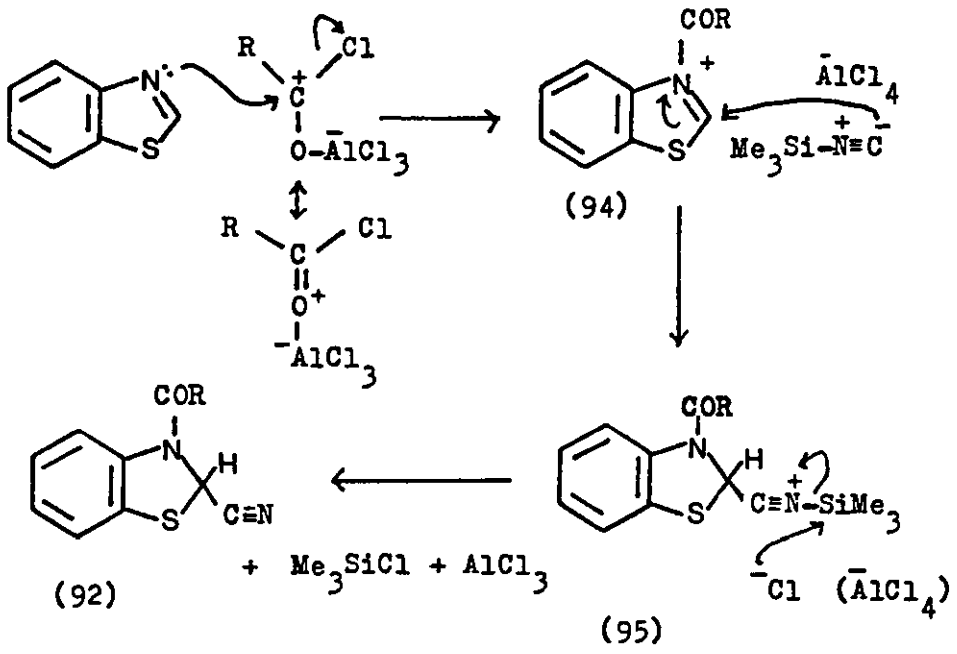
$$R_3C\text{-}Cl + (CH_3)_3Si\text{-}CN \xrightarrow[CH_2Cl_2]{SnCl_4} R_3C\text{-}CN + (CH_3)_3Si\text{-}Cl$$

They proposed two mechanisms each involving isonitrile participation. Applying their mechanisms to our substrates with aluminium chloride as the catalyst would provide pathways A and B.

Mechanism A

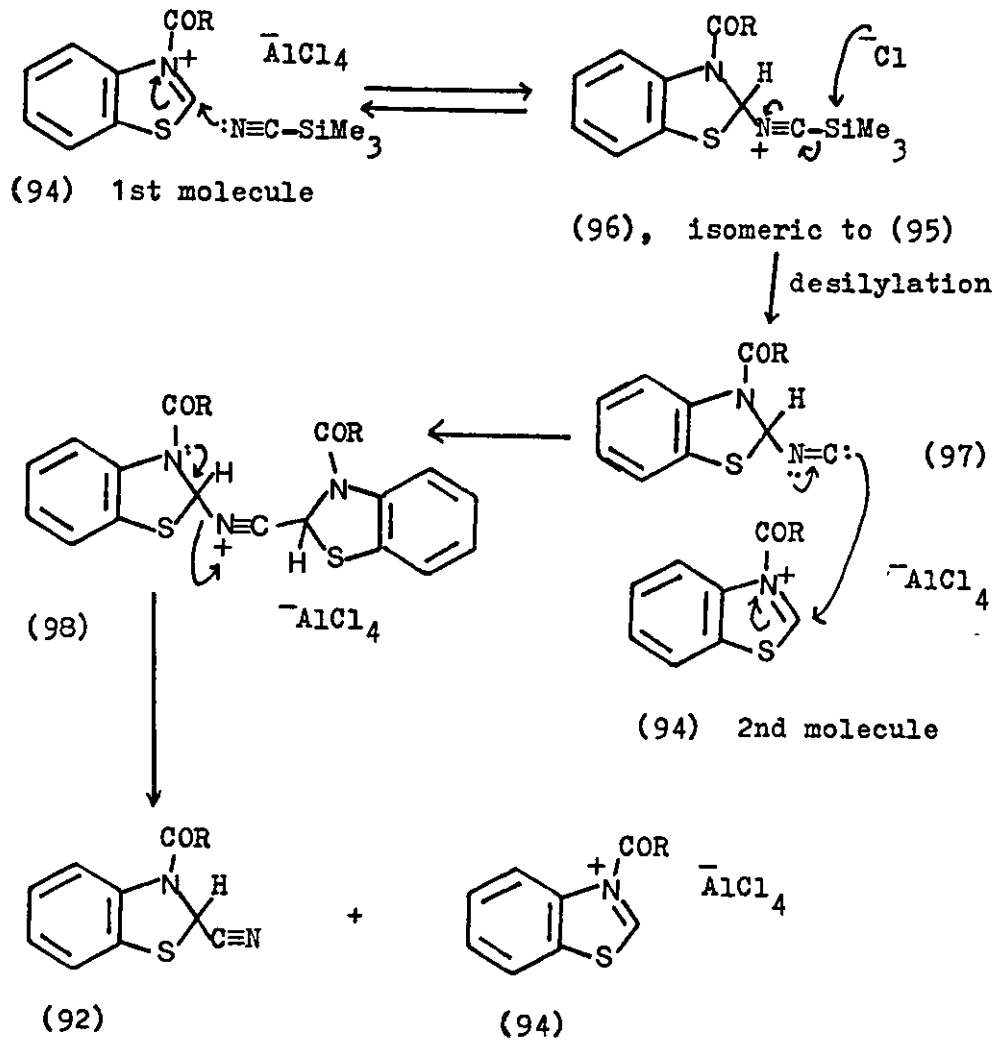
$(CH_3)_3Si\text{-}CN \rightleftharpoons (CH_3)_3Si\text{-}\overset{+}{N}\equiv\overset{-}{C}$

(75) nitrile (93) isonitrile




In this mechanism, it is proposed that it is the isonitrile (93) which could actually be the reacting species, and that the intermediate nitrilium ion (95) is rapidly desilylated to the Reissert compound (92) and trimethylsilyl chloride.

Mechanism B

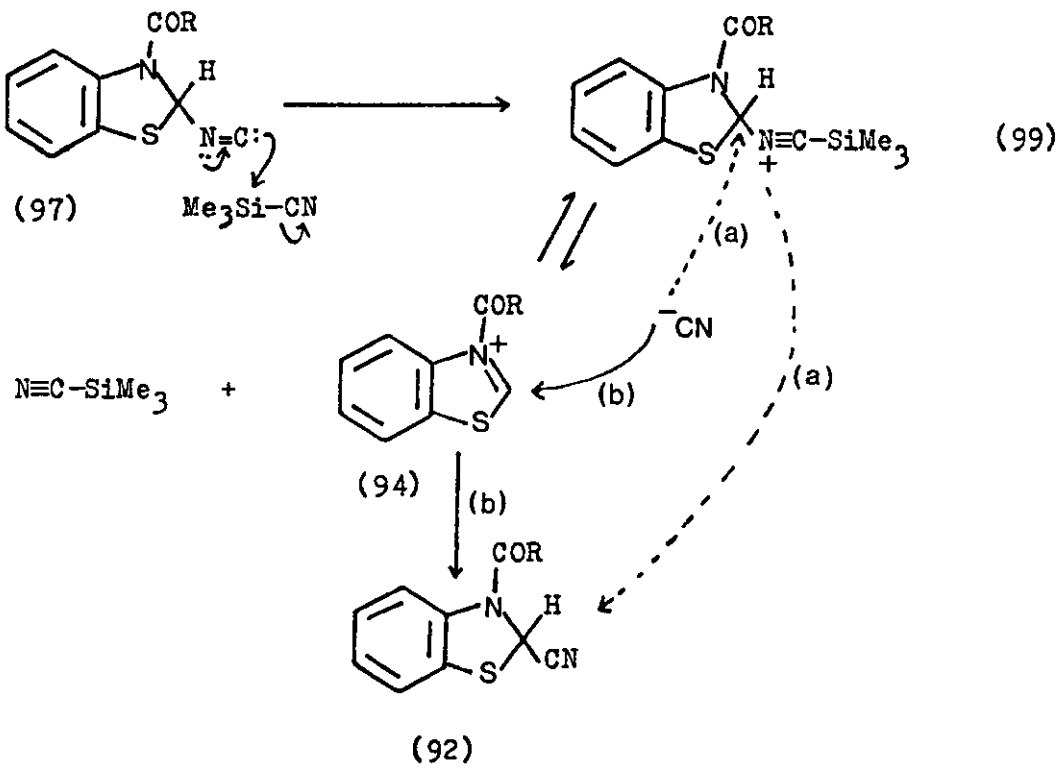



This mechanism involves two moles of the reacting substrate (94). The first molecule is attacked by trimethylsilyl cyanide acting as a nucleophile to give the nitrilium ion (96) which is isomeric to (95). This intermediate (96) is rapidly desilylated to give the isonitrile isomer (97) of the Reissert compound which then attacks a second molecule of the substrate (94) to give the new nitrilium ion (98), and hence leading to the product Reissert compound (92).

Reetz et al[75] favour a mechanism of type B for the cyanation of tertiary alkyl chlorides. But in our case, it is thought this mechanism is unlikely as it involves two moles of the substrate (94) to give the nitrilium ion (98), which is a rather bulky intermediate.

This steric factor could be reduced by an alternative pathway for the isonitrile (97), i.e. in that it could attack a second molecule of trimethylsilyl cyanide liberating $^{-}CN$ and giving (99) (Scheme 36).

Scheme 36

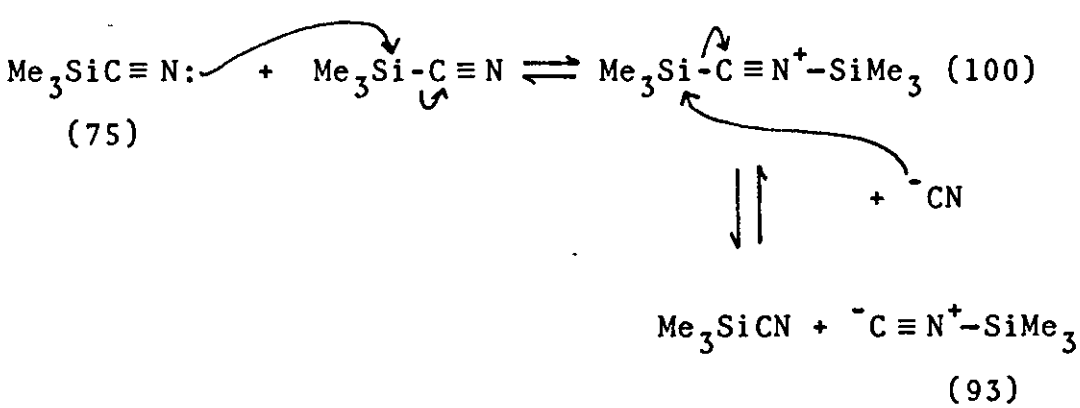



The cyanide could then either re-attack (99) at position-2 liberating $Me_3SiCN$ by $S_N2$ displacement [route (a)] or attack a second molecule of (94) [route (b)] which could be

provided from equilibration of (99) as shown in Scheme 36. Either process would give the Reissert compound (92).

Mechanism A is a plausible one, i.e. where it is proposed that it could be the trimethylsilyl isonitrile (93) which is the reacting species, continuous replenishment being possible. But also, it must be recognised that although trimethylsilyl cyanide (ir, $\vartheta_{max}$ 2200cm$^{-1}$, (C≡N)) does exist in equilibrium with the isonitrile (ir, $\vartheta_{max}$ 2095cm$^{-1}$, (-$^{+}$N≡C$^{-}$)), the equilibrium strongly favours trimethylsilyl cyanide.[76] This statement itself begs the question as to whether the $Me_3SiCN$/$Me_3SiNC$ equilibration could provide the cyanide ion required for the Reissert reaction (Scheme 37).

Scheme 37



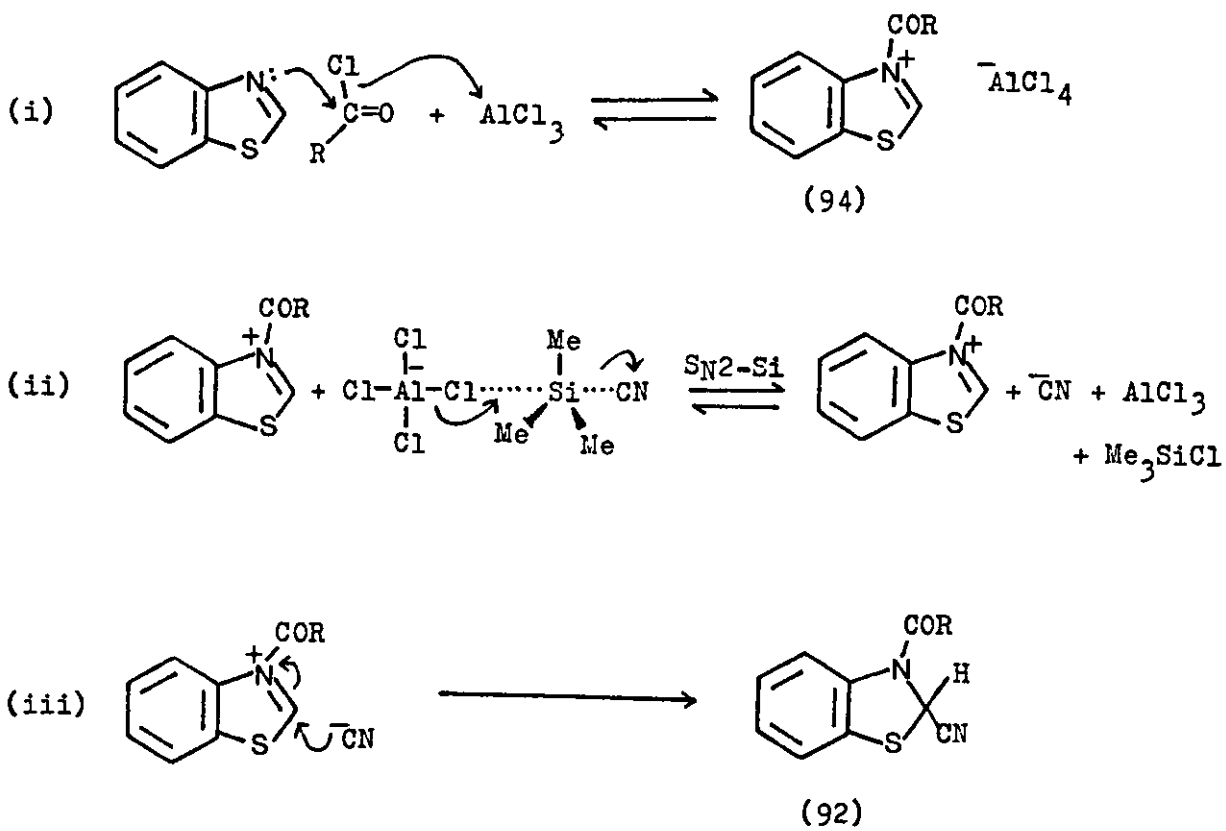

Unless a cyclic mechanism is involved, unlikely in view of the linear requirements of the sp hybridised CN system, the equilibration could be depicted as shown in Scheme 37.

Reissert compound formation would thus depend on cyanide ion escaping from cation (100), i.e. not being held as a tight ion pair. If cation (100) survived until work-up, two moles of $Me_3SiCN$ would be required stoichiometrically per mole of

heterocycle. This is not observed to be the case. The cation (100) could, however, breakdown by attack by chloride ion at either of the silicon atoms.

However, it could be that a more simple mechanism is available which does not involve isonitrile participation, but instead, involving liberation of cyanide ion via a $S_N2$-Si[77] type substitution, as outlined in Scheme 38.

Scheme 38

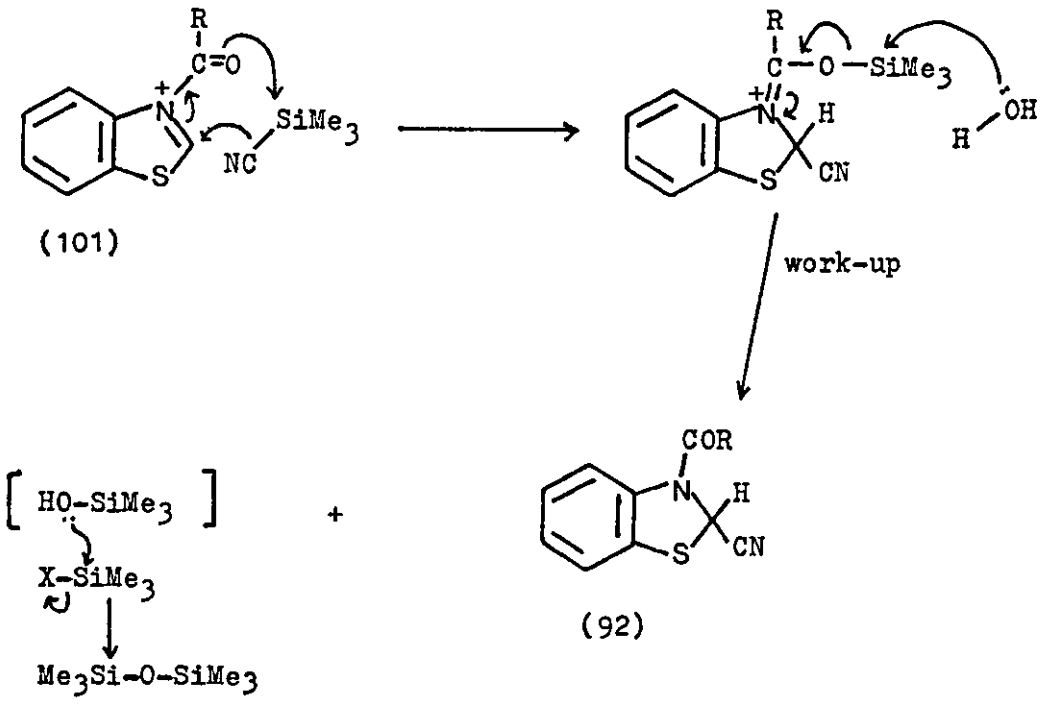



This mechanism depends upon step (ii) producing cyanide ions which would react rapidly with the cation (94) to give the Reissert compound (92). Step (ii) involves the formation of $Me_3SiCl$ from $Me_3SiCN$, which is the reverse of the

preparation of trimethylsilyl cyanide and so equilibrium may favour the left side. However, as cyanide was used up in step (iii), continuous replenishment by step (ii) would occur.

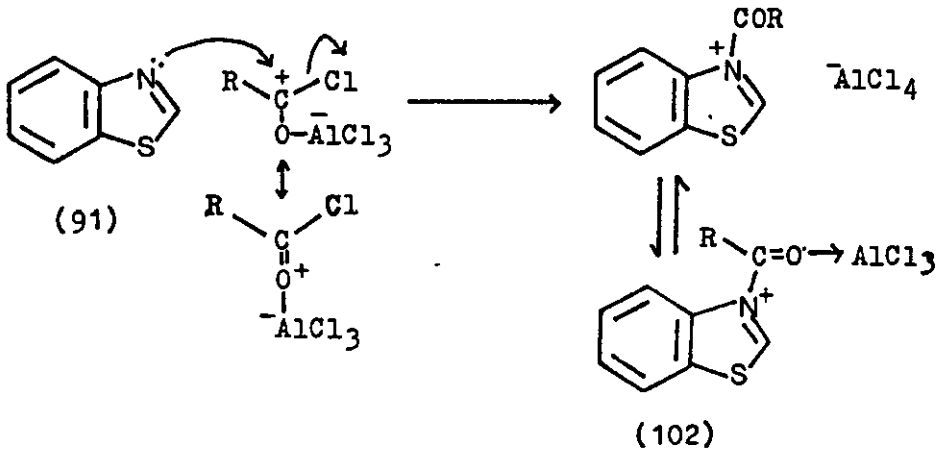
At the Seventh East Midlands Regional Symposium of the Royal Society of Chemistry (Perkin Division)[68], Professor W.D. Ollis (Sheffield University) asked if a cyclic mechanism for the involvement of trimethylsilyl cyanide had been considered as shown in Scheme 39.

Scheme 39




Although this is an interesting and reasonable suggestion, it can be pointed out that there will be competition between attack of the carbonyl oxygen of cation (101) on silicon (of $Me_3SiCN$) and coordination with the aluminium (of the $AlCl_3$) (102).

i.e.




Furthermore, the cyclic mechanism shown in Scheme 39, could not be applied generally to all the examples we have encountered, because of steric reasons. The subject is discussed further later in the thesis (p.142).

ii) The use of tri-n-butyltin cyanide as an alternative cyanating reagent

An alternative reagent to trimethylsilyl cyanide which is commercially available is tri-n-butyltin cyanide ($nBu_3SnCN$) (103). We would anticipate that the use of the tin reagent may release $^-CN$ readily due to the Sn-CN bond being weaker than the Si-CN bond.[78]

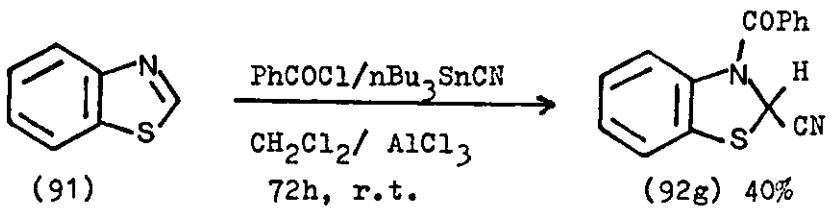
Thus we set out to study the application of this reagent (103) to the Reissert method using benzothiazole as the heterocycle. We deliberately used reaction conditions which were parallel to those used with trimethylsilyl cyanide so that we may compare yields from these two reagents, should a Reissert compound be obtained in this situation.

We found that when benzothiazole, benzoyl chloride and $nBu_3SnCN$ (103) in molar ratios of 1:1:1.3 were stirred at room temperature for 72 hours in the presence of a catalytic amount of $AlCl_3$, the Reissert compound 3-benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g) was isolated in 40% yield, m.p. 140-142°C, authentic sample m.p. 140-141°C.[67] The yield compares with 44% from use of trimethylsilyl cyanide (p.57) (Scheme 40).

We found the work-up involved in the isolation of the Reissert compound (92g) by this method was not as straightforward as that observed when $Me_3SiCN$ was used as the cyanating reagent. Recrystallisation from ethyl acetate was not sufficient to purify the crude product, as indicated by analytical tlc and by pmr which showed impurities from the butyl groups of the tin reagent. But the Reissert compound

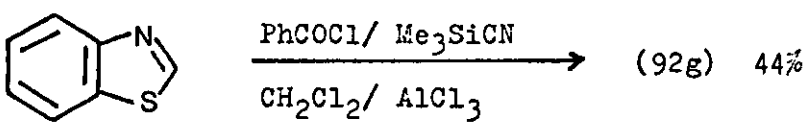
(92g) was isolated pure after using preparative tlc (3 x 1m silica gel plates) with 25:75 ethyl acetate and petroleum ether as the eluent.

Scheme 40




(91) (92g) 40%

Whereas,

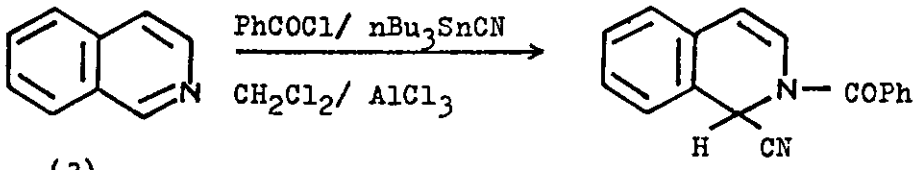



(92g) 44%

In view of the practical difficulties and the lack of improvement in yield, we did not pursue the study with benzothiazole as heterocycle.

Following our work, two reports[79a,b] of the use of tri-n-butyltin cyanide in Reissert reactions have appeared. The approaches were with six-membered ring heterocycles. Popp and Kant studied isoquinoline, quinoline, phthalazine and phenanthridine. They, like us, found that the yields of the corresponding Reissert compounds were comparable with those when $Me_3SiCN$ was used. The relevant results are shown below (Scheme 41), with the yields from trimethylsilyl cyanide in brackets.

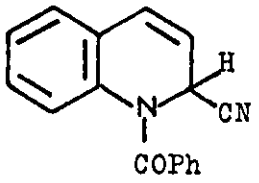
Scheme 41



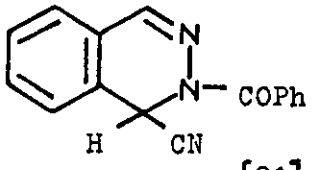

(3)

(2) 96% (84%[80])

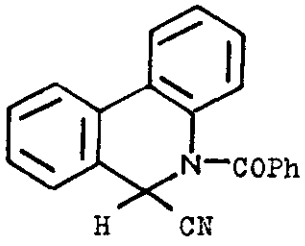
Similarly,




(1) 83% (89%[80])



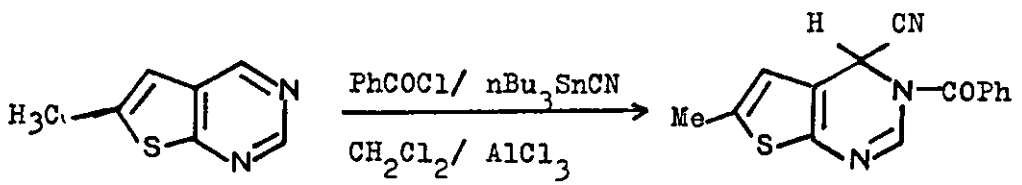

(71) 95% (88%[81])




(104) 91% (90%[42])

New and co-workers[79] have applied the use of the tin reagent (103) to the heterocycle 6-methylthieno[2,3-d]-pyrimidine (105) in the Reissert reaction with benzoyl chloride and a catalytic amount of $AlCl_3$ to yield the Reissert compound (106) in 68% yield after flash chromatography (Scheme 42). The same reaction failed with trimethylsilyl cyanide as reagent.[79]

Scheme 42




(105) (106) 68% (0%)

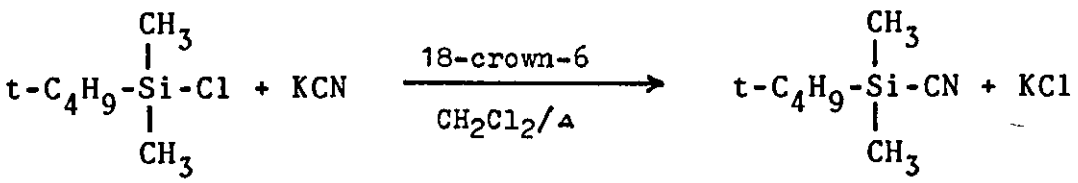
The use of tri-n-butyltin cyanide is thus seen to be an effective source of cyanide for the preparation of Reissert compounds. Although the yield from benzothiazole as the starting heterocycle was not exceptionally high, the tin reagent may prove to be as useful as trimethylsilyl cyanide in the preparation of Reissert compounds from some of the more delicate heterocyclic systems.

We have carried out a brief and unsuccessful study on the preparation of t-butyldimethylsilyl cyanide (t-Bu$Me_2$SiCN) (107), to use as an alternative source of cyanide to trimethylsilyl cyanide ($Me_3$SiCN)(75) and tri-n-butyltin cyanide ($nBu_3$SnCN)(103) in the Reissert application. t-Butyldimethylsilyl cyanide (107) has been found to be superior to $Me_3$SiCN in the direct preparation of stable silylated cyanohydrins.[82,83]

We followed the method of Hwu, Lazar and Corless[84] in an attempt to prepare t-Bu$Me_2$SiCN. Potassium cyanide: t-butyldimethylsilyl chloride: 18-crown-6 in the mole ratio of 1:1.3:0.31 was used, with dichloromethane as the solvent. The 18-crown-6 was used as a phase transfer catalyst[85] to solubilise the potassium and thus enhance the action of the

cyanide ion (Scheme 43). The mixture was refluxed gently for 72 hours and according to Hwu et al[84], the product could be obtained by sublimation in 75% yield.

Scheme 43



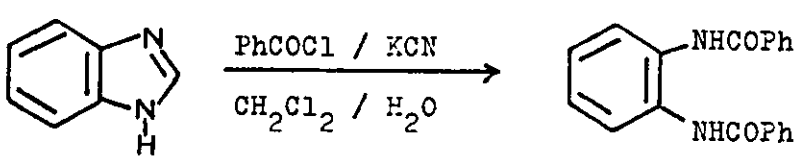
(107)

We have attempted to carry out this preparation, but we have been unsuccessful in isolating t-$BuMe_2SiCN$. The step which gave particular difficulty was the sublimation. A cold finger containing solid $CO_2$ was required. Crystals were deposited on the cold finger but when the equipment was dismantled to scrape off the product, the crystals very rapidly turned to an oil which could not then be induced to crystallise. The t-$BuMe_2SiCN$ is recorded as having a melting point of 74-75°C.[84] In view of these difficulties, further study of this preparation was discontinued.

## iii) Alternative procedures used in an attempt to synthesise benzothiazole Reissert compounds

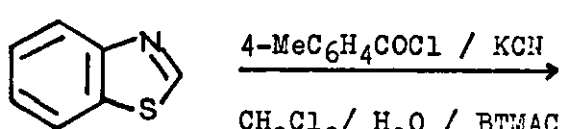
### a) Use of two-phase reaction conditions

As discussed in the Introduction, attempts by previous workers[14a] to form a Reissert compound from the five-membered ring heterocycle benzimidazole (16) with benzoyl chloride and potassium cyanide under two-phase reaction conditions ($CH_2Cl_2/H_2O$) resulted in ring opening of the heterocycle to structure (19).[14a] A mechanism was proposed for the ring opening (Scheme 5, p.7).




(16) (19)

We found that when we treated benzothiazole (91) with 4-methylbenzoyl chloride and potassium cyanide in a reaction medium of dichloromethane and water, using benzyltrimethylammonium chloride (BTMAC) as the phase-transfer catalyst, we recovered only the starting heterocycle but no ring opening was observed.

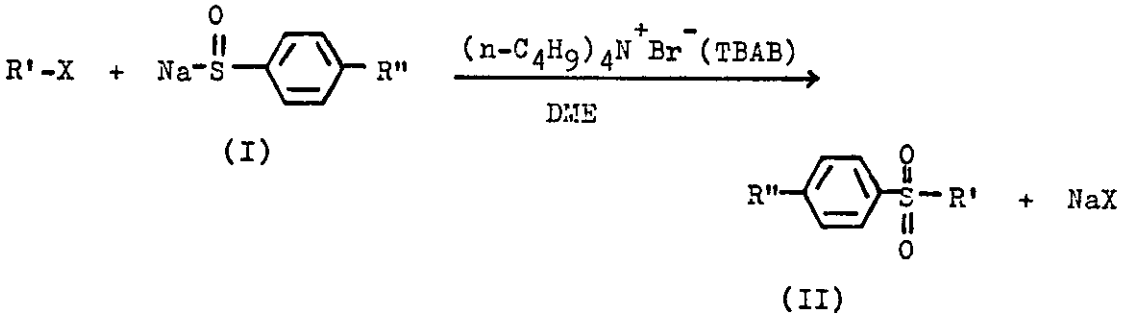



(91) recovered (91) 93%

b) Use of potassium cyanide under solid/liquid phase transfer catalysis conditions

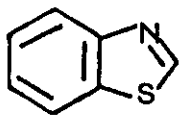
We made a brief study on the use of the phase-transfer catalyst tetrabutylammonium bromide (TBAB) for solid/liquid phase transfer in the Reissert reaction with benzothiazole i.e. using a single liquid phase.

Wildeman and van Leusen[86] reported the synthesis of sulphones (I) in high yields by alkylation of sodium aryl-sulphinates (II) in an aprotic medium, using a catalytic amount of tetrabutylammonium bromide.




(I) (II)

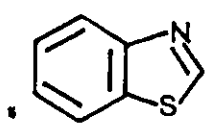
We found treatment of benzothiazole with benzoyl chloride and potassium cyanide, in the molar ratios of 1:1:1 in dichloromethane as the single liquid phase using TBAB (10% mole of KCN) and refluxing for 2.5 hours, resulted in recovery of benzothiazole (60%) and the isolation of benzoyl cyanide (23%). The latter product was obtained from flash column chromatography of the crude material after the work-up. Benzoyl cyanide was identified by its melting point (29-31$^{o}$C), infrared peaks at 2220cm$^{-1}$ (C ≡ N) and 1680cm$^{-1}$ (C = 0) and proton nmr spectral data, which were identical to those of a commercial sample of the compound.



PhCOCl / KCN
$CH_2Cl_2$ / TBAB
reflux, 2.5h

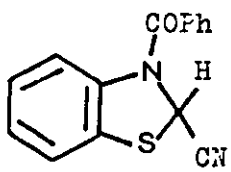
(91) + PhCOCN
60% 23%

We repeated the above reaction using the same molar ratios of the substrates but, in this case, progress of the reaction was followed by analytical tlc. The reaction was eventually halted after gentle refluxing for six hours, followed by stirring at room temperature for 18 hours. After the work-up, which included washing with 5% hydrochloric acid and 5% sodium hydroxide, we recovered benzothiazole (67%) and benzoyl chloride (9.3%) together with the Reissert compound 3-benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g) in a low yield of 6%, m.p. 140-142°C.



(91)

PhCOCl / KCN
$CH_2Cl_2$/ TBAB
reflux 6h, r.t. 18h



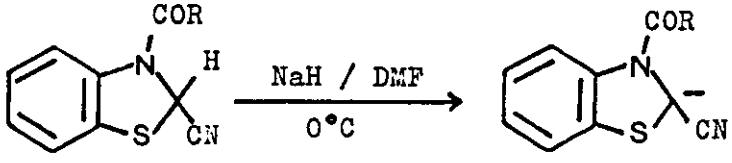
(92g) 6%

+ (91) 67% + PhCOCl, 9.3%

This result represents the first preparation of a Reissert compound from the five-membered ring heterocycle benzothiazole using an inorganic cyanide source under single phase reaction conditions albeit in very poor yield.

## Part II Some Chemistry of Benzothiazole Reissert Compounds

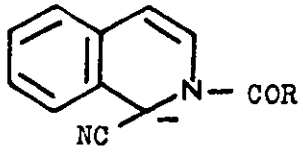
We found that, as with the six-membered ring Reissert compounds, the conjugate bases of the novel five-membered ring Reissert compounds (92) could be readily generated with sodium hydride in dimethylformamide at 0°C, giving an immediate red colouration and evolution of hydrogen gas.




(92) (108)

Although the carbanion centre in (108) lacks the direct resonance stabilisation that the benzene ring affords to the benzylic anion of the isoquinoline Reissert system (20), it benefits from stabilisation by the $\alpha$-sulphur atom.

$\alpha$-Carbanion stabilisation by sulphur is well known and has been attributed[1] to overlap of the unshared electron pair with an empty d orbital ($p\pi - d\pi$ bonding).[87a,b]



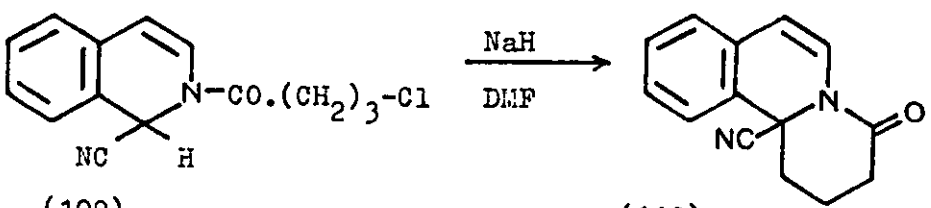

(20)

Assuming the carbanion in (108) is planar,[87c] p orbital overlap would also occur with the planar amide system, and hence with the benzene ring, and similarly with the sp orbital of the nitrile.

Once generated, Reissert anions of type (108) could be applied to a variety of synthetic schemes.

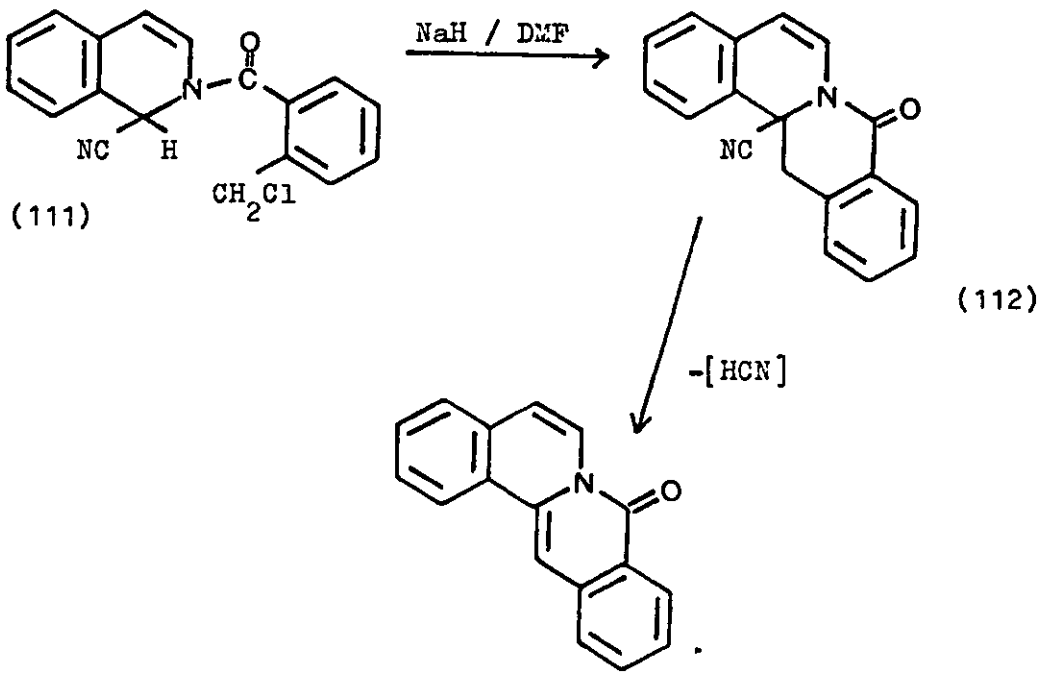
i) Intramolecular alkylation reactions: formation of tri- and tetracyclic ring systems

H.W. Gibson et al[88] showed that suitably substituted isoquinoline Reissert compounds could be made to undergo intramolecular alkylation and cyclisation upon treatment with a strong base. Thus treatment of the isoquinoline Reissert compound (109) with sodium hydride in dimethylformamide afforded (110).



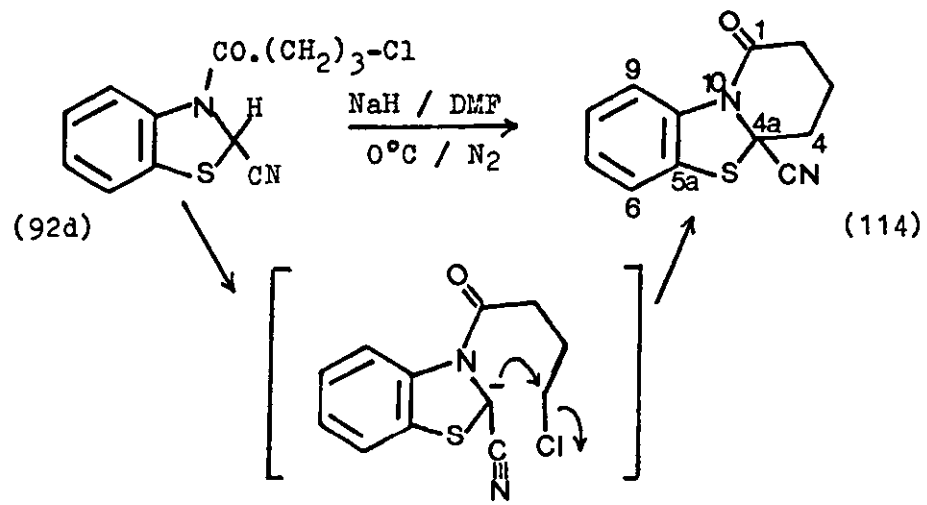

(109) (110)

Other workers[89,90] reported the intramolecular cyclisation of the isoquinoline Reissert compound (111) prepared from 2-chloromethylbenzoyl chloride to give the tetracyclic system (112) after treatment with base. Cyclisation was accompanied by elimination of hydrogen cyanide in situ to give (113). The work was extended to provide berbine alkaloid derivatives and analogues.[19b,52,89,90]




We investigated similar schemes with the appropriately substituted benzothiazole Reissert compounds. We found that the reaction of 3-(4-chlorobutanoyl)-2-cyano-2,3-dihydrobenzothiazole (92d)(1 mole) with sodium hydride (1 mole) in dimethylformamide at 0-5°C for 2 hours and under an atmosphere of nitrogen, resulted in a smooth intramolecular cyclisation to give the novel tricyclic derivative (114). Recrystallisation from ethanol provided 4a-cyano-2,3,4,4a-tetrahydro-1-oxo-1H-pyrido[2,1-b]benzothiazole (114) as light yellow rhombs in 88% yield, m.p. 92-93°C (Scheme 44).

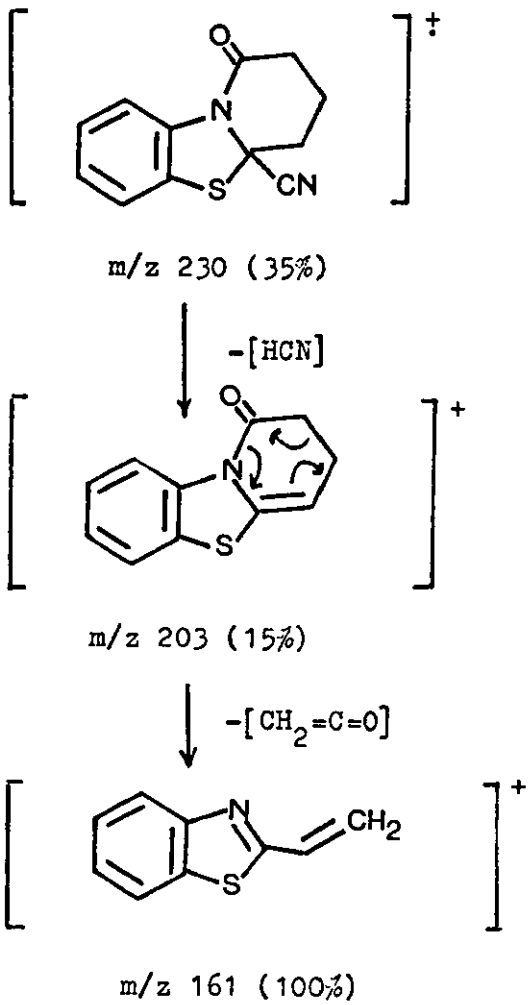
Scheme 44




The infrared of the compound (114) showed a weak nitrile absorption frequency at 2230cm$^{-1}$ and the lactam carbonyl at 1678cm$^{-1}$. The proton nmr showed a multiplet at δ2.90-2.10 for the six aliphatic protons.

The mass spectrum of (114) showed the molecular ion at m/z 230 with 35% relative intensity. A fragment at m/z 203 suggested the loss of HCN from the molecular ion and the base peak at m/z 161 corresponded to the further loss of the elements of ketene. The fragmentation pattern may be represented as follows (Scheme 45).

Scheme 45

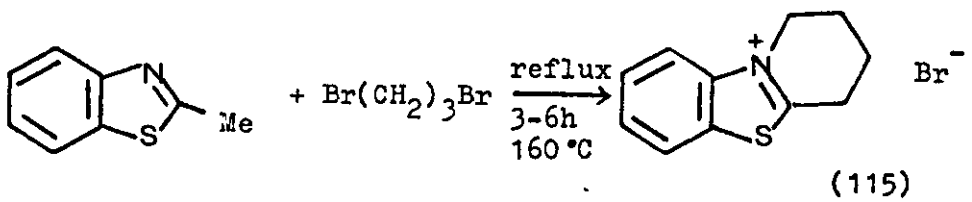



The formula of (114) was also confirmed by satisfactory microanalytical data.

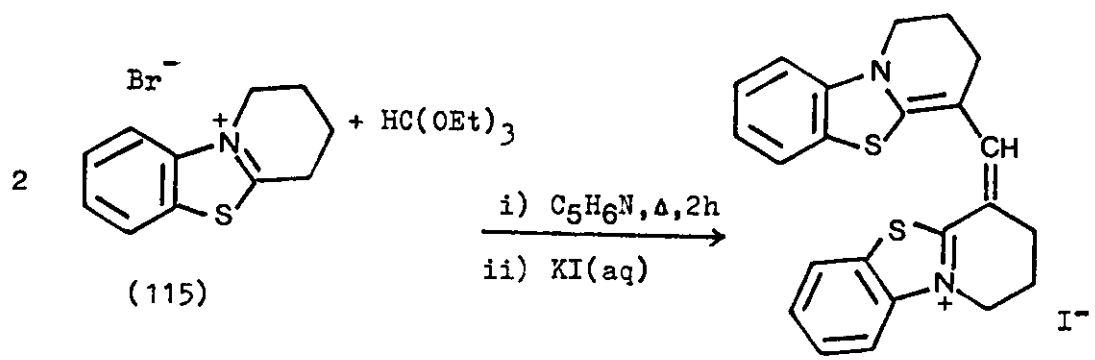
The synthesis of (114) represents a new and efficient route to the pyrido[2,1-b]benzothiazole ring system. There are several other reports of the formation of the tricycle in the literature, but mainly in the form of the pyrido[2,1-b]benzothiazolium salt.[91-93] Schwarz and de Smet[91a] first reported in 1940, the preparation of 1,2,3,4-tetrahydropyrido[2,1-b]benzothiazolium bromide (115) by reaction of 2-methylbenzothiazole and 1,3-dibromopropane (Scheme 46). This

intermediate (115) was subsequently condensed with triethyl orthoformate ($HC(OEt)_3$) in pyridine to form the carbocyanine (116).

Scheme 46



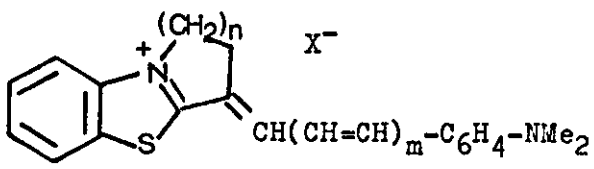

(115)




(115)

(116) $\lambda_{max}$ 565nm

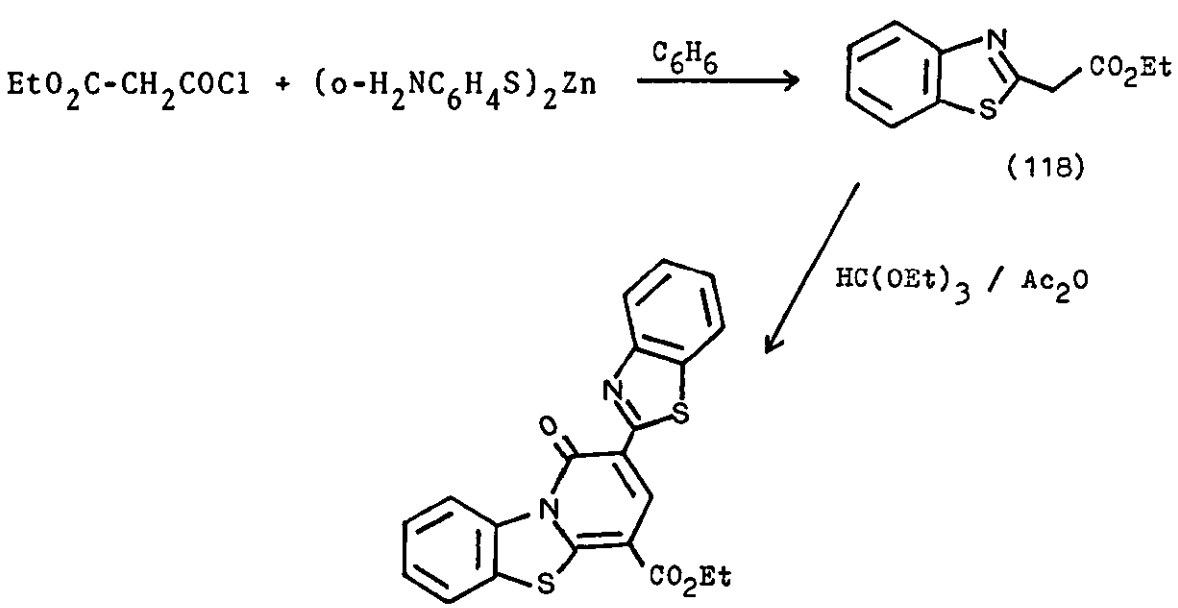
Cyanine dyes with structures such as (116)[91] and (117)[93] and other derivatives[94] of the pyrido[2,1-b]benzothiazole ring system have found application as photographic spectral sensitizers for red-sensitive silver halide emulsions.



(117, e.g.: n = 2, m = 0, x = Br, $\lambda_{max}$ 515 nm)

Nys and van Dormael[95] prepared the carbocyanine (119) by the condensation of ethyl 2-benzothiazoleacetate (118) with triethyl orthoformate in acetic anhydride (Scheme 47). The carbocyanine (119) was also found to have photographic sensitizer properties.[95]

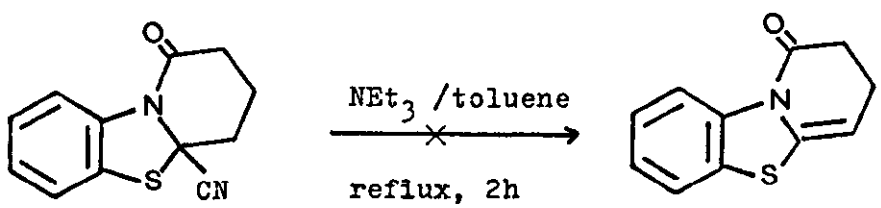
Scheme 47



(118)

(119)

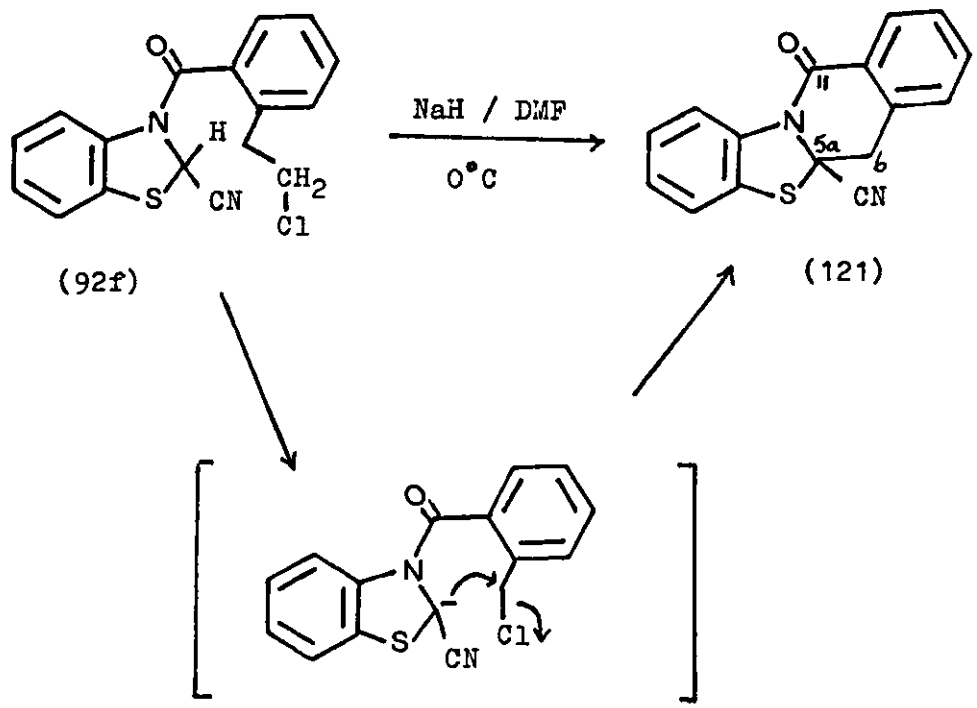
We attempted to remove HCN from structure (114) by refluxing triethylamine in toluene for two hours, but only recovered starting material was isolated. So it appears that the tricyclic system (114) is relatively stable.




(114) (120)

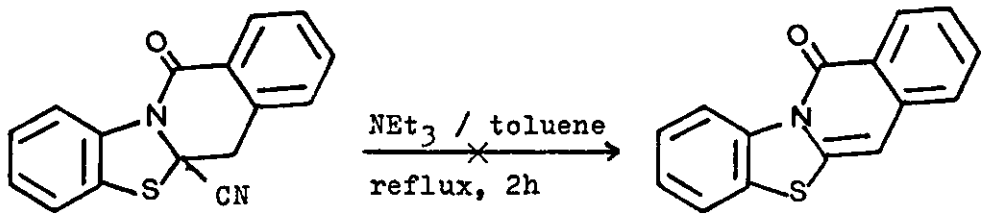
It is also appropriate to mention that the novel pyrido[2,1-b]benzothiazole derivative (114) has been sent for screening for antineoplastic activity after a request was made by the Brussels Laboratory of the National Institutes of Health, National Cancer Institute, Bethseda, Maryland, U.S.A., for a sample of this compound.

We achieved an analogous cyclisation with 3-(2-chloromethylbenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92f) and sodium hydride in DMF, to give the tetracyclic system (121) which is the benzo-analogue of the tricyclic system (114), also in high yield. Recrystallisation from ethyl acetate gave the benzothiazolo[3,2-b]isoquinoline system (121) as yellow prisms in 76% yield, m.p. 157-159°C.




The infrared of compound (121) showed the presence of a nitrile as a weak absorption at 2220cm$^{-1}$ and the lactam carbonyl at 1665cm$^{-1}$. The mass spectrum indicated the molecular ion at m/z 278 (7.2% relative intensity) and the base peak at m/z 251 corresponding to the loss of HCN from $M^{+}$. The structure of (121) was further confirmed by satisfactory microanalytical data.

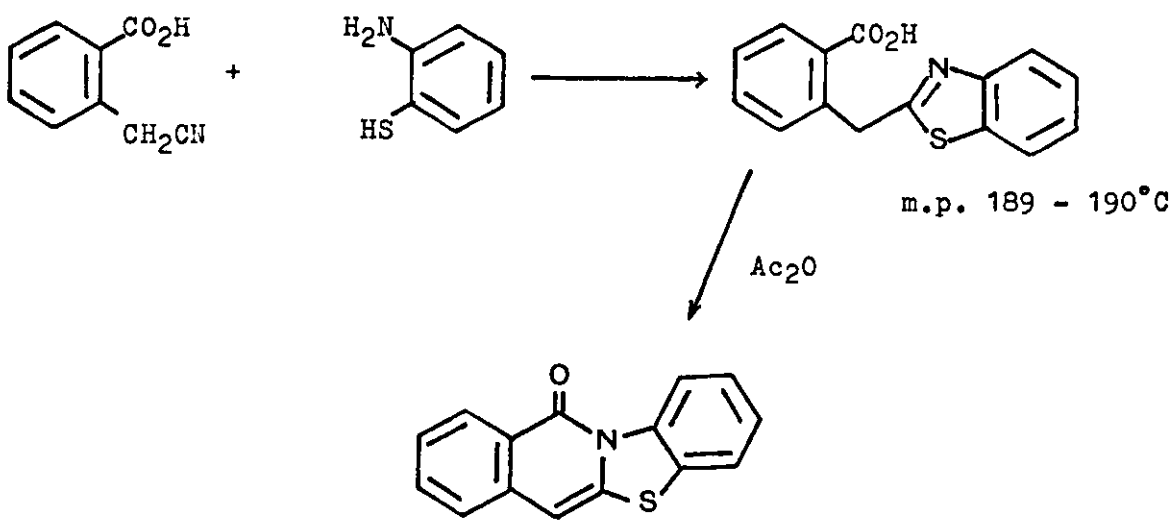
Once again, reflux of (121) with triethylamine and toluene yielded only recovered starting material instead of the compound (122) from expected loss of hydrogen cyanide.




(121) (122)

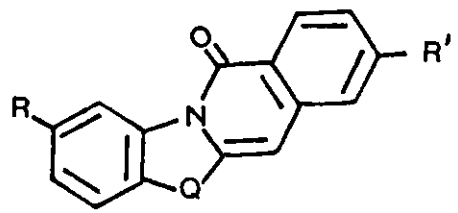
There are only a few previous reports of the tetracyclic system in the literature.[96-98] The sequence of reactions used by Schefczik[96a] to synthesise the benzothiazolo[3,2-b]-isoquinoline system is described in Scheme 48. The author[96a] obtained compound (122) by his method in 85%, m.p. 177-178°C.

Scheme 48




(122)

Schefczik has prepared a series of compounds with the general structure (123) and some of the derivatives have been found to be useful as intermediates for dyes.[96b]




| e.g. (123) | Q | R | $R^1$ |
|---|---|---|---|
| a) | O | H | H |
| b) | O | Ph | H |
| c) | O | H | $NMe_2$ |
| d) | S | H | NHCOPh |

The intramolecular cyclisation of the benzothiazole Reissert compounds (92d, f) thus provide new and efficient synthesis of the novel tri- and tetracyclic ring systems.

ii) Intermolecular alkylation reactions: formation of 2-alkylbenzothiazoles

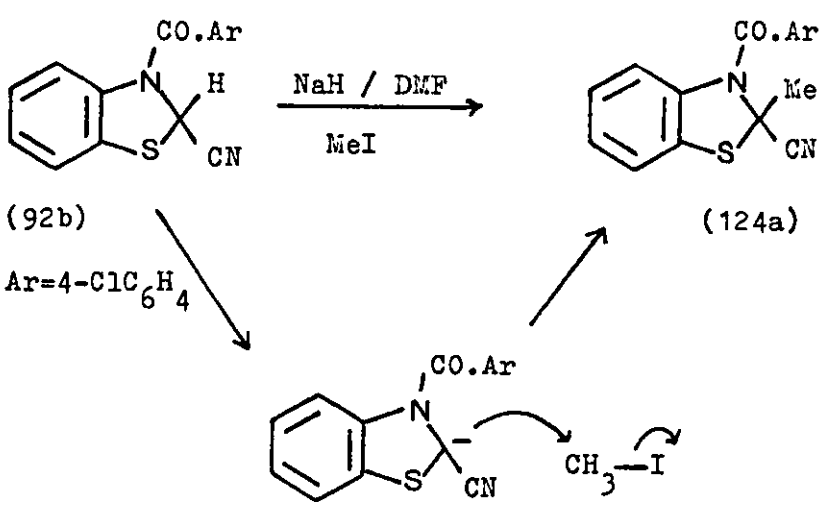
As described in the Introduction, the conjugate base of the isoquinoline Reissert compound (20) has been found to participate in nucleophilic displacement reactions with alkyl halides to give the substituted Reissert compound (21), subsequent base hydrolysis giving 1-alkylisoquinolines.[8a,23,99]

If this procedure could be applied to the novel benzothiazole Reissert compounds, then it would provide a new route to 2-alkylbenzothiazoles.

We studied the reaction of the Reissert compound 3-(4-

chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92b) (1 mole) with methyl iodide in the presence of sodium hydride (1.2 mole) and dimethylformamide. The anion formation was indicated by the appearance of a red colouration. The colour gradually faded to light orange as the reaction progressed. After work-up, 3-(4-chlorobenzoyl)-2-cyano-2,3-dihydro-2-methyl-benzothiazole (124a) was obtained in 55% yield, m.p. 118-120°C (Scheme 49).

Scheme 49

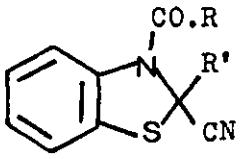



The infrared spectrum of compound (124a) showed an amide absorption frequency at 1662cm$^{-1}$ and a weak cyano peak at 2223cm$^{-1}$. In the proton nmr, the methyl protons appeared as a singlet at δ2.20ppm, and the C-2 proton, which was observed at δ6.42 in the original Reissert compound, was absent. The structure of the alkylated compound (124a) was further confirmed by satisfactory microanalytical data.

This approach was extended to prepare the 2-methyl

derivative from the chloroformate derived Reissert compound (92e) using methyl iodide and the protons of the methyl group in the product (124b) were observed at δ 2.25ppm.

A further derivative (124c) was obtained from (92e) and benzyl bromide, the results are summarised in Table 4. this last reaction is analogous to the important route to 1-benzylisoquinolines via the appropriate Reissert compound,[23] a procedure much used in the synthesis of alkaloids.



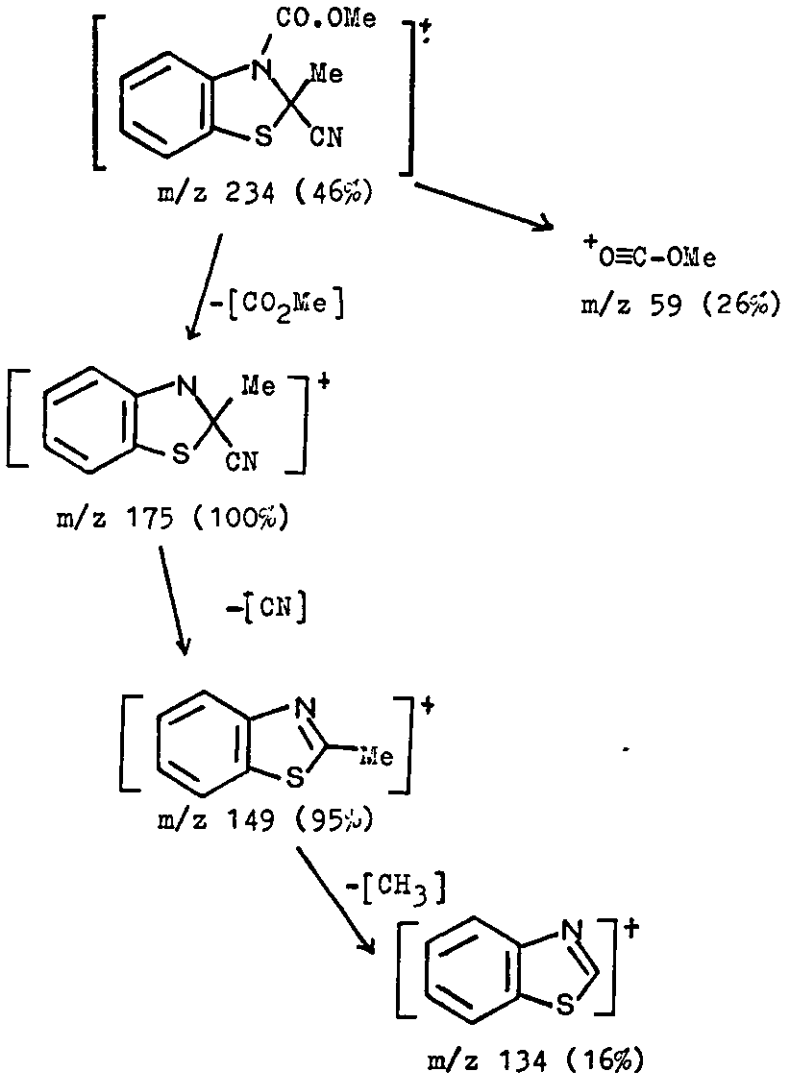

(124)

Table 4

| Compound | | | Yield/ % | m.p./ °C | ir(C=0) ϑmax/ $cm^{-1}$ | pmr δ /ppm |
|---|---|---|---|---|---|---|
| 124 | R | $R^1$ | | | | |
| a | 4-$ClC_6H_4$ | $CH_3$ | 55 | 118-120 | 1662 | 2.20,s,$CH_3$ |
| b | $CH_3O$ | $CH_3$ | 85 | 63-65 | 1728 | 2.25,s,$CH_3$<br>4.02,s,$OCH_3$ |
| c | $CH_3O$ | $C_6H_5CH_2$ | 63 | 112-114 | 1728 | 3.70,s,$CH_2$<br>4.01,s,$OCH_3$ |

All the above compounds gave satisfactory microanalytical data. The mass fragmentation pattern of compound (124b) is described in Scheme 50. The molecular ion was observed at m/z 234 with relative intensity of 46%, and the base peak occurred at m/z 175, resulting from α-cleavage to carbonyl.

Scheme 50

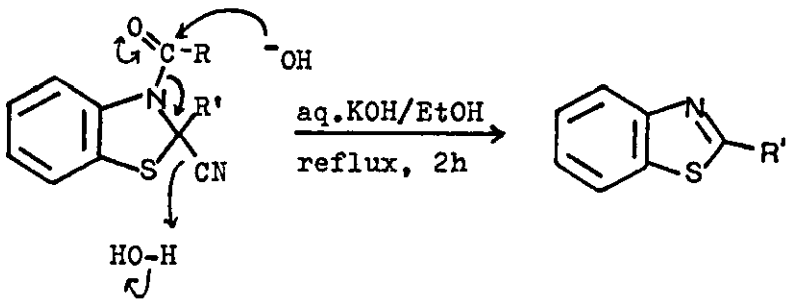



iii) Base catalysed hydrolysis reactions

The alkylated Reissert compounds (124a-c) were hydrolysed[30] in the presence of potassium hydroxide in aqueous ethanol for two hours by refluxing to yield 2-methyl-

benzothiazole (125) and 2-benzylbenzothiazole (126), though in only modest yields (Scheme 51).

Scheme 51




(124a) R = 4-$ClC_6H_4$ , $R^1$ = Me

(124b) R = MeO , $R^1$ = Me

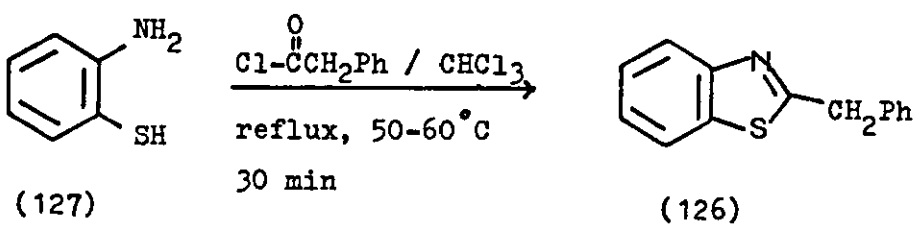
(124c) R = MeO , $R^1$ = $CH_2Ph$

(125) $R^1$ = $CH_3$

(126) $R^1$ = $CH_2Ph$

2-Methylbenzothiazole (125) was obtained in 30% and 25% yields from the Reissert compounds (124a) and (124b) respectively. The ir and pmr of the products were identical to those of the commercial sample of 2-methylbenzothiazole.

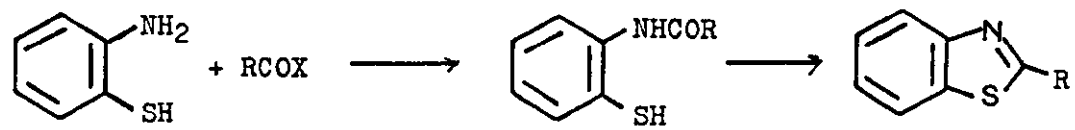
2-Benzylbenzothiazole (126) was obtained in 23%, m.p. 108-111°C from the Reissert compound (124c). Compound (126) has been prepared previously by the condensation of 2-aminothiophenol with phenylacetyl chloride in chloroform to give 2-benzylbenzothiazole (126) in 55% yield, m.p. 112°C.[101]




(127) (126)

The conversion of (127) to (126) as shown, is typical of one of the most used routes to 2-substituted benzothiazoles. Acid chlorides or anhydrides[102] are most often employed, although the acids themselves[103] as well as their esters[104] have been used successfully (Scheme 52).

Scheme 52

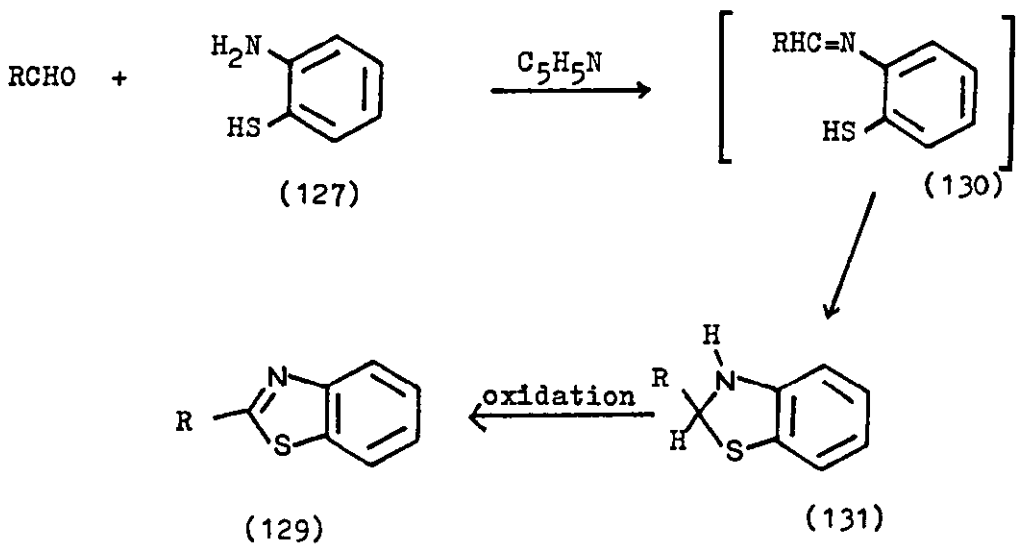



(127) (128) (129)

The o-acylaminothiophenols (128), which are intermediates in this reaction have been found to cyclise readily[105] to give benzothiazoles (129).

An alternative literature approach to such compounds (129) is by the reaction of aldehydes with o-aminothiophenols. This yields either 2,3-dihydrobenzothiazoles (131) or, by ring closure and oxidation, benzothiazoles (129), depending on the aldehyde and the thiophenol employed (Scheme 53). Aliphatic aldehydes give only the dihydro derivatives, the oxidative ring closure pathway occurring readily in the case of aromatic aldehydes.

Scheme 53

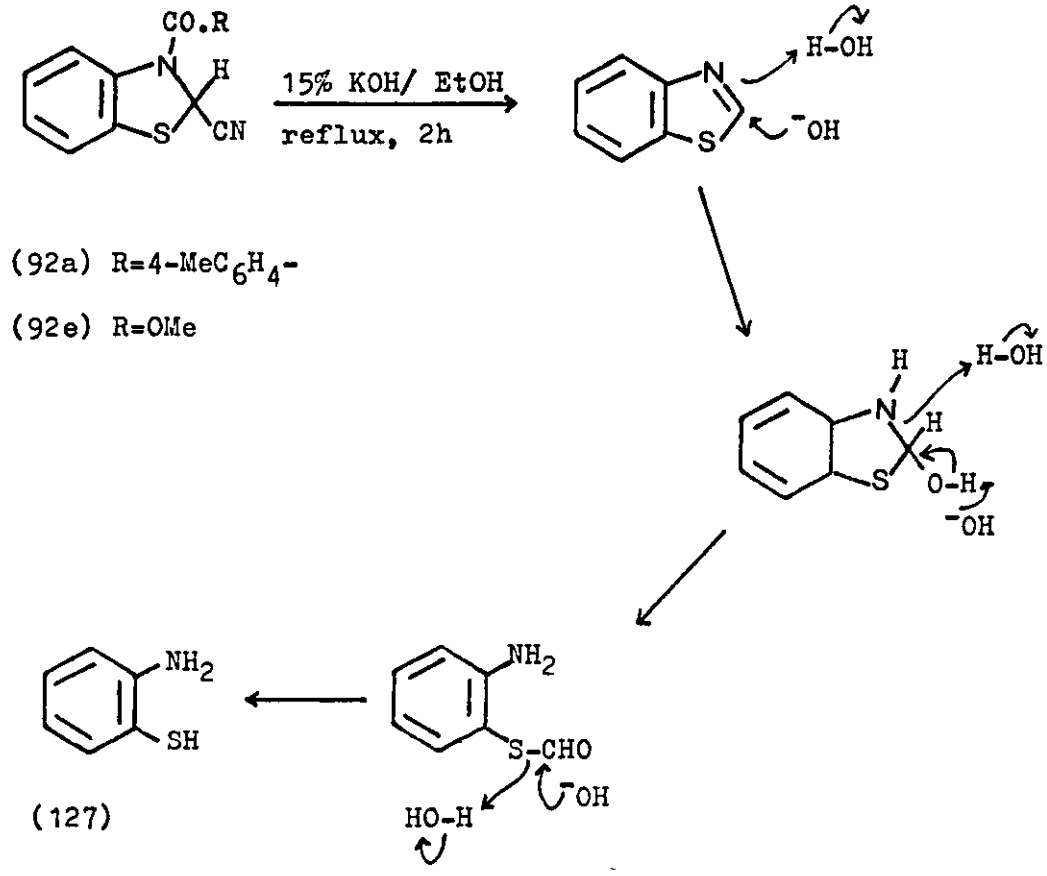



Thus we have achieved a different route to the synthesis of 2-substituted benzothiazoles, although yields from these base-catalysed hydrolysis reactions have not been optimised. We later examined the conversion under different conditions as described below (p.96 and p.97 ).

When the unsubstituted Reissert compound 2-cyano-2,3-dihydro-3-(4-methylbenzoyl)benzothiazole (92a) was refluxed with aqueous potassium hydroxide (15%) and ethanol for two hours, after the work-up, 2-aminothiophenol (127) was isolated in 46% yield, m.p. 17-20°C, lit[106] 19-21°C. The ir and pmr spectra were identical to those of a commercial sample of 2-aminothiophenol.

We had hoped to isolate benzothiazole from this reaction since, from previous work,[30] base-hydrolysis of a Reissert compound regenerated the starting aromatic heterocycle (Scheme 54). But instead, hydrolysis continued to cause ring opening of the heterocycle and eventually give 2-aminothiophenol.

Scheme 54




(92a) R=4-MeC$_6$H$_4$-

(92e) R=OMe

(127)

The isolation of the thiophenol (127) was confirmed not only by its characteristic smell but also by the melting point of its hydrochloride salt (132).


(127)

(132) dec. 210°C,
lit[107] 216°C

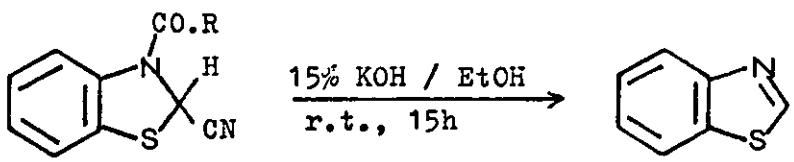
When a similar hydrolysis was carried out under reflux

using the unsubstituted chloroformate derived Reissert compound 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e), 2-aminothiophenol (127) was again isolated in 70% yield, m.p. 18-20°C.

The hydrolysis conditions used were thus too severe to prevent the benzothiazole ring opening. We therefore carried out the same two reactions but with no heating involved, simply stirring at room temperature. The progress of the hydrolysis was monitored by analytical tlc and in both cases, the reaction had completed after 15 hours.

Hence, we found that the base-catalysed hydrolysis of the Reissert compound (92a) yielded benzothiazole in 50% with ir and pmr identical to authentic material.

Similarly, base-catalysed hydrolysis of the Reissert compound (92e) at room temperature gave benzothiazole in 41%, b.p. 90°C/5mmHg.




(91)

(92a) R = 4-$MeC_6H_4$

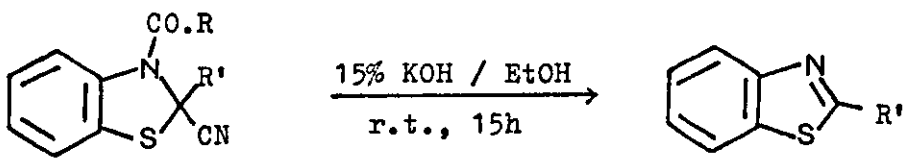
(92e) R = MeO

Therefore, regeneration of the starting aromatic heterocycle was successful under the milder conditions used.

We then extended the use of these reaction conditions to the synthesis of 2-alkylbenzothiazoles from the alkylated

Reissert compounds. We applied the method to the two examples used previously i.e. compounds (124b) and (124c) (Scheme 51) in the hope that the use of the milder hydrolysis conditions would result in higher yields of 2-alkylbenzothiazoles.

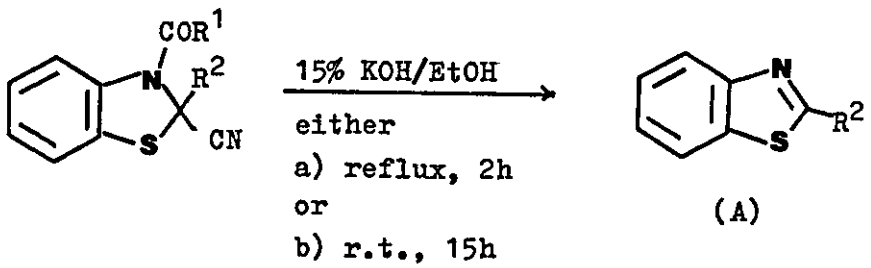
Indeed, we found that hydrolysis of the alkylated Reissert compounds (124b) and (124c) in the presence of potassium hydroxide in aqueous ethanol at room temperature yielded 2-methylbenzothiazole (125) and 2-benzylbenzothiazole (126) in 61% and 53% respectively. The yields are usefully higher than those observed when hydrolysis was carried out under reflux. i.e.




(124b) R = MeO , $R^1$ = Me (125) $R^1$ = $CH_3$

(124c) R = MeO , $R^1$ = $CH_2Ph$ (126) $R^1$ = $CH_2Ph$

The results from the base-catalysed hydrolysis reactions are summarised in Table 5:-




(A)

Table 5

| $R^1$ | $R^2$ | Yield of (A)/% | |
|---|---|---|---|
| | | (a) after reflux/2h | (b) after r.t./15h |
| 4-$MeC_6H_4$ | H | ring opens | 50 |
| MeO | H | ring opens | 41 |
| MeO | Me | 35 | 61 |
| MeO | $CH_2Ph$ | 23 | 53 |

iv) Retro-Reissert reactions with chloroformate derived substrates using carboxylic acids

It can be seen that base-catalysed hydrolysis procedures discussed above are examples of a "retro-Reissert" reaction whereby the aromatic heterocycle is regenerated.

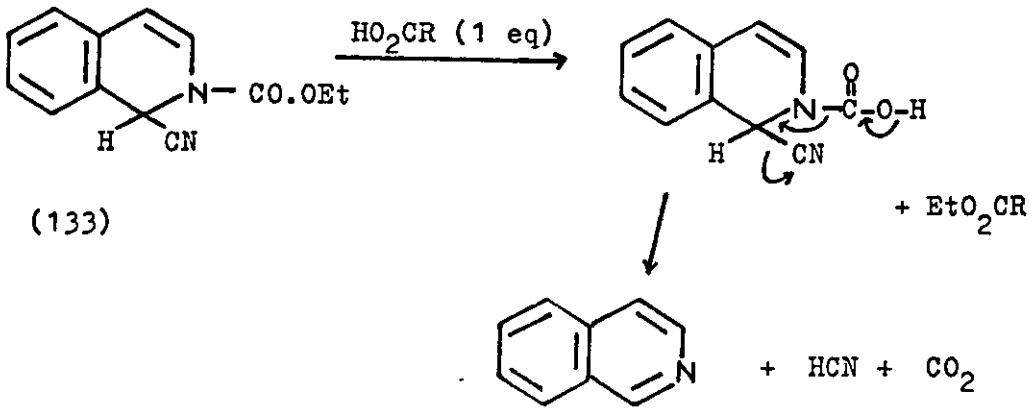
Tsizin and co-workers[108] observed recently that when 1-cyano-2-ethoxycarbonyl-1,2-dihydroisoquinoline (133) or 2-cyano-1-ethoxycarbonyl-1,2-dihydroquinoline (134) were heated with an equimolar quantity of n-hexanoic, cyclohexanecarboxylic or benzoic acid, a retro-Reissert reaction occurred, regenerating isoquinoline or quinoline respectively.

The method thus avoids hydrolytic conditions, providing in these cases, an alternative to the base-catalysed procedure usually used to achieve the retro-Reissert process.

The process is a transesterification, presumably via the mixed anhydride, giving the ethyl ester of the acid concerned, together with hydrogen cyanide and carbon dioxide. The

reaction course, as presented by the Russian workers[108], is shown in Scheme 55.

Scheme 55

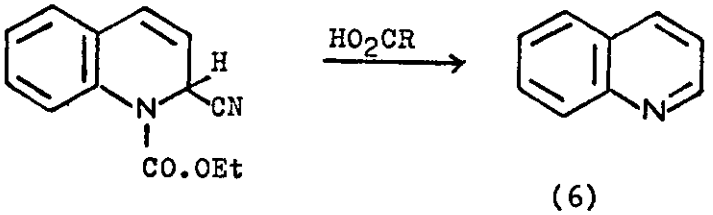



(133)

(3)

R = $C_5H_{11}$ , cyclo-$C_6H_{11}$ , $C_6H_5$

Similarly,




(134)

(6)

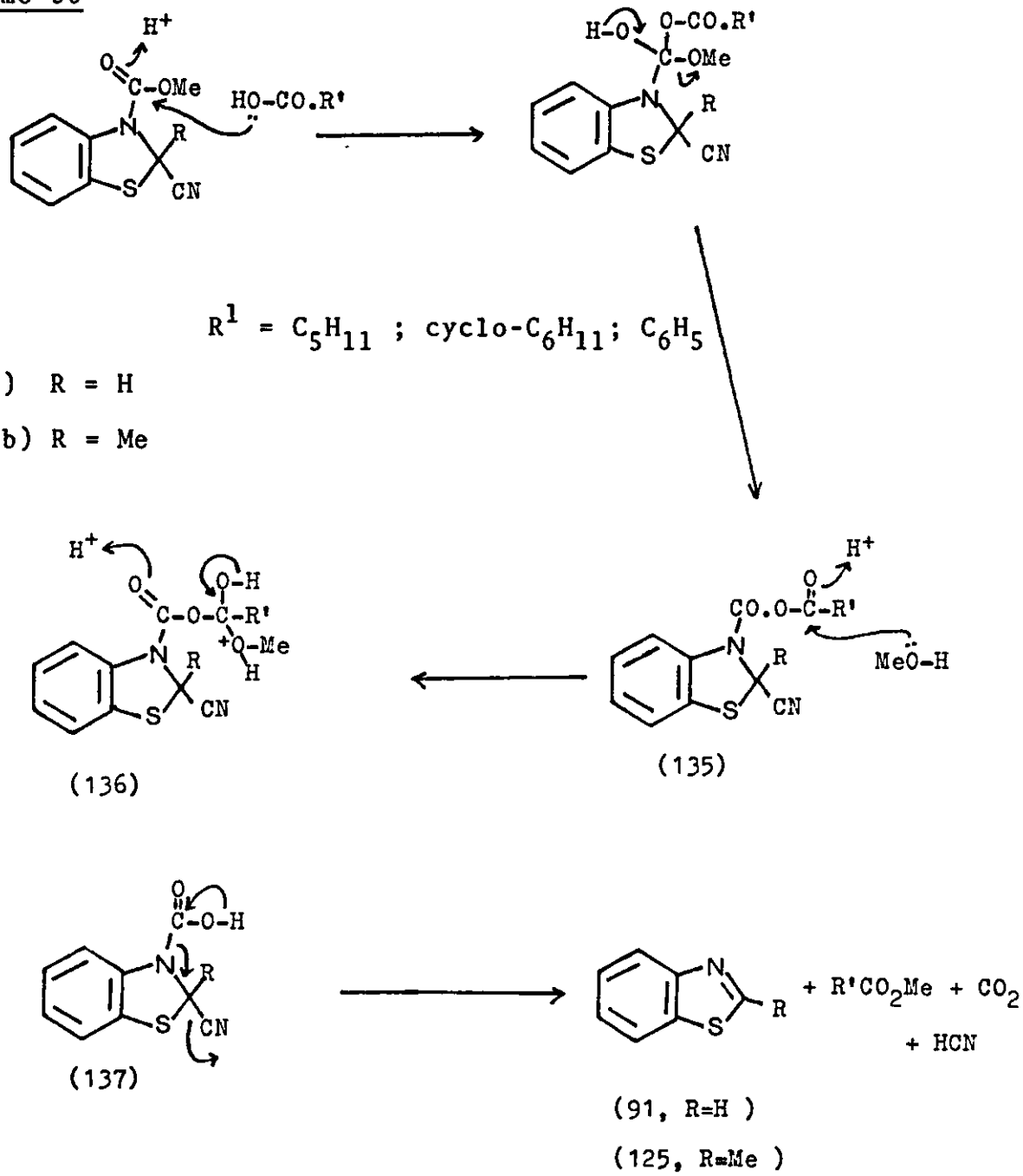
Tsizin and co-workers[108] did not report application of their method to alkylated Reissert compounds and also their quoted yields were determined by means of gas liquid chromatography (glc), rather than product isolation.

We have applied this procedure to Reissert compounds derived from the five-membered ring heterocycle benzothiazole. We have found that the Reissert compound 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e) and its 2-methyl derivative

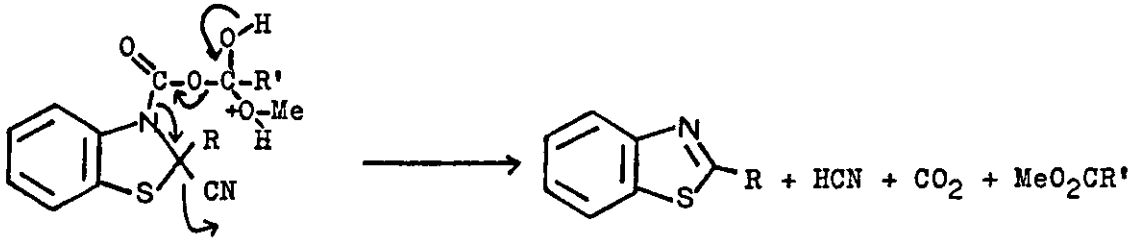
(124b) can be converted to their corresponding aromatic heterocycles, i.e. benzothiazole (91) and 2-methylbenzothiazole (125) which were isolated in yields of 35-59% (Table 6).

We found that better yields were obtained (Table 6) when the Reissert compound was heated with two equivalents of the acid at 130-140$^{o}$C for four hours. It could be that the excess acid assisted in the catalysis of the reaction in going from the mixed anhydride intermediate (135) (Scheme 56) to the subsequent cleavage of the carbamic acid (137) to give the product (91) or (125).

Scheme 56




An alternative breakdown of intermediate (136) proceeding directly to the benzothiazole (91) or (125), without involvement of the carbamic acid (137), could also occur.



(136)

Our results are summarised in Table 6 below:-

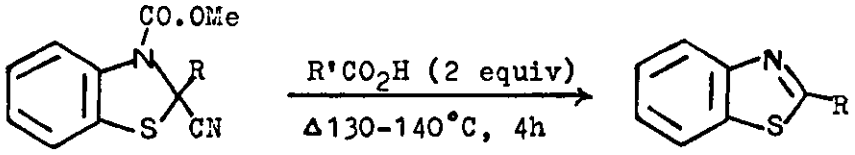


Table 6

| R | $R^1CO_2H$(2equiv) | Yield[a]/% | B.p./°C |
|---|---|---|---|
| H | $n\text{-}C_5H_{11}CO_2H$ | 53[b](48) | 90/5mmHg[c] |
| H | $(CH_2)_5CHCO_2H$ | 39[d](26) | 90/5mmHg[c] |
| H | $PhCO_2H$ | 35[e](18) | 90/5mmHg[c] |
| Me | $n\text{-}C_5H_{11}CO_2H$ | 59 | 95/5mmHg[c] |

[a] Use of one equivalent of the acid gave the yields in brackets. [b] 79% based on recovered starting material. [c] identical with commercial sample. [d] 70% based on recovered starting material. [e] 50% based on recovered starting material.

From the results, it would appear that n-hexanoic acid was the most effective in this retro-Reissert conversion. The use of cyclohexanecarboxylic and benzoic acids proved less efficient.

The main value of the base-catalysed retro-Reissert process previously has been to regenerate the aromatic heterocycle after an alkylation step at the carbon alpha to the nitrile.

We have, therefore, successfully extended the method to include a 2-alkylated Reissert compound from benzothiazole (124b). This gave 2-methylbenzothiazole in an isolated yield of 59% which is comparable with the yield of 61% by the base hydrolysis at room temperature (p.96) and thus the method provides a satisfactory alternative procedure for the process.

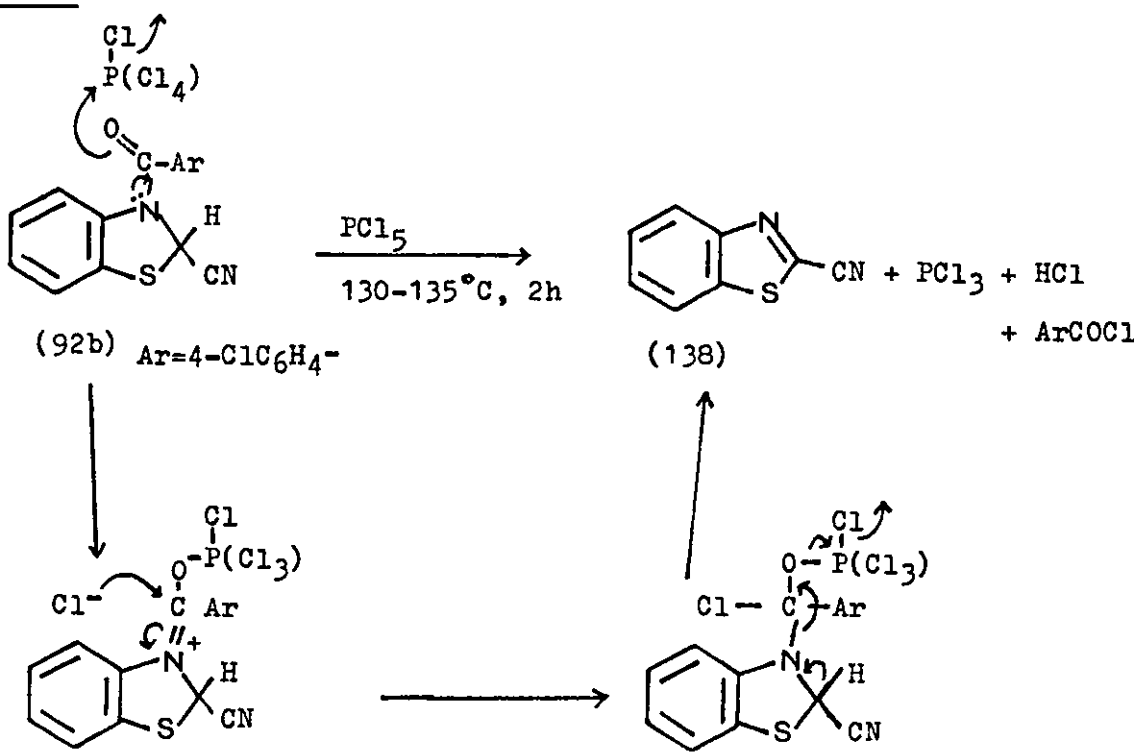
v) Benzothiazole Reissert compound cleavage with phosphorus pentachloride: formation of 2-cyanobenzothiazole

Kaufmann and Dandliker[109] and later workers[110-112] showed that N-benzoyl-1-cyano-1,2-dihydroisoquinoline could be cleaved to isoquinaldonitrile, benzoyl chloride, phosphorus trichloride and hydrogen chloride, and that the quinoline analogue similarly gave quinaldonitrile as heterocyclic product. Thionyl chloride and sulphuryl chloride have also been used as reagents,[109] and the reaction applied to substituted and fused Reissert substrates.[113-115]

By following the method of G.W. Kirby et al,[113] for the cleavage of 2-benzoyl-4-chloro-1-cyano-1,2-dihydroisoquinoline by heating with phosphorus pentachloride, the cleavage of 3-(4-chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92b) gave

2-cyanobenzothiazole (138) in 56% yield, m.p. 72-75°C, lit[116] 71-73°C. We suggest a possible mechanism below (Scheme 57).

Scheme 57

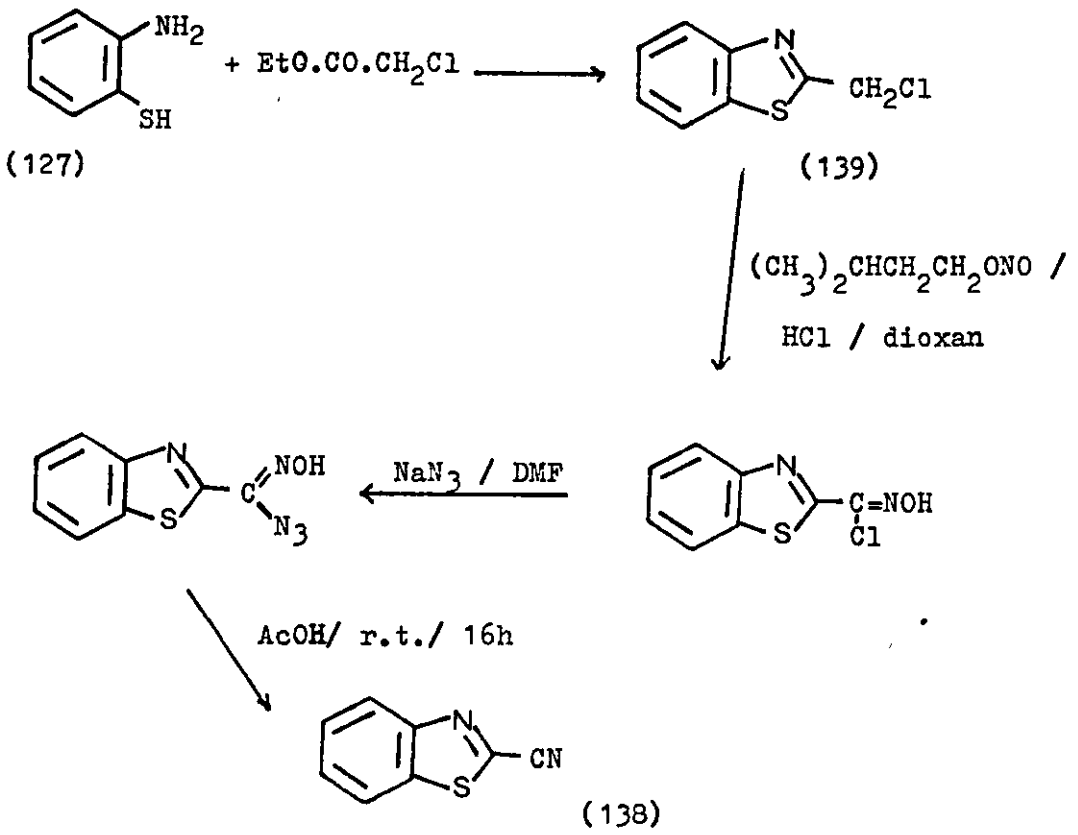



The infrared of compound (138) showed a fairly strong nitrile absorption at 2220cm$^{-1}$ which is in contrast to the weak nitrile observed at 2223cm$^{-1}$ of the starting Reissert compound (92b). The ir also indicated the absence of the amide carbonyl at 1660cm$^{-1}$. Nmr showed the proton at C-2 of the starting material (92b) at ∂6.42ppm had disappeared and the four aromatic protons of the product appear as a multiplet at ∂ 8.35-7.58ppm.

2-Cyanobenzothiazole has been previously prepared[116] starting with the condensation of o-aminothiophenol with ethyl

chloroacetate to give 2-chloromethylbenzothiazole (139) and reacting this in sequence with isoamyl nitrile, sodium azide and stirring in acetic acid (Scheme 58a).

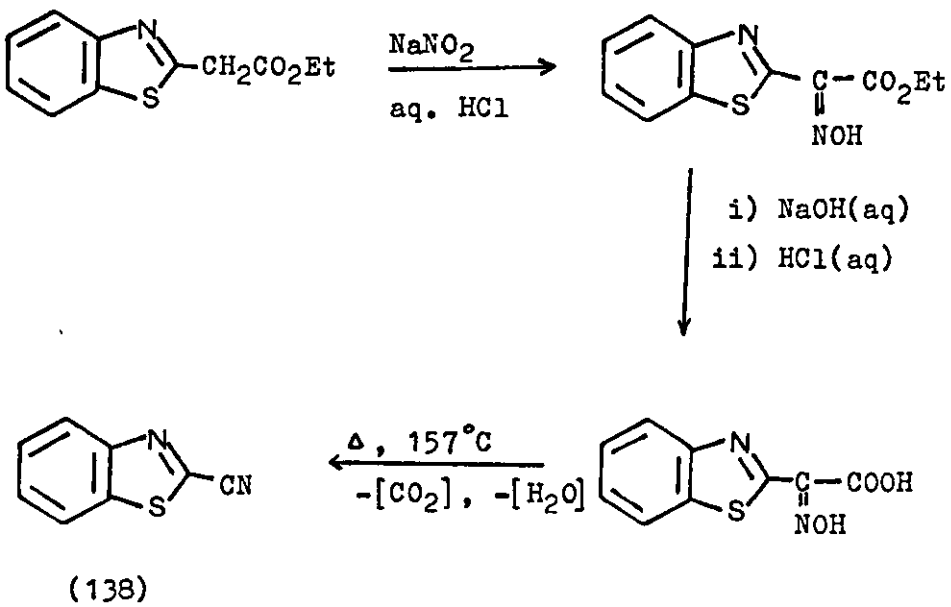
Scheme 58a




Although this procedure gives 2-cyanobenzothiazole (138) in an overall yield of 62% from (127) compared to our overall yield of 48% from benzothiazole (91), our reaction sequence and the time involved are considerably shorter.

Another method for the synthesis of 2-cyanobenzothiazole (138) was reported by Baudet and co-workers,[117] starting from ethyl 2-benzothiazoleacetate, to give the product (138) in an overall yield of 46% (Scheme 58b).

Scheme 58b




(138)

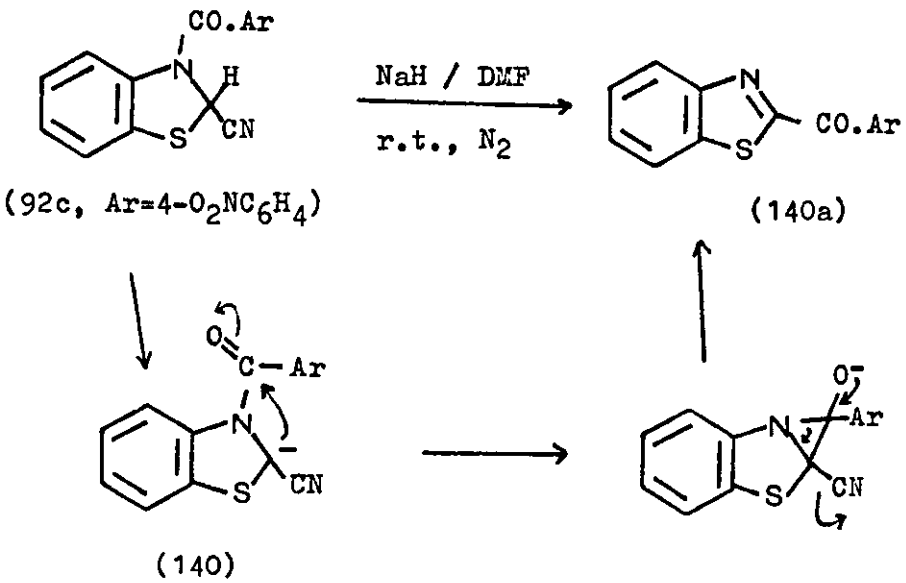
vi) Attempted 1,2-rearrangement reaction

The conjugate base (140) of the Reissert compound 2-cyano-2,3-dihydro-3-(4-nitrobenzoyl)benzothiazole (92c) was generated by treating with sodium hydride at room temperature. A deep blue colouration was observed with the evolution of hydrogen gas.

The behaviour of the conjugate base (140) was studied in the absence of any added electrophile at room temperature in an inert atmosphere of nitrogen gas. It was anticipated that the anion (140) may undergo an intramolecular 1,2-rearrangement via an aziridine intermediate and elimination of cyanide ion to give as product 2-(4-nitrobenzoyl)benzothiazole (140a)(Scheme 59).

Analogous intramolecular 1,2-rearrangements have been reported with the conjugate bases of isoquinoline and quinoline Reissert compounds[99b] and of phthalazine Reissert compounds,[62] to give the corresponding C-acyl heterocycle.

Scheme 59




(92c, Ar=4-$O_2NC_6H_4$)

(140a)

(140)

An inert atmosphere of nitrogen gas was used in order to avoid a competing reaction of the Reissert anion (140) with atmospheric oxygen (Scheme 24, p.36).

The Reissert anion (140) solution was allowed to stand at room temperature for 6 hours, its initial colour was deep blue, but gradually changed to a red-brown colour. A bright red gum-like residue was obtained after work-up, and analytical tlc indicated the presence of many components in the crude product. Preparative tlc (2 x 1m silica gel plates) was used in an attempt to separate the components, using a 40:60 mixture of ethyl acetate and petroleum ether (b.p. 40-60$^{o}$C) as the eluent.

The largest fraction collected was a light orange amorphous solid (49mg) which could not be satisfactorily purified. The infrared spectrum of this solid showed a carbonyl absorption at 1685cm$^{-1}$ and the proton nmr showed absence of the C-2H of the original Reissert compound (92c) at $\partial$6.30ppm. The mass spectrum

showed the molecular ion at m/z 284, corresponding to the wanted 2-(4-nitrobenzoyl)benzothiazole (140a).

So it appears that a 1,2-rearrangement of (92c) had occurred to give the product (140a), but only in a very low yield. The other fractions collected were of such negligible yields that they were not identified.

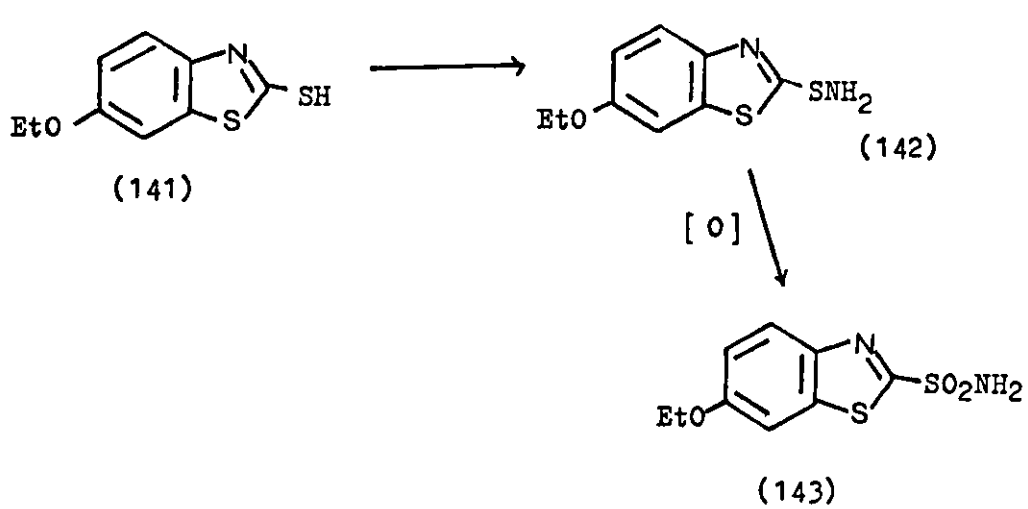
The five-membered ring Reissert compounds thus provide a new and potentially versatile means of extending the chemistry of these ring systems.

## Part III Potential Biological Interest of Benzothiazole Reissert Compounds

We have found novel five-membered ring Reissert compounds may be prepared from benzothiazole. As mentioned earlier (p.59), the Reissert compound derived from methyl chloroformate (92e) has been sent to the Brussels Laboratory of the National Institutes of Health, National Cancer Institute, Bethseda, Maryland, U.S.A. for screening for antineoplastic activity. It would be of interest to see if these benzothiazole Reissert compound would show other potential biological activity.

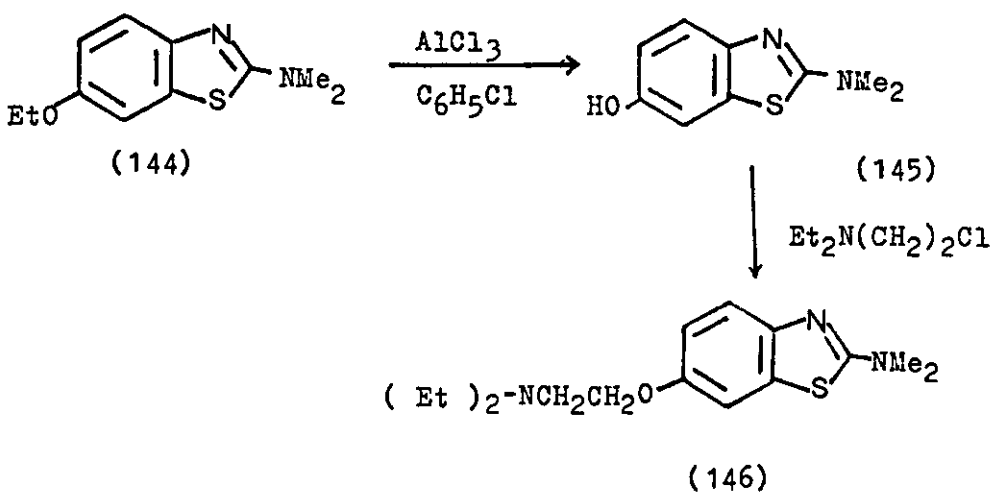
Some substituted benzothiazoles have found use pharmacologically. Ethoxysolamide (143) is a sulphonamide with diuretic activity.[118a] This may be prepared by reaction of the substituted benzothiazole (141) with sodium hypochlorite in a mixture of sodium hydroxide and ammonia to afford the sulphenamide (142). Oxidation with permanganate led to the sulphonamide (143)(Scheme 60).[118b]

Scheme 60



Dianthiazole (146) is active as an antifungal agent[118a] and is also derived from benzothiazole. Compound (146) may be prepared by cleavage of the ether function of the substituted benzothiazole (144) with aluminium chloride followed by alkylation of the sodium salt of the resulting phenol (145) with 2-diethylaminoethyl chloride (Scheme 61).[118c]

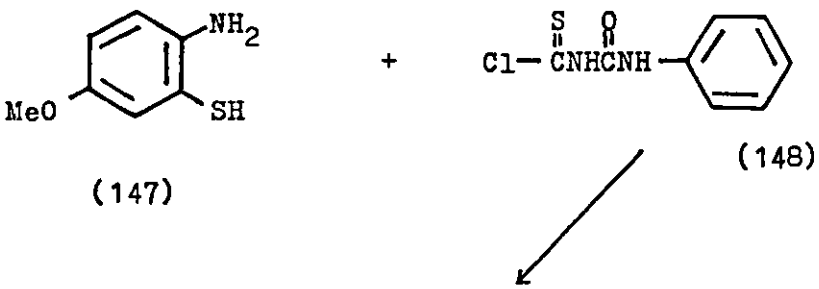
Scheme 61



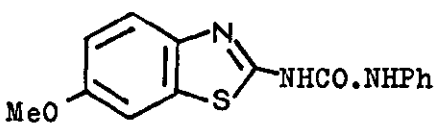

(144) (145) (146)

Another example of a substituted benzothiazole with pharmacological activity is the anthelmintic agent frentizole (149).[119a] Reaction of the aminophenol (147) with reagent (148) obtained from phenylurea and thiophosgene leads to frentizole (149)(Scheme 62).[119b]

Scheme 62

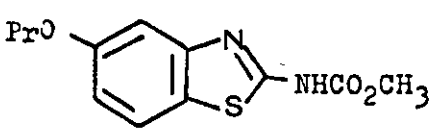



(147) (148)




(149)

The anthelmintic agent tioxidazole (150) is similarly prepared.[119b]




(150)

The examples described above demonstrate the various areas of biological activity where the novel five-membered ring Reissert compounds from benzothiazole and their derivatives may be of potential use.

## CHAPTER III INDAZOLE REISSERT COMPOUNDS

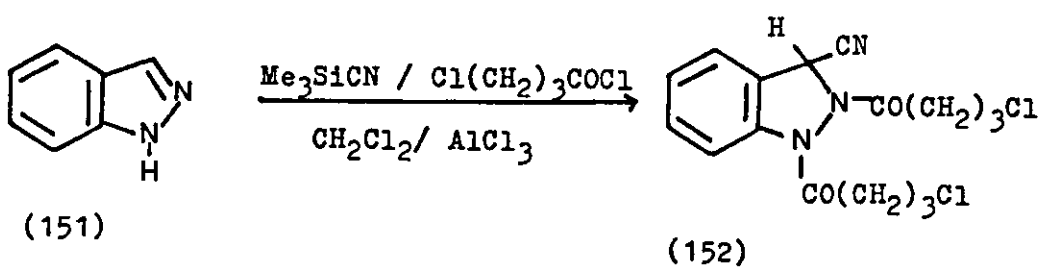
### Part I The Synthesis of Reissert Compounds from Indazoles

Having successfully prepared from benzothiazole the first examples of five-membered ring Reissert compounds,[67] we proceeded to examine the behaviour of other such heterocycles to the single phase reaction medium approach. Indazole (151) is a five-membered ring diazaheterocycle which has not been studied previously for Reissert compound formation.

#### i) The use of trimethylsilyl cyanide under single phase reaction conditions

Following the same method as used for the preparation of a benzothiazole Reissert compound, use of 4-chlorobutanoyl chloride with trimethylsilyl cyanide gave 1,2-bis(4-chlorobutanoyl)-3-cyano-2,3-dihydroindazole (152). This was obtained in 66% yield, b.p. 85°C/10mmHg, using indazole: trimethylsilyl cyanide: 4-chlorobutanoyl chloride in the molar ratio of 1:2:2 (Scheme 63).

Scheme 63

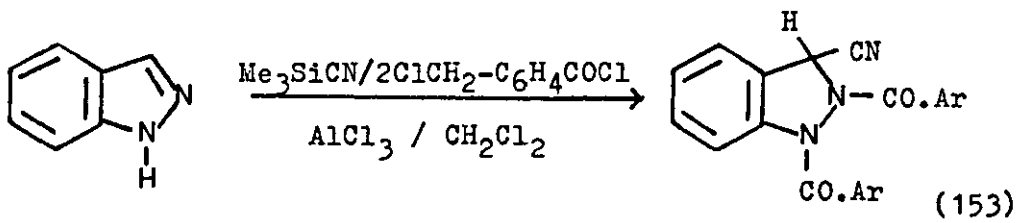



(151) (152)

The infrared spectrum of this product (152) showed the carbonyl absorption frequency at 1715cm$^{-1}$ and a weak cyano

peak at 2230cm$^{-1}$. The proton nmr included a slightly broad singlet at ∂8.50 attributed to the C-7H; its significant downfield shift may be rationalised by probable intramolecular hydrogen bonding occurring with the amide carbonyl at position -1. The compound (152) gave a satisfactory microanalysis and a single spot was observed on analytical tlc.

A similar Reissert compound was formed in 40% yield using two moles of 2-chloromethylbenzoyl chloride, m.p. 86-89°C (153). The infrared spectrum of this compound showed the carbonyl absorption at 1685cm$^{-1}$ and a weak cyano peak at 2220cm$^{-1}$. Compound (153) gave a correct microanalysis and a single spot was observed on analytical tlc.




(151) (153)

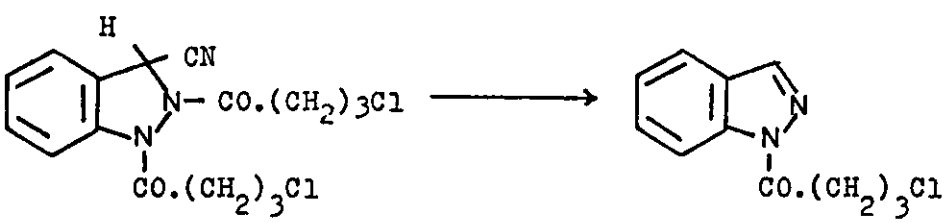
Ar= 2-ClCH$_2$-C$_6$H$_4$-

Both compounds (152) and (153) changed to a deep red colour on mixing a small sample of each with sodium hydride in dimethylformamide, hence reinforcing the fact that it was the Reissert compounds which have been isolated.

But mass analysis of compounds (152) and (153) by both electron impact and chemical ionisation modes gave rather unexpected results. With compound (152), the highest peaks appeared at m/z 222 and 224. The molecular ion cluster

expected at m/z 357/355/353 was absent. In the case of compound (153), the highest peaks were observed at m/z 270 and 272 and the molecular ion cluster absent. These observations suggested compounds (152) and (153) either readily lose the elements of $Cl(CH_2)_3COCN$ or 2-$ClCH_2C_6H_4COCN$ respectively in the mass spectrometer or are unstable and have either decomposed or hydrolysed, perhaps by moisture in the air, to the N-acylated indazoles (154) and (155)(Scheme 64).

Scheme 64




(152) m.wt. 253/355/357 (154) m.wt. 222/224

and

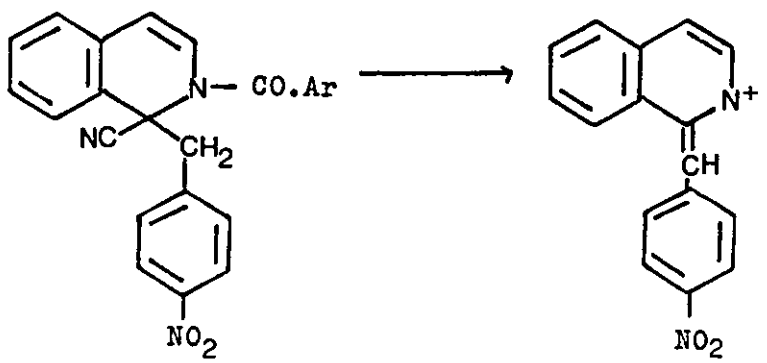

Ar= 2-$ClCH_2C_6H_4$ -

(153) m.wt. 449/451/453 (155) m.wt. 270/272

An example of this absence of the molecular ion in mass analysis was observed by Mrs. N.M. Enwerem in this Department,[120] with some derivatives of an isoquinoline

Reissert compound (156). The highest fragment observed (157) corresponded to the loss of the elements ArCO.HCN from the molecular ion (Scheme 65).

Scheme 65




(157)

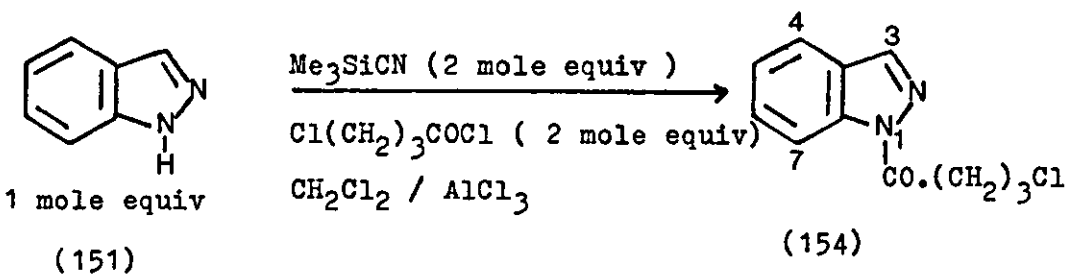
(156) Ar = $C_6H_5$-;
= 4-$CH_3OC_6H_4$-;
= 4-$ClC_6H_4$-

On repeating the reaction for the preparation of compound (152), we were unable to isolate (152), but instead obtained the monoacylated heterocycle (154). This was isolated as a solid product which, on recrystallisation from ethyl acetate, gave colourless needles in 85% yield, m.p. 28-29$^{o}$C and a single spot was observed on analytical tlc (Scheme 66).

The infrared of (154) showed a carbonyl absorption at 1710cm$^{-1}$ but no cyano peak was observed. Also, no deep colour was observed on mixing a small sample of this compound with sodium hydride in dimethylformamide, unlike compound (152) which turned deep red. The proton nmr showed the presence of one 4-chlorobutanoyl chain only from the integration. The C-7H

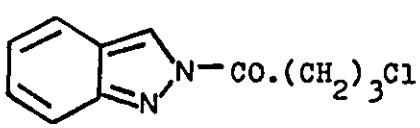
was observed as a broad singlet at ∂8.55[121] and the C-3H as a singlet at ∂8.22ppm.[121] An accurate mass analysis of the N-(4-chlorobutanoyl)indazole (154) showed molecular ions at m/z 222 (4.45%) and m/z 224 (1.5%). Microanalysis was also correct.

Scheme 66



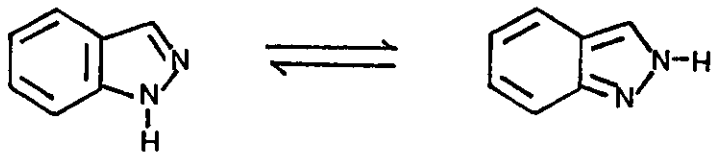

The same product (154) was obtained when the reaction was undertaken, using one mole equivalent of each reagent.

An alternative product from this reaction (Scheme 66) would be the 2-acyl derivative (158). But in general, the 1-acylated indazoles are more stable than the 2-acyl derivatives.[122] In the cases where 2-acylated indazoles have been prepared, it was found that long standing or heating caused isomerisation of the 2-derivative into the 1-acylated compound.[122] The ease of this rearrangement varies considerably with the acyl group involved,[123] being rather slow with benzoyl derivatives. But with groups such as bromoacetyl and trichloroacetyl, the only isolable product is the 1-acylindazole.[124]



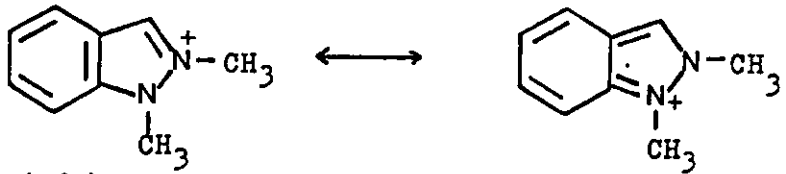

(158)

The 2-acylated indazole requires the carbocyclic ring to be present in the o-quinonoid form (158). The difficulty of accounting for the properties of indazole by a single conventional formula led to the suggestion that it could best be represented by a tautomeric equilibrium.[122] Spectroscopic and other physical measurements, however, show that the benzenoid form (151) clearly predominates ( >95%).[125] Isomerism can arise when the imino hydrogen is replaced. i.e.



(151) (159)

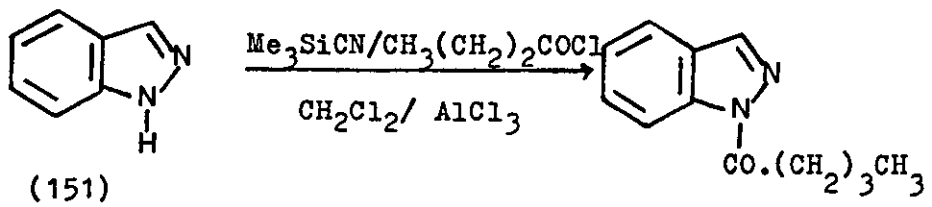
It has been found that the treatment of either 1-methylindazole or 2-methylindazole with methyl iodide yields the same indazolium salt.[126] The 1,2-dimethylindazolium cation could be represented as a resonance hybrid with the two structures, (160) and (161), as the important contributors.



(160) (161)

We also found that reaction of indazole, butanoyl chloride and trimethylsilyl cyanide in molar ratios of 1:2:2 respectively, gave only 1-butanoylindazole (162) in 38%, m.p. 34-36$^{o}$C (Scheme 67). The product (162) was identified from its spectral data.

Scheme 67




(151) (162)

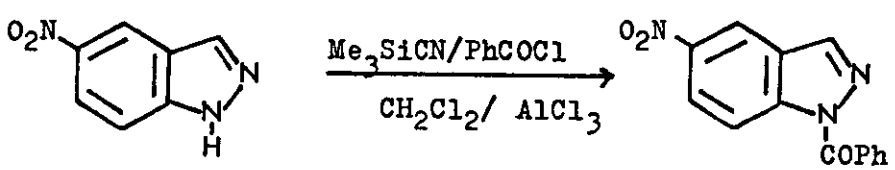
The infrared spectrum showed a strong carbonyl absorption at 1713cm$^{-1}$ and the proton nmr indicated the C-3H at ∂8.18 ppm with the C-7H observed at ∂8.58. Accurate mass analysis of compound (162) gave the anticipated molecular ion at m/z 188 with 14% relative intensity. This compound also gave a satisfactory microanalysis.

ii) Attempted synthesis from 5-nitroindazole

a) Under single phase reaction conditions

When 5-nitroindazole (163), which is available commercially, was treated with benzoyl chloride and trimethylsilyl cyanide in molar ratios of 1:2:2 respectively, we found that once again, only N-acylation occurred to give 1-benzoyl-5-nitroindazole (164) in 79% yield, m.p. 205-207°C (Scheme 68).

Scheme 68



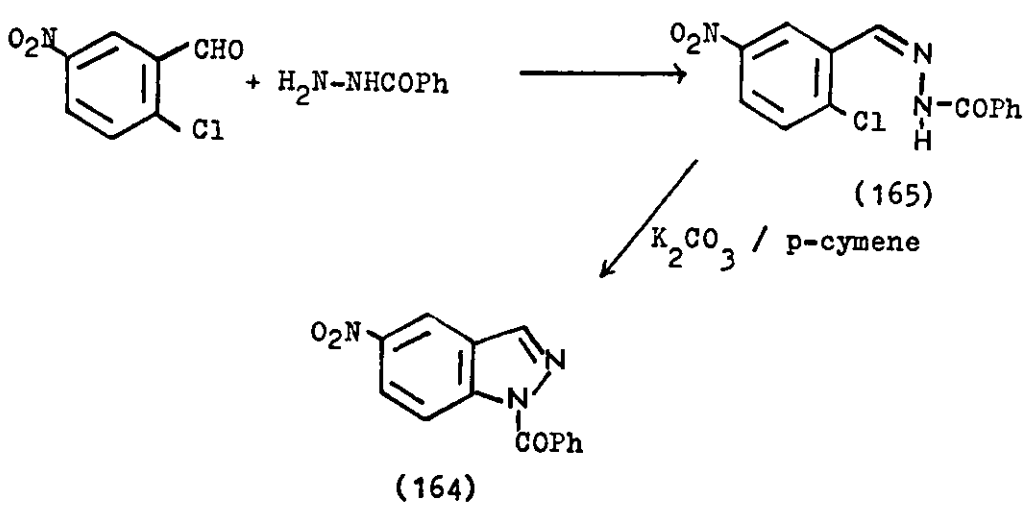

(163) (164)

The amide carbonyl was observed in the infrared spectrum at 1695cm$^{-1}$ and both mass and microanalytical data were satisfactory for compound (164).

This benzoylated 5-nitroindazole (164) was subsequently used in reaction with trimethylsilyl cyanide and benzoyl chloride, this time in molar ratios of 1:1.2:1 under a single phase reaction conditions. But, after work-up, we found that only 1-benzoyl-5-nitroindazole (164) was recovered and no Reissert compound was isolated.

Compound (164) has been previously prepared by direct acylation.[124a] Another method was to boil 2-chloro-5-nitrobenzaldehyde benzoylhydrazone (165)[127] with potassium carbonate in p-cymene, to give the product in 45% yield, m.p. 192-193°C (Scheme 69).

Scheme 69




(164)

This synthesis (Scheme 69) was an example of the preparation of an authentic 1-acyl derivative of indazole by ring closure.

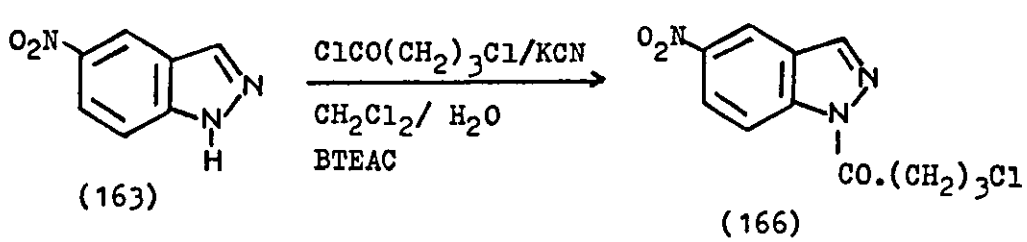
b) Under two phase reaction conditions

We next went on to investigate the reaction of 5-nitroindazole (163) with an acid chloride and potassium cyanide under two phase conditions, i.e. $CH_2Cl_2/H_2O$. The question posed was, would the five-membered ring heterocycle undergo ring opening as occurs with benzimidazole under alkaline conditions[14a,128] as discussed in the Introduction (p.7)?

On reaction of 5-nitroindazole (163) with 4-chlorobutanoyl chloride and potassium cyanide in a two phase system, using benzyltriethylammonium chloride (BTEAC) as the phase transfer catalyst, we isolated 1-(4-chlorobutanoyl)-5-nitroindazole (166). Flash column chromatography[63] was used to purify the crude product and compound (166) was obtained in 88% yield, m.p. 116-118°C (Scheme 70).

The infrared spectrum of the product showed the carbonyl absorption at 1720cm$^{-1}$ and the proton nmr showed an integration characteristic of one chlorobutanoyl chain. The compound (166) also gave correct microanalysis and mass spectral data.

Scheme 70

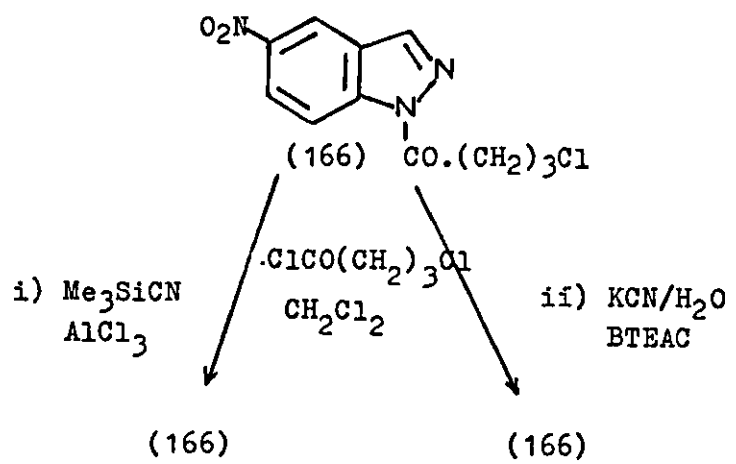



(163) (166)

No Reissert analogue was isolated from this reaction but also no ring opening was observed.

The 1-acylated 5-nitroindazole (166) was consequently used as the starting heterocycle in (i) a single phase reaction with trimethylsilyl cyanide and (ii) a two phase reaction with aqueous potassium cyanide. The acid chloride used in both cases was 4-chlorobutanoyl chloride (Scheme 71). But in both cases, we found that the starting 1-(4-chlorobutanoyl)-5-nitroindazole (166) only was isolated.

Scheme 71




From these observations, it appears that indazole (151) and 5-nitroindazole (163) undergo N-acylation readily with a variety of aryl and aliphatic acid chlorides to give stable 1-acylindazoles. It is also evident that the indazole nucleus is less susceptible to ring opening than benzimidazole (16), under hydrolytic conditions.

Due to the disappointing outcome from the reactions studied so far, with respect to the isolation of the stable novel Reissert compounds from indazole, we switched our attention to the study of N-methylindazole as the starting heterocycle.

## Part II 1-Methylindazole Reissert Compounds

### i) The Synthesis of 1-methylindazole Reissert compounds

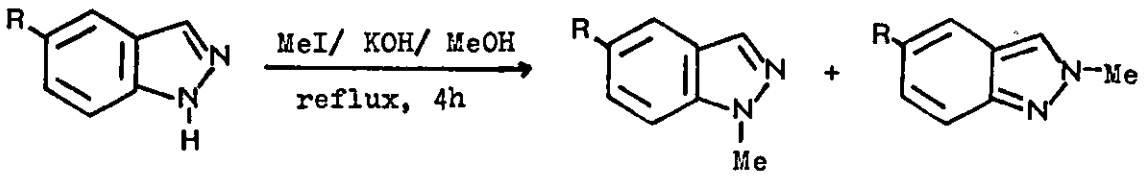
#### a) N-methylation of indazole

Indazole was readily methylated[129] with methyl iodide in methanolic potassium hydroxide under reflux to give a mixture of 1-methyl- and 2-methylindazole (Scheme 72).

The products were separated by flash column chromatography[63] using a 50:50 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C) as the eluent. The first fraction collected was 1-methylindazole (167) in a yield of 55%, m.p. 60-62°C, lit[129] 61°C, and showed the N-Me signal in the nmr at $\partial$4.15. The second fraction was the 2-methylindazole (168), yield 34%, m.p. 47-49°C, lit[129] 56°C, with $\partial_H$ 4.00 (NMe).

5-Nitroindazole was similarly methylated to give a mixture of 1-methyl-5-nitroindazole (169) and 2-methyl-5-nitroindazole (170). The two isomers were separated by flash column chromatography[63] using a 50:50 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C). The first fraction collected was 1-methyl-5-nitroindazole (169) in 39% yield as yellow needles, m.p. 155-158°C, lit[129] 154°C. The second fraction was 2-methyl-5-nitroindazole (170), obtained as yellow needles (35%), m.p. 135-137°C, lit[129] 130°C (Scheme 72).

Scheme 72




(151, R=H )
(163, R=$NO_2$ )

(167, R=H ) $\partial_H$4.15(NMe)

(168, R=H ) $\partial_H$4.00(NMe)

(169, R=$NO_2$ ) $\partial_H$4.18(NMe)

(170, R=$NO_2$ ) $\partial_H$4.31(NMe)

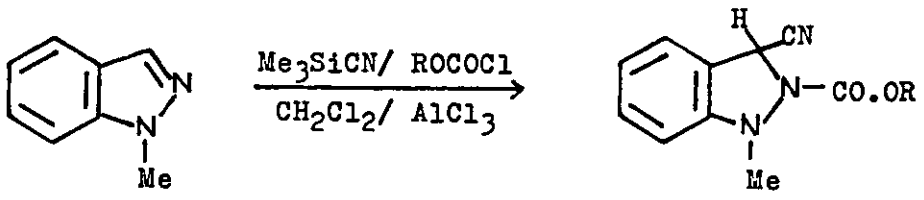
Palmer and co-workers[129] carried out a detailed analysis on the proton nmr of indazoles. Whereas our observed chemical shifts for the N-Me protons in (169) and (170) were within 0.05 ppm of the values of Palmer et al,[129] they recorded the NMe resonance in (167) as ∂3.95 and in (168) as ∂3.80. They, like us, used $CDCl_3$ as solvent but solution concentrations may have been different.

b) Formation of Reissert compounds from 1-methylindazole

We examined the suitability of 1-methylindazole (167) as a starting heterocycle in the Reissert approach.

We found that treatment of 1-methylindazole (167) with trimethylsilyl cyanide with various chloroformates in the presence of aluminium chloride in dry dichloromethane gave the novel 2-(alkoxycarbonyl)-3-cyano-2,3-dihydro-1-methylindazole (171)(Scheme 73).[68,69]

Scheme 73

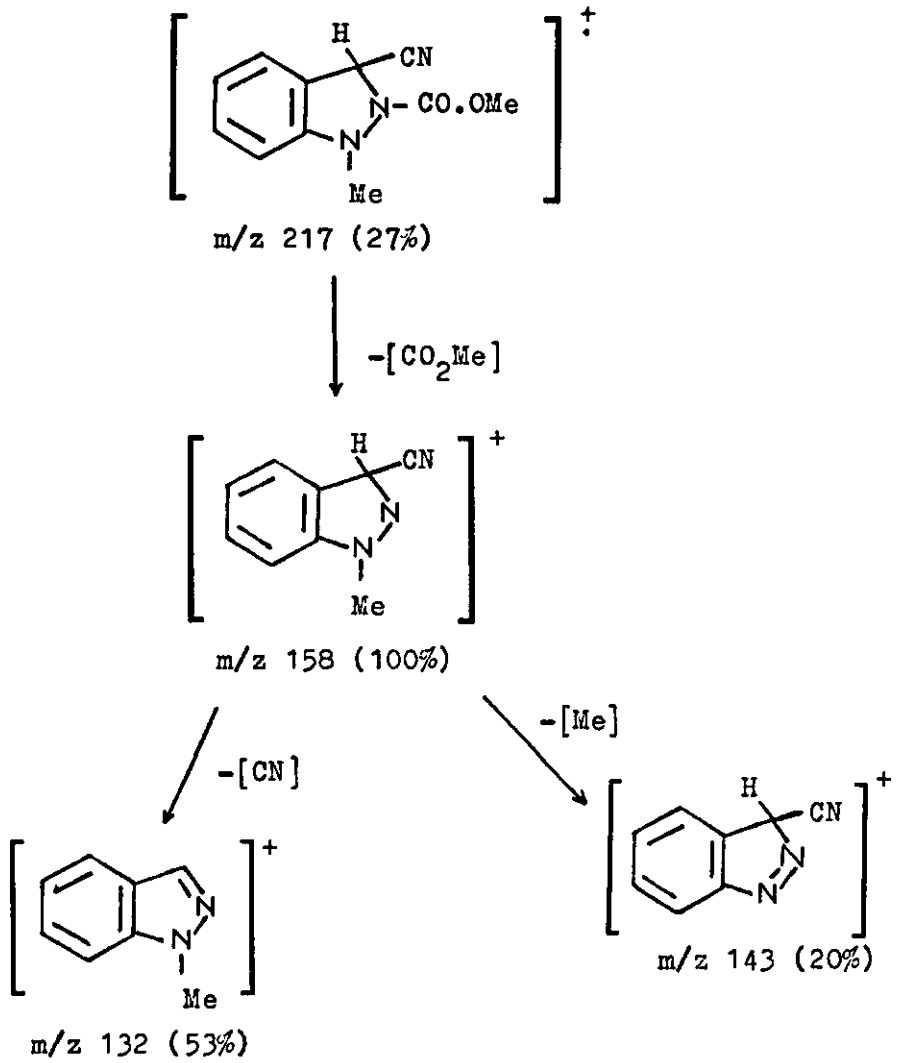



(167) (171)

The reaction of 1-methylindazole (167), trimethylsilyl cyanide and methyl chloroformate in molar ratios of 1:1.2:1.2 under single phase conditions led to the formation of the novel Reissert analogue 3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a) in 57% yield, m.p. 141-143°C (Table 7), obtained after preparative tlc.

The infrared spectrum of this product (171a) showed the carbonyl absorption frequency at 1730cm$^{-1}$ and a weak cyano group at 2215cm$^{-1}$. The proton nmr included a sharp singlet at ∂6.0, attributed to C-3H. The mass spectrum showed the molecular ion at m/z 217 with a relative intensity of 27%. The fragmentation pattern is shown in Scheme 74. Loss of $CO_2R$, by α-cleavage to carbonyl, gives the base peak, as observed with the Reissert compounds in other series. The product (171a) also gave a satisfactory microanalysis.

Scheme 74




Two other novel Reissert analogues of 1-methylindazole have been synthesised from using ethyl and phenyl chloroformate. The three products are the first examples of chloroformate-derived Reissert compounds from the five-membered ring heterocycle indazole and the results are summarised as follows (Table 7).

Table 7

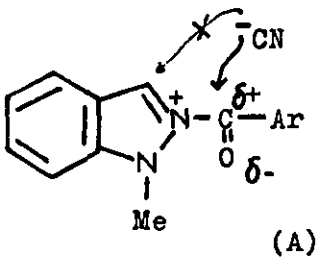
| 171 | R | Yield/ % | m.p./ °C | ir(KBr)C=O;C≡N $\vartheta_{max}/cm^{-1}$ | C-3H;N-$CH_3$ δ/ppm |
|---|---|---|---|---|---|
| a | $CH_3$- | 57 | 141-143 | 1730;2215 | 6.00;3.20 |
| b | $CH_3CH_2$- | 17 | 118-120 | 1735;2210 | 5.98;3.20 |
| c | $C_6H_5$- | 32 | 114-117 | 1730;2230 | 6.10;3.23 |

As was observed with the benzothiazole Reissert compounds (92)(p.58), the indazole-derived analogues also showed absorption frequencies due to the cyano group in the range of 2230-2210$cm^{-1}$. These absorptions were of weak intensity, but clearly discernible, whereas in Reissert compounds derived from six-membered ring heterocycles, the nitrile absorption normally cannot be distinguished from background.

An anticipated feature from the nmr spectra of the products (171) was that the singlet due to the N-$CH_3$ group in each case had moved upfield to ca.∂ 3.20 from ∂4.15 in the original 1-methylindazole (167). This upfield shift is due to the lost aromatic character and hence deshielding by the hetero ring.

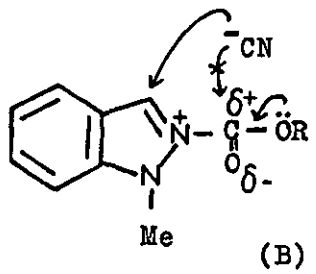
The use of 1-methylindazole and trimethylsilyl cyanide in reaction with benzoyl and 4-methylbenzoyl chloride was found to give only the recovered starting heterocycle.

The unusual behaviour whereby 1-methylindazole Reissert analogues could be prepared from chloroformates but not from aroyl chlorides may be rationalised by considering the intermediates (172) and (173) involved.




(A)

(172)




(B)

(173)

In (172) and (173), the site competing with C-3 for attack by $^{-}CN$ is the carbonyl carbon, but in (173) the electrophilicity is reduced by the adjacent oxygen, as in an ester. The consequence of pathway (A) would be the production of aroyl cyanide, but none was isolated and so hydrolysis of ArCOCN could have occurred.

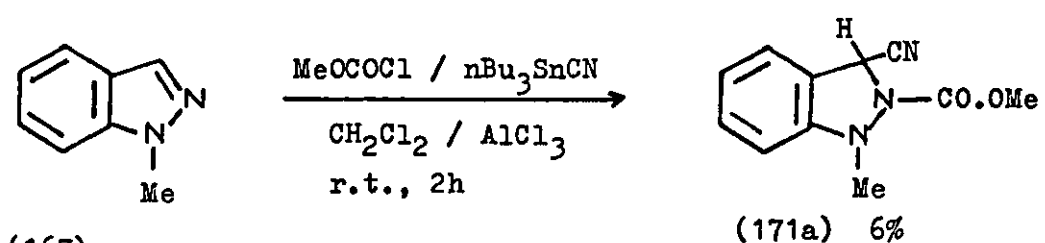
Although we were successful in preparing chloroformate derived Reissert compounds from 1-methylindazole, we found the isolation and purification procedures more tedious than experienced with the benzothiazole series. Preparative tlc was used in all cases in order to obtain samples pure enough for acceptable spectral characterisation; this may have contributed to the low yields of product obtained.

We found that when 1-methyl-5-nitroindazole (169) was treated with trimethylsilyl cyanide and methyl chloroformate in dichloromethane, only starting heterocycle (169) was recovered and no Reissert analogue was isolated. Since 1-methylindazole had given the corresponding Reissert compound (57%) under the same conditions, it suggests the 5-nitro group has reduced the reactivity of the heterocycle, presumably reducing the nucleophilicity of N-2 by inductive electron withdrawal; a 4- or 6-nitro isomer could also do so mesomerically.

c) The use of tri-n-butyltin cyanide as an alternative cyanating reagent

As discussed earlier in Chapter II (p.69), an alternative reagent to trimethylsilyl cyanide which is commercially available is tri-n-butyltin cyanide, n-$Bu_3SnCN$ (103). We had found this cyanide source to be effective for the preparation of the five-membered ring Reissert compound, 3-benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g), obtained in 40% yield (cf. 44% from $Me_3SiCN$ (75)).

We found that when 1-methylindazole, methyl chloroformate and $nBu_3SnCN$ in molar ratios of 1:1:2 were stirred at room temperature for 72 hours in the presence of a catalytic amount of $AlCl_3$, the Reissert compound 3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a) was isolated in 6% yield, m.p. 140-142°C after flash column chromatography. We also recovered 1-methylindazole (85%) and the yield of the Reissert compound (171a) based on this recovery was 38%. The yield of the Reissert compound (171a) from the use of trimethylsilyl cyanide was 57% and so it appears that this latter reagent is superior to $nBu_3SnCN$ (103) in this reaction.




(167) (171a) 6%

d) Attempted Synthesis from 1-methylindazole under two phase reaction conditions

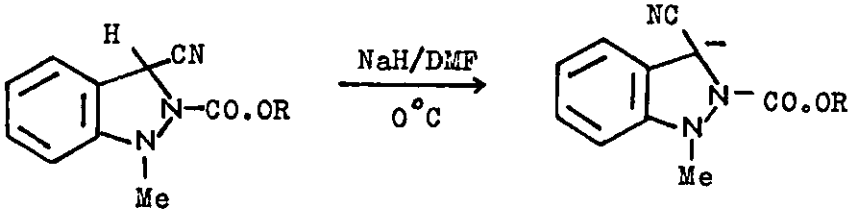
We found that on reaction of 1-methylindazole (167) with

methyl chloroformate and potassium cyanide in a two phase system $CH_2Cl_2/H_2O$, using benzyltriethylammonium chloride (BTEAC) as the phase transfer catalyst, 90% of the starting heterocycle (167) was recovered after the reaction mixture had been stirred at room temperature for 72 hours. Under these conditions, no evidence of ring opening of 1-methylindazole was found.

1-methylindazole was also recovered (87%) when the reaction was repeated but under reflux for two hours before stirring at room temperature for 15 hours.

ii) Alkylation of 1-methylindazole Reissert compounds

We found that, as with the five-membered ring Reissert compounds from benzothiazole, the conjugate bases of the novel Reissert compounds from 1-methylindazole (171) could readily be generated with sodium hydride in dimethylformamide at $0^{\circ}C$, giving an immediate red/orange colouration and evolution of hydrogen gas.



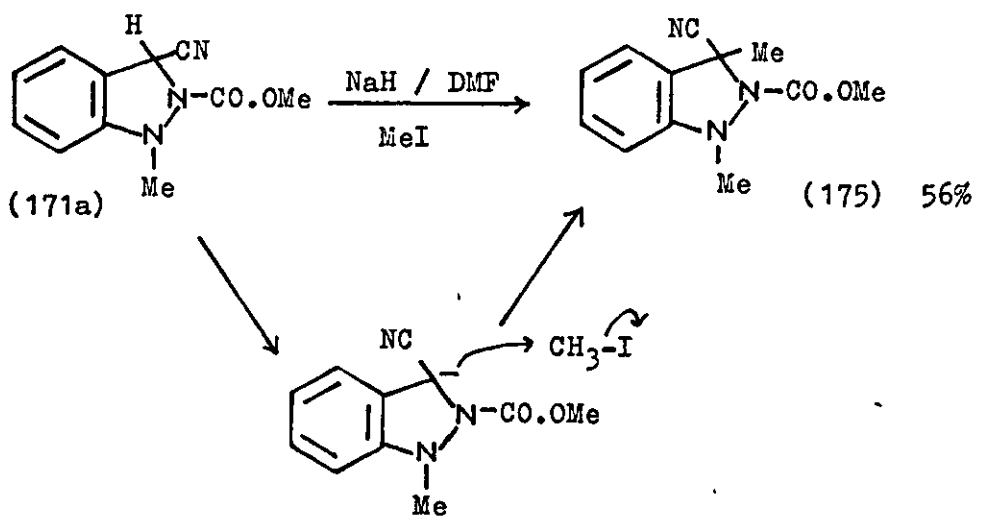

(171) (174)

As observed in the Introduction, the conjugate bases of isoquinoline Reissert compounds and others undergo nucleophilic displacement reactions with alkyl halides to give the substituted Reissert compound which, on subsequent base hydrolysis, gives the 1-alkylisoquinoline etc.[8a,23,99] We have shown this procedure can be applied to the novel benzothiazole Reissert compounds to

provide a new route to 2-alkylbenzothiazoles.

We studied the reaction of the Reissert compound 3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a)(1 mole) with methyl iodide in the presence of sodium hydride (1 mole) and dimethylformamide. The anion formation was indicated by the appearance of an orange colour which faded to light yellow as the reaction progressed. After preparative tlc (2 x 1m silica gel plates) of the crude material, using as solvent system a 40:60 mixture of ethyl acetate: petroleum ether (b.p. 40-60°C), 3-cyano-2,3-dihydro-1,3-dimethyl-2-methoxycarbonylindazole (175) was obtained in 56% yield, m.p. 68-70°C (Scheme 75).

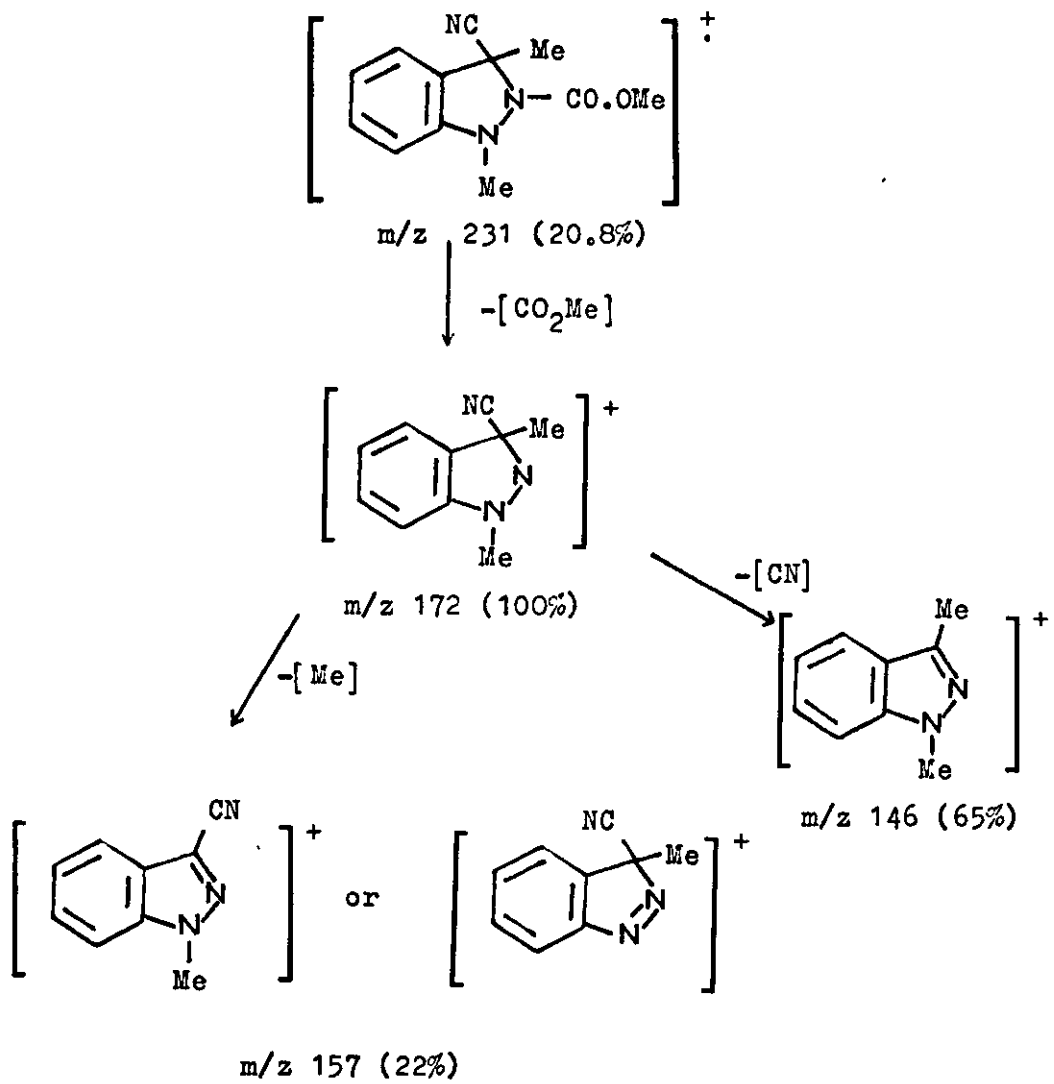
Scheme 75



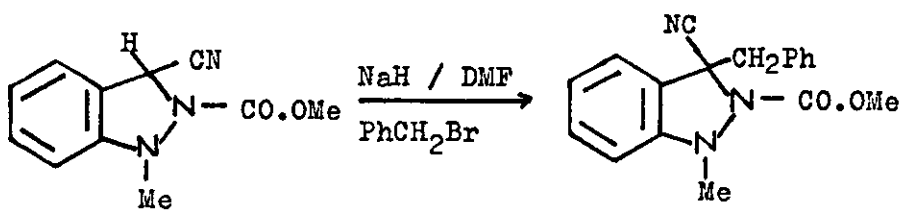

The infrared spectrum of compound (175) showed the carbonyl absorption frequency at 1718cm$^{-1}$ and a weak cyano absorption at 2300cm$^{-1}$. In the proton nmr, three sharp singlets were observed, ∂3.85ppm represented the three protons of the $OCH_3$ group, ∂3.10 the N-$CH_3$ and ∂2.05 the C-3$CH_3$ group. The

structure of the alkylated compound (175) was further confirmed by satisfactory microanalytical data and accurate mass measurement. The mass fragmentation pattern is described in Scheme 76. As with previous Reissert compounds α-cleavage to carbonyl of the amidic N-C bond provided the base peak.

Scheme 76



This approach was extended to prepare the 3-benzyl derivative from the Reissert compound (171a) using benzyl bromide. 3-Benzyl-3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (176) was obtained in 89% yield, m.p. 112-114°C after preparative tlc (2 x 1m silica gel plates) using a 20:80 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C) as eluent.



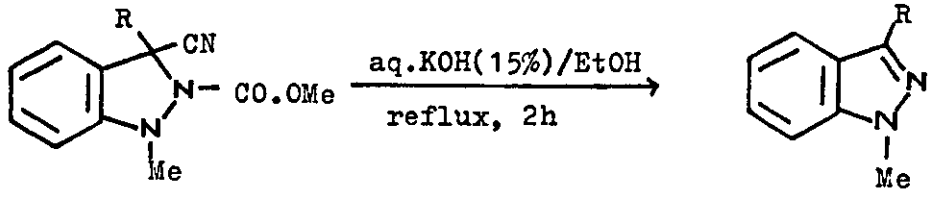

(171a) (176) 89%

The infrared spectrum of compound (176) showed the carbonyl absorption at 1720cm$^{-1}$, but unlike the methylated compound (175), the 3-benzyl derivative did not show the cyano absorption at 2300cm$^{-1}$ or thereabouts. This may reflect the greater conformational demand of the benzyl group compared with methyl, possibly altering the average environment of the CN, relative to the C=O. The proton nmr showed two sharp singlets, one at ∂3.85 ($OCH_3$) and the other at ∂3.10 ($N\text{-}CH_3$). A singlet at ∂3.55 with an integration of two protons was assigned to the $CH_2$ of the benzyl group. The C-2 proton, observed at ∂6.0ppm in the original Reissert compound (171a), was absent. The compound (176) also gave a correct accurate mass measurement and satisfactory microanalytical data.

iii) Base-catalysed hydrolysis reactions

The alkylated Reissert compounds (175) and (176) were hydrolysed[30] in the presence of potassium hydroxide (15%) in aqueous ethanol for two hours to yield by refluxing, their corresponding 1,3-disubstituted indazoles, although in the low yields of 15% and 13% respectively.

Scheme 77




(175) R=Me

(176) R=$CH_2Ph$

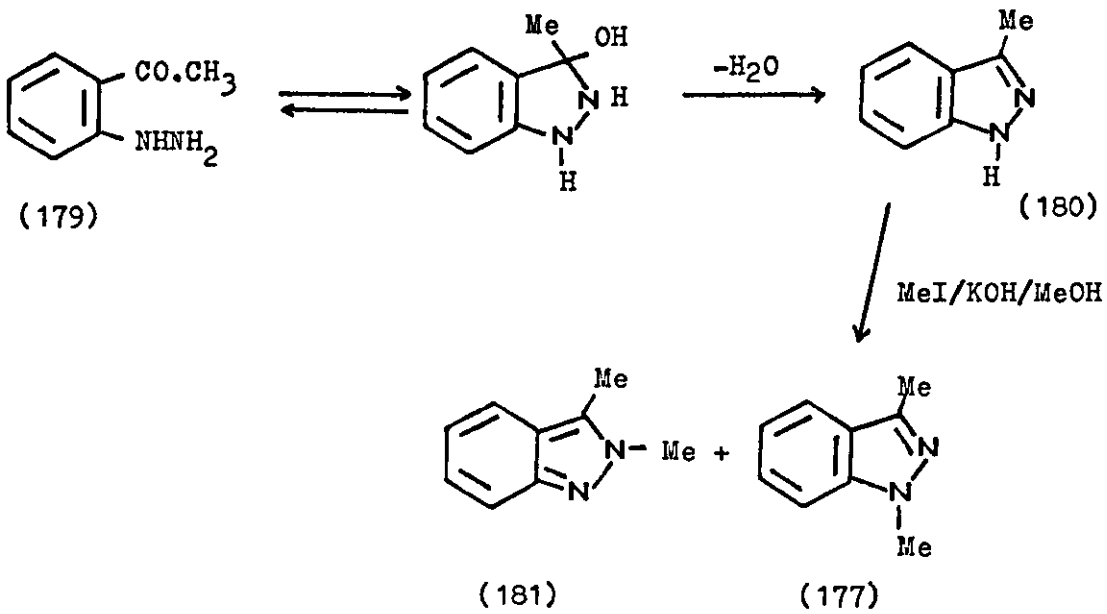
(177) R=Me (15%)

(178) R=$CH_2Ph$ (13%)

1,3-Dimethylindazole (177), m.p. 35-38°C, lit[129] 35°C, showed in the proton nmr, two sharp singlets, at ∂4.00 (N-$CH_3$) and ∂2.57 (C-3$CH_3$). The N-$CH_3$ group has moved downfield from ∂3.10 in the Reissert compound (175). This downfield shift reflects the regained aromaticity of the heterocyclic ring and is comparable with that observed in the original heterocycle 1-methylindazole (∂4.20, N-$CH_3$).

1,3-Dimethylindazole (177) can be prepared by N-methylation of 3-methylindazole (180),[129] the latter being available from the dehydration of o-hydrazinoacetophenone (179)[130] (Scheme 78).

Scheme 78

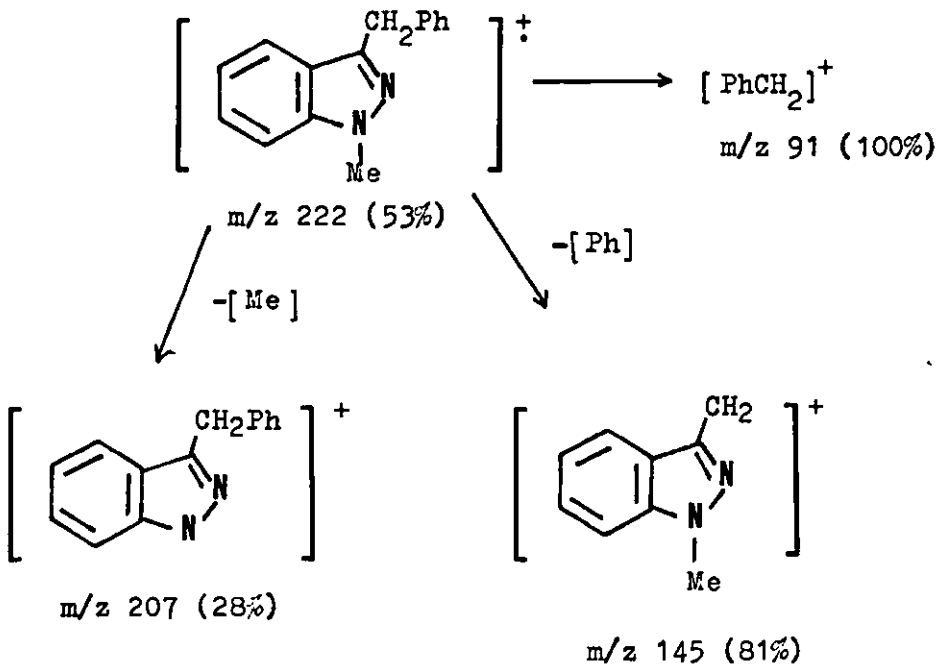



(179) (180) (181) (177)

But this preparation also gave 2,3-dimethylindazole (181), with the methylation ratio of 1,3- to 2,3-dimethylindazole being 65:35. The two products require separation by chromatography on alumina.

Under the hydrolytic conditions described in Scheme 77, we obtained 3-benzyl-1-methylindazole (178) from the Reissert compound (176) in 13% yield, b.p. 125°C/10mmHg. In the proton nmr, the N-$CH_3$ group was observed as a singlet at ∂4.05ppm and the $CH_2$ of the benzyl group was observed as a singlet at ∂4.36. The compound (178) gave correct accurate mass analysis and satisfactory microanalytical data. The mass fragmentation pattern of compound (178) is described in Scheme 79, showing m/z 91 ($CH_2Ph$) for the base peak.

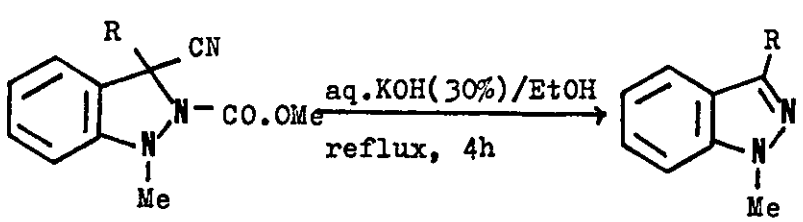
Scheme 79




Thus, we have achieved a different route to the synthesis of 1,3-disubstituted indazoles, although the yields from these base-catalysed hydrolysis reactions were low.

In an attempt to increase the yields of (177) and (178), we carried out the hydrolyses using 30% aqueous potassium hydroxide and refluxing for four hours (Scheme 80).

Scheme 80




(175) R=Me

(176) R=$CH_2Ph$

(177) R=Me

(178) R=$CH_2Ph$

These conditions gave improved yields: 1,3-dimethylindazole (177) was obtained in 40% yield and 3-benzyl-1-methylindazole (178) in 38% yield, thus providing a reasonable though not ideal route to 3-alkylindazoles.

## Part III 2-Methylindazole Reissert Compounds

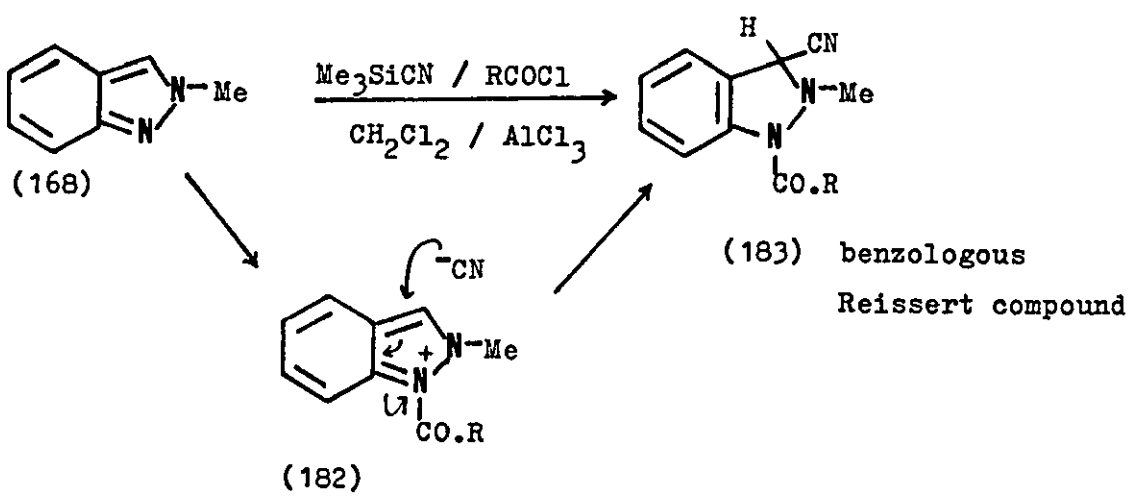
### i) The Synthesis of Benzologous Reissert Compounds

Encouraged by the success in obtaining chloroformate-derived Reissert compounds (171) from 1-methylindazole, we considered it would be of interest to study the reaction of the 2-methyl isomer under similar conditions.

We appreciated that a "conventional" Reissert reaction across the 7a, 1 C=N would be unlikely to occur but recognised that a 1,4- addition to the diene system of the hetero ring may take place. Such a process would be assisted by the restoration of aromaticity in the carbocyclic ring and the product would be a benzologous Reissert compound.

We found that such an addition does occur giving, to our knowledge, the first examples of benzologous Reissert compounds. Treatment of 2-methylindazole (168) with trimethylsilyl cyanide and an acid chloride in the presence of a Lewis acid catalyst ($AlCl_3$) in dry dichloromethane gave the 1-acyl-3-cyano-2,3-dihydro-2-methylindazole (183) (Scheme 81).

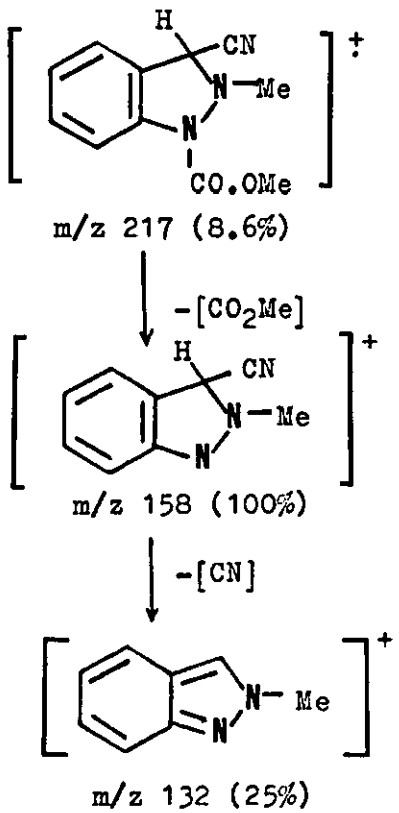
Scheme 81



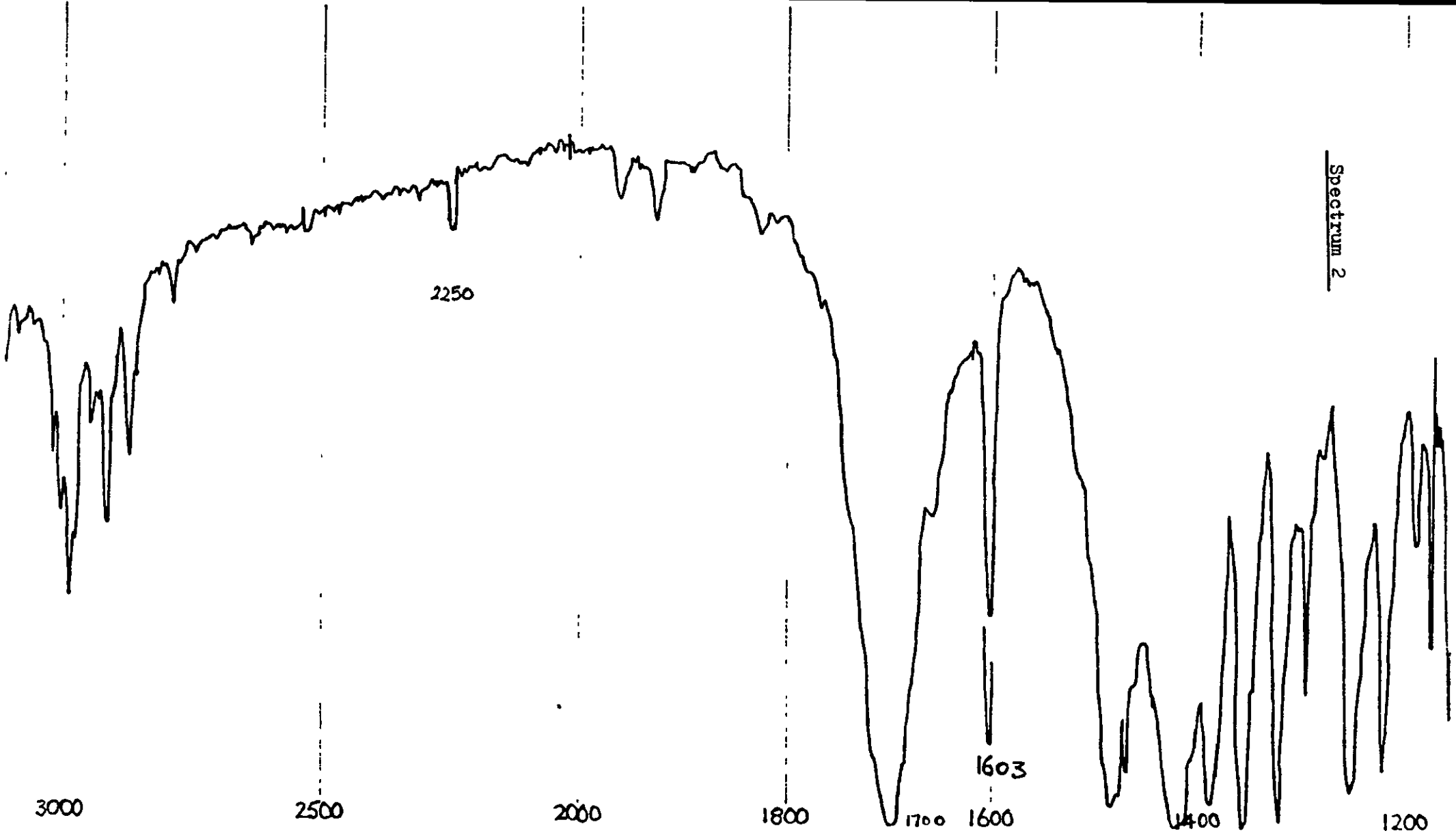
3-Cyano-2,3-dihydro-1-methoxycarbonyl-2-methylindazole (183a) was synthesised from treatment of 2-methylindazole with trimethylsilyl cyanide and methyl chloroformate in molar ratios of 1:1.2:1.2 under single phase reaction conditions. This Reissert analogue was obtained, after flash column chromatography of the crude material using ethyl acetate as the eluent, in 38% yield, m.p. 138-140$^{o}$C.

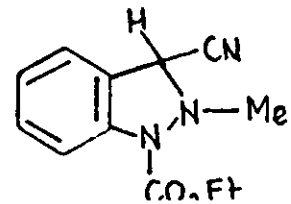
The infrared spectrum of compound (183a) showed the strong carbonyl absorption at 1705cm$^{-1}$ and a cyano absorption of medium intensity was observed at 2226cm$^{-1}$. The proton nmr spectrum showed two sharp singlets at resonances of $\partial$4.00ppm and $\partial$ 2.80 assigned to the $OCH_3$ and $N\text{-}CH_3$ groups respectively. The C-3H was observed as a singlet at $\partial$5.02ppm, this assignment was confirmed by addition of a small amount of sodium hydride to the 'Hnmr sample followed by quenching with $D_2O$ which resulted in the disappearance of the C-3H signal from a subsequent 'Hnmr spectrum; the C-3 proton had been exchanged with $D_2O$. The product (183a) also gave a correct accurate mass and satisfactory microanalysis. The mass fragmentation pattern of the product is described below (Scheme 82). Again, $\alpha$-cleavage to carbonyl of the N-C bond provides the base peak.

Scheme 82




This procedure was extended to the preparation of two other benzologous Reissert compounds from 2-methylindazole using ethyl chloroformate, and benzoyl chloride. The results are summarised in Table (8) and the infrared spectrum of compound (183b) is reproduced (Spectrum 2).

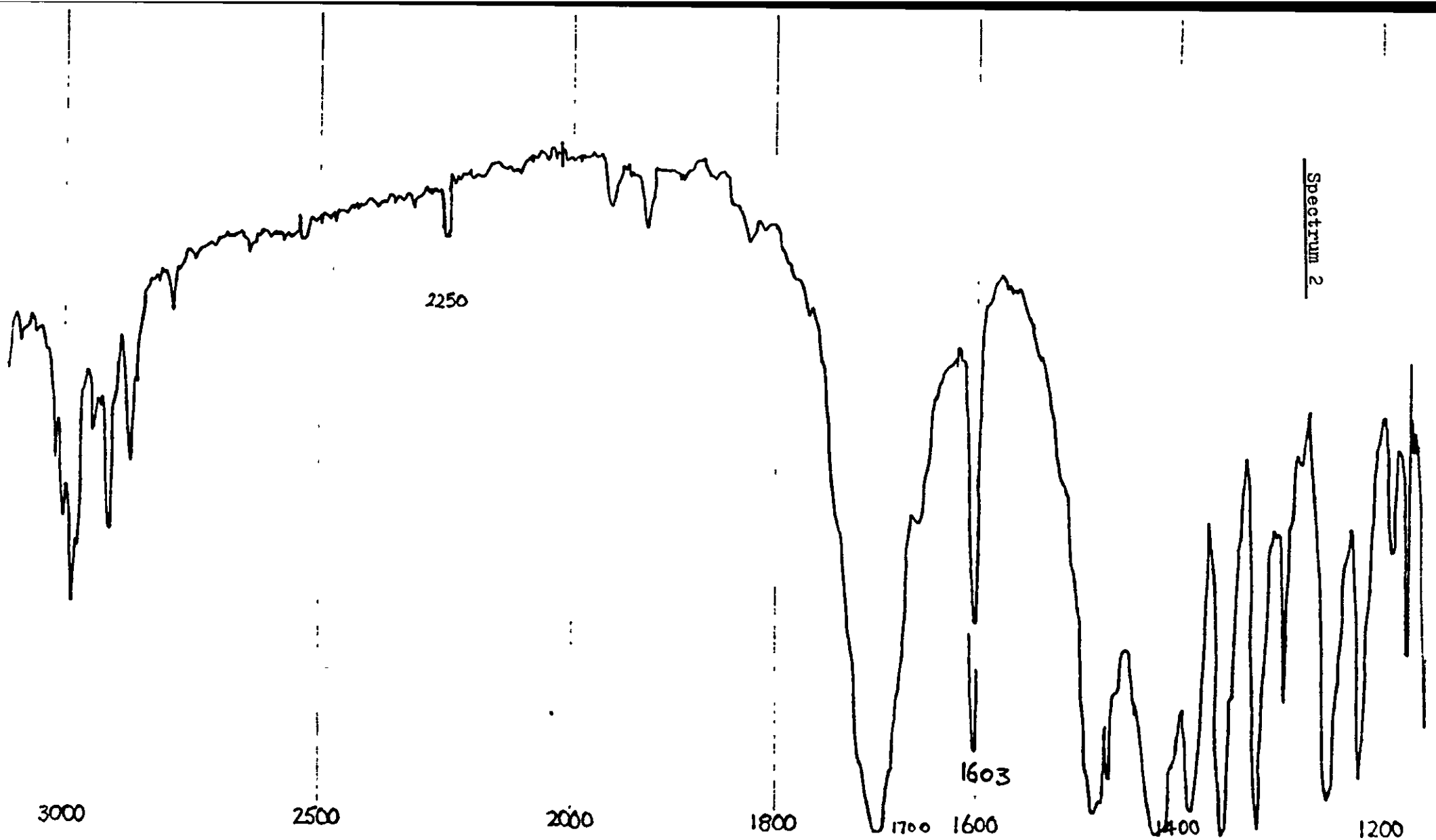


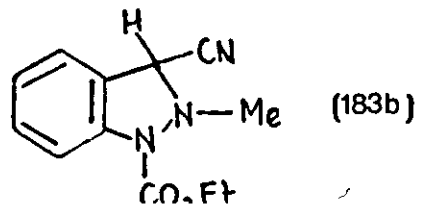




(183b)

KBr disc

138a




(183b)

KBr disc

138a

Table 8

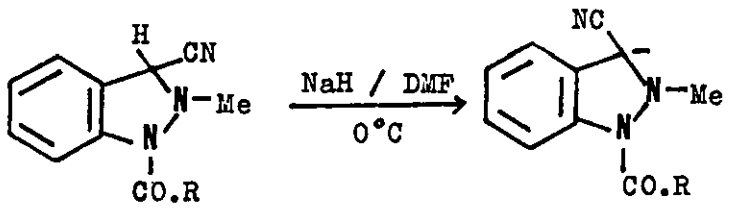
| 183 | R- | Yield/ % | m.p./ °C | $\vartheta_{max}/cm^{-1}$ | | ∂/ppm C-3H |
|---|---|---|---|---|---|---|
| | | | | C=O | C≡N | |
| a | MeO | 38 | 138-140 | 1705 | 2226 | 5.02 |
| b | EtO | 48 | 101-102 | 1700 | 2250 | 5.00 |
| c | Ph | 15 | 134-135 | 1650 | 2250 | 4.85 |

These first examples of benzologous Reissert compounds gave satisfactory accurate mass and microanalytical data. The aromaticity of the benzenoid ring has been restored in going from 2-methylindazole (168) which has an ortho quinonoid-type structure, to the product Reissert compound (183).

Treatment of 2-methyl-5-nitroindazole (170) with trimethylsilyl cyanide and methyl chloroformate under single phase reaction conditions led only to the starting heterocycle (170) being recovered (96%).

ii) Formation of 2,3-dimethylindazole (181)

We reported previously (p.128 ) that the conjugate base of the novel Reissert compound from 1-methylindazole (171) was readily generated with sodium hydride in dimethylformamide at 0°C. Hence we observed a red colour change on addition of sodium hydride to a sample of the benzologous Reissert compound (183) in dimethylformamide, which was indicative of the generation of its conjugate base (184).




(183) (184)

As described earlier in this chapter, the conjugate base of the 1-methylindazole Reissert compound (171a) was found to participate in nucleophilic displacement reactions with methyl iodide and benzyl bromide to give 3-substituted Reissert compounds which, on subsequent base hydrolysis, provided a route to 1,3-disubstituted indazoles.

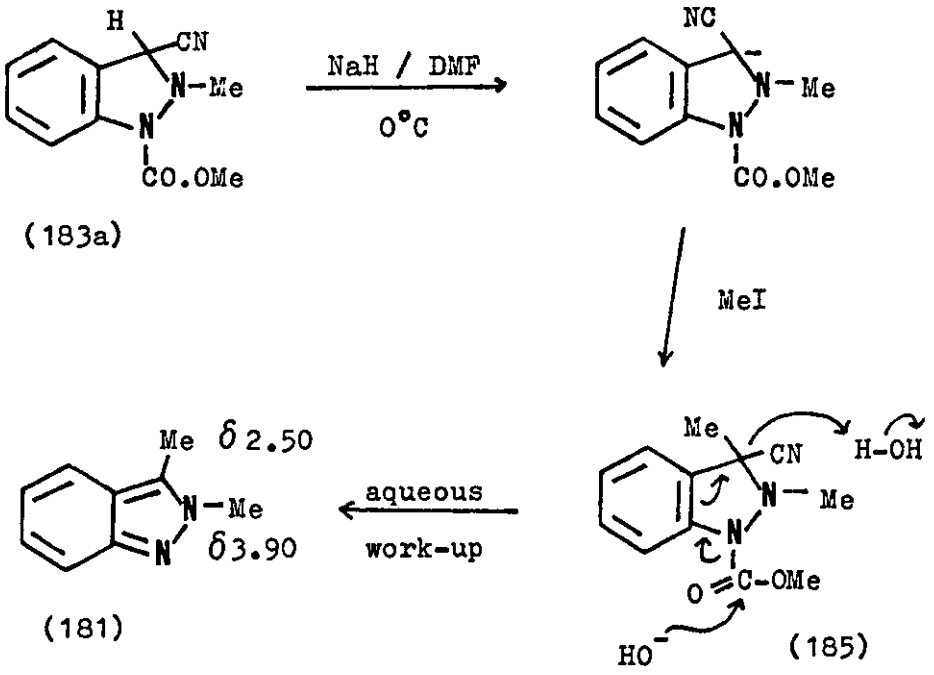
We studied the reaction of the benzologous Reissert compound (183a), 3-cyano-2,3-dihydro-1-methoxycarbonyl-2-methylindazole (1 mole) with methyl iodide in the presence of sodium hydride (1 mole) and dimethylformamide at 0°C. The reaction mixture immediately became orange which faded to light yellow on continued stirring for 24 hours.

After the work-up, which involved pouring the reaction mixture into ice and extraction of the organic material, the expected product was the 3-alkylated benzologous Reissert compound (185). But the solid, m.p. 80-82°C, isolated from preparative tlc of the crude oil using ethyl acetate as the eluent, did not show spectral features characteristic of the expected methylated Reissert compound. The infrared of the solid did not show a strong absorption due to a carbonyl group, nor was a nitrile absorption observable. Proton nmr showed two sharp

singlets, one resonance at ∂3.90 and the other at ∂2.45. Mass analysis showed the molecular ion at m/z 146, which was also the base peak.

From these spectral data and the melting point, it would appear that the product obtained was 2,3-dimethylindazole in 30% yield, lit[129] 79-80°C. This must mean that the 3-methylated Reissert compound (185) had been formed but on aqueous work-up, hydrolysis occurred which led to the isolation of the 2,3-dimethylindazole (181)(Scheme 83).

Scheme 83

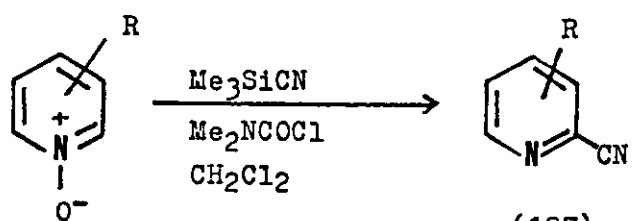



Thus, we have in this example, achieved a direct route to a 2,3-disubstituted indazole from the benzologous Reissert compound (183a), without carrying out the usual step of base-catalysed hydrolysis of the alkylated Reissert compound.

## Part IV Further discussion of the mechanistic involvement of trimethylsilyl cyanide in the formation of five-membered ring Reissert compounds

Earlier in the thesis, we had discussed several possible mechanistic pathways for the formation of benzothiazole Reissert compounds using trimethylsilyl cyanide (p.61 ). We now extend this discussion to include the formation of Reissert compounds from 1-methyl and 2-methylindazoles using this source of cyanide.

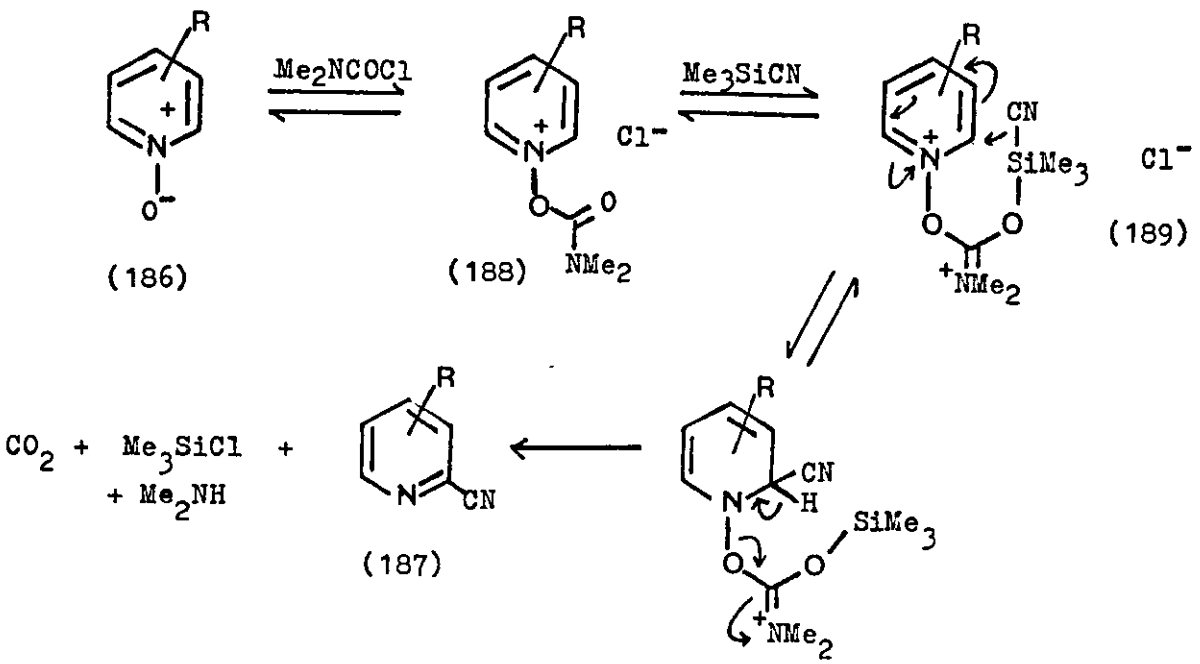
Fife[131] has recently reported the conversion of pyridine-1-oxides to 2-cyanopyridines (187) by treatment of the N-oxide with trimethylsilyl cyanide and dimethylcarbamoyl chloride in dichloromethane.




(186) (187)

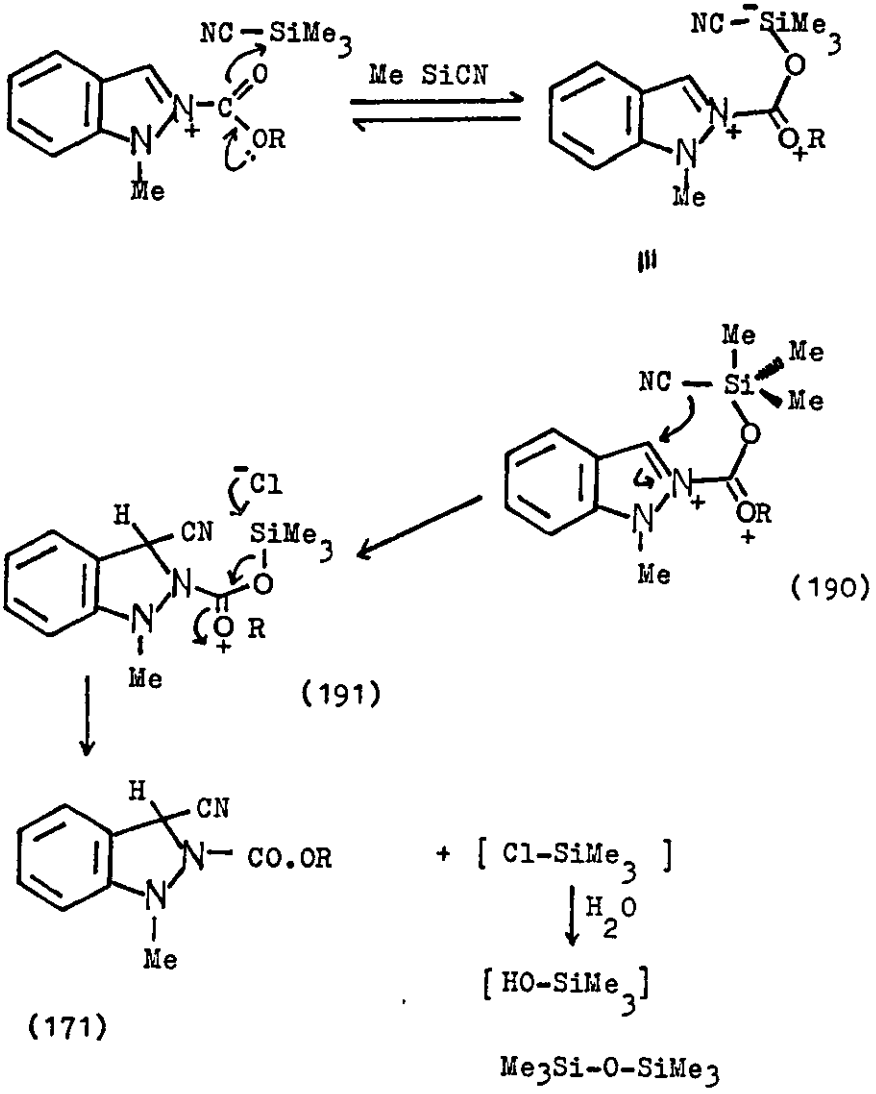
This was a modification of the Reissert-Henze[132] reaction to provide a wide variety of substituted 2-cyanopyridines. In this reaction, Fife found no evidence of $\gamma$-cyanation under the conditions used. The mechanism he proposed to explain the high regioselectivity of the reaction involved an interaction between trimethylsilyl cyanide and the acyloxypyridinium intermediate (188)(Scheme 84).

Scheme 84



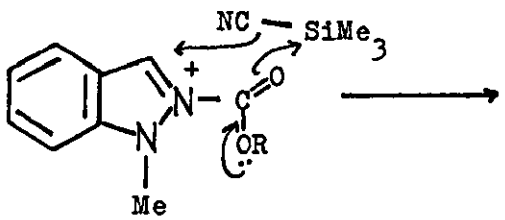

Applying an analogous mechanism to our substrates of 1-methylindazole, a chloroformate and trimethylsilyl cyanide with a catalytic amount of aluminium chloride in the Reissert reaction would provide us with pathway C.

Mechanism C




Intermediates such as (190) which include a trigonal bipyramidal silicon have been proposed by Corriu for a number of reactions of silicon reagents.[133]

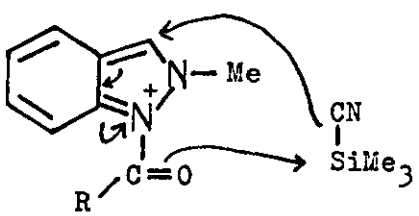
Mechanism C is similar to the one we discussed earlier which implied a concerted delivery of CN involving a six-centre cyclic intermediate (Scheme 39, p.67). Applying this suggestion to our substrates would give intermediate (192) which would then follow the pathway described in Mechanism C to give the product Reissert compound (171).




(191) (171)

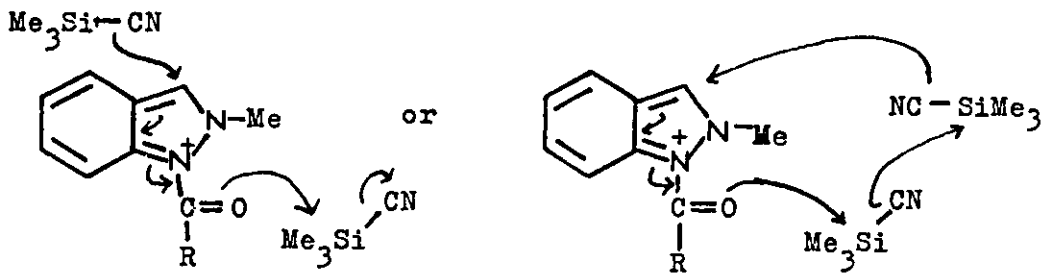
(192)

This type of mechanism, whether concerted or a stepwise regiospecific delivery of cyanide is feasible in the cases of conventional Reissert compound formation where the cyano group adds to the carbon atom adjacent to the imminium nitrogen. But these proposals would not appear applicable in the examples of benzologous Reissert compound formation from 2-methylindazole (183). Assuming the intermediate (193) is planar, the carbonyl oxygen would be too far away from the C-3 position to allow CN to be delivered in a similar manner.




(193)

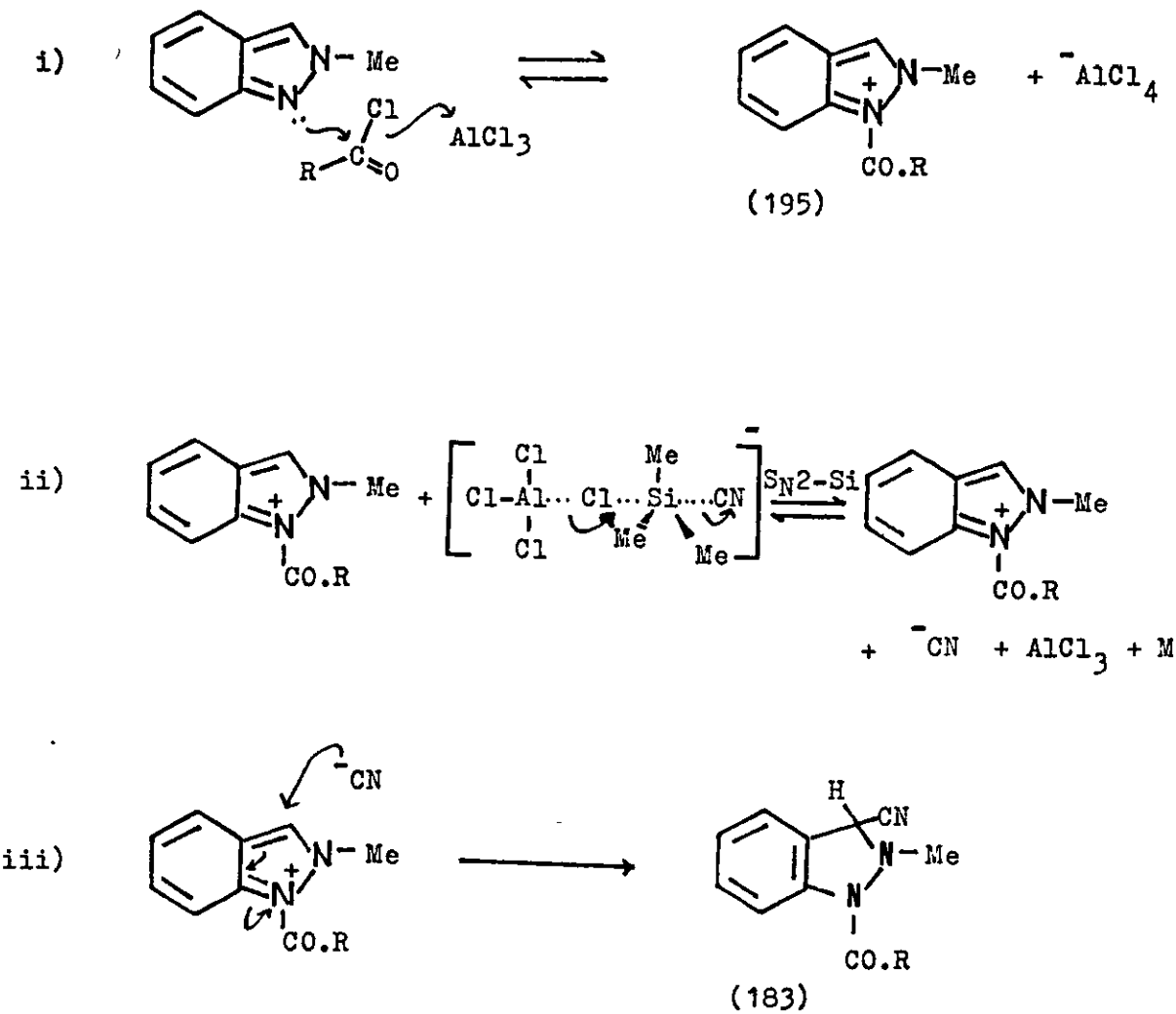
If the involvement of trimethylsilyl cyanide does include a cyclic mechanism, then it is unlikely the mechanism will work with a 1:1 molar ratio of $Me_3SiCN$ and the Reissert compound. A cyclic mechanism with two molecules of $Me_3SiCN$, involving a 10-centre intermediate (194) is unlikely to occur from the entropy point of view.




(194)

Therefore, it seems that a more simple mechanism is available which would adequately explain the formation of the "conventional" Reissert compounds from benzothiazole and 1-methylindazole, and the "unconventional" benzologous Reissert compounds from 2-methylindazole (Scheme 85).

Scheme 85

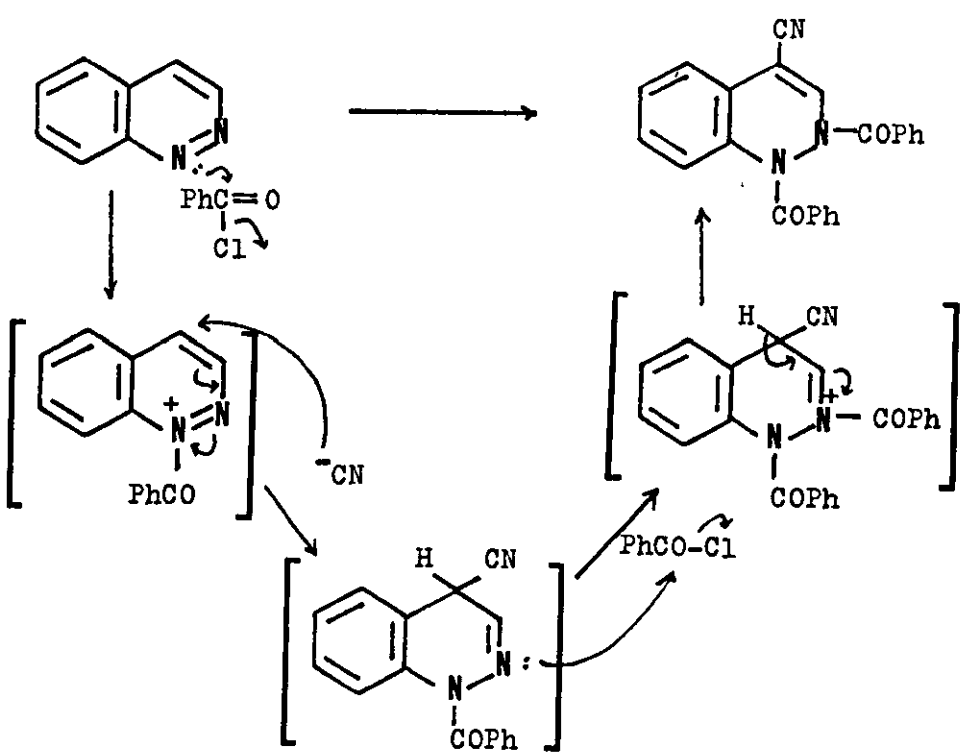



This mechanism, involving liberation of cyanide ion by attack of chloride via an $S_N2$-Si[75] type substitution, was earlier described in Scheme 38 (p.66) for the formation of benzothiazole Reissert compounds. It depends upon step (ii) producing cyanide ions which would react rapidly with the cation (195) to give the Reissert compound (183), hence, driving the reaction to the right. Chloride can be provided from the $AlCl_4^-$ anion, or

directly if it is the counter ion to (195) in the absence of $AlCl_3$. Reissert reactions with $Me_3SiCN$ proceed in the absence of $AlCl_3$ but usually work better with the catalyst present.[19a]

Although to our knowledge, compounds (183) are the first examples of the isolation of benzologous Reissert compounds, a similar structure could be postulated as an intermediate in the pathway of an attempted Reissert reaction with cinnoline. Bhattacharjee and Popp[48] reported that treatment of cinnoline with benzoyl chloride and trimethylsilyl cyanide in the molar ratio 1:2:2, in the presence of aluminium chloride gave, as the sole product 1,2-dibenzoyl-4-cyano-1,2-dihydrocinnoline (62). The authors[48] did not provide a mechanism for its formation but we have suggested the following earlier in this thesis (Scheme 16, p.25).

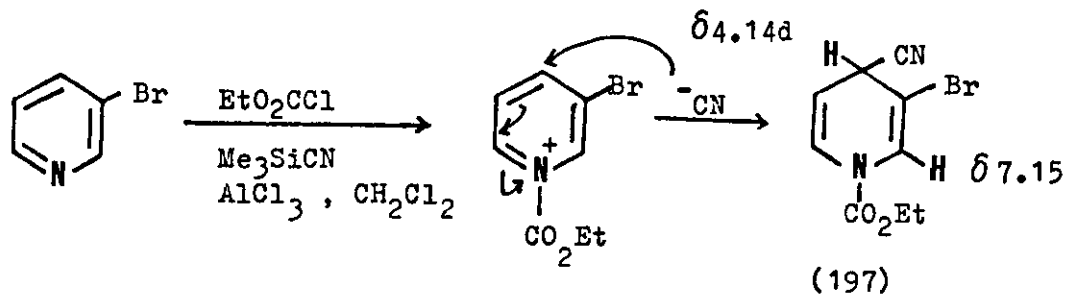
Scheme 16




(196)

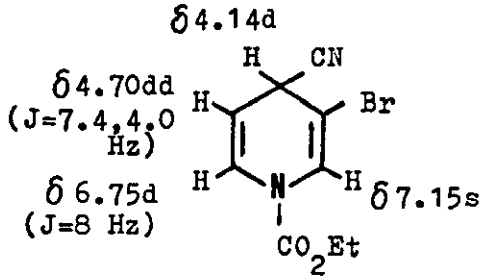
Thus, intermediate (196) has a benzologous Reissert compound structure.

The nearest equivalent to an isolatable benzologous Reissert compound which has been reported is a vinylogous Reissert compound, recently observed in the pyridine series. The Reissert reaction with pyridine and aliphatic or aromatic acid chlorides fails, but it succeeds with chloroformates.[54,134,135] Kant and Popp[54] have reported recently that, whereas pyridine and substituted pyridines with ethyl chloroformate and $Me_3SiCN$ usually give regiospecific cyanation at the 2-position, 3-bromopyridine gives 3-bromo-4-cyano-1-ethoxycarbonyl-1,4-dihydropyridine (197) as exclusive product, i.e. a vinylogous Reissert compound.

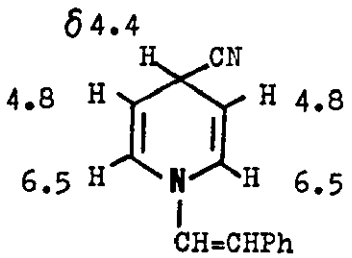



(197)

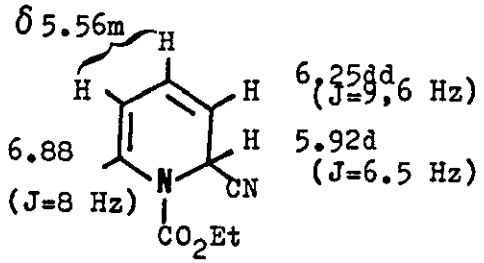
The assignment of isomer (197) was on the basis of spectral data.[54] We compare this with data for compounds (198)[135] and (200).[134]




(197)[54]




(198)[135]




(200)[134]

The authors list the nmr data for structures (197) and (200) without assignments: we show likely allocations. It can be seen that the coupling constant data appears slightly inconsistent for both (197) and (200), on a first order basis.

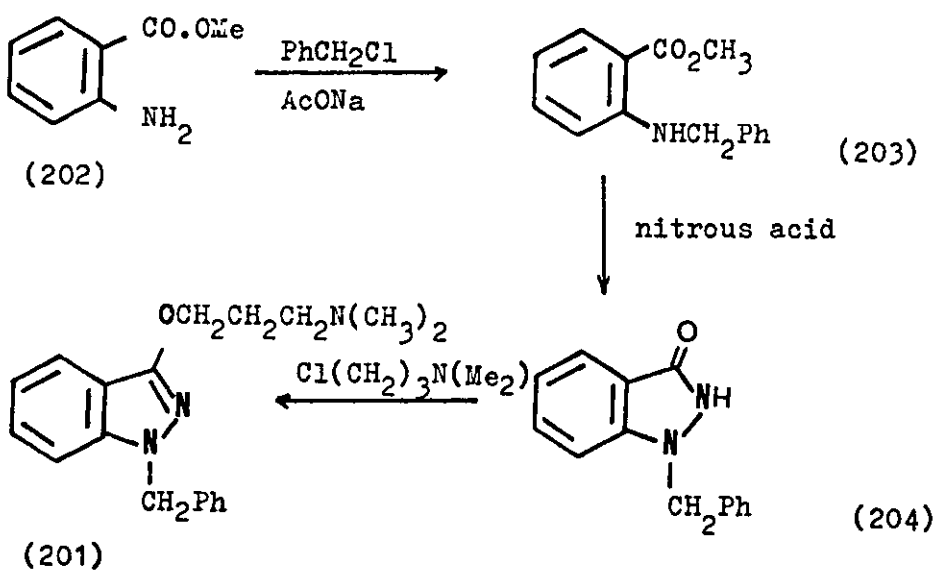
From the various mechanisms discussed, it appears that the one involving liberation of cyanide ion via an $S_N2$-Si type substitution is applicable to the formation of Reissert compounds from benzothiazole, 1-methylindazole, benzologous Reissert analogous from 2-methylindazole, and, as an intermediate, from cinnoline, and the vinylogous Reissert compound from 3-bromo-pyridine.

## Part V Potential Biological Interest of Reissert Compounds from Indazoles

We have found novel five-membered ring Reissert compounds may be prepared from indazole, 1-methyl- and 2-methylindazole. From the latter two series of compounds, we have achieved different routes to the synthesis of 1,3- and 2,3-disubstituted indazoles.

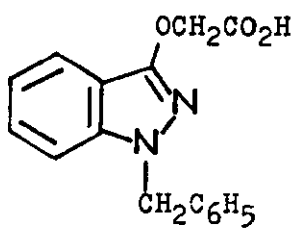
Some compounds with the indazole nucleus have been reported to be of medicinal interest as nonsteroidal antiinflammatory agents or analgesics.[136] Benzydamine (201) is a fairly potent nonsteroidal antiinflammatory agent with antipyretic and analgesic properties. A procedure for the synthesis of (201) is described in Scheme 86.[137]

Scheme 86



Alkylation of the amine of anthranilic acid methyl ester (202) with benzyl chloride in the presence of sodium acetate was reported to give (203). Treatment with nitrous acid led to the nitrosamine which cyclised spontaneously to the 3-ketoindazole system (204). On heating the sodium salt of (204) with 2-dimethylaminopropyl chloride, benzydamine (201) was obtained.[137]

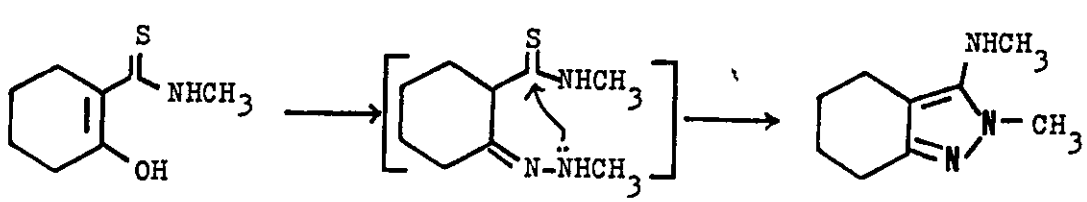
Bendazac (205)[138] is another example of a nonsteroidal antiinflammatory agent with the indazole nucleus.




(205)

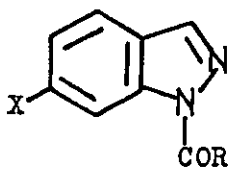
Reduction of the benzene ring in the indazole nucleus may also be compatible with biological activity. The analgesic agent, tetrydamine (206) has been prepared by reaction of N-methyl-2-thiocarbamoylcyclohexanone (207) with methyl hydrazine, probably with the intermediacy of the alkylhydrazone (208)(Scheme 87).[139]

Scheme 87

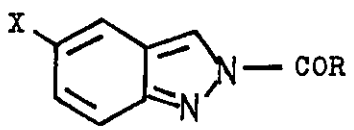



(207) (208) (206)

Substituted indazoles of the type (209) and (210) have been synthesised by Kingsbury and co-workers[140] as potential anthelmintics.



(209)



(210)

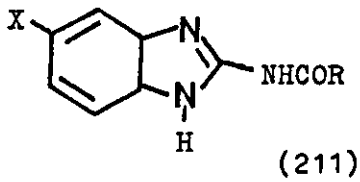
e.g.

| | X, | R | X, | R |
|---|---|---|---|---|
| (a) | H | OMe | H | $OCH_3$ |
| (b) | H | $OCH_2Ph$ | H | $OCH_2Ph$ |
| (c) | H | 2-furyl | H | quinoxalin-2-yl |
| (d) | $NO_2$ | $N(CH_3)$-n-$C_6H_{13}$ | Cl | $N(CH_3)$-n-$C_6H_{13}$ |

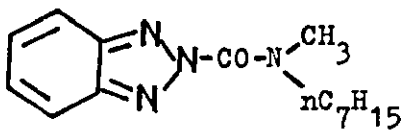
But Kingsbury et al[140] have found the indazole nucleus to be less attractive than the benzimidazole nucleus for the preparation of new anthelmintics. Substituted benzimidazoles of type (211) have been reported to have the broadest spectrum of activity as anthelmintics against the intestinal nematodes of sheep.[141a] Benzothiazoles (212) with 1- and 2-carbamoyl substituents are also reported to have broad-spectrum anthelmintic activity.[141b]

e.g.

| (211) | $\underline{X_2}$ | $\underline{R}$ |
|---|---|---|
| (a) | H | OMe |
| (b) | $n\text{-}C_4H_9$ | OMe |
| (c) | H | $N(CH_3)\text{-}n\text{-}C_7H_{15}$ |
| (d) | H | 2-furyl |




(211)

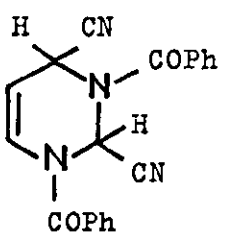



(212)

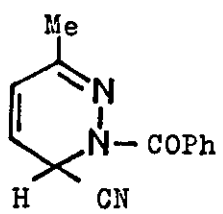
The examples described above, thus demonstrate the various areas where the novel indazole Reissert compounds and their derivatives may be of potential medicinal interest.

## CHAPTER IV A BRIEF INVESTIGATION INTO THE USE OF THE MONOCYCLIC FIVE-MEMBERED RING HETEROCYCLE PYRAZOLE IN THE REISSERT APPROACH

As mentioned in the Introduction (p.27), the first two examples of monocyclic Reissert compounds were recently prepared by Popp and co-workers[19c] from pyrimidine (68) and 3-methylpyridazine (69) using trimethylsilyl cyanide under single phase conditions, in yields of 59% and 41% respectively.

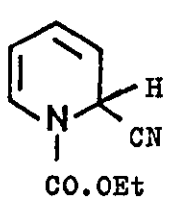



(68)




(69)

Reuss et al[53] reported some time ago, the preparation of a pyridine Reissert compound (70) in 25% yield using sodium cyanide and ethyl chloroformate under two-phase reaction conditions ($CH_2Cl_2/H_2O$).




(70)

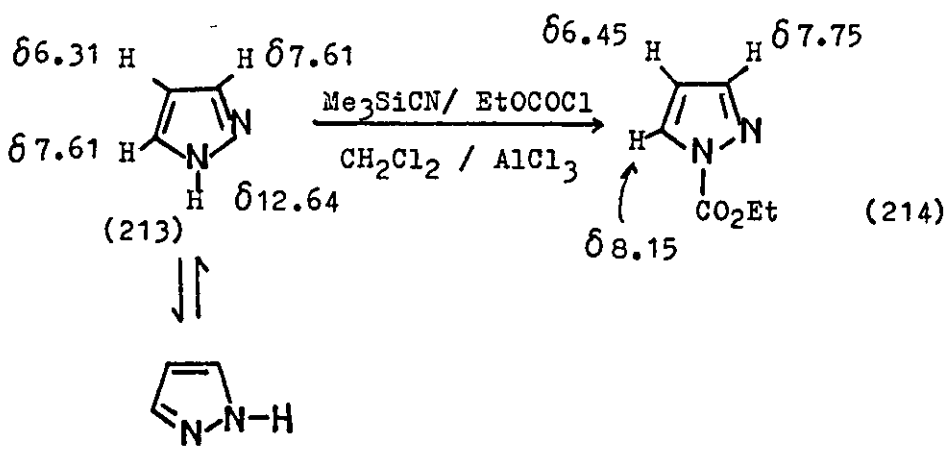
The yield of the Reissert compound (70) was improved considerably to 92% by Popp et al[54] in 1985 using trimethylsilyl cyanide in a single phase medium. Popp et al[54] and Cooney et al[134] also found that the use of the phase transfer

catalyst benzyltrimethylammonium chloride (1%) under two-phase reaction conditions gave compound (70) in 75-92% yield.

There are no previous reports of monocyclic five-membered ring Reissert compounds. We have carried out a brief study on the use of the monocyclic five-membered diazaheterocycle pyrazole (213) in the Reissert method.

We found that treatment of pyrazole with trimethylsilyl cyanide and ethyl chloroformate in molar ratios of 1:2:2 under single phase reaction conditions, gave an oil which was identified as N-ethoxycarbonylpyrazole (214), obtained in 58% yield, b.p. 85°C/4mmHg (Scheme 88). The infrared spectrum of the compound showed a strong carbonyl absorption at 1735cm$^{-1}$ and the proton nmr showed the characteristic splitting pattern of an ethyl group. The compound also gave satisfactory mass and microanalytical data.

Scheme 88

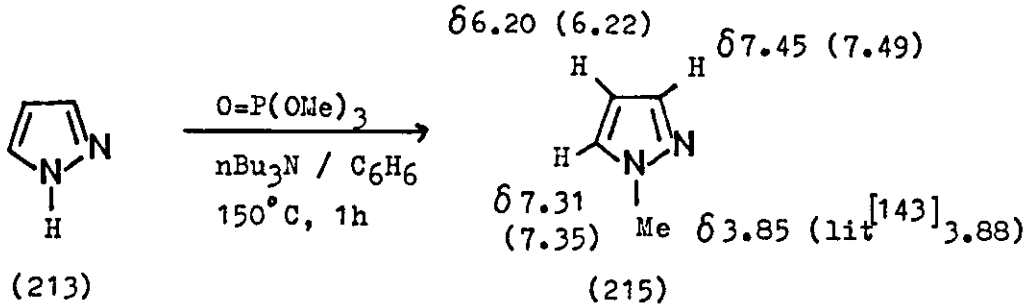


Further reaction of compound (214) with trimethylsilyl cyanide and ethyl chloroformate gave only recovered (214), 94%.

Thus, we proceeded to examine the usefulness of N-methylated pyrazole as the starting heterocycle in the Reissert approach. We have seen in Chapter III, 1-methylindazole, the benzo-analogue of pyrazole, had yielded Reissert compounds from chloroformates.

We followed the method of Yamauchi and Kinoshita[142] to methylate pyrazole by heating with trimethyl phosphate and tri-n-butylamine at 150°C for an hour (Scheme 89). 1-Methylpyrazole (215) was obtained in 27% yield, b.p. 125-128°C/760mmHg, lit[142] 128°C/760mmHg.

Scheme 89



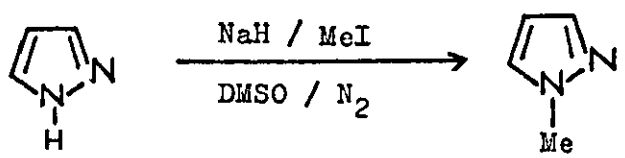

(213) (215)

Yamauchi and Kinoshita[142] have claimed a yield of 90% using this method, but we have found the product to be contaminated with the base tri-n-butylamine and required at least two distillations before pure 1-methylpyrazole was obtained.

We subsequently found pyrazole was readily methylated with methyl iodide and sodium hydride in dimethylsulphoxide (Scheme 90). The reaction mixture was stirred at 0°C for 3 hours and under a nitrogen atmosphere. The product 1-methylpyrazole was

obtained in 72% yield, b.p. 126-128°C. In the proton nmr, the N-$CH_3$ group was observed as a singlet at ∂3.85ppm.

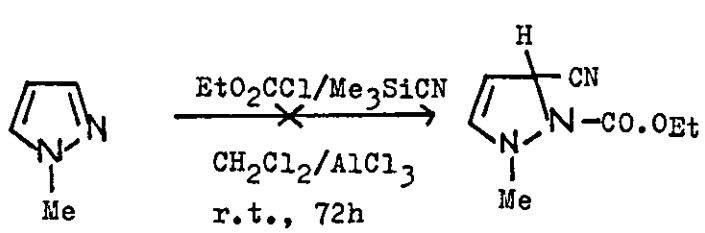
Scheme 90




(213) (215)

We also found that dimethylformamide may be used in place of DMSO, the yield of 1-methylpyrazole using DMF was 69%, but the product contained traces of the solvent even after distillation. The product obtained from using DMSO was found to be pure after distillation.

But on using 1-methylpyrazole in the Reissert reaction with ethyl chloroformate and trimethylsilyl cyanide in dichloromethane with a catalytic amount of $AlCl_3$, we recovered only the starting heterocycle (92%).




(215)

The same result was observed on using the same substrates as above, but this time, the reaction mixture was refluxed for six hours and stirred at room temperature for 48 hours.

The starting heterocycle 1-methylpyrazole was also recovered when the reaction was carried out with benzoyl chloride and trimethylsilyl cyanide.

From this brief study, we were unable to isolate a Reissert analogue from pyrazole, but further investigation is necessary before this heterocycle is regarded as unsuitable for use in this reaction.

## EXPERIMENTAL

Unless otherwise stated, the following conditions applied.

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian EM 360A Spectrometer (60 MHz) or Perkin- Elmer R32 Spectrometer (90 MHz) in solutions of $CDCl_3$ and/or DMSO-$d_6$, with tetramethylsilane (TMS) as internal reference. The following abbreviations are used in the presentation of these spectra:

s = singlet, d = doublet, t = triplet, q = quartet,
m = multiplet, br = broad.

Infrared spectra were recorded as KBr discs, nujol mulls or liquid films by means of a Perkin-Elmer 177 grating spectrometer. The ultraviolet spectra were recorded on a Shimadzu UV-160 spectrophotometer in ethanol. Mass spectra were obtained on a Kratos MS80 Spectrometer with DS-55 data system. Elemental analyses were carried out at the University of Manchester.

Column chromatography was normally carried out by the flash chromatography technique[63,64] with Merck silica gel 60 for column chromatography (0.040-0.063mm mesh). Column diameters were 10mm, 30mm, 40mm and 50mm. After use, column recycling was effected by flushing the column first with acetone then ethyl acetate at 2in/min and finally, with the desired eluent. Thin layer chromatography (tlc) used plates 5 x 5cm, 20 x 20cm and 20 x 100cm (0.5mm layers), made from kieselgel 60 PF 254 & 366.

Commercial grade solvents and reagents were used except for the following, which were purified as follows. Dichloromethane ethyl acetate, chloroform and petroleum ether (b.p. 40-60°C) were dried over calcium chloride overnight and distilled. Petroleum ether was stored over sodium wire and the others over molecular sieves type 4A. Dimethylformamide (DMF) and dimethylsulphoxide (DMSO) were dried over $CaH_2$ overnight and distilled, both were stored over molecular sieves (4A). N-methylpyrrolidinone was freshly distilled when required and stored over potassium hydroxide pellets. Triethylamine was also freshly distilled when required. Diethyl ether was dried over $LiAlH_4$ overnight, distilled and stored over sodium wire. The $LiAlH_4$ residues were destroyed by addition of ethyl acetate. Sodium hydride (50% or 80% suspension in oil) was washed with dry light petroleum (b.p. 40-60°C) before use.

All solutions were dried by means of anhydrous magnesium sulphate, unless otherwise stated.

## CHAPTER I: THE USE OF PHTHALAZINE REISSERT COMPOUNDS IN HETEROCYCLIC SYNTHESES

### Phthalazine (33)

A 3-necked round bottom flask (500ml) was fitted with a reflux condenser, pressure-equalising dropping funnel (250ml) and a nitrogen inlet. o-Phthalic dicarboxaldehyde (13.4g, 0.1 mol) was dissolved in ethanol (100ml), the mixture being warmed slightly to aid dissolution. This was then added dropwise to an ice-cooled solution of hydrazine hydrate (64% solution, 5.5g, 0.11 mole) in ethanol (100ml). The reaction mixture was stirred constantly and addition of the o-phthalic dicarboxaldehyde solution was completed in one hour.

The reaction mixture was stirred for another hour at $0^{o}C$ and a further 3 hours at room temperature, under a nitrogen atmosphere throughout the reaction time.

Ethanol was removed in vacuo and a pale yellow oil was obtained which solidified on cooling. The crude product was kept in a vacuum desiccator with conc. $H_2SO_4$ overnight to remove excess of hydrazine.

Phthalazine (33) was obtained as cream-coloured needles from recrystallisation with diethyl ether (11.8g, 91%), m.p. $88\text{-}90^{o}C$, lit[55] $90\text{-}91^{o}C$.

$\nu_{max}$ (KBr), 1615 (C=N), 1575 $cm^{-1}$ (N=N)

$\delta_H$ (60MHz, $CDCl_3$), 9.30 (2H, s, C-1H & C-4H),
7.8-7.2 (4H, m, aromatic).

Trimethylsilyl cyanide (75)

Safe handling of cyanide

Safety spectacles and rubber gloves were worn during the preparation of trimethylsilyl cyanide. The toxicity of this compound is not known but it was assumed that on hydrolysis, it may produce HCN and hexamethyldisiloxane, $Me_3SiOSiMe_3$. The same handling precautions were taken as with the use of KCN in the preparation of Reissert compounds. A supply of capsules of the heart stimulant amyl nitrite was kept ready, work was carried out in the presence of a colleague. All manipulations, including weighing and filtrations etc. were carried out in a fume cupboard. After use, all the apparatus, tissue papers and gloves etc. were placed in a large beaker containing an alkaline solution of ferrous sulphate, overnight.

The cyanide residues from the distillation of trimethylsilyl cyanide were likewise destroyed by treatment with an excess of strongly alkaline ferrous sulphate solution overnight in the fume cupboard before disposal. This process converts any cyanide residues to the non-toxic Prussian Blue (iron III ferrocyanide) which precipitates.[23] The steps are as follows:-

$$Fe^{2+} + 2CN^- \longrightarrow Fe(CN)_2$$

$$Fe(CN)_2 + 4CN^- \longrightarrow Fe(CN)_6^{4-}$$

$$Fe^{2+} \xrightarrow{[O]} Fe^{3+}$$

$$Na^+ + Fe^{3+} + Fe(CN)_6^{4-} \longrightarrow NaFe[Fe(CN)_6]$$

$$Fe^{3+} + Fe(CN)_6^{4-} \longrightarrow Fe_4[Fe(CN)_6]_3$$

i) Method[56] using KCN: $Me_3SiCl$: N-methylpyrrolidinone in 5:5:1 molar ratio with KI catalyst

Freshly distilled N-methylpyrrolidinone (9.9g, 0.1 mol) was added gradually from a pressure-equalising dropping funnel to a stirred suspension of dry potassium cyanide (32.6g, 0.5 mol, ground and stored in a desiccator overnight), potassium iodide (8.3g, 0.05 mol) in trimethylsilyl chloride (54.1g, 0.5 mol).

The mixture was stirred vigorously and heated to gentle reflux with an oil bath. Cooling was by a solid $CO_2$ - acetone condenser and the reaction mixture was kept under a blanket of $N_2$ during the course of reaction.

After refluxing for 3 hours, the mixture was allowed to stir at room temperature overnight after which the product was distilled directly using a Vigreux column. Three fractions were collected.

The first fraction collected at 56-60°C was recovered trimethylsilyl chloride (37g, which was subsequently re-useable).

The second fraction was collected at 90-110°C (3.5g) and appeared to be impure trimethylsilyl cyanide.

$\nu_{max}$(liquid film), 3200 (OH), 2200 (C≡N), 2095$cm^{-1}$($\overset{+}{N}\equiv C^-$)

The third fraction was collected at 116-118°C and showed

$\nu_{max}$(liquid film),2970(CH),2910(CH),2200(C≡N),2095$cm^{-1}$($\overset{+}{N}\equiv C^-$)

The infrared spectrum of the third fraction was identical with that of an authentic commercial sample (Aldrich Chemical Company)[146] showing the fraction to be pure trimethylsilyl cyanide (75), (17.3g, 35%). Yield based on recovered trimethylsilyl chloride, 85%, (lit[56] yield 86-87%, b.p. 112-117°C).

ii) Method[57] using NaCN (0.75 mol), $Me_3SiCl$ (0.60 mol) and an excess of N-Methylpyrrolidinone, with NaI catalyst

A 500ml 3-necked round bottom flask was fitted with a dropping funnel, a condenser containing solid $Co_2$/acetone, and a nitrogen inlet.

Dry sodium cyanide (37.65g, 0.75 mol) and anhydrous sodium iodide (0.05 mol) as a catalyst were placed into the flask. N-Methylpyrrolidinone (50ml, 51.65g) was added and the suspension was stirred vigorously, keeping the reaction mixture at 105-110°C with an oil bath. Trimethylsilyl chloride (65g, 0.6 mol) was added dropwise from the pressure-equalising dropping funnel.

Addition of trimethylsilyl chloride was completed after 2.5 hours and, after cooling, the product was fractionally distilled to give trimethylsilyl cyanide as a colourless liquid (75) (10.7g, 18%) b.p. 116-120°C (lit[57] yield 65-80%, b.p. 116-118°C).

Storage

In a fume cupboard, the product (75) was placed into a dry round bottom flask, dry nitrogen was gently blown over the

surface and the flask sealed with a subaseal septum cap. This was stored in a tin half filled with soda ash, which would neutralise any HCN produced in the event of a breakage, and with a layer of self-indicating silica-gel above it. When used in an experiment, the trimethylsilyl cyanide was transferred into the reaction mixture by means of a dry syringe.

All the equipment used in this procedure was subsequently treated to destroy any cyanide residues, by the method described previously (p.163).

2-Benzoyl-1-cyano-1,2-dihydrophthalazine (71)

To a well stirred solution of phthalazine (5.0g, 0.038 mol) in dry dichloromethane (50ml) and trimethylsilyl cyanide (3.8g, 5.1ml, 0.038 mol) was added anhydrous aluminium chloride (0.1g). After several minutes, benzoyl chloride (5.5g, 0.038 mol) was added dropwise over 30 minutes. The reaction mixture was stirred at room temperature for 24 hours. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane layer was dried over anhydrous potassium carbonate and filtered. After concentration of the solvent and recrystallisation from ethanol, the title compound (71) was obtained as cream-coloured prisms (8g, 80%), m.p. 165-166°C, lit[28] 163-164°C.

$\nu_{max}$ (KBr), 2250 (C≡N), 1650 (C=O), 1575cm$^{-1}$ (C=N)

$\delta_H$(60MHz,$CDCl_3$),7.80-7.30(10H,m,aromatic),6.75(1H,s,C-1H)

4-Methylphenyl phthalazin-1-yl carbinol (81a)

Sodium hydride (0.96g of 50% oil dispersion, to provide 0.48g, 0.02 mol of NaH) was washed free of oil by stirring the slurry with dry petroleum ether (40-60°C)(20ml) in a 3-necked round bottom flask, the solvent was removed by using a micropipette. The flask was fitted with a nitrogen inlet, a pressure-equalising dropping funnel and a $N_2$-exit bubbler. Dimethylformamide (5ml) was added and the resulting slurry cooled to 0°C in an ice-bath. A mixture of 2-benzoyl-1-cyano-1,2-dihydrophthalazine (2.6g, 0.01 mol) and freshly distilled p-methylbenzaldehyde (1.2g, 0.01 mol) in DMF (45ml) was added dropwise over a period of 15 minutes, with constant stirring. A dark red-brown colour resulted, indicating the generation of the Reissert anion by the NaH. The reaction mixture was allowed to stir at room temperature for 24 hours under an atmosphere of $N_2$.

The mixture was poured on to ice (ca. 200g). The solid obtained was recovered by filtration, washed with water and dried in a vacuum desiccator overnight. Recrystallisation from ethanol gave cream-coloured needles of the title compound (81a) (0.4g, 16%) m.p. 141-143°C.

$\nu_{max}$ (KBr): 3310 (OH), 1600$cm^{-1}$ (C=N)

$\delta_H$(90MHz,$CDCl_3$):7.9-7.2(8H,m,aromatic),6.56(1H,s,C<u>H</u>OH)
4.38(1H,br,OH,exchangeable with $D_2O$),
2.43(3H,s,$CH_3$)

m/z, 250($M^{\ddagger}$,26%),233(14%,$M^{\ddagger}$-OH),119(100%,4-$MeC_6H_4CO$)
91(79%,4-$MeC_6H_4$-)

Found: C, 76.6; H, 5.6; N, 11.1 $C_{16}H_{14}N_2O$
requires: C, 76.8; H, 5.6; N 11.2%

3,4-Dimethoxyphenyl phthalazin-1-yl ketone (84)

A mixture of 2-benzoyl-1-cyano-1,2-dihydrophthalazine (2.0g, 7.7mmol) and 3,4-dimethoxybenzaldehyde (1.3g, 7.7mmol) in DMF (40ml) was added dropwise to NaH (0.37g of 50% oil dispersion to provide 0.19g, 7.7mmol of NaH), with cooling at 0°C and under an atmosphere of $N_2$. After the addition was completed, the reaction mixture was stirred at room temperature for 16 hours before pouring on to crushed ice (ca. 150g). A peach coloured precipitate was formed, but on filtering, changed into a sticky gum. On trituration with ethanol, this gum became a stable solid, m.p. 170-174°C. An infrared spectrum of the crude product in the form of a KBr disc indicated a strong absorption frequency at 1710$cm^{-1}$, which suggested the presence of an ester.

The crude material was used without further purification. It was refluxed directly in a solution of ethanol (75ml) and aqueous potassium hydroxide (16%, 75ml) for 3 hours. The reaction mixture was then diluted with water (100ml) and ethanol was removed under reduced pressure. The solution was extracted with dichloromethane (2 x 100ml) and the organic layer was washed several times with water before drying over anhydrous magnesium sulphate.

Concentration of the $CH_2Cl_2$ gave an oil which on trituration with $MeOH/CH_2Cl_2$ resulted in cream-coloured needles of the title compound (84)(0.11g, 5%) m.p. 227-228°C, lit[30] 214-215°C.

$\nu_{max}$ (KBr), 1653 (C=O), 1590$cm^{-1}$ (C=N)

Reduction of the Ketone (84) to 3,4-dimethoxyphenyl phthalazin-1-yl carbinol (82)

The ketone (84)(0.1g, 0.34mmol) in methanol (7.5ml) was cooled to 0.5°C and sodium borohydride (0.13g, 3.4mmol) was added in small portions. The mixture was stirred at 0°C for one hour and a further 30 minutes at room temperature. 5% Hydrochloric acid (7.5ml) was added and the methanol was removed under reduced pressure. After dilution with water (12.5ml), the solution was extracted with dichloromethane (2 x 15ml), dried over anhydrous potassium carbonate and filtered. Evaporation of $CH_2Cl_2$ and recrystallisation from ethanol gave cream-coloured needles of the title compound (82)(0.07g, 67%) m.p. 233-234°C, lit[30] 235-236°C.

$\nu_{max}$ (KBr), 3450 (OH), 1600$cm^{-1}$ (C=N)

$\delta_H$ (90MHz,$CDCl_3$),8.10-7.30(8H,m,aromatic),6.40(1H,s,C<u>H</u>OH),
5.45(1H,br,OH exchangeable with $D_2O$),
3.85(6H,s,OMe)

m/z, 296 ($M^+$ 1%), 165 (100%, 3,4-$Me_2C_6H_3CO$)

## Preparation of α-(phthalazin-1-yl)benzyl benzoate esters (80b-d)

### General Procedure (A)

Sodium hydride (0.37g of 50% oil dispersion to provide 0.19g, 7.7mmol of NaH) was washed free of oil using petroleum ether (40-60°C) in a 3-necked round bottom flask and the solvent was removed by using a micropipette. The flask was fitted with a nitrogen inlet, a pressure-equalising dropping funnel and a $N_2$-exit bubbler. Dimethylformamide (5ml) was added and resulting slurry was cooled to 0-5°C with an ice-bath. Stirring was begun and a mixture of 2-benzoyl-1-cyano-1,2-dihydrophthalazine (2.0g, 7.7mmol) and the freshly distilled aromatic aldehyde (7.7mmol) in DMF (35ml) was added over a period of 15 minutes. The reaction mixture was kept at 0-5°C for 1 hour and then stirred overnight at room temperature with an atmosphere of $N_2$ throughout reaction time.

The mixture was poured into ice cold water, any solid obtained was filtered and dried in a vacuum desiccator overnight. The aqueous solution was made neutral by adding dilute hydrochloric acid and extracted with dichloromethane (2 x 50ml). The combined extracts were washed with water (5 x 50ml), dried over anhydrous potassium carbonate, filtered and evaporated.

The crude product was either directly recrystallised from an appropriate solvent or first purified by column chromatography to give the ester as described below.

α-(Phthalazin-1-yl)-4-methoxybenzyl benzoate (80b)

Use of 2-benzoyl-1-cyano-1,2-dihydrophthalazine (2.0g, 7.7mmol), sodium hydride (0.37g, 7.7mmol of 50% oil dispersion) and 4-methoxybenzaldehyde (1.05g, 7.7mmol) in the general method (A) (p.170) gave a brown oil. From analytical tlc (silica gel), the crude product showed the presence of two components and flash column chromatography[63] (p.160) was carried out to separate the components.

A column with diameter 40mm was used and the eluent was a 80:20 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C). Two fractions were collected, the first (0.2g) m.p. 168-170°C, was not characterised. The second fraction was found to be the title compound (80b). Recrystallisation from ethanol gave pale yellow prisms (1.9g, 66%) m.p. 138-140°C.

$\nu_{max}$ (KBr), 1694cm$^{-1}$ (C=O)

m/z, 370.1374($M^+$ 0.1%, $C_{23}H_{18}N_2O_3$ requires 370.1377), 105(100%, $C_6H_5CO$), 77(56%, $C_6H_5$).

α-(Phthalazin-1-yl)benzyl benzoate (80c)

Use of 2-benzoyl-1-cyano-1,2-dihydrophthalazine (2.0g, 7.7mmol), sodium hydride (0.37g of 50% oil dispersion, 7.7 mmol) and benzaldehyde (0.78g, 7.7mmol) in the general method (A) gave a pale orange precipitate which was purified by flash column chromatography.

A 40mm diameter column was used and the solvent system was a 80:20 mixture of ethyl acetate and light petroleum (b.p.

40-60°C). The title compound (80c) was obtained as colourless prisms from recrystallisation with ethanol (1.9g, 72%) m.p. 168-170°C.

$\nu_{max}$ (KBr), 1700cm$^{-1}$ (C=0)

m/z, 340.1216($M^+$ 1%, $C_{22}H_{16}N_2O_2$ requires 340.1212)
105 (100% $C_6H_5CO$), 77 (89%, $C_6H_5$).

α-(Phthalazin-1-yl)-4-chlorobenzyl benzoate (80d)

Use of 2-benzoyl-1-cyano-1,2-dihydrophthalazine (2.0g, 7.7mmol), 4-chlorobenzaldehyde (1.1g, 7.7mmol) and sodium hydride (0.37g of 50% oil dispersion, 7.7mmol) in the general method (A) gave an oil which solidified on trituration with ethanol. Recrystallisation of the solid from ethanol gave the title compound (80d) (1.7g, 58%) m.p. 155-157°C.

$\nu_{max}$ (KBr), 1695cm$^{-1}$ (C=0)

Aryl phthalazin-1-yl carbinols (81)

General Procedure (B)

A mixture of the α-(phthalazin-1-yl)benzyl benzoate, aqueous potassium hydroxide (16%) and ethanol was placed into a round bottom flask fitted with a condenser at the top of which was a T-piece supplied with nitrogen gas on one side and a bubbler on the other. The mixture was refluxed for 8 hours under a nitrogen atmosphere. The reaction mixture was then cooled and diluted with water. Most of the ethanol was evaporated and the solution

extracted with dichloromethane (2 x 30ml). The aqueous solution was neutralised with dilute hydrochloric acid and extracted with dichloromethane (2 x 10ml). The extracts were combined, washed with water, dried over anhydrous magnesium sulphate and filtered. The crude product was recrystallised from an appropriate solvent to give the title compound as described below.

4-Methoxyphenyl phthalazin-1-yl carbinol (81b)

Use of ester (80b)(0.8g, 2.2mmol), ethanol (35ml) and aqueous potassium hydroxide solution (16%, 35ml) in the general procedure (B) yielded, after recrystallisation from ethanol, the title compound (81b) as colourless needles (0.5g, 84.5%), m.p. 166-168°C.

$\nu_{max}$ (KBr), 3410 (OH), 1600cm$^{-1}$ (C=N)

$\delta_H$ (90MHz, $CDCl_3$), 8.45-6.81 (9H, m, aromatic), 6.53 (1H, s, CHOH), 5.80 (1H, br, OH, exchangeable with $D_2O$), 3.80 (3H, s, OMe)

m/z, 266.1062($M^+$ 26%, $C_{16}H_{14}N_2O_2$ requires 266.1055), 135 (100%, 4-$MeOC_6H_4CO$)

Found: C, 71.7; H, 5.3; N, 10.1 $C_{16}H_{14}N_2O_2$
requires: C, 72.2; H, 5.3; N, 10.5%.

Phenyl phthalazin-1-yl carbinol (81c)

Use of ester (80c) (0.91g, 2.7mmol), ethanol (35ml) and aqueous potassium hydroxide solution (16%, 35ml) in the general

procedure (B), after recrystallisation from ethanol yielded the title compound (81c) as colourless crystals (0.36g, 56.5%), m.p. 173-175°C, lit[18a] 172-175°C

$\nu_{max}$ (KBr), 3400 (OH), 1590cm$^{-1}$ (C=N)

$\delta_H$ (90MHz, $CDCl_3$), 8.10-7.30 (10H, m, aromatic), 6.15 (1H, s, C<u>H</u>OH), 5.40 (1H, br, OH, exchangeable with $D_2O$)

m/z, 236.0952 ($M^+$ 82%, $C_{15}H_{12}N_2O$ requires 236.0949), 105 (73%, $C_6H_5CO$-), 77 (100%, $C_6H_5$-).

Found: C, 75.8; H, 5.1; N, 11.8% $C_{15}H_{12}N_2O$
requires: C, 76.25; H, 5.1; N, 11.9%.

<u>4-Chlorophenyl phthalazin-1-yl carbinol (81d)</u>

Use of ester (80c)(0.61g, 1.6mmol), ethanol (35ml) and aqueous potassium hydroxide solution (16%, 35ml) in the general procedure (B) yielded the <u>title compound (81d)</u> as colourless prisms after recrystallisation from ethanol (0.14g, 32%), m.p. 172-174°C. The product gave a single spot on analytical tlc.

$\nu_{max}$ (KBr), 3400 (OH), 1600cm$^{-1}$ (C=N)

$\delta_H$ (90MHz, $CDCl_3$), 8.25-7.40 (9H, m. aromatic), 6.30 (1H, s, C<u>H</u>OH), 5.30 (1H, br, OH, exchangeable with $D_2O$)

m/z, 272.0530 ($M^{+}$ 10.43%, $C_{15}H_{11}N_2O^{37}Cl$ requires 272.0520), 270.0560 ($M^{+}$ 32.42%, $C_{15}H_{11}N_2O^{35}Cl$ requires 270.0562), 76 (100%, $C_6H_4$-).

1-Aryl-3H-oxazolo[4,3-a]phthalazin-3-one (89)(90)

General Procedure

This procedure involved the use of toxic phosgene gas and hence, all preparations were carried out in an efficient fume cupboard.

Dried diethyl ether (25ml) was placed into a two-necked round bottom flask fitted with an inlet tube and a cardice condenser (containing solid $CO_2$ in acetone) with an outlet connected to a Dreschel bottle charged with aqueous ammonium hydroxide (this was used as an indicator of the rate at which phosgene was being passed into the reaction flask and to destroy excess of phosgene).

The round bottom flask was kept over an ice-bath and phosgene gas was bubbled at a rate of 3 bubbles per second over 30 minutes. During this time, approximately 4 grams of phosgene was dissolved into the diethyl ether. In a separate flask, the aryl phthalazin-1-yl carbinol was dissolved in dry dichloromethane (10ml) and dry ether (15ml) and dry triethylamine (5ml) was added. The ethereal phosgene solution was added dropwise to this mixture via a pressure-equalising dropping funnel over 15 minutes, with cooling by an ice-bath. A vigorous reaction took place, with the evolution of white fumes and a thick suspension was observed.

After stirring overnight, the mixture was poured on to ice-water, no precipitate was obtained. The layers were separated and the organic layer washed with 8% aqueous sodium bicarbonate and 5% hydrochloric acid solution. The organic layer was dried over magnesium sulphate and filtered. After evaporation of the solvent, the residue was recrystallised from dichloromethane/methanol to give the product as detailed below.

1-(4-Methoxyphenyl)-3H-oxazolo[4,3a]phthalazin-3-one (89)

Use of carbinol (81b)(0.4g, 15mmol) in dichloromethane (10ml) and dried diethyl ether (15ml), triethylamine (5ml) and phosgene (4g) in diethyl ether (25ml) in the general procedure (C) gave the title compound (89) as pale orange cyrstals (0.15g, 34%), m.p. 210-214°C, lit[39] 213-216°C. The product gave a single spot on analytical tlc.

$\nu_{max}$ (KBr), 1745 (C=O), 1600cm$^{-1}$ (C=N)

$\delta_H$ (90MHz, $CDCl_3$), 8.35-7.10 (9H, m, aromatic), 3.90 (3H, s, OMe)

m/z, 292.0902 ($M^+$ 1.18%, $C_{17}H_{12}N_2O_3$ requires 292.0848), 264 (18%, $m^+$ - CO), 135 (100%, 4-$MeC_6H_4CO$), 77 (26%), 44 (15%, $CO_2$)

$\lambda_{max}$ (EtOH), 265 (log $\epsilon$ 3.97), 292 (3.82), 332nm (3.51).

1-Phenyl-3H-oxazolo[4,3-a]phthalazin-3-one (90)

Use of carbinol (81c)(0.35g, 15mmol) in dichloromethane (10ml) and dried diethyl ether (15ml), triethylamine (5ml) and phosgene (3.5g) in diethyl ether (25ml) in the general procedure (C) gave the title compound (90) as yellow crystals (0.18g, 48%), m.p. 148-150°C. The product gave a single spot on analytical tlc.

$\nu_{max}$ (KBr), 1755 (C=O), 1590cm$^{-1}$ (C=N)

$\delta_H$ (90MHz, $CDCl_3$), 8.10-7.20 (10H, m, aromatic)

m/z, 262.0625 ($M^+$ 0.6%, $C_{16}H_{10}N_2O_2$ requires 262.0742),
234(29%, $M^+$-[CO]), 105(43%,$C_6H_5CO$), 77(42%, $C_6H_5$)

$\lambda_{max}$ (EtOH), 252 (log $\varepsilon$ 3.67), 270 (3.42), 350nm (3.59).

## CHAPTER II: BENZOTHIAZOLE REISSERT COMPOUNDS

### Part I The Synthesis of Benzothiazole Reissert Compounds

### General Procedure (D)

To a well stirred solution of benzothiazole in dry dichloromethane (25ml) and trimethylsilyl cyanide was added anhydrous aluminium chloride (0.1g). After several minutes, the acid chloride in dry dichloromethane (15ml) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 72 hours. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane layer was dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure and recrystallised from the appropriate solvent to yield the product.

### 2-Cyano-2,3-dihydro-3-(4-methylbenzoyl)benzothiazole (92a)

Use of benzothiazole (1.90g, 0.014 mole), trimethylsilyl cyanide (1.50g, 2.02ml, 0.0154 mol), anhydrous aluminium chloride (0.1g) and 4-methylbenzoyl chloride (2.16g, 0.014 mol) in the general procedure (D) yielded the title compound (92a). Recrystallisation from ethyl acetate gave colourless needles (3.18g, 87%), m.p. 158-160°C.

$\nu_{max}$ (KBr), 2225 (C≡N), 1663cm$^{-1}$ (C=O)

$\delta_H$(90MHz, $CDCl_3$), 7.40-7.25(8H,m,aromatic), 6.3(1H,s,C-2H)
2.40 (3H,s,$CH_3$)

m/z, 280.0677 ($M^+$ 16%, $C_{16}H_{12}N_2OS$ requires 280.0670),
119 (100%, 4-$MeC_6H_4CO$)

Found: C, 68.25; H, 4.2; N, 9.7 $C_{16}H_{12}N_2OS$
requires: C, 68.6; H, 4.3; N, 10.0%

3-(4-Chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92b)

Use of benzothiazole (0.95g, 7mmol), trimethylsilyl cyanide (0.75g, 1.01ml, 7.7mmol), anhydrous aluminium chloride (0.1g) and 4-chlorobenzoyl chloride (1.23g, 7mmol) in the general procedure (D) gave the title compound (92b). Recrystallisation from ethyl acetate yielded pale yellow rhombs (1.8g, 85%), m.p. 115-118°C.

$\nu_{max}$ (KBr), 2223 (C ≡ N), 1660$cm^{-1}$ (C=0)

$\delta_H$ (90MHz, $CDCl_3$), 7.65-7.02 (8H, m, aromatic), 6.42
(1H, s, C-2H)

m/z,302.0081($M^+$1.07%,$C_{15}H_9N_2OS^{37}Cl$ requires 302.0095),
300.0104 ($M^+$3%,$C_{15}H_9N_2OS^{35}Cl$ requires 300.0104),
139 (100%, 4-$ClC_6H_4CO$).

Found: C, 59.9; H, 2.9; N, 9.2 $C_{15}H_9N_2OSCl$
requires: C, 59.9; H, 3.0; N, 9.3%

2-Cyano-2,3-dihydro-3-(4-nitrobenzoyl)benzothiazole (92c)

Use of benzothiazole (2g, 0.015mol), trimethylsilyl cyanide (1.93g, 2.6ml, 0.018mol), anhydrous aluminium chloride (0.1g)

and 4-nitrobenzoyl chloride (2.8g, 0.015mol) in the general procedure (D), after recrystallisation from ethyl acetate yielded the title compound (92c) as yellow crystals (4.39g, 94%), m.p. 191-193°C.

$\nu_{max}$(KBr), 1675 (C=O), 1340 and 1280cm$^{-1}$ (aromatic N=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.25-7.00(8H, m, aromatic),
6.3 (1H, s, C-2H)

m/z, 311.0370 ($M^+$ 24%, $C_{15}H_9N_3O_3S$ requires 311.0365)
161 (18%, $M^+$-[4-$NO_2C_6H_4CO$]), 104(100%, $C_6H_4CO$).

Found: C, 58.0; H, 2.9; N, 13.5 $C_{15}H_9N_3O_3S$
requires: C, 57.9; H, 2.9; N, 13.5%

3-(4-Chlorobutanoyl)-2-cyano-2,3-dihydrobenzothiazole (92d)

Use of benzothiazole (1.90g, 0.014 mol), trimethylsilyl cyanide (1.5g, 2.02ml, 0.0154 mol), anhydrous aluminium chloride (0.1g) and 4-chlorobutanoyl chloride (1.98g, 0.014 mol) in the general procedure (D), gave the title compound (92d) as colourless plates after recrystallisation from ethyl acetate (3.12g, 84%), m.p. 104-105°C.

$\nu_{max}$ (KBr), 2250 (C≡N), 1670cm$^{-1}$ (C=O)

$\delta_H$(90MHz,$CDCl_3$), 7.45-7.20(4H,m,aromatic), 6.72(1H,s,C-2H),
3.70(2H,t,$C\underline{H}_2Cl$), 2.88(2H,t,$C\underline{H}_2$-CO)
2.24(2H,m,$CH_2$)

m/z, 268.0189($M^+$ 3.4%, $C_{12}H_{11}N_2OS^{37}Cl$ requires 268.0251),
266.0244($M^+$ 10.06%, $C_{12}H_{11}N_2OS^{35}Cl$ requires 266.0280),
105 (100%, 4-Cl$(CH_2)_3CO$).

Found: C, 54.1; H, 4.2; N, 10.4 $C_{12}H_{11}N_2OSCl$
requires: C, 54.0; H, 4.2; N, 10.5%.

2-Cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)

Use of benzothiazole (1.90g, 0.014 mol), trimethylsilyl cyanide (1.5g, 2.02ml, 0.0154 mol), anhydrous aluminium chloride (0.1g) and methyl chloroformate (1.32g, 0.014 mol) in the general procedure (D), the title compound (92e) was obtained as colourless needles after recrystallisation from ethyl acetate (2.42g, 78%) m.p. 101-102°C.

$\nu_{max}$ (KBr), 2225 (C≡N), 1735$cm^{-1}$ (C=O)

$\delta_H$(90MHz, $CDCl_3$), 7.35-7.15(4H, m, aromatic), 6.43
(1H, s, C-2H), 3.95 (3H, s, $CH_3$)

m/z, 220.0306 ($M^+$ 58%, $C_{10}H_8N_2O_2S$ requires 220.0310),
135 (100%, $C_7H_5NS$).

Found: C, 54.5; H, 3.7; N, 12.65 $C_{10}H_8N_2O_2S$
requires: C, 54.5; H, 3.7; N, 12.7%

3-(2-Chloromethylbenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92f)

Use of benzothiazole (1.90g, 0.014 mol), trimethylsilyl cyanide (1.5g, 2.02ml, 0.0154 mol), anhydrous aluminium

chloride (0.1g) and 2-chloromethylbenzoyl chloride (1.95ml; 0.014 mol) in the general method (D) yielded the title compound (92f) after recrystallisation from ethyl acetate, as pale yellow plates (3.23g, 73%), m.p. 188-190°C.

$\nu_{max}$ (KBr), 2223 (C≡N), 1665cm$^{-1}$ (C=O)

$\delta_H$(90MHz, $CDCl_3$), 7.60-7.05 (8H, m, aromatic), 6.43 (1H, s, C-2H), 4.55-4.42(2H, m, $CH_2$)

m/z, 316.0251($M^+$1.14%,$C_{16}H_{11}N_2OS^{37}Cl$ requires 316.0254), 314.0231($M^+$3.09%,$C_{16}H_{11}N_2OS^{35}Cl$ requires 314.0274), 153(100%, 2-$ClCH_2C_6H_4CO$)

Found: C, 60.7; H, 3.5; N, 8.6 $C_{16}H_{11}N_2OSCl$
requires: C, 61.05; H, 3.5; N, 8.9%

3-Benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g)

Use of benzothiazole (0.95g, 7mmol), trimethylsilyl cyanide (0.75g, 1.01ml, 7.7mmol), anhydrous aluminium chloride (0.1g) and benzoyl chloride (0.98g, 7mmol) in the general procedure (D) gave the title compound (92g) as pale yellow crystals after recrystallisation from ethyl acetate (0.82g, 44%), m.p. 140-141°C.

$\nu_{max}$ (KBr), 1655cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.75-7.30(9H, m, aromatic), 6.4 (1H, s, C-2H)

m/z, 266.0513 ($M^+$ 10.14%, $C_{15}H_{10}N_2OS$ requires 266.0514),
105 (100%, $C_6H_5CO$), 77(29%, $C_6H_5$)

Found: C, 67.9; H, 4.0; N, 10.05 $C_{15}H_{10}N_2OS$
requires: C, 67.65; H, 3.8; N, 10.5%

2-Cyano-2,3-dihydro-3-(4-methoxybenzoyl)benzothiazole (92h)

Use of benzothiazole (0.95g, 7mmol), trimethylsilyl cyanide (0.75g, 1.01ml, 7.7mmol), anhydrous aluminium chloride (0.1g) and 4-methoxybenzoyl chloride (1.2g, 7mmol) in the general procedure (D) yielded the title compound (92h) after recrystallisation from ethyl acetate to give pale yellow plates, (0.4g, 19%), m.p. 122-123.5°C.

$\nu_{max}$ (KBr), 2240 (C≡N), 1675$cm^{-1}$ (C=O)

$\delta_H$(90MHz, $CDCl_3$), 7.45-6.95(8H, m, aromatic), 6.41
(1H, s, C-2H), 3.92 (3H, s, $CH_3$)

m/z, 296.0619($M^+$1.67%, $C_{16}H_{12}N_2O_2S$ requires 296.0637),
135 (100%, 4-$MeOC_6H_4CO$)

Found: C, 65.2; H, 4.3; N, 9.2 $C_{16}H_{12}N_2O_2S$
requires: C, 64.85; H, 4.1; N, 9.45%

The use of tri-n-butyltin cyanide in the Reissert reaction

3-Benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g)

Benzothiazole (0.34g, 2.5mmol) and tri-n-butyltin cyanide (1.0g, 3.2mmol) were dissolved in dry dichloromethane (20ml) and stirred in presence of aluminium chloride (0.05g). Benzoyl chloride (0.35g, 2.5mmol) in dichloromethane (10ml) was added dropwise to the reaction mixture. After stirring at room temperature for 72 hours, the reaction mixture was washed with water, 5% aqueous sodium hydroxide, water and 5% HCl and water again before the organic layer was dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave an oil which crystallised on standing. Analytical tlc showed impurities and so preparative tlc (3 x 1m silica gel plates) was used to purify the crude product. The eluent used was a 25:75 mixture of ethyl acetate and light petroleum ether (b.p. 40/60). The title compound (92g) was obtained in 40% yield, m.p. 140-142°C, authentic sample m.p. 140-141°C.[67]

$\nu_{max}$ (KBr), 1660cm$^{-1}$ (C=O)

$\delta_H$ (60MHz, $CDCl_3$), 7.60-6.80(9H, m, aromatic), 6.35 (1H, s, C-2H)

iii) Alternative procedures used in an attempt to synthesise benzothiazole Reissert compounds

a) Use of two-phase reaction conditions

To a well stirred solution of benzothiazole (91)(2g, 0.015 mol) in dichloromethane (25ml) was added a mixture of potassium cyanide (3g, 0.045 mol) and benzyltrimethylammonium chloride (0.3g, 10% mole of KCN) dissolved in water (15ml). 4-Methylbenzoyl chloride (4.6g, 0.03 mol) in dichloromethane (10ml) was added dropwise over 5 minutes.

The reaction mixture was stirred at room temperature for 48 hours, after which it had acquired a red-brown appearance. The two layers were separated and the organic layer was washed with water , 5% hydrochloric acid, water, 5% sodium hydroxide and water before drying over anhydrous magnesium sulphate. Evaporation of the dichloromethane under reduced pressure resulted in an oil which gave a single spot on analytical tlc and was identified as recovered benzothiazole (1.85g, 93%).

b) Use of potassium cyanide under solid/liquid phase catalysis conditions

i) Isolation of benzoyl cyanide and recovery of benzothiazole

To a well stirred mixture of benzothiazole (91)(2.7g, 0.02 mol), potassium cyanide (1.3g, 0.02 mol) and tetrabutylammonium bromide (TBAB)(0.13g, 10% mole of KCN) in dichloromethane (15ml) was added a solution of benzoyl chloride (2.8g, 0.02 mol) in dichloromethane (10ml) dropwise over 5 minutes. The reaction mixture was refluxed gently for 2.5 hours, cooled and the

following washes were carried out; 5% hydrochloric acid, water, 5% sodium hydroxide and water. The organic layer was dried over anhydrous magnesium sulphate, filtered and the solvent evaporated under reduced pressure. A crude oil was obtained which showed two spots on analytical tlc.

The two components were separated by flash column chromatography[63] using a column with diameter of 30mm, and the eluent chosen was a 30:70 mixture of ethyl acetate and petroleum ether (b.p. 40/60).

The first fraction collected was identified as benzoyl cyanide obtained in a yield of 23%, m.p. 29-31°C, lit[147] 30-32°C. The ir and nmr spectra were identical with those of a commercial sample.[148]

ii) Isolation of 3-benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g) and recovery of benzothiazole and benzoyl chloride

A solution of benzoyl chloride (1.4g, 0.01 mol) in dichloromethane (10ml) was added dropwise over five minutes to a well stirred mixture of benzothiazole (1.35g, 0.01mol), potassium cyanide (0.65g, 0.01 mol) and TBAB (0.065g, 10% mole of KCN) in dichloromethane (15ml). The reaction mixture was refluxed gently for 6 hours, followed by stirring at room temperature for a further 18 hours before washing with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude oil obtained showed three spots on analytical tlc and so flash column chromatography was undertaken to separate the components. A column with diameter of

30mm was used and the eluent chosen was a 15:85 mixture of ethyl acetate and petroleum ether (b.p. 40/60).

Fraction one was identified as unreacted benzoyl chloride (9.3%) and fraction two was recovered benzothiazole (67%) and the third fraction was found to be the Reissert compound 3-benzoyl-2-cyano-2,3-dihydrobenzothiazole (92g) obtained in 6% yield, m.p. 140-142$^{o}$C, lit[67] 140-141$^{o}$C.

## CHAPTER II: BENZOTHIAZOLE REISSERT COMPOUNDS

### Part II: Some Chemistry of Benzothiazole Reissert Compounds

#### (i) Intramolecular alkylation reactions

#### 4a-Cyano-2,3,4,4a-tetrahydro-1-oxo-1H-pyrido[2,1b]benzothiazole (110)

3-(4-Chlorobutanoyl)-2-cyano-2,3-dihydrobenzothiazole (92d) (1.07g, 4mmol) in dry dimethylformamide (15ml) was added dropwise to a stirred solution of sodium hydride (0.2g of 50% oil dispersion to give 0.1g, 4mmol of NaH) in dimethylformamide (5ml) at 0°C, under a nitrogen atmosphere. The reaction mixture was stirred for 2 hours under these conditions before pouring on to crushed ice (ca. 30g). A light yellow precipitate was obtained which was filtered and dried. Recrystallisation from ethanol gave the title compound (110) as pale yellow rhombs (0.81g, 88%), m.p. 91-93°C.

$\nu_{max}$ (KBr), 2230 (C≡N), 1673cm$^{-1}$ (C=O)

$\delta_H$(90MHz, $CDCl_3$), 8.15-7.15 (4H, m, aromatic),
2.90-2.10 (6H, m, aliphatic)

m/z, 230.0521 ($M^+$ 35%, $C_{12}H_{10}N_2OS$ requires 230.0513)
203 (15%, $M^+$ - [HCN]), 161 (100%, $C_3H_5CO$)

$\lambda_{max}$ (EtOH), 257.2 (log $\epsilon$ 3.56), 282nm (sh, 3.09)

Found: C, 62.7; H, 4.3; N, 12.5 $C_{12}H_{10}N_2OS$
requires: C, 62.6; H, 4.4; N, 12.2%

5a-cyano-5a,6-dihydro-11-oxo-11H-benzothiazolo[3,2-b]isoquinoline (121)

3-(2-Chloromethylbenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92f)(0.63g, 2mmol) in dry dimethylformamide (10ml) was added dropwise to a stirred solution of sodium hydride (0.15g of 50% oil dispersion to give 0.075g of NaH) in DMF (5ml) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for two hours under these conditions and then at room temperature overnight, still under a nitrogen atmosphere. A yellow precipitate was obtained on pouring the reaction mixture on to crushed ice (ca. 30g), which was filtered and dried. Recrystallisation from ethyl acetate gave the title compound (121) as yellow prisms (0.42g, 76%), m.p. 157-159°C.

$\nu_{max}$ (KBr), 2220 (C≡N), 1665cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.70-7.25(8H, m, aromatic)
4.15-3.65 (2H, q, aliphatic)

m/z, 278.0508 ($M^{\cdot+}$ 7.2%, $C_{16}H_{10}N_2OS$ requires 278.0514),
251 (100%, $M^+$ -[HCN])

$\lambda_{max}$ (EtOH), 241 (log ε 3.89), 280 (3.57), 315nm (3.45)

Found: C, 68.7; H, 3.6; N, 10.0 $C_{16}H_{10}N_2OS$
requires: C, 69.05; H, 3.6; N, 10.1%

(ii) Intermolecular alkylation of benzothiazole Reissert compounds (92)

General Procedure (E)

The Reissert compound (92) in dry dimethylformamide was added dropwise to a well stirred solution of sodium hydride and alkyl halide in dry dimethylformamide under a nitrogen atmosphere. The mixture was stirred at 0°C for one hour and then overnight at room temperature. After this time, the reaction mixture was poured into ice cold water with stirring. The oily residues obtained were extracted with dichloromethane and the extract was washed several times with water before drying over anhydrous magnesium sulphate. On evaporation of the solvent, the residue was either recrystallised from an appropriate solvent or purified by flash column chromatography to give the alkylated Reissert compound (124).

3-(4-Chlorobenzoyl)-2-cyano-2,3-dihydro-2-methylbenzothiazole (124a)

Use of 3-(4-chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92b)(0.6g, 2mmol) in DMF (15ml), sodium hydride (0.1g of 50% oil dispersion to give 0.05g, 2mmol of NaH) in DMF (5ml) and methyl iodide (1.42g, 10mmol) in the general procedure (E) gave the title compound (124a) after purification by flash column chromatography, using 15% ethyl acetate and 85% petroleum ether (b.p. 40-60°C) as eluent. Yield of (124a) was (0.34g, 55%), m.p. 118-120°C.

$\nu_{max}$ (KBr), 2223 (C≡N), 1662cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.50-6.65 (8H, m, aromatic),
2.20 (3H, s, $CH_3$)

m/z, 316.0244($M^+$ 1.85%, $C_{16}H_{11}N_2OS^{37}Cl$ requires 316.0251)
, 314.0279($M^+$ 4.63%, $C_{16}H_{11}N_2OS^{35}Cl$ requires 214.0281)
, 139 (100%, 4-$ClC_6H_4CO$)

Found: C, 60.9; H, 3.45; N, 8.8 $C_{16}H_{11}N_2OSCl$
requires: C, 61.05; H, 3.5; N, 8.9%

2-Cyano-2,3-dihydro-3-methoxycarbonyl-2-methylbenzothiazole (124b)

Use of 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)(1.1g, 5mmol) in DMF (15ml), sodium hydride (0.18g of 80% oil dispersion to give 0.144g, 6mmol of NaH) in DMF (5ml) and methyl iodide (2.84g, 20mmol) in the general procedure (E) gave a brown oil. This was purified by flash column chromatography using a column with 20mm diameter and 15% ethyl acetate 85% petroleum ether (b.p. 40/60) as eluent. The title compound (124b) was obtained after recrystallisation from petroleum ether (40/60) as colourless plates (1g, 85%), m.p. 63-65°C.

$\nu_{max}$ (KBr), 2248 (C≡N), 1728$cm^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.95-7.10 (4H, m, aromatic), 4.02
(3H, s, OMe), 2.25 (3H, s, Me)

m/z, 234.0464 ($M^+$46%, $C_{11}H_{10}N_2O_2S$ requires 234.0463)
175 (100%, $M^+$ - $CO_2Me$), 149 (95%, $C_8H_7NS$),
134 (16%, $C_7H_4NS$), 59 (26%, $CO_2Me$)

Found: C, 56.65; H, 4.3; N, 11.9 $C_{11}H_{10}N_2O_2S$
requires: C, 56.4; H, 4.3; N, 12.0%

2-Benzyl-2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (124c)

Use of 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)(0.88g, 4mmol) in DMF (15ml), sodium hydride (0.12g of 80% oil dispersion to give 0.096g, 4mmol of NaH) in DMF (5ml) and benzyl bromide (1.71g, 10mmol) in the general procedure (E) gave the title compound (124c) as light yellow needles after recrystallisation from ethyl acetate (0.78g, 63%), m.p. 112-114°C).

$\nu_{max}$ (KBr), 2255 (C≡N), 1728cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.80-7.05 (9H, m, aromatic), 4.01 (3H, s, OMe), 3.7 (2H, s, $CH_2$)

m/z, 310.0772 ($M^+$ 2.8%, $C_{17}H_{14}N_2O_2S$ requires 310.0776)
175 (100%, $C_9H_7N_2S$), 91 (40%, $CH_2Ph$)

Found: C, 65.8; H, 4.7; N, 8.9 $C_{17}H_{14}N_2O_2S$
requires: C, 65.8; H, 4.55; N, 9.0%

(iii) Base catalysed hydrolysis reactions

Formation of 2-methylbenzothiazole (125)

(a) From alkylated Reissert compound (124a)

3-(4-Chlorobenzoyl)-2-cyano-2,3-dihydro-2-methylbenzothiazole (124a)(0.46g, 1.5mmol), ethanol (10ml) and aqueous potassium

hydroxide (15%, 10ml) was refluxed for two hours. The reaction mixture was cooled and diluted with water (10ml). Most of the ethanol was evaporated under reduced pressure and the aqueous solution brought to pH7 with dilute hydrochloric acid. The neutralised solution was extracted with dichloromethane (2 x 20ml) and the combined extracts were washed with water, dried over anhydrous magnesium sulphate and filtered. Evaporation of the solvent gave a yellow oil, which, on purification by preparative tlc using 25:75 of ethyl acetate and petroleum ether (40/60) as eluent, gave 2-methylbenzothiazole (125) as a colourless oil (0.062g, 30%), b.p. 95°C/5mmHg, lit[149] 150°C/15mmHg.

The infrared[150a] and proton nmr[150b] were identical to those of the commercial sample of 2-methylbenzothiazole.

$\delta_H$ (60MHz, $CDCl_3$), 7.65-7.10 (4H, m, aromatic), 2.90 (3H, s, $CH_3$)

(b) <u>From alkylated Reissert compound (124b)</u>

Use of 2-cyano-2,3-dihydro-3-methoxycarbonyl-2-methyl-benzothiazole (124b)(0.4g, 1.7mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the same procedure as used for the hydrolysis of (124a), gave 2-methylbenzothiazole (125) as a colourless oil (0.092g, 35%), b.p. 95°C/5mmHg. The ir and pmr were identical to those of the commercial sample.

$\delta_H$ (60MHz, $CDCl_3$), 7.70-7.05 (4H, m, aromatic), 2.80 (3H, s, $CH_3$)

2-Benzylbenzothiazole (126)

Use of 2-benzyl-2-cyano-2,3-dihydro-3-methoxycarbonyl-benzothiazole (124c)(0.31g, 1mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the same procedure as used for the hydrolysis of (124a) gave 2-benzylbenzothiazole (126) as light yellow needles after purification by preparative tlc using 20:80 of ethyl acetate and petroleum ether (40/60) as eluent. Yield of (126) was (0.051g, 23%) m.p. 108-111°C, lit[101] 112°C.

$\delta_H$ (90MHz, $CDCl_3$), 8.20-7.48 (9H, m, aromatic),
4.51 (2H, s, $CH_2$)

Formation of 2-aminothiophenol (127)

(a) From 2-cyano-2,3-dihydro-3-(4-methylbenzoyl)benzothiazole (92a)

Use of compound (92a)(0.5g, 1.8mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the same procedure as used for the hydrolysis of (124a) gave 2-aminophenol (127) after the work-up. The product had a characteristic smell and was obtained in 46% yield, m.p. 17-20°C, lit[106] 19-21°C. The ir and pmr spectra were identical to those of the commercial sample of 2-aminophenol.

$\nu_{max}$($CHCl_3$), 3500 and 3300 (NH), 1610$cm^{-1}$ (NH and aromatic CH)

$\delta_H$ (60MHz, $CDCl_3$), 7.25-6.50 (4H, m, aromatic),
4.20 (2H, br, $NH_2$)

The presence of the thiophenol (127) was further confirmed by the preparation of its salt from hydrochloric acid. 2-Aminothiophenol (127) was heated gently with concentrated HCl and allowed to cool on standing. Yellow needles were formed which were filtered and dried. The crystals were subsequently found to have a decomposition temperature of 210°C, lit[107] 216°C.

(b) From 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)

Use of compound (92e)(0.43g, 1.94mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the same procedure as used for the hydrolysis of (124a), gave 2-aminothiophenol (127) in 70% yield, m.p. 18-20°C, lit[106] 19-21°C. The ir and pmr spectra were identical to those of the commercial sample.

Base-catalysed hydrolysis at room temperature

General Procedure (F)

Reissert compound, ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) were stirred at room temperature for 15 hours before dilution with water (10ml). Most of the ethanol was evaporated under reduced pressure and the aqueous solution brought to pH7 with dilute hydrochloric acid. The neutralised solution was extracted with dichloromethane (2 x 20ml) and the organic extracts washed with water before drying over anhydrous magnesium sulphate. Evaporation of the solvent gave a residue which was purified by distillation or recrystallisation.

Formation of benzothiazole (91)

(a) From 2-cyano-2,3-dihydro-3-(4-methylbenzoyl)benzothiazole (92a)

Use of compound (92a)(0.5g, 1.8mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the general procedure (F) gave benzothiazole (0.12g, 50%), b.p. 90°C/5mmHg, lit[151] 119-20°C/25mmHg. The ir and pmr spectra were identical to those of a commercial sample of benzothiazole.

(b) From 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)

Use of compound (92e)(0.4g, 1.8mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the general procedure (F) gave benzothiazole (0.098g, 41%), b.p. 90°C/5mmHg. The ir and pmr spectra were identical to those of a commercial sample of benzothiazole.

Formation of 2-methylbenzothiazole (125)

Use of 2-cyano-2,3-dihydro-3-methoxycarbonyl-2-methyl-benzothiazole (124b)(0.4g, 1.7mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the general procedure (F) yielded 2-methylbenzothiazole (125)(0.15g, 61%), b.p. 95°C/5mmHg. The ir and pmr spectra were identical to those of a commercial sample of (125).

$\delta_H$ (60MHz,$CDCl_3$), 7.60-7.05 (4H,m,aromatic),2.85 (3H,s,$CH_3$)

Formation of 2-benzylbenzothiazole (126)

Use of 2-benzyl-2-cyano-2,3-dihydro-3-methoxycarbonyl-benzothiazole (124c)(0.5g, 1.6mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the general procedure (F), yielded 2-benzylbenzothiazole (126) after recrystallisation from ethyl acetate - petroleum ether (40-60), (0.19g, 53%), m.p. 107-110°C, lit[101] 112°C.

$\delta_H$ (90MHz,$CDCl_3$), 8.30-7.50 (9H,m,aromatic), 4.40(2H,s,$CH_2$)

(iv) Retro-Reissert reaction with chloroformate derived substrates using carboxylic acids

General Procedure (G)

A mixture of the Reissert compound (2.7mmol) and acid (n-hexanoic, cyclohexanecarboxylic or benzoic)(5.4mmol) was heated at an oil bath temperature of 130-140°C for 4 hours. The reaction mass was cooled, dissolved in chloroform (30ml), and washed with 20% sodium hydroxide (50ml). The chloroform layer was extracted with 50% hydrochloric acid (50ml) and this acid layer was subsequently brought up to pH7 with sodium hydroxide solution. The neutralised solution was extracted with chloroform (2 x 50ml) and dried over anhydrous magnesium sulphate. Concentration of the solvent gave the aromatic heterocycle.

Formation of benzothiazole (91)

(a) Use of 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)(0.6g, 2.7mmol) and n-hexanoic acid (0.63g, 5.4mmol) in

the general procedure (G) gave benzothiazole in 53% yield, b.p. 90°C/5mmHg, lit[151] 119-20°C/25mmHg. The ir and pmr spectra were identical to those of a commercial sample of benzothiazole.

(b) Use of 2-cyano)2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)(0.6g, 2.7mmol) and cyclohexanecarboxylic acid (0.69g, 5.4mmol) in the general procedure (G) gave benzothiazole in 39% yield, b.p. 90°C/5mmHg. The ir and pmr spectra were identical to those of a commercial sample of benzothiazole.

(c) Use of 2-cyano-2,3-dihydro-3-methoxycarbonylbenzothiazole (92e)(0.6g, 2.7mmol) and benzoic acid (0.66g, 5.4mmol) in the general procedure (G) gave benzothiazole in 35% yield, b.p. 90°C/5mmHg. The ir and pmr spectra were identical to those of a commercial sample of benzothiazole.

Formation of 2-methylbenzothiazole (125)

Use of 2-cyano-2,3-dihydro-3-methoxycarbonyl-2-methyl-benzothiazole (124b)(0.63g, 2.7mmol) and n-hexanoic acid (0.63g, 5.4mmol) in the general procedure (G) gave 2-methylbenzothiazole (125) in 59% yield, b.p. 95°C/5mmHg, lit[149] 150°C/15mmHg. The ir and pmr spectra were identical to the authentic sample of (125).

$\delta_H$ (60MHz,$CDCl_3$), 8.02-7.20(4H,m,aromatic), 2.80 (3H,s,$CH_3$)

(v) Benzothiazole Reissert compound cleavage with phosphorus pentachloride: formation of 2-cyanobenzothiazole (138)

The Reissert compound 3-(4-chlorobenzoyl)-2-cyano-2,3-dihydrobenzothiazole (92b)(0.5g, 1.7mmol) was heated with phosphorus pentachloride (0.5g) at an oil bath temperature of 130-135°C for two hours. The reaction mixture was cooled, dissolved in chloroform (15ml) and treated with water (15ml). The chloroform layer was washed with dilute aqueous sodium hydroxide and then water before drying over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave a brown solid which showed two components on analytical tlc. Separation by preparative tlc (2 x 1m silica gel plates) using 10:90 of ethyl acetate and petroleum ether (40/60) gave 2-cyanobenzothiazole (138) as the first fraction (0.15g, 56%), m.p. 72-75°C, lit[116] 71-73°C.

$\nu_{max}$ (KBr), 2220cm$^{-1}$ (C≡N)

$\delta_H$ (90MHz, $CDCl_3$), 8.35-7.58 (4H, m, aromatic)

m/z, 160.0086 ($M^+$ 100%, $C_8H_4N_2S$ requires 160.0095)
108 (42%, $M^+ - C_2N_2$)

(vi) Attempted 1,2-rearrangement reaction

2-Cyano-2,3-dihydro-3-(4-nitrobenzoyl)benzothiazole (92c) (0.5g, 0.0016mol) in dry dimethylformamide (10ml) was added dropwise to a well stirred solution of 50% oil dispersion of

sodium hydride (0.15g, to give 0.077g, 0.0032mol of NaH) in dry DMF (5ml) under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for six hours before pouring on to ice-water (ca. 30g). The organic material was extracted with dichloromethane (2 x 30ml) and the combined extracts were washed several times with water before drying over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave a red gum which, on analytical tlc, indicated the presence of several components. Preparative tlc (2 x 1m silica gel plates) using a 40:60 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C) yielded a light orange amorphous solid (49mg) which could not be satisfactorily purified. This material was subsequently identified as 2-(4-nitrobenzoyl)benzothiazole (140a) from spectral data, yield 11%.

$\nu_{max}$ ($CHCl_3$), 1685 (C=0), 1330 and 1285$cm^{-1}$ (N=0)

$\delta_H$ (90MHz, $CDCl_3$), 7.75-7.10 (8H,m,aromatic)

m/z, 284.0264 ($M^{\ddagger}$ 0.11%, $C_{14}H_8N_2O_3S$ requires 284.0256),
104 (100%, $C_6H_4CO$), 76 (30%, $C_6H_4$)

## CHAPTER 3 INDAZOLE REISSERT COMPOUNDS

### Part I: The Synthesis of Reissert Compounds from Indazoles

#### 1,2-Bis(4-chlorobutanoyl)-3-cyano-2,3-dihydroindazole (152)

To a well stirred solution of indazole (0.83g, 7mmol) in dry dichloromethane (25ml) and trimethylsilyl cyanide (1.4g, 1.9ml, 14mmol) was added anhydrous aluminium chloride (0.1g). 4-Chlorobutanoyl chloride (2g, 14mmol) in dry dichloromethane (15ml) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 72 hours. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane layer was dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure to give an oil. This was purified by distillation to yield the title compound (152) (1.63g, 66%), b.p. 85°C/10mmHg. The product gave a single spot on analytical tlc.

$\nu_{max}$ (liquid film), 2230 (C≡N), 1715cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.5 (1H, br. s, C-7H),
8.12-7.3 (4H, m, aromatic & C-3H),
3.88-3.72 (4H, 2 x t, $C\underline{H}_2$-Cl),
3.58-3.40 (4H, 2 x t, $COC\underline{H}_2$),
2.54-2.18 (4H, m, -$\underline{C}H_2$-)

Found: C, 54.6; H, 5.0; N, 12.2 $C_{16}H_{17}N_3O_2Cl_2$
requires: C, 54.25; H, 4.8; N, 11.9%

m/z, 357, 355 and 353 ($M^+$ 0%), 224 (4%, $C_{11}H_{11}N_2O^{37}Cl$), 222 (11%, $C_{11}H_{11}N_2O^{35}Cl$), 117 (100%, $C_7H_5N_2$)

1,2-Bis(2-chloromethylbenzoyl)-3-cyano-2,3-dihydroindazole (153)

Use of indazole (0.83g, 7mmol), trimethylsilyl cyanide (1.4g, 1.9ml, 14mmol), anhydrous aluminium chloride (0.1g) and 2-chloromethylbenzoyl chloride (2.6g, 14mmol) as in the above procedure for the preparation of compound (152), gave the title compound (153) as pale yellow needles after recrystallisation from ethyl acetate. Yield (1.3g, 40%), m.p. 86-89°C, the product also gave a single spot on analytical tlc.

$\nu_{max}$ (KBr), 2220 (C≡N), 1685$cm^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.7 (1H, br.s, C-7H),
8.22-7.33 (12H, m, aromatic & C-3H),
5.06 (2H, s, $CH_2$), 4.8 (2H, s, $CH_2$)

Found: C, 63.95; H, 3.9; N, 9.0 $C_{24}H_{17}N_3O_2Cl_2$
requires: C, 64.0; H, 3.8; N, 9.3%

m/z, 449, 451 and 453 ($M^+$0%), 272 (30%, $C_{15}H_{11}N_2O^{37}Cl$)
270(100%,$C_{15}H_{11}N_2O^{35}Cl$),153(62%,2-$ClCH_2C_6H_4CO$)
117(20%, $C_7H_5N_2$)

1-(4-Chlorobutanoyl)indazole (154)

Trimethylsilyl cyanide (1.39g, 1.9ml, 14mmol) was added to a well stirred solution of indazole (0.825g, 7mmol) in dry dichloro-

methane (25ml) with anhydrous aluminium chloride (0.1g). 4-Chlorobutanoyl chloride (2g, 14mmol) in dry dichloromethane (15ml) was added dropwise over 10 minutes and the reaction mixture was stirred at room temperature for 72 hours. The solution was washed with 5% hydrochloric acid, water, 5% sodium hydroxide and water. The organic layer was dried over anhydrous magnesium sulphate. After filtering, dichloromethane was removed in vacuo to give a yellow oil which solidified on cooling in an ice-bath. Recrystallisation from ethyl acetate yielded the title compound (154) (1.3g, 85%), as colourless needles, m.p. 28-29°C.

$\nu_{max}$ ($CHCl_3$), 1710$cm^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.55 (1H, br.s, C-7H), 8.22 (1H, s, C-3H),
7.87-7.34 (3H, m, aromatic),
3.86-3.70 (2H, t, $CH_2$-Cl),
3.56-3.40 (2H, t, $CH_2$-CO),
2.50-2.20 (2H, quintet, -$CH_2$-)

m/z, 224.0535 ($M^{\ddagger}$ 1.5%, $C_{11}H_{11}N_2O^{37}Cl$ requires 224.0530),
222.0563 ($M^{\ddagger}$ 4.45%, $C_{11}H_{11}N_2O^{35}Cl$ requires 222.0559),
117 (100%, $C_7H_5N_2$)

Found: C, 59.4; H, 5.2; N, 12.3 $C_{11}H_{11}N_2OCl$
requires: C, 59.3; H, 5.0; N, 12.6%

1-Butanoylindazole (162)

Use of indazole (0.83g, 7mmol), trimethylsilyl cyanide (1.4g, 1.9ml, 14mmol), anhydrous aluminium chloride (0.1g) and butanoyl

chloride (1.5g, 14mmol) as in the procedure for the preparation of compound (154) led to the formation of a light yellow oil. Flash column chromatography[63] using a column with 30mm diameter and 20% ethyl acetate, 80% petroleum ether (40/60) as the eluent, the title compound (162) was isolated in 38% yield as colourless prisms, m.p. 34-36°C.

$\nu_{max}$ (KBr), 1713cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.58 (1H, br, C-7H), 8.18 (1H, s, C-3H), 7.85-7.30 (3H, m, aromatic), 3.32-3.16 (2H, t, CO-C$\underline{H}_2$), 2.13-1.70 (2H, sextet, C-C$\underline{H}_2$-C), 1.18-1.00 (3H, t, $CH_3$)

m/z, 188.0956 ($M^+$ 13.6%, $C_{11}H_{12}N_2O$ requires 188.0950)
117 (100%, $C_7H_5N_2$)

Found: C, 70.4; H, 6.6; N, 14.95 $C_{11}H_{12}N_2O$
requires: C, 70.2; H, 6.4; N, 14.9%

1-Benzoyl-5-nitroindazole (164)

To a well stirred solution of 5-nitroindazole (1.14g, 7mmol) in dry dichloromethane (25ml) and trimethylsilyl cyanide (1.4g, 1.9ml, 14mmol) was added anhydrous aluminium chloride (0.1g). Benzoyl chloride (2g, 14mmol) in dry dichloromethane (15ml) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 72 hours before the solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and

water. The dichloromethane was dried over anhydrous magnesium sulphate and filtered. Evaporation of the solvent gave a solid which, on recrystallisation from ethyl acetate, gave the title compound (164) as cream-coloured plates. Yield of the product (1.5g, 79%), m.p. 205-207°C, lit[127] 192-193°C.

$\nu_{max}$(KBr), 1695 (C=O), 1600 (C=C), 1520 & 1350cm$^{-1}$($NO_2$conj)

$\delta_H$ (90MHz, $CDCl_3$), 8.95-8.10 (4H, m, aromatic),
7.90-7.35 (5H, m, aromatic ($C_6H_5$))

m/z, 267.0661 ($M^+$ 18%, $C_{14}H_9N_3O_3$ requires 267.0659)
105 (100%, $C_6H_5CO$), 77 (33%, $C_6H_5$)

Found: C, 63.0; H, 3.1; N, 15.2 $C_{14}H_9N_3O_3$
requires: C, 62.9; H, 3.4; N, 15.7%

1-(4-Chlorobutanoyl)-5-nitroindazole (166)

A mixture of potassium cyanide (7.8g, 0.12mol) and benzyltriethylammonium chloride (0.4g; 5% mole of KCN) in water (15ml) was added to a well stirred solution of 5-nitroindazole (6.5g, 0.04mol) in dichloromethane (70ml). 4-Chlorobutanoyl chloride (11.3g, 0.08mol) in dichloromethane (15ml) was added dropwise over 15 minutes. The reaction mixture changed to a dark brown colour on addition of the acid chloride, but was allowed to stir at room temperature for 16 hours before the two layers were separated. The organic layer was washed with water, 5% hydrochloric acid, water and 5% sodium hydroxide before drying

over anhydrous magnesium sulphate. Evaporation of the solvent gave a dark brown solid which was subsequently purified by flash column chromatography,[63] using 40% ethyl acetate 60% petroleum ether (40/60) as the eluent. The title compound (166) was obtained as colourless plates, yield (9.4g, 88%), m.p. 116-118°C.

$\nu_{max}$ (KBr), 1720 (C=O), 1515 & 1360cm$^{-1}$ ($NO_2$conj)

$\delta_H$ (90MHz, $CDCl_3$), 8.5-8.10 (4H, m, aromatic), 3.80-3.60 (2H, t, $C\underline{H}_2$-Cl), 3.50-3.30 (2H,t,CO-$C\underline{H}_2$), 2.55-2.10 (2H, m, C-$C\underline{H}_2$-C)

m/z,269.0267($M^{\cdot+}$2.95%,$C_{11}H_{10}N_3O_3$ $^{37}Cl$ requires 269.0381)
267.0405($M^{\cdot+}$7%, $C_{11}H_{10}N_3O_3$ $^{35}Cl$ requires 267.0411)
162 (100%, 5-$O_2N$-$C_7H_4N_2$)

Found: C, 49.5; H, 3.7; N, 15.7 $C_{11}H_{10}N_3O_3Cl$
requires: C, 49.4; H, 3.8; N, 15.7%

## Part II: 1-Methylindazole Reissert Compounds

### (i) The synthesis of 1-methylindazole Reissert Compounds

#### (a) Methylation of indazole (151) to 1-methylindazole (167) and 2-methylindazole (168)

A mixture of indazole (5g, 0.0425mol), methyl iodide (15g, 0.11mol) and potassium hydroxide (5g, 0.085mol) in methanol (50ml) was heated under reflux for four hours. After cooling, the reaction mixture was diluted with water (50ml). The mixture was extracted with dichloromethane (2 x 50ml) and dried over anhydrous magnesium sulphate. A portion of the dichloromethane solution was evaporated and directly investigated by 'Hnmr spectroscopy; the presence of two N-methyl resonances was evident. Analytical tlc of the crude product also showed the presence of two components.

Flash column chromatography[63] was employed to separate the two products. The eluent used was a 50:50 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C).

The first fraction collected was 1-methylindazole (167) (3.1g, 55%) as colourless needles m.p. 60-62°C, lit[129] 61°C.

$\delta_H$ (90MHz, $CDCl_3$), 8.02 (1H,s,H-3), 7.83-7.75(1H,d,H-4), 7.48 (1H,br.s,H-7), 7.40-7.38(1H,m,H-6), 7.35-7.10 (1H,m,H-5), 4.15 (3H,s,N-Me)

The second fraction was 2-methylindazole (168) obtained in a yield of (1.9g, 34%) as cream-coloured plates, m.p. 47-49°C, lit[129] 56°C.

$\delta_H$ (90MHz, $CDCl_3$), 7.90-7.82(1H,d,H-7), 7.73-7.66(1H,d,H-3),
7.43-7.02(3H,m,aromatic)
4.00 (3H,s,N-Me)

Methylation of 5-nitroindazole to 1-methyl-5-nitroindazole (169) and 2-methyl-5-nitroindazole (170) by the above procedure yielded two products after flash column chromatography[63] using a 50:50 mixture of ethyl acetate and petroleum ether (40/60).

The first fraction was 1-methyl-5-nitroindazole (169) obtained as yellow needles (0.84g, 39%), m.p. 155-158°C, lit[129] 154°C.

$\delta_H$(90MHz, $CDCl_3$), 8.78(1H,d,H-4), 8.40-8.25(1H,q,H-6)
8.23(1H,s,H-3), 7.56-7.46(1H,d,H-7)
4.18(3H,s,N-Me)

The second fraction was 2-methyl-5-nitroindazole (170) obtained as yellow needles, (0.75g, 35%), m.p. 135-137°C, lit[129] 130°C.

$\delta_H$ (90MHz, $CDCl_3$), 8.78(1H, d, H-4), 8.26(1H, s, H-3)
8.23-8.08 (1H, q, H-6), 7.83-7.72
(1H, d, H-7), 4.31 (3H, s, N-Me)

(b) Formation of Reissert compounds from 1-methylindazole (167)

General Procedure (H)

To a well stirred solution of 1-methylindazole in dry dichloromethane (25ml) and trimethylsilyl cyanide was added

anhydrous aluminium chloride (0.1g). The chloroformate in dry dichloromethane (15ml) was added dropwise over 10 minutes and the reaction mixture stirred at room temperature for 72 hours. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane layer was dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure and the crude product was purified by means of preparative tlc (silica gel) using an appropriate solvent system.

3-Cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a)

Use of 1-methylindazole (1.1g, 8.3mmol), trimethylsilyl cyanide (1.04g, 1.4ml, 10mmol), anhydrous aluminium chloride (0.1g) and methyl chloroformate (0.94g, 10mmol) in the general procedure (H) yielded a crude product which showed two spots on analytical tlc.

Preparative tlc (4 x 1m silica gel plates) using a 20:80 mixture of ethyl acetate and petroleum ether (40/60) gave two fractions.

The first fraction collected was found to be recovered starting 1-methylindazole (0.15g).

The second fraction yielded the title compound (171a) as colourless prisms (1.2g, 57%), m.p. 141-143°C.

$\nu_{max}$ (KBr), 2215 (C≡N), 1730cm$^{-1}$ (C=O)

$\delta_H$ (90MHz,$CDCl_3$), 7.55-6.95 (4H,m,aromatic), 6.0 (1H,s,C-3H), 3.92 (3H,s,OMe), 3.20(3H,s,N-Me)

m/z, 217.0857($M^+$ 27%, $C_{11}H_{11}N_3O_2$ requires 217.0851),
158 (100%, $M^+ - CO_2Me$), 132 (53%, $C_8H_8N_2$)

Found: C, 61.0; H, 5.1; N, 19.4 $C_{11}H_{11}N_3O_2$
requires: C, 60.8; H, 5.1; N, 19.3%

3-Cyano-2,3-dihydro-2-ethoxycarbonyl-1-methylindazole (171b)

Use of 1-methylindazole (1.5g, 11.4mmol), trimethylsilyl cyanide (1.5g, 2ml, 13.7mmol), anhydrous aluminium chloride (0.1g) and ethyl chloroformate (1.5g, 13.7mmol) in the general procedure (H) yielded a crude product which showed two components on analytical tlc.

Preparative tlc (4 x 1 m silica gel plates) using a 20:80 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C) enabled the separation of the two components.
The first fraction was recovered 1-methylindazole (0.4g).
The second fraction collected was found to be the title compound (171b), obtained as colourless rhombs (0.45g, 17%), m.p. 118-120°C.

$\nu_{max}$ (KBr), 2210 (C≡N), 1735$cm^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 8.20-7.00(4H,m,aromatic), 5.98(1H,s,C-3H),
4.50-4.25 (2H,q,$C\underline{H}_2$),
3.20 (3H,s,N-Me), 1.45-1.30 (3H,t,$C\underline{H}_3$)

m/z, 231.0999 ($M^+$ 19%, $C_{12}H_{13}N_3O_2$ requires 231.1008)
158 (100%, $M^+ - CO_2Et$)

Found: C, 62.2; H, 5.7; N, 18.0 $C_{12}H_{13}N_3O_2$
requires: C, 62.3; H, 5.7; N, 18.2%

3-Cyano-2,3-dihydro-1-methyl-2-phenoxycarbonylindazole (171c)

Use of 1-methylindazole (0.8g, 6mmol), trimethylsilyl cyanide (0.74g, 1ml, 7.3mmol), anhydrous aluminium chloride (0.1g) and phenyl chloroformate (1.14g, 7.3mmol) in the general procedure (H) yielded a crude product which showed two components on analytical tlc.

Preparative tlc (4 x 1m silica gel plates) using a 50:50 mixture of ethyl acetate: petroleum ether (40/60) gave separation of the two components.

The first fraction was found to be the title compound (171c) obtained as colourless prisms (0.54g, 32%), m.p. 114-117°C.

$\nu_{max}$ (KBr), 2230 (C≡N), 1730cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.50-6.75 (9H,m,aromatic),
6.10 (1H,s,C-3H), 3.23 (3H,s,N-Me)

m/z, 279.1013 ($M^+$ 27%, $C_{16}H_{13}N_3O_2$ requires 279.1008)
158 (100%, $M^+$ - $CO_2Ph$), 77 (18%, $C_6H_5$)

Found: C, 68.9; H, 4.7; N, 15.0 $C_{16}H_{13}N_3O_2$
requires: C, 68.8; H, 4.7; N, 15.05%

The second fraction was found to be recovered 1-methylindazole (0.24g).

(c) The use of tri-n-butyltin cyanide as an alternative cyanating reagent

3-Cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a)

1-Methylindazole (0.33g, 2.5mmol) and tri-n-butyltin cyanide (1.58g, 5mmol) were dissolved in dry dichloromethane (20ml) and stirred in the presence of aluminium chloride (0.05g). Methyl chloroformate (0.47g, 2.5mmol) in dichloromethane (10ml) was added dropwise to the reaction mixture. After stirring at room temperature for 72 hours, the reaction mixture was washed with water, 5% hydrochloric acid, water and 5% sodium hydroxide and water before the organic layer was dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave an oil which showed two major components on analytical tlc.

Flash column chromatography was used to separate the two fractions and the eluent was a 20:80 mixture of ethyl acetate: petroleum ether (b.p. 40-60$^{o}$C).
The first fraction collected was found to be recovered 1-methylindazole (0.28g, 85%). The second fraction was the title compound (171a), but proton nmr of this still showed the presence of impurities from the butyl groups of the tin reagent. Preparative tlc (1m silica gel plate) was used with a 20:80 mixture of ethyl acetate: petroleum ether (b.p. 40-60$^{o}$C) as the solvent system, to purify the Reissert compound. 3-Cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a) was obtained in 6% yield, m.p. 140-142$^{o}$C, identical with the sample we had prepared previously (p.182).

$\nu_{max}$ (KBr), 2315 (C≡N), 1720cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.60-6.90 (4H,m,aromatic), 6.00 (1H, s,C-3H), 3.91 (3H,s,OMe), 3.20 (3H,s,N-Me)

(d) Attempted synthesis of Reissert compound from 1-methylindazole under two-phase reaction conditions

A mixture of potassium cyanide (2.22g, 0.034mol) and benzyltriethylammonium chloride (0.11g, 5% mol of KCN) in water (10ml) was added to a well stirred solution of 1-methylindazole (1.5g, 0.011mol) in dichloromethane (20ml). Methyl chloroformate (2.70g, 0.028mol) in dichloromethane (10ml) was added dropwise over 10 minutes. The reaction mixture changed to a dark brown colour on addition of the chloroformate, but was allowed to stir at room temperature for 72 hours before the two layers were separated. The organic layer was washed with water, 5% hydrochloric acid, water and 5% sodium hydroxide and water before drying over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure gave a brown solid which, on recrystallisation from ethyl acetate/petroleum ether (b.p. 40-60°C), was found to be recovered 1-methylindazole (90%), m.p. 61-63°C, lit[129] 61°C.

1-Methylindazole was also recovered (87%) when the reaction was repeated but with heating under reflux for two hours before stirring at room temperature for 15 hours.

(ii) Alkylation of 1-methylindazole Reissert compounds

3-Cyano-2,3-dihydro-1,3-dimethyl-2-methoxycarbonylindazole (175)

A solution of 3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a)(0.3g, 1.4mmol) in dry dimethylformamide (10ml) was added dropwise to a well stirred solution of sodium hydride (0.067g of 50% oil dispersion to give 0.033g, 1.4mmol of NaH) and methyl iodide (1g, 7mmol) in dry DMF (5ml), under a nitrogen atmosphere. The orange-coloured reaction mixture was stirred at 0°C for two hours and at room temperature for a further 24 hours. After this time, the reaction mixture was poured on to ice-water (ca. 25g). No precipitate was formed and so the mixture was extracted with dichloromethane (2 x 25ml). The organic layer was washed several times with water before drying over anhydrous magnesium sulphate. On evaporation of the solvent under reduced pressure, a light yellow oil was obtained. Preparative tlc (2 x 1m silica gel plates) with a 20:80 mixture of ethyl acetate: petroleum ether (b.p. 40-60°C) as the solvent system was used to purify the oil.

The title compound (175) was obtained pure in 56% yield, m.p. 68-70°C.

$\nu_{max}$ (KBr), 2300 (C≡N,w) 1718cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.35-6.65 (4H,m,aromatic),
3.85 (3H,s,$OCH_3$), 3.10 (3H,s,$NCH_3$)
2.05 (3H,s,C-$3CH_3$)

m/z, 231.1000 ($M^{+}$ 20.8%, $C_{12}H_{13}N_3O_2$ requires 231.1008),
172 (100%, $M^{+}$ - $CO_2Me$), 157 (22%), 146 (65%)

Found: C, 62.2; H, 5.8; N, 18.1 $C_{12}H_{13}N_3O_2$
requires: C, 62.3; H, 5.7; N, 18.2%

3-Benzyl-3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (176)

Use of 3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (171a)(0.22g, 1mmol) in dry DMF (10ml), sodium hydride (0.05g of 50% oil dispersion to give 0.025g, 1mmol of NaH) and benzyl bromide (0.85g, 5mmol) in dry DMF (15ml) by the above procedure gave an oil which, on purification by preparative tlc (2 x 1m silica gel plates) using a 20:80 mixture of ethyl acetate: petroleum ether (b.p. 40-60°C) as the eluent, yielded the title compound (176) (0.27g, 89%), m.p. 112-114°C.

$\nu_{max}$ (KBr), 1720$cm^{-1}$ (C=0)

$\delta_H$ (90MHz, $CDCl_3$), 7.25-6.45 (9H,m,aromatic),
3.85 (3H,s,$OCH_3$), 3.55 (2H,s,$C\underline{H}_2$)
3.10 (3H,s,$NCH_3$)

m/z, 307.1310 ($M^{+}$ 7.2%, $C_{18}H_{17}N_3O_2$ requires 307.1321),
281 (19%, $M^{+}$ - CN), 216 (100%, $M^{+}$ -$CH_2Ph$)

Found: C, 70.6; H, 5.65; N, 13.7 $C_{18}H_{17}N_3O_2$
requires: C, 70.3; H, 5.6; N, 13.7%

(iii) Base-catalysed hydrolysis reactions

(a) Using 15% potassium hydroxide in aqueous ethanol

Formation of 1,3-dimethylindazole (177)

3-Cyano-2,3-dihydro-1,3-dimethyl-2-methoxycarbonylindazole (175)(0.2g, 0.87mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) were refluxed for two hours. The reaction mixture was cooled and diluted with water (10ml). Most of the ethanol was evaporated under reduced pressure, and the aqueous solution brought to pH7 with dilute hydrochloric acid. The neutralised solution was extracted with dichloromethane (2 x 15ml) and the extracts were washed with water, dried over anhydrous magnesium sulphate and filtered. Evaporation of the solvent gave a pale yellow oil which crystallised on standing. 1,3-Dimethylindazole (177) was obtained as cream-coloured needles after recrystallisation from petroleum ether (40/60)(19mg, 15%), m.p. 35-38°C, lit[129] 35°C.

$\delta_H$ (90MHz, $CDCl_3$), 7.72-7.10 (4H,m,aromatic), 4.00 (3H,s, $N\text{-}CH_3$), 2.57(3H,s,$C\text{-}3CH_3$)

Formation of 3-benzyl-1-methylindazole (178)

Use of 3-benzyl-3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (176)(0.45g, 1.5mmol), ethanol (10ml) and aqueous potassium hydroxide (15%, 10ml) in the above procedure gave a pale yellow oil which showed one spot on analytical tlc. The title compound (178) was obtained in 13% yield after distillation, b.p. 125°C/10mmHg.

$\delta_H$ (90MHz, $CDCl_3$), 7.90-7.20 (9H,m,aromatic),
4.36 (2H,s,$C\underline{H}_2$), 4.05 (3H,s,N-$CH_3$)

m/z, 222.1156 ($M^+$ 53%, $C_{15}H_{14}N_2$ requires 222.1157)
207 (28%, $M^+ - CH_3$), 145 (81%, $M^+ - C_6H_5$),
91 (100%, $C_6H_5CH_2$)

Found: C, 80.5; H, 6.6; N, 12.05 $C_{15}H_{14}N_2$
requires: C, 81.0; H, 6.4; N, 12.3%

(b) Using 30% potassium hydroxide in aqueous ethanol
Formation of 1,3-dimethylindazole (177)

3-Cyano-2,3-dihydro-1,3-dimethyl-2-methoxycarbonylindazole (175)(0.4g, 1.74mmol), ethanol (10ml) and aqueous potassium hydroxide (30%, 10ml) were refluxed for four hours . The reaction mixture was cooled and diluted with water (20ml). Most of the ethanol was evaporated under reduced pressure, and the aqueous solution brought to pH7 with dilute hydrochloric acid. The neutralised solution was extracted with dichloromethane (2 x 25ml) and the extracts were washed with water before drying over anhydrous magnesium sulphate. Evaporation of the solvent gave an oil which solidified on cooling. Recrystallisation from petroleum ether (b.p. 40-60°C) gave 1,3-dimethylindazole as cream-coloured needles (0.1g, 40%), m.p. 34-36°C, lit[129] 35°C. The product gave a single spot on analytical tlc and spectral data were identical to those obtained with the previous sample of (177).

Formation of 3-benzyl-1-methylindazole (178)

Use of 3-benzyl-3-cyano-2,3-dihydro-2-methoxycarbonyl-1-methylindazole (176)(0.61g, 2mmol), ethanol (10ml) and aqueous potassium hydroxide (30%, 10ml) in the above procedure resulted in an oil (0.15g) which was purified by distillation to give 3-benzyl-1-methylindazole (178) in 38% yield, b.p. 125°C/10mmHg. The spectral data of the product from this hydrolysis were identical to those obtained previously.

## PART III 2-Methylindazole Reissert Compounds

### (i) The Synthesis of Benzologous Reissert Compounds

### General Procedure (I)

To a well stirred solution of 2-methylindazole in dry dichloromethane (25ml) and trimethylsilyl cyanide was added anhydrous aluminium chloride (0.1g). The acid chloride in dry dichloromethane (15ml) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 72 hours, after which it was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane layer was dried over anhydrous magnesium sulphate and filtered. After evaporation of the solvent, flash column chromatography with the appropriate eluent was used to isolate the product pure.

### 3-Cyano-2,3-dihydro-1-methoxycarbonyl-2-methylindazole (183a)

Use of 2-methylindazole (1.98g, 0.015mol), trimethylsilyl cyanide (1.78g, 2.40ml, 0.018mol), anhydrous aluminium chloride (0.1g) and methyl chloroformate (1.7g, 0.018mol) in the general procedure (I) gave an oil which was purified by flash column chromatography using ethyl acetate as the eluent. The title compound (183a) was obtained as colourless prisms (1.2g, 38%), m.p. 138-140°C.

$\nu_{max}$ (KBr), 2226 (C≡N,m) 1705cm$^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.87-7.20 (4H,m,aromatic), 5.02(1H,s,C-3H), 4.00 (3H,s,$OCH_3$), 2.80(3H,s,$NCH_3$)

m/z, 217.0853 ($M^+$ 8.6%, $C_{11}H_{11}N_3O_2$ requires 217.0851),
158 (100%, $M^+$ - $CO_2Me$), 132 (25%)

Found: C, 61.1; H, 5.1; N, 19.0 $C_{11}H_{11}N_3O_2$
requires: C, 60.8; H, 5.1; N, 19.3%

3-Cyano-2,3-dihydro-1-ethoxycarbonyl-2-methylindazole (183b)

Use of 2-methylindazole (1.32g, 0.01mol), trimethylsilyl cyanide (1.19g, 1.60ml, 0.012mol), anhydrous aluminium chloride (0.1g) and ethyl chloroformate (1.3g, 0.012mol) in the general procedure (I) gave a crude solid which showed two spots on analytical tlc.

Flash column chromatography was used to separate the components with 50% ethyl acetate 50% petroleum ether (40/60) as the eluent. The first fraction collected was found to be the title compound (183b), obtained as colourless prisms after recrystallisation from ethyl acetate, (1.1g, 48%), m.p. 101-102°C.

$\nu_{max}$ (KBr), 2250 (C≡N, m) 1700$cm^{-1}$ (C=O)

$\delta_H$ (90MHz, $CDCl_3$), 7.80-7.05 (4H,m,aromatic), 5.0(1H,s, C-3H), 4.55-4.10 (2H,q,$C\underline{H}_2$), 2.80 (3H,s,N-$CH_3$), 2.65-1.25 (3H,t, $C\underline{H}_3$)

m/z, 231.1004 ($M^+$ 9.8%, $C_{12}H_{13}N_3O_2$ requires 231.1008)
158 (100%, $M^+$ - [$CO_2Et$])

Found: C, 62.5; H, 5.8; N, 18.4 $C_{12}H_{13}N_3O_2$
requires: C, 62.3; H, 5.7; N, 18.2%

The second fraction was found to be recovered 2-methylindazole (0.3g).

1-Benzoyl-3-cyano-2,3-dihydro-2-methylindazole (183c)

Use of 2-methylindazole (0.97g, 7.6mmol), trimethylsilyl cyanide (0.90g, 1.2ml, 9.12mmol), anhydrous aluminium chloride (0.1g) and benzoyl chloride (1.30g, 9.12mmol) in the general procedure (I) resulted in a crude oil which showed two spots on analytical tlc.

Flash column chromatography using a 50:50 mixture of petroleum ether (b.p. 40-60°C) as the eluent gave separation of the two components. The first fraction collected, after recrystallisation from ethyl acetate, was found to be the title compound (183c), obtained as colourless rhombs (0.3g, 15%), m.p. 134-135°C.

$\nu_{max}$ (KBr), 2250 (C≡N, m) 1650cm$^{-1}$ (C=O)

$\delta_H$(90MHz, $CDCl_3$), 8.15-7.05 (9H,m,aromatic), 4.85(1H,s, C-3H), 2.43 (3H,s,N-$CH_3$)

m/z, 263.1054 ($M^+$ 3.5%, $C_{16}H_{13}N_3O$ requires 263.1058), 158 (15%, $M^+$ - COPh), 105 (100%, COPh), 77 (42%, Ph)

Found: C, 72.7; H, 5.1; N, 15.6 $C_{16}H_{13}N_3O$
requires: C, 73.0; H, 5.0; N, 16.0%

(ii) Formation of 2,3-dimethylindazole (181)

A solution of 3-cyano-2,3-dihydro-1-methoxycarbonyl-2-methylindazole (0.5g, 2.3mmol) in dry dimethylformamide (10ml) was added dropwise to a well stirred solution of sodium hydride (0.07g of 80% oil dispersion to give 0.056g, 2.3mmol of NaH) in dry DMF (5ml), under a nitrogen atmosphere. The red coloured reaction mixture was stirred at $0^{o}C$ for two hours and then at room temperature for 24 hours. The reaction mixture was poured on to ice (ca. 30g), no precipitate was formed and so the solution was extracted with dichloromethane (2 x 30ml). The organic layer was washed several times with water to remove the final traces of DMF, before drying over anhydrous magnesium sulphate. The solvent was filtered and on evaporation of the solvent under reduced pressure, a light yellow oil was obtained. Preparative tlc (2 x 1m silica gel plates) using ethyl acetate as the eluent yielded a solid which showed a single spot on analytical tlc. Recrystallisation from ethyl acetate gave 2,3-dimethylindazole as cream-coloured prisms (100mg, 30%), m.p. $80-82^{o}C$, lit[129] $79-80^{o}C$.

$\delta_H$ (90MHz, $CDCl_3$), 7.85-7.00 (4H,m,aromatic),
3.90 (3H,s,N-$CH_3$), 2.45 (3H,s,C-3$CH_3$)

m/z, 146.0843 ($M^{+}$ 100%, $C_9H_{10}N_2$ requires 146.0844)

## CHAPTER IV: A BRIEF INVESTIGATION INTO THE USE OF THE MONOCYCLIC FIVE-MEMBERED RING HETEROCYCLE PYRAZOLE IN THE REISSERT APPROACH

### 1-Ethoxycarbonylpyrazole (214)

To a well stirred solution of pyrazole (0.68g, 0.01mol) in dry dichloromethane (15ml) and trimethylsilyl cyanide (1.98g, 2.70ml, 0.02mol) was added anhydrous aluminium chloride (0.1g). Ethyl chloroformate (2.17g, 0.02mol) in dry dichloromethane (10ml) was added dropwise over five minutes. The reaction mixture was stirred at room temperature for 72 hours. The solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The dichloromethane layer was dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure to give an oil, which was distilled. One fraction was collected at 100°C/5mmHg (0.82g) and identified as 1-ethoxycarbonylpyrazole (58%).

$\nu_{max}$ (liquid film), 1735cm$^{-1}$ (C=0)

$\delta_H$ (90MHz, $CDCl_3$), 8.15 (1H,d,C-5H), 7.75 (1H,d,C-3H),
6.45 (1H,q,C-4H),
4.55 (2H,q,$C\underline{H}_2$), 1.50 (3H,t,-$C\underline{H}_3$)

m/z, 140.0586 ($M^+$ 27%, $C_6H_8N_2O_2$ requires 140.0586)
68 (100%, $C_3H_4N_2$)

found: C, 51.7; H, 5.9; N, 20.3 $C_6H_8N_2O_2$
requires: C, 51.4; H, 5.75; N, 20.0%

1-Methylpyrazole (215)

a) Using trimethyl phosphate and tri-n-butylamine[142]

A mixture of pyrazole (1.92g, 0.028mol) and trimethyl phosphate (2.0g, 0.14mol) was heated at an oil bath temperature of 150°C for one hour. The mixture was cooled and dry benzene (50ml) was added, followed by addition of 30% aqueous potassium hydroxide (100ml). The solution was vigorously stirred for 10 minutes before the two layers were separated. The organic layer was washed several times with water before drying over anhydrous magnesium sulphate. Benzene was evaporated under reduced pressure and an oil was obtained. Distillation gave, as a clear oil, 1-methylpyrazole (215)(0.6g, 27%), b.p. 125-128°C/760mmHg, lit[142] 128°C/760mmHg.

$\delta_H$ (90MHz, $CDCl_3$), 7.45 (1H,d,C-3H), 7.31 (1H,d,C-5H), 6.20 (1H,q,C-4H), 3.85 (3H,s,$CH_3$)

b) Using methyl iodide and sodium hydride in DMSO

Pyrazole (2g, 0.03mol) in dry dimethylsulphoxide (15ml) was added dropwise to a stirred solution of sodium hydride (1.35g of 80% oil dispersion to give 1.08g, 0.045mol of NaH) in dimethyl sulphoxide (5ml) at 0°C, under a nitrogen atmosphere. The reaction mixture was stirred for three hours before pouring on to ice-water (ca. 50ml). The organic material was extracted with dichloromethane (2 x 50ml) and this was washed with water several times to remove remnants of DMSO. The organic solvent was dried over anhydrous magnesium sulphate and filtered. Evaporation of

the solvent under reduced pressure gave an oil which, on distillation, yielded 1-methylpyrazole (215)(1.78g, 72%), b.p. 126-128°C/760mmHg. The proton nmr was identical to that of the product from method (a) above.

Dimethylformamide was used in place of DMSO as the solvent in this reaction. The yield of 1-methylpyrazole (215) obtained was 69%.

Attempted synthesis of a Reissert analogue from 1-methylpyrazole

Ethyl chloroformate (1.30g, 0.012mol) in dry dichloromethane (10ml) was added dropwise to a well stirred solution of 1-methylpyrazole (0.82g, 0.01mol) and trimethylsilyl cyanide (1.18g, 1.6ml, 0.012mol) with a catalytic amount of $AlCl_3$ (0.1g) in dry dichloromethane (20ml). The reaction mixture was stirred at room temperature for 72 hours before washing with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The organic layer was dried over anhydrous magnesium sulphate and filtered. Dichloromethane was evaporated under reduced pressure, resulting in a clear oil. Distillation of the oil identified it as the starting 1-methylpyrazole (215)(92%), b.p. 126-128°C/760mmHg. The proton nmr of this product was identical to that of the starting material.

On repeating this reaction with the same substrates as above, this time refluxing the reaction mixture for six hours and stirring at room temperature for 48 hours, 1-methylpyrazole was recovered (88%), b.p. 126-128°C/760mmHg.

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# Reissert Compound Formation with Five-membered Ring Heterocycles using Trimethylsilyl Cyanide

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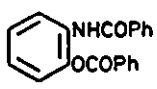
Treatment of benzothiazole with trimethylsilyl cyanide and an acid chloride in $CH_2Cl_2$ gives the *N*-acyl-2-cyano-2,3-dihydrobenzothiazole in good yield, benzoxazole similarly is converted into a five-membered ring Reissert compound, providing the first examples in these series

Formation of Reissert compounds from a wide range of aromatic six-membered ring nitrogen heterocycles by use of an acid chloride and a source of cyanide has been utilized as a key step for the modification of the heterocyclic ring in a variety of different ways [1] Attempts to extend the method to five-membered ring analogues have failed because under the normal two-phase conditions of Reissert compound formation ring opening occurs For example, we have observed that benzoxazole with benzoyl chloride and potassium cyanide in $CH_2Cl_2$–$H_2O$ gives (**1**) in high yield, analogous products result from benzothiazole and benzimidazole

We now report the formation in good yield of Reissert compounds from five-membered ring heterocycles utilizing trimethylsilyl cyanide[2] as the source of cyanide in a single phase system For example, treatment of benzothiazole (1 mol) with *p*-toluoyl chloride (1 mol) and trimethylsilyl cyanide (1 1 mol) in the presence of a catalytic amount of aluminium chloride in anhydrous $CH_2Cl_2$ for 72 h at room temperature gives Reissert compound (**2**, R = 4-$MeC_6H_4$), 86%, as pale yellow needles from ethyl acetate, m p 158—160 °C, $\nu_{max}$ (KBr) 1662 $cm^{-1}$, $\delta_H$ 7 4—7 2 (8H) 6 3 (1H, s, C-2-H), and 2 4 (3H) † Use of other aroyl chlorides gave (**2**, R = Ph), 44%, m p 140—141 °C, and (**2** R = 4-$ClC_6H_4$) 85%, m p

† All new compounds gave satisfactory microanalytical data

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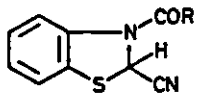


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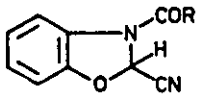


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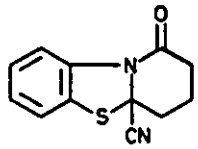


(4)

115—118 °C. 4-chlorobutanoyl chloride gave (2, R = $Cl[CH_2]_3$) 84%, m p. 104—105 °C, and ethyl chloroformate provided (2, R = EtO), 72%, m p. 89—90 °C.

Similarly benzoxazole has been converted in good yields into Reissert compounds (3) Use of benzoyl chloride provided (3, R = Ph), 50%, m p. 104 5—105 5 °C, $\nu_{max}$(KBr) 1670 $cm^{-1}$, $\delta_H$ 7 6—6 8 (9H) and 6 7 (1H, s, C-2-H). Also obtained were (3, R = 2-$ClCH_2C_6H_4$), 43%, m p 106—108 °C, (3, R = $Cl[CH_2]_3$), 47%, m p. 86—87 5 °C; and (3, R = EtO), 52%, m p 74—75 °C.

Carbanion generation at C-2 in both series can be achieved by treatment of the Reissert compound with sodium hydride in *N,N*-dimethylformamide, an immediate red colouration being given with evolution of hydrogen. The process can be used to effect further heterocyclic modification. For example, intramolecular cyclisation results when the anion of the benzothiazole Reissert compound (2, R = $Cl[CH_2]_3$) is stirred under nitrogen for 2 h at 0—5 °C, providing the novel tricyclic derivative (4), m p 92—93 °C, 83%, $\nu_{max}$(KBr) 1678 $cm^{-1}$, $\delta_H$ 8 15—7 15 (4H) and 2 9—2 1 (6H). Also, treatment of the anion of *N*-benzoyl-2-cyano-2,3-dihydrobenzoxazole (3, R = Ph) with MeI gives alkylation at C-2, which when followed by base hydrolysis provides 2-methylbenzoxazole, b p 178 °C, $\delta_H$ 7 85—7 25 (4H), 2 6 (3H) ‡

The five-membered ring Reissert compounds provide a new and potentially versatile means of extending the chemistry of these ring systems

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‡ I r spectrum identical with that of an authentic sample