STUDIES CONCERNING THE SYNTHESIS OF PYRROLO[2,1-a]PHTHALAZINES AND RELATED SYSTEMS

by

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A Doctoral Thesis

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

To my wife

and

to my parents

and Mateen

ACKNOWLEDGEMENTS

I would like to express my deep and sincere gratitude to Dr. B.C. Uff for the excellent and considerate guidance and encouragement he provided throughout the course of this project and for the knowledge he imparted to me.

I am also grateful to Dr. C.B. Chapleo of Reckitt & Colman Ltd., Pharmaceutical Division, Hull, for helpful discussions and arranging for the pharmacological testing to be carried out.

I would like to thank the following for enthusiastic technical assistance; Mr. M. Harris (n.m.r. spectra), Mr. A. J. Greenfield (mass spectra), Mr. W.E. Marriott, Mr. A.T. Kowalski and Mr. J.Kershaw.

I would like to thank my parents for their love, understanding and encouragement.

Except where otherwise stated, the material presented is original and has not been submitted for a degree at this or any other university.

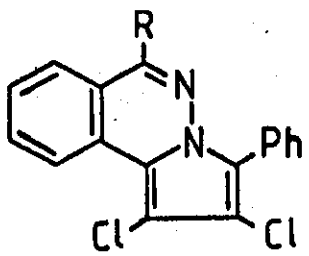
"We must now highly resolve to arise and lay hold of all those instrumentalities that promote the peace and well-being and happiness, the knowledge, culture and industry, the dignity, value and station, of the entire human race."

'Abdu'l-Baha (1875)

SUMMARY

The purpose of the work was to study the synthesis of the pyrrolo[2,1-a]phthalazine system, and of the related systems, and routes to substituted derivatives with a view to producing compounds of potential antihypertensive activity. The effect of substitution particularly at and in the region of the 6-position of pyrrolo[2,1-a]phthalazine, was of interest, by analogy with the substituted phthalazine antihypertensive agent, hydralazine.

Our studies have produced 27 new pyrrolo[2,1-a]phthalazines, which were available for pharmacological examination and are summarized below:



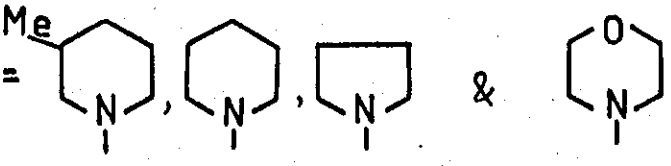
(X)

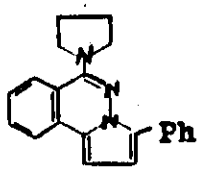
(i) Cl at position-6 ,

(X), R = Cl

(ii) N-functions at position-6 ,

a) amino ,

(X), R= 

and 

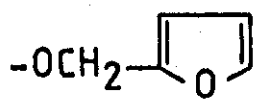
b) hydrazino ,

(X) : R = Me—N(—)—NH$_2$, NH(—)—NH$_2$

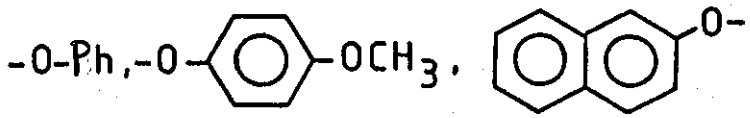
O-functions at position-6 :

(iii) O-alkyl and O-aryl :

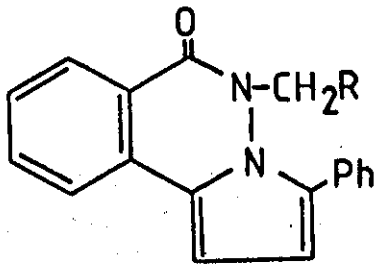
(X) : R = -OMe , -OEt , -O-Pr-n , -OPr-i ,

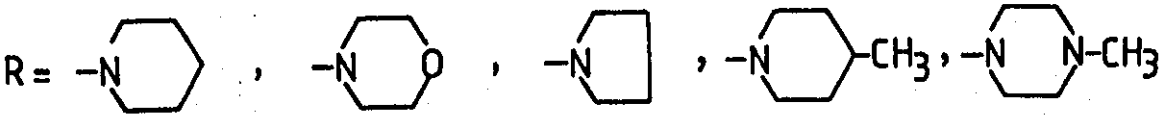


, -OCH$_2$—CH=CH$_2$,

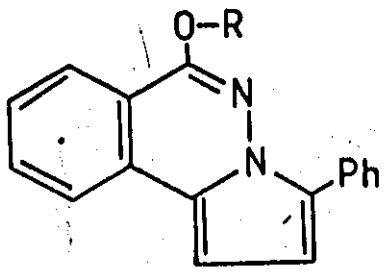


(iv) C-6 carbonyl and N-5-aminoalkyl :



R = 

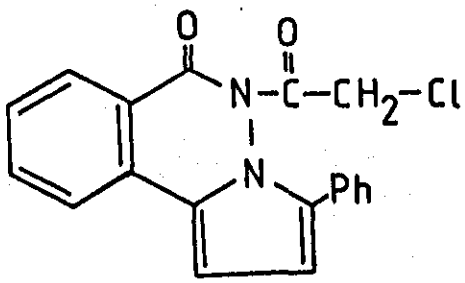
(v) O-acyl and carbonates :



(Z)

(Z), R = 

(vi) C-6 carbonyl and N-5 acyl :



From the compounds submitted for pharmacological examination, four showed encouraging antihypertensive activity and these compounds are doubly underlined above.

Studies have been also carried out on the synthesis of tricyclic systems related to pyrrolo[2,1-a]phthalazine, since earlier studies in this Department have suggested such a system may have antihypertensive properties.

Condensation of 3-methylisoquinoline-N-methoxycarbonyl-Reissert compound with 4-fluorophenyl isothiocyanate has been found to give the tetrahydroimidazo[5,1-a]isoquinoline system.

Condensation of phthalazine-2-methoxycarbonyl-Reissert compound with 4-fluorophenyl, 1-naphthyl and methyl isothiocyanates leads to formation of the novel imidazo[5,1-a]phthalazine system. A bis-imidazo[5,1-a]phthalazinyl disulphide is also produced, and evidence for its structure has been obtained by mass spectrometry using the direct chemical ionisation technique.

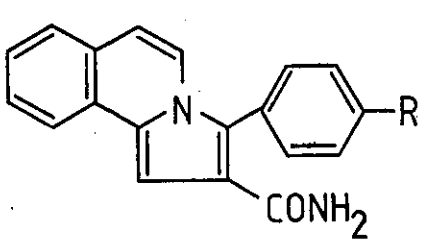
CONTENTS

INTRODUCTION

"But there is another alchemy, operative and practical.... which not only can yield wealth and very many other things for the public welfare but it also teaches how to discover such things as are capable of prolonging human life for much longer periods than can be accomplished by nature".

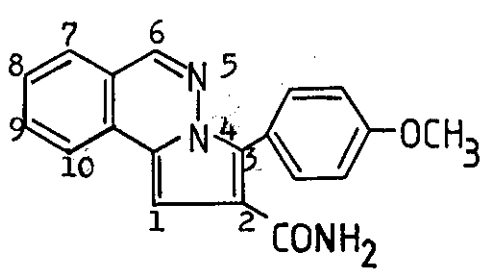
Roger Bacon (c. 1220 - c. 1292)

At the outset of this work in Autumn 1978 a student in this Department, R.S Budhram, had just completed a study of the synthesis and chemistry of certain tricyclic systems containing a bridgehead nitrogen.[1-3] Examples of three of the ring systems he studied had been submitted for pharmacological examination as potential antihypertensive agents. The ring systems concerned were the pyrrolo-[2,1-a]isoquinoline system (e.g 1 and 2), the pyrrolo[2,1-a]phthalazine system (e.g 3) and the imidazo[5,1-a]isoquinoline system (e.g 4).



(1) : R = OCH_3

(2) : R = CH_3



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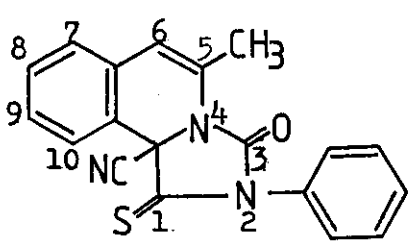
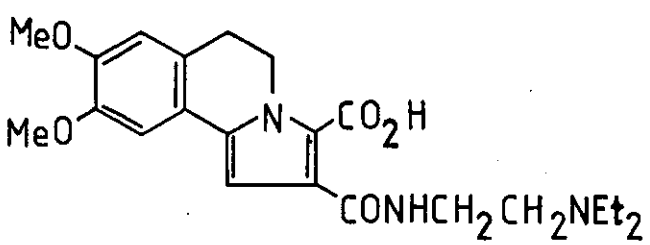


(4)

The compounds each showed antihypertensive activity (Table 1) and were considered lead compounds for possible further research. The tests were carried out because an earlier report by C. Casagrande et al.[4] has shown a number of pyrrolo[2,1-a]isoquinolines to have antihypertensive activity, of which (5) was the most active (Table 1). The activities of these tricyclic compounds are compared with the activities of two antihypertensive agents in current clinical use, hydralazine (6) and α-methyldopa (7), in Table 1.



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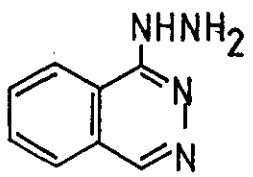

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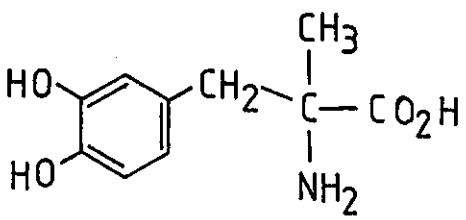


(7)

Table 1

Antihypertensive Activity

Drug	Species	Dose mg/Kg	Route	Response
(1)**	rat	100	p.o	15% reduction in MABP after 5h.
(2)**	rat	100	p.o	16% reduction in MABP after 5h.
(3)**	rat	100	p.o	13% reduction in MABP after 5h.
(4)**	rat	100	p.o	12% reduction in MABP after 5h.
(5)*	dog	5	i.v	25% reduction in femoral arterial blood pressure, lasting 1-2 h.
(5)*	dog	20	i.v	40% reduction in femoral arterial blood pressure, lasting 1-2 h.
(5)*	rabbit	50-60	i.v	60-50% reduction in arterial blood pressure, lasting 1.5-2h.
(6)**	rat	3	i.p	41.6$\pm$5.7% reduction in MABP after 5h.
(7)**	rat	200	i.p	36.7$\pm$4.3% reduction in MABP after 5h.

p.o = per oral
i.p = intraperitoneal
MABP = mean arterial blood pressure
i.v = intravenous

** Data for these compounds were kindly obtained by Reckitt & Colman, Pharmaceutical Division, Hull.

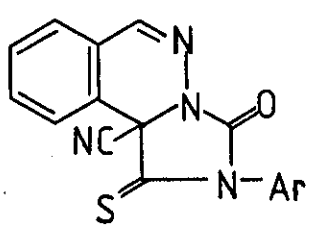
* C.Casagerande, A. Invernizzi, R.Ferrini and G.G Ferrari, J.Med. Chem 1968, 11, 765.

It can be pointed out that Casagerande's most active compound (5) loses its activity after two hours whereas Budhram's compounds (1-4) although less pronounced in action have the desirable property of sustaining their effect for at least five hours.

Budhram's compound (3) contains the phthalazine system as part of its structure, which is also present in the important anti-hypertensive drug mentioned above, hydralazine (6), [5-14] i.e. 1-hydrazinylphthalazine. It seemed of particular interest therefore, to develope a study of the pyrrolo[2,1-a]phthalazine system (e.g 3) with a view, in particular, of modifying the system in the region of positions - 6 and - 5, i.e. the region of space occupied by the hydrazinyl substituent in hydralazine (6).

The hope would be that such compounds might favourably augment the antihypertensive activities separately shown by the tricyclic system (3) and by hydralazine (6). This study is described in Parts I and II of the Discussion section of this thesis.

The other interesting area of study to develope from Budhram's work would be to attempt to extend his synthetic work to further tricyclic systems In keeping with our other work, the synthesis of the novel imidazo[5,1-a]phthalazine system (e.g 8) could be attempted. This work is described in Part III of the Discussion section.



(8)

The remainder of this Introduction discusses (A) the disease of hypertension, (B) antihypertensive agents (including hydralazine) and (C) routes to the synthesis of pyrrolo[2,1-a]phthalazines and related structures.

(A) The Disease of Hypertension

Hypertension is the presence of an increase in blood pressure above normal within the arteries and arterioles. [15]

The blood pressure is usually considered to be abnormally high, when the resting systolic pressure exceeds 140 mm Hg and the diastolic pressure exceeds 90 mm Hg. [16-17] However when judging the normality of the arterial pressure, age (arterial pressure increases with age [15]) and sex of individuals (females tolerate hypertension better than males),[16] as well as environmental factors (high incidence in industrialized countries, absent in primitive populations[15]) must also be taken into account. [18-21]

Hypertension may be of primary or secondary origin.[22-24] Secondary hypertension is a condition which arises as a result of a known cause of elevated arterial pressure. Among its more important causes are kidney disease and diabetes. Some conditions of secondary hypertension can be corrected by surgery.[15] Most cases of hypertension are however due to conditions of primary origin and no precise causal anomaly can be detected. This form of hypertension is known as essential (or primary) hypertension.[25-28]

Arterial pressure is a function of cardiac output, blood volume and the resistance of peripheral arterioles.[29] There is a direct correlation between diastolic or systolic blood pressure and the death rate.[30] It has been estimated that approximately 15% of the adult American population suffer from high blood pressure.[31-32] Sustained elevation of blood pressure results in significant vascular damage throughout the body.[33-34] Elevated blood pressure has deleterious effects on the smooth muscle of the heart and the blood vessels.[35]

It is for this reason that three common immediate causes of death in the hypertensive population are stroke, representing damage to cerebral blood vessels, heart failure (the inability of the heart muscle to cope with the demand for blood), and kidney failure (uremia), the inability of the kidneys to remove waste products effectively.[35,44] Hence correlations between hypertension and mortality statistics must not be restricted to deaths recorded as directly due to hypertensive disease. In England and Wales in 1979 of the 593,019 deaths, 298,436 (50.32%) were due to diseases of the circulatory system (Table 2).[36] Within that group 6,506 (1.10%) were recorded as due to hypertensive disease (Table 3).[36]

Table 2 Causes of death in England and Wales, 1979

Cause of Death			% of total deaths
I	Infections and parasitic diseases	2,273	0.383
II	Neoplasms	129,638	21.86
III	Endocrine, nutritional and metabolic diseases and immunity disorders	6,462	1.09
IV	Diseases of blood and blood-forming organs	1,729	0.291
V	Mental disorders	3,211	0.542
VI	Diseases of the nervous system and sense organs	6,934	1.17
VII	Diseases of the circulatory system	298,436	50.324
VIII	Diseases of the respiratory system	85,925	14.49
IX	Diseases of the digestive system	16,255	2.74
X	Diseases of the genitourinary system	7,913	1.33
XI	Complications of pregenancy, childbirth and the puerperium	74	0.012
XII	Diseases of the skin and subcutaneous tissue	439	0.074
XIII	Diseases of the musculoskeletal system and connective tissue	3,047	0.514
XIV	Congenital abnormalities	3,498	0.59
XV	Certain conditions originating in the perinatal period	3,424	0.58
XVI	Signs, symptoms and ill-defined conditions	2,608	0.44
XVII	Injury and poisoning	21,153	3.57
		593,019	100

Table 3 Deaths due to diseases of the circulatory system in England and Wales, 1979[36]

			% of total deaths (all causes)
Deaths (all causes) England and Wales 1979		593,019	100
VII	Diseases of the circulatory systems	298,436	50.32
	Acute rheumatic fever	3	-
	Chronic rheumatic heart disease	3,396	0.57
	Hypertensive disease	6,506	1.10
	Ischaemic heart disease	155,647	26.26
	Diseases of pulmonary circulation	4,329	0.73
	Other forms of heart disease	32,090	5.41
	Cerebrovascular disease	74,378	12.54
	Diseases of the arteries, arterioles and capillaries	17,404	2.93
	Diseases of the veins and lymphatics and other diseases of the circulatory system	4,683	0.78
		298,436	50.32

(B) Antihypertensive Agents

It is well recognised that lowering of blood pressure with pharmacological agents is effective in reducing the incidence of death in patients suffering from hypertension. Progress in the treatment of hypertensions has come only in recent years.[37,38]

Though many compounds have been synthesised, only few are useful for therapy. A hypotensive drug should have a prolonged effect with not rapid but a slow reduction of blood pressure. Further, increased doses should not cause a more pronounced fall in blood pressure, but a more prolonged effect.[39] It should be effective in the recumbent position and during the sleep. It is desirable that its action is free of side-effects in order that it may be used for long term therapy. For example it should not produce nausea and drowsiness[40].

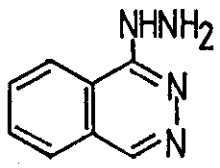
The use of a single drug in doses adequate to control blood pressure can lead to considerable side-effects which occur with nearly all antihypertensive drugs. Therefore in many cases of hypertension use of a single drug can seldom be successful for antihypertensive therapy. The use of two or more drugs in combination usually leads to lower doses of individual drugs, to less trouble from side-effects and to better control of the hypertension.[41-42]

Antihypertensive drugs maybe classified according to their mode of action as shown in Table 4.[43]

Table 4 Classification of Antihypertensive Drugs

Site of Action	Mode of Action	Drug	Trade Name
Arteriolar smooth muscle	Direct vasodilatation	Hydralazine	Apresoline
		Diazoxide	Hyperstat
		Minoxidil	
		Nitroprusside	Nipride
Alpha adrenergic receptors	Receptor blockade	Phentolamine	Regitine
		Phenoxybenzamine	Dibenzyline
		Prazosin	Minipress
Beta adrenergic receptors	CNS effect Myocardial depression Renin release Inhibition	Propranolol	Inderal
Sympathetic fibers	Blockade of NE release (also depletion)	Guanethidine	Ismelin
	Inhibition of MAO	Pargyline	Eutonyl
Paravertebral ganglia	Ganglionic blockade	Chlorisondamine	Ecolid
Central nervous system	Depression of C-V control center	Clonidine	Catapres
	False neurotransmitter	Methyldopa	Aldomet
	NE depletion	Reserpine	Many
Carotid sinus	Reflex sympathetic depression	Veratrum alkaloids	
Kidney	Sodium excretion Volume depletion	Chlorothiazide	Saluric

The structures of the compounds listed in the third column of Table 4 are shown below:



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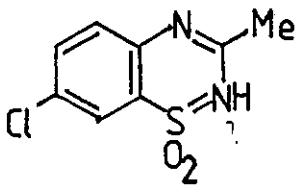
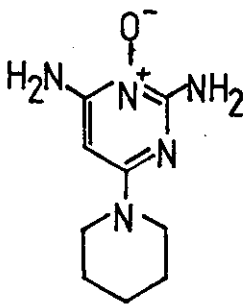
hydralazine



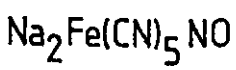
(9)

diazoxide



(10)

minoxidil



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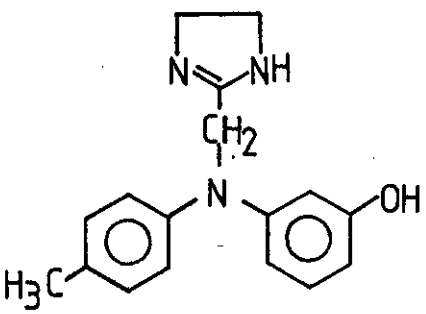
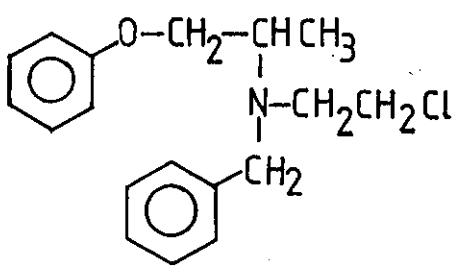
sodium nitroprusside



(12)

phentolamine



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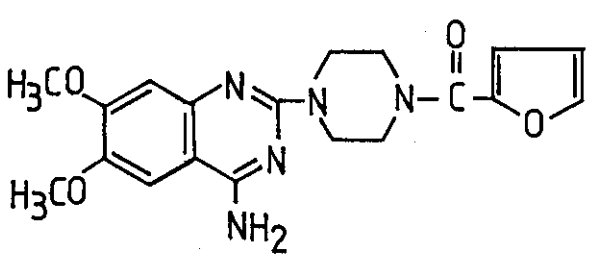
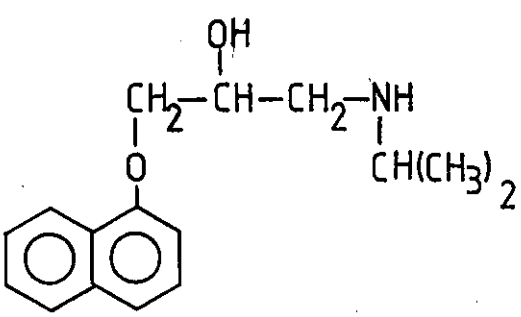
phenoxybenzamine



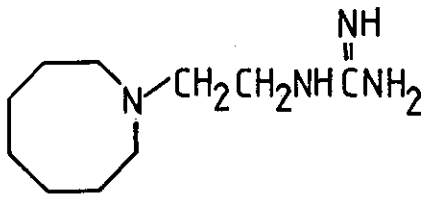
(14)

prazosin



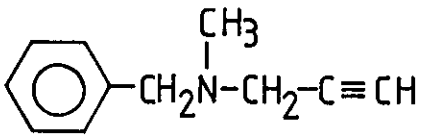
(15)

propranolol



(16)

guanethidine



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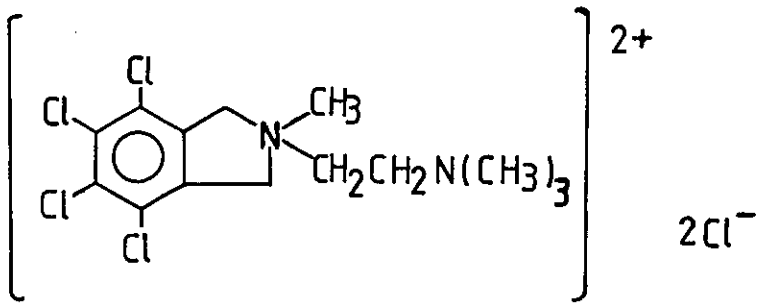
pargyline



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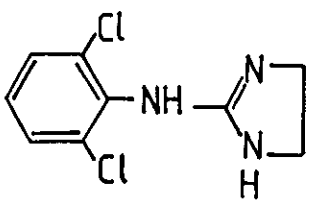
chlorisondamine chloride



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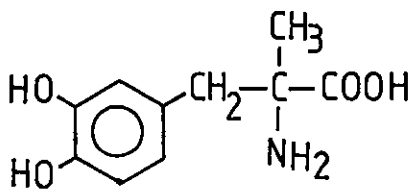
clonidine



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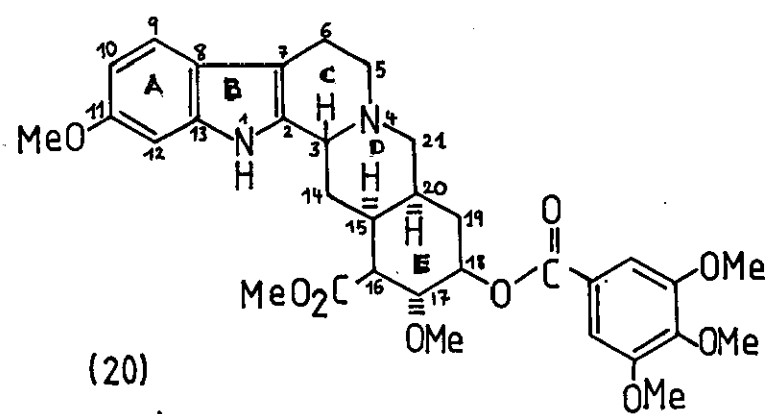
α-methyldopa



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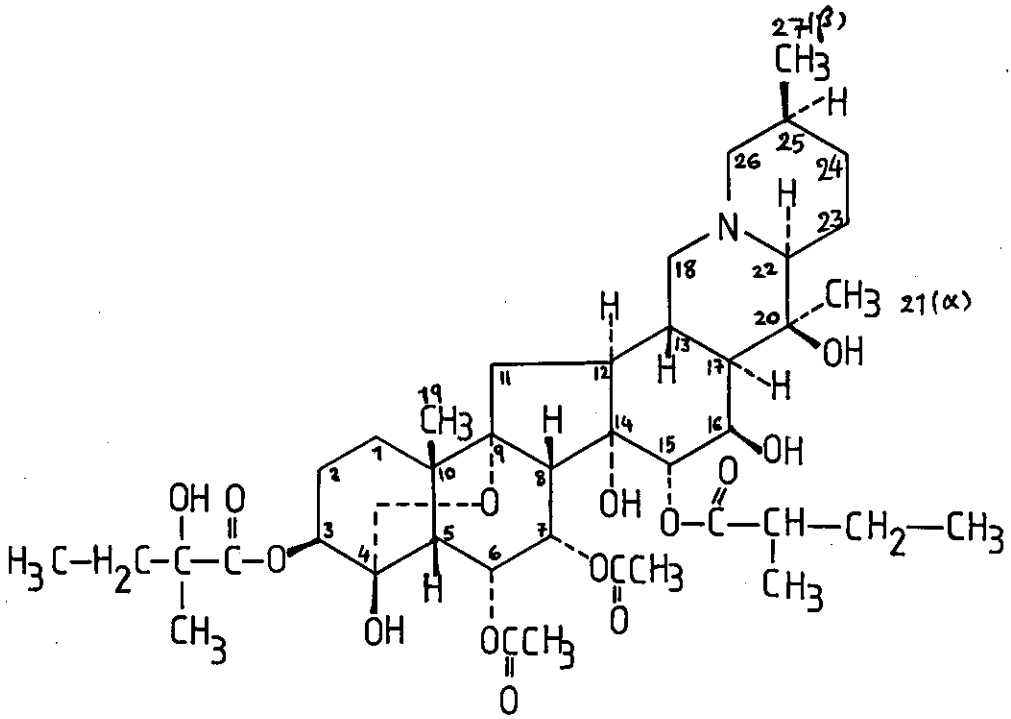
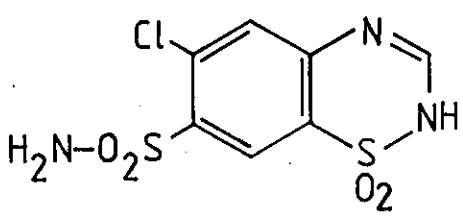
reserpine



(21)

protoveratrine A



(22)

chlorothiazide

Of the above, the most important can be narrowed down to those shown in Table 5.[45]

Table 5 Principal antihypertensive agents (adult dosage per 24 hours)[45]

1.	Diuretics,	e.g. chlorothiazide (Saluric, 500mg)
2.	β.Blockers	e.g. propranolol (Inderal, 80-240mg)
3.	Hydralazine	(Apresoline, 25-100mg)
4.	α-Methyldopa	(Aldomet, 500-1500mg)
5.	Clonidine	(Catapres, 0.3-0.6mg)
6.	Guanethidine	(Ismelin, 400-1200mg)

In a patient with essential hypertension, aged 45 years or over, the first antihypertensive drug usually prescribed is a thiazide diuretic. In subjects less than 45 years old, a β-blocker is usually first prescribed. If in either case arterial pressure decreases insufficiently then a combination of β-blocker and diuretic is prescribed.

If this combination fails to produce the desired fall in pressure then a third antihypertensive drug is added, usually hydralazine, α-methyldopa, clonidine or guanethedine.[46]

The drug which our studies principally relate to is hydralazine, which falls in the class of direct vasodilators and we now discuss four members of this group in more detail, viz. hydralazine, sodium nitroprusside, minoxidil and diazoxide.[47-49]

i) Hydralazine

As the name implies the vasodilators have a direct dilating action on blood vessels, relaxing vascular smooth muscle and reducing peripheral resistance significantly. In most patients with chronic essential hypertension abnormally high peripheral vascular resistance is the proximate cause of elevated arterial pressure.[31,50,51,59] Their cardiac output is generally within the

normal range. Yet most antihypertensive drugs that elicit their hypotensive effect by depressing the sympathetic nervous system decrease cardiac output. While blood pressure decreases, the abnormally low cardiac output results in decreased tissue perfusion to the heart, brain and kidneys, a hemodynamic situation which is hardly desirable nor chronically tolerated. The hemodynamic goal in most chronic essential hypertension therapy should be to specifically reduce peripheral vascular resistance, without sympathodepression.[31]

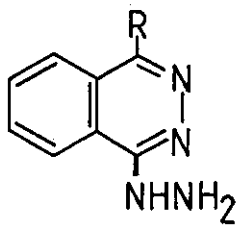
Hydralazine, first reported in 1950 by Gross, Druey and Meier[11] and marketed in 1953 by CIBA in Switzerland,[53-56] acts directly on constricted arteriolar smooth muscle. However, the decrease in vascular resistance caused by therapy with hydralazine activates the baroreceptors, resulting in a reflex increase in sympathetic discharge which increases heart rate, stroke volume, and cardiac output.[31,52] It is for this reason therefore that hydralazine is normally administered in combination with β-adrenergic blockers which eliminates the reflex action. The diuretic also often added offsets the sodium and water retention caused by hydralazine.[31] Hypertensive control is achieved and the rate of use of hydralazine in the treatment of hypertension has expanded during recent years.[11,57]

However hydralazine does have side-effect liability including the promotion of a lupus erythematosus- like syndrome,[31] nausea, vomiting, weakness, flushing, headache, tachycardia and nasal congestion,[58] hence the continued search for an improved drug.

Although the mode of action of hydralazine in reducing blood pressure is still uncertain,[47] one must assume that the free hydrazino group in hydralazine is an essential constituent of its therapeutic, blood-pressure lowering action.[60] The hydrazino group in hydralazine is highly reactive, and is believed to react with enzymes in the organism, particularly those enzymes with an aldehydic function.[61] Druey et al.[53-55] and many other groups of workers have synthesised structural analogous and derivatives of hydralazine. Table 6 shows, that the replacement of hydrogen at

the 4-position in 1-hydrazinophthalazine by a methyl or an ethyl group does not reduce, but still retains good activity.[60] However no improvement over hydralazine and dihydralazine (1,4-dihydrazinylphthalazine) antihypertensive activities are observed.

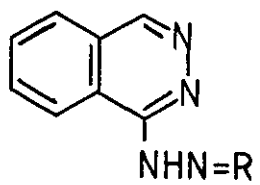
Table 6 4-Substituted hydralazines



R	Activity	References
H	good	(11)
CH_3	good	(11)
C_2H_5	good	(54)
C_6H_5	fair to low	(54)

As shown in Table 7, hydrazones of hydralazine retain the antihypertensive activity.[60]

Table 7 Hydrazones of hydralazine

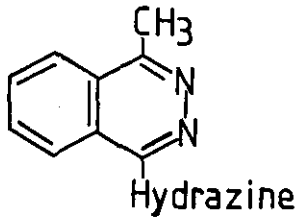


R	Activity	References
CH_2	good	(54)
$CHCH_3$	good	(53)
$C(CH_3)_2$	good	(54)
$CH(C_6H_5)$	fair	(54)

The hydrazones shown in Table 7 were chemically rather unstable.[60] The good activity of hydrazone derivatives is probably due to cleavage and degradation of these compounds in the organism, into hydralazine.[60]

The N,N-alkyl substituted derivatives of 1-hydrazinophthalazine (Table 8), are chemically more stable compared to the hydrazone derivatives of hydralazine. However these compounds show less activity in comparison with hydralazine.[60]

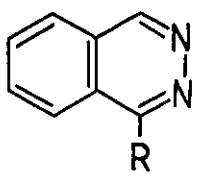
Table 8 N-Alkylhydrazinophthalazines

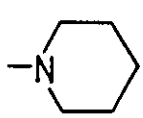
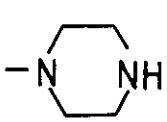


Hydrazine	Activity	References
$N(CH_3)NH_2$	fair	(54)
$N(CH_3)NHCH_3$	none	(54)

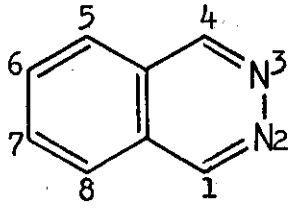
Druey[60] examined the replacement of the hydrazino group in hydralazine by other radicals. The activity of these compounds (see Table 9), although pronounced in terms of milimeter of mercury, were not significant in comparison with hydralazine activity.[60]

Table 9 Various 1-Substituted phthalazines



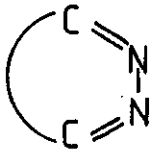
R	Activity	References
-H	none	(61)
$-NH_2$	none	(61)
	none	(61)
	hypotensive	(61)
-OH	none	(61)
-SH	low	(53)

Druey and co-workers[61] concluded that the structural requirement for all molecules related to hydralazine, having vasodilator activity, was the sequence -C=N-N=C- in a six-membered heteroaromatic system with the hydrazino group (or its hydrazone) attached to one of the carbons as illustrated by structure (24).



(23)

phthalazine



(24)

Furthermore the following empirical structure-activity relationships were defined.[53,60,61]

(a) The hydrazine group must be present in the 1-position of phthalazine (23). The hydrazino group is necessary structural feature for prolonged hypotensive activity.

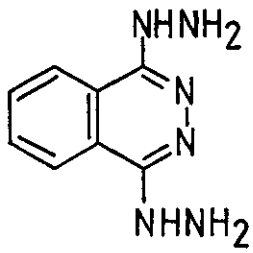
(b) Antihypertensive activity does not alter to a significant degree by carbon substitution in phthalazine ring.

(c) The benzene ring of phthalazine (23) may be replaced by pyridine.

(d) Hydrazones of hydralazine retain activity.

In spite of the fact that many compounds have been synthesised in order to produce a better hypotensive activity than hydralazine, very few types of compounds have been found to display a hydralazine like activity.[61]

1-Hydrazinophthalazine and 1,4-dihydralazine (25), as free bases are rather unstable compounds.[61] In the form of their salts with strong acids they are stable. Hydralazine hydrochloride occurs as, a white or slightly yellowish crystalline powder and is soluble in water to the extent of about 3 percent.[39] A 2 per cent aqueous solution has a pH of 3.5 to 4.5.[39]

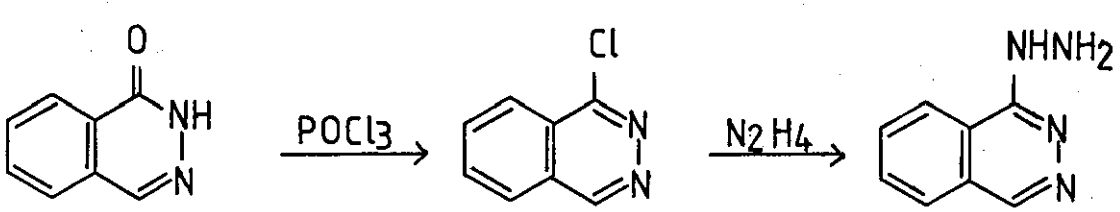


(25)

Hydralazine is used for the treatment of uremia, and is beneficial to the patients with impaired renal functions.[22] It is also used in the treatment of moderate grade to severe hypertension.[22] The side effect of hydralazine arise, when, it is used alone in large doses.[39]

Hydralazine hydrochloride has been extensively used in the treatment of hypertension.[5] The drug is readily absorbed after oral administration,[39] but it should not be administered alone, in which case it may have serious side-actions, including jaundice,[5] and conditions which resemble acute rheumatism.[22] Hydralazine is available as tablets, containing 10, 25, 50, and 100 mg and 1ml ampules (20 mg/ml) for intramuscular or intravenous administration.

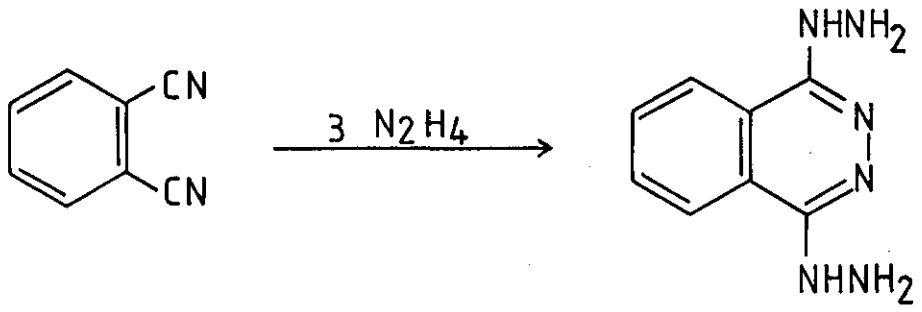
Hydralazine (6), is commonly prepared on a large-scale from 1-chlorophthalazine (27) by the following route.[62,63]



(26) (27) (6)

Phthalazinone (26) is converted into 1-chlorophthalazine (27), by refluxing with phosphor-us oxychloride for 30 minutes. The 1-chlorophthalazine then reacts with hydrazine hydrate in refluxing ethanol for 2 hours to give hydralazine (6).

Dihydralazine (25) can be obtained analogously from 1,4-dichlorophthalazine. Another method which is of interest for the industrial production, yields dihydralazine (25) in one step.[64] The starting material of this reaction is the commercially available phthalodinitrile (28).[64]



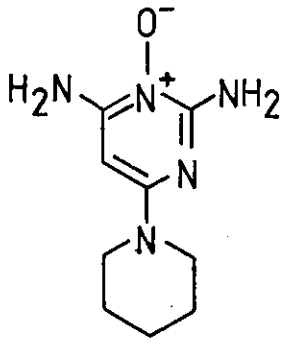
(28) (25)

ii) Sodium nitroprusside (Nipride)

$Na_2Fe(CN)_5NO.2H_2O$

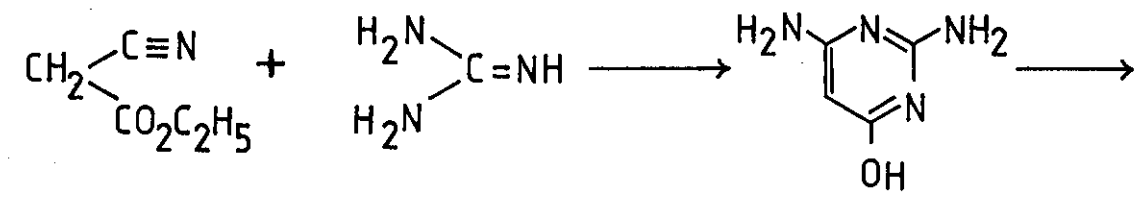
Sodium nitroprusside was one of the first drugs used in the treatment of hypertension. It is a highly potent vasadilator and short-acting hypotensive agent.[65] Sodium nitroprusside is not used for long-term antihypertensive therapy, because of its unwanted side-effects. These include nausea, vomiting, headache, dizziness, disorientation and muscle pain. Sodium nitroprusside may be used in the treatment of hypertensive crises and for controlled hypertension during general anesthesia.[65,66]

iii) Minoxidil

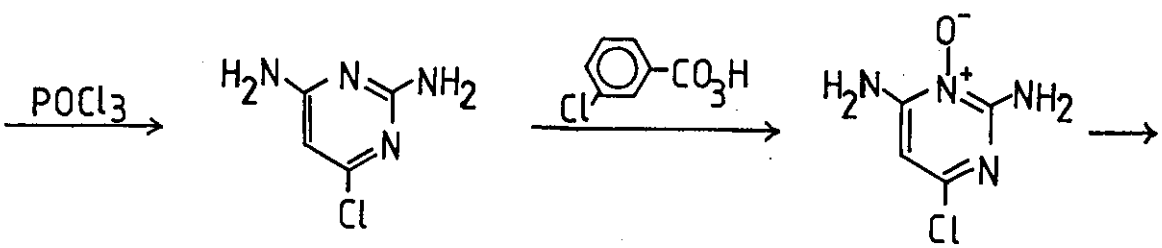


Minoxidil reduces peripheral resistance by a direct action on blood vessels. It is a potent vasodilator of long duration.[65] Minoxidil is used for the treatment of severe hypertension.[67] The daily dose, taken once daily, is 10 to 40 mg. Minoxidil has a longer duration of action compared to hydralazine. Minoxidil is used in combination with other drugs. Its side-effects include tachycardia (rapid action of heart). The combined use of minoxidil and β-blockers have proved effective for the control of severe hypertension.[65,67,68]

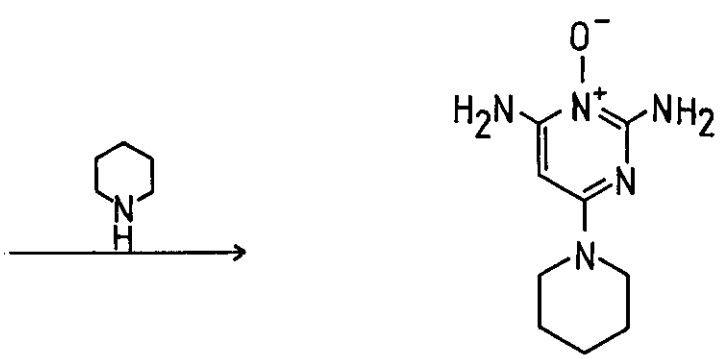
The synthesis of minoxidil is outlined below.[69] Condensation of ethyl cyanoacetate (29) with guanidine (30) in the presence of sodium ethoxide affords the starting pyrimidine (31). Reaction with phosphorus oxychloride replaces the hydroxyl group by chlorine to give (32). Treatment of (32) with metachloroperbenzoic acid, leads to the N-oxide (33). Further displacement of the halogen with piperidine affords minoxidil (10).



(29) (30) (31)

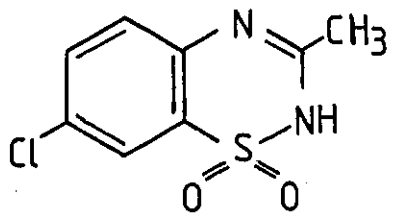


(32) (33)

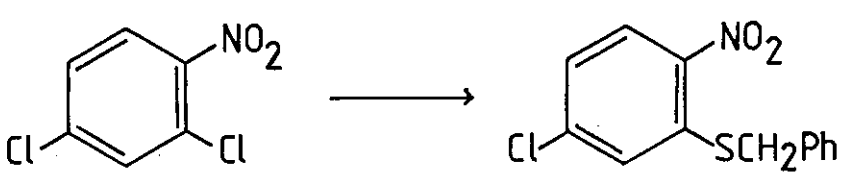


(10)

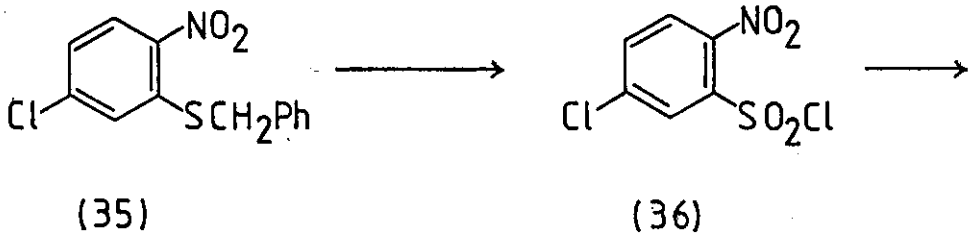
iv) Diazoxide



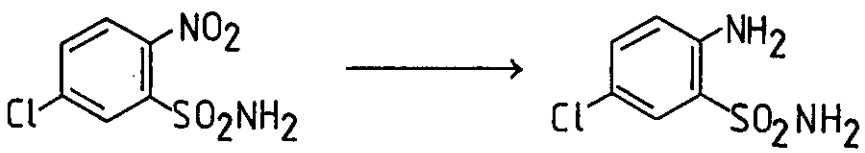
Diazoxide has been known since the early 1960's.[70] It is commonly considered as a peripheral dilating hypotensive agent. Diazoxide[71,72] bears a structural resemblance to the diuretic agent chlorothiazide (22), but unlike chlorothiazide, it is devoid of diuretic activity.[73-75] Diazoxide may be used in hypertensive crises, in emergencies and malignant hypertension. It is given by a rapid intravenous injection and the response is immediate. Diazoxide retains its action for as long as 24 hours. In patients with an impaired blood supply to the heart or brain, however, use of diazoxide will result in a rapid fall in blood pressure and will produce a significant reduction of blood to these organs. In these cases, use of sodium nitroprusside is preferred to diazoxide.[65]



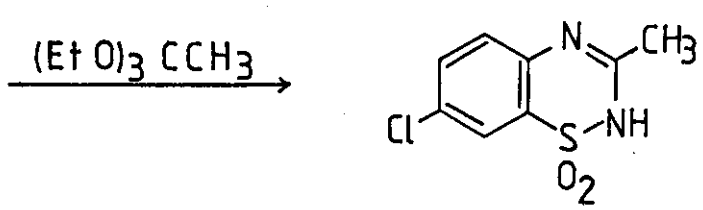
(34) (35)



(35) (36)



(37) (38)



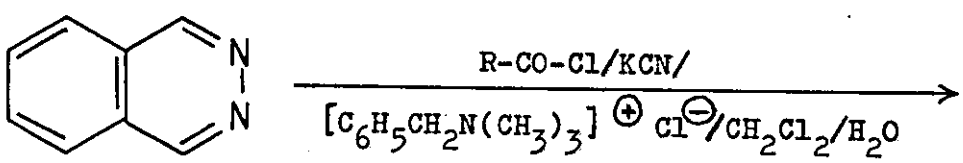
(9)

Diazoxide (9) is synthesised as outlined above, starting from 2,4-dichloronitrobenzene (34).[76] Benzylthiol anion displaces, surprisingly the ortho-chlorine, by nucleophilic substitution to give (35). Debenzylation with concomitant oxidation is achieved with aqueous chlorine. Treatment of the sulphonyl chloride (36) with ammonia gives the sulphonamide (37). Reduction of the nitro group gives the amine (38) and the ring is closed by means of ethyl orthoacetate.[75]

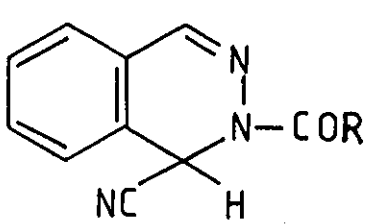
(C) Some Current Studies on

Pyrrolo[2,1-a]phthalazines & Related Systems

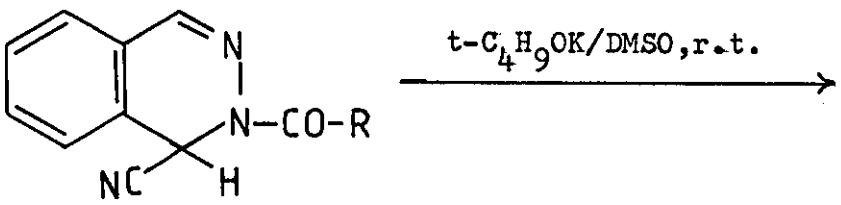
At the outset of our work, B.C. Uff and R.S Budhram had reported a new synthesis of the pyrrolo[2,1-a]phthalazine system.[2] The phthalazine Reissert compound (39) was prepared from phthalazine (23) by treatment with an acid chloride and potassium cyanide, in a two-phase system and in the presence of a phase transfer catalyst. The reaction of potassium t-butoxide in dimethyl sulphoxide with (39) then generates the carbanion (40) which on treatment with acrylonitrile provided the 3-arylpyrrolo[2,1-a]phthalazine-2-carboxamide (41) in good yield (54 - 65%).



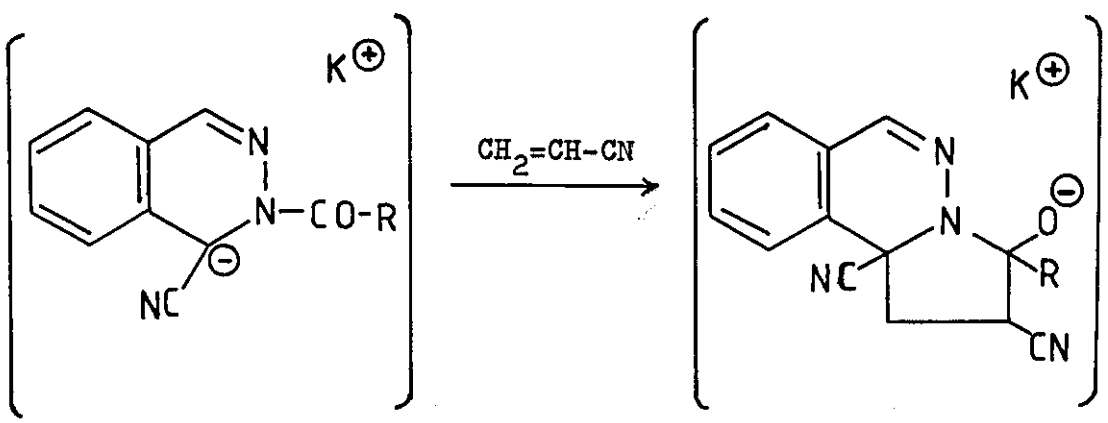
(23)



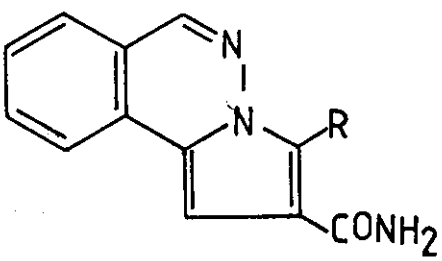
(39)



(39)



(40)

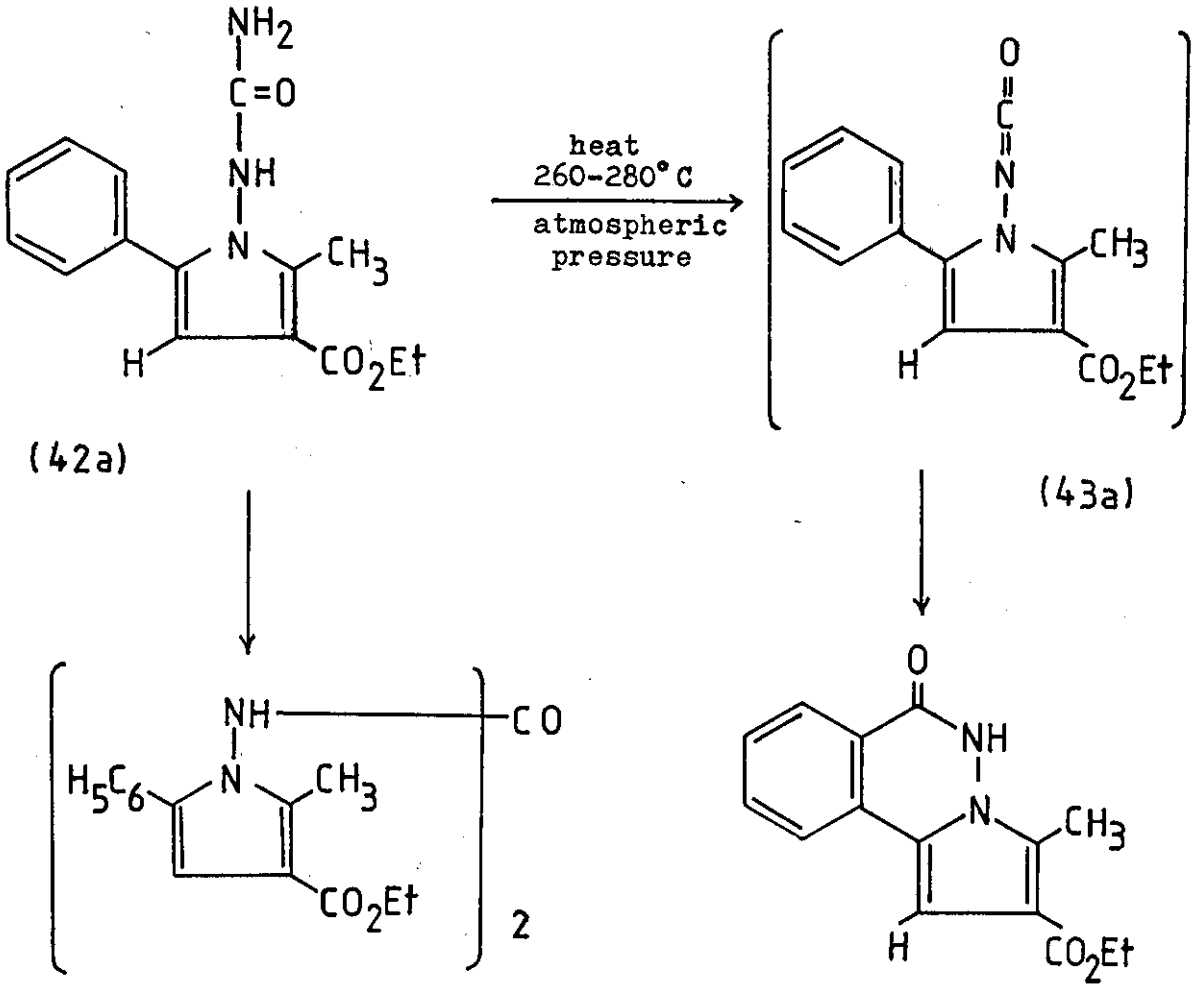


R=C_6H_5;4-CH_3-C_6H_4;

4-CH_3O-C_6H_4-;4-Cl-C_6H_4

(41)

In a somewhat different approach, pyrrolo[2,1-a]phthalazines (44a), (44b) were synthesised by Sprio et al.[77]



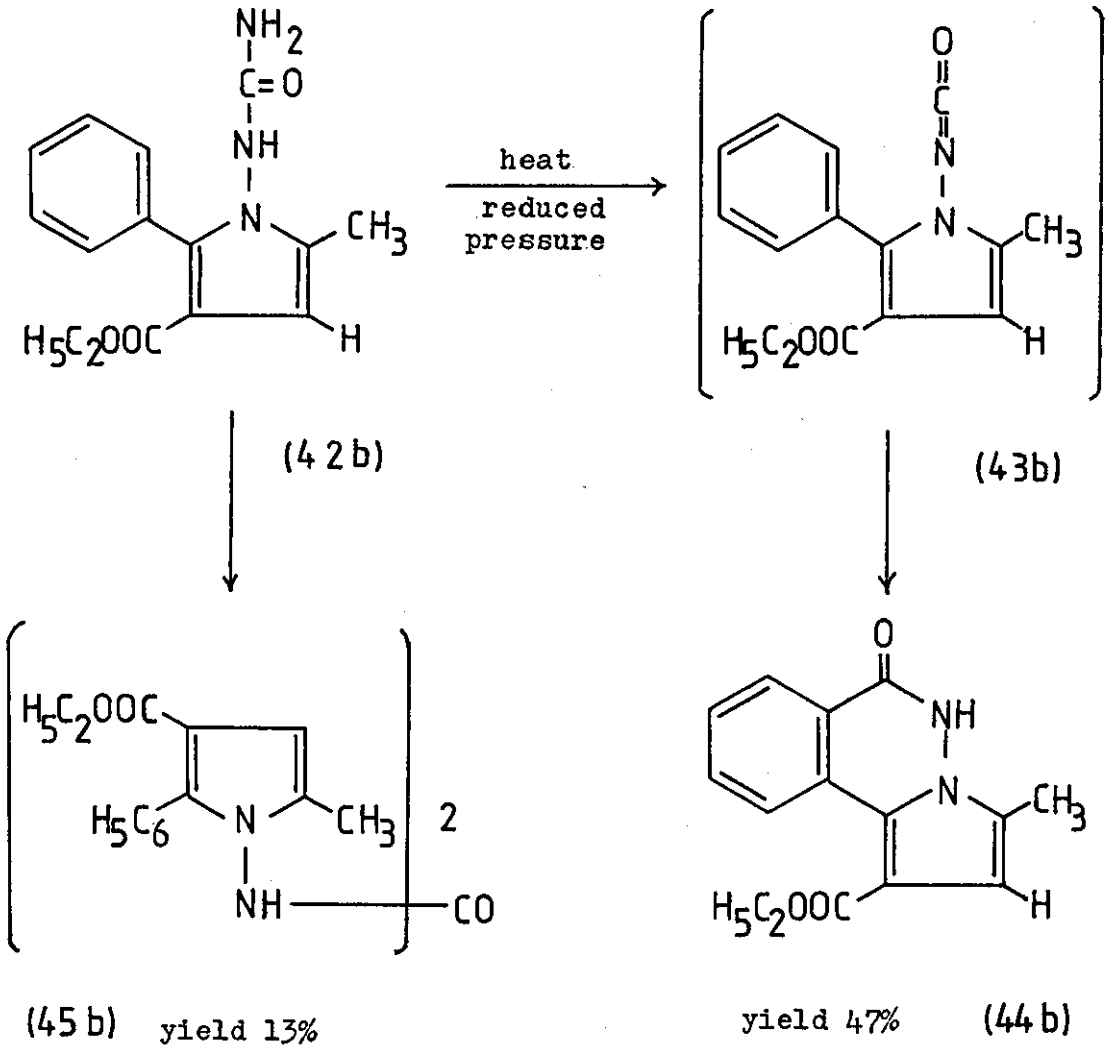
(42a)

(43a)

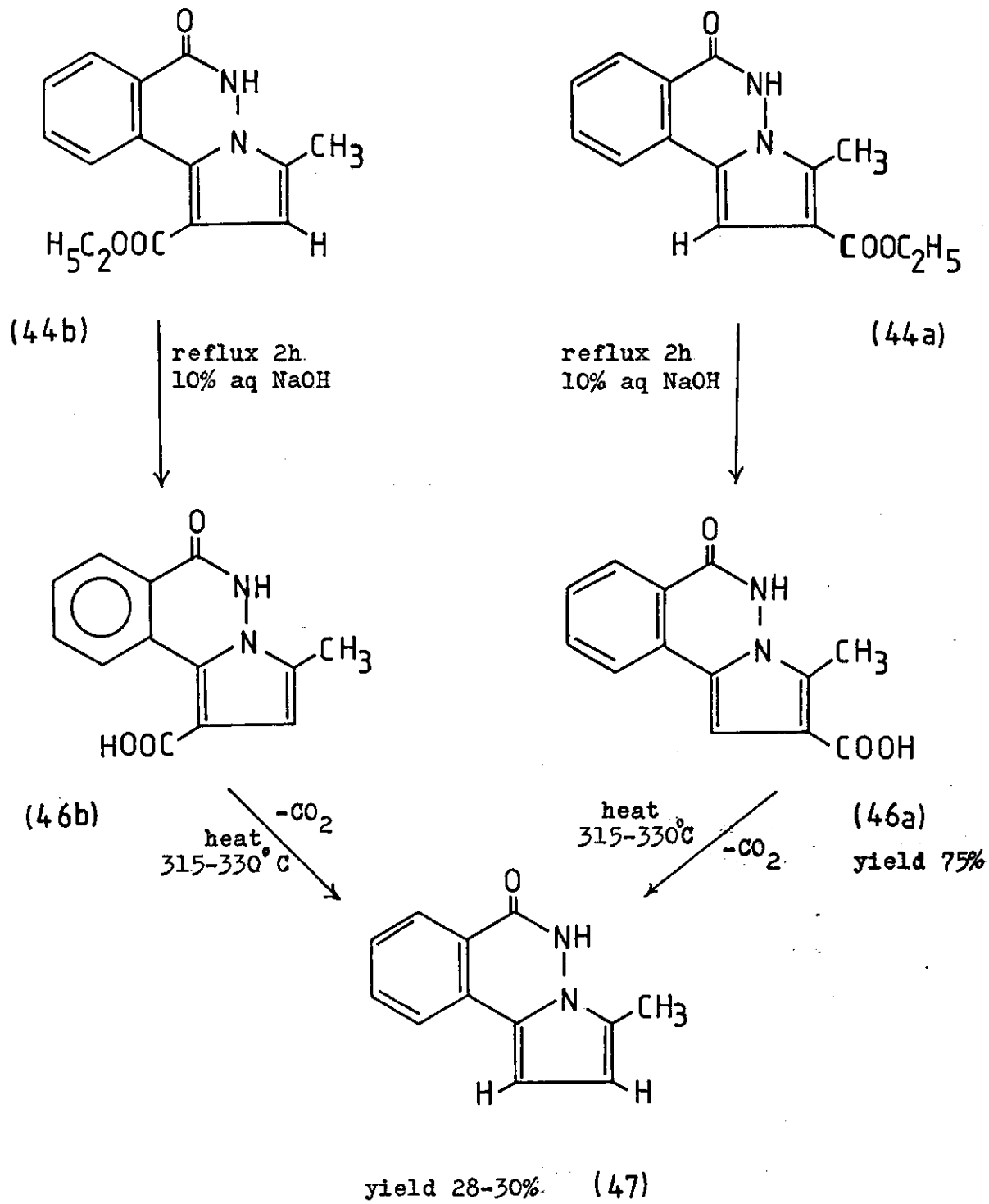
(45a) yield 23%

yield 21% (44a)

Cyclisation of N-ureidopyrrole (42a) and (42b) having a phenyl group at the α-position was achieved, by heating (42a) at 260°C-280°C at atmospheric pressure for 30 minutes[77] and by distillation of (42b) at reduced pressure, respectively.



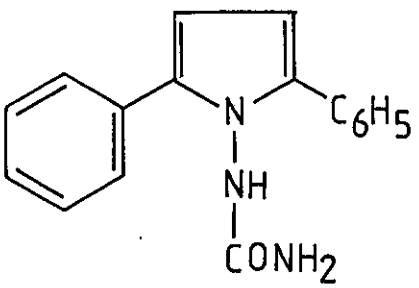
From the fusion mixture, some "dimerised" starting materials (45a) and (45b) were also isolated in 23% and 13% yield, respectively. Further hydolysis and decarboxylation of 44a, b afforded (47) in 30% yield.[77]



Formation of (47) is thought to occur by a reaction pathway in which initial loss of ammonia leads to generation of an isocyanate

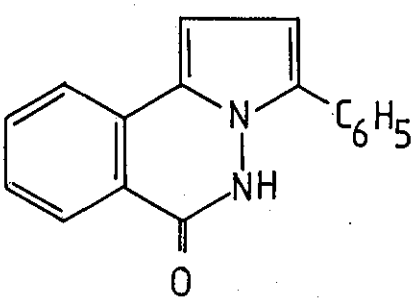
group. Electrophilic attack by the isocyanate group on the benzene ring effects cyclisation and thereby formation of the pyrrolo[2,1-a]phthalazin-6(5H)one.

In another experiment Sprio et al.[77] have pyrolysed 2,5-diphenyl-1-ureidopyrrole (48). In this case however, in addition to the pyrrolo[2,1-a]phthalazin-6(5H)one (49), they isolated another product, which proved to be 1-amino-2,5-diphenylpyrrole (50),. These authors[77] indicated that the formation of an intermediate such as (51) would also explain the formation of an N-aminopyrrole (50), namely through hydrolysis of the isocyanate group. It could also arise by direct hydrolysis of compound (48).

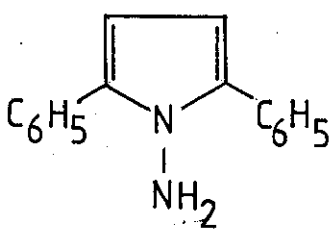


(48)

heat 260-280° C/30 min/N_2
atmospheric pressure

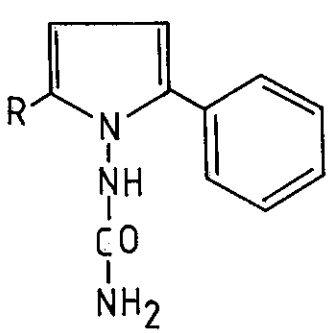


+

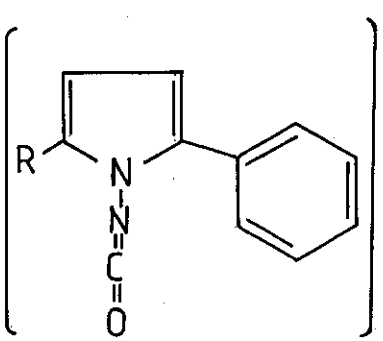


(49) yield 37%

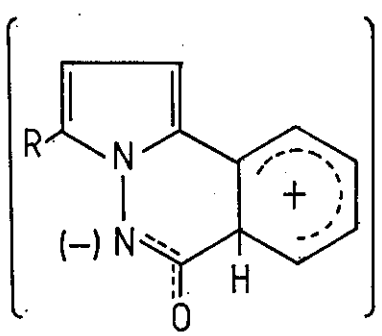
yield 27% (50)

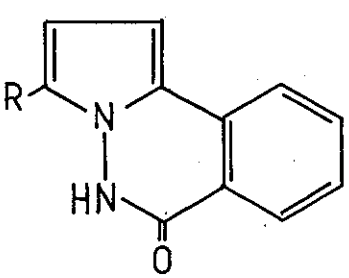


heat
$-NH_3$

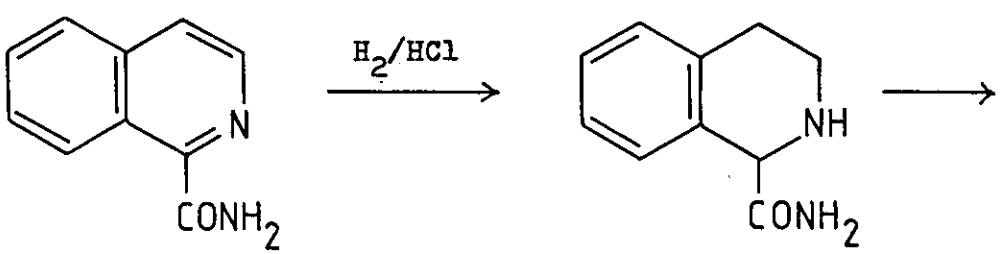


(51)

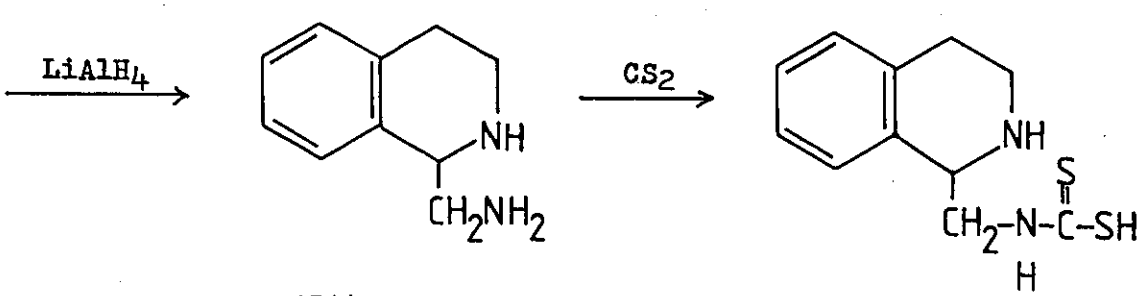




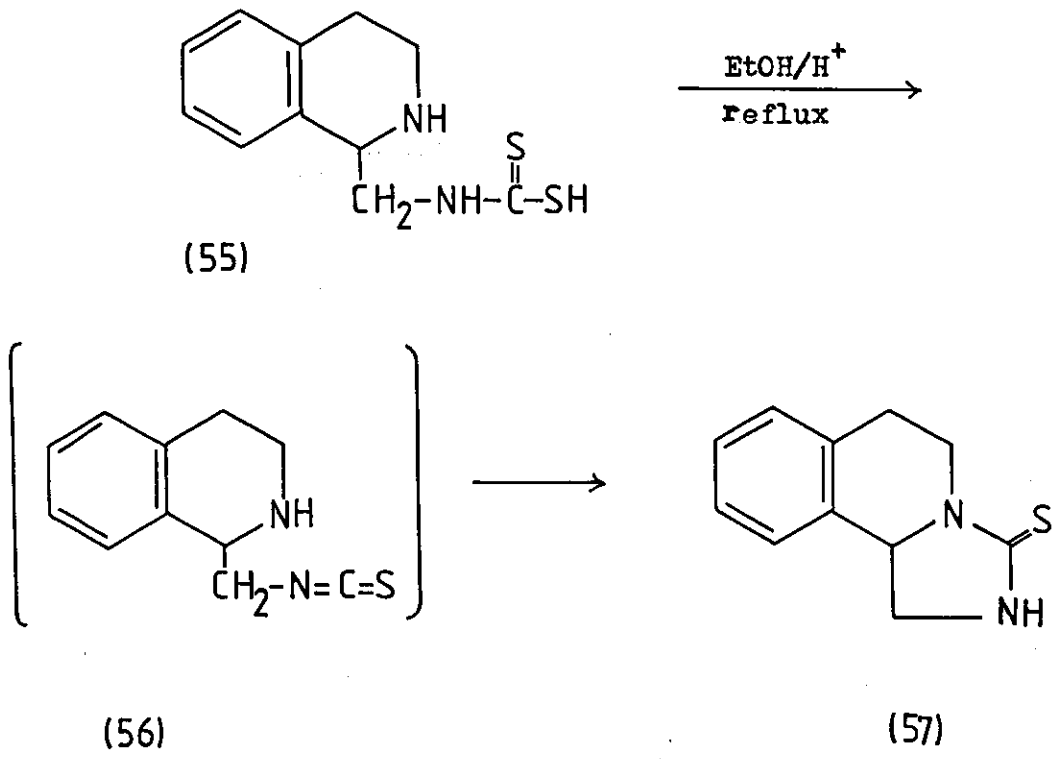
Tetrahydoimidazo[5,1-a]isoquinoline has been prepared by F.D. Popp et al.[78] by the following procedure. Hydrogenation of isoquinaldamide hydrochloride (52), under 3-atmospheres of hydrogen, yielded, tetrahydroisoquinaldamide (53). This compound (53), was then reduced with lithium aluminium hydride to give 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (54). The diamine (54), was reacted with carbon disulphide to give the dithiocarbamic derivative of 1,2,3,4-tetrahydroisoquinoline (55), which loses H_2S on heating with acid and cyclises to the tetrahydroimidazo[5,1-a]isoquinoline (57), via the isothiocyanate -derivative (56).[78]



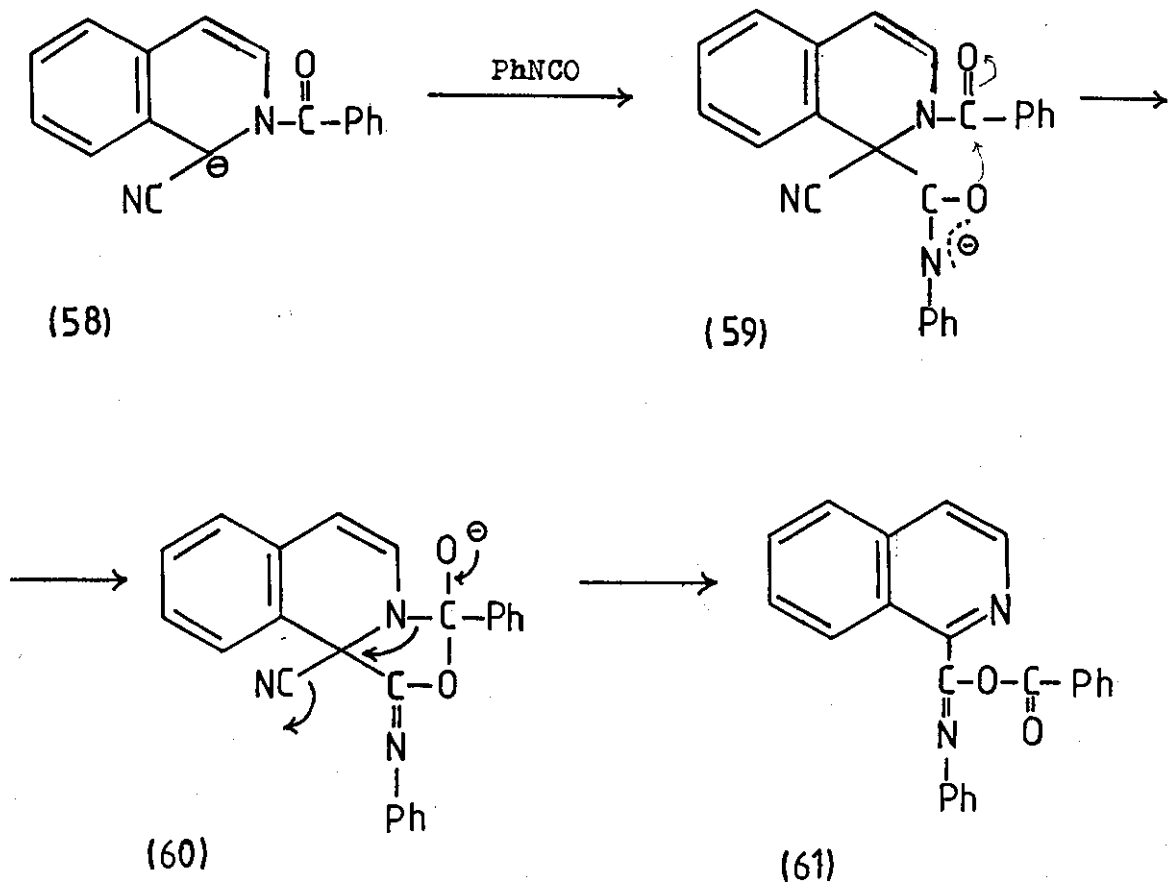
(52) (53)



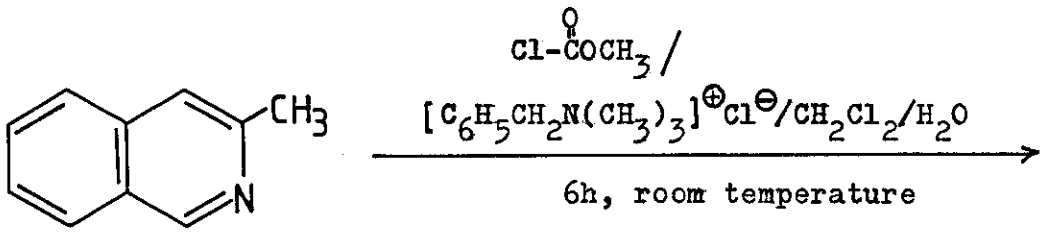
(54) (55)



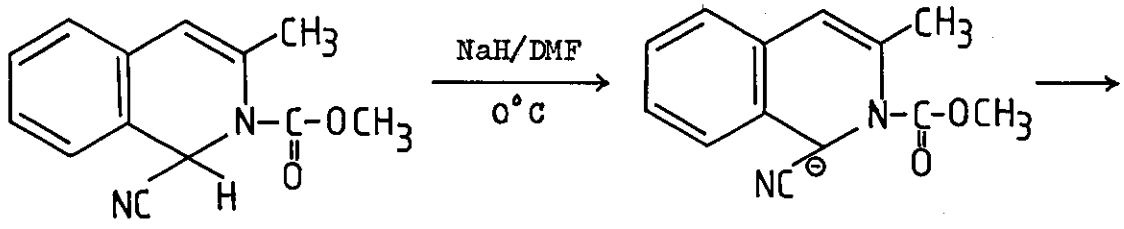
The condensation of phenyl isocyanate with the anion of 2-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (58), has been reported to give O-benzoyl-N-phenylisoquinaldimidate (61).[79] This reaction presumably proceeds by initial addition of (58) to the carbonyl carbon of phenyl isocyanate, to form (59), which then provides (61), via a tricyclicoxazolo-intermediate (60).[79] An important driving force for formation of (61), is likely to be the gain in resonance energy accompanying the ring opening step.



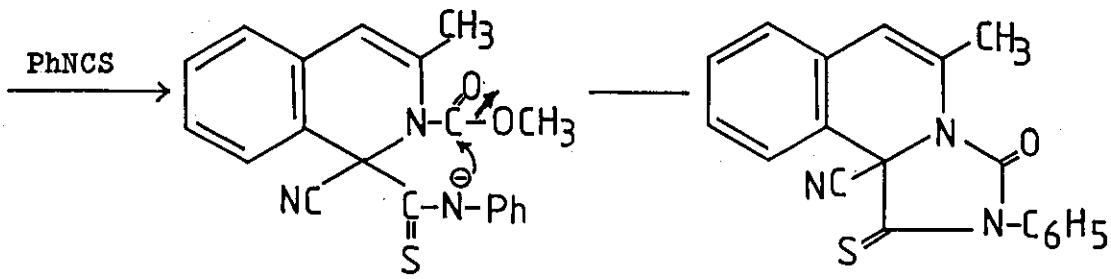
In order to prevent this ring opening, B.C. Uff and R.S. Budhram[80-81] have used Reissert compounds of the type (63), derived from chloroformates,[82] which possess a potential leaving group (i.e. -OR group, R = Alkyl or phnyl). The authors[80-81] studied the reaction of phenyl isothiocyanate with the anion of (63), which was generated by use of sodiumhydride in dimethylformamide at $0^{o}C$, and obtained 10b cyano-5-methyl-N-phenyl -1,2,3, 10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (4) as major product and a co-product whose structure was unknown at the out -set of the writer's studies.


Cl-COCH3 /
[C6H5CH2N(CH3)3]⊕Cl⊖/CH2Cl2/H2O
6h, room temperature
CH3
N

(62)


CH3
N-C-OCH3
O
NC
H
NaH/DMF
0°C
CH3
N-C-OCH3
O
NC⊖

(63)


PhNCS
CH3
O
N-C-OCH3
NC
C-N⊖-Ph
S
CH3
N
O
NC
N-C6H5
S

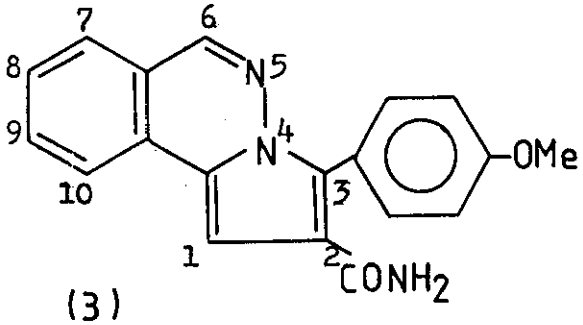
(4)

DISCUSSION

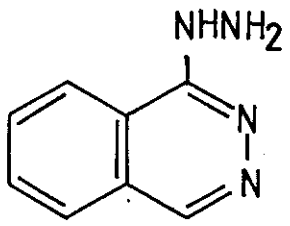
PART I

SYNTHESIS OF PYRROLO[2,1-a]PHTHALAZINES

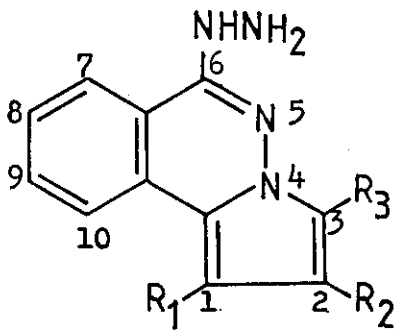
As described in the Introduction, we wished to study the chemistry of the pyrrolo[2,1-a]phthalazine system with a view to synthesizing a range of substituted derivatives. This would permit an assessment of the antihypertensive activity of the system as initially revealed by derivative (3) and related compounds in the work of R.S. Budhram and B.C. Uff.[1-3] Also, if a hydrazino-substituent could be introduced at position-6, as in (64), this would represent the tricyclic analogue of the important clinical antihypertensive agent, hydralazine (6), and so may show augmented activity over both hydralazine and compound (3).



(3)



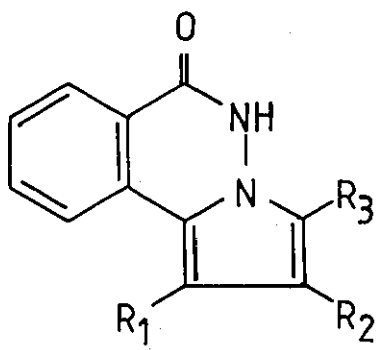
(6)



(64)

In Part I of the Discussion we describe the synthesis of the tricyclic system and in Part II studies with the pyrrolo[2,1-a]phthalazines.

We used the method of Plescia, Aiello and Sprio,[77] in order to obtain the pyrrolo[2,1-a]phthalazin-6 (5H)-one system (65) as our key intermediate. This structure was selected because of the functionalisation at positions-5 and-6 in the form of an amide unit. This functionalisation has been well explored in the phthalazine series[85] and should offer similar opportunities for modification in the tricyclic system. Sprio's synthesis also provided various functionalities at position -1, -2, and -3 to assist further diversification of our approach.



(65)

49 : R_1 = H R_2 = H R_3 = C_6H_5

44a : R_1 = H R_2 = COOEt R_3 = CH_3

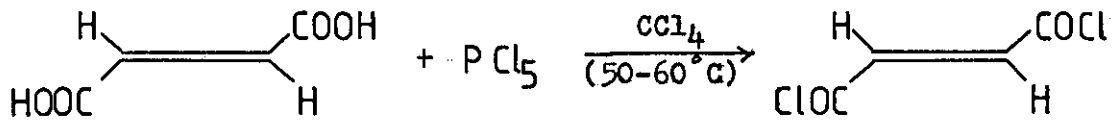
44b : R_1 = COOEt R_2 = H R_3 = CH_3

The Scheme and detailed preparation of phthalazinones (65) was as follows:

i) 3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (49)

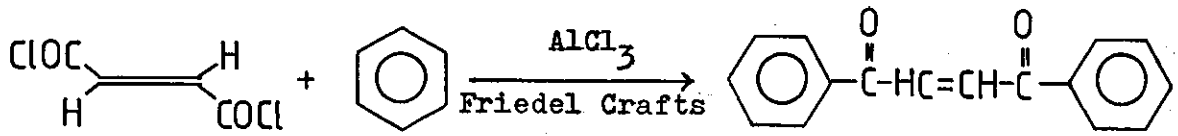
The approach was first to build the pyrrole ring from a 1,4-diketone, viz. 1,2-dibenzoylethane. This latter compound could be synthesised in three steps from fumaric acid.

Fumaryl chloride (67) was prepared in 27% yield by the reported method of Yang et al.,[86] through the reaction of fumaric acid (66) and phosphorus pentachloride in carbon tetrachloride for 2 hours at (50-60°C).



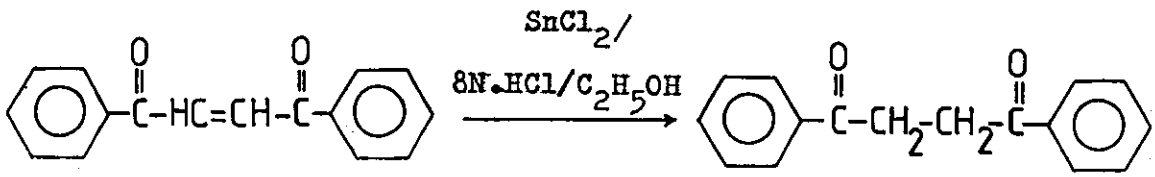
(66) (67) yield 27%

Trans-1,2-dibenzoylethylene (68) was prepared in 61% yield, by the reported method of Lutz et al.,[87] through the Friedel Crafts reaction of fumaryl chloride, dry benzene and aluminium chloride.



(67) (68) yield 61%

The synthesis of 1,2-dibenzoylethane (69), in 76% yield has been reported by Lutz et al.[88]:

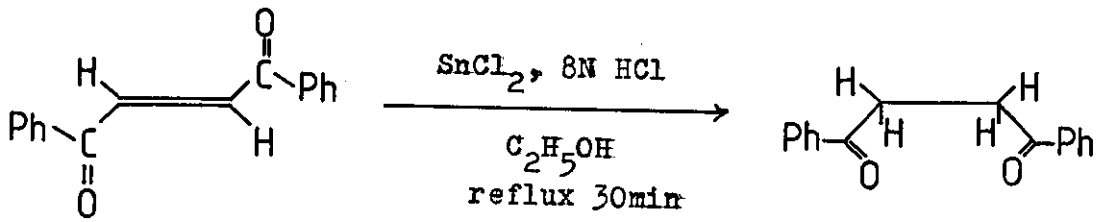


(68) (69) yield 76%

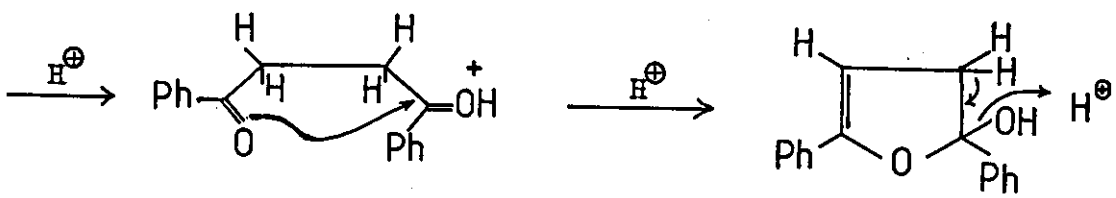
Based on the above method, in the first attempted preparation a hot solution of trans-1,2-dibenzoylethylene (68) in ethanol was added to a hot suspension of stannous chloride in 8N HCl and ethanol. No reaction time was reported by Lutz et al.[88] and so the mixture

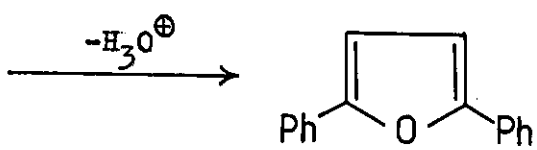
was refluxed for 30 minutes by which time a clear solution was obtained. This was then diluted with H_2O. A product was obtained as a colourless sharp melting solid, melting point 89-90°C. However Lutz et al.,[88] reported a melting point for 1,2-dibenzoylethane of 145-147°C. In the n.m.r. 60MHz ($CDCl_3$), our product showed only protons in the aromatic region, with resonances at δ7.1-7.9(10H,m) and δ6.7 (2H,m,aromatic) and no CH_2 resonances at ca δ3. The i.r. (nujol mull) showed ν_{max} 1600cm^{-1} (C=C), 1030cm^{-1} (C-O-C), and no carbonyl absorption in the region of 1680cm^{-1}. The mass spectrum of the compound showed m/e 220[$M^{+\cdot}$] as molecular ion and base peak. We therefore deduced the product obtained was, 2,5-diphenylfuran (70) given in 49% yield. Further investigation in the literature showed that 2,5-diphenylfuran has been synthesised in 86% yield, m.p 89.5-90°C[90] by treating trans-1,2-dibenzoylethylene with a refluxing mixture of conc. hydrochloric and acetic acid, for 15 minutes and then pouring into water. Thus we have shown that the same reduction and cyclisation takes place if the acetic acid is replaced by ethanol with a 30 minute reflux time, and using 8N HCl rather than conc. (12N) HCl.

A likely mechanism for the formation of 2,5-diphenylfuran (70) is as follows:



(68) (69)

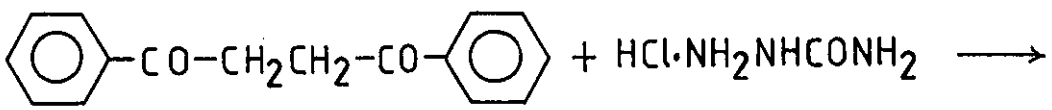




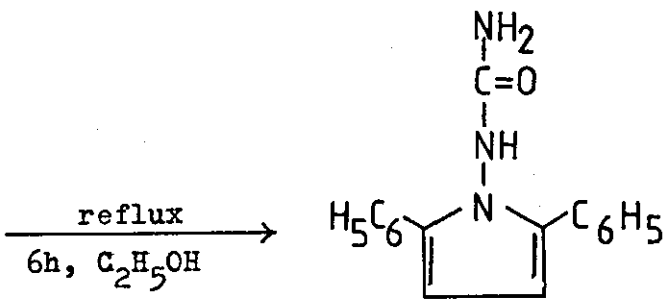
(70)

In the next repeated experiment for the synthesis of 1,2-dibenzoylethane, we again used 8N HCl (as originally used by Lutz *et al.*,[88] but the hot ethanolic suspension mixture of $SnCl_2$/HCl and *trans*-1,2-dibenzoylethylene was diluted with water *immediately* after mixing and not after 30 minutes. This gave 1,2-dibenzoylethane in 70% yield. The literature yield[88] was 76%.

1,4-Dicarbonyl compounds react with ammonia or primary amines to give pyrroles. The cyclisation of 1,2-dibenzoylethane was effected with one equivalent of semicarbazide hydrochloride as the amine, in ethanol and provided the 2,5-diphenyl-1-ureidopyrrole (48) in 48% yield.[89] Semicarbazide hydrochloride was used to provide the necessary nitrogen and carbon atoms for the subsequent ring closure to the tricyclic system.

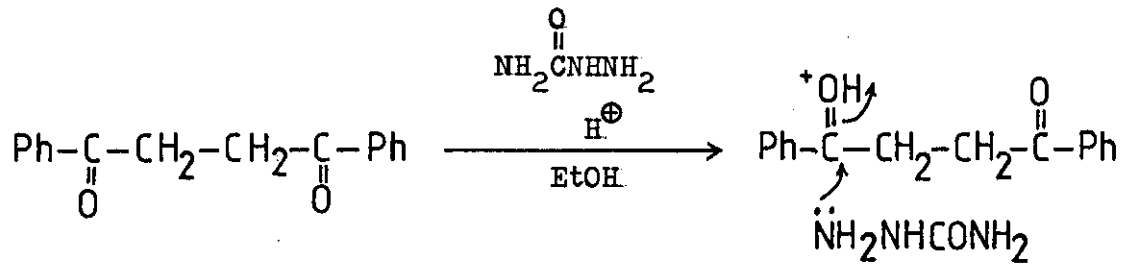


(69)

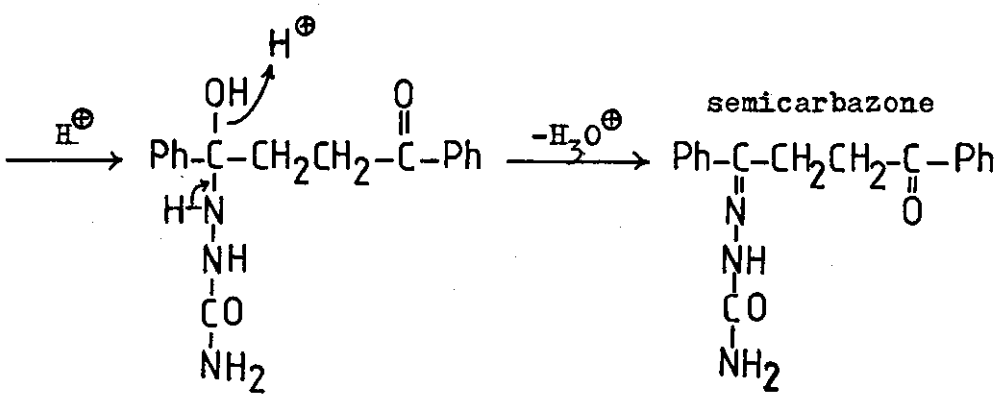


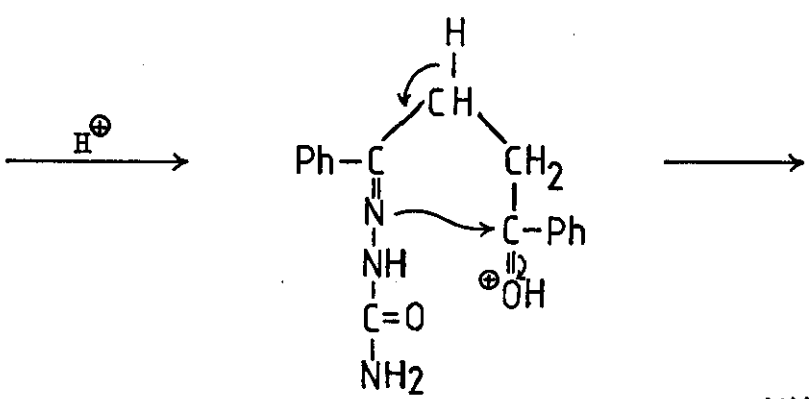
(48) yield 48%

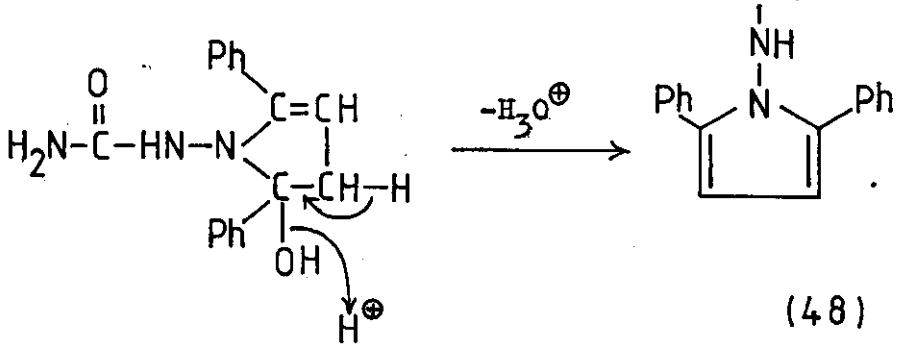
A possible mechanism for the formation of 2,5-dipenyl-1-ureidopyrrole (48) is via the semicarbazone which then cyclises to the product.



(69)



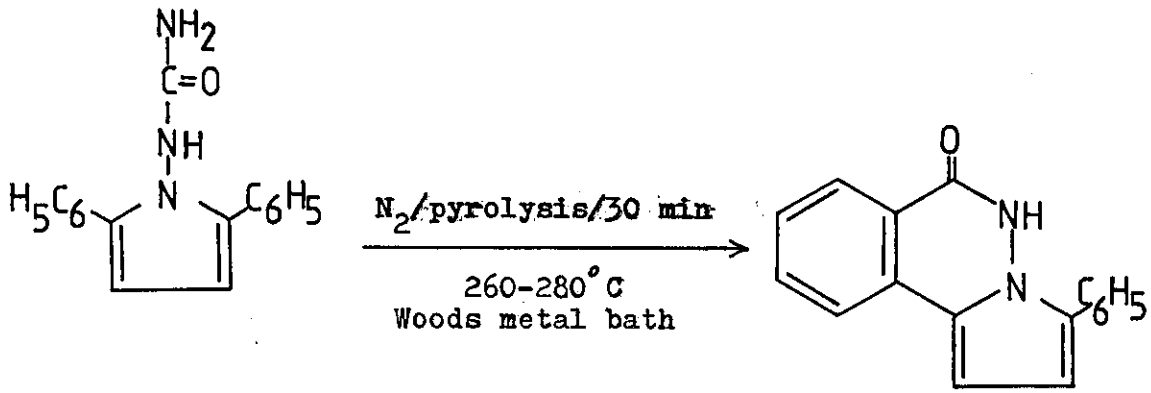




(48)

The compound (48) was then heated at 260-280°C under a nitrogen atmosphere for 30 minutes on a Woods metal bath. Wood's metal is an alloy of 50% Bi; 25% Pb; 12.5% Sn and 12.5% Cd. The resultant brown mixture was chromatographed on a silica gel column. Elution with cyclohexane - toluene (4:1) and further elution with toluene provided the 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (49) as yellow needles in 30% yield. The literature yield was 37%.

A possible mechanism of this reaction is discussed in the Introduction (p. 33).



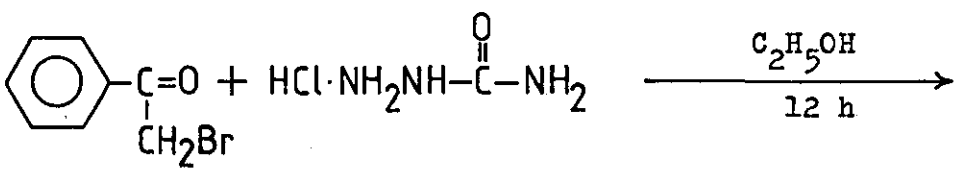
(48) (49)

The product (49) showed a carbonyl absorption at ν_{max} 1660cm^{-1} in the i.r. In the n.m.r. the two hydrogens of the pyrrole ring showed as a doublets at δ6.5 and 6.7, and the NH as a broad band at δ12.0.

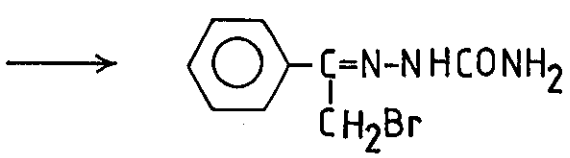
ii) 2-Ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthalazin-6(5H)-one (44a)

The title compound (44a) was prepared by a different procedure since the 1,4-diketone pyrrole precursor required is unsymmetrical.

ω-Bromoacetophenone semicarbazone (72) was prepared in 80% yield by the reported method of Sprio et al., [89] through the reaction of phenacyl bromide (71) and semicarbazide hydrochloride in ethanol for 12 hours at room temperature.

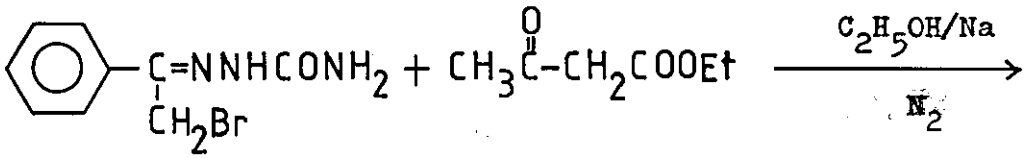


(71)

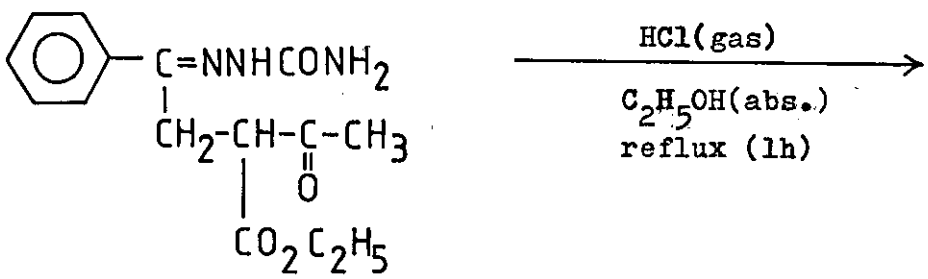


(72) yield 80%

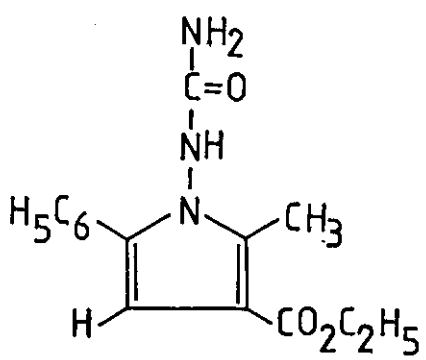
For the preparation of 3-ethoxycarbonyl-2-methyl-5-phenyl-1-ureidopyrrole (42a), we used the method of Sprio and Madonia, [89] which involves the reaction of ethyl acetoacetate, sodium ethoxide and ω-bromoacetophenone semicarbazone, followed by the introduction of gaseous HCl in dry ethanol and a reflux period of 1 hour as shown on page 48.


C=NNHCONH2
CH2Br
CH3C-CH2COOEt
O
C2H5OH/Na
N2

(72)

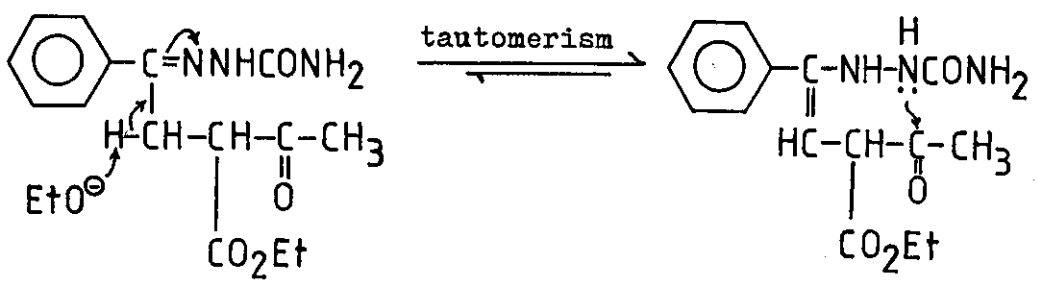

C=NNHCONH2
CH2-CH-C-CH3
O
CO2C2H5
HCl(gas)
C2H5OH(abs.)
reflux (1h)

(73)


NH2
C=O
NH
N
H5C6
CH3
H
CO2C2H5

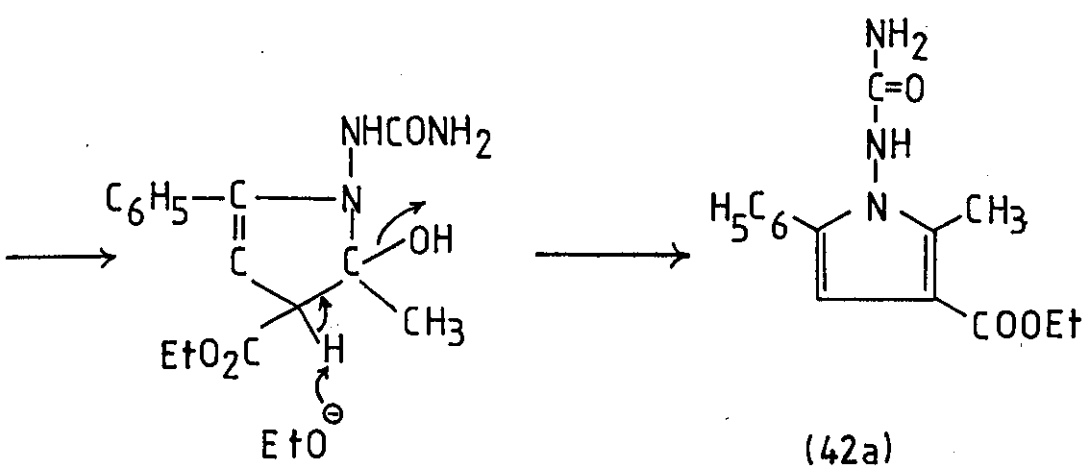
(42a)

Following the first step in the above method, the expected intermediate semicarbazone (73) reported melting point 120°C,[89] could not be isolated. However the product obtained showed a melting point of 248°C. The mass spectrum of this compound showed m/e 287 [$M^{+\cdot}$] as molecular ion and base peak. These data correspond to the cyclised product 3-ethoxycarbonyl-2-methyl-5-phenyl-1-ureido-pyrrole (42a). The n.m.r. 60 MHz ($DMSOd_6$), of this product showed δ9.25(1H,s,NH), δ7.1-7.5(5H, m, aromatic), δ6.45(1H,s,1H pyrrole), δ6.12 (2H, broad, NH_2), δ4.2 (2H,q, $CO_2\underline{CH_2}CH_3$), δ3.4 (3H,s,CH_3 at pyrrole) δ1.35(3H, t, $CO_2CH_2\underline{CH_3}$). The mechanism of the cyclisation may involve the following:



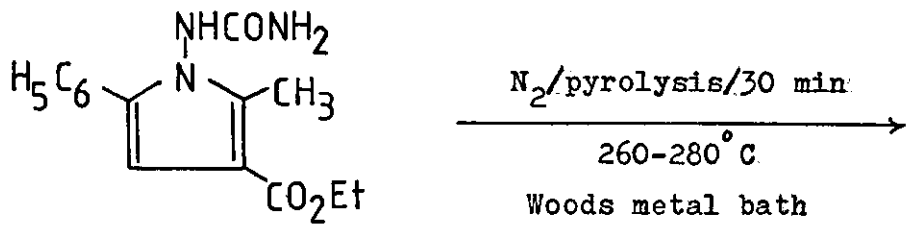
(73) imine

(74) enamine

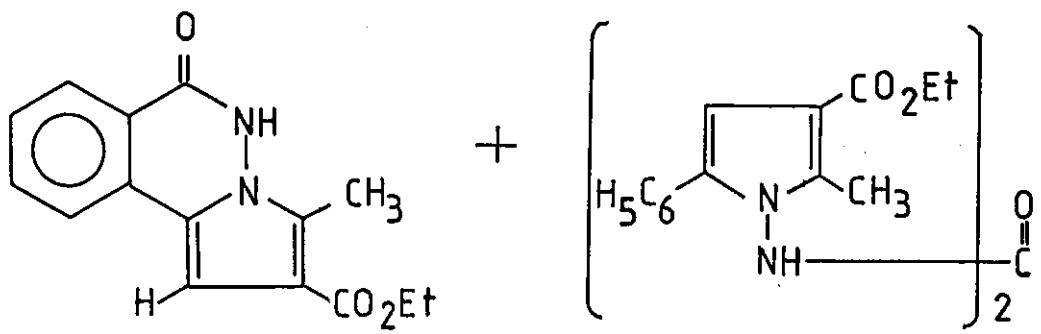


(42a)

Pyrolysis of the pyrrole (42a) was carried out by the reported method of Plescia, Aiello and Sprio.[77] The compound (42a) was heated at 260-280°C under a nitrogen atmosphere for 30 minutes.



(42a)



(44a) yield 7%

(45a)

The resultant brown mixture was chromatographed on a silica gel column. Elution with toluene - ethyl acetate (9:1) removed the 2-

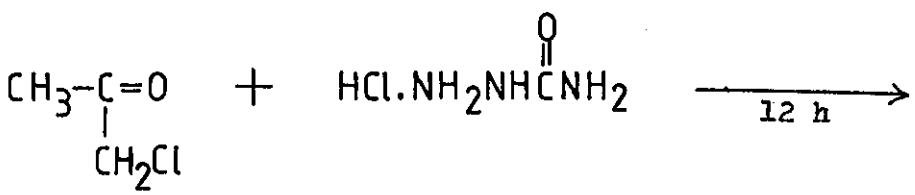
-ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthalazin-6 (5H)-one (44a) in only 7% yield. The literature yield was 21%. The n.m.r. 60 MHz ($DMSOd_6$), of this compound showed δ1.3 (3H, t, $CO_2CH_2\underline{CH_3}$), δ2.6 (3H, s, CH_3 at pyrrole), δ4.1 (2H, q, $CO_2\underline{CH_2}CH_3$), δ7.1-8.1 (5H, m, aromatic), δ13.5 (1H, broad, NH), and in the i.r. this compound showed ν_{max} 1660cm^{-1} and 1700cm^{-1} (2XCO).

Further elution with toluene - ethyl acetate (8:2) removed (45a) which was not isolated pure.

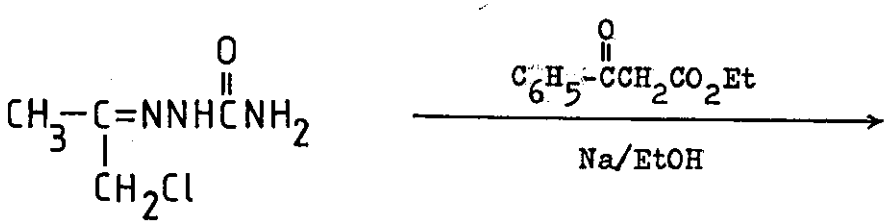
iii) 1-Ethoxycarbonyl-3-methylpyrrolo[2,1a]phthalazin-6(5H)-one (44b)

The title compound again required an unsymmetrical pyrrole and was approached via the monosemicarbazone of a 1,4-diketone.

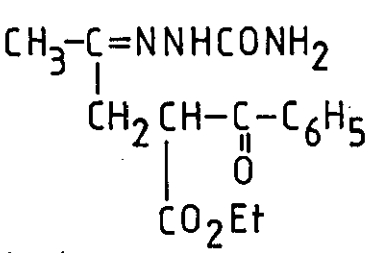
The reaction of chloroacetone (75) with semicarbazide hydrochloride in ethanol at room temperature for 12 hours afforded chloroacetone semicarbazone (76), in 62% yield.



(75)

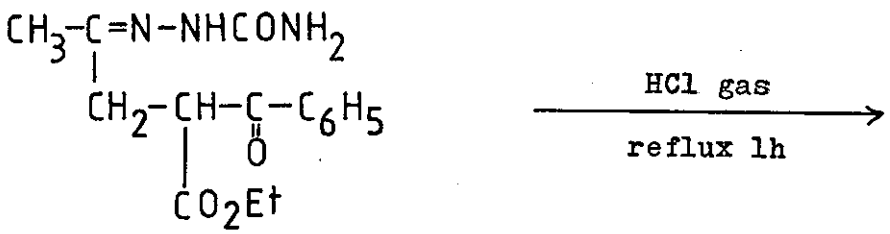


(76) yield 62%

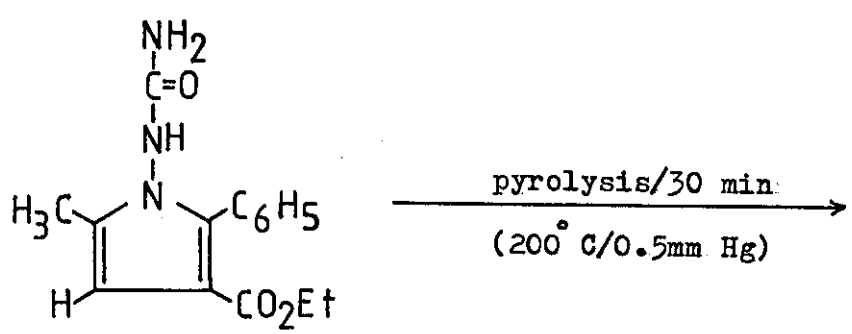


(77) yield 50%

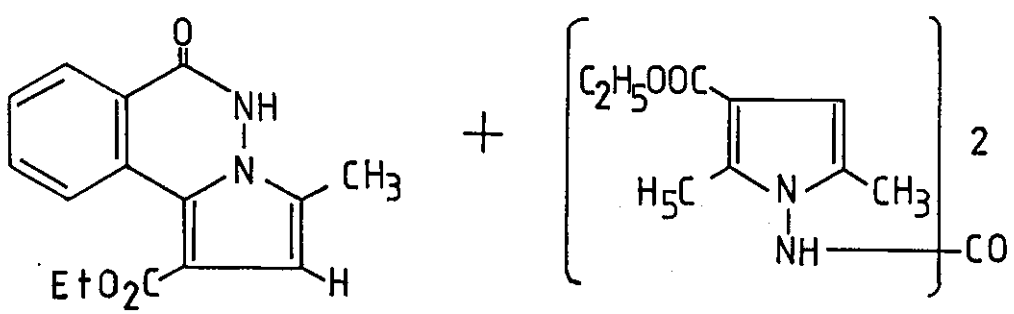
The chloroacetone semicarbazone was then converted in 50% yield, to the ethyl 2-benzoyl-4-semicarbazonopentanoate (77), on treatment with ethyl benzoylacetate and sodium ethoxide in dry ethanol and under a nitrogen atmosphere. The cyclisation of the ester (77) in a solution of dry ethanol which was saturated with gaseous HCl provided the 3-ethoxycarbonyl-5-methyl-2-phenyl-1-ureidopyrrole (42b), in good yield (80%).



(77)



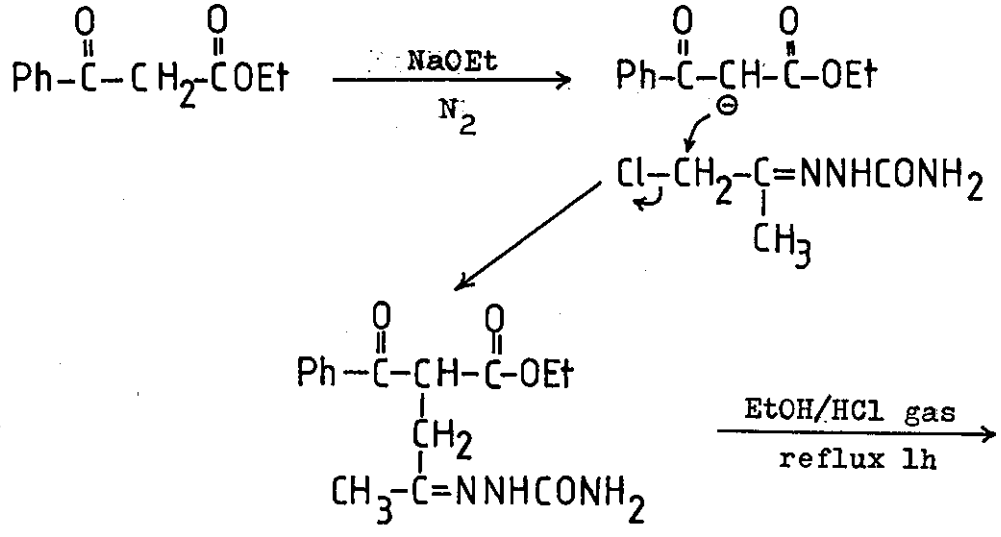
(42b) yield 80%



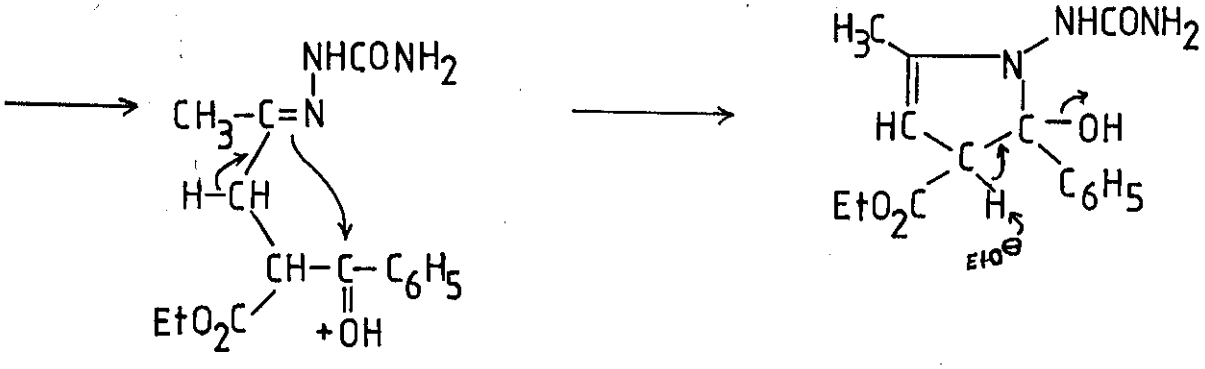
(44b) yield 11%

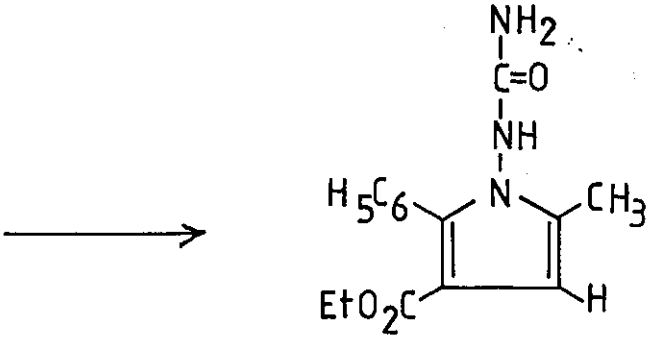
(45b)

A likely mechanism is outlined:



(77)





(42b)

It should be noted that in the base catalysed mechanism of (73) the phenyl ring may be assisting in conjugation and stabilisation of the enamine structre (74). This is in contrast to the cyclisation of ethyl 2-benzoyl-4-semicarbazonopentanoate (77), which was not cyclised directly but by introduction of gaseous HCl in dry ethanol and a reflux period of 1 hour.

It is notable that the one-pot formation of the pyrrole (42a) occurs at room temperature.

Pyrolysis of 3-ethoxycarbonyl-5-methyl-2-phenyl-1-ureidopyrrole (42b) on a Woods metal bath at 200°C/0.5mm Hg, gave a yellow liquid which was distilled and solidified on standing. The resultant yellow solid was purified by fractional recrystallisation from ethanol and provided 1-ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthalazin-6(5H)-one (44b) in only 11% yield. The reported yield by Sprio et al.[77], was 47%. In the i.r. this compound showed ν_{max} 1660cm^{-1} and 1700cm^{-1} (2 x CO) and in the n.m.r. 60 MHz (DMSOd_6): δ1.3 (3H, t, $CO_2CH_2\underline{CH_3}$), δ2.4 (3H, s, CH_3, at pyrrole), δ4.2 (2H, q, $CO_2\underline{CH_2}CH_3$), δ6.8 (1H, s, 1H at pyrrole), δ7.5-8.3 (3H,m,H_7,H_8 and H_9), δ10.6 (1H, m, H_{10}), δ13.0 (1H, broad, NH).

A second product N,N' - bis (1-pyrrolyl) urea (45b) also reported by Sprio et al.[77], was present to a minor extent and not isolated pure.

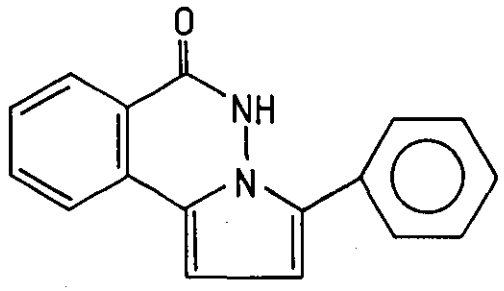
Our studies had provided three pyrrolo[2,1-a]phthalazin-6(5H)-one (49), (44a) and (44b) in yields, for the final cyclisation step, of 30%, 7% and 11%, respectively. In view of the disappointing low yields in these last two cases, which we could not improve, we restricted

our subsequent studies to compound (49), 3-phenylpyrrolo[2,1-*a*]phthalazin-6(5H)-one.

PART II

STUDIES WITH PYRROLO[2,1-a]PHTHALAZINES

As described in Part I we had prepared satisfactorily 3-phenylpyrrolo [2,1-a]phthalazin-6(5H)-one (49) which we now wished to modify particularly in the 5- and 6- positions and possibly elsewhere also.

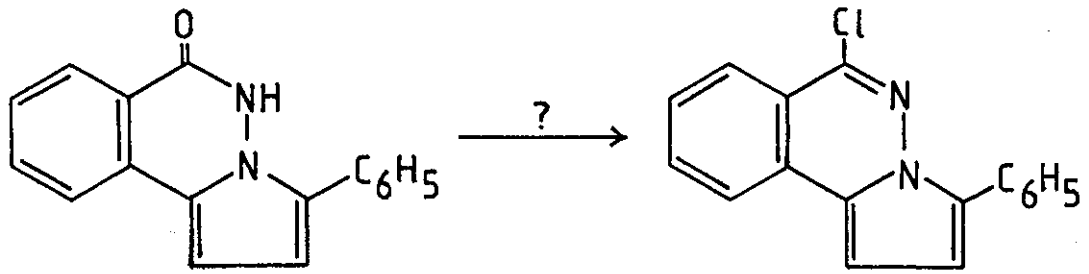


(49)

A. Syntheses of Pyrrolo[2,1-a]phthalazines substituted at Position -6

i) Substitution by chlorine at position -6

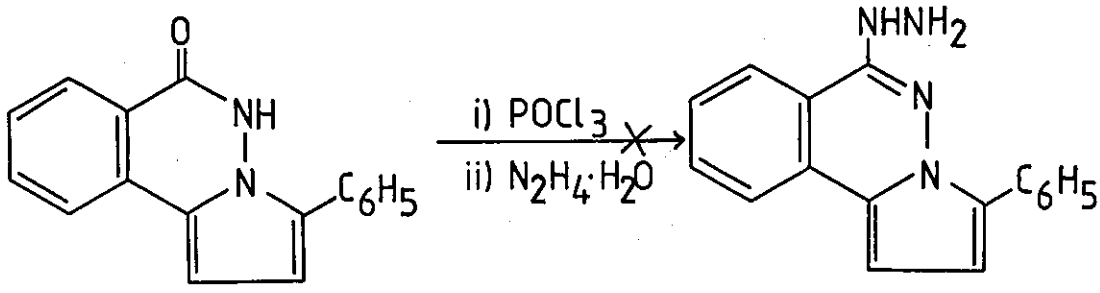
We first investigated converting 3-phenylpyrrolo[2,1-a]phthalazin -6(5H)-one (49) to the chlorophthalazine (78) since chlorine is a good leaving group and substitution of the product by various nucleophiles could be then investigated.



(49) (78)

As mentioned in the introduction (p. 21) 1-chlorophthalazine (27) is made in high yield (78-96%) by refluxing, phthalazin-1(2H)-one, with $POCl_3$.[91-93] Therefore we first examined the reaction of 3-phenylpyrrolo [2,1-a]phthalazin-6(5H)-one with one equivalent phosphorous oxychloride and a reflux period of 30 minutes. However only the staring material was recovered. This reaction was repeated with a large excess of $POCl_3$ and a reflux period of 5 hours. The product obtained was a yellow solid m.p. 112-115°C, which unfortunately could not be obtained pure. The melting point of the staring material was 186°C, and a sodium fusion test on the impure product proved the presence of chlorine. This compound in the i.r. showed ν_{max} 1635cm^{-1} (C=N). Our product proved very unstable at room temperature i.e. the compound on standing at room temperature after 2 hours turned dark yellow, dark brown and then to black, indicating decomposition. Similar observations for 1-chlorophthalazine have been reported,[94-97] and 1-chlorophthalazine has to be used fresh because of its instability.[95] It undergoes a gradual transformation, on standing at room temperature, into higher melting substances.[93,94]

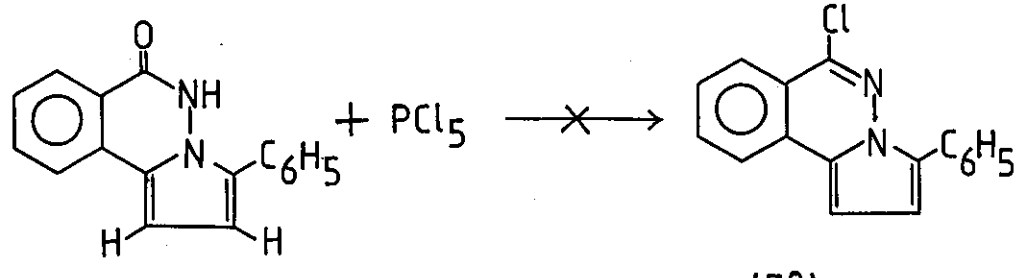
Immediate reaction of our product with hydrazine hydrate in ethanol on a hot water bath for 2 hours, gave a green solid, (m.p.109°-112°C). This compound on standing at room temperature after 30 minutes turned to dark brown and then to black.



(49) (79)

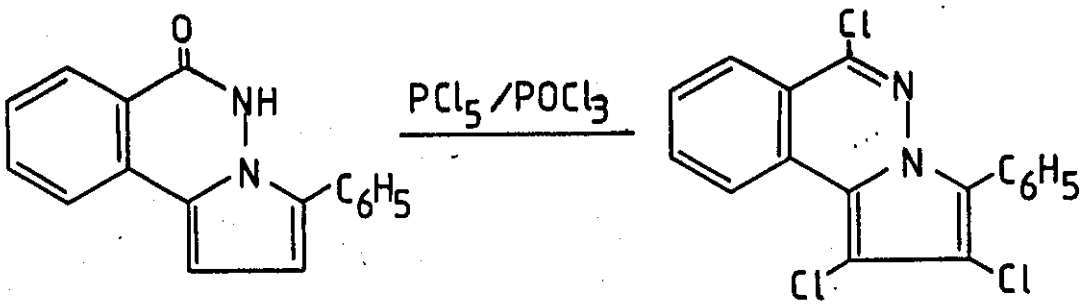
The 1-hydrazinophthalazine itself, is known to be very unstable,[61,98] but it forms stable salts with strong acids (e.g. HCl). We therefore treated the crude product (79) with a saturated solution of gaseous HCl in absolute ethanol at 0°C.[53a] However no HCl salt could be obtained. Instead a black gum which could not be crystallised was obtained. In view of these difficulties this approach was not further investigated.

An alternative route for preparation of 1-chlorophthalazine involves heating the phthalazin-1(2H)-one with PCl_5.[99-102] Therefore the reaction of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one with PCl_5 in carbon tetrachloride at room and reflux temperatures was studied. However the mixture even after refluxing for 14 days did not give the required chloro-derivative (78). Here again a yellow solid was obtained m.p. 148-150°C, ν_{max} 1630cm^{-1} (C=N). A sodium fusion test proved the presence of chlorine. The mass spectrum of this compound showed m/e 294 as a base peak, and highest m/e 350 and could not be identified.



(49) (78)

Another alternative route for converting phthalazine to 1-chlorophthalazine involves the heating of the phthalazin-1(2H)-one with $POCl_3/PCl_5$ mixture.[103,104] Using this mixture with 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one and a reflux period of 90 minutes the reaction provided chlorination at C-6 but also in the pyrrolo ring at positions -1 and -2. The trichloro derivative (80) was given in 63% yield.

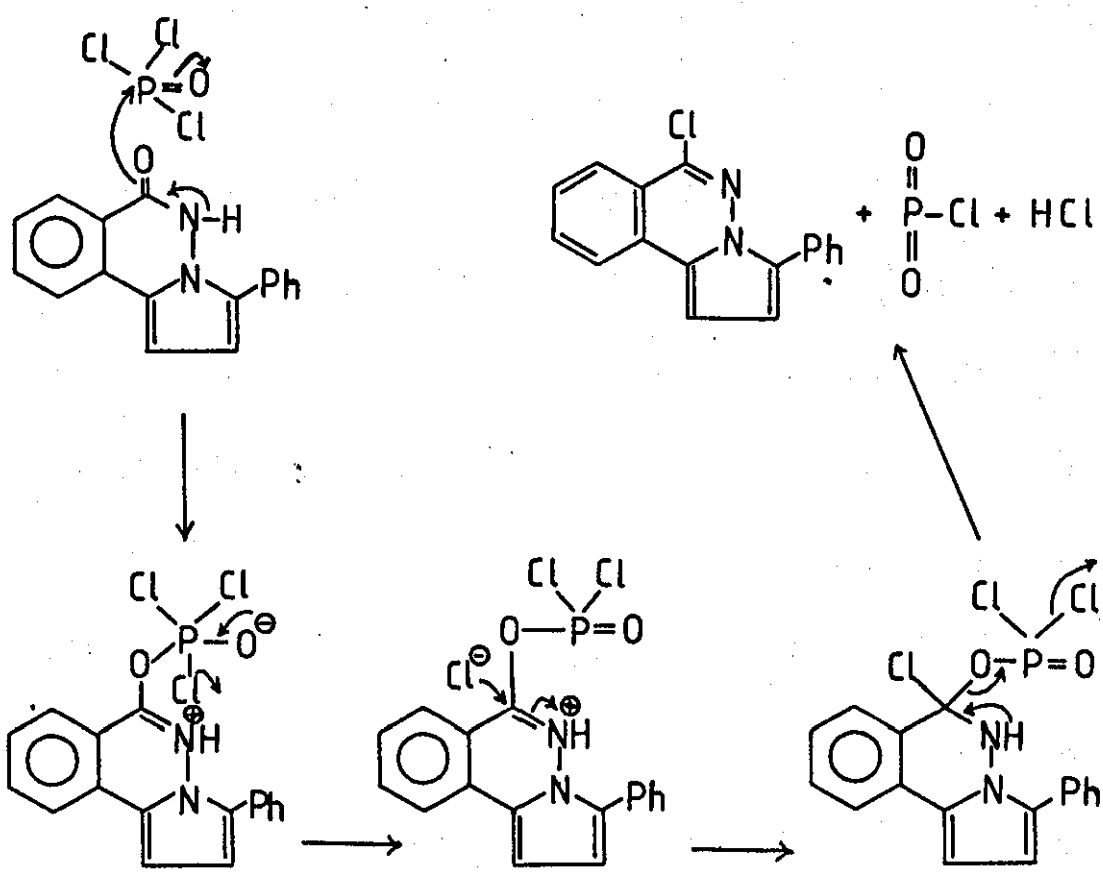


(49) (80)

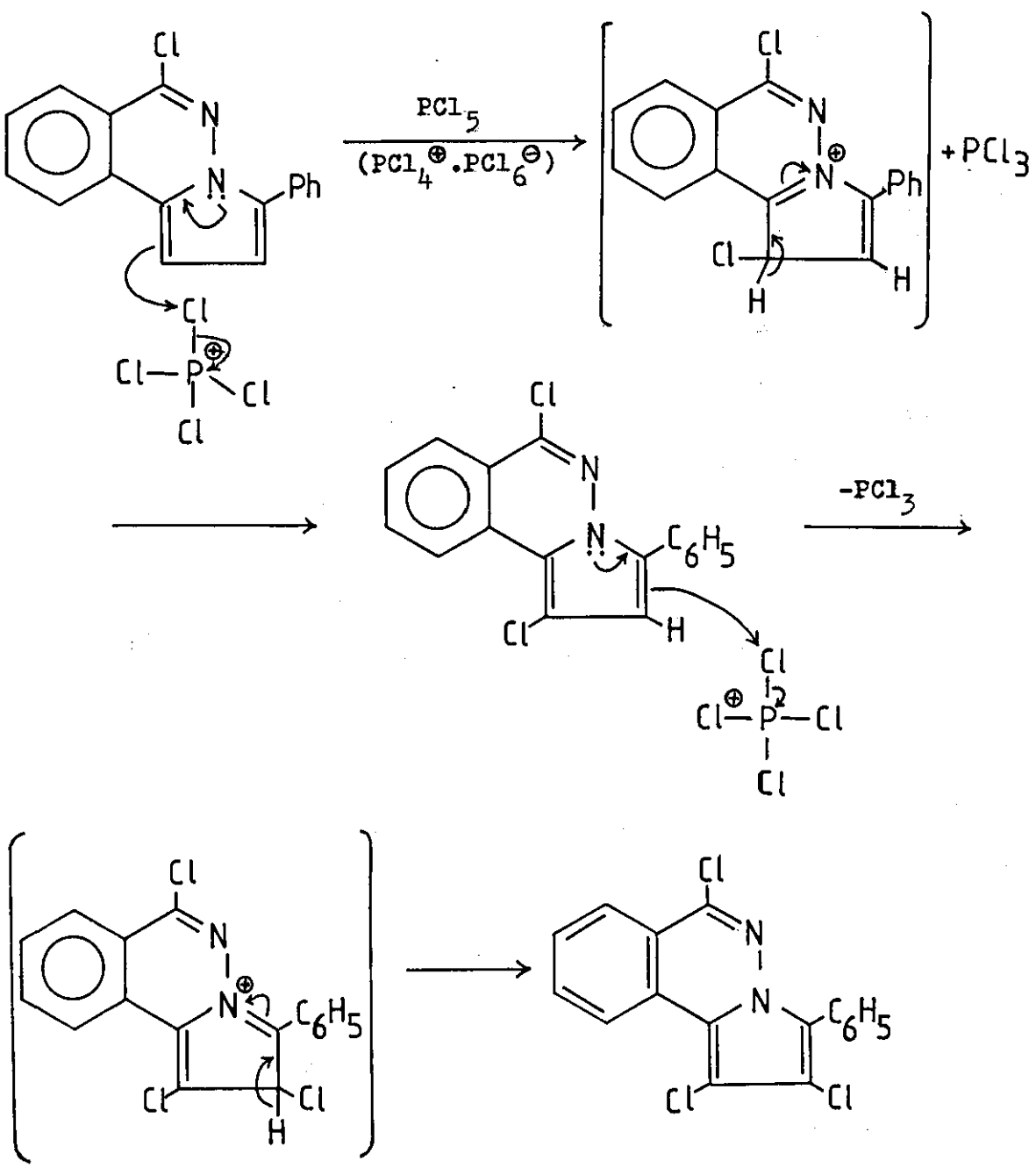
The structure of (80) was deduced as follows. The mass spectrum of the compound showed a molecular ion cluster at m/e 346, 348, 350, 352, in the relative ratios of 27:27:9:1, in accord with the molecular formula of (80). The cluster also represented the base peak. By means of a binomial expansion $(a + b)^n$ the intensity of molecular-ion clusters owing to halogen isotopes may be calculated were n is the number of the halogen atoms, a is the relative abundance of the lighter isotope and b is the relative

abundance of the heavier isotope. In general n halogen atoms produce a cluster of (n + 1) peaks spaced two mass units apart. If three chlorine atoms are present: n=3, a=3, b=1, (as ^{35}Cl : ^{37}Cl occur in the relative abundance of 3:1) then $a^3 + 3a^2b + 3ab^2 + b^3 = 27 + 27 + 9 + 1$. In the i.r. the carbonyl peak of (49) at 1660cm^{-1} was absent but there was a peak at ν_{max} 1615 (C=N). In the 60 MHz n.m.r. ($CDCl_3$), this compound showed a multiplet at δ7.2-8.9 (m, aromatic). The characteristic two doublets at δ6.5 and δ6.7 for the protons at pyrrole ring in the staring 3-phenylpyrrolo[2,1-a] phthalazin-6(5H)--one had disappeared. We had also obtained correct analytical data for this compound.

The possible mechanism for the chlorination of 3-phenylpyrrolo [2,1-a] phthalazin-6(5H)-one using $POCl_3/PCl_5$ mixture may be as follows:



The chlorination of the pyrrole ring is due to phosphorus pentachloride acting as an electrophilic reagent as the pyrrole ring is an electron rich system. The chlorination at C-6 is nucleophilic in character whereas the chlorination at C-1 and C-2 is electrophilic in character.



(80)

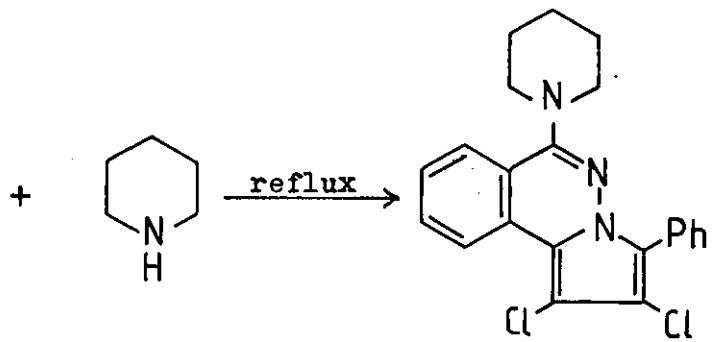
Electrophilic chlorination by phosphorus pentachloride has been reported for a number of activated aromatic compounds, including mesitylene,[105] aniline derivatives, [106] and polynuclear hydrocarbons such as anthracene.[107] The mechanism of the reaction probably involves the PCl_5 ionising to $\overset{+}{P}Cl_4\ \overset{-}{P}Cl_6$, so that the $\overset{+}{P}Cl_4$ behaves as the source of the electrophilic chlorine atom.[108] This also has been demonstrated in the case of alkenes, for example cyclohexene is converted to trans-1,2-dichloro-cyclohexane.[109, 105]

The 1,2,6-trichloro-product (80) appeared stable and could be stored satisfactorily for several weeks without deterioration. Since the 6-monochloro-derivative had proved unstable we decided to continue our studies with the trichloro-compound to examine in particular its susceptibility to nucleophilic substitution. It was hoped that the 6-position would be preferentially susceptible since normally a pyrrole system is not susceptible to nucleophilic substition. [110,111] It was recognised however that the two chlorines at C-1 and C-2 may have modified the situation. Substition at C-6 however should occur readily since the system is analogous to a 2-chloropyridine.[112]

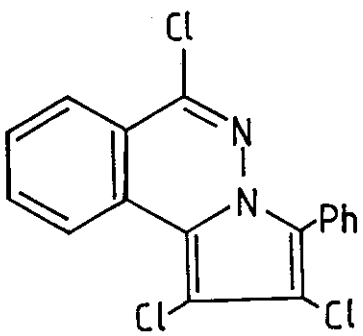
If substitution at C-6 could be achieved,then possibly the residual chlorines at C-1 and C-2 could be removed reductively.

ii) Substitution by nitrogen functions at position -6

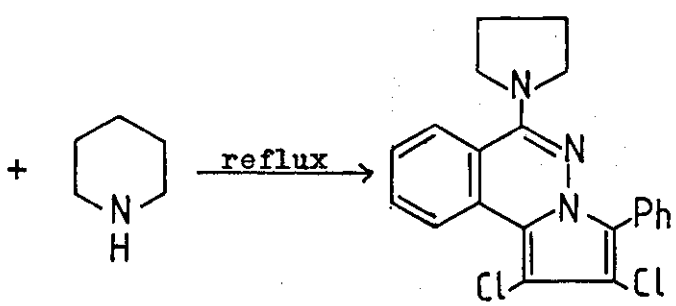
Substitution of the trichloro-compound (80) was first studied using a variety of amines. Treatment with morpholine, piperidine and pyrrolidine provided mono-amino substitution products in which two of the chlorines of (80) remained present. This occured even when a large excess of the nucleophile was used. In these cases it was convenient to use the amine as the solvent for the reaction.



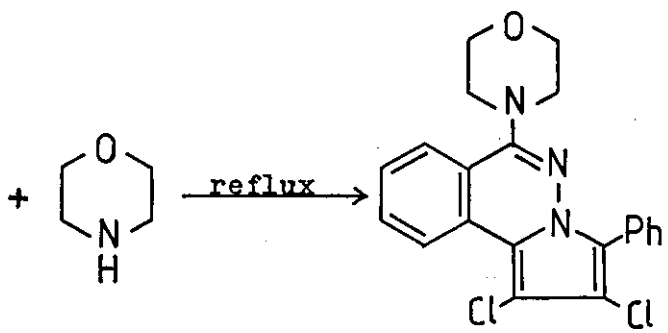
(81) yield 45%



(80)



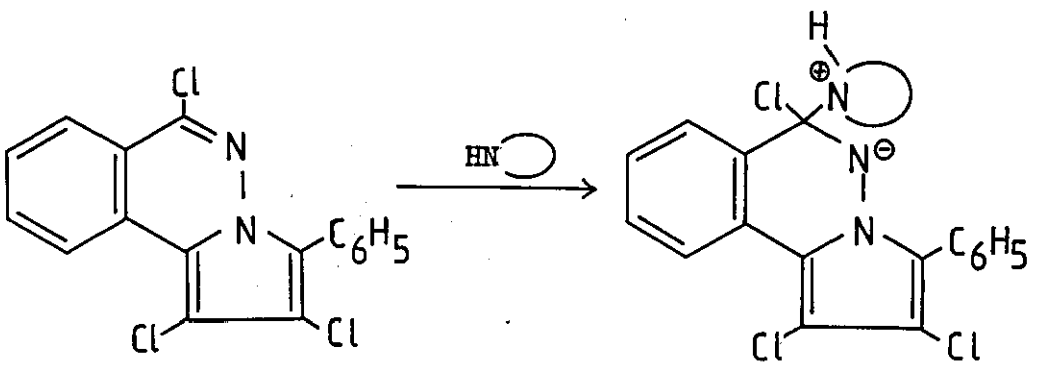
(82) yield 76%



(83) yield 38%

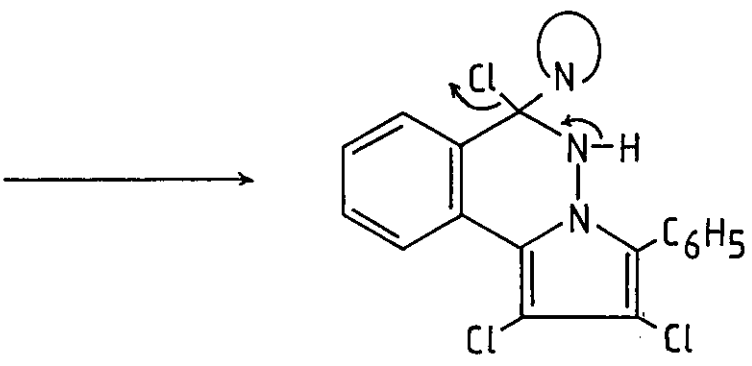
In order to investigate which chlorine was displaced by the nucleophilic attack of these bases (i.e.pyrrolidine, piperidine, morpholine), it was hoped to be able to distinguish between the various positions of each of dichlorophthalazines, so obtained, with the help of ^{13}C n.m.r. Unfortunately the spectra obtained showed overlap of the signals of the

^{13}C-Cl with the other aromatic carbons of these compound and therefore no useful information could be obtained. However it was considerd reasonable to assume that the chlorine atom at 6-position of (80) was substituted by the bases (i.e. pyrrolidine, morpholine, piperdine) in view of the earlier discussion. The pyridazine moiety is very electron deficient compared to the pyrrole moiety and therefore a nucleophile will be directed to the former. The attack of secondary amine at C-6 results in the stabilisation of the negative charge by the nitrogen atom of the ring (at position-5) producing structure (a) which leads to (c) via (b) or its conjugate base. The excess of amine present will absorb the HCl produced to assist the progress of the reaction, as shown on p. 66.

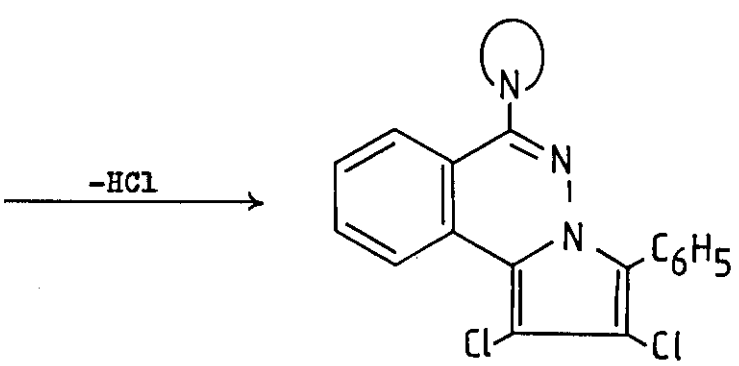


(80)

(a)



(b)

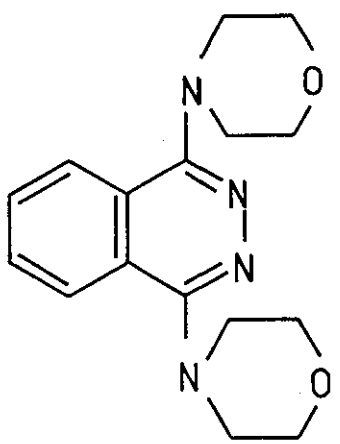


(c)

The three 6-amino-1,2-dichloro-3-phenylpyrrolo[2,1-a]phthalazines (81), (82), and (83), were colourless, pale yellow to yellow crystalline compounds and satisfactory analytical and spectroscopic data were obtained for each. The two chlorines were revealed in the mass spectrum by the

M, M + 2, M + 4 cluster in the ratio 9:6:1.

In 1969 D.Parsons et al.[113] studied the hypotensive activities of some 1-aminophthalazines, e.g. (84).



(84)

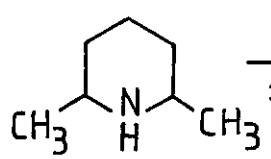
These authors found products including (84) showed significant hypotensive activity and also antiinflammatory and respiratory stimulent activity, without demonstrable adverse toxicity. We hoped to submit samples of our products for pharmacological study.

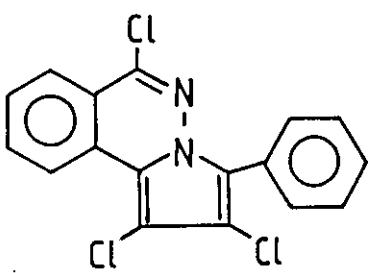
We next decided to study the reaction of 1,2,6-trichloro-3-phenylpyrrolo[2,1-a]phthalazine (80) with some other primary and secondary amines shown on p.68.

The reaction of 1,2,6-trichloro-3-phenylpyrrolo[2,1-a]phthalazine (80) with an excess of diethylamine and a reflux period of 72 hours gave the starting material only.

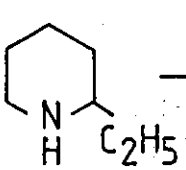
The reason for no substitution occuring in this case may be due to the low reflux temperature (diethylamine b.p. 55°C).

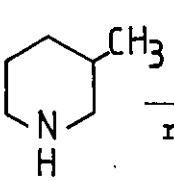
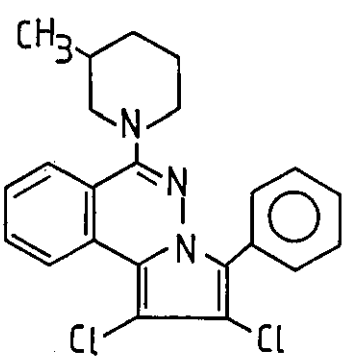
+ $HN(C_2H_5)_2$ —(dry toluene, reflux 72 h)→ starting material recovered

+  —(dry toluene, reflux 6 days)→ starting material recovered



(80)

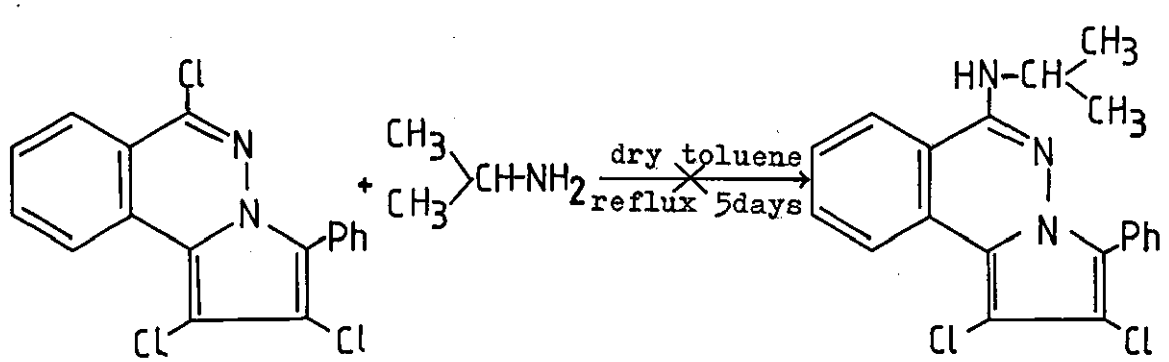
+  —(dry toluene, reflux 6 days)→ starting material recovered

+  —(dry toluene, reflux 6 days)→ 

(85) yield 40%

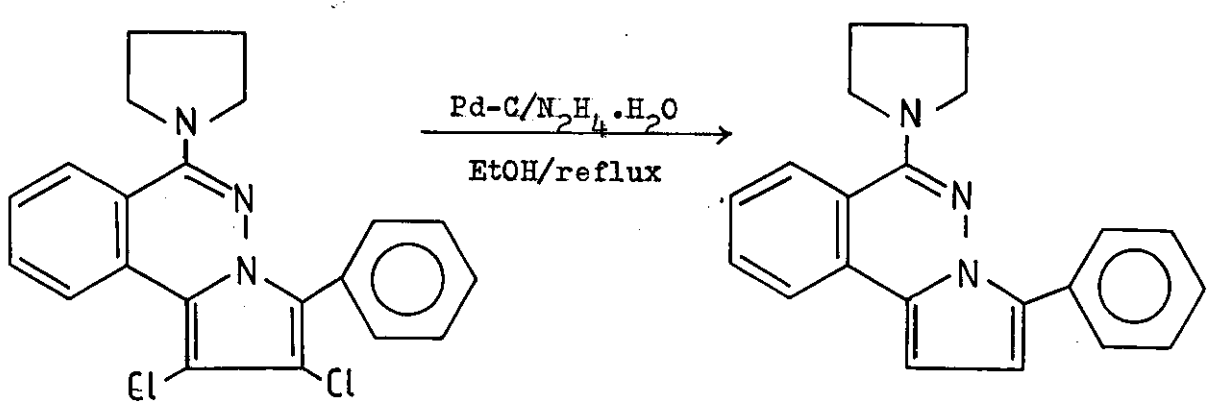
The reaction of trichloro-compound (80) with 2,6-dimethyl and 2-ethylpiperidine after prolonged reflux (6 days) again provided only starting material (80). The reason for no substitution in these cases seems likely to be due to steric factors, the 2,6-dimethyl and 2-ethyl groups preventing satisfactory access of the nucleophile at C-6 to replace chlorine. This suggestion is supported by the observation that use of 3-methylpiperidine after a similar period of reflux (6 days) in dry toluene provided the desired 1,2-dichloro-6-(3-methylpiperidino)-3-phenylpyrrolo[2,1-a] phthalazine (85) in 40% yield. Satisfactory analytical and spectroscopic data was obtained for compound (85).

The reaction of 1,2,6-trichloro-3-phenylpyrrolo[2,1-a] phthalazine (80) with an excess of isopropylamine (b.p. 34°C) in dry toluene and prolonged reflux (5 days) was carried out. Attempts were made to purify the product (86) by means of column chromatography, using neutral alumina (Camag of Brockmann activity I), and $CHCl_3$ as eluent. However compound (86) could not be isolated pure. It seems likely that as with diethylamine the low boiling point of the amine caused the reaction not to proceed satisfactorily.



(80) (86)

Mosby et al.[114] have reported the dehalogenation of some aromatic compounds by the use of hydrazine hydrate and 10% palladium-on-charcoal.[114-116] We used this method in order to investigate the dechlorination of our 6-amino-1,2-dicholor-3-phenylpyrrolo[2,1-a]phthalazine system. This reaction was carried out successfully with the 1,2-dichloro-3-phenyl-6-pyrrolidinopyrrolo[2,1-a]phthalazine (82). Dissolving compound (82) in ethanol and addition of 10% palladium-on-charcoal and hydrazine hydrate and a reflux period of 90 minutes, gave the dechlorinated product (87) in 40% yield. Satisfactory analytical data was obtained for this crystalline pale yellow compound m.p. 110-112°C.

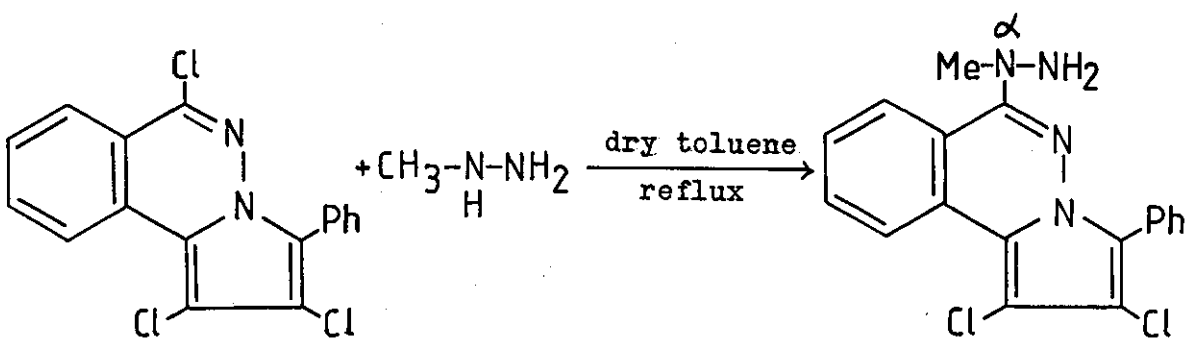


(82) (87) yield 40%

This important result extended the versatility of our approach, showing that although trichlorination was necessary to give an adequately stable compound with chlorine at position -6, the 1- and 2-chloro-groups could be regarded as protecting groups, readily removable after the C-6 chlorine had been replaced by a suitable nucleophile.

It was thought important, however to submit for testing products both with and without the 1- and 2-chloro-groups since their effect on the pharmacological activity was unknown.

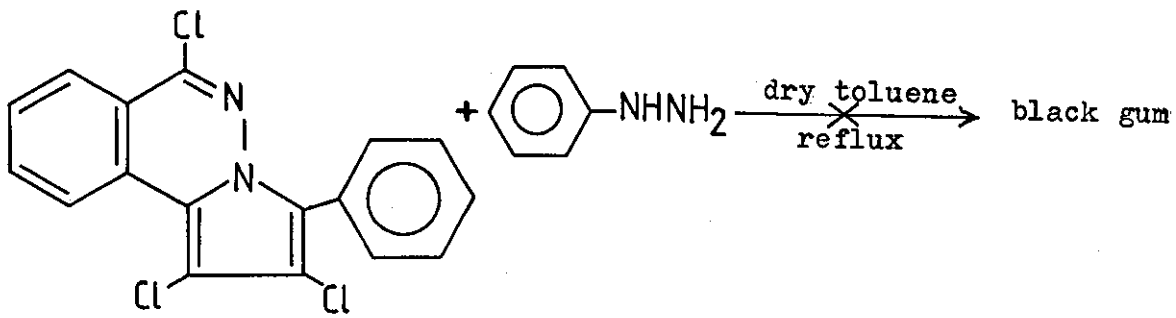
The reaction of trichloro compound (80) with methylhydrazine was next studied. Excess of the reagent was refluxed with (80) for 6 days to give 1,2-dichloro-6-(α-methylhydrazino)-3-phenylpyrrolo[2,1-a]phthalazine (88) in moderate yield (36%). In the 60 MHz n.m.r. ($CDCl_3$) this compound showed resonances at δ3.0 (3H, s, -N-Me) δ5.2 (2H, br, NH_2), and δ7.0-8.8 (9H, m, aromatic) in accord with the structure (88) and in the i.r. ν_{max} (KBr) 3320cm^{-1} (br, NH_2), 1600cm^{-1} (C=C). Satisfactory analytical data was obtained for this crystalline pale yellow compound m.p. 169-171°C. Methylhydrazine contains two basic nitrogen atoms, one primary and one secondary. The latter is known to be the more nucleophilic of the two,[117-118] benefitting from the inductive electron release of the adjacent Me-group. The structure proposed for the product (88) is in accord with the substitution being effected by the secondary nitrogen.



(80) (88) yield 36%

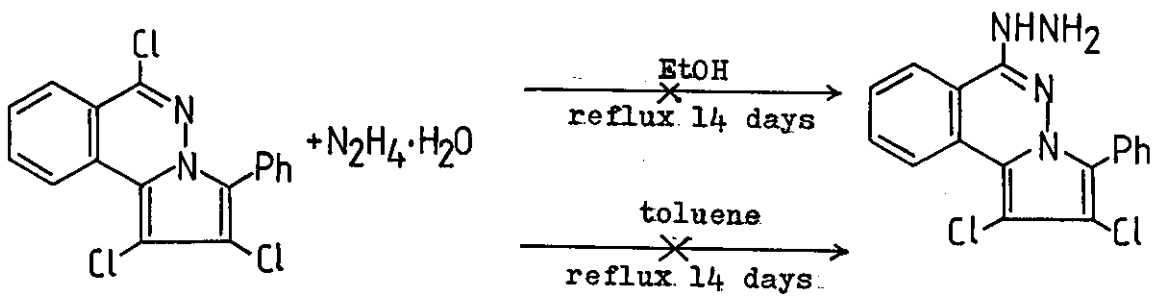
The product (88) provides an example of a 6-hydrazinopyrrolo[2,1-a]phthalazine and it may have interesting pharmacology, it was submitted for testing.

On repeating the above reaction but using phenylhydrazine we only obtained, after prolonged reflux (6 days), a dark yellow gum, which was very unstable and became black after 20 minutes. It could not be purified by chromatography on a neutral alumina column, nor by attempted conversion to a hydrochloride salt.



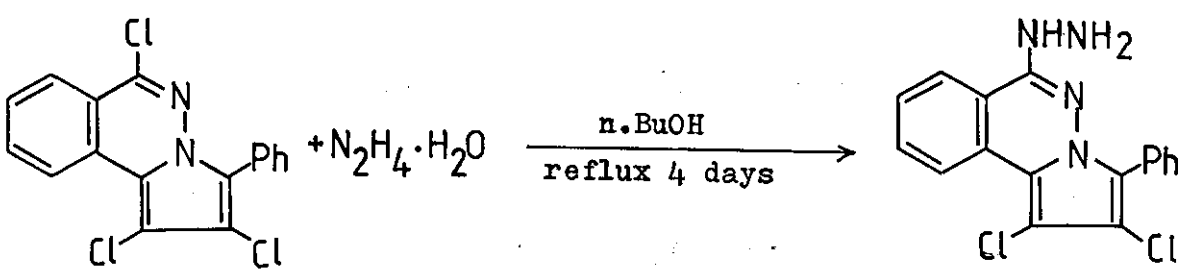
(80)

We next studied direct substitution of the trichloro-compound (80) with hydrazine.



(80) (89)

The trichloro compound (80) was not soluble in $N_2H_4 \cdot H_2O$. Therefore, we first attempted this reaction in ethanol as a polar solvent and refluxed the mixture for (14 days). However no reaction was taking place (as shown by t.l.c.) and the starting trichloro compound (80) was recovered. This reaction was next repeated in toluene as a higher boiling but less polar solvent compared to ethanol. However, again the starting material (80) was recovered, even after prolonged reflux (14 days). We needed a high boiling polar solvent which could also be easily removed at reduced pressure, without application of high temperature as the hydralazines are generally known to be unstable to high temperature.[61,98] Therefore this reaction was repeated with n-butanol (b.p. 117°C) and a reflux period of four days. We were happy to obtain the desired hydralazine derivative (89) in 55% yield.



(80) (89) yield 55%

The mass spectrum of this compound showed the molecular-ion peak as base peak with the characteristic molecular-ion cluster due to two chlorine atoms: M, M + 2, M + 4 with the intensity ratios of 9:6:1 respectively, at m/e 342, 344, and 346. Accurate mass measurement for M^+ gave 342.0431, $C_{17}H_{12}N_4{}^{35}Cl_2$ requires 342.0438. A satisfactory

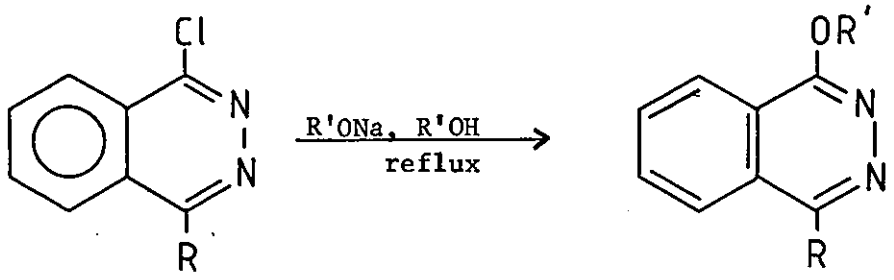
microanalysis was also obtained.

This key compound was submitted for pharmacological testing.

iii) Substitution by oxygen functions at position-6

We next turned our attention to the synthesis of a range of 6-oxygenated-pyrrolo[2,1-a]phthalazines, in order to compare the antihypertensive activities of the products with hydralazine.

1-Alkoxyphthalazines (90) are prepared, by refluxing the corresponding 1-Chlorophthalazines with the sodium alkoxides in the appropriate alcohol for 20 minutes to 3 hours.[119-125]

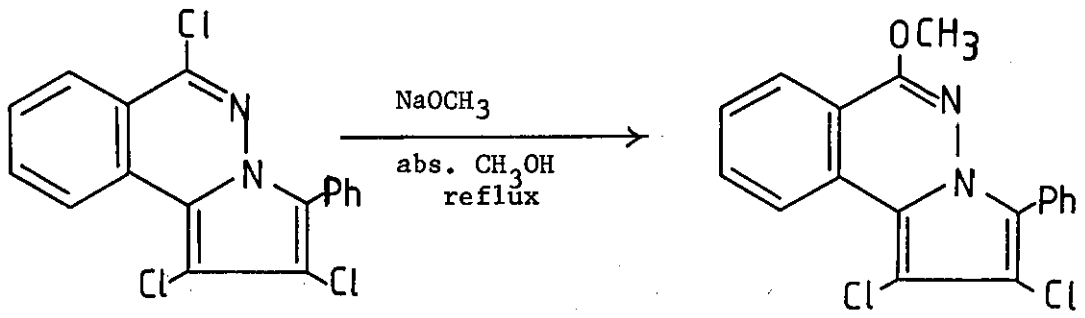


(90)

R = H, alkyl

R' = alkyl

The reaction of trichloro compound (80) with freshly prepared sodium methoxide in abs. methanol was carried out. We obtained 1,2-dichloro-6-methoxy-3-phenylpyrrolo[2,1-a]phthalazine in good yield (81%).

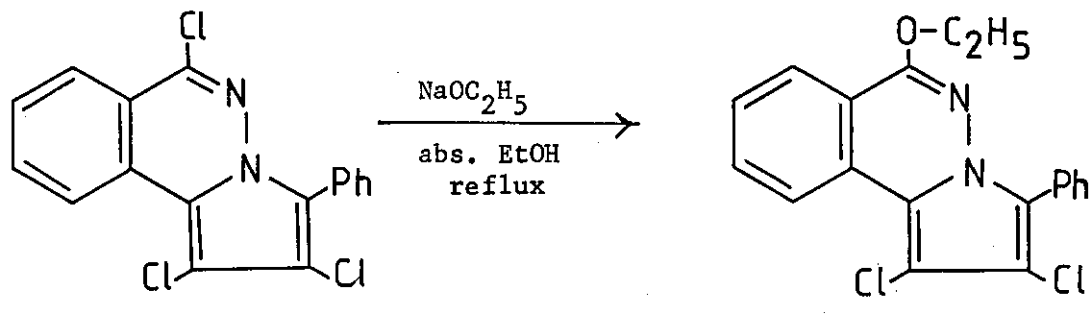


(80) (91)

In the n.m.r. 60 MHz ($CDCl_3$), this compound showed the methoxy group at δ3.85 and in the i.r. showed ν_{max} 1630cm^{-1} (C=N), 1260cm^{-1} and 1100cm^{-1} (C-O-C). The mass spectrum of this compound showed the molecular-ion as base peak m/e 342 and the characteristic molecular-ion cluster due to two chlorine atoms: M, M + 2, M + 4, with the intensity ratios of 9:6:1, respectively at m/e 342, 344, and 346.

Satisfactory analytical data was obtained for this crystalline pale yellow compound, m.p. 116-118°C.

The reaction of trichloro-compound (80) with freshly prepared sodium ethoxide in abs. ethanol similarly gave 1,2-dichloro-6-ethoxy-3-phenylpyrrolo[2,1-a]phthalazine (92), though in moderate yield (37%)

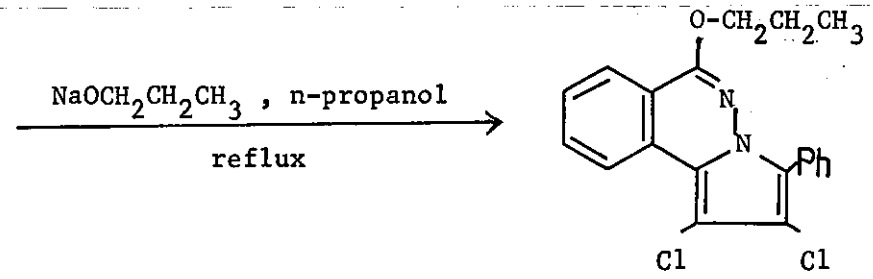


(80) (92)

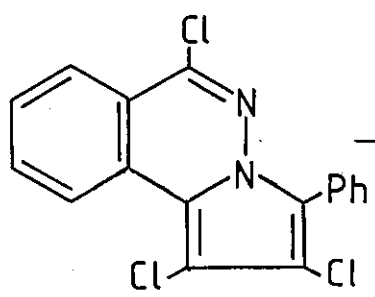
In the n.m.r. 60 MHz ($CDCl_3$), this compound showed the typical triplet-quartet pattern, of the ethyl group at δ1.4 (t, CH_3), δ4.3 (q, CH_2).

The mass spectrum of this compound showed features similar to (91) and the product was obtained analytically pure.

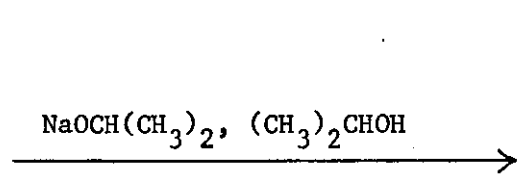
Having established the general method we then used n-propoxide, iso-propoxide and the anion of the furfuryl alcohol as nucleophile as shown below .These would provide a variety of sterochemistries around the 6-position to relate to pharmacological activity.

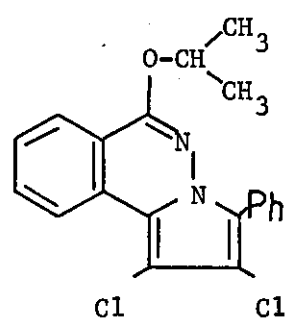


(93) yield 49%

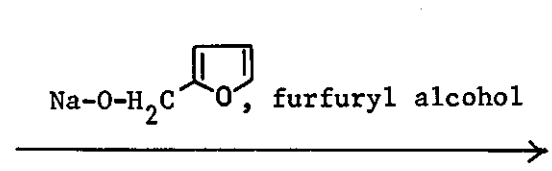


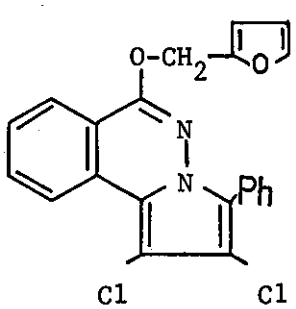
(80)





(94) yield 65%

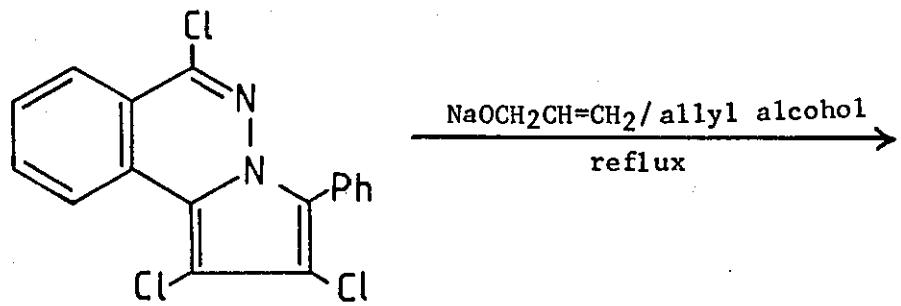




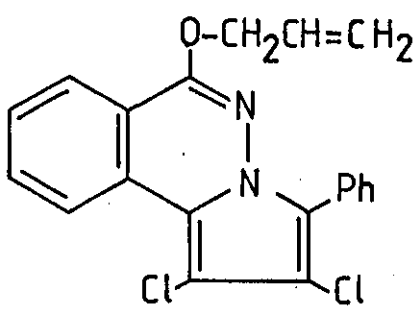
(95) yield 60%

Each of the three products (93, 94, 95) gave satisfactory spectroscopic and analytical data and were pale yellow crystalline compounds.

The reaction of trichloro-compound (80) with freshly prepared sodium allyloxide in dry allyl alcohol was carried out to provide an example of an alkenyl oxide side chain at C-6. We obtained 1,2-dichloro-3-phenyl-6-(prop-2-enyloxy)-pyrrolo[2,1-a]phthalazine (96) in good yield (57%). Satisfactory analytical and spectroscopic data were obtained for this pale yellow crystalline compound m.p. 129-131°C.



(80)

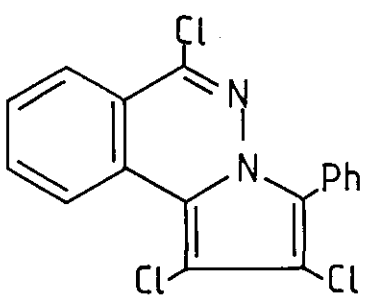


(96) yield 57%

We next turned our attention to achieving 6-aryloxy substitutions.

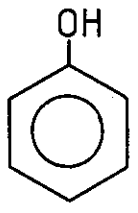
The reaction of 1-chlorophthalazine with phenol in presence of potassium carbonate on heating at 100°C for 1-2 hours gives the corresponding 1-phenoxyphthalazine.[55,126]

The reaction of trichloro-compound (80) with an excess of phenol in presence of K_2CO_3 and heating at 100°C for 12 hours, did not give the desired product (97). Instead the staring trichloro-compound (80) was recovered. This reaction was repeated at higher temperatures. We obtained 1,2-dichloro-3-phenyl-6-phenoxypyrrolo[2,1-a]phthalazine (97) in 69% yield, when the reactants were heated at 190°C for 19 hours on a Woods metal bath.



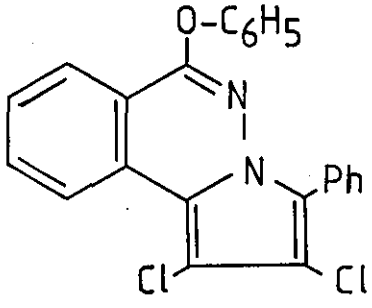
(80)

+



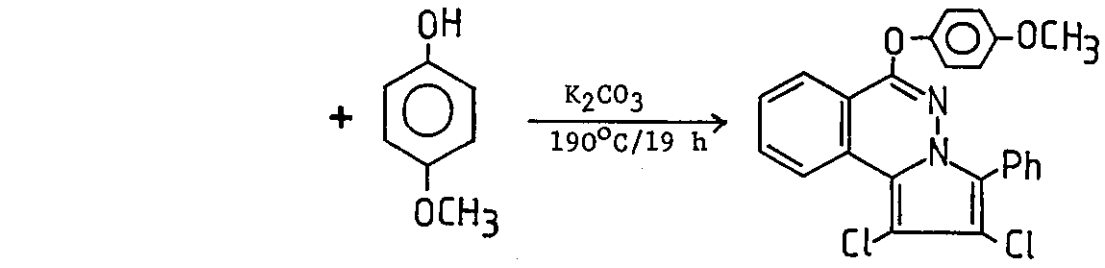
phenol

$\xrightarrow[190^{o}C/19\ h]{K_2CO_3}$

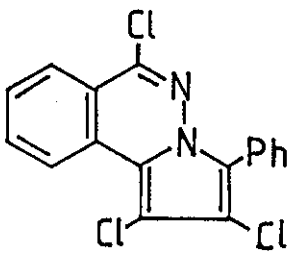


(97) yield 69%

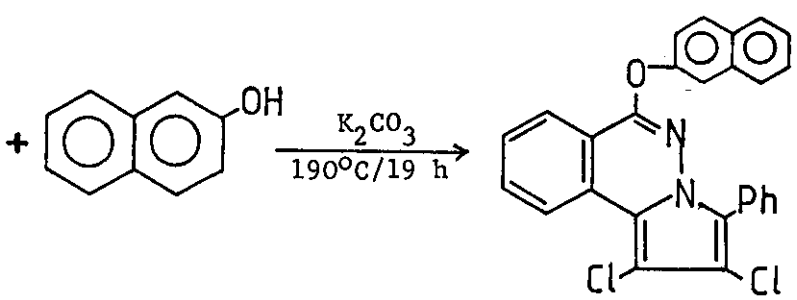
Similar reactions of trichloro-compound (80) with 4-methoxyphenol and also with 2-naphthol, in presence of K_2CO_3 at 190°C for 19 hours, gave us 1,2-dichloro-6-(4′-methoxyphenoxy)-3-phenylpyrrolo[2,1-a]phthalazine (98), and 1,2-dichloro-6-(2-naphthoxy)-3-phenylpyrrolo[2-1-a]phthalazine (99), respectively. Satisfactory spectroscopic and analytical data were obtained for these pale yellow crystalline compounds.



(98) yield 40%



(80)



(99) yield 70%

B. Syntheses of Pyrrolo[2,1-a]phthalazine-Derivatives, Functionalised at Positions -5 and/or -6.

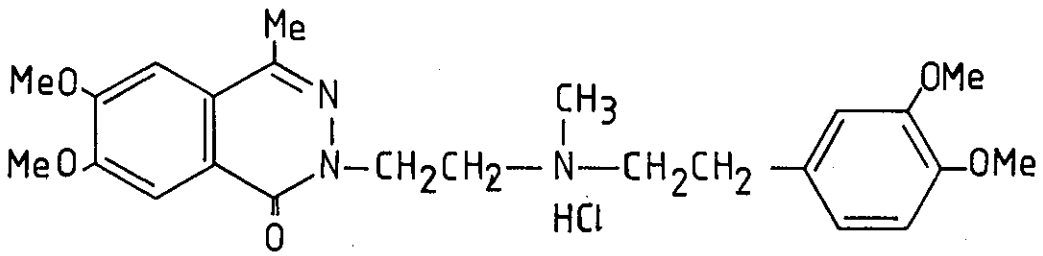
i) Formation of Mannich-Base Derivatives

Having obtained a considerable range of pyrrolo[2,1-a]phthalazines, substituted at positions 6-, we next sought examples in which both the 6- and 5- positions were modified since substitutions in both positions will in part occupy the area of space of importance with respect to the receptor site for likely activity.

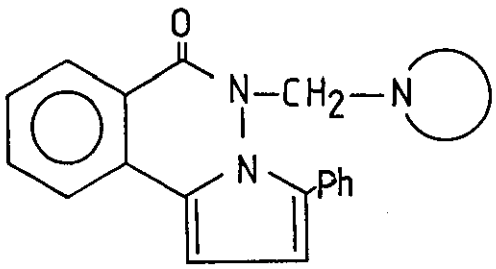
In 1979 Eberlin et al.[127] reported that the N-(β-aminoethyl)-phthalazin-1 (2H)-one derivative (100) was a pharmacologically useful heart rate reducer and mild antihypertensive.[127]

Mannich-bases of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (101) which have a similar type of structure to (100), should be accessible from 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one by the Mannich reaction.

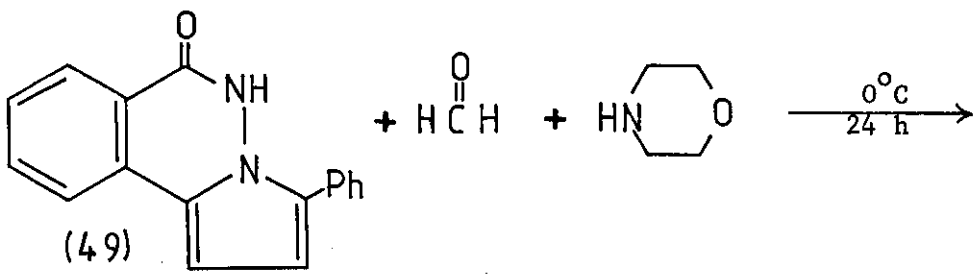
The reaction of 3-phenylpyrrolo[2,1-a]phthalazin-6-(5H)-one with morpholine and aqueous formaldehyde in ethanol at 0°C for 24 hours, provided 5-(morpholinyl-N-methyl)-3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (102). This compound was purified on a short column of Hyflo supercel, using $CHCl_3$ as eluent and we obtained (102) in 55% yield.



(100)



(101)

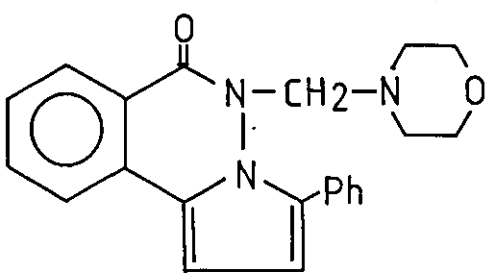


(49)

ν_{max}(KBr)1660cm^{-1}

u.v. λ_{max} nm logϵ 250(3.11),

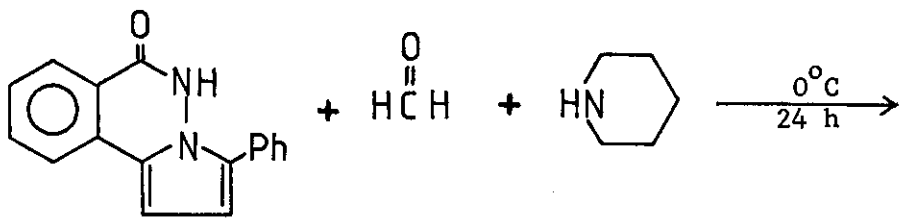
293(3.61), 333(3.53)



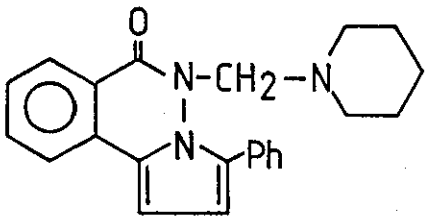
(102) yield 55%

In the 60 MHz n.m.r. ($CDCl_3$), this compound showed δ6.6-8.3 (11H, m, aromatic), δ3.90 (2H, s, N-CH_2-N), δ3.61 (4H, m, protons at 3 & 5 postions of morpholine) δ2.72 (4H, m, protons at 2 & 6 positions of morpholine), and in the i.r. ν_{max} (KBr) 1628cm^{-1} (C=O) and in the u.v. λ_{max} nm log ε 252(3.25), 290(3.67), 335(3.47). These λ_{max} values accord closely with those of the starting material suggesting similar chromophores. Satisfactory analytical data was obtained for this pale yellow, crystalline compound, m.p. 207-209°C.

The reaction of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one with piperidine and aqueous formaldehyde in ethanol at 0°C for 24 hours, provided 3-phenyl-5-(piperidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6-(5H)-one (103). This compound after purification on a short column of Hyflo supercel using $CHCl_3$ as eluent, gave us (103) in good yield (60%).



(49)

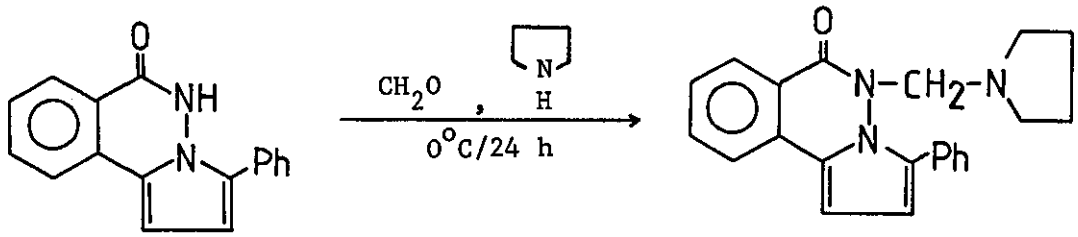


(103) yield 60%

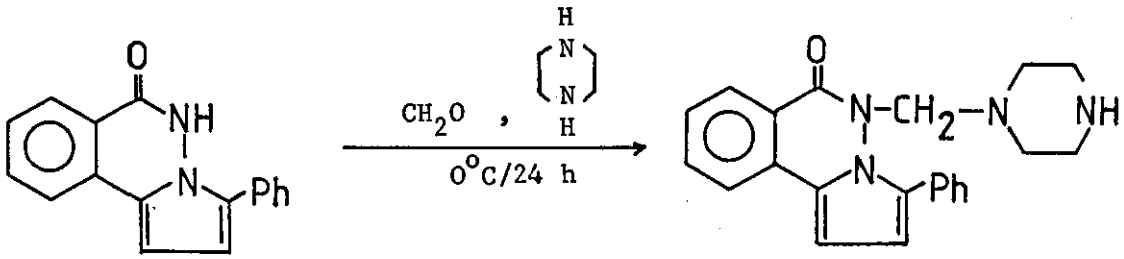
In the nmr 60 MHz ($CDCl_3$), this compound showed δ3.90 (2H, s, N-CH_2-N) and other peaks in accord with structure (103), and in the

in the i.r. ν_{max} (KBr) 1628cm^{-1} (C=O) and in the u.v. λ_{max} nm log ϵ 248(3.15), 286(3.52), 330(3.37). Satisfactory analytical data was obtained for this pale yellow, crystalline compound, m.p. 203-205°C.

Mannich reaction of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one with pyrrolidine was also carried out and the desired compound (104) was obtained in 45% yield. In the n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50) the expected peaks were present including δ3.95 (2H, s, N-CH_2-N) and in the i.r. ν_{max} ($CHCl_3$) 1628cm^{-1} (C=O), and in the u.v. λ_{max} nm log ϵ 240(3.18), 272(3.38), 332(2.92).



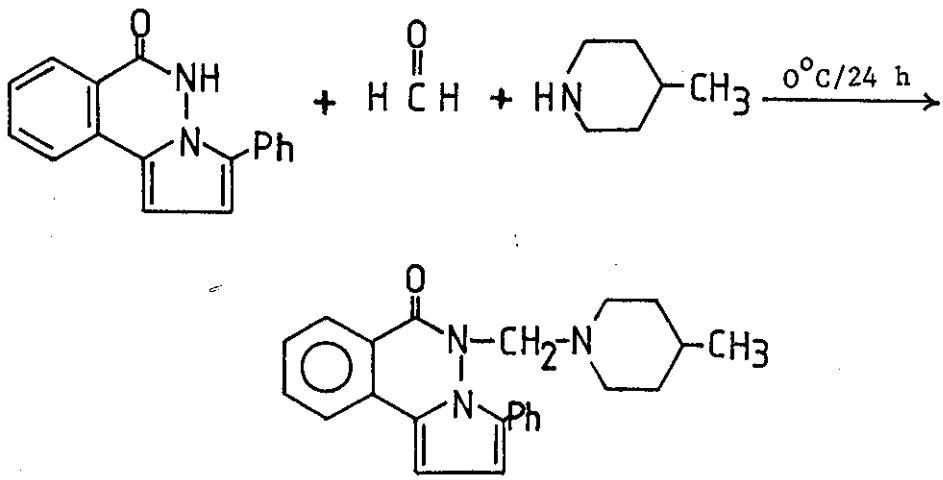
(104) yield 45%



(105)

We have attempted to prepare 3-phenyl-5-(piperazino-N-methyl)-pyrrolo[2,1-a]phthalazin-6 (5H)-one (105). However compound (105) could not be isolated pure.

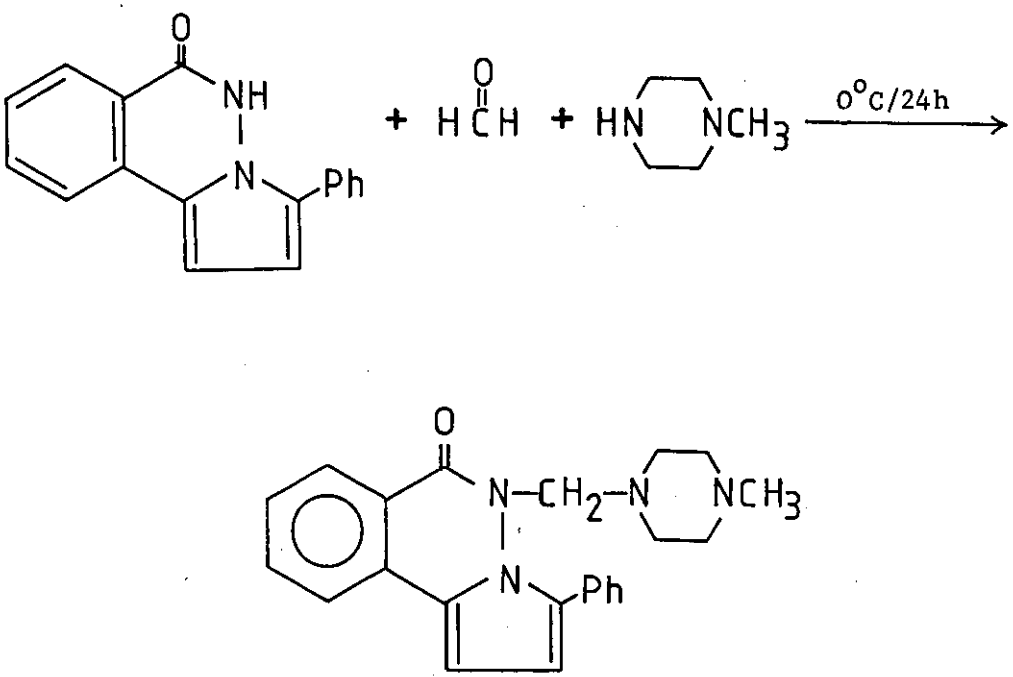
We were happy to obtain 3-phenyl-5-(4-methylpiperidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6(5H)-one (106) in 51% yield.



(106) yield 51%

In the nmr 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), the expected peaks were present including δ3.85 (2H, s, N-CH_2-N) and in the i.r. ν_{max} (KBr) 1628cm^{-1} (C=O) and in the u.v. λ_{max} nm log ε 248(3.28), 284(3.55) 328(3.29).

Finally in this series we obtained 3-phenyl-5-(4-methylpiperazino-N-methyl)-pyrrolo[2,1-a]phthalazin-6(5H)-one (107) in 55% yield.

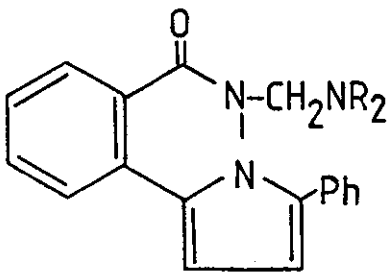


(107) yield 55%

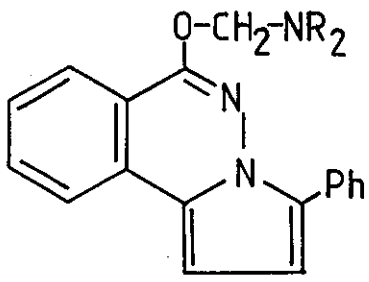
In the n.m.r. 60 MHz ($CDCl_3/DMSOd_6$, 50:50) the expected peaks were present including δ3.85 (2H, s, N-CH_2-N), and in the i.r. ν_{max} (KBr) 1628cm^{-1} (C=O) and in the u.v. λ_{max}^{nm} log ∈ 252(3.26), 285(3.50), 330 (3.38). Satisfactory analytical data were obtained for these (106 & 107) compounds.

The Mannich-bases obtained, were submitted for pharmacological testing for antihypertensive activity.

The structures shown for the above five Mannich bases assume N-alkylation (101a) rather than O-alkylation (101b).

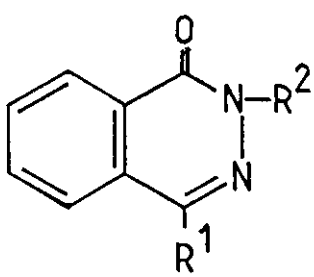


(101 a)



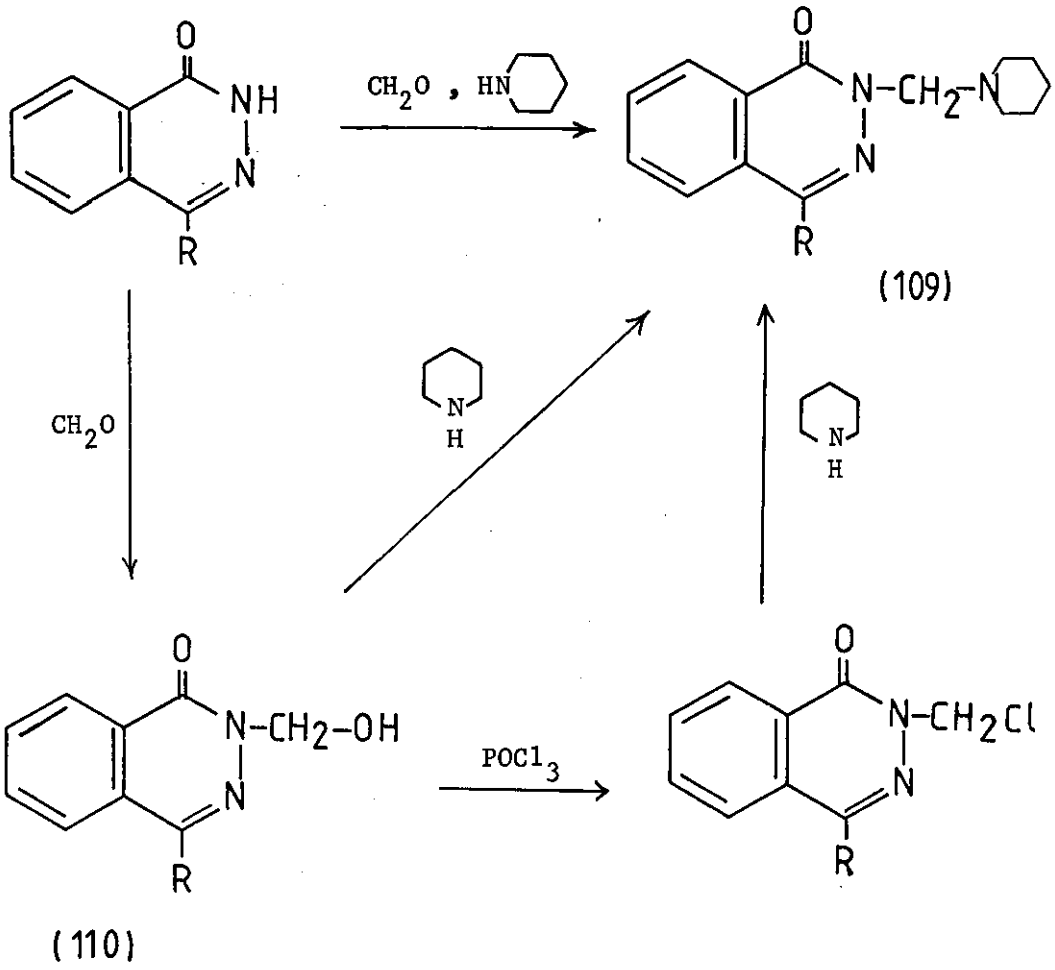
(101 b)

This follows from the work of Mustafa et al.[128], who synthesised a range of phthalazine analogues of type (108), where R^1= H, Me, C_6H_5 R^2=CH_2NR_2



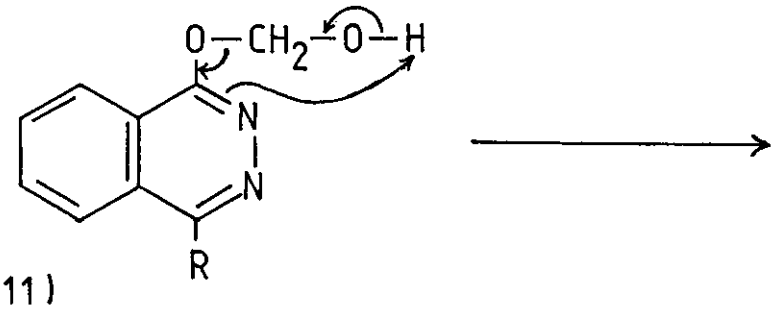
(108)

For structure proof they [128] synthesised the piperidine Mannich-base (109) by three routes as shown:

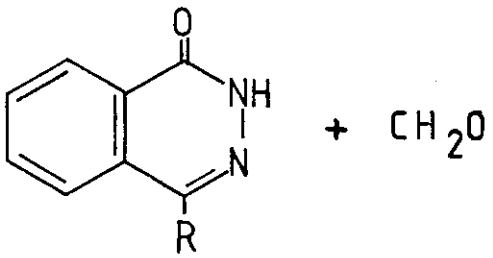


The N-hydroxymethyl derivative (110) was isolated separately for R = Me or C_6H_5.

The alternative structure for(110) would be (111).

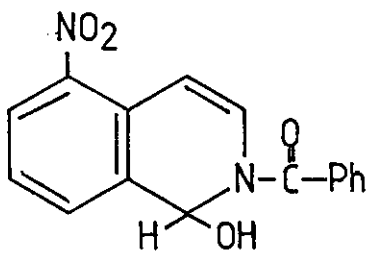


(111)

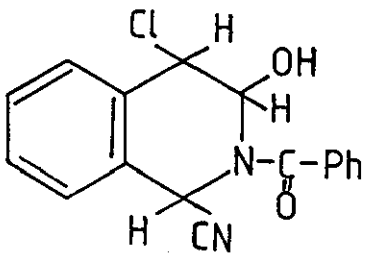


(111a)

One would anticipate that the hydroxymethylimidate (111) if formed would immediately break down in to the stable lactam (111a) and formaldehyde. In the N-hydroxymethyl form (110), the lactam unit is preserved and there are many other examples known of stable carbinolamides e.g. (112),[129] and (113).[130]

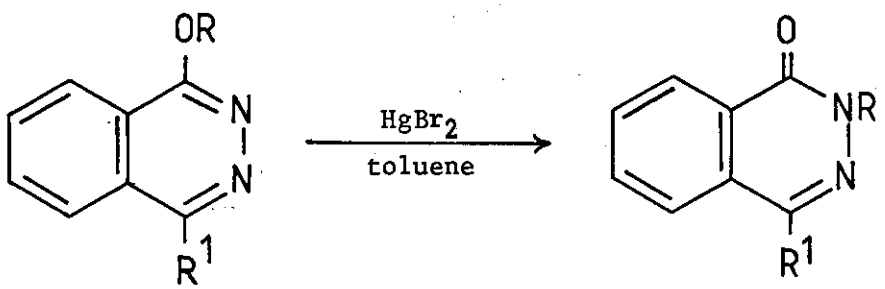


(112)



(113)

If therefore structure (110) is correct, it follows that structure (109) is correct unless an N to O rearrangement is taking place in each of the two routes from (110) to (109). Although an O to N alkyl migration is known (Scheme 1)[131], the reverse process has not been recorded to our knowledge.[132]



R = glucosyl

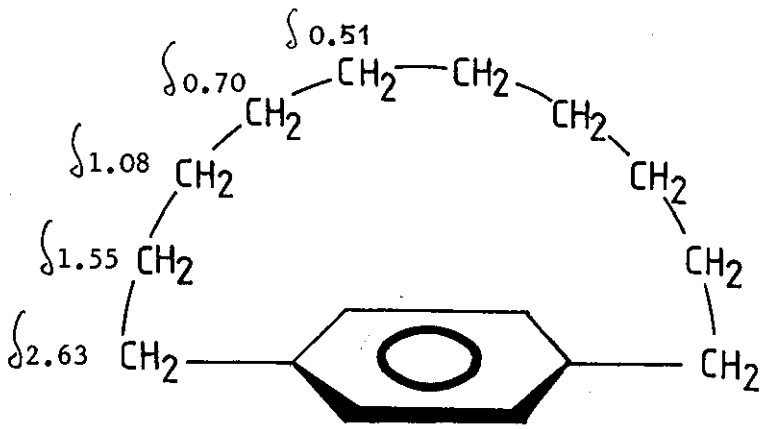
R^1 = H, Cl, Ph

Scheme 1

In all our Mannich-bases, the amide carbonyl at C-6 appears in the i.r. at ν_{max} 1628cm^{-1} and the N-CH_2-N methylene at δ3.90 in the n.m.r.

The CH_2 group must be heavily shielded by the face of the 3-phenyl group because in Mustafa's [128] phthalazinone analogue (109, R=H) we have observed the same group to be at δ5.0.

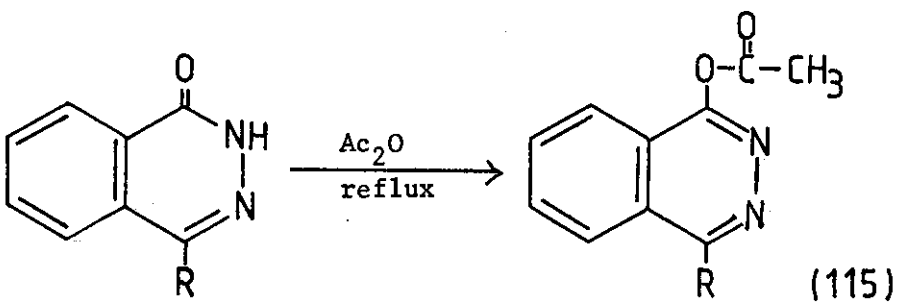
Similar shielding occurs in [10]-paracyclophane (114).[133]



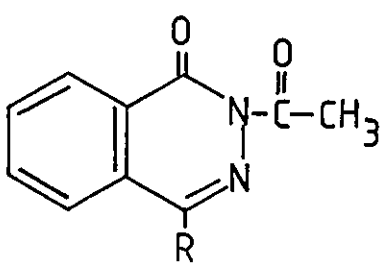
(114)

(ii) Acylation Reactions

Treatment of phthalazin-1(2H)-one with refluxing acetic anhydride gives a mono-acetyl derivative. The literature is in conflict as to the structure of the product. The two proposals are the O-acetyl compound (115),[134] and the N-acetyl compound (116).[135]



(115)



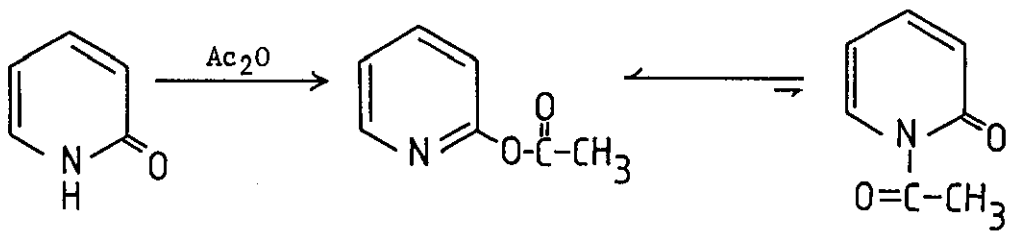
(116)

Structure (115)(R=-$CH(CH_3)_2$), is supported,[134] by the i.r. showing ν_{max} 1757 cm^{-1}, in accord with an aryl ester.[134] However other workers,[136] defined the product as the N-acetyl isomer (116) (R=-$CH(C_2H_5)CH_3$), although they quote an infrared absorption at ν_{max} 1754 cm^{-1}.[136]

Structure (116), (R=H),[135] is claimed to be supported by the n.m.r. showing no change in chemical shift for a signal assigned to C-8 H at

δ 8.52 after acetylation. Loss of the C=O at C-1, it is argued,[135] would noticably modify the deshielding of the C-8 H. Further work on the N-acylation of phthalazin-1(2H)-one has been reported, however no spectroscopic or other relevent data were provided.[137,138]

In the analogous case of the acetylation of 2(1H)-pyridone, McKillop *et al.*[139] have shown an equilibrium to occur, favouring the O-acetyl structure (117), (9:1) at room temperature, the N-acetyl(118) being more evident (40%) at -40°C. At room temperature the equilibrium mixture shows a carbonyl stretching bond at 1730-1760 cm^{-1} for (117) and a medium band at 1650-1675 cm^{-1} which is assigned[139] to (118).[139]

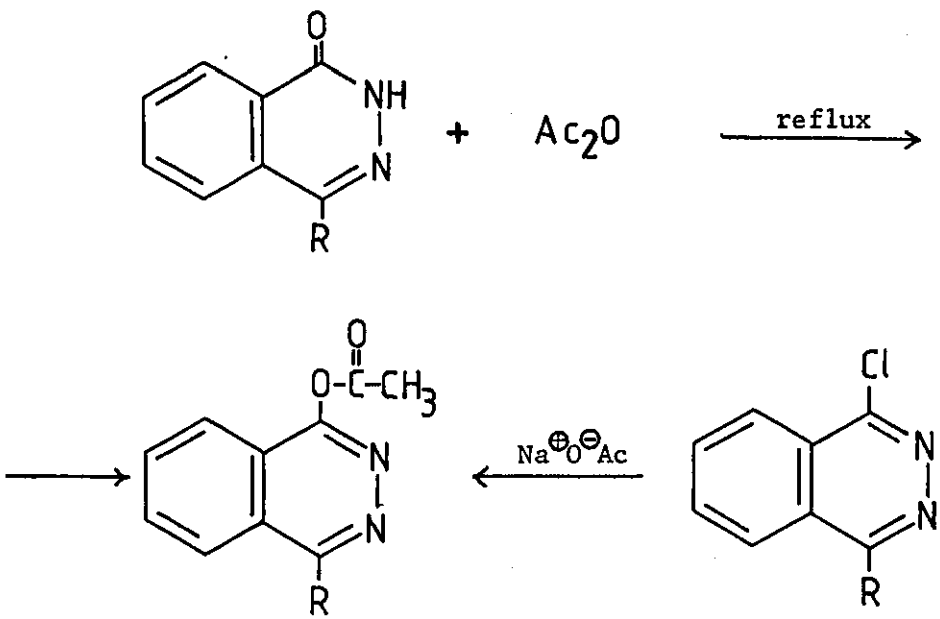


(117) (118)

Unfortunately in our starting material, 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one, the nine protons of the benzo and phenyl rings all occur in a multiplet at δ 7.0-8.2 with none displaced to lower field.

Aebi and Hofstetter,[134] have obtained 1-acetoxy-4-isopropyl-phthalazine (115) (R=-$CH(CH_3)_2$), by refluxing 4-isopropylphthalazin-

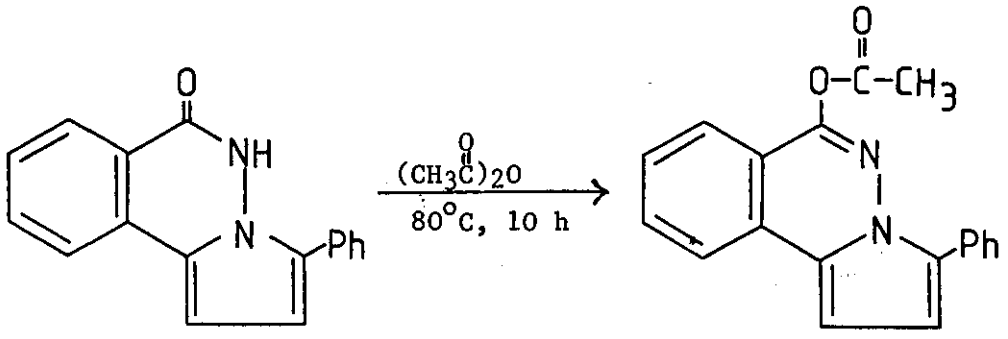
1(2H)-one with acetic anhydride and by reacting 1-chloro-4-isopropyl-phthalazine with sodium acetate.[134]



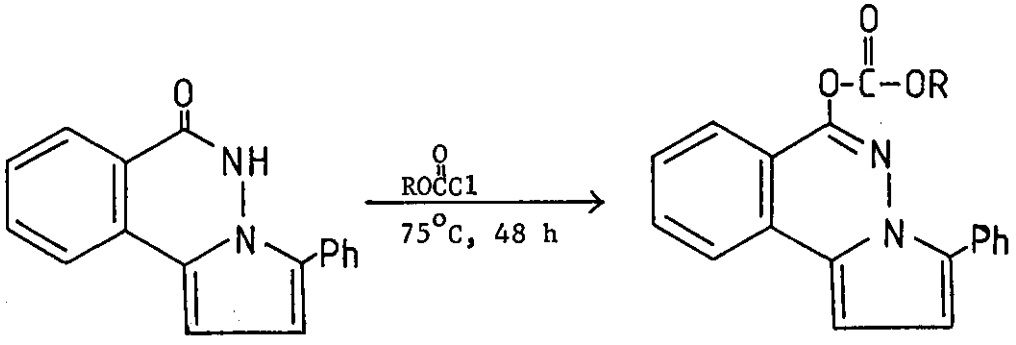
(115) R = $CH(CH_3)_2$

Their assignment of structure (115) was supported by i.r. data of (115) (R=-$CH(CH_3)_2$) ; -O-$\overset{O}{\overset{\|}{C}}$-$CH_3$(C=O, 1757 cm^{-1}), and 1220 cm^{-1} (C-O-$\overset{O}{\overset{\|}{C}}$, C-O of acetyl group).

We carried out five acylations, obtaining crystalline mono-acyl derivatives in each case, with satisfactory microanalyses. The acylating agents were acetic anhydride, methyl chloroformate, ethyl chloroformate, phenyl chloroformate and chloroacetyl chloride. The spectroscopic data appear to suggest the following reactions have occured.

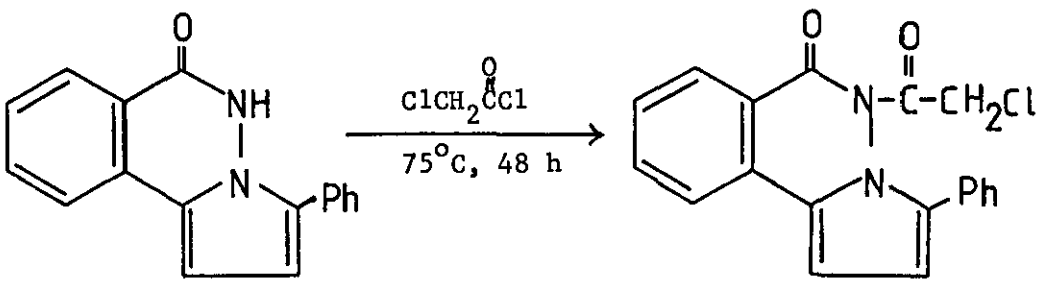


(49) (119)



(49)

(120) R = Me
(121) R = Et
(122) R = Ph



(49) (123)

The spectroscopic data obtained is summarised in Table 10.

Table 10

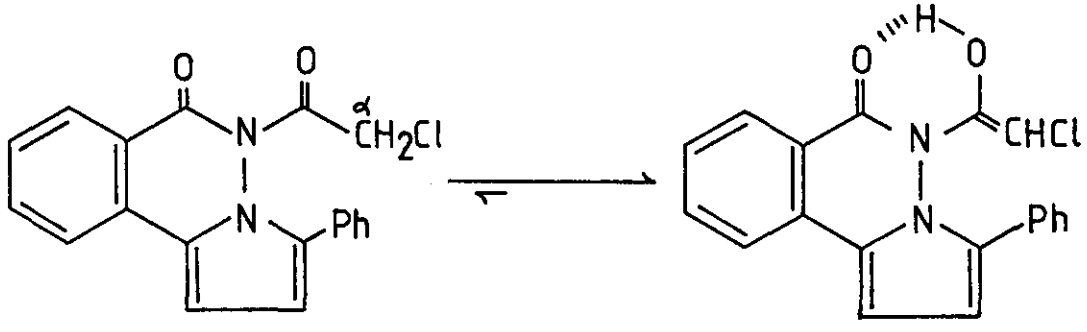
Compounds Text No.	ν_{max} cm^{-1}	λ_{max} nm (log ∈)
(49)	1660	250(3.11), 293(3.61), 333(3.53)
(119)	1760 , 1620	250(2.56), 290(3.08), 333(2.8)
(120)	1770 , 1622	250(3.10), 291(3.65), 334(3.44)
(121)	1775 , 1626	250(3.03), 290(3.52), 335(3.29)
(122)	1780 , 1626	250(3.50), 293(3.94), 328(3.84)
(123)	1636 , 1624	—— , 280(3.57), 352(3.03)

In none of the products is the envelope of aromatic proton absorptions significantly changed from that of the starting material(49), i.e. δ 7.0-8.2 .

The i.r.-data obtained, for the O-acyl-derivatives (119, 120, 121, 122) ν_{max} ca. (1760 cm^{-1},C=O) differentiates between the two possible structural isomers, and the carbonyl absorption for the O-acyl-derivatives is in accord with the observation of Aebi & Hofstetter mentioned above.[134]

It is of interest to note, that the u.v.-spectrum of the N-acyl-derivative (123), shows a λ_{max} at 352 nm, ca. 20 nm, higher, compared to the average λ_{max} value, obtained for the O-acyl-derivatives (119, 120, 121, 122) at $\sim$ 330 nm .

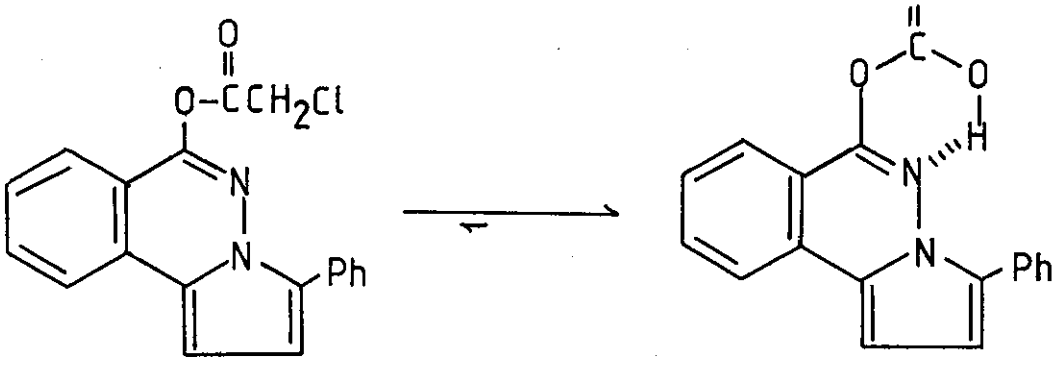
The exceptional N-acylation by chloroacetyl chloride is surprising. Possibly the product is particularly stabilized by hydrogen bonding in the enol form (124), being a 1,3-dicarbonyl compound. The electron withdrawing chlorine atom would assist loss of an α-proton in (123), promoting enolisation.



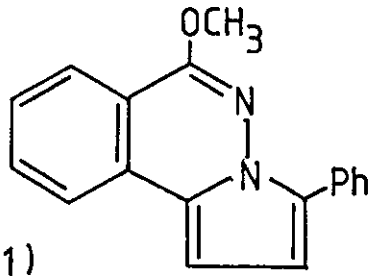
(123) (124)

The relatively long reflux time (2 days) would promote the formation of the most thermodynamically stable product.

Although we are showing the structure of the product as (123), the alternative isomer (125) cannot rigorously be excluded on the data available because the enolisation and H-bonding argument just advanced could also be applied to the O-chloroacetyl isomer as shown below in the equilibrium (125) $\rightleftharpoons$ (126). Although no good analogies are available it is possible that the infrared data could be in accord with (126). The relevant peaks appear at ν_{max} 1636, 1624, 1210, and 1115 cm^{-1}. The O-acetyl derivative (119) shows ν_{max} 1620 cm^{-1}(C=N), and 1188 cm^{-1} (C-O ether); and the carbonates (120, 121, 122) ν_{max} 1622-1626 cm^{-1} (C=N), and 1220-1225 cm^{-1}, 1200 cm^{-1} (C-O ether). The simple ethers such as (91) shown ν_{max} 1630 cm^{-1} (C=N).



(125) (126)



(91)

ν_{max} 1630 cm^{-1} (C=N)

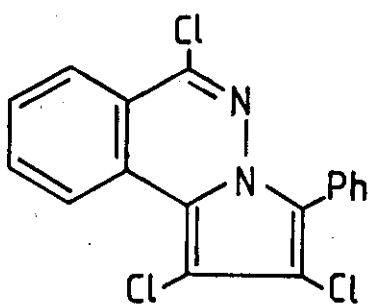
PART II C

PHARMACOLOGY

Our studies described above had produced 27 new pyrrolo[2,1-a]phthalazines which together with the starting 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-ones were available for pharmacological examination and listed below.

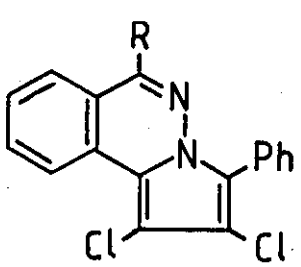
Samples for Pharmacology (Antihypertensive Testing)

(II A i) Cl at position-6



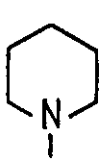
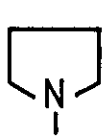
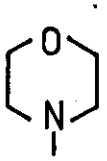
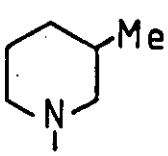
(80)

(II A ii) N-function at position-6

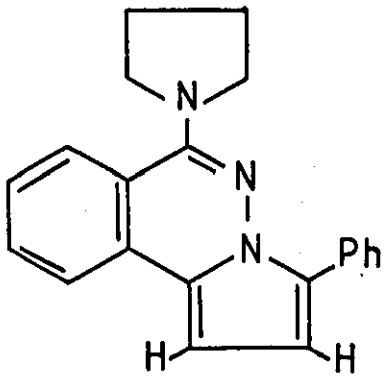


(X)

(a) amino :

(X), R=    

(81) (82) (83) (85)



(87)

(b) hydrazino :

(X), R = Me—N(—)—NH$_2$, NHNH$_2$

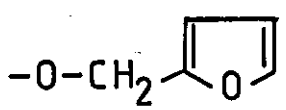
(88) (89)

(II A iii) O-function at position-6

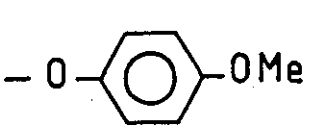
O-alkyl and O-aryl :

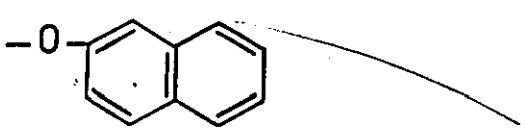
(X), R = -OMe , -OEt , -OPr-n , -OPr-i ,

(91) (92) (93) (94)

 , -OCH$_2$CH=CH$_2$, -OPh ,

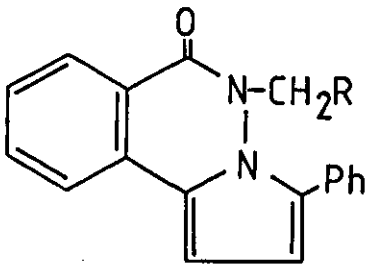
(95) (96) (97)

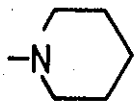
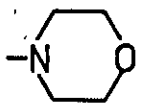
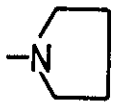
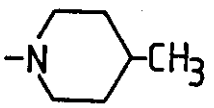
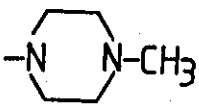
 ,



(98) (99)

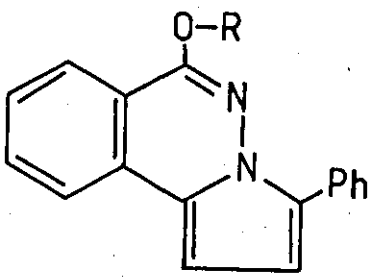
(II B i) C-6 carbonyl and N-5 alkylamino



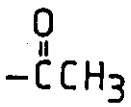
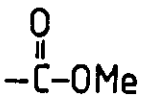
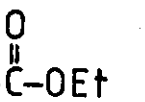
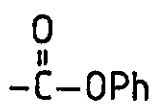
R=  ,  ,  ,  , 

(103) (102) (104) (106) (107)

(II B ii) O-acyl

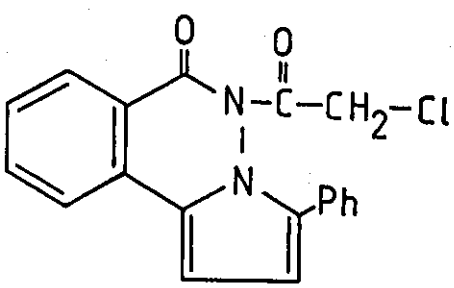


(Z)

(Z), R=  ,  ,  , 

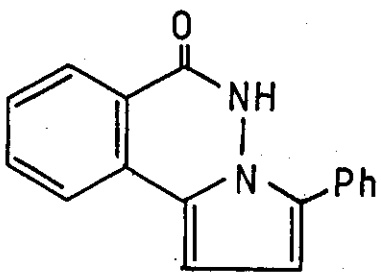
(119) (120) (121) (122)

(II B iii) C-6 carbonyl and N-5 acyl

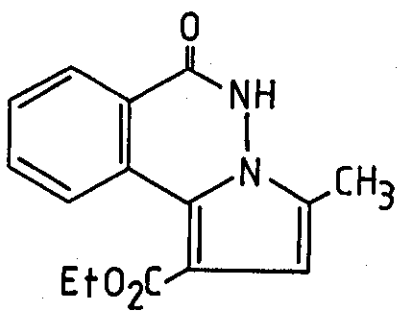


(123)

C-6 carbonyl and N-5 H



(49)



(44b)

From the compounds submitted to Reckitt & Colman, Pharmaceutical Division, Hull, nine compounds were selected for testing, for anti-hypertensive activity, representing most of the structural classes listed above. The compounds selected were (85, 88, 89, 92, 95, 96, 102, 119 & 49). These compounds are underlined in the above list, e.g. (119).

The screening results are summarized overleaf. We are indebted to Reckitt & Colman, Pharmaceutical Division, Hull for These data.

The nine compounds were each tested in normotensive rats* using a dose of 10 or 100mg/Kg as shown, administered by the intraperitoneal route. The percentage fall in mean arterial blood pressure (MABP) was recorded at specified times. The heart rate (HR) was also monitored.

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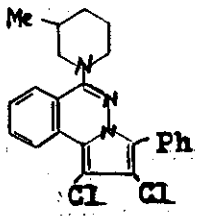
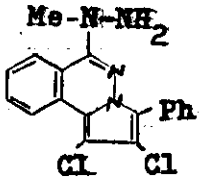
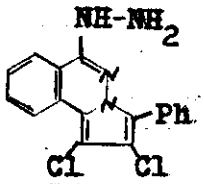
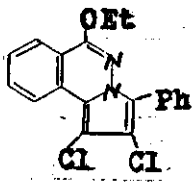
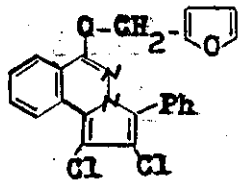
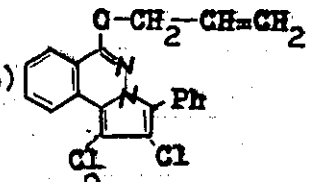
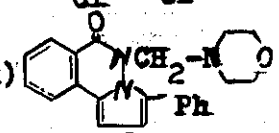
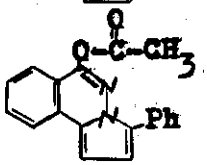
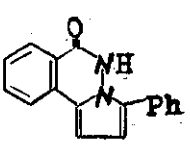
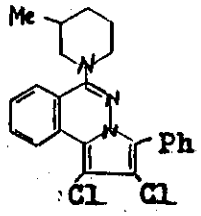
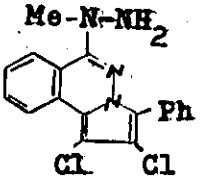
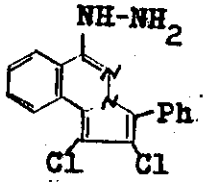
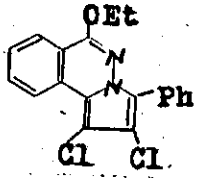
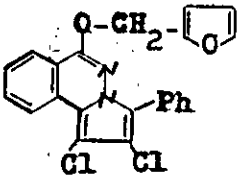
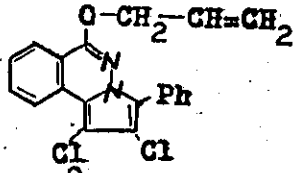
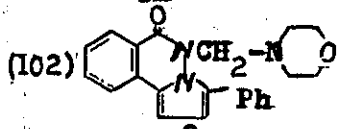
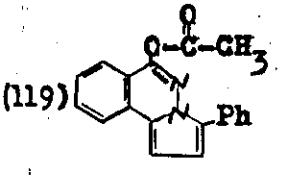
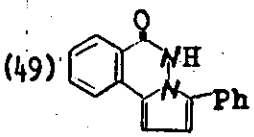
* i.e. having normal arterial blood pressure

Screening Results	Dose mg/kg (i.p.)	Response: Normotensive rats	Response: DOCA Hypertensive rats
(85) 	100	inactive	—
(88) 	100	inactive	—
(89) 	10	20 mm Hg fall (15%) in MABP at 2h 20% rise in HR at 3h	—
(92) 	100	20 mm Hg fall (15%) in MABP	27 mm Hg fall (16%) in MABP at ½h (persisting for 3h) 51% rise in HR at 2h (falling off at 3h)
(95) 	100	inactive	—
(96) 	10	13 mm Hg fall (10%) in MABP at 1h Negligible effect on HR	—
(102) 	100	inactive	—
(119) 	100	22 mm Hg fall (17%) in MABP	Negligible effect on MABP 32% rise in HR at 1h (falling off at 3h)
(49) 	100	inactive	—

i.p. = intraperitoneal
MABP = mean arterial blood pressure
HR = heart rate

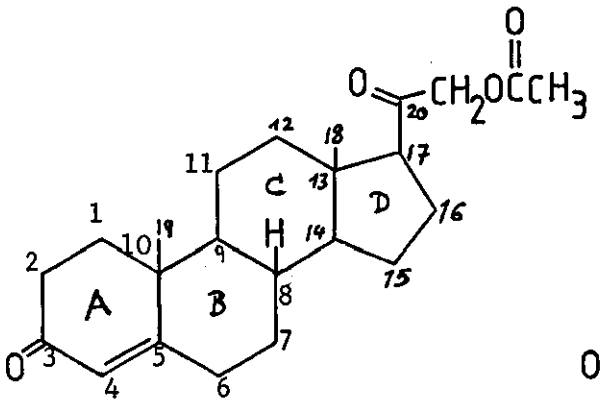
Screening Results	Dose mg/kg (i.p.)	Response: Normotensive rats	Response: DOCA Hypertensive rats
(85) 	100	inactive	—
(88) 	100	inactive	—
(89) 	10	20 mm Hg fall (15%) in MABP at 2h 20% rise in HR at 3h	—
(92) 	100	20 mm Hg fall (15%) in MABP	27 mm Hg fall (16%) in MABP at ½h (persisting for 3h) 51% rise in HR at 2h (falling off at 3h)
(95) 	100	inactive	—
(96) 	10	13 mm Hg fall (10%) in MABP at 1h Negligible effect on HR	—
(102) 	100	inactive	—
(119) 	100	22 mm Hg fall (17%) in MABP	Negligible effect on MABP 32% rise in HR at 1h (falling off at 3h)
(49) 	100	inactive	—

i.p. = intraperitoneal
MABP = mean arterial blood pressure HR = heart rate

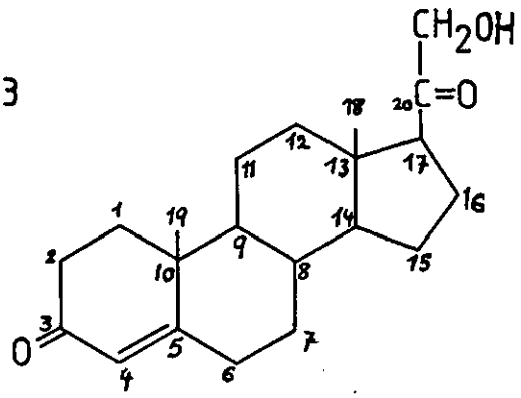
Two of the active compounds (92) and (119) were also tested in DOCA hypertensive rats.

Metacorticoid hypertension can be induced by chronic administration of 11-deoxycorticosterone acetate (DOCA) (127), to unilaterally nephrectomised rats, maintained on 1% sodium chloride drinking solution.[140,141] The incidence of elevated arterial blood pressure promoted, resembles, both physiologically and morphologically, the syndrome of human essential hypertension.

Deoxycorticosterone (128) is a hormone secreted by the adrenal cortex and generally promotes retention of salt and water.[142] Excessive production of deoxycorticosterone has been associated with high blood pressure and is probably responsible for hypertension by a sodium retention mechanism.



(127)



(128)

It can be seen from the screening results that of the nine compounds tested, four were active as antihypertensive agents, viz the 6-hydrazino-, the 6-ethoxy- and the 6-allyloxy-1,2-dichloro-3-phenylpyrrolo[2,1-a]phthalazine and the 6-acetyl-3-phenylpyrrolo[2,1-a]phthalazine, structures (89), (92), (96), and (119), respectively.

The inactive compounds, included the representative (85) of the 6-amino-substituted system and the 6-α-methylhydrazino derivative (88). This suggests that with C-6 N-substituted pyrrolo[2,1-a]phthalazines the most effective group is (unsubstituted) hydrazino-, a result in common with the hydralazine series as mentioned in the introduction (p. 16).

Of the C-6 -OR substituted examples, three with small OR groups were active but the more bulky furfuryloxy derivative (95) caused activity to be lost.

Both the two representatives pyrrolo[2,1-a]phthalazin-6(5H)-one derivatives (102) and (49) were inactive, i.e. with (102), and without (49), N-5 substitution.

Of the three active compounds carrying C-6 -OR groups (92), (96) and (119), one of these (119) lacks 1,2-dichloro groups. This suggests that the chloro groups are not significant in determining whether the compounds are antihypertensive. The chloro groups may affect toxicity levels of the compounds, but no toxicity tests were carried out.

The most active of our compounds is the 6-hydrazino derivative (89), producing in normotensive rats a fall of 15% in MABP at 2 hours, with a dose of only 10mg/Kg. However this antihypertensive activity

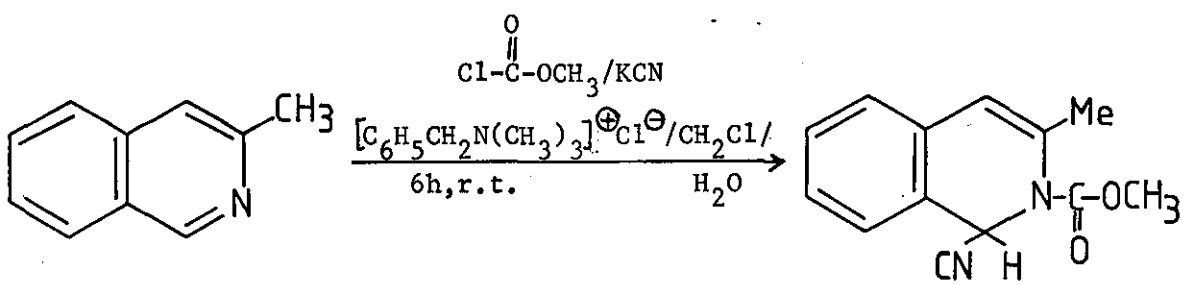
could only be classed as moderate when compared with the clinical drug hydralazine which causes [143] a maximum fall of 31% in MABP in normotensive rats at a dose of 5mg/Kg. The effect is seen at 2 hours after dosage. Hydralazine simultaneously causes a rise in heart rate of 18% at 2 hours. Our analogue (89) causes a rise of 20% in HR at 3 hours.

It is significant that our 6-alkoxy derivative (96) at the same dosage (10mg/Kg) produced a 10% fall in MABP at 1 hour but had negligible effect on HR. The 6-ethoxy and 6-acetyl derivatives (92) and (119) tested at 100mg/Kg, caused considerable increases in HR of 51% and 32%, respectively. The pharmacologists were unable to say what was causing this adverse effect; further detailed study of the animals would be required. The compounds (92) and (119) caused falls of 15% and 17%, respectively in the MABP of normotensive rats, and surprisingly only the ethoxy derivative (92) caused a fall in MABP, 16%, in DOCA hypertensive rats.

PART III

SYNTHESIS OF IMIDAZO[5,1-a]PHTHALAZINES AND RELATED SYSTEMS

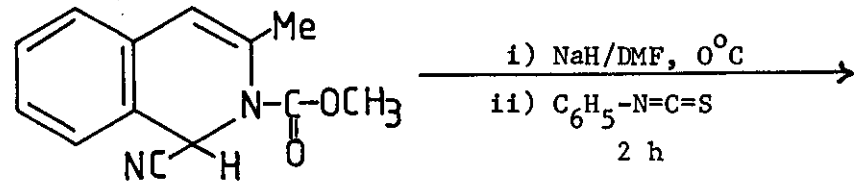
As discussed in the Introduction (p.27), phthalazine Reissert compounds are prepared from phthalazine by treatment with an acid chloride and potassium cyanide in a two-phase system incorporating a phase transfer catalyst. B.C. Uff and co-workers [80,81,144] have, for example, synthesised N-methoxycarbonyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (63) from 3-methylisoquinoline, methyl chloroformate, and KCN in a two phase system (CH_2Cl_2/H_2O) and in the presence of benzyltrimethylammonium chloride as a phase transfer catalyst, in 64% yield.



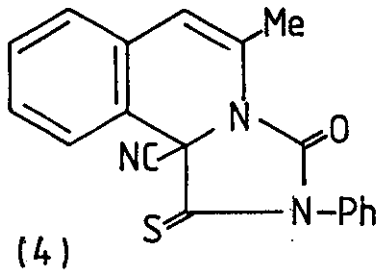
(63)

B.C. Uff and R.S. Budhram[80,81,144] studied the reaction of phenyl isothiocyanate with the anion of (63), which was generated by use of sodium hydride in dimethylformamide at 0°C, and obtained 10b-cyano-5-methyl-N-phenyl-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (4) as a yellow solid (m.p. 168°C) in 58% yield and a co-product

unidentified at the outset of our work.



(63)

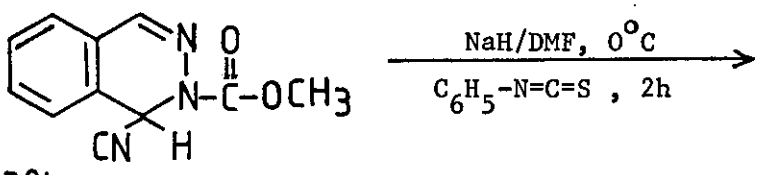


(4)

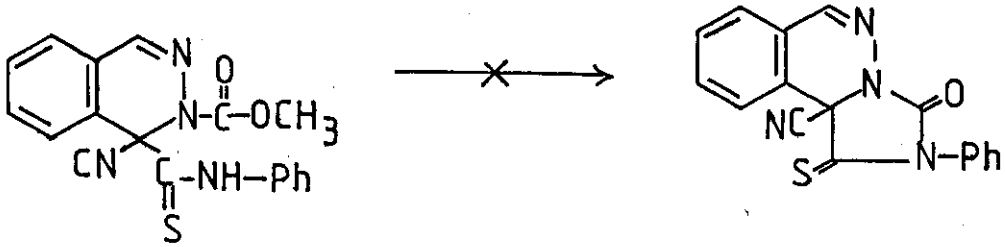
+ unknown

(129)

B.C, Uff and R.S. Budhram[145] also attempted to use the above method for synthesis of the novel imidazo[5,1-a]phthalazine (132). However they found that cyclisation under the same conditions but using 2-methoxycarbonylphthalazine Reissert compound (130), did not occur and instead the open-chain addition compound (131) was obtained.

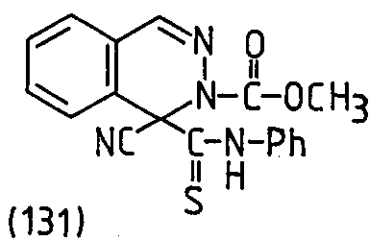


(130)



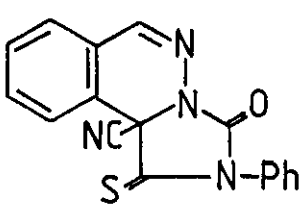
(131) (132)

B.C. Uff and A.S. Mallard,[146] have recently shown that cyclisation of thiocarboxide (131) can be achieved, However, when compound (131) is refluxed in dry toluene over molecular sieves type 4A for 21 hours, to give (132) as minor product and an unknown compound (133) as major product.



(131)

dry toluene, reflux(21h)
molecular sieves
type 4A



(132)

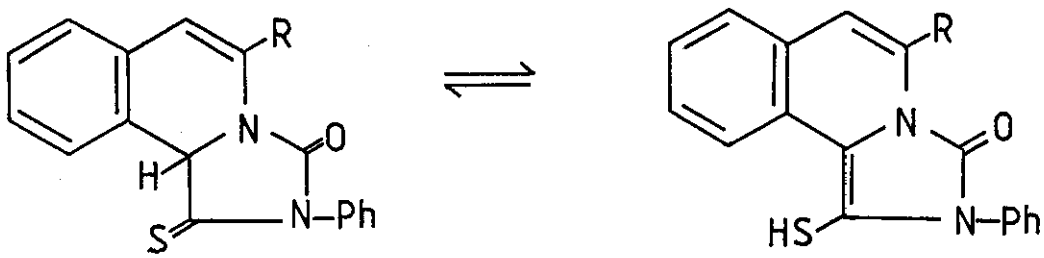
+ unknown

(133)

We decided to study — the above cyclisations in order to assess the generality or otherwise of the synthesis of imidazo[5,1-a]phthalazines and imidazo[5,1-a]isoquinolines, using other isothiocyanates.

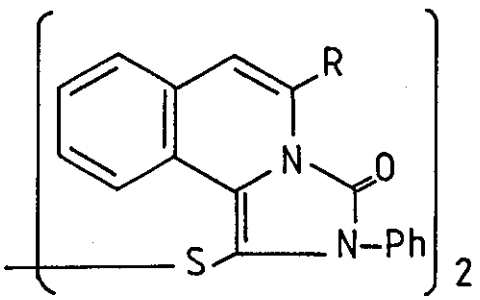
Also it was of interest to elucidate the structure of the co-product (133) from the cyclisation.

The earlier co-product (129) from the isoquinoline cyclisation was thought by Budhram,[147] to be the thione structure (134a, R=H) or its ene-thiol tautomer (134b,R=H).[147]

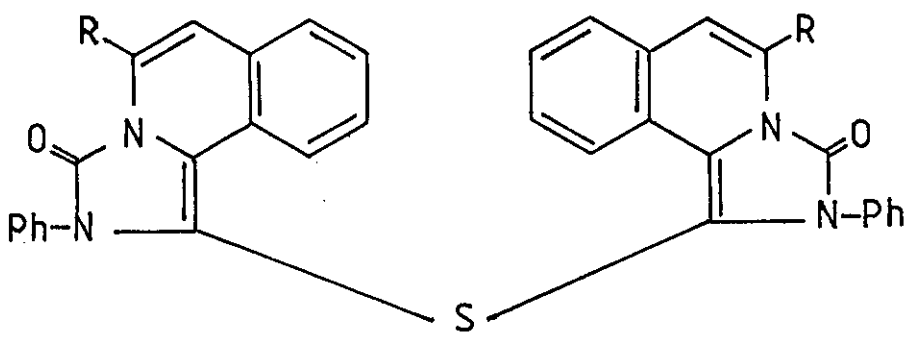


(134a) (134b)

The compound gave an acceptable microanalysis for (134a, R=H) but osmometry indicated a higher molecular weight, of 522, comparable, within the 10% accuracy of the method, with either the disulphide (F, R=H, m.wt.=582), or the mono sulphide (G, R=H, m.wt. = 550).



(F)

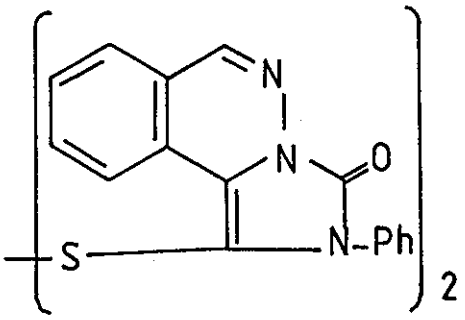


(G)

The mass spectrum of the compound ($R=CH_3$) showed no peak corresponding to the disulphide (F, $R=CH_3$, m.wt.=610) but did show a small peak at M^+ 578.1789 corresponding to mono-sulphide (G, $R=CH_3$, m.wt.=578.1777).[148]

An X-ray study in the Department has recently been carried out,[149] and the results studied and reported by A.S. Mallard.[146] The data show the structure of the co-product from unsubstituted isoquinoline Reissert compound cyclisation with PhNCS, to be the disulphide (F, R=H). Hence with the 3-methylisoquinoline sequence the co-product (129) will be (F, $R=CH_3$). Compound (129) was given in 25% yield.[152]

It seemed likely to us, therefore, that the structure of the co-product (133) in the phthalazine cyclisation was the disulphide shown :



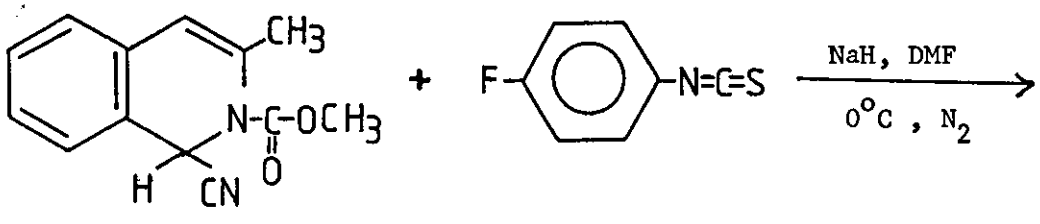
(133)

We hoped to find evidence to support this proposal.

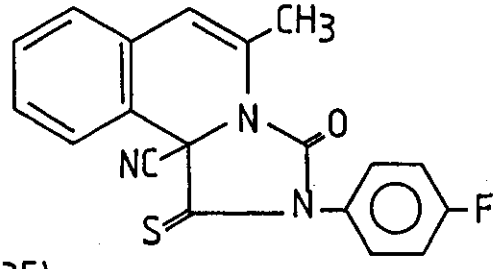
We first sought to extend the examples of imidazo[5,1-a]isoquinoline formation. Preparation of the starting Reissert compounds, required potassium cyanide, and the special precautions for handling cyanide and disposing of cyanide residues are summarized in the experimental section (p.176).

The reaction of 4-fluorophenyl isothiocyanate with the anion of

(63), which was generated by use of sodium hydride in dimethylformamide at 0°C and under a dry nitrogen atmosphere provided 10b-cyano-5-methyl-N-(4-fluorophenyl)-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (135) in 52% yield.



(63)



(135)

It was surprising that no disulphide derivative of (135) was isolated. However in the preparations of the imidazo[5,1-a]isoquinoline series the disulphide has usually been the minor prduct.[146,150]

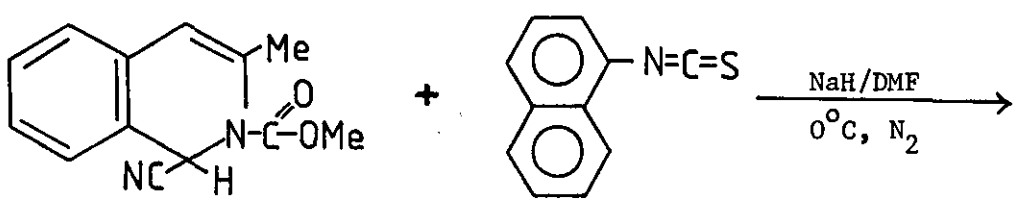
The infrared spectrum of our compound (135) showed a remarkably high carbonyl absorption at ν_{max} (KBr) 1775 cm^{-1} (C=O, strong intensity). Similar values were reported by Budhram [150] e.g. compound (4), which showed C=O at 1780 cm^{-1}.[150]

In the n.m.r. 60MHz ($CDCl_3$), our compound (135) showed δ 2.53 (3H, s, C5-Me), δ 6.38 (1H, br, C6-H), δ 7,1-7.7 (7H, m, aromatic) and δ 8.4 (1H,d, C10-H) and in the u.v. ($CHCl_3$) λ_{max} nm log ε 252(3.79),

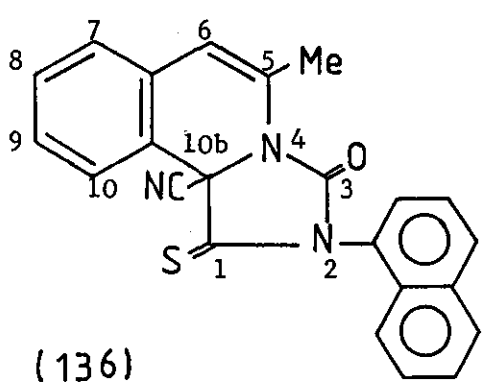
279(3.97).

Satisfactory analytical data was obtained for this crystalline yellow compound m.p. 158-160°C.

We next looked at the reaction of 1-naphthyl isothiocyanate with the anion of (63), which was generated by use of sodium hydride in dimethylformamide at 0°C and under a dry nitrogen atmosphere provided impure 10b-cyano-5-methyl-N-(naphth-1-yl)-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (136).



(63)

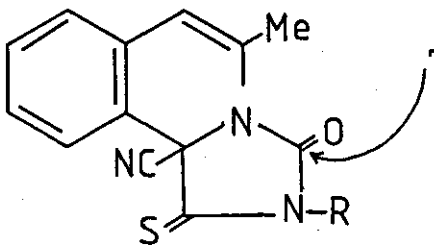


(136)

Again as with (135) no disulphide derivative of (136) could be isolated.

The infrared spectrum of our compound (136) showed similar high carbonyl absorption at ν_{max} (KBr) 1775 cm^{-1} (C=O, strong intensity). This high carbonyl absorption of 1775-1780 cm^{-1} is a characteristic for

the tricyclic imidazo[5,1-a]isoquinoline system (137).[150]

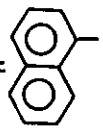


ν_{max} 1775-1780 cm^{-1}

(137)

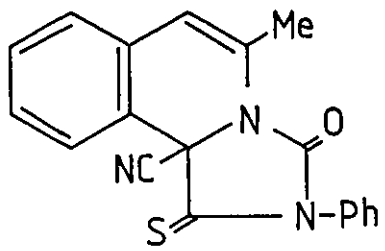
(4) R=  , ν_{max} 1780 cm^{-1} (C=O)

(135) R=F-  , ν_{max} 1775 cm^{-1}(C=O)

(136) R=  , ν_{max} 1775 cm^{-1}(C=O)

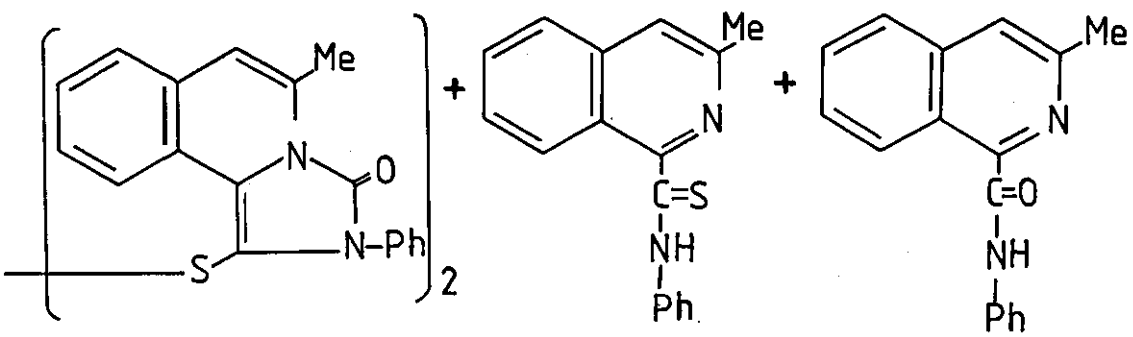
In the n.m.r. 60 MHz ($CDCl_3$), our compound (136) showed δ 3.15 (3H, s, Me), δ 6.31 (1H, br, C6-H), δ 6.6-8.1 (10H,m, aromatic) and δ 8.48 (1H,m,C10-H). However compound (136) could not be isolated analytically pure. Attempts at purification by recrystallisation from toluene, ethyl acetate, ethanol, methanol,or mixture of these solvents and also purification by column chromatography on neutral alumina (act I), using chloroform-methanol (3:1) as eluent, were all unsuccessful.

Hydrolysis of compound (4) was studied by Budhram,[145] using 30% aqueous sodium hydroxide at room temperature for ~ 12.5 hours, and he isolated compound (129) plus two other products(138) and (139). The structure of compound (129) was later confirmed by X-ray studies,[149] to be the bis-imidazo[5,1-a]isoquinolinyl disulphide.[149]



30% aq. NaOH, dioxan
12.5h room temperature

(4)



(129) yield 34%

(138) yield 18%

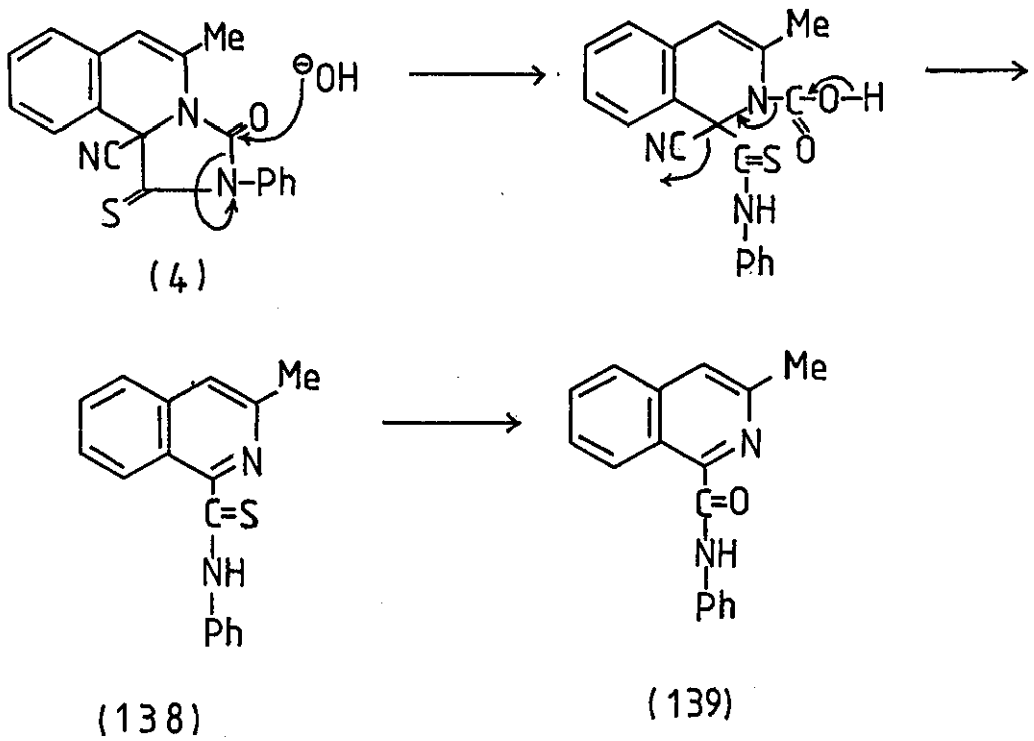
(139) yield 12%

However hydrolysis of compound (4), using 90% sodium hydroxide provided Budhram only compound (139). This compound (139), was also obtained when compound (138) was hydrolysed using 30% sodium hydroxide.[151,152]

The following mechanism for the formation of (138) and (139) was suggested by Budhram.[151] (See p. 116).

Hydrolysis of compound (4) by base attack at the hydantoin carbonyl carbon, and decarboxylation accompanied by loss of cyanide produces first the thioanilide (138) which is hydrolysed further to the anilide (139). Budhram[151] showed (138) gave (139) on treatment with 30% NaOH.

Such hydrolyses are not unusual.[153]

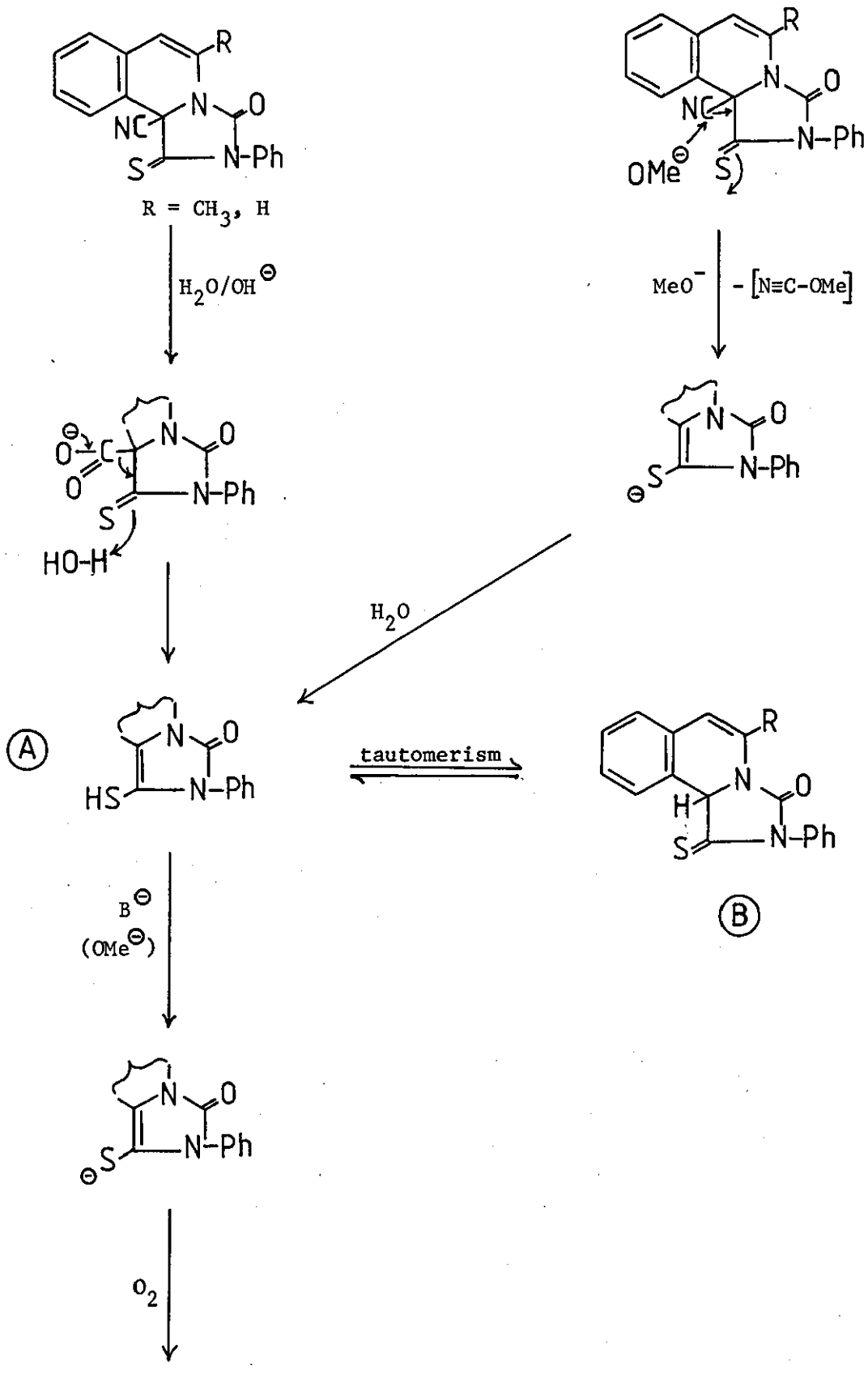


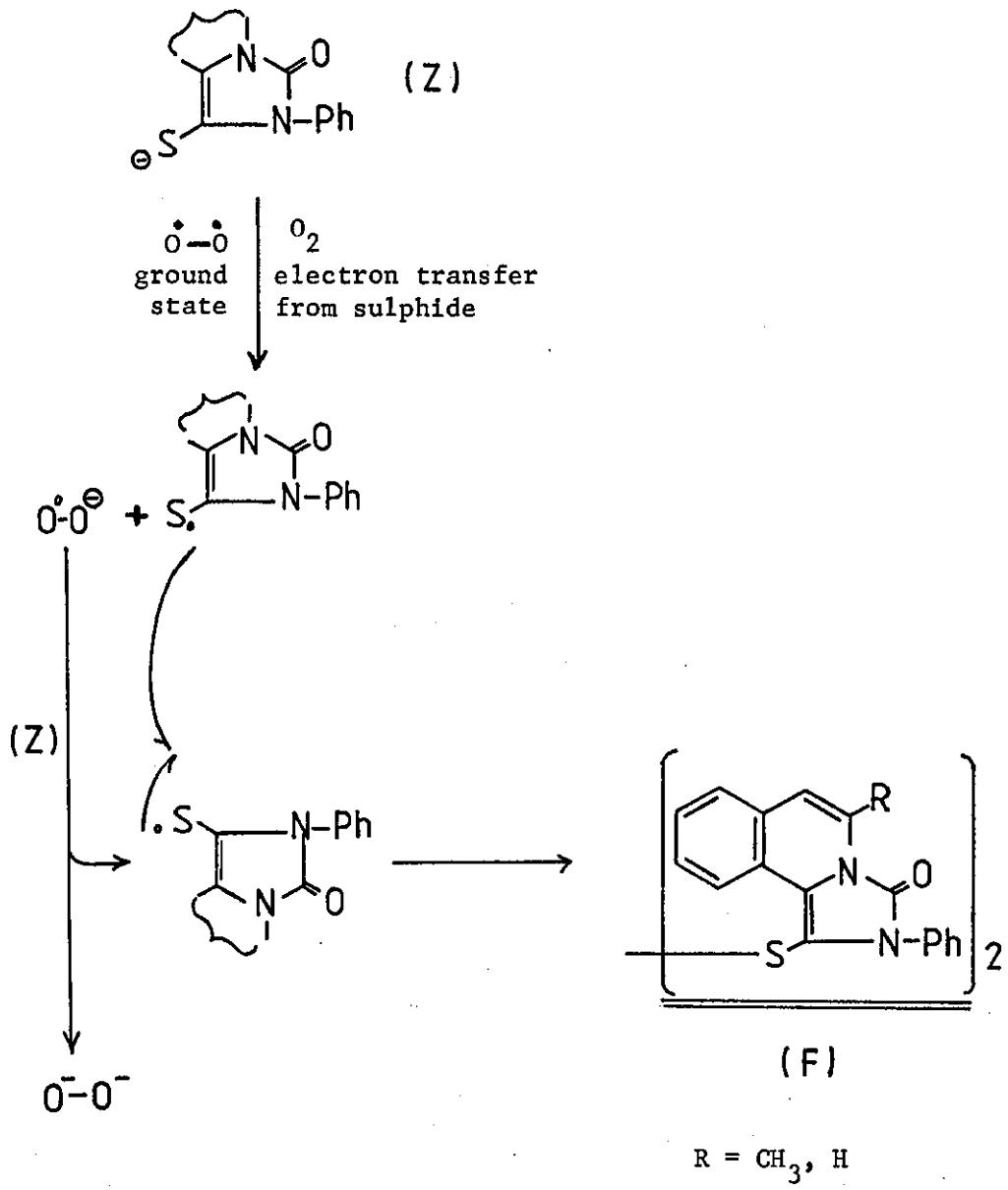
(4)

(138)

(139)

Formation of the disulphide linkage is probably preceded by either cyanide hydrolysis and decarboxylation during work-up of this reaction, or possibly by direct displacement of CN by $CH_3O^{\ominus}$, liberated during the cyclisation. Both mechanisms then could proceed via oxidative coupling of (A) (tautomer of B), as shown on p.117 . Air oxidation of thiols to disulphides is well known and involves sulphide conversion to a sulphur radical by electron transfer to oxygen.[154]


R
N
O
NC
S
N-Ph
R = CH3, H
H2O/OH⊖
OMe⊖
MeO⁻
- [N≡C-OMe]
HO-H
H2O
A
B
HS
tautomerism
B⊖
(OMe⊖)
O2

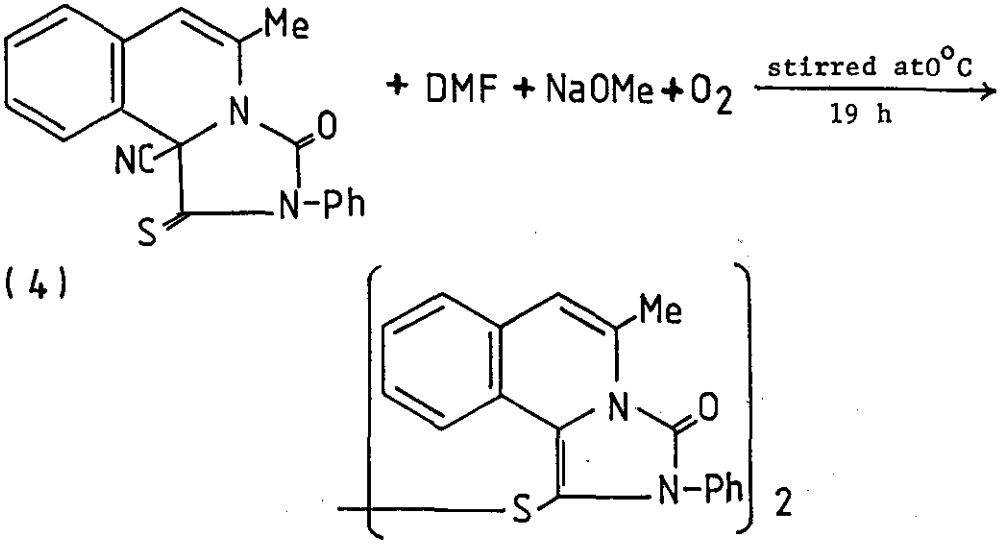


As mentioned on p.115 Budhram studied the hydrolysis of compound (4) using 30% sodium hydoxide, and isolated the disulphide (129).[151]

In order to find out whether or not $CH_3O^{\ominus}$, (which is liberated on cyclisation of the Reissert compound) (e.g. 63), plays any role in the cyano group removal, prior to disulphide linkage, we decided to carry out the following experiments.

The reaction of compound (4) with one molar equivalent of sodium methoxide in dry dimethylformamide at 0°C under a dry oxygen atmosphere was carried out. The sample of compound (4) used by us had been prepared by R.S. Budhram.[152] The reaction was followed by t.l.c. every 30 minutes. The t.l.c. of the yellow solution after 3 hours showed only one spot corresponding to the tricyclic starting material (4). The period of 3 hours is longer than the original cyclisation (2 hours).[152]

After 7 hours it was observed that the mixture had changed slightly more red, and the t.l.c. showed disulphide appearance as a weak spot. After 19 hours the red colour had deepened and t.l.c. showed a strong disulphide spot and only a weak spot corresponding to starting material. The mixture was then evaporated at (70°C/0.1 mm Hg). Infrared spectrum of the product showed ν_{max} 1710 cm^{-1}. This product was then columned on neutral alumina, using toluene-ethyl acetate (4:1) as eluent and the disulphide (129), m.p. 244-246°C, was isolated, identical with a sample prepared previously by Budhram.[152]



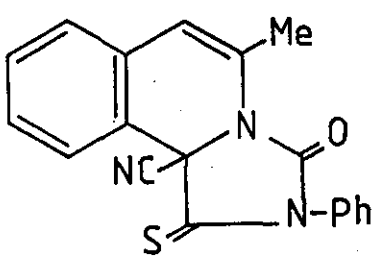
(4)

(129)

It seems that direct cyano-group displacement by $MeO^{\ominus}$ after 2 hours at 0°C (i.e. conditions of the original experiment) is not occuring. The slow appearance of the disulphide (129) after 19 hours, may have been a product of slow hydrolysis due to some moisture gaining access to the system e.g. by taking and replacing the stopper during the t.l.c. examination.

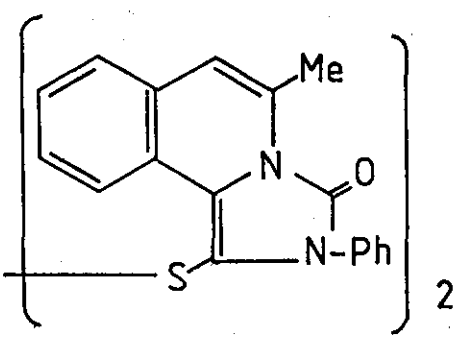
As mentioned above ,in order to evaporate the dimethylformamide, after stirring at 0°C, the mixture was heated at (70°C/0.1 mm Hg) for 30 minutes.

In order to find out whether or not heat is necessary for the convertion of the tricyclic imidazo[5,1-a]isoquinoline (4) to the disulphide (129), following reaction was carried out :



(4)

+ DMF + NaOMe + O_2 —stirred at 70°C, 24 h, anhydrous conditions→



(129)

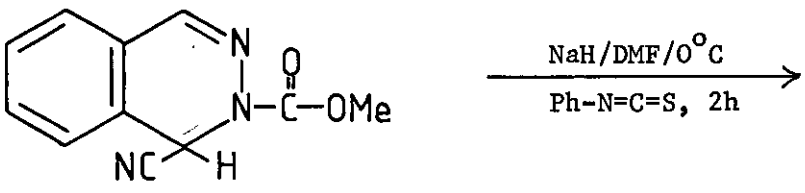
The reaction of compound (4) with one molar equivalent of sodium methoxide in dry dimethylformamide at 70°C under a dry oxygen atmosphere

was examined. The reaction was followed by t.l.c. every ½ hour, samples being withdrawn by insertion of a syringe through a septum cap to avoid access of moisture. However even after heating the mixture for 24 hours, the t.l.c. showed tricyclic imidazo[5,1-a]isoquinoline(4) as a major spot and only a small trace of the disulphide (129). The mixture was then poured on to crushed ice. The precipitate formed on warming to room temperature was filtered off and the starting material (4), was recovered. The yellow filtrate was extracted with chloroform. Concentration of yellow chloroform-extracts under reduced pressure also provided the tricyclic imidazo[5,1-a]isoquinoline (4). No disulphide (129), could be isolated, in the above reaction.

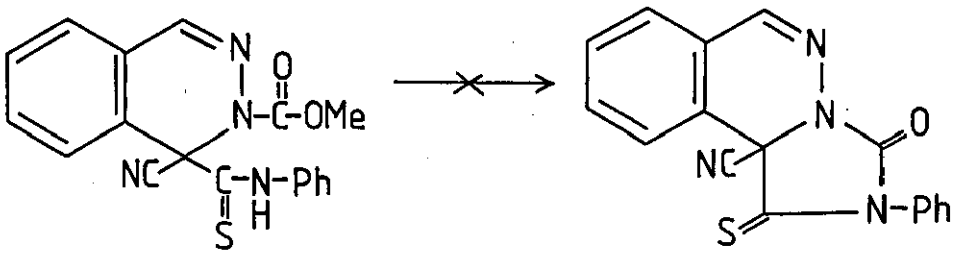
It seems therefore that under anhydrous conditions, methoxide does not cause cyanide displacement and hence disulphide formation. Access of water and hence $HO^{\ominus}$ seems to be the cause of cyanide loss (by hydrolysis and decarboxylation) and this can occur during work-up or by access of moisture during the reaction. Displacement of CN by direct attack by $MeO^{\ominus}$ and liberation of methyl cyanate, MeOCN, has been proposed once before in the literature to our knowledge but the proposal was not substantiated[155] on further experimental study. It can be noted that if methyl cyanate were formed it might trimerise [156] or rearrange to the isocyanate, MeNCO.[156]

As mentioned above B.C. Uff and R.S. Budhram [145,145a] studied the reaction of phenyl isothiocyanate with the anion of phthalazine Reissert compound (130), generated by use of sodium hydride in dimethylformamide at $0^{o}C$, and obtained the open-chain addition compound (131), no

cyclisation could be achieved. This was unexpected, as similar reaction of related isoquinoline Reissert compounds under the same conditions provided a tricyclic product, imidazo[5,1-a]isoquinoline, as earlier discussed in this chapter (p.108).



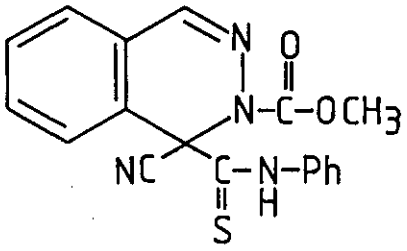
(130)



(131)

(132)

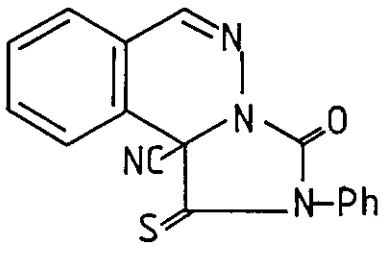
As mentioned on p.109, B.C. Uff and A.S. Mallard,[125] have recently shown that cyclisation of the thiocarboxamide (131) can be achieved, when compound (131) is refluxed in dry toluene over molecular sieves type 4A for 21 hours, to give (132) as minor product and an unknown compound (133) as major product.



dry toluene, reflux(21h)

molecular sieves type 4A

(131) open-chain addition compound



+ unknown

(133)

(132)

It seemed likely, that the structure of the compound (133) was the disulphide shown on (p.111), as earlier discussed in this chapter (p.109) . We hoped to find out evidence to support this proposal.

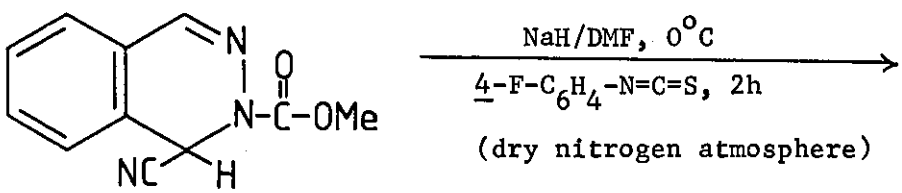
We decided to study the above cyclisations in order to assess the generality or otherwise of the novel synthesis of imidazo[5,1-a]phthalazines, using other isothiocyanates.

The approach was first to build up the open-chain addition compound from phthalazine Reissert anion on treatment with other isothiocyanates at $0^{\circ}C$.

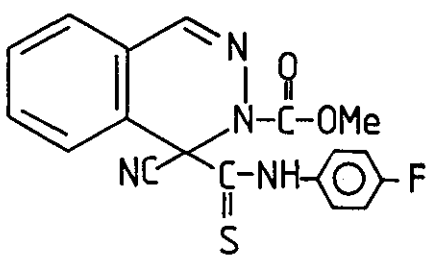
Preparation of the starting Reissert compound, required potassium cyanide, and the usual precautions were taken for handling cyanide and disposing of cyanide residues p.176 .

The reaction of 4-fluorophenyl isothiocyanate with the anion of

phthalazine Reissert compound (130), generated by use of sodium hydride in dimethylformamide at 0°C, provided 1-(4-fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (140) in 37% yield.



(130)



(140)

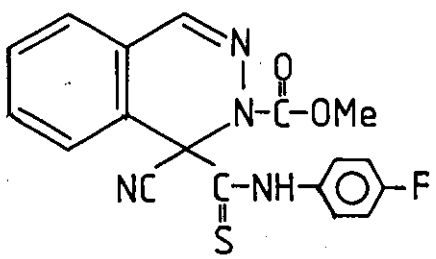
In the 60MHz n.m.r.($CDCl_3$/DMSOd6, 50:50), this compound showed δ 3.90 (3H,s, -O-Me), δ 6.8-8.25 (9H, m, aromatic) and δ 11.25(1H,br, NH), and in the i.r. ν_{max}(KBr) 3200 cm^{-1}(NH), 1730 cm^{-1} (C=O).

Satisfactory analytical data was obtained for this crystalline pale yellow compound, m.p. 181-183°C .

Cyclisation of the open-chain addition compound (140), was achieved when this compound (140) was refluxed in dry toluene over molecular sieves type 4A for 21 hours, and provided two compounds (141) and (142).

Compound (141) in the 60 MHz n.m.r. ($CDCl_3$) showed, δ 6.2-7.8 (7H, m. aromatic), δ 8.14 (1H, m. C6-H), δ 8.52 (1H, m, C10-H). The infrared

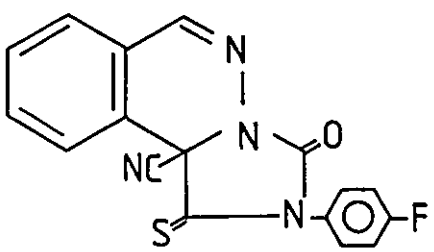
spectrum of our compound (141)showed high carbonyl absorption of 1778cm^{-1} (C=O). As mentioned earlier (p.114) similar values were obtained for the tricyclic imidazo[5,1-a]isoquinoline system (137) of 1775-1780 cm^{-1}. Compound (141) in the u.v. showed λ_{max} nm log ε 210(4.65), 278(4.35), 316(3.97). In the mass spectrum of this compound (141), the following principal fragments were observed : m/e 336(M^{+}, 36%), 310(14%), 199(6%), 173(23%), 155(26%), 153(100%), 137(20%). (See Scheme A).



(140)

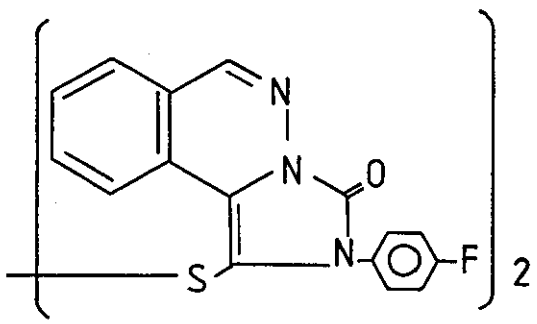
toluene, reflux(21h)

molecular sieves type 4A

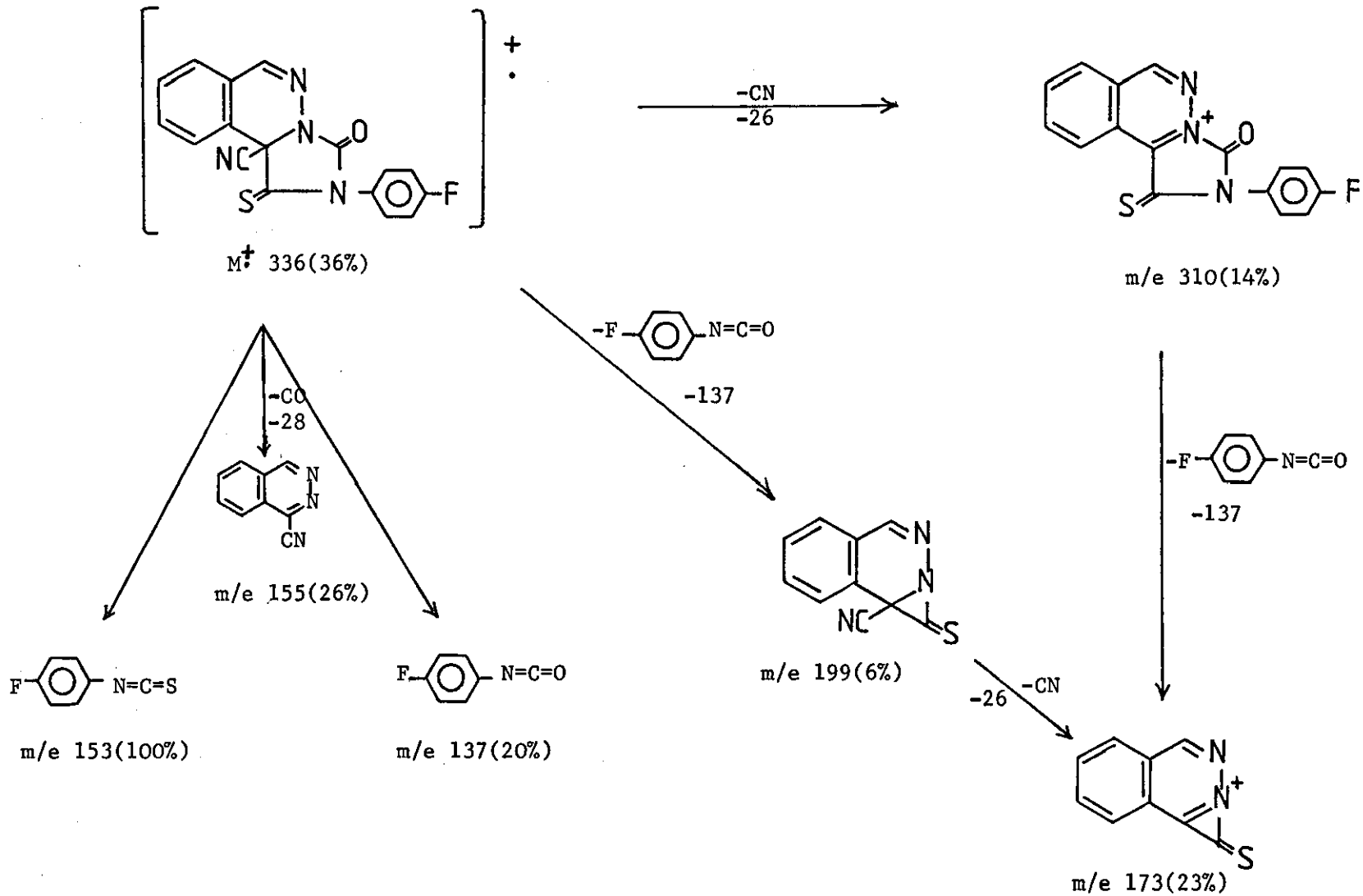


(141)

+



(142)


-CN
-26
M+ 336(36%)
m/e 310(14%)
-F N=C=O
-137
-CO
-28
m/e 155(26%)
-F N=C=O
-137
F N=C=S
m/e 153(100%)
F N=C=O
m/e 137(20%)
m/e 199(6%)
-26
-CN
m/e 173(23%)

Scheme A

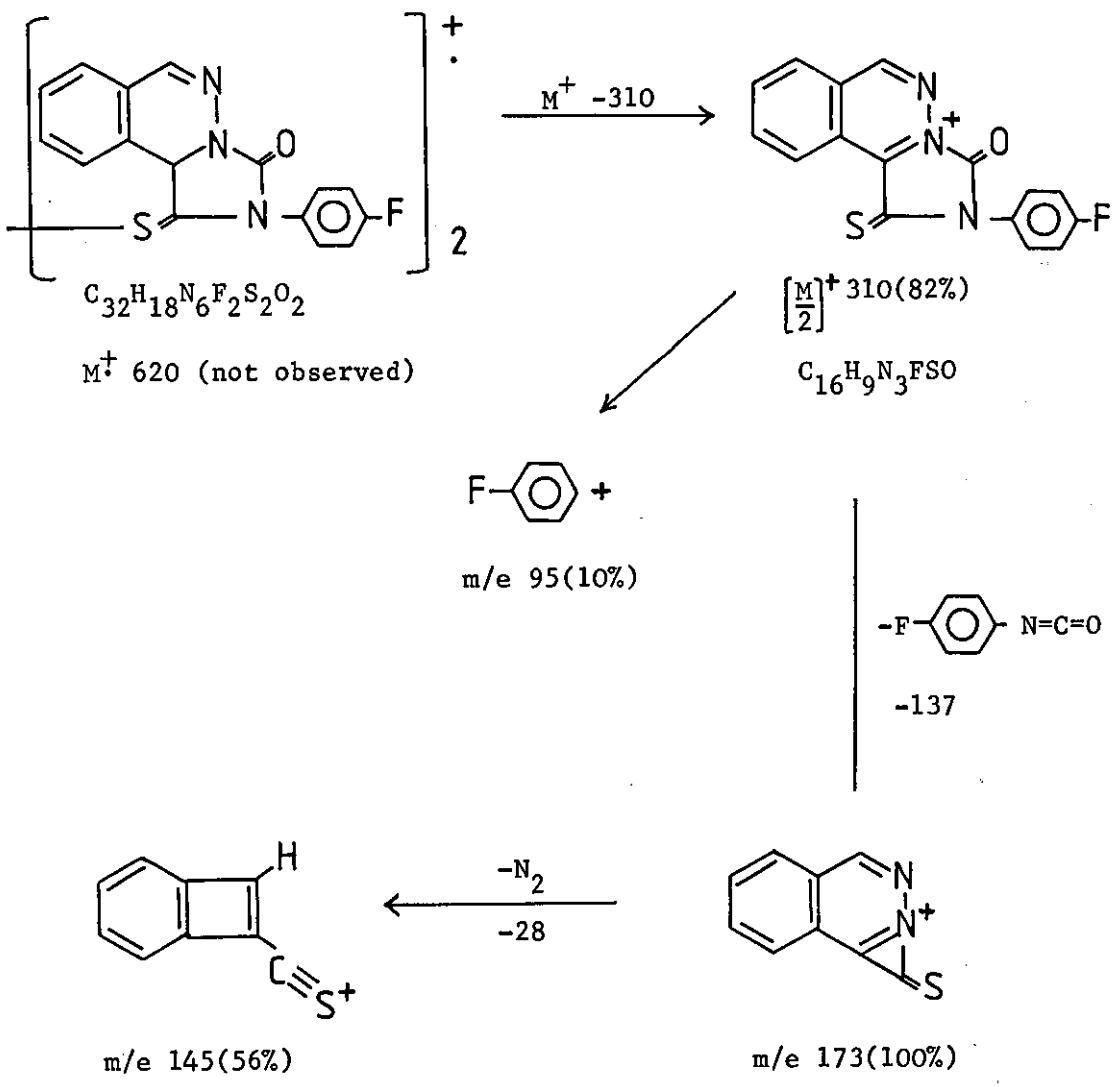
Accurate mass measurement for this compound (141), obtained by PCMU, Harwell, showed M^+ 336.0482 ($C_{17}H_9N_4FSO$ requires 336.0.480). However this compound (141) could not be isolated analytically pure, although it showed only one spot on t.l.c. Attempts at purification by recrystallisation from toluene, ethyl acetate, ethanol, methanol, or mixture of these solvents, and also purification by column chromatography on neutral alumina (act I) using chloroform as eluent, were all unsuccessful. Decomposition to and contamination with traces of disulphide (142) seems the most likely explanation, since the accurate mass data clearly showed compound (141) to be formed.

Concentration of the dark maroon filtrate under reduced pressure gave the bis[2-(4-fluorophenyl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthlazin-1-yl] disulphide (142) in 29% yield. This compound (142), in the i.r. showed ν_{max} 1715 cm^{-1} (C=O), and 1600 cm^{-1} (C=C), and in the u.v. λ_{max} nm log ε 224(4.5),250(4.20),268(4.35),344(3.52),444(3.21).

Comparison of the i.r. data obtained for (141) and (142), shows a fall in (C=O) wavelength absoption from 1778 cm^{-1}, to 1715 cm^{-1}, respectively, indicative of the change in saturation of the imidazo ring in (141), on removal of the cyano group, and loss of the thio-imide unit $S{=}\overset{|}{C}\text{-}\underset{|}{N}\text{-}\overset{|}{C}{=}O$.

Also the u.v. shows a shift to longer wavelength, the colour being dark maroon in (142), compared to the yellow colour of (141). The u.v. spectrum of bis-imidazo[5,1-a]phthalazinyl disulphide (142), includes λ_{max} at 444 nm , ca. 100 nm, higher, compared to the λ_{max} - value, obtained for (141) at λ_{max} 316 nm.

In the accurate mass spectrum of (142) the molecular ion at M^{+} 620 was absent but there showed however, $\left[\frac{M}{2}\right]^{+}$ peak at m/e 310.0448, ($C_{16}H_9N_3FSO$ requires 310.0450). Principal fragments obtained were as follows: m/e 310$\left[\frac{M}{2}\right]^{+}$ (82%),173(100%),145(56%), 95(10%).(See Scheme B).



Scheme B

Satisfactory analytical data was obtained for this crystalline dark maroon compound, m.p. 249-296°C.

As mentioned above, in the mass spctrum of bis-imidazo[5,1-a]phthalazinyl disulphide (142), M^+ 620.09000 was not observed and only $\left[\frac{M}{2}\right]^+$ could be seen. This is because of molecular ions generated in these types of compounds are not sufficiently stable, when electron-impact ionisation is used. In fact molecular-ions of many classes of compounds suffer decomposition in the mass spectrometry, due to the large excess of energy (70 ev), imparted to these molecules.[157]

Chemical ionisation (CI) is a valuable technique in mass spectrometry,[157,158] for faciliating the identification of molecular-ions, particularly in cases where the molecular ion is too labile for observation by more usual EI technique.[157,158]

Chemical ionisation usually occurs by a proton transfer from a reactant ion gas (ammonia, or hydrocarbons commonly used), to the substrate.[159]

$$XH^+ + AB \longrightarrow ABH^+ + X$$

AB = substrate

X = reactant gas (commonly used : ammonia, methane).

Hydrocarbons (particularly methane) are often used as reactant ion gas.

On electron impact, in case of the use of hydrocarbons (e.g.methane)

as reactant gas, the following reactions may take place :[157]

$$CH_4^{+\bullet} + CH_4 \longrightarrow CH_5^+ + CH_3^\bullet$$

$$CH_3^+ + CH_4 \longrightarrow C_2H_5^+ + H_2$$

The $C_2H_5^+$ and CH_5^+ then induce the sample ions to ionise by a proton transfer.

For many type of compounds parent ion therefore appears at M+1 .

In cases of thermally labile compounds, which normally decompose using direct probe techniques, CI provides better quality spectra.[159-162]

As mentioned earlier, in the (EI) accurate mass measurement for compound (142), obtained by PCMU, Harwell, M^+ 620.09000 peak was not observed. Compound (142) was submitted for CI mass spectrometry using ammonia as reactant gas on a VG Micromass mass spectrometer. The obtained mass spectrum and fragmentation pattern for this compound (142) are shown (Scheme C, & p.132).

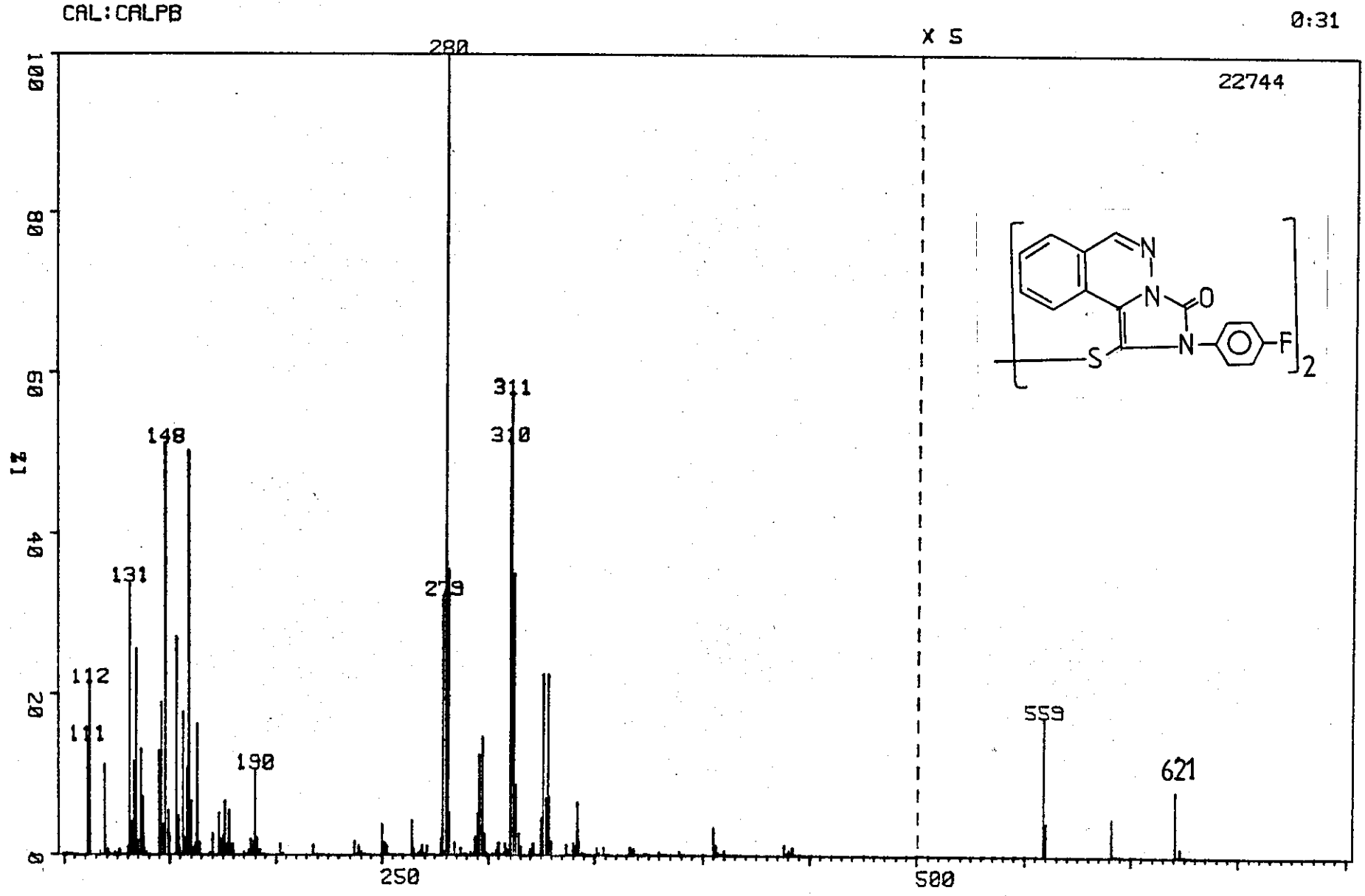
It can be seen immediately that , at last, the disulphide molecular ion has been detected in the form of an (M+1) peak at m/e 621 (2%). This provides the first direct evidence for the molecular structure of the bis-imidazo[5,1-a]phthalazinyl disulphide. It pleasingly complements the X-ray data for the disulphide structure in the analogous imidazo[5,1-a]isoquinoline series.

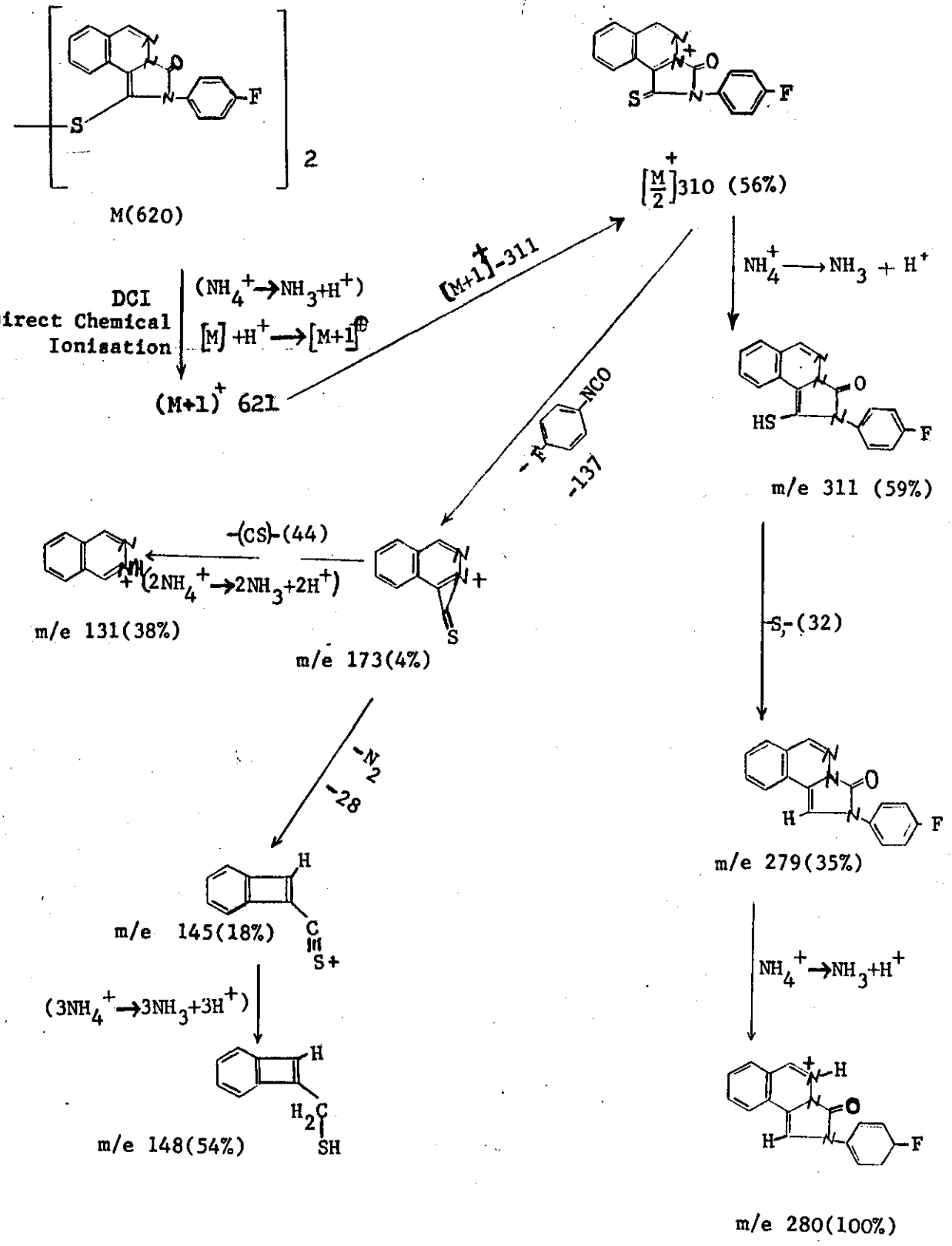
In the CI spectrum for (142) the peak at $(M+1)^+$ 621, arises by the following procedure :

$$NH_4^+ \longrightarrow NH_3 + H^+$$

$$[M] + H^+ \longrightarrow [MH]^+$$

m/e 620 m/e 621


PAUL6 12 GG53 DCI NH3
CAL:CALPB
0:31
X 5
280
22744
100
80
60
40
20
0
%
148
131
112
111
190
279
311
310
559
621
250
500
N
N
O
N
S
F
2

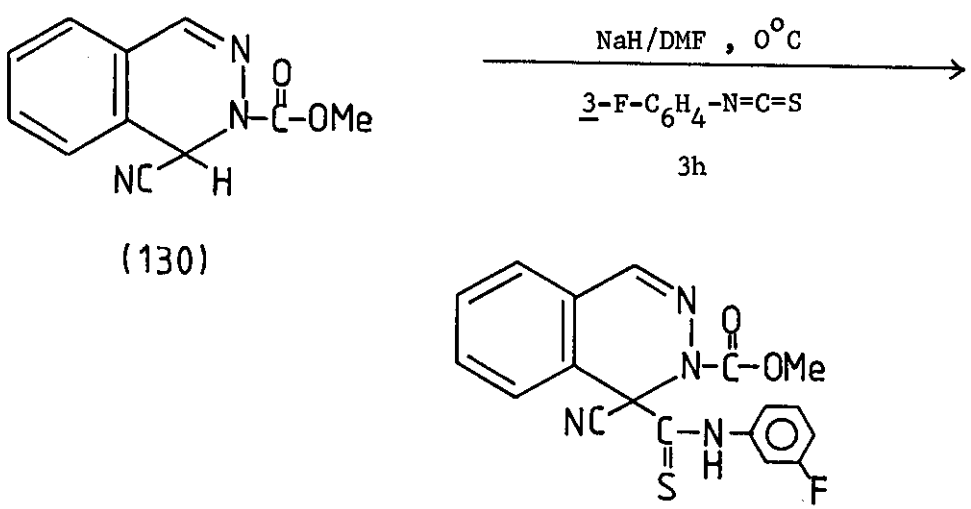

M(620)
DCI
Direct Chemical
Ionisation
$(NH_4^+ \rightarrow NH_3+H^+)$
$[M]+H^+ \rightarrow [M+1]^+$
$(M+1)^+$ 621
$[M+1]^+ - 311$
$[\frac{M}{2}]^+ 310$ (56%)
$NH_4^+ \rightarrow NH_3 + H^+$
m/e 311 (59%)
-137
-(CS)-(44)
$(2NH_4^+ \rightarrow 2NH_3+2H^+)$
m/e 131(38%)
m/e 173(4%)
-S,-(32)
m/e 279(35%)
$-N_2$
-28
m/e 145(18%)
$(3NH_4^+ \rightarrow 3NH_3+3H^+)$
m/e 148(54%)
$NH_4^+ \rightarrow NH_3+H^+$
m/e 280(100%)

Scheme C

Our final objective was to assess the generality of the above synthesis of the novel imidazo[5,1-a]phthalazine system. We wished to use a variety of isothiocyanates.

The approach was first to construct the open-chain addition compound from phthalazine Reissert anion on treatment with 3-flurophenyl isothiocyanate.

The reaction of 3-fluorophenyl isothiocyanate with the anion of (130), which was generated by use of sodium hydride in dimethylformamide at 0°C and under a dry nitrogen atmosphere, provided 1-(3-fluorphenyl-aminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (143) in 41% yield.



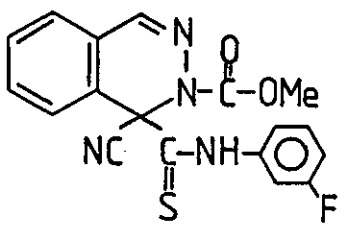
(130)

(143)

In the i.r., this compound showed ν_{max} (KBr) 3240 cm^{-1} (NH), 1738 cm^{-1}(C=O), 1550 cm^{-1} and 1130 cm^{-1}(CSNH) and in the n.m.r. 60MHz ($CDCl_3$), this compound showed δ 3.90(3H, s, -OMe), δ 6.7-8.3 (9H, m, aromatic), and δ 9.15(1H, br, NH). Satisfactory analytical data was

obtained for this crystalline, pale yellow compound m.p. 168-169°C .

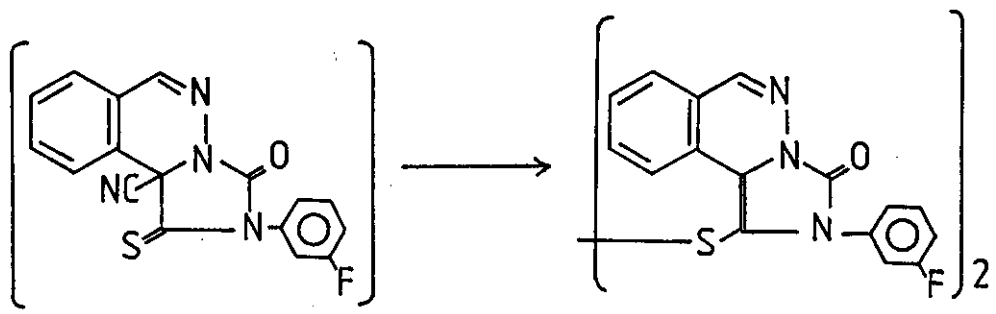
Cyclisation of thiocarboxamide (143), was then achieved, when compound (143) was refluxed in dry toluene over molecular sieves type 4A for 21 hours. The product was bis[2-(3-fluorophenyl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (145). No intermediate (144) was isolated.



(143)

toluene, reflux(21h)

molecular sieves type 4A



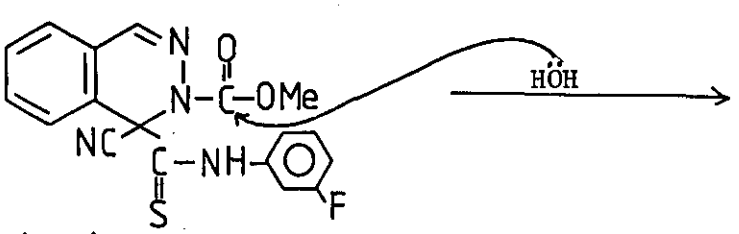
(144) (145)

In the i.r. the disuphide (145) showed ν_{max} (KBr)1712 cm^{-1}(C=O), 1600 cm^{-1} (C=C), and in the u.v. λ_{max} nm log ε 250(4.92), 268(4.98), 328(4.63).

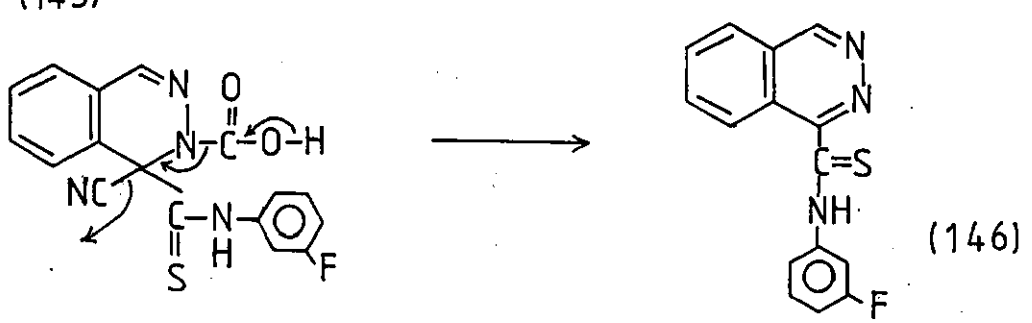
In the mass spectrum of compound (145), neither M^{+} peak at m/e 620, nor $[M-32]^{+}$ peak at m/e 588 could be seen. However as mentioned earlier (p.128) the $\left[\frac{M}{2}\right]^{+}$ peak, characteristic in all mass spectra obtained

for the bis-imidazo[5,1-a]phthalazinyl disulphides, was observed in the mass spectrum of this compound. The accurate mass obtained for this compound (145) M^{+} (not observed), however showed $\left[\frac{M}{2}\right]^{+}$ peak at m/e 310.0451 ($C_{16}H_9N_3SFO$ requires 310.0450). The compound (145), could not be isolated analytically pure. Attempts at purification by recrystallisation from toluene, ethyl acetate, ethanol, methanol,or mixture of these solvents and also purification by column chromatography on neutral alumina (act I), using chloroform-methanol (3:1) as eluent were all unsuccessful.

The above reaction was repeated three times under the same conditions but the product (145) could not be isolated analytically pure. However in addition to (145), we also obtained in one experiment 1-(3-fluorophenylaminothiocarbonyl)phthalazine (146). Formation of (146), could be as a result of hydrolysis of the open-chain addition compound(143), duringwork-up, or use of insufficiently dried solvent (toluene), during the reaction.

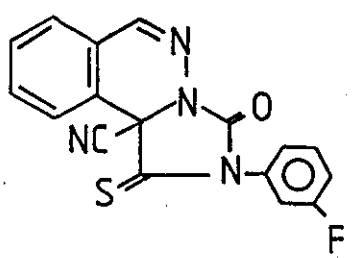


(143)



(146)

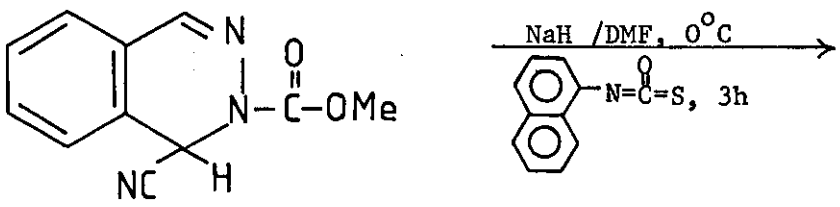
In the i.r. compound (146) showed ν_{max} (KBr) 3250 cm^{-1} (NH), 1495 cm^{-1} and 1380 cm^{-1} (C=S), and in the n.m.r. 60 MHz ($CDCl_3$) δ 7.1-8.3 (9H,m, aromatic), δ9.25 (1H, br, NH). Satisfactory analytical data was obtained for this crystalline pale yellow compound m.p. 188-191°C. It was surprising that no tricyclic imidazo[5,1-a] phthlazine derivative (144) was isolated. However in the imidazo [5,1-a]phthalazine series the disulphide was seen to be the major product in a number of cases (see below).



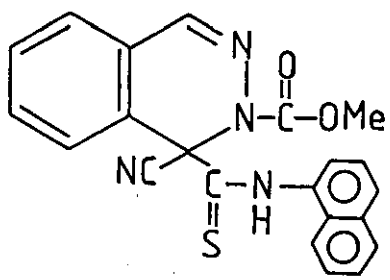
(144)

Our next synthesis with phthalazine Reissert anion used with 1-naphthyl isothiocyanate.

The reaction of 1-naphtyl isothiocyanate with the anion of (130) generated by use of sodium hydride in dimethylformamide at 0°C and under a dry nitrogen atmosphere, provided 1-(naphth-1-yl-aminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (147) in 39% yield.



(130)

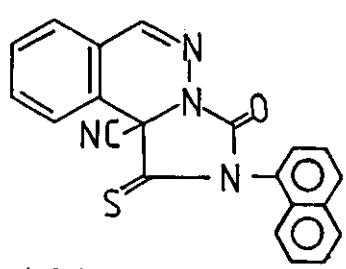


(147)

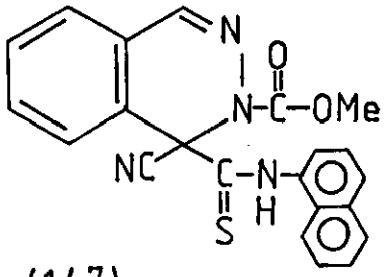
In the i.r. this compound showed ν_{max} (KBr) 3186 cm^{-1}(NH), 1735 cm^{-1} (C=O), 1500 cm^{-1} and 1145 cm^{-1} (CSNH), and in the n.m.r. 60 MHz ($CDCl_3$/DMSOd6, 50:50), δ3.95 (3H,s, OMe), δ 7.2-8.3(12H, m, aromatic), δ 9.36 (1H, br, NH). However this compound (147), again resisted attempts at purification even after careful column chromatography on neutral alumina, using chloroform-methanol as a eluent.

Cyclisation of thiocarboxamide (147), was successfully achieved when compound (147) was refluxed in dry toluene over molecular sieves type 4A for 21 hours. This provided pure bis[2-(naphth-1-yl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (149) in 43% yield.

Again it was noted that no tricyclic imidazo[5,1-a]phthalazine (148) was isolated.

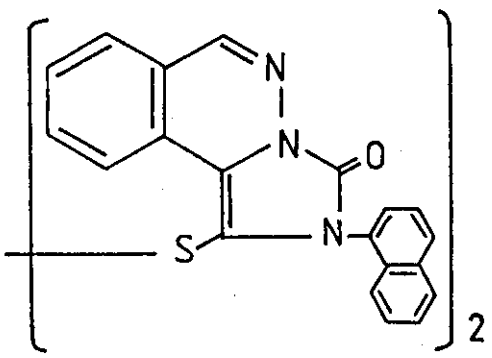


(148)



(147)

toluene , reflux(21h)
molecular sieves
type 4A



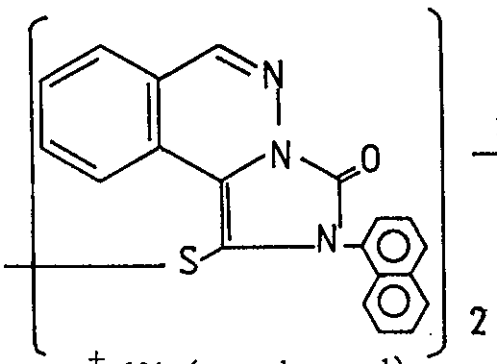
(149)

In the i.r. compound (149) showed ν_{max} (KBr) 1721 cm^{-1} (C=O), 1600 cm^{-1} (C=C, aryl), and in the u.v. λ_{max} nm log ε 220(4.28), 276(3.64), 350(3.4),440(3.04).

Satisfactory analytical data was obtained for this crystalline dark maroon compound, m.p. 261-263°C.

In the mass spectrum of this compound (149), neither $M^{+\cdot}$ peak at m/e 684, nor $[M-32]^+$ peak at m/e 652 could be seen.

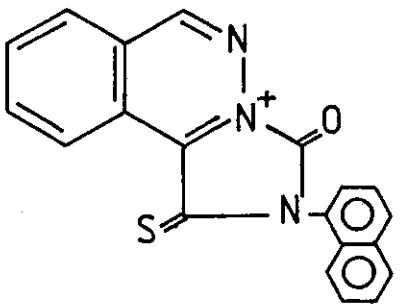
Compound (149), showed the characteristic $\left[\frac{M}{2}\right]^+$ peak at m/e 342.0697 ($C_{20}H_{12}N_3OS$ requires 342.0701). Principal fragments obtained were as follows : $M^{+\cdot}$ (not observed), m/e : 342 $\left[\frac{M}{2}\right]^+$ (61%), 173 (100%), 145 (46%), 127(12%). (See Scheme D).



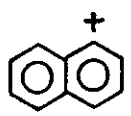
M^+ 684 (not observed)

$C_{40}H_{24}N_6O_2S_2$

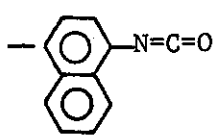
$M^+ - 342$



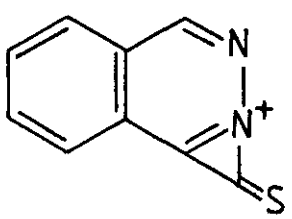
$\left[\frac{M}{2}\right]^+$ 342(61%) $C_{20}H_{12}N_3OS$



m/e 127(12%)



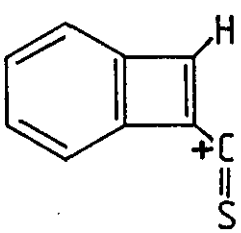
(-169)



m/e 173(100%)

$-N_2$

-28

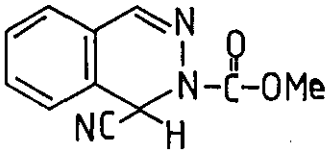


m/e 145(56%)

Scheme D

So far we have studied the above cyclisation in order to assess the generality or otherwise of the synthesis of novel imidazo[5,1-a]o phthalazine, using aryl isothiocyanates. We lastly studied one example using an alkyl isothiocyanate.

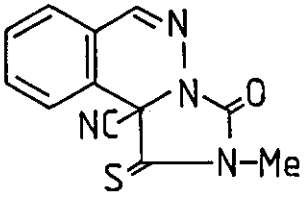
The reaction of methyl isothiocyanate with the anion of (130), generated by use of sodium hydride in dimethylformamide at $0^{\circ}C$ and under a dry nitrogen atmosphere directly provided two compounds (150) and (151).



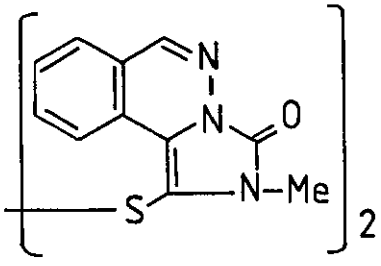
(130)

i) NaH/DMF, $0^{\circ}C$

ii) Me-N=C=S , 3h



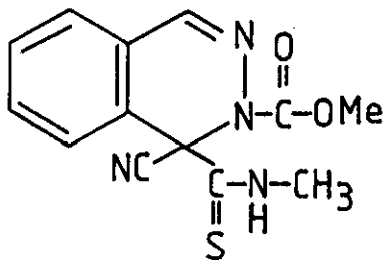
&



(150)

(151)

It was surprising that no open-chain addition compound (152) was isolated, as in the cases of using aromatic isothiocyanates, mentioned above.



(152)

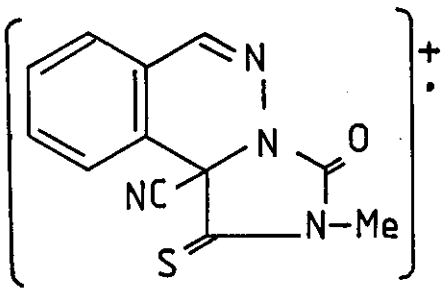
The above reaction was first studied by A.S. Mallard in this Department. She obtained compound (151) in 8% and impure compound (150) in 5% yield, respectively. Satisfactory analytical data was obtained by her for (151), however she was unable to isolate compound (150) pure.

We obtained compound (150) as pale yellow needles in 6% yield. In the n.m.r. 60 MHz ($CDCl_3$), this compound showed δ 3.42(3H,s, Me), δ 7.16-7.85 (3H, m, aromatic, C7-H, C8-H and C9-H), δ 8.1 (1H,m,C6-H), δ 8.58(1H, m, ClO-H), in the i.r. ν_{max} 1770 cm^{-1} (C=O), 1600 cm^{-1}, and 1165 cm^{-1} (C=S), and in the u.v. λ_{max} nm log ε 210(3.80), 270(3.65), 316(3.35).

In the mass spectrum of this compound (150) principal fragments obtained were as follows : M^{+} 256(65%), m/e: 173(7%),155(100%),127(26%). (See Scheme E).

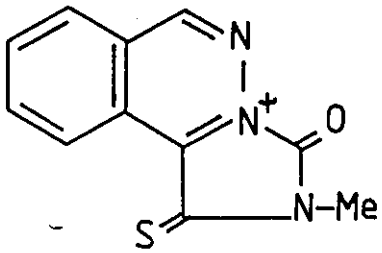
Accurate mass measurement obtained for this compound (150), showed M^{+} 256.0415 ($C_{12}H_8N_4SO$ requires 256.0416). Satisfactory analytical data was obtained for this crystalline, pale yellow new compound m.p. 197-199°C.

In the above reaction, concentration of the dark maroon filtrate under reduced pressure gave us bis[2-methyl-3-oxo-2,3-dihydroimidazo



$M^{+\cdot}$ 256 (65%)

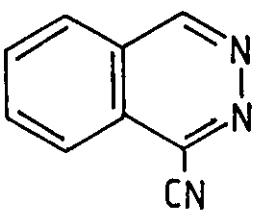
-CN
-26



m/e 230(4%)

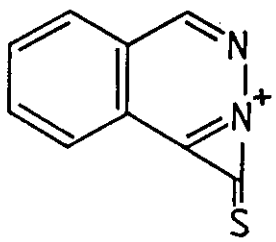
-CS
-44

-Me-N=C=O
(-57)



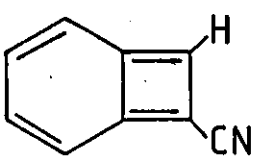
m/e 155(100%)

-MeN=C=O
(-57)



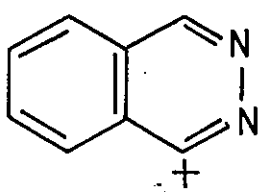
m/e 173(7%)

$-N_2$
-28



m/e 127(26%)

-CS
(-44)

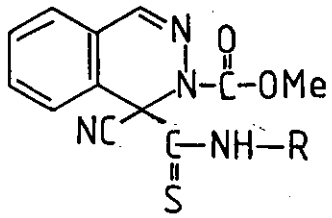


m/e 129(7%)

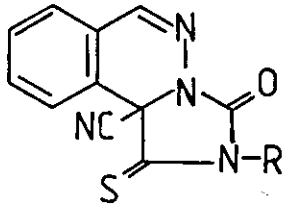
Scheme E

[5,1-a]phthalazin-1-yl] disulphide (151) in 9% yield. In the i.r. this compound (151) showed ν_{max} 1715 (C=O) and in the u.v. λ_{max} n.m. log ε 246(3.93), 270(4.29), 340(3.56).

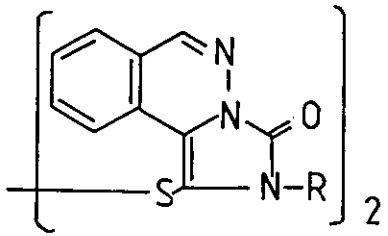
Table 11



(Q)



(M)



(T)

	R	ν_{max} cm^{-1}(C=O)		yield%		R	ν_{max} cm^{-1}(C=O)		yield%		R	ν_{max} cm^{-1}(C=O)		yield%
Q	(131) C_6H_5**	1730	✓	67	M	(132) C_6H_5*	1780	✓	20	T	(133) C_6H_5*	1712 23	✓	14
Q	(140) 4-F-C_6H_4	1730	✓	37	M	(141) 4-F-C_6H_4	1778	m s	40	T	(142) 4-F-C_6H_4	1715	✓	29
Q	(143) 3-F-C_6H_4	1738	✓	41	M	(144) 3-F-C_6H_4	—		0	T	(145) 3-F-C_6H_4	1712	m s	39
Q	(147) $C_{10}H_7$	1735	×	39	M	(148) $C_{10}H_7$	—		0	T	(149) $C_{10}H_7$	1721	✓	43
Q	(152) Me	—		0	M	(150) Me	1770	✓	6	T	(151) Me	1715	✓	9
												1710	✓	4

* Data from A.S. Mallard.[146]

** Data from R.S. Budhram.[1]

Table 11 shows a summary of our imidazo[5,1-a]phthalazine work described above. As Table 11 shows, for the open-chain addition compound (Q) ν_{max} 1730-1738 cm^{-1} (C=O) was observed, while the infrared spectrum of the tricyclic imidazo[5,1-a]phthalazine system (M) showed a remarkably high carbonyl absorption of ν_{max} 1770-1780 (C=O). For the disulphide derivatives (T) ν_{max} of 1712-1721 cm^{-1} (C=O) was observed.

In conclusion our studies have shown that the imidazo[5,1-a] phthalazine system, either in the form of the tricyclic compound (M) or disulphide (T), or both, can be synthesized from a 2-alkoxycarbonyl-phthalazine Reissert compound and alkyl or aryl isothiocyanates.

It would be worthwile in the future scaling-up the higher yielding reactions, to provide adequate material for pharmacological testing for antihypertensive activity as this was shown present in the analogous imidazo[5,1-a]isoquinoline system (4) mentioned earlier (p.1).

Our work together with complementary studies by A.S. Mallard has been presented and published in abstract form.[165] A copy of the abstract is bound at the end of this thesis.

EXPERIMENTAL

Unless otherwise stated the following conditions apply.

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded by a Varian EM360A spectrometer (60MHz) and Perkin-Elmer R32 spectrometer (90MHz) in solutions of deuteriochloroform and/or $DMSOd_6$ with tetramethylsilane (TMS) as internal reference. The following abbreviations are used in the presentation of these spectra: s = singlet, d = doublet, q = quartet, t = triplet m = multiplet, br = broad.

Infrared spectra were recorded as KBr discs, nujol mulls, liquid films or chloroform solutions by means of Perkin-Elmer 177 grating spectrophotometer and the quoted absorbances are strong except where indicated (m = medium, w = weak). The ultraviolet spectra were recorded on a Unicam S P 800 spectro photometer. Mass spectra were obtained on an A.E.I.MS12 machine. Accurate mass measurements were carried out by P.C.M.U.on an A.E.I. MS50 Machine.

Column chromatography was, unless otherwise stated, on neutral alumina (Camag) of Brockmann activity 1. Preparative thin layer chromatography was also an alumina, 0.75mm layer, Merck GF_{254}. Thin layer chromatography (t l c) used plates 5 cm x 20 cm, 10 cm x 20 cm, or 20 cm x 20 cm, with alumina GF_{254} (0.75mm layers)

Commercial grade solvents were used except for the following which were purified as follows. Light petroleum (40-60^{o}C) diethyl

ether and toluene, were distilled and dried over sodium wire. Dimethylformanide DMF, was distilled as follows,[83] A mixture of DMF (250g), C_6H_6 (30g) and H_2O (12g) were fractionally distilled. First benzene, water, amines and ammonia were collected, boiling range 83-105°C at 760mm Hg and then at reduced pressure DMF was distilled b.p. 54-56°C at 14mm Hg, stored over molecular sieves (3A) and protected from light.

'Super dry' ethanol[84] was prepared by warming a mixture of magnesium turnings (5g), iodine (0.5g) and ethanol (75ml, 99%), until the iodine had disappeared.[84] Absolute alcohol (900ml) was then added and the mixture was refluxed for 30 minutes. The alcohol was then distilled off. The super-dry ethanol (purity exceeds 99.95 per cent), is exceedingly hygroscopic, and precautions were taken to protect the distillate from atmospheric moisture.

EXPERIMENTAL

PART 1 SYNTHESIS OF PYRROLO[2,1-a]PHTHALAZINES

Fumaryl chloride (67)

A mixture of fumaric acid (50g, 0.43mol) and phosphorus pentachloride (100g, 0.48mol) in carbon tetrachloride (200ml), was heated at (50-60°C) with stirring for 3 hours, and then fractionated, using a Vigreux column to afford fumaryl chloride (67) as a colourless liquid (33g, 50%) b.p. (62-64°C/13mm), [lit,[86] (b.p. 62-64°C/13mm)] n.m.r. 60MHz ($CDCl_3$) δ7.1(2H, s, CH=CH).

Trans-1,2-dibenzoylethylene (68)

A mixture of finely powdered anhydrous aluminium chloride (206g; 1.54mol) and dry benzene (1060ml) was stirred and heated on a water bath at 50-60°C, the water bath removed after 30 minutes and fumaryl chloride (90g; 0.58mol) was added dropwise during 30 minutes. The mixture turned dark red and evolved hydrogen chloride rapidly. The mixture was refluxed gently for 10 minutes with stirring. The pasty red mixture was poured portion-wise upon ice (2kg) to which was added conc. HCl (40ml). The reaction mixture was stirred for 30 minutes. The mixture was washed with hot water (4 x 300 ml) and extracted with benzene (4 x 50ml). The combined benzene extract was concentrated, and recrystallised from ethanol to afford trans-1,2-dibenzoylethylene (68) (85g; 61%) as yellow needles, m.p. 109-111°C [(lit.,[87] m.p. 109-110°C)]. ν_{max} (nujol mull) 1660cm^{-1} (C=O); 1600 (C=C) n.m.r. 60MHz ($CDCl_3$) δ7.35 (2H, m, CH=CH); 7.5 (4H, m, aromatic); 7.6-8.15 (6H, m, aromatic).

2,5-Diphenylfuran (70)

Into a hot suspension of stannous chloride (8g, 0.035mol) in a solution of hydrochloric acid (8N, 12ml) and ethanol (4ml), was added with stirring a hot solution of trans-1,2-dibenzoylethylene (8g, 0.03mol) in ethanol (40ml). The mixture was stirred and refluxed for 30 minutes and then diluted with water (4ml), cooled and filtered, to give 2,5-dipenylfuran (3.7g; 49%). Recrystallisation from ethanol gave colourless plates m.p. 89-90°C [(lit.,[90] 89.5-90°C)].

1,2-Dibenzoylethane (69)

Into a hot suspension of stannous chloride (8g; 0.03mol) in a solution of hydrochloric acid (8N, 12ml), and ethanol (95%, 4ml) was added dropwise with stirring a hot solution of trans-1,2-dibenzoylethane (8g;0.03mol) in ethanol (95%, 40ml). The mixture was then diluted immediately, with water (4ml), cooled and filtered. The product was recrystallised from ethanol to afford (5.67g, 70%) of 1,2-dibenzoylethane (69) as pale yellow neeldes m.p. 144-147°C, [(lit.,[88] m.p 145-147°C)]. ν_{max} (nujol mull) 1680cm^{-1} (C=O) 1600cm^{-1} (C=C aromatic); n.m.r. 60MHz ($CDCl_3$) δ3.4 (4H, s, 2 x CH_2); 7.1-8.2 (10H, m, aromatic).

2,5-Diphenyl-1-ureidopyrrole (48)

To a solution of 1,2-dibenzoylethane (3.6g; 15m·mol) in ethanol (75ml) was added at room temperature a solution of semicarbazide hydrochloride (1.8g; 16m·mol) in H_2O (5ml) and the mixture was refluxed for 6 hours. The mixture was concentrated under reduced

pressure. The product was purified by fractional recrystallisation from ethanol to afford 2,5-diphenyl-1-ureidopyrrole (2g; 48%) as pale-yellow needles m.p. 238-239°C, [(lit.[89] m.p 239°C)]; ν_{max} (nujol mull) 3310cm^{-1} (br, NH and NH_2), 1650cm^{-1} (C=O); n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$) δ5.18 (2H, br , NH_2), 6.20 (2H, s, H_1 and H_2 pyrrole), 6.9-7.8 (10H, m, aromatic), 9.25 (1H, br., NH).

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (49)

2,5-Diphenyl-1-ureidopyrrole (1g, 3m.mol) was heated under N_2 atmosphere on a Woods metal bath at 260-280°C for 30 minutes. The resultant brown mixture was chromatographed on a column (20 x 3cm) of silica gel (25g). Elution with cyclohexane-toluene (4:1) and further elution with toluene, afforded 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (280mg; 30%) as yellow needles m.p. 185-186°C (petroleum ether 40-60°C) [(lit.[77] m.p. 185-186°C)]; ν_{max} (KBr) 1660cm^{-1} (C=O); n.m.r. 60 MHz ($CDCl_3$); δ6.5 (1H, d, H_1 or H_2 pyrrole CH, J= 3.0 Hz), 6.70 (1H, d, H_2 or H_1 pyrrole CH, J= 3.0 Hz), 7.0-8.2 (9H, m, C_6H_5 and C_6H_4); 12.0 (1H, br , NH);

u.v. λ_{max} nm log ε 250(3.11), 293(3.61), 333 (3.53).

ω- Bromoacetophenone semicarbazone (72)

To a solution of bromoacetophenone (10g; 0.05mol) in ethanol (20ml) a solution of semicarbazide hydrochloride (6g; 0.054mol) and potassium acetate (6g; 0.06mol) in water (10ml) was added. After standing for 12 hours at room temperature a solid was separated off, which was recrystallised from ethanol to afford ω-bromoacetophenone semicarbazone (10.3g-80%) as colourless to pale-yellow needles m.p. 146-148°C (lit.[89] 146-148°C). ν_{max} (nujol mull) 3470, 3360cm^{-1} (NH), 1720cm^{-1} (C=O); n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), δ4.52 (2H, s, $-CH_2$ Br), 6.2 (2H, br, NH_2), 7.2-7.9 (5H, m, aromatic), 9.8 (1H, s, NH).

3-Ethoxycarbonyl-2-methyl-5-phenyl-1-ureidopyrrole(42a)

To a solution of sodium ethoxide which was prepared from sodium (1.2g) and absolute ethanol (8ml), ethyl benzoylacetate (6.5g, 0.05mol) was added dropwise under stirring and a dry nitrogen atmosphere at $0^{o}C$. As the mixture began to solidify more absolute ethanol (8ml) was added until a clear solution was obtained. To the mixture was then added under cooling at $10^{o}C$, ω-bromoacetophenone semicarbazone (12.8g, 0.05mol) and absolute ethanol (30ml), and the mixture was shaken at room temperature for 24 hours. The product was then diluted with H_2O (20ml) and was extracted with ether (3 x 40mol). The ether extract was dried ($MgSO_4$), and concentrated. The oily product was then crystallised from ethanol to give a product, 3.5g, m.p. 248-250^{o}C, identified as 3-ethoxycarbonyl-2-methyl-5-phenyl-1-ureidopyrrole (42a) (lit.[89], m.p. 248^{o}C), hence the percentage yield was 24%. ν_{max} (nujol mull) 3400cm^{-1} and 3300cm^{-1} (NH), 1685cm^{-1} (shld. at 1715cm^{-1} C=O); n.m.r. 60 MHz ($DMSOd_6$), δ1.35 (3H, t, CH_2-CH_3, J= 5.0 Hz), 3.4 (3H, s, Me), 4.2 (2H, q, $\underline{CH_2}$ CH_3, J= 5.0 Hz), 6.12 (2H, br, NHz), 6.45(1H, s, H at pyrrole), 7.1-7.5 (5H, m, aromatic), 9.25 (1H, s, NH). Mass spectrum (relative intensity), m/e:287(M^{+},100%), 228 (61%), 215(30%) 200 (36%), 183(21%), 170(15%), 104(15%), 77(21%).

2-Ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthalazin-6(5H)-one(44a)

3-ethoxycarbonyl-2-methyl-5-phenyl-1-ureidopyrrole (1g; 0.003mol) was heated under N_2 atmosphere on a Woods metal bath at 260-280^{o}C for 30 minutes. The resultant brown mixture was chromatographed on a column (20 x 3 cm) of silica gel (25g). Elution with toluene-ethyl acetate (9:1) afforded 2-ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthalazin-6(5H) -one (44a), (70mg, 7%) as yellow needles m.p. 226-229^{o}C (ethanol), [(lit.[77], m.p. 225-228^{o}C)]; ν_{max} (nujol mull) 1660cm^{-1} and 1700cm^{-1} (2 x CO);n.m.r. 60 MHz ($DMSOd_6$), δ1.3 (3H, t, $CO_2CH_3\underline{CH_3}$, J= 7.0 Hz)

2.6 (3H, s, CH_3 at pyrrole, (4.1 (2H, q, CO_2 $\underline{CH_2}CH_3$, J= 7.0 Hz), 7.1-8.1 (5H, m, aromatic), 13.5(1H, br , NH). Further elution with toluene ethyl acetate (8:2) afforded (45a) as pale yellow needles which could not be isolated pure m.p. 271-276°C, [(lit.[77], m.p. 275-278°C)]. ν_{max} (KBr), 3300cm^{-1} (br, 2xNH), 1720cm^{-1} (br) and 1665cm^{-1} (C=O),1230cm^{-1} (C-O-C); n.m.r. 60 MHz ($DMSOd_6$), δ1.2 (6H, t, 2 x CH_2-$\underline{CH_3}$, J= 7.0 Hz), 2.2 (6H, s, 2 x CH_3) 4.2 (4H, q, 2 x $\underline{CH_2}$ CH_3), 6.5 (2H, s, 2 x CH), 7.1-7.7 (10H, m, 2 x C_6H_5), 10.2 (2H, s, 2 x NH).

Chloroacetone semicarbazone (76)

To a solution of chloracetone (15g; 0.16mol) in ethanol (35ml) a solution of semicarbazide hydrochloride (19.5g; 0.17mol) and potassium acetate (18.0g; 0.18mol) in water (25ml) was added. After standing for 12 hours at room temperature a solid was separated off which was recrystallised from ethanol to afford chloroacetone semicarbazone (16.9g; 70%) as colourless needles m.p 163-165°C [(lit.[89], 164°C)]. ν_{max} (nujol mull) 3470cm^{-1} (NH), 1700cm^{-1} (C=O); n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$), δ1.9 (3H, s, CH_3) 4.2 (2H, s, CH_2), 6.37(2H, br, NH_2), 9.47 (1H, s, NH).

Ethyl 2-benzoyl-4-semicarbazidopentanoate (77)

To a stirred solution of sodium ethoxide which was prepared from sodium (1g) and absolute ethanol (10ml) was added ethyl benzoylacetate (7.8g, 0.04mol) at 0°C under a dry nitrogen atmosphere. As the mixture began to solidify, more absolute ethanol (8ml) was added until a clear solution was obtained. To the mixture was then added with cooling to 10°C, chloroacetone semicarbazone (6g, 0.04mol) and absolute ethanol (20ml), and the mixture was shaken at room temperature for 5 hours and left at room temperature for 48 hours. The product was filtered and recrystallised from ethanol to afford ethyl 2-benzoyl-4-semicarbazido-

pentanoate (6g; 50%). Recrystallisation from ethanol gave colourless needles m.p. 152-155°C [(lit.[89] 155°C)] . ν_{max} (nujol mull) 3460cm^{-1} (NH), 1730cm^{-1} (shld. at 1715cm^{-1}) (C=O), 1680cm^{-1} ($CONH_2$), 1250cm^{-1} (C-O-C); n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), δ1.2 (3H, t, $-CH_2\underline{CH_3}$, J = 5.0 Hz), 1.8 (3H, s, CH_3). 2.9 (2H, d, $-CH-\underline{CH_2}-C(=N)-CH_3$, J= 5.0 Hz), 4.1 (2H, q, $\underline{CH_2}CH_3$, J= 5.0 Hz), 5.1 (1H, t, $\underline{CCH}\ CH_2$, J= 5.0 Hz), 5.8 (2H, br, NH_2), 7.2-8.3 (5H, m, aromatic), 9.0(1H, s, NH).

3-Ethoxycarbonyl-5-methyl-2-phenyl-1-ureidopyrrole(42b)

Ethyl 2-benzoyl-4-semicarbazidopentanoate (2g; 6m.mol) in absolute ethanol (20ml) and a solution of dry ethanol (2ml) which was saturated with gasous hydrogen chloride, were refluxed for 1 hour, and the precipitate was crystallised from ethanol to afford 3-ethoxycarbonyl-5-methyl-2-phenyl-1-ureidopyrrole (1.5g; 80%) as colourless needles m.p. 218-220°C [(lit.[89] m.p. 218°C)] ν_{max} (nujol mull) 3460cm^{-1} and 3300cm^{-1} (NH), 1685cm^{-1} (shld. at 1710cm^{-1}) (C=O), 1600cm^{-1} (C=C); n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50) δ1.2 (3H, t, $-OCH_2\underline{CH_3}$), 2.1(3H, s, CH_3), 4.0 (2H, q, $-CO_2-\underline{CH_2}-CH_3$), 5.85 (2H, br, NH_2), 6.25 (1H, s, H_4-pyrrole), 7.2-7.4 (5H, m, aromatic), 8.95 (1H, s, NH).

1-Ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthalazin-6(5H)-one (44b)

3-Ethoxycarbonyl-5-methyl-2-phenyl-1-ureidopyrrole (1g, 3m·mol) was heated on a Woods metal bath to 200°C at 0.5mm in a microdistillation apparatus. A yellow liquid was distilled which solidified on standing. The product was purified by fractional recrystallisation from ethanol to afford 1-ethoxycarbonyl-3-methylpyrrolo[2,1-a]phthazin-6(5H)-one (100mg; 11%) as yellow needles, m.p. 216-218°C [(lit.[77] m.p. 216-218°C)] ν_{max} (nujol mull) 1660 and 1700cm^{-1} (2 x CO); n.m.r. 60 MHz ($DMSOd_6$), δ1.3 (3H, t, $CH_2\underline{CH_3}$, J= 7.0 Hz), 2.4 (3H, s, CH_3), 4.2 (2H, q, $\underline{CH_2}CH_3$, J=7.0 Hz), 6.8 (1H, s,pyrrole CH),

7.5-8.3 (3H, m, H_7, H_8 and H_9) 10.6 (1H, m, H_{10}), 13.0 (1H, br, NH).

A second product N,N'- bis (1-pyrrolyl) urea derivative (45b) was also obtained by fractional recrystallisation from ethanol, which could not be isolated pure, m.p. 324-328°C, [(lit.[77], m.p. 328-330°C)]. ν_{max} (nujol mull) 3300cm^{-1} (br 2 x NH), 1720cm^{-1} (br) and 1665 cm^{-1} (C=O).

PART II

A Syntheses of Pyrrolo[2,1-a]phthalazines. Substituted at Position-6

i) Substitution by chlorine

Attempted formation of 1-chloro-3-phenylpyrrolo[2,1-a]phthalazine (78) and its conversion to 1-hydrazinyl-3-phenylpyrrolo[2,1-a]phthalazine (79)

a) Using one equivalent of phosphorus oxychloride

3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (1g, 3m.mol) and phosphorus oxychloride (0.58g, 3m·mol) were refluxed for 30 minutes. The brown product was cooled and poured into ice (100g) and stirred. The mixture was basified to pH 8 with NH_4OH solution. The yellow crystals obtained were filtered, washed with water (30ml) and dried. The product obtained was the starting material (49) as yellow needles (0.93g, 93%, recovery) identified by its i.r. spectrum ν_{max} (nujol mull) 1660cm^{-1} (C=O) and m.p. 184-186°C [lit.[77] m.p. 185-186°C].

b) Using an excess of phosphorus oxychloride

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (2g, 6m.mol) and phosphorus oxychloride (12g, 0.08mol) were refluxed for 5 hours. The brown product was cooled and poured into ice (100g) and stirred. The mixture was basified to pH8 with NH_4OH solution. The yellow crystals obtained were filtered, washed with water (30ml) and dried. Recrystallisation from CCl_4 gave a product (1.1g, 51%, based on compound (78)), as yellow needles m.p. 112-115°C, i.r. ν_{max} (nujol mull) 1635cm^{-1} (C=N), which

was very unstable at room temperature (i.e.the compound on standing at room temperature after 2 hours turned dark yellow, dark brown, and then to black, indicating decomposition). A sodium fusion test, on impure product proved the presence of chlorine. Immediate reaction of this chloro-derivative (1g, 0.3mmol) with hydrazine hydrate (10.4g, 0.2mol) in ethanol (30 ml) on a hot water bath and a reflux period of 2 hours, gave a green solid (0.39g, 40%, based on compound (79)), (m.p. 109-112^{o}C, decompostion), which after standing for 30 minutes at room temperature turned dark brown and then black, indicating decompostion. Treatment of the crude product (79), (0.3g, 1m.mol) with a saturated solution of gaseous HCl in absolute ethanol (10ml) at 0^{o}C gave a black gum which could not be crystallised. In view of these difficulties this approach was not further investigated

c) Using phosphorus pentachloride

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.55g, 2m.mol) and phosphorus pentachoride (0.6g, 3m.mol) were refluxed in carbon tetrachloride (20ml) for 14 days. The mixture was concentrated under reduced pressure and then poured into ice (50g) and stirred. The mixture was basifed to pH8 with NH_4OH solution. The yellow crystals obtained were filtered, washed with water (30ml) and dried. Recrystallisation from CCl_4 gave a product (0.2g, 38%, based on compound 78) as yellow needles, m.p.148-150^{o}C, ir ν_{max} (nujol mull) 1630cm^{-1} (C=N), n.m.r. 60 MHz ($CDCl_3$) δ7.0-8.2 (m, aromatic). A sodium fusion test, on impure product proved the presence of chlorine. The mass spectrum of this compound showed m/e 294 as a base peak, and highest m/e 350 and could not be identified.

1,2,6-Trichloro-3-phenylpyrrolo[2,1-a]phthalazine (80)

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (2g, 7m.mol) and phosphorous pentachloride (6g, 0.03 mol) and phosphorus oxychloride (19g, 0.13mol)

were heated at 70°C for 90 minutes. The brown product was cooled and poured into ice (100g) and stirred. The mixture was basifed to pH8 with NH_4OH solution. The yellow crystals obtained were filtered, washed with water (30ml) and dried in a vacuum desiccator over calcium chloride. The product was recrystallised, from carbon tetrachloride to afford 1,2,6-trichloro-3-phenylpyrrolo[2,1-a]phthalazine (80) (1.7g; 63%) as yellow needles, m.p. 206-208°C, from carbon tetrachloride.

ν_{max} (KBr) 1615cm^{-1} (C=N);

n.m.r. 90 MHz ($CDCl_3/DMSOd_6$, 50:50) δ7.2-8.9 (m, aromatic);

u.v. λ_{max} nm log ε 200 (2.96), 253(2.55), 285(2.92), 316(2.44).

Mass spectrum (relative intensity), m/e 352(4%), 350(33%), 348(100%) 346(base peak, 100%), 312(8%), 310(10%), 276(58%), 208(6%), 155(23%) 138(28%).

$C_{17}H_9N_2{}^{35}Cl_3$ requires M^+, 346.

Found: C,58.1; H,2.5; N,8.0 % $C_{17}H_9N_2Cl_3$

requires C,58.7; H,2.6; N,8.1%.

ii) Substitution by nitrogen functions at position-6

Synthesis of 6-amino-1,2-dichloro-3-phenylpyrrolo[2,1-a]phthalazines

General Procedure

1,2,6-Trichloro-3-phenylpyrrolo[2,1-a]phthalazine (3m.mol) and an excess of amine (0.1mol) were refluxed for 19 hours. If the trichloropyrrolo[2,1-a]phthalazine was not soluble in the amine, the mixture was refluxed in dry toluene (25ml). The mixture was then concentrated under reduced pressure till dryness and the yellow oil or solid obtained was crystallised, to give the product.

1,2-Dichloro-3-phenyl-6-piperidinopyrrolo[2,1-a]phthalazine (81)

Use of the above procedure with 1,2,6-trichloro-3-phenylpyrrolo[2,1-a]phthalazine (1g,3m.mol) and piperidine (8g, 0.09mol) gave 1,2-dichloro-3-phenyl-6-piperidinopyrrolo[2,1-a]phthalazine (81), (0.52g, 45%) as pale yellow needles, m.p. 151-153°C from cyclohexane.

ν_{max} (KBr) 1620cm^{-1} (C=N);

n.m.r. 90 MHz ($CDCl_3$), δ1.7 (6H, m, protons at 3,4 and 5-positions of piperidine), 3.2 (4H,m, protons at 2 and 6 positions of piperidine); 7.1-8.8 (9H,m, aromatic). Mass spectrum (relative intensity) m/e 399(11%), 397(66%), 395(100%), 311(22%), 276(27%), 91(23%), $C_{22}H_{19}N_3{}^{35}Cl_2$ requires, M^+ 395.

Found:	C, 66.4	; H,4.8	; N,10.9 %	$C_{22}H_{19}N_3Cl_2$
requires	C,66.7	; H,4.8	; N,10.6 %.	

1,2-Dichloro-3-phenyl-6-pyrrolidinopyrrolo[2,1-a]phthalazine (82)

Use of 1,2,6-trichloro-3-phenylpyrrolo[2,1-a]phthalazine (1g, 3m.mol) and pyrrolidine (8g, 0.1mol) in the general procedure gave 1,2-dichloro-3-phenyl-6-pyrrolidinopyrrolo[2,1-a]phthalazine (82), (0.84g, 76%) as pale yellow needles m.p. 169-171°C from cylohexane.

ν_{max} (nujol mull) 1615cm^{-1} (C=N);

n.m.r. 60 MHz ($CDCl_3$), δ 1.86 (4H, m, protons at 3 & 4 positions of pyrrolidine), 3.50 (4H, m, protons at 2 & 5 positions of pyrrolidine), 7.0-9.1 (9H, m, aromatic).

Found: C,65.6 ; H, 4.5 ; N, 10.8 % $C_{21}H_{17}N_3Cl_2$

Requires C,66.0 ; H, 4.5 ; N, 11.0 %

1,2-Dichloro-6-morpholino-3-phenylpyrrolo[2,1-a]phthalazine (83)

Use of 1,2,6-trichloro-3-phenylpyrrolo[2,1-a]phthalazine (0.7g, 2m.mol) in the general procedure gave 1,2-dichloro-6-morpholino-3-phenylpyrrolo[2,1-a]phthalazine (83), (0.3g, 38%) as yellow needles m.p. 145-148°C, from dry toluene.

ν_{max} (nujol mull) 1615cm^{-1} (C=N);

n.m.r. 60 MHz ($CDCl_3$), δ 2.95 (4H, m, protons at 2 & 6 positions of morpholine), 3.55 (4H, m, protons at 3 & 5 postions of morpholine), 6.95-8.8 (9H, m, aromatic).

Mass spectrum (relative intensity) m/e 401 (12%), 399 (66%), 397 (100%) 312 (37%), 276 (83%), 208 (8%), 174 (12%), 138 (41%). $C_{21}H_{17}N_3{}^{35}Cl_2$ requires $M^{\ddagger}$ 397.

Found: C, 63.0 ; H, 4.3 ; N, 10.55 %, $C_{21}H_{17}N_3Cl_2O$

Requires C, 63.3 ; H, 4.3 ; N, 10.5 %.

1,2-Dichloro-6-(3-methylpiperidino)-3-phenylpyrrolo[2,1-a]phthalazine (85)

1,2,6-Trichloro-3-phenylpyrrolo[2,1-a]phthalazine (1g, 3.mol), 3-methylpiperidine (8g, 0.09mol) and dry toluene (20ml) were refluxed for 6 days.

The mixture was concentrated under reduced pressure till dryness. A yellow oil was obtained, which was crystallised from toluene to afford 1,2-dichloro-6-(3-methylpiperidino)-3-phenylpyrrolo[2,1-a]phthalazine (85) (0.47g, 40%), pale yellow needles m.p. 129-131°C from toluene.

ν_{max} (nujol mull) 1615cm^{-1} (C=N).

Found: C, 67.5 ; H, 5.25 ; N, 10.1 %, $C_{23}H_{21}N_3Cl_2$

requires C, 67.3 ; H, 5.2 : N, 10.2 %.

3-Phenyl-6-pyrrolidinopyrrolo[2,1-a]phthalazine (87)

To a solution of 1,2-dichloro-6-pyrrolidinopyrrolo[2,1-a]phthalazine (0.1g; 10%) in ethanol (10ml) was added palladium charcoal (0.1g, 10%) and hydrazine hydrate (8g, 0.16mol). The mixture was refluxed for 90 minutes. The catalyst was filtered off and the filtrate was evaporated at reduced pressure. The colourless crystals obtained, were washed with H_2O (20ml) filtered, dried and recrystallised from cyclohexane to afford 3-phenyl-6-pyrrolidinopyrrolo[2,1-a]phthalazine (87), (30mg; 40%) as light yellow needles m.p. 110-112°C from cyclohexane.

ν_{max} (nujol mull) 1615cm^{-1} (C=N).

Found : C, 80.3 ; H, 6.0 ; N, 13.2 %, $C_{21}H_{19}N_3$

requires C, 80.5 ; H, 6.1 ; N, 13.4 %.

1,2-Dichloro-6-(α-methylhydrazino)-3-phenylpyrrolo[2,1-a]phthalazine (88)

3-Phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (0.8g; 0.002mol) in dry toluene (10ml) and methylhydrazine (10ml) were refluxed for

6 days. The mixture was concentrated under reduced pressure till dryness. A yellow oil was obtained, which was crystallised from toluene to afford 1,2-dichloro-6-(α-methylhydrazino)-3-phenylpyrrolo[2,1-a]phthalazine (88) (0.3g; 36%) pale yellow needles m.p. 169-171°C from toluene.

ν_{max} (KBr) 3320cm^{-1} (br, NH_2), 1600cm^{-1} (C=C),

n.m.r. 60 MHz ($CDCl_3$), δ3.0 (3H, s, -N-Me), 5.2 (2H, br, NH_2), 7.0-8.8 (9H, m, aromatic).

Found: C, 60.5 ; H, 3.9 ; N, 15.4 %, $C_{18}H_{14}N_4Cl_2$

requires C, 60.5 ; H, 3.95; N, 15.7 %.

1,2-Dichloro-6-hydrazinyl-3-phenylpyrrolo[2,1-a]phthalazine (89)

3-Phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (0.4g; 0.001mol) in dry n-butanol (10ml) and hydrazine hydrate (15ml, 0.3mol) were refluxed for 4 days. The mixture was concentrated under reduced pressure, to give an oil. Trituration of the oil with ethanol afforded 1,2-dichloro-6-hydrazinyl-3-phenylpyrrolo[2,1-a]phthalazine (89) (0.21g; 55%) pale yellow needles m.p. 246-248°C from ethanol.

ν_{max} ($CHCl_3$) 3420cm^{-1}(NH&NH_2), 1630cm^{-1} (C=N);

n.m.r. 60 MHz ($CDCl_3$) δ4.2 (1H, t, NH), 6.3 (2H, d, NH_2, D_2O exchangable), 6.8-8.9 (9H, m, aromatic).

Mass spectrum (relative intensity) m/e 346(9.1%), 342(100% base peak), 311(24%), 276(18.5%). Accurate mass m/e 342.0431, ($C_{17}H_{12}N_4{}^{35}Cl_2$ requires 342.0438).

Found: C, 60.05 ; H, 3.6 ; N, 15.6 %, $C_{17}H_{12}N_4Cl_2$

requires C, 59.5 ; H, 3.5 ; N, 16.3 %.

iii) Substitution by oxygen functions at position-6

Synthesis of 6-alkoxy-and 6-aryloxy-1,2-dichloro-3-phenylpyrrolo[2,1-a]phthalazines

General Procedure

To sodium alkoxide which was freshly prepared from sodium (0.02mol) and appropriate dry alcohol (20ml), a solution of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (4m.mol) in the same solvent (10ml) was added at room temperature. The mixture was refluxed for 72 hours. Further dry alcohol was added to destroy any excess of sodium and the solvent was evaporated under reduced pressure. The residue was suspended in water and extracted with chloroform (3 x 40ml). The chloroform extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The yellow solid obtained was recrystallised to give the product.

The 6-phenoxy and 6-(2-naphthoxy)-derivatives of 3-phenylpyrrolo[2,-1-a]phthalazine were synthesised by heating a mixture of 3-phenylpyrrolo[2,-1-a]phthalazine (0.003mol) with the corresponding phenol or naphthol (0.04mol) and anhydrous potassium carbonate (0.014mol) at 190°C for 19 hours. The obtained brown solid was then treated with NaOH (20ml, 40%) and cold water (50ml) and extracted with chloroform (3 x 40ml). The chloroform extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give the product.

1,2-Dichloro-6-methoxy-3-phenylpyrrolo[2,1-a]phthalazine (91)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g, 3m.mol)

with sodium methoxide (1.1g; 0.02mol) and dry methanol (15ml) in the general procedure (p. 162) gave 1,2-dichloro-6-methoxy-3-phenylpyrrolo[2,1-a]phthalazine (91) (0.8g; 81%) light yellow needles m.p. 116-118°C from CCl_4.

ν_{max} (KBr) 1630cm^{-1} (C=N), 1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C);

n.m.r. 60 MHz ($CDCl_3$), δ3.85 (3H, s, OMe), 7.1-8.6 (9H, m, aromatic),

Found: C, 62.8 ; H, 3.4 ; N, 7.9 %, $C_{18}H_{12}N_2Cl_2O$

requires C, 63.0 ; H, 3.5 ; N, 8.2 %.

1,2-Dichloro-6-ethoxy-3-phenlypyrrolo[2,1-a]phthalazine (92)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g, 3m.mol) with sodium ethoxide (1.4g, 0.02mol) and dry ethanol (15ml) in the general procedure (p. 162) gave 1,2-dichloro-6-ethoxy-3-phenylpyrrolo[2,1-a]phthalazine (92) (0.3g, 37%) pale yellow needles, m.p. 125-127°C, from CCl_4.

ν_{max} (KBr) 1630cm^{-1} (C=N), 1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C);

n.m.r. 60 MHz ($CDCl_3$), δ1.4 (3H,t, CH_3), 4.3 (2H,q, OCH_2), 7.1-8.8 (9H, m, aromatic).

Found: C, 63.55 ; H, 3.8 ; N, 7.5 %, $C_{19}H_{14}N_2Cl_2O$

requires C, 63.9 ; H, 3.95; N, 7.8%.

1,2-Dichloro-3-phenyl-6-propoxpyrrolo[2,1-a]phthalazine (93)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g, 3m.mol) with sodium propoxide (1.7g, 0.02mol) and dry 1-propanol (15ml) in the general procedure (p. 162) gave 1,2-dichloro-3-phenyl-6-propoxypyrrolo-[2,1-a]phthalazine (93) (0.51g, 49%) pale yellow, needles, m.p. 128-130°C from cyclohexane.

ν_{max} (nujol mull) 1630cm^{-1} (C=N), 1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C);

n.m.r. 60 MHz ($CDCl_3$) δ1.21 (3H, t, Me) 1.93 (2H, m, $-CH_2$-Me) 4.22 (2H, t, -O-CH_2-), 7.0-8.8 (9H, m, aromatic).

Found: C, 64.9 ; H, 4.2 ; N, 7.4 %, $C_{20}H_{16}N_2Cl_2O$

requires C, 64.7 ; H, 4.3 ; N, 7.55%.

1,2-Dichloro-6-isopropoxy-3-phenylpyrrolo[2,1-a]phthalazine (94)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g, 3m.mol) with sodium isopropoxide (1.7g, 0.02mol) and dry isopropanol (15ml) in the general procedure (p. 162) gave 1,2-Dichloro-6-isopropoxy-3-phenylpyrrolo[2,1-a]phthalazine (94) (0.6g, 56%) pale yellow needles, m.p. 124-126°C from isopropanol.

ν_{max} (KBr) 1630cm^{-1} (C=N), 1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C),

n.m.r. 60 MHz ($CDCl_3$), δ1.3 (6H, m, 2 x Me), 3.95 (1H, m, O-CH); 6.7-8.8 (9H, m, aromatic).

Found: C, 64.9 ; H, 4.0 ; N, 7.5 %, $C_{20}H_{16}N_2Cl_2O$

requires C, 64.7 ; H, 4.3 ; N, 7.5 %.

1,2-Dichloro-6-furfuryloxy-3-phenylpyrrolo[2,1-a]phthalazine (95)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g, 3m.mol) with sodium furfuryloxide (2.6g; 0.02mol) and dry furfuryl alcohol (15ml) in the general procedure (p. 162) gave 1,2-dichloro-6-furfuryloxy-3-phenylpyrrolo[2,1-a]phthalazine (95) (0.7g; 60%) pale yellow needles m.p. 126-128°C from cyclohexane.

ν_{max} (KBr) 1630cm^{-1} (C=N), 1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C);

n.m.r. 60 MHz ($CDCl_3$), δ4.2 (2H,s, -O-CH_2-), 6.9-8.8 (12H, m, aromatic)

Found: C, 64.3 ; H, 3.8 ; N, 6.7 %, $C_{22}H_{14}N_2Cl_2O$

requires C, 64.6 ; H, 3.4 ; N, 6.8 %.

1,2-Dichloro-3-phenyl-6-(prop-2-enyloxy)-pyrrolo[2,1-a]phthalazine (96)

Use of 3-phenyl-1,2,6-trichloro[2,1-a]phthalazine (1g; 3m.mol) with sodium allyloxide (1.7g, 0.02mol) and dry allyl alcohol (15ml) in the general procedure (p. 162) gave 1,2-dichloro-3-phenyl-6-(prop-2-enyloxy)-pyrrolo[2,1-a]phthalazine (96) (0.6g; 57%) pale yellow needles, m.p. 129-131°C from ethanol.

ν_{max}(KBr) 1630cm^{-1} (C=N),1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C);

n.m.r. 60 MHz ($CDCl_3$), δ4.75 (2H, d, -O-$\underline{CH_2}$-CH=CH_2), 5.41 (2H, m, O-CH_2-CH=$\underline{CH_2}$) 5.8-6.4 (1H, m, -O-CH_2-$\underline{CH}$=CH_2) 7.1-8.9 (9H, m, aromatic).

Found: C, 65.0 ; H, 3.9 ; N, 7.4 %, $C_{20}H_{14}N_2Cl_2O$

requires C, 65.05; H, 3.8 ; N, 7.6 %.

1,2-Dichloro-6-phenoxy-3-phenylpyrrolo[2,1-a]phthalazine(97)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g; 3 m.mol) with phenol (4g; 0.04 mol) and potassium carbonate (2g; 0.014 mol) in the general procedure (p. 162) gave 1,2-dichloro-6-phenoxy-3-phenylpyrrolo[2,1-a]phthalazine (97) (0.8g; 69%) pale yellow, needles, m.p. 148-150°C from cyclohexane.
ν_{max} (KBr) 1628cm^{-1} (C=N), 1600cm^{-1} (C=C), 1090cm^{-1} (C-O-C);
n.m.r. 60 MHz ($CDCl_3$), δ 6.8-8.9 (m, aromatic).
Found: C, 68.2 ; H, 3.4 ; N, 6.8 % , $C_{23}H_{14}N_2Cl_2O$
requires C, 68.2 ; H, 3.5 ; N, 6.9 %.

1,2-Dicholoro-6-(4-methoxyphenoxy)-3-phenylpyrrolo[2,1-a]phthalazine (98)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (0.6g; 2 m.mol) with p-methoxyphenol (3g; 0.02 mol) and potassium carbonate (2g; 0.014 mol) in the general procedure (p.162) gave 1,2-dichloro-6-(4-methoxyphenoxy)-3-phenylpyrrolo[2,1-a]phthalazine (98) (0.3g; 40%) pale brown, plates, m.p. 162-164°C from cyclohexane.
ν_{max} (KBr) 1630cm^{-1} (C=N), 1600cm^{-1} (C=C), 1100cm^{-1} (C-O-C);
n.m.r. 60 MHz ($CDCl_3$), δ 3.78 (3H, s, OMe), 6.5-8.9 (13H, m, aromatic)
Found: C, 66.6 ; H, 3.9 ; N, 6.3 %, $C_{24}H_{16}N_2Cl_2O_2$
requires C, 66.2 ; H, 3.7 ; N, 6.4 % .

1,2-Dichloro-6-(2-naphthoxy)-3-phenylpyrrolo[2,1-a]phthalazine (99)

Use of 3-phenyl-1,2,6-trichloropyrrolo[2,1-a]phthalazine (1g, 3m.mol) with 2-naphthol (5.7g; 0.04mol) and potassium carbonate (2g; 0.014mol) in the general procedure (p. 162) gave 1,2-dichloro-6-(2-napnthoxy)-3-phenylpyrrolo[2,1-a]phthalazine (99) (0.9g, 70%) pale yellow needles, m.p. 161-163°C from cyclohexane.

ν_{max} (nujol mull) 1620cm^{-1} (C=N) 1600cm^{-1} (C=C) 1160cm^{-1} (C-O-C)

n.m.r. 60 MHz ($CDCl_3$) δ6.7-8.9 (m, aromatic)

Found: C, 71.4 ; H, 3.9 ; N, 5.7%, $C_{27}H_{16}N_2Cl_2O$

requires C, 71.2 ; H, 3.5 ; N, 6.15%.

B. Syntheses of Pyrrolo[2,1-a]phthalazine-Derivatives, Functionalised at Positions -5 and/or -6.

i) Formation of Mannich-Base Derivatives

General Procedure

To a stirred suspension of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.66g, 3m.mol) in ethanol and the appropriate amine (4mmol) was added formaldehyde (0.2ml of a 40% W/V aqueous solution, 0.0025m) at $0^{o}C$. Stirring was continued for 24 hours at $0^{o}C$. The solvent was removed under reduced pressure and the residue columned on Hyflo supercel (8g) and eluted with chloroform, until a dark band reached the bottom of the column. Evaporation of the eluate and trituration with diethyl ether gave the product, which was further purified by recrystallisation from ethanol or methanol.

5-(Morpholino-N-methyl)-3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (102)

Use of the above procedure with 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.66g, 3m.mol), morpholine (0.4g, 4m.mol) and formaldehyde solution (0.2ml) in the general procedure gave 5-(Morpholino-N-methyl)-3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (102) (0.49g, 55%) as pale yellow needles, m.p. 207-209^{o}C from methanol.
ν_{max} (KBr) 1628cm^{-1} (C=O) n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), δ2.72 (4H, m, protons at 2 & 6 positions of morpholine), 3.61 (4H, m, protons at positions 3 & 5 of morpholine), 3.9 (2H, s, N-CH_2-N), 6.6-8.3 (11H, m, aromatic); uv. λ_{max} nm log ϵ 252(3.25), 290(3.67), 335(3.47).

Found: C, 73.4 ; H, 5.9 ; N, 11.5 %, $C_{22}H_{21}N_3O_2$
requires C, 73.5 ; H, 5.9 ; N, 11.7 %.

3-Phenyl-5-(piperidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6-(5H)-one (103)

Use of 3-phenylpyrrolo[2,1-a]phthalzin-6-(5H)-one (0.66g, 3m.mol) piperidine (0.4g, 4m.mol) and formaldehyde solution (0.2ml) in the general procedure gave 3-phenyl-5-(piperidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6-(5H)-one (103) (0.5g, 60%) as pale yellow needles, m.p. 203-205°C from methanol.
ν_{max} (KBr) 1628cm^{-1} (C=O) n.m.r 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), δ1.5 (6H, m, protons at 3,4 & 5 positions of piperidine), 2.57(4H, m, protons at 2 & 6 positions of piperidine), 3.9 (2H, s, N-CH_2-N), 6.3-8.2 (11H, m, aromatic); u.v. λ_{max} nm log ∈ 248(3.15), 286(3.52), 330(3.37).
Found: C, 77.1 ; H, 6.5 ; N, 11.4 %, $C_{23}H_{23}N_3O$
requires C, 77.3 ; H, 6.5 ; N, 11.6 %.

3-Phenyl-5-(pyrrolidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6-(5H)-one (104)

Use of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.66g, 3m.mol) pyrrolidine (0.4g, 4m.mol) and formaldehyde solution (0.2ml) in the general procedure gave 3-phenyl-5-(pyrrolidino-N-methyl)-pyrrolo[2,1-a]phthalzin-6(5H)-one (104) (0.38g, 45%) as greenish yellow, needles, m.p. 188-190°C from ethanol.
ν_{max} ($CHCl_3$/$DMSOd_6$, 50:50), δ1.74 (4H, m, protons at 3 & 4 positions of pyrrolidine), 2.62 (4H, m, protons at 2 & 5 postions of pyrrolidine), 3.85 (2H, s, N-CH_2-N), 6.6-8.4 (11H, m, aromatic); u.v. λ_{max}nm log ∈ 240(3.18), 272(3.38), 332(2.92).

Found: C, 76.3 ; H, 6.0 ; N, 11.4 % $C_{22}H_{21}N_3O$
requires C, 76.9 ; H, 6.2 ; N, 12.2 %.

3-Phenyl-5-(4-methylpiperidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6(5H)-one (106)

Use of 3-phenylpyrrolo[2,1-a]phthalzin-6-(5H)-one (0.66g, 3m.mol), 4-methylpiperidine (0.42g, 4m.mol) and formaldehyde solution (0.2ml) in the general procedure p. 168, gave 3-phenyl-5-(4-methylpiperidino-N-methyl)-pyrrolo[2,1-a]phthalazin-6(5H)-one (106) (0.47g, 51%) as pale yellow needles, m.p. 190-192°C from ethanol.
ν_{max} (KBr) 1628cm^{-1} (C=O), n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), δ0.78 (3H, m, Me), 1.3 (5H, m, protons at 3, 4 & 5 positions of piperidine), 2.6 (4H, m, protons at 2 & 6 positions of piperidine), 3.85 (2H, s, N-CH_2-N); u.v. λ_{max} nm log ∈ 248(3.28), 284(3.55), 3 28(3.29).
Found: C, 77.3 ; H, 6.5 ; N, 10.9 %, $C_{24}H_{25}N_3O$
requires C, 77.6 ; H, 6.8 ; N, 11.3 %.

3-Phenyl-5-(4-methylpiperazino-N-methyl)-pyrrolo[2,1-a]phthalazin-6(5H)-one (107)

Use of 3-phenylpyrrolo[2,1-a]phthlazin-6(5H)-one (0.66g, 3m.mol), 4-methylpiperazine (0.43g, 4m.mol) and formaldehyde solution (0.2ml) in the general procedure gave 3-phenyl-5-(4-methylpiperazino-N-methyl)-pyrrolo[2,1-a]phthalazin-6(5H)-one (107), (0.5g, 55%) as pale yellow needles, m.p. 231-233°C from methanol.
ν_{max} (KBr) 1628cm^{-1} (C=O);
n.m.r. 60 MHz ($CDCl_3$/$DMSOd_6$, 50:50), δ2.1(3H, s, Me), 2.6 (8H, m, protons at piperazine), 3.85(2H, s, N-CH_2-N), 6.3-8.2 (11H, m, aromatic).

UV λ_{max} nm log ϵ 252 (3.26), 285 (3.50), 330(3.38).

Found: C, 73.8 ; H, 6.5 ; N, 14.9 %, $C_{23}H_{24}N_4O$

requiresC, 74.2 ; H, 6.5 ; N, 15.0%.

2-(Morpholino-N-methyl)-phthalazin-1(2H)-one (109,R=H)

To a stirred suspension of phthalazin-1(2H)-one (1.46g, 0.01mol) in methanol (40ml) was added formaldehyde solution (2.5ml of a 40% W/V aqueous solution, 0.031m) and morpholine (1.74g, 0.02mol). Stirring was continued for 1 hour at room temperature and then the solution was refluxed for 1 hour. The solvent was removed under reduced pressure. Trituration of the residue with diethyl ether gave the 2-(morpholinyl-N-methyl)-phthalazin-1(2H)-one (1.4g, 57%) as colourless needles m.p. 136-138°C (lit.[128], 136°C).

ν_{max} (nujol mull) 1628cm^{-1} (w), 1640cm^{-1} (C=O) ;

n.m.r. 60 MHz ($CDCl_3$) δ2.75 (4H, m, protons at 2 & 6 positions of morpholine), 3.68 (4H, m, protons at 3 & 5 positions of morpholine), 5.0 (2H, s, N-CH_2-N), 7.1-8.6 (5H, m, aromatic);

u.v. λ_{max} nm log ϵ 251 (3.08), 285(3.08), 315 (2.78).

ii) Acylation Reactions

6-Acetoxy-3-phenylpyrrolo[2,1-a]phthalazine (119)

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.5g; 2 m·mol), and acetic anhydride (10g; 0.09 mol) were heated at 80°C under stirring for 10 hours. The mixture was stirred for a further 1 hour at room temperature and then poured on to crushed ice (200g). The precipitate formed on warming to room temperature was filtered off, washed with H_2O (2 x 20ml) and dried in a vacuum desiccator over calcium chloride, to give 6-acetoxy-3-phenylpyrrolo[2,1-a]phthalazine (119) (0.4g; 69%) as yellow needles, m.p. 122-124°C from methanol.

ν_{max} (nujol mull) 1760cm^{-1} (-O-$\overset{O}{\overset{\|}{C}}$-$CH_3$, C=O); 1620cm^{-1} (C=N), 1188cm^{-1} (-C-O-$\overset{O}{\overset{\|}{C}}$-, C-O of acetyl group).

uv λ_{max} nm log ϵ 209 (3.14), 250 (2.56), 290(3.08), 333(2.8),

n.m.r. 60MHz ($CDCl_3$) δ 2.55(3H, s, -O-$\underset{O}{\overset{\|}{C}}$-Me), 6.9-7.1 (2H, m, protons at pyrrole), 7.2-8.1 (9H, m, aromatic).

Found : C, 75.2 ; H, 4.7 ; N, 9.3 %, $C_{19}H_{14}N_2O_2$

requires C, 75.5 ; H, 4.7 ; N, 9.3 % .

Condensation of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one, with methyl, ethyl, and phenyl chloroformate

General Procedure

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.002 mol) and methyl, ethyl, or phenyl chloroformate (0.1 mol) were heated at 75°C under stirring for 2 days. The dark green solution obtained was cooled to 15°C and then poured on to crushed ice (200g). The precipitate formed on warming to room temperature was filtered off, washed with H_2O (2 x 20ml) and dried in a vacuum desiccator over calcium chloride to give the product.

Methyl 3-phenylpyrrolo[2,1-a]phthalazin-6-yl carbonate (120)

Use of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.5g; 2 m·mol) and methyl chloroformate (10ml; 0.13 mol) in the general procedure p.173, gave methyl 3-phenylpyrrolo[2,1-a]phthalazin-6-yl carbonate (120) (0.4g; 67%) as greenish yellow, needles, m.p.136-137°C from methanol.

ν_{max} (nujol mull) 1770 cm^{-1} (O-$\overset{O}{\overset{\|}{C}}$-$OCH_3$, C=O), 1622$cm^{-1}$ (C=N), 1225cm^{-1} (-C-O-$\overset{O}{\overset{\|}{C}}$, C-O); u.v. λ_{max} nm log ∈ 213(3.50), 250(3.10), 291(3.65) 334(3.44); n.m.r. 60MHz ($CDCl_3$), δ 3.90(3H, s, $\underset{O}{\overset{\|}{C}}$-OMe), 6.88 (2H, br., protons at pyrrole), 7.1-8.1(9H, m, aromatic).

Found : C, 71.7 ; H, 4.3 ; N, 8.9 % , $C_{19}H_{14}N_2O_3$

requires C, 71.7 ; H, 4.4 ; N, 8.8 % .

Ethyl 3-phenylpyrrolo[2,1-a]phthalazin-6-yl carbonate (121)

Use of 3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.5g; 2 m·mol) and ethyl chloroformate (10 ml; 0.10 mol) in the general procedure p.173, gave ethyl 3-phenylpyrrolo[2,1-a]phthalazin-6-yl carbonate (121) (0.38g, 60%) as yellow needles m.p. 138-140°C from ethanol.

ν_{max} (KBr) 1775 cm^{-1} (O-$\overset{O}{\overset{\|}{C}}$-OEt, C=O), 1626 cm^{-1} (C=N), 1600 cm^{-1} (C=C), 1220 cm^{-1} (C-O-$\overset{O}{\overset{\|}{C}}$, C-O);

uv. λ_{max} nm log ϵ 214(4.22), 250(3.03), 290(3.52), 335(3.29);

n.m.r. 60 MHz($CDCl_3$). δ 1.5 (3H, t, CH_3), 4.5 (2H, q, O-$\overset{O}{\overset{\|}{C}}$-O-$\underline{CH_2}CH_3$), 6.88 (2H, br, protons at pyrrole), 7.1-8.2 (9H, m, aromatic).

Found ; C, 72.3 ; H, 4.9 ; N, 8.2 %, $C_{20}H_{16}N_2O_3$

requires C, 72.3 ; H, 4.9 ; N, 8.4 % .

Phenyl 3-phenylpyrrolo[2,1-a]phthalazin-6-yl carbonate (122)

Use of 3-phenylpyrrolo[2,1-a]phthalazin-6-(5H)-one (0.5g,2 m·mol) and phenyl chloroformate (20 ml; 0.1 mol) in the general procedure p.173 gave phenyl 3-phenylpyrrolo[2,1-a]phthalazin-6-yl carbonate (122) (0.41 g; 56 %) as greenish yellow, needles, m.p. 141-143°C from ethanol.

ν_{max} (nujol mull) 1780 cm^{-1} (O-$\overset{O}{\overset{\|}{C}}$-O-$C_6H_5$, C=O) ; 1626 cm^{-1} (C=N), 1220 cm^{-1} & 1200 cm^{-1} (-C-O-$\overset{O}{\overset{\|}{C}}$, C-O) ; uv λ max nm log ϵ 211(4.12), 250(3.50), 293(3.94), 328(3.84); n.m.r. 60 MHz ($CDCl_3$), δ 6.90 (2H, br., protons at pyrrole), 7.1-8.2(14H, m, aromatic).

Found : C, 75.7 ; H, 4.1 ; 7.5 % , $C_{24}H_{16}N_2O_3$

requires C, 75.8 ; H, 4.2 ; 7.4 % .

5-(Chloromethylcarbonyl)-3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (123)

3-Phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (0.5g; 2 m·mol) and chloroacetyl chloride (10g; 0.09 mol) were heated at 75°C under stirring for 2 days. The dark green solution was cooled to 15°C and then poured on to crushed ice (300g). The precipitate formed on warming to room temperature was filtered off, washed with H_2O(2x30 ml) and dried in a vacuum desiccator over calcium chloride to give 5-(chloromethylcarbonyl)-3-phenylpyrrolo[2,1-a]phthalazin-6(5H)-one (123) (0.46g; 65 %) as greenish yellow, needles, m.p. 246-249°C from methanol.

ν_{max} (KBr) 1636 cm^{-1} (phthalazinone, C=O), 1624 cm^{-1} (-N-C(=O)-CH_2Cl , C=O), 1600 cm^{-1} (C=C), 1210 cm^{-1} (-C-O-C(=O), C-O), 1115 cm^{-1} (C-O-C);

n.m.r. 60 MHz ($CDCl_3$/DMSO d6, 50:50), δ 4.90 (2H, m, -N-C(=O)-$\underline{CH_2}$-Cl), 6.6-8.4 (11 H, m, aromatic);

u.v. λ max nm log ϵ 216(3.52), 280(3.57), 352(3.03).

Found : C, 67.7 ; H, 4.0 ; N, 7.9 % , $C_{19}H_{13}N_2ClO_2$

requires C, 67.8 ; H, 3.9 ; N, 8.3 % .

PART III

SYNTHESIS OF IMIDAZO[5,1-a]PHTHALAZINES AND RELATED SYSTEMS

Safe handling of potassium cyanide

The synthesis of Reissert compound involved the use of toxic cyanide salt KCN. Therefore the following precautions were practised. Safety glasses and rubber gloves were worn during Reissert compound formation and a supply of amyl nitrate was ready. All manipulations, including weighing and filtration were carried out in a fume-cupboard. The cyanide bottle was placed on a piece of filter paper, potassium cyanide then weighed into a beaker by using a spoon-type spatula. After use all the apparatus, the filter paper, and the rubber gloves, were thoroughly washed with an alkaline solution of ferrous sulphate. These washings were collected in a beaker and combined with the original aqueous layer and the aqueous washings of the dichloromethane layer, during the Reissert compound formation, which also contained cyanide residues.

These cyanide residues were destroyed prior to disposal by making the solution strongly basic with sodium hydroxide and then adding, with stirring, a large excess of ferrous sulphate.[164,164a] The resulting suspension was then left overnight in the fume cupboard before disposal. This process converted cyanide to the nontoxic,

prussian blue (ferric ferrocyanide), which precipitates. Reactions involved are as follows:[164]

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

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

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

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

$$4\,Fe^{3+} + 3[Fe^{II}(CN)_6]^{4-} \longrightarrow Fe^{III}_4[Fe^{II}(CN_6)]_3$$

For the synthesis of phthalazine Reissert compound (130), see p.184 .

The 2-methoxycarbonyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile (63) and 10b-cyano-5-methyl-N-phenyl-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (4), were authentic samples provided by R.S.Budhram.[1]

Imidazo[5,1-a]isoquinolines

p.112.

10b-Cyano-5-methyl-N-(4-fluorophenyl)-1,2,3,10b-tetrahydro-imidazo[5,1-a]isoquinolin-3-one-1-thione (135)

Sodium hydride (0.24g, 0.011 mol) (50 % suspension in oil) was washed with petroleum ether (5 ml, boiling range 40-60°C) and suspended in dimethylformamide (25 ml) and stirred at 0°C under a dry nitrogen atmosphere.

The Reissert compound N-methoxycarbonyl-3-methyl-1,2-dihydro-isoquinoline-1-carbonitrile(2.4g, 0.01 mol) in dimethylformamide (10 ml) was added dropwise during 6 minutes. The mixture was stirred for a further 15 minutes to allow complete formation of the Reissert anion (hydrogen was evolved). A solution of 4-fluorophenyl isothiocyanate (1.8 g, 0.012 mol) in dimethylformamide (10 ml) was added dropwise over 5 minutes. The mixture was stirred for a further 2 hours at 0°C then poured on to crushed ice (400g) and neutralised with 2N.HCl to pH 7. The precipitate formed on warming to room temperature was filtered off and dried in a vacuum desiccator under calcium chloride, to give 10b-cyano-5-methyl-N-(4-fluorophenyl)-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (135),(1.86 g; 52%) yellow needles m.p. 158-160°C from toluene- light petroleum (boiling range 60-80°C).

ν_{max} (KBr) 2240 cm^{-1} (CN), 1775 cm^{-1} (C=O), 1650 cm^{-1} (C=C),

1600 (aryl C=C) and 1145 cm^{-1} (C=S) ; uv. λ_{max} ($CHCl_3$) nm log ε 252 (3.79) , 279 (3.97); n.m.r. 60 MHz ($CDCl_3$), δ 2.53 (3H, s, C5-Me) , 6.38 (1H, br, C6-H), 7.1-7.7 (7H, m, aromatic), 8.4 (1H, split doublet, C10-H) .

Found : C, 65.2 ; H, 3.5 ; N, 11.8 % , $C_{19}H_{12}N_3FSO$

requires C, 65.3 ; H, 3.5 ; N, 12.0 % .

Attempted preparation of 10b-cyano-5-methyl-N-(naphth-1-yl)-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (136)

Sodium hydride (0.3g, 0.012 mol)(50% suspension in oil) was washed with petroleum ether (6 ml, boiling range 40-60°C) and suspended in dimethylformamide (25 ml) and stirred at 0°C under a dry nitrogen atmosphere.

The Reissert compound N-methoxycarbonyl-3-methyl-1,2-dihydro-isoquinoline-1-carbonitrile (1.5g, 0.005 mol) in dimethylformamide (10 ml) was added dropwise during 6 minutes. The mixture was stirred for a further 15 minutes to allow complete formation of the Reissert anion (hydrogen was evolved). A solution of 1-naphthylisothiocyanate (0.96 g, 0.0052 mol) in dimethylformamide (10 ml) was added dropwise over 5 minutes. The mixture was stirred for a further 2 hours at 0°C, then poured on to crushed ice (350g) and neutralised with 2N.HCl to pH 7. The precipitate formed on warming to room temperature was filtered off and dried in a vacuum desiccator under calcium chloride,

to give 10b-cyano-5-methyl-N-(naphth-1-yl)-1,2,3,10b-tetrahydro-imidazo[5,1-a]isoquinolin-3-one-1-thione (136) (0.21 g; 11%) pale yellow needles m.p. 151-153°C from toluene-light petroleum (boiling range 60-80°C). However this compound could not be isolated analytically pure.

ν_{max} (KBr), 1775 cm^{-1} (C=O), 1600 cm^{-1} (aryl C=C) and 1140 cm^{-1}(C=S); n.m.r. 60 MHz ($CDCl_3$), δ3.15 (3H, s, C5-Me), 6.31 (1H, br, C6-H), 6.6-8.1 (10H, m, aromatic), 8.48 (1H, m, C10-H).

Reaction of 10b-cyano-5-methyl-N-phenyl-1,2,3,10b-tetrahydro-imidazo[5,1-a]isoquinolin-3-one-1-thione (4) with sodium methoxide in dimethylformamide at 0°C for 19 hours

Sodium methoxide was prepared from Na (0.04 g, 0.001 mol) in dry methanol (5 ml) under a dry nitrogen atmosphere and stirring at room temperature for 2 hours . Methanol was then removed using a vacuum pump, to leave sodium methoxide as a white powder. To the freshly prepared sodium methoxide powder (0.05g, 0.001 mol) was added under a dry oxygen atmosphere*, a solution of 10b-cyano-5-methyl-N-phenyl-1,2,3,10b-tetrahydroimidazo[5,1-a] isoquinolin-3-one-1-thione (4) (0.33 g, 0.001 mol) in dry dimethylformamide (15 ml), and the mixture was stirred at 0°C. The reaction was followed by t.l.c. every 30 minutes. The t.l.c. of the yellow solution miture after 3 hours showed only one spot, corresponding to the starting material. After 7 hours it was observed that the mixture had become slightly more red, and the t.l.c. showed disulphide appearance as a weak spot. After 19 hours the red colour had deepened and t.l.c. showed strong disulphide spot and only a weak spot corresponding to starting material. The mixture was then evaporated at (70°C/0.1 mm Hg). Infrared spectrum of the product showed ν_{max} 1710 cm^{-1}. This product was then columned

* The oxygen used was from an oxygen cylinder which was passed through a Dreschel bottle containing silica gel (self indicating 2.5-6 mm, 4-7 mesh, 240 g), and the blue colour remained throughout the reaction after 19 hours.

on neutral alumina, using toluene-ethyl acetate (4:1) as eluent and the bis [5-methyl-N-phenyl-3-oxo-2,3-dihydroimidazo[5,1-a]isoquinolin-1-yl] disulphide (129) (0.12g, 21%), was isolated as dark maroon rods m.p. 244-246°C {(lit., [152] m.p.245-246°C)}.

Reaction of 10b-cyano-5-methyl-N-phenyl-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (4) with sodium methoxide in dimethylformamide at 70°C for 24 hours

To a freshly prepared sodium methoxide powder (see p. 181) (0.05 g, 0.001 mol) was added under a dry oxygen atmosphere (see footnote p.181) a solution of 10b-cyano-5-methyl-N-phenyl-1,2,3,10b-tetrahydroimidazo[5,1-a]isoquinolin-3-one-1-thione (4),(0.33g, 0.001mol) in dry dimethylformamide (15 ml), and the mixture was stirred at 70°C. The samples being withdrawn by insertion of a syringe through a rubber septum cap to avoid access of moisture. After heating the mixture at 70°C for 24 hours, the t.l.c. still showed starting tricyclic compound (4) as a major spot and only a small trace of the disulphide (129). The mixture was then poured on to crushed ice (150g). The precipitate formed on warming to room temperature was filtered off and the starting material (4) (0.18 g) was recovered. Extraction of the yellow filtrate with chloroform (3x50 ml), and concentration of yellow chloroform-extracts under reduced pressure also provided the

the tricyclic starting material (4), (0.09 g). The total yield of the recovered starting material was (0.27 g, 91%) recrystallised from toluene-petroleum ether (boiling range 60-80°C) as yellow needles, m.p. 166-168°C [(lit.,[152] m.p. 167-168°C)]. The trace of disulphide (129) revealed by t.l.c. did not prove sufficient to isolate.

Phthalazine (23)

O-Phthalaldehyde (26.8 g; 0.2 mol) in ethanol (200 ml) was added dropwise with stirring, under nitrogen, to an ice cooled solution of hydrazine hydrate (30 g; 0.6 mol) in ethanol (200 ml). The rate of addition, approximately one and a half hours , was adjusted to maintain the reaction mixture at -10°C. The resulting light yellowish reaction mixture was kept with stirring for an additional one hour at 0°C. The solution was thereafter permitted to reach room temperature and kept at room temperature for 2 hours.

The ethanol together with excess hydrazine and small amounts of water were removed under reduced pressure, in a rotary evaporator. A yellowish oil was obtained, which on cooling solidified to a pale yellow solid. The yellow solid was placed overnight in a vacuum desiccator, containing a small beaker of concentrated sulphuric acid.

The crude phthalazine (25.8 g; 99%) was then dissolved in diethyl ether, by refluxing on a water bath, treated with charcoal (0.5 g) and filtered. The colourless solution upon evaporation yielded colourless needles, m.p. 90-93°C, [(lit.[163] m.p. 90-91°C)]. ν_{max} (nujol mull), 1600cm^{-1} (C=N); n.m.r. 60MHz($CDCl_3$), δ 7.8 (4H, m, aromatic), 9.45 (2H, m, C-1H & C-4H).

2-Methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (130)

This reaction involves highly toxic cyanide salts. Cyanide residues are collected and disposed off separately, and the entire sequence is performed in an efficient fume cupboard.

Phthalazine (15 g; 0.115 mol), was added to methylene chloride (230 ml), in a three-necked round bottomed flask (1000 ml), fitted with a pressure equalising dropping funnel (250 ml). Potassium cyanide (30 g; 0.462 mol) was dissolved in distilled water (45 ml) containing benzyltrimethylammonium chloride (1.5 g; 5% by wt of KCN) and the solution was added to the phthalazine mixture in the flask. The mixture was stirred vigorously, using a magnetic stirrer bar, and during this time methyl chloroformate (43.2 g; 0.456 mol) was added dropwise from the dropping funnel over a period of two hours. Stirring was then continued at room temperature for an additional 8 hours.

The resulting pale yellow reaction mixture was transferred into a separating funnel and the two layers were separated. The aqueous layer was extracted with methylene chloride (4x100ml). The combined methylene chloride extracts were then washed successively with water (100 ml), 2N hydrochloric acid (1x40 ml) , 2N sodium hydroxide (1x40ml) and finally water (3x120 ml). The organic layer was dried over anhydrous potassium carbonate (50 g) and filtered. The solvent was evaporated off under reduced pressure, in a rotary evaporator, to give a dark yellow oil which on standing at room temperature yielded a crude yellow solid. T.l.c. examination on the crude product revealed the presence of two products, phthalazine and Reissert compound. The

yellow mixture was chromatographed on a column (90x3 cm) of alumina (150 g, act.I). Elution with dry diethyl ether, then chloroform-diethyl ether (2:1), produced -2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (5.9 g, 24% ; 31% if based on recovered phthalazine 3.6g).

The Reissert compound was recrystallised from diethyl ether as colourless rhombs m.p. 164-165°C. ν_{max} (nujol mull) 2238 (CN), 1700(N-C=O), and 1620 cm^{-1}(C=N); n.m.r. 60 MHz ($CDCl_3$/DMSO-d6) δ 3.95(3H, s, OMe), 6.62(1H, s, C1-H), 7.1-7.7(4H, m, aromatic), 7.88 (1H, s, C4-H) .

Imidazo[5,1-a]phthalazine

1-(4-Fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (140)

Sodium hydride (0.26g, 0.011 mol) (50% suspension in oil) was washed with light petroleum boiling range (40-60°C) and suspended in dimethylformamide (20 ml) and stirred at 0°C under a dry nitrogen atmosphere. The Reissert compound, 2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (3.42 g, 0.017 mol) in dimethylformamide (20 ml) was added dropwise during 10 minutes. The mixture was stirred for a further 15 minutes to allow complete formation of the dark blue phthalazine Reissert anion(hydrogen was evolved). A solution of 4-fluorophenyl isothiocyanate (2.8g, 0.02 mol) in dimethylformamide (10ml) was added dropwise over 5 minutes. The mixture was stirred for a further 3 hours at 0°C, then poured on to crushed ice (400 g) and neutralised with 2N.HCl to pH 7. The precipitate formed on warming to room temperature was filtered off and dried in a vacuum desiccator over calcium chloride, to give 1-(4-fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (140) (2.1g, 37%) pale yellow needles m.p. 181-183°C from ethanol. ν_{max} (KBr) 3200 cm^{-1} (NH), 1730 cm^{-1}(C=O), 1500 cm^{-1} and 1145 cm^{-1} (CSNH); n.m.r. 60MHz ($CDCl_3$/DMSOd6, 50:50), δ 3.90(3H,s, OMe), 6.8-8.25 (9H, m, aromatic), 11.25 (1H, br, NH).

Found : C, 58.4 ; H, 3.6 ; N, 15.0 % , $C_{18}H_{13}N_4SFO$

requires C, 58.7 ; H, 3.5 ; N, 15.2 % .

10b-Cyano-2-(4-fluorophenyl)-1,2,3,10b-tetrahydroimidazo[5,1-a]phthalazin-3-one-1-thione (141)

A mixture of the 1-(4-fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (140) (2g, 5 m mol) and molecular sieves type 4A (12 g) was refluxed in dry toluene (20 ml) under a dry nitrogen atmosphere for 21 hours. The mixture was cooled and filtered . After storage of the filtrate in a refrigerator for one day the resulting yellow crystalline precipitate was collected and recrystallised from toluene-petroleum ether boiling range (60-80°C), 1:4, to give 10b-cyano-2-(4-fluorophenyl)-1,2,3,10b-tetrahydroimidazo[5,1-a]phthalazin-3-one-1-thione (141) (0.78 g, 40%), pale yellow needles m.p. 150-151°C, from toluene-petroleum ether boiling range (60-80°C).

ν_{max} (KBr) 1778 cm^{-1} (C=O), 1648 cm^{-1}(C=N), 1600 cm^{-1} (aryl C=C) and 1180 cm^{-1}(C=S) ; u.v. λ_{max} nm log ε 210(4.65) , 278(4.35), 316(3.97) ; n.m.r. 60 MHz ($CDCl_3$), δ 6.2-7.8 (7H, m, aromatic), 8.14 (1H, m, C6-H) , 8.52(1H, m, C10-H) .

Mass spectrum : (P.C.M.U.) m/e : M^+ 336 (36%), 310(14%), 199(6%), 173(23%), 155(26%), 153(100%), 137(20%) .

Accurate mass M^+ 336.0482 ($C_{17}H_9N_4FSO$ requires 336.0480).

However this compound (141), could not be isolated pure for

microanalysis, although, it showed only one spot on t.l.c. examination on neutral alumina, using $CHCl_3$ as eluent. Attempts at purification by recrystallisation from toluene, ethyl acetate, ethanol, methanol, or mixture of thses solvents and also purification by column chromatography on neutral alumina (act I) using chloroform as eluent, were all unsuccessful.

Concentration of the dark maroon filtrate under reduced pressure gave the bis [2-(4-fluorophenyl)-3-oxo-2,3-dihydroimidazo[5,1-a]= phthalazin-1-yl] disulphide (142), (0.99 g, 29%), dark maroon plates m.p. 294-296°C from ethanol-ethylacatate (1:9).

ν_{max} (KBr) 1715 cm^{-1}(C=O), and 16600 cm^{-1}(C=C); u.v. λ_{max} nm log ε 206(4.67), 224(4.50), 250(4.20), 268(4.35), 344(3.52), 444(3.21).

Mass spectrum (P.C.M.U.) m/e : M^+ 620.0900 (not observed), $\left[\frac{M}{2}\right]^+$ 310(82%), 173(100%), 145(56%), 95(10%) 76(4%) .

Accurate mass, m/e : M^+ 620.0900 (not observed), $\left[\frac{M}{2}\right]^+$ 310.0448 , ($C_{16}H_9N_3FSO$ requires 310.0450).

Mass spectrum (VG Micromass, CI mode with NH_3 as reactant gas) m/e$(M+1)^+$ 621 (2%), 311(59%), 310(56%), 279(35%), 280(100%), 148(54%).

Found : C, 60.0 ; H, 3.1 ; N, 13.3 % $C_{32}H_{18}N_6S_2O_2.H_2O$

requires C, 60.2 ; H, 3.2 ; N, 13.2 % .

1-(3-Fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (143)

Sodium hydride (0.3 g, 0.012 mol) (50% suspension in oil) was washed with light petroleum boiling range 40-60°C, and suspended in

dimethylformamide (20 ml) and stirred at 0°C under a dry nitrogen atmosphere. The Reisset-compound, 2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile(2.73 g, 0.013 mol)in dimethylformamide (20 ml) was added dropwise during 10minutes. The mixture was stirred for a further 15 minutes to allow complete formation of the dark blue phthalazine Reissert anion (hydrgen was evolved). A solution of 3-fluorophenyl isothiocyanate (2.24 g, 0.016 mol) in dimethylformamide (10 ml) was added dropwise over 5 minutes. The mixture was stirred for a further 3 hours at 0°C, then poured on to crushed ice (400 g) and neutralised with 2N.HCl to pH7 . The precipitate formed on warming to room temperature was filtered off and dried in a vacuum desiccator over calcium chloride, to give 1-(3-fluorophenylamino-thiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (143) (1.9 g, 41%), pale yellow needles m.p. 168-169°C from ethanol. ν_{max} (KBr) 3245 cm^{-1} (NH), 1738 cm^{-1}(C=O), 1550 cm^{-1} and 1130 cm^{-1} (CSNH) ; n.m.r. 60 MHz ($CDCl_3$), δ3.90 (3H, s, OMe), 6.7-8.3(9H, m, aromatic), 9.15(1H, br, NH) .

Found : C, 58.4 ; H, 3.5 ; N, 15.1 , $C_{18}H_{13}N_4FSO$

requires C, 58.7 ; H, 3.5 ; N, 15.2 .

Attempted preparation of bis[2-(3-fluorophenyl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (145)

A mixture of 1(3-fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (143) (1g, 3 m mol) and molecular sieves type 4A (6g) was refluxed in dry toluene (10ml) under a dry

nitrogen atmosphere for 21 hours. The mixture was cooled and filtered. After storage of the filtrate in a refrigerator for one day the resultingdark maroon crystalline precipitate was collected and recrystallised from ethanol, to give bis [2-(3-fluorophenyl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (145), (0.14g, 8%), concentration of the dark maroon filtrate also provided compound (145), (0.15 g, 31%), hence the total yield was (0.65g, 39%), dark maroon plates m.p. > 350°C, from ethanol. ν_{max} (KBr) 1712 cm^{-1}(C=O), 1600 cm^{-1} (C=C), u.v. λ_{max} nm log ε 250(4.92) , 268(4.98),328(4.63). Mass spectrum : (P.C.M.U.), m/e, $M^{+\cdot}$ 620.0900 (not observerd), 310$\left[\frac{M}{2}\right]^{+\cdot}$ (54%); 173(77%), 145(54%), 95(91%), 76(33%) .
Accurate mass : m/e, $M^{+\cdot}$ 620.0900 (not observed), $\left[\frac{M}{2}\right]^{+}$ 310.0451 ($C_{16}H_9N_3SFO$ requires 310.0450). This compound however could not be isolated analytically pure even after careful column chromatography on alumina (act I) and using chloroform-methanol (3:1) as eluent.

1-(3-Fluorophenylaminothiocarbonyl)phthalazine (146)

A mixture of 1-(3-fluorophenylaminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthlazine-1-carbonitrile (143) (3 g, 9 m mol) and molecular sieves type 4A (20 g) was refluxed in dry toluene (30 ml) under a dry nitrogen atmosphere for 21 hours. After storage of the filtrate in a refrigerator for one day the resulting dark maroon crystalline precipitate was collected and recrystallised from ethanol to give impure disulphide (145), (0.14 g, 3%), m.p. > 350°C, from ethanol, ν_{max} (KBr) 1712 cm^{-1} (C=O), 1600 cm^{-1}(C=C).

Concentration of dark maroon filtrate at reduced pressure provided 1-(3-fluorophenylaminothiocarbonyl)phthalazine (146),(0.23g, 10%), yellow needles m.p. 188-191°C, from ethanol, ν_{max} (KBr) 3250cm^{-1} (NH), 1495 cm^{-1} and 1380 cm^{-1} (C=S), n.m.r. 60MHz ($CDCl_3$), δ 7.1-8.3 (9H, m, aromatic), 9.25 (1H, br, NH).

Found : C, 63.6 ; H, 3.7 ; N, 14.7 % $C_{15}H_{10}N_3FS$

requires C, 63.6 ; H, 3.6 : N, 14.8 % .

Attempted preparation of 1-(naphth-1-yl-aminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (147)

Sodium hydride (0.44g, 0.018 mol) (50% suspension in oil) was washed with light petroleum boiling range 40-60°C, and suspended in dimethylformamide (20 ml) and stirred at 0°C under a dry nitrogen atmosphere. The Reissert compound, 2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (3.42 g, 0.017 mol) in dimethylformamide (20 ml) was added dropwise during 10 minutes. The mixture was stirred for a further 15 minutes to allow complete formation of the dark blue phthalazine Reissert anion (hydrogen was evolved). A solution of 1-naphthyl isothiocyanate (3.65 g, 0.02 mol) in dimethylformamide (10 ml) was added dropwise over 5 minutes. The mixture was stirred for a further 3 hours at 0°C, then poured on to crushed ice (400 g) and neutralised with 2N.HCl to pH 7 . The precipitate formed on warming to room temperature was filtered off and dried in a vacuum desiccator over calcium chloride, to give 1-(naphth-1-yl-aminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile(147),

(2.4 g, 39%), as pale yellow m.p. 221-222°C from ethanol. ν_{max} (KBr) 3186 cm^{-1}(NH), 1735 cm^{-1} (C=O), 1500 cm^{-1} and 1145 cm^{-1} (CSNH) ; n.m.r. 60 MHz ($CDCl_3$/DMSOd6, 50:50), δ 3.95 (3H, s, OMe), 7.2-8.3 (12H, m, aromatic), 9.36 (1H, br, NH).

This compound however could not be isolated analytically pure. An attempt to purify this compound by coloumn chromatography on alumina (act I, 60 g) was undertaken using, chloroform-methanol (5:2) as eluent. However even after careful column chromatography this compound could not be isolated pure.

Bis[2-(naphth-1-yl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (149)

A mixture of 1-(naphth-1-yl-aminothiocarbonyl)-2-methoxycarbonyl-1,2-dihydrophthalazine (147), (isolated impure as mentioned above, 2g, 5 m.mol), and molecular sieves type 4A(12 g) was refluxed in dry toluene (20ml) under a dry nitrogen atmosphere for 21 hours. The mixture was cooled and filtered . After storage of the filtrate in a refrigerator for one day the resulting dark maroon crystalline precipitate was collected and recrystallised from ethanol, to give bis [2-(naphth-1-yl)-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (149), (0.3g, 9%), concentration of the dark maroon filtrate also provided compound (149), (1.16 g, 34%), hence the total yield was (1.46 g, 43%), dark maroon needles, m.p. 261-263°C, from ethanol. ν_{max} (KBr) 1721 cm^{-1} (C=O), 1600 cm^{-1} (C=C); u.v. λ_{max} nm log ε 220(4.28) 276(3.64) 350(3.4) 440(3.04). Mass spectrum : (P.C.M.U.), m/e : M^+ 684.1402 (not observed), 342$\left[\frac{M}{2}\right]^+$ (61%), 173 (100%), 145 (46%), 127 (12%) .

Accurate mass m/e : $M^{+\cdot}$ 684.1402 (not observed), $\left[\frac{M}{2}\right]^{+}$ 342.0697 ($C_{20}H_{12}N_3OS$ requires 342.0701).

Found : C, 67.5 ; H, 3.6 ; N, 11.7 % $C_{40}H_{24}N_6S_2O_2.1\frac{1}{2}H_2O$ requires C, 67.5 ; H, 3.8 ; N, 11.8 % .

10b-Cyano-2-methyl-1,2,3,10b-tetrahydroimidazo[5,1-a]phthalazin--3-one-1-thione (150)

Sodium hydride (0.36 g, 0.015 mol) (50% suspension in oil) was washed with light petroleum (boiling range 40-60°C) and suspended in dimethylformamide (20 ml) and stirred at 0°C under a dry nitrogen atmosphere. The Reissert-compound, 2-methoxycarbonyl-1,2-dihydrophthalazine-1-carbonitrile (3.0 g, 0.014 mol) in dimethylformamide (20 ml) was added dropwise during 10 minutes. The mixture was stirred for a further 15 minutes to allow complete formation of the dark blue phthalazine Reissert anion (hydrogen was evolved). A solution of methyl isothiocyanate (1.19 g, 0.016 mol) in dimethylformamide (10 ml) was added dropwise over 5 minutes. The mixture was stirred for a further 3 hours at 0°C, then poured on to crushed ice (450 g), and neutralised with 2N.HCl to pH 7. The precipitate formed on warming to room temperature was filtered off and dried in a vacuum desiccator over calcium chloride, to give 10b-cyano-2-methyl-1,2,3,10b-tetrahydroimidazo[5,1-a]phthalazin-3-one-1-thione (150), (0.2 g, 6%), pale yellow needles, m.p. 197-199°C, from toluene-petroleum ether boiling range 60-80°C . ν_{max} (nujol mull) 1770 cm^{-1} (C=O), 1600 cm^{-1} (C=C), and

1165 cm^{-1}(C=S); u.v. λ_{max} nm log ϵ 210(3.80), 270(3.65), 316(3.35); n.m.r. 60MHz ($CDCl_3$) δ 4.32 (3H, s, Me), 7.16-7.85 (3H, m, aromatic, C7-H, C8-H and C9-H), 8.1 (1H, m, C6-H), 8.58 (1H, m, C10-H).

Mass spectrum : (P.C.M.U.), m/e : M^{+} 256 (65%), 199(5%), 173 (7%), 155(100%), 127 (26%).

Accurate mass M^{+} 256.0415 ($C_{12}H_8N_4SO$ requires 256.0416).

Found : C, 56.1 ; H, 2.9 ; N, 21.6 % $C_{12}H_8N_4SO$

requires C, 56.2 ; H, 3.1 ; N, 21.9 % .

Concentration of the dark maroon filtrate under reduced pressure gave bis[2-methyl-3-oxo-2,3-dihydroimidazo[5,1-a]phthalazin-1-yl] disulphide (151) (0.61 g; 9%) maroon needles m.p. 300-302°C from ethanol, lit.[146] m.p. 300-302°C . ν_{max} (nujol mull) 1715 cm^{-1} (C=O), and 1600 cm^{-1} (C=C).

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HETEROCUMULENES IN CYCLISATION WITH N-ALKOXYCARBONYL-REISSERT COMPOUND CARBANIONS: FORMATION OF IMIDAZO[5,1-a]PHTHALAZINES AND RELATED SYSTEMS

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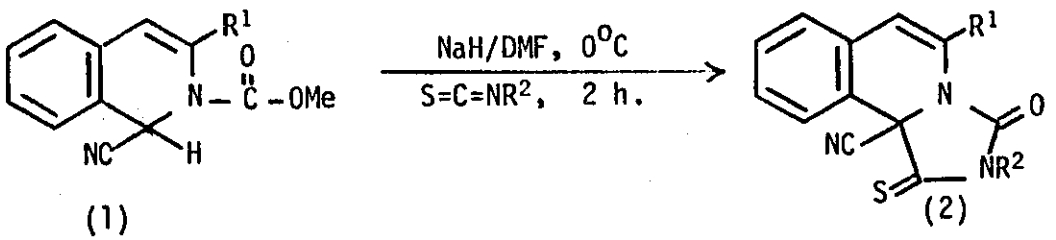
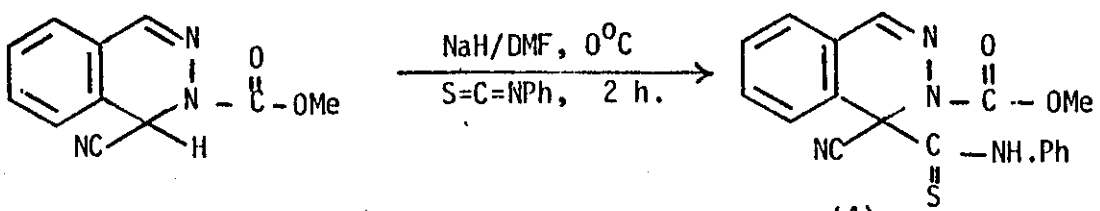
We have shown that cyclisation occurs on treatment of an isothiocyanate with the carbanion of N-alkoxycarbonylisoquinoline Reissert compound (1) at 0°C to give the tricyclic imidazo[5,1-a]isoquinoline system (2).[1]



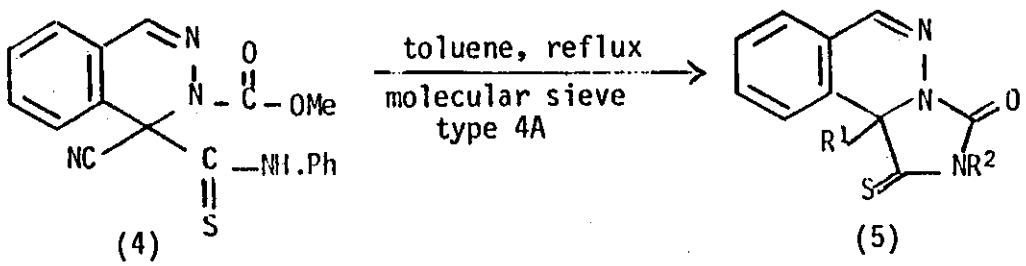
(1) (2)

We have examined application of this approach to provide a synthesis of the novel imidazo[5,1-a]phthalazine system (5). However, we found that cyclisation under the same conditions, but using the carbanion from N-methoxycarbonylphthalazine Reissert compound (3), failed, giving on work-up the open-chain addition compound (4).



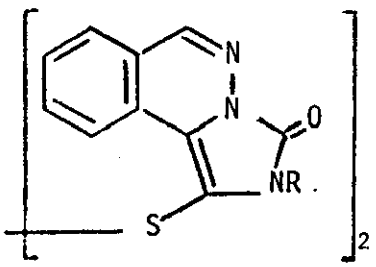
(3) (4)

A mild route for converting esters to amides involves heating the ester with an amine in the presence of molecular sieves.[2] Using this reagent with the thiocarboxamide (4) we observed smooth cyclisation to give the required imidazo[5,1-a]phthalazine system (5, R^1 = CN, R^2 = Ph).

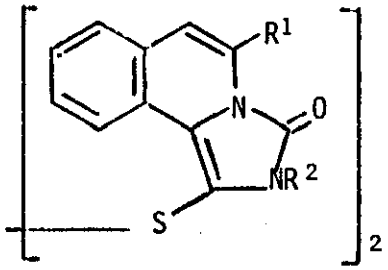


(4) (5)

Attempts to obtain compounds of type (5, R^1 = CN, R^2 = aryl, alkyl) from the anion of (3) by raising the temperature of the original reaction also gave the required ring system but in the form of the bis-imidazo[5,1-a]phthalazinyl disulphide (6, R = aryl, alkyl).



(6)



(7)

Analogous disulphides in the imidazo[5,1-a]isoquinoline series (7) have also been obtained as co-products in the synthesis of compounds (2, R^1 = H, Me; R^2 = Me, Ph), and the structure of (7, R^1 = H, R^2 = Ph) has been confirmed by X-ray studies.[3] Formation of the disulphide linkage probably proceeds by oxidative coupling of (5, R^1 = H) or its tautomer, the cyano-group first being removed either by hydrolysis under work-up conditions and decarboxylation or possibly by direct displacement by the MeO^- liberated on cyclisation.[4]

References

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4. Cf. R. Marshall and D. M. Smith, J. Chem. Soc. (C), 1971, 3510.