THE CHEMISTRY OF HYDRAZIDES AND THIOHYDRAZIDES

SOME ASPECTS OF THE CHEMISTRY OF HYDRAZIDES AND THIOHYDRAZIDES

By

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SCOPE AND CONTENTS:

In order to study the mechanism of their conversion into hydrazides and thiohydrazides, a number of hydrazidic halides were treated with compounds containing a nucleophilic oxygen or sulfur atom.

The initial products of these reactions were formed from the displacement of the α-halogen atom of the hydrazidic halide. In cases where there was sufficient activation the group attached to oxygen or sulfur was transferred to nitrogen in the presence of base.

Some hydrazides and thiohydrazides containing displaceable groups in the 2-position of an N-aryl ring yielded benzoxadiazines and benzothiadiazines respectively under basic conditions. The reactions exhibited the characteristics of bimolecular nucleophilic aromatic substitutions.

The synthesis of four novel heterocyclic ring systems is described.

ACKNOWLEDGEMENTS

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INTRODUCTION

The chemistry of hydrazidic halides has been under investigation for more than half a century. The majority of the work has been concerned with the preparations and reactions of compounds of general structure (1) where R_1 and R_2 have been aryl groups, X chlorine or bromine and R_3 mostly hydrogen. The term hydrazidic halide is relatively new[1] and the older literature refers to ω-halogenoarylaldehyde arylhydrazones[2] or

$$\begin{matrix} R_1C{=}N{-}NR_2R_3 \\ | \\ X \end{matrix} \qquad (1)$$

benzarylhydrazidic halides[3].

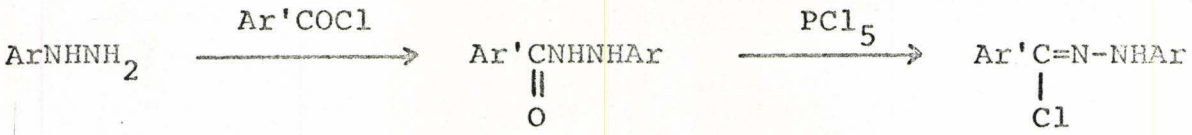
A. PREPARATION OF HYDRAZIDIC HALIDES

There are two general methods for the preparation of these compounds and these are given in reaction schemes (i) and (ii).

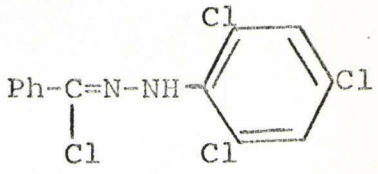
SCHEME (i)

$$ArNHNH_2 \xrightarrow{Ar'CHO} Ar'CH{=}N{-}NHAr \xrightarrow[AcOH]{Cl_2 \text{ or } Br_2} \begin{matrix} Ar'C{=}N{-}NHAr \\ | \\ X \end{matrix}$$

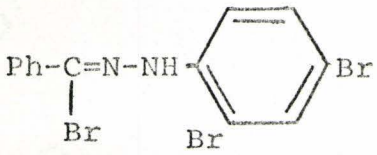
SCHEME (ii)



Scheme (i) involves the action of the halogen (bromine or chlorine) on a hydrazone and is normally done at room temperature. As expected the N-aryl ring undergoes attack as well as the α-position. Chlorination of benzaldehyde phenylhydrazone[4] gives the tetrachloro-derivative (2), whereas bromination yields the tribromocompound (3) under the same conditions[5,6].

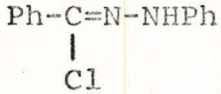


(2)



(3)

Scheme (ii) involves the action of phosphorus pentachloride on the aroyl derivative of a hydrazine. Thus N-benzoyl-N'-phenylhydrazine yields N-α-chlorobenzylidene-N'-phenylhydrazine[7] (4).

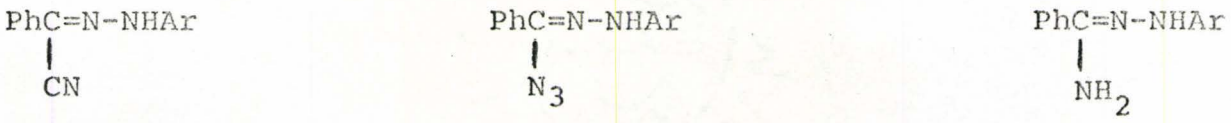


(4)

In this case the N-aryl ring is not attacked. The use of phosphorus pentabromide, however, leads to bromination in the ring, presumably because of the presence of free bromine in the mixture.

B. GENERAL REACTIONS OF HYDRAZIDIC HALIDES

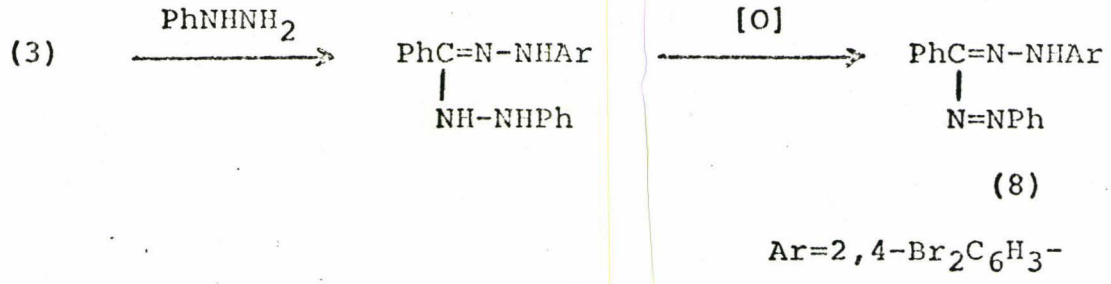
The halogen substituent of hydrazidic halides is open to facile displacement by a variety of nucleophiles. Thus potassium cyanide, sodium azide and ammonia convert (3) into (5), (6) and (7) respectively[2,10].



(5) (6) (7)

Ar=2,4-$Br_2C_6H_3$-

Derivatives of ammonia, such as primary and secondary amines, hydrazine and substituted hydrazines react in an analogous manner. Reaction of phenylhydrazine with (3) serves as a useful test for the presence of the reactive α-halogen atom since the intermediate hydrazidine is rapidly oxidised to the formazyl derivative (8)[7] which is generally bright red or yellow in colour. Coloured products are formed when hydrazidic halides are boiled with ethanolic potassium hydroxide solution. These probably arise through partial hydrolysis to the hydrazine, which then reacts with unchanged halide in the manner indicated above[2].



One of the main synthetic appeals of hydrazidic halides is that they behave in many reactions like 1,3-dipolar species[8]. Treatment of (4) with triethylamine has been shown to give the diphenylnitrilimine at 20°[3]. In the presence of norbornene, 94% of the exo-adduct was formed. Some further pyrazolines and pyrazoles are listed in scheme (iii). The structures of the adducts were all confirmed, except that the relative orientation in the bis-adduct of norbornadiene was uncertain.

C. CONVERSION OF HYDRAZIDIC HALIDES INTO HYDRAZIDES AND THIOHYDRAZIDES

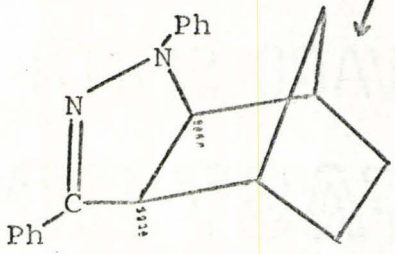
The conversion of hydrazidic halides into hydrazides was not made until recently[15,16], although the preparation of acetylated hydrazides by this route has been known since 1925[2]. The mechanism proposed by Chattaway and Walker involved N-acetylation as the first step, followed by nucleophilic displacement of the α-halogen atom by hydroxide ion, as shown below. However the same workers also observed that direct action of hydroxide ion on (3) merely gave the formazan in the manner already described.

The reaction of hydrazidic halides with acetate ion was investigated at a later date by Burgess and Gibson[12]. These

SCHEME (iii)

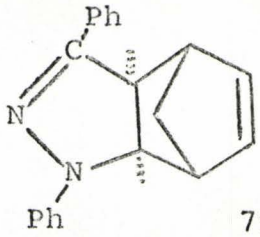
(4) + NEt_3 — BENZENE, 20° → $Et_3NH^+Cl^-$ + $PhC\equiv\overset{+}{N}-\bar{N}-Ph$

Norbornene



94%

Norbornadiene (10 equiv.)



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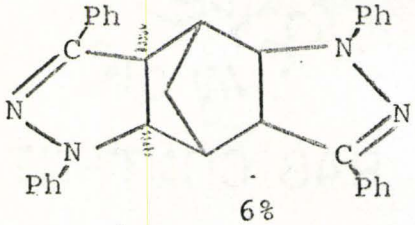

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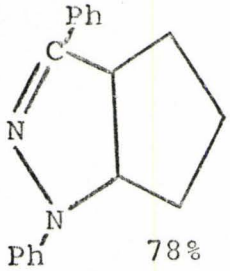
Cyclopentene



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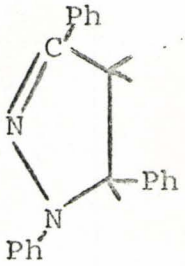
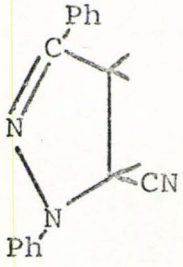
Styrene



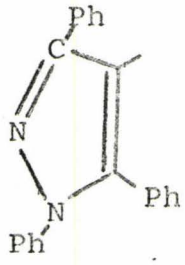
88%

Acrylonitrile



85%

Phenylacetylene



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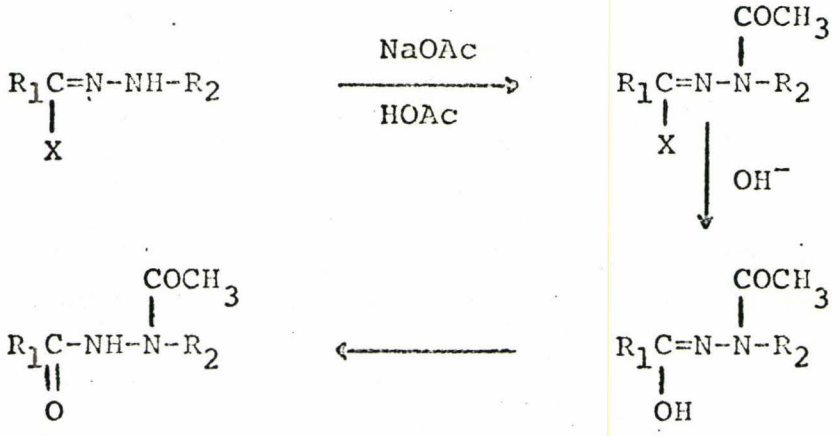
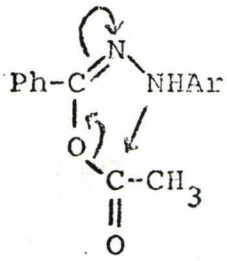


workers favoured a mechanism involvingan O→N migration of the intermediate acetoxycompound (9) to give (10)



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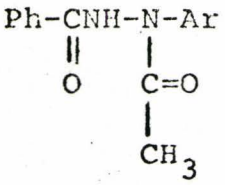
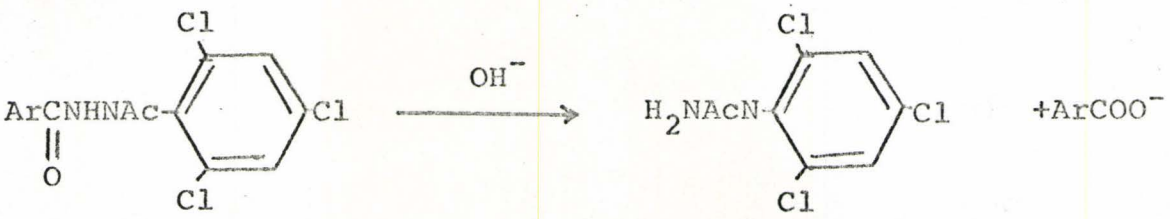


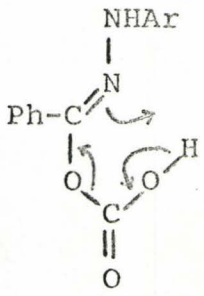
(10)

Ar=2,4-$Br_2C_6H_3$-

Attempts to remove the acetyl group from acetylated hydrazides by hydrolysis usually result in the recovery of a benzoic acid derivative and an arylhydrazine. Only in very few cases is the acetyl group removed cleanly[13]. In cases where the N-aryl nucleus is trisubstituted the acetyl group remains although the hydrazide suffers hydrolysis[14].



The conversion of hydrazidic halides directly to hydrazides was eventually realised by two groups of workers at almost the same time. Barnish and Gibson[16] reported that (3) reacts with potassium hydrogen carbonate in dry dimethylformamide to give the hydrazide (12) and carbon dioxide. Decarboxylation of the intermediate α-hydrogen carbonate (11) could occur directly with nitrogen participation or via the anion.



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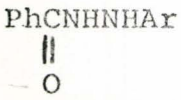
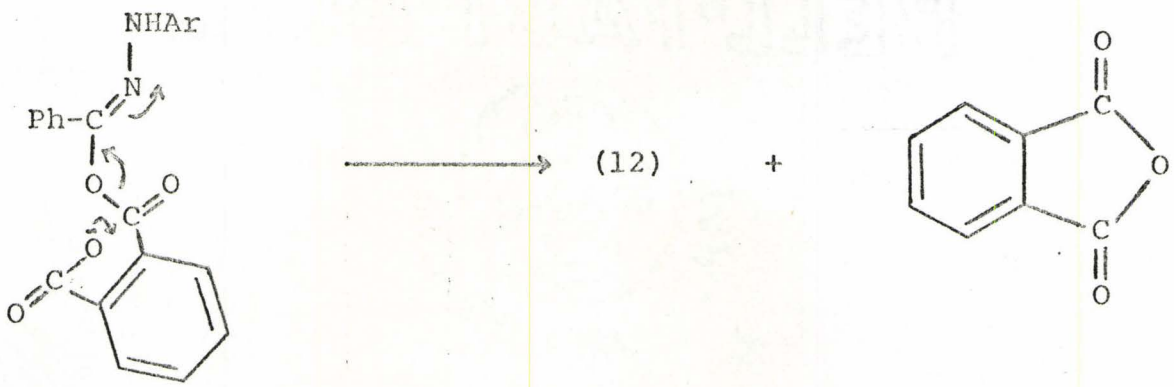


(12)

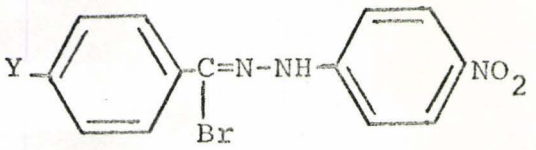
Ar=2,4-$Br_2C_6H_3$-

Moreover (3) reacts with potassium hydrogen phthalate in dry acetonitrile to give (12) and phthalic anhydride. In this case, attack of the carboxylate ion on the juxtaposed carbonyl group in the intermediate α-hydrogen phthalate (13) yields the hydrazide.



(13)

At the same time Scott and Aylward noted[15] that hydrazidic halides are hydrolysed in 50% aqueous dioxan in good yields. These workers reported kinetic and thermodynamic data on the hydrolysis of a series of compounds of general formula (14), and attributed the negative ρ value (-0.92 at 75°) to the development of carbonium ion character during the reaction. Stabilisation of such carbonium ions can be achieved by delocalisation of the charge onto the hydrazino nitrogen and into the aryl ring containing Y. The relatively low value of ρ was considered to represent an overall effective delocalisation of charge in the transition state rather than poor development of

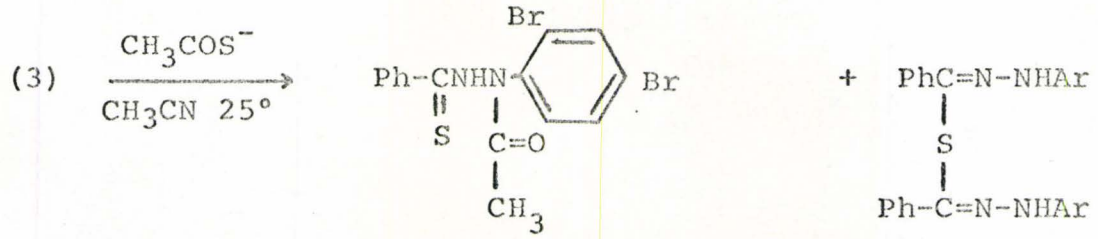


(14)

Y = H
CH_3
$(CH_3)_2CH$
Br
Cl

carbonium ion character therein.

The conversion of hydrazidic halides to acetylated thiohydrazides was realised by Callaghan and Gibson[17] who used potassium thioacetate in acetonitrile at room temperature. Thus (3) yielded (15) together with the hydrazidic sulfide (16) in relative yields which appeared to depend on the amount of water present in the reaction mixture.



(15)

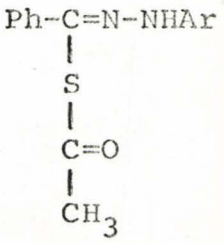
(16)

Ar=2,4-$Br_2C_6H_3$-

The acetylated thiohydrazide was thought to be formed in a manner analogous to the acetylated hydrazide discussed previously. Compound (15) was identified by its mass spectrum and its i.r. spectrum since compounds of this type appeared to

be thermally unstable and microanalyses were repeatedly inaccurate.

The appearance of the hydrazidic sulfide (16) was of some interest since the potassium thioacetate used did not contain sulfide ion. The intermediate thioacetate (17) was thought to be deacetylated either by excess thioacetate or by water followed by further reaction of the derived ion (18) with (3) to produce (16). Subsequent S→N hydrazidyl transfer was also considered a possibility.



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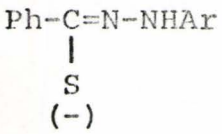


(18)

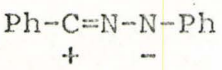
Ar=2,4-$Br_2C_6H_3$-

The occurrence of the hydrazidic sulfide (16) in the reaction of (3) with thioacetate ion in refluxing acetonitrile had previously been noted[18] and was thought to be formed in a manner akin to that outlined above. The other isolable product of the hot reaction was a benzothiadiazine produced by a process involving the displacement of the ortho-bromine substituent from (15). The formation of this compound was important to the present work and will be discussed at greater length in section (E) of the Introduction.

D. THE SMILES REARRANGEMENT

An O→N transfer of a phenyl group analogous to the O→N migration of the acetyl group proposed by Burgess and Gibson had been observed earlier by Huisgen and co-workers[19]. When the tetrazole (19) and phenol were boiled together under reflux for three hours (21) was obtained in good yield. Since (19) is thought to give the 1,3-dipolar species (20) under these conditions the intermediate in this reaction may be envisaged as (22).

(19)



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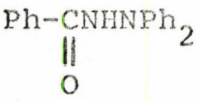


(21)

Huisgen repeated the reaction in refluxing thiophenol and obtained the unrearranged thiophenoxy compound (23). The structure of (23) was established by acidic hydrolysis to N-benzoyl-

(22)

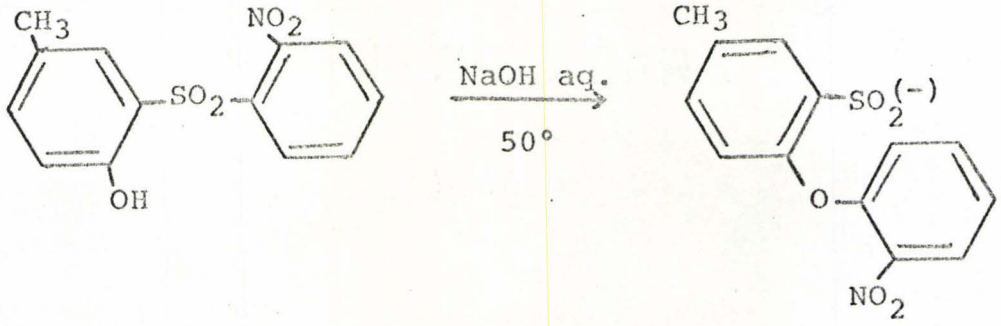
-N'-phenylhydrazine.

This O→N migration is only one example of a much broader series of rearrangements studied by Smiles and co-workers[20,21].

(19) $\xrightarrow[\Delta]{PhSH}$ Ph-C(SPh)=N-NHPh

(23)

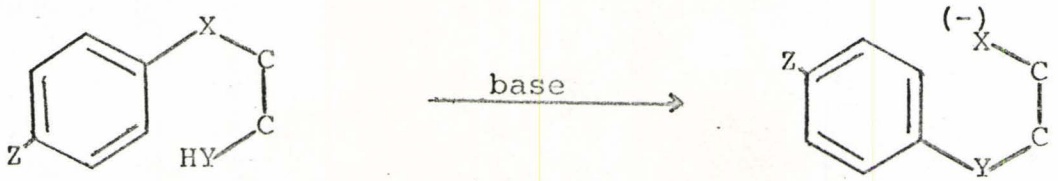
A typical Smiles rearrangement is represented by the transformation of 2-hydroxy-5-methyl-2'-nitrodiphenyl sulfone (24) into 4-methyl-2'-nitro-2-sulfinodiphenyl ether (25) under the influence of a slight excess of aqueous sodium hydroxide at 50°[22].



(24) (25)

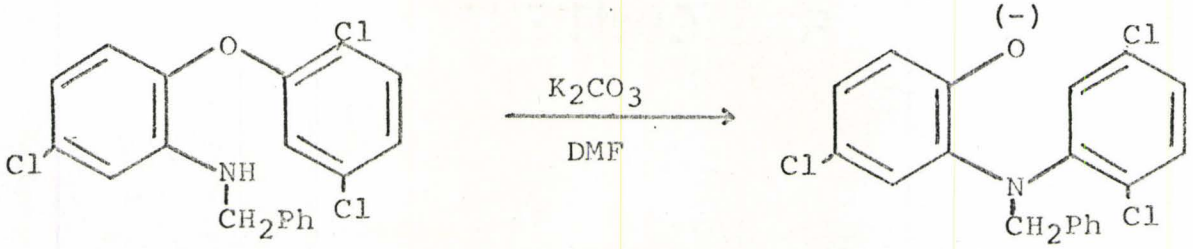
Smiles recognised, and provided evidence for[23], the various factors governing the rearrangement of compounds of general structure (26), in which the carbon atoms joining X and Y may be part of an aromatic ring, into (27).

The ease of the rearrangement depends on the activation present in the aromatic ring as well as the nature of X and Y[21].



(26) (27)

Few rearrangements occur without activation although the first rearrangements that Smiles reported were in unactivated naphthalene derivatives[24]. Smiles later worked with compounds containing nitro groups and sulfonyl groups[25]. More recently activation by chlorine has been observed in the transformation of (28) into (29)[26].

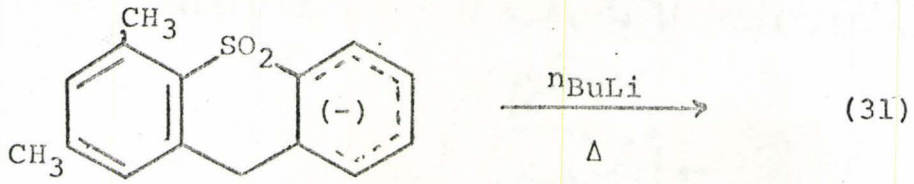


(28) (29)

Truce has reported the rearrangement of some o-methyl-diaryl sulfones, e.g. (30) into (31) with butyl lithium[27].

Later work by Drozd has shown that the initial product in this reaction is (32)[28].

(30) (31)

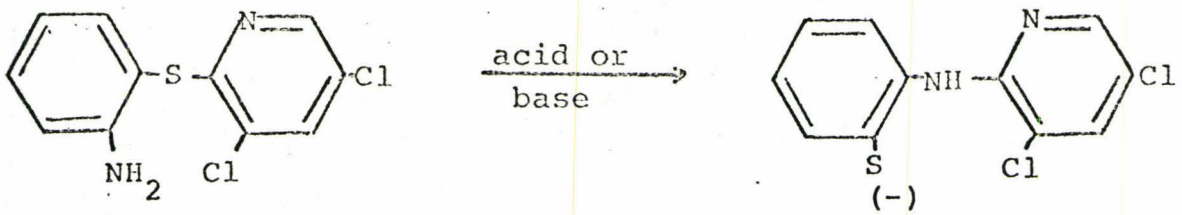


(32) (31)

Rearrangement of (33) reported recently[29] is an unusual example of a Smiles Rearrangement.

(33)

References to the Smiles rearrangement involving activation by a pyridine ring have become increasingly common in recent years, mainly because of the work of Maki and co-workers. A typical example is the transformation of (34) into (35). These reactions are catalysed by acid or base. Peck[31] has reported a rearrangement activated by a quinoline nucleus



(34) (35)

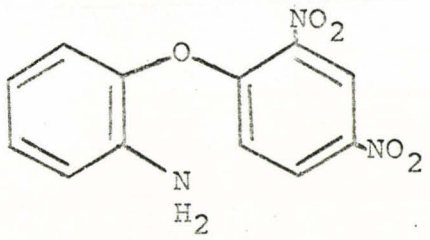
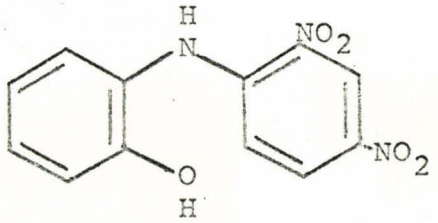
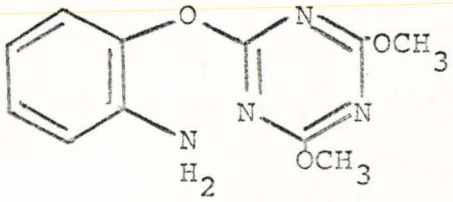
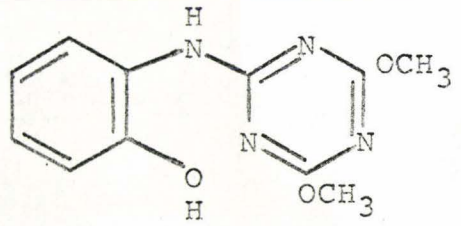
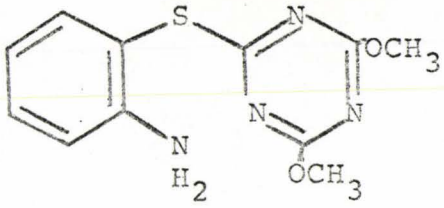
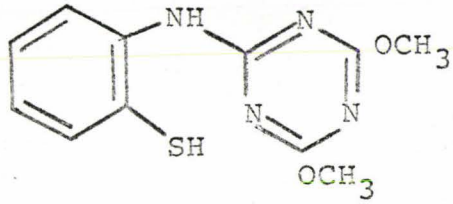
and reference has also been made to a rearrangement involving the s-triazine system[32].

Recently a report of a photochemical Smiles rearrangement has appeared in the literature[33]. The preliminary results are shown in Table I. It was found that the Smiles rearrangement products were accompanied by some side-reaction products, and that no rearrangement occurred without u.v. light in the solvents used and at room temperature.

E. CYCLISATION OF SOME THIOHYDRAZIDES

In their attempts to convert hydrazidic halides into thiohydrazides, Barnish and Gibson examined the reaction of (3) with thioacetate ion[18]. A hydrazidic thioacetate (17) formed by displacement of the α-halogen atom by the more nucleophilic centre of the ambident thioacetate ion was envisaged as the primary product. Partial or complete rearrangement to the N-acetylthiohydrazide (15) was thought to be the most likely subsequent reaction. However, in the event, no compound (15) was isolated in this series of reactions at room temperature in dry

Table 1. The Photo-Smiles Rearrangements of Some Aromatic Compounds at Room Temperature.

Substance	Solvent	Radiation source	Irradiation time hr.	Photo-Smiles rearrangement product
	Benzene	H(>3000Å)	24	
	Benzene	H(>3000Å)	50	
	Ethanol	L(2537Å) and H(>3000Å)	30 24	

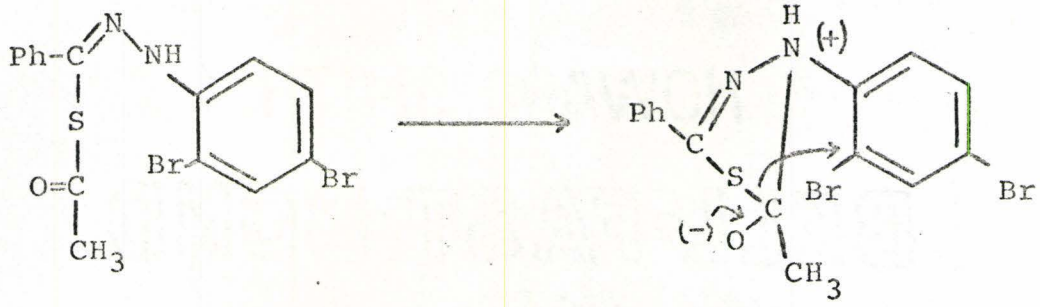
H: High pressure mercury lamp. L: Low pressure mercury lamp.

acetonitrile, nor in the same solvent at reflux temperatures. As already noted (section (C)) the cold reaction gave the hydrazidic sulfide (16) as the only isolable product (71%). In the hot reaction the yield of sulfide dropped to 16% and a second product (14%) was isolated and eventually formulated as 4-acetyl-7-bromo-2-phenyl-4H-benzo[1,3,4]thiadiazine (36). After performing the necessary control experiments the authors provided a mechanism for the formation of (36) via the displacement of the transiently activated 2-bromine atom in the protonated species (37) (scheme iv). Thus the move towards completion of the S→N acetyl transfer is accompanied by addition of the incipiently negative sulfur to the 2-position of the halogenated benzene ring in a synchronous process leading to (38). However they could not dismiss the alternative mechanism which allows completion of the acetyl transfer and addition of the negative sulfur to the 2-position as two discrete processes.

It was noted that the yield of benzothiadiazines was dependent on the identity of the 2-substituent, the ease of displacement being in the order F>>Br>Cl (not at all). The nature of the 4-substituent also appeared to be important. In all the cases examined only hydrazidic halides containing a 4-halogen substituent could be made to undergo benzothiadiazine formation. From this it was tentatively concluded[34] that the 4-substituent had to be capable of increasing the nucleophilicity of the nitrogen atom by electron release for the formation of (37)*, and then be capable of augmenting the electron-

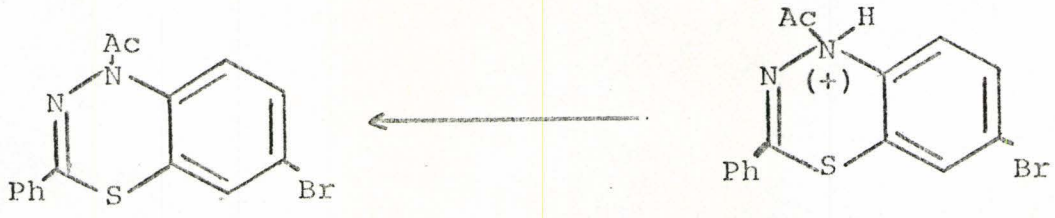
*But see H. J. Van Opstall, Rec. trav. chim., 1933, 52, 906.

SCHEME (iv)



(17)

(37)

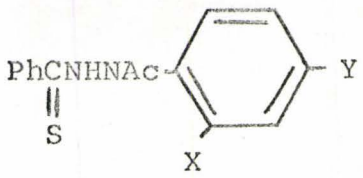


(36)

(38)

deficiency of the 2-carbon atom by an inductive effect to allow the formation of (38) and subsequently the final product (36). The observation that no benzothiadiazine formation was observed with a 4-methyl, a 4-hydrogen or a 4-carboethoxy substituent could be explained along these lines.

Callaghan and Gibson[17] recently reported that the ease of displacement of the 2-substituent had been extended to F>I>Br>Cl (not at all) where the 4-position was occupied by bromine. These same workers investigated the reactions of acetylthiohydrazides of general structure (39) in proton-exchange systems. They envisaged the possible formation of the zwitterion

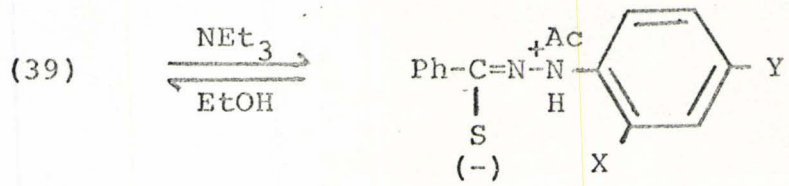


X = F, Cl, Br, I

Y = halogen, $-SO_2NMe_2$, $-CF_3$, -H

(39)

(40), albeit in low concentration, with subsequent benzothiadiazine formation in favourable cases. In fact (40) was directly analogous to the species considered by Barnish and Gibson to



(40)

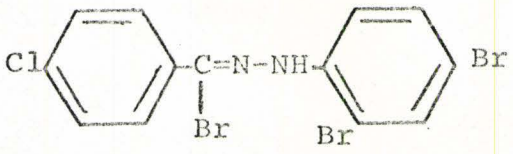
result from complete transfer of the acetyl group in (37) prior to the attack by the negative sulfur at the 2-position of the benzene ring. They found that the identity of the 2-halogen was not as critical as in the hot thioacetate reactions. However chlorine was still immovable and no benzothiadiazine was observed with hydrogen in the 4-position. In refluxing ethanol-triethylamine the cyclisation appeared to be extremely facile in most cases and yields in excess of 80% were common, irrespective of the leaving group. It was shown that the acetyl group was necessary for ring-closure to proceed.

There thus remained the possibility that the benzothiadiazine formation observed by Barnish and Gibson in the reactions of hydrazidic halides and thioacetate ion was not entirely synchronous as represented by (37) but rather involved a step-wise process leading to the formation of such intermediates as (40). The presence of small amounts of thioacetate ion dissolved in acetonitrile could constitute a weak proton exchange system and, as such, lead to cyclisation. Perhaps fortuitously (15) and thioacetate ion were found to yield (36) in exactly the same yield (14%) as had been observed earlier in the reaction of (3) with thioacetate ion.

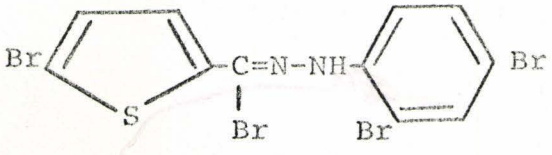
DISCUSSION

The aim of the present research was two-fold; to test the acetyl transfer mechanism proposed for the formation of (10)[12] and (15)[17] and then to effect the cyclisations of suitably substituted hydrazides and thiohydrazides in basic media to give oxadiazines and thiadiazines respectively. To this end a series of hydrazidic halides was prepared in which two were not reported in the literature.

The bromination of p-chlorobenzaldehyde phenylhydrazone by the method of Chattaway and Walker[2] for the bromination of benzaldehyde phenylhydrazone gave N-α-bromo-p-chlorobenzylidene--N'-(2,4-dibromophenyl)hydrazine (41) in 61% yield, based on the aldehyde.



(41)

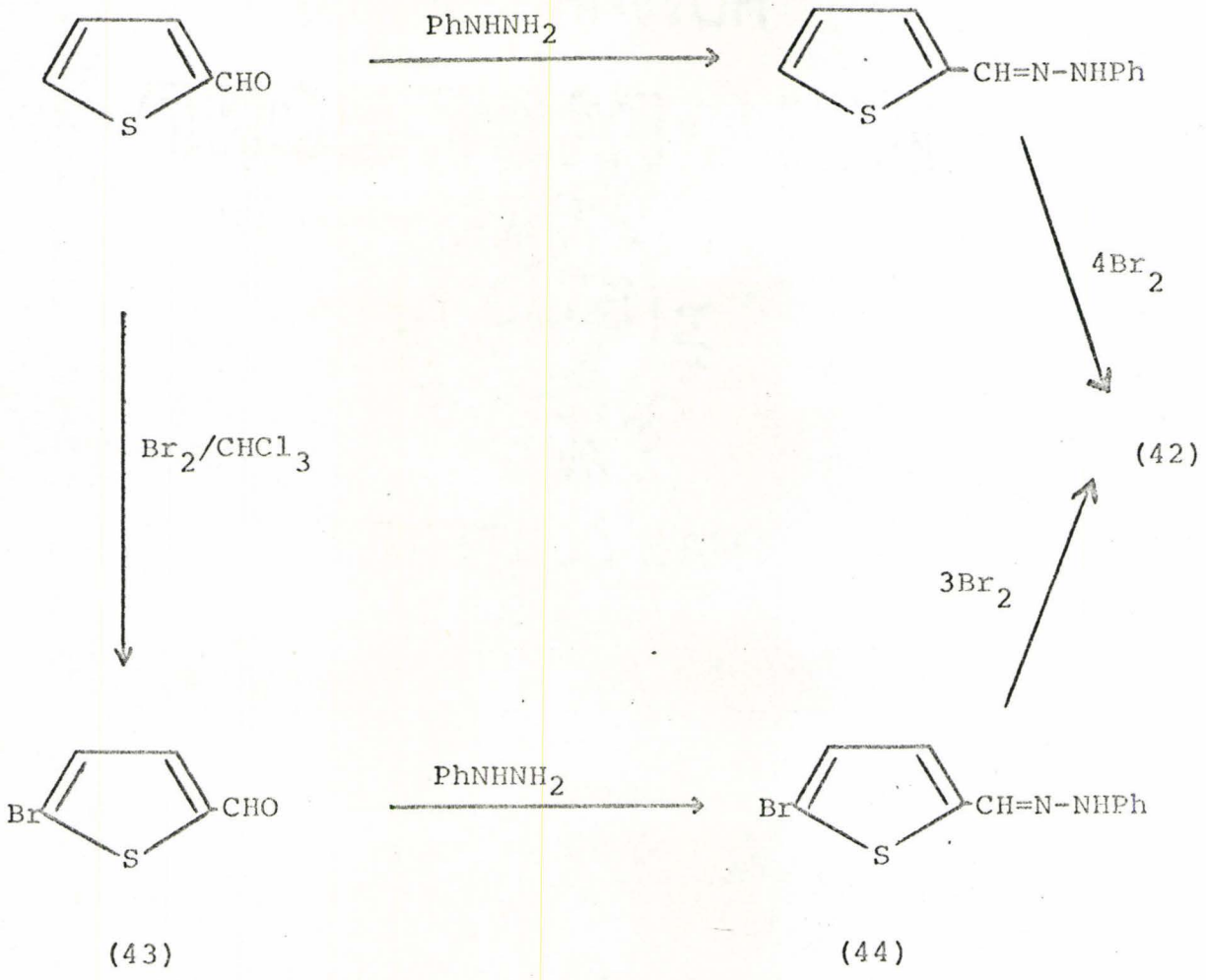


(42)

The action of four equivalents of bromine on thienyl--2-aldehyde phenylhydrazone in acetic acid at room temperature produced a compound in 65% yield which was eventually formulated

as N-α,5-dibromo-2-thienylidene-N'-(2,4-dibromophenyl)hydrazine (42). The details are given in scheme (v). The p.m.r. spectrum of (42) showed an AB quartet for the thiophene ring protons with a coupling constant of 4.0 Hz., which is consistent only with β-β' coupling[35]. An alternative synthesis of (42) was devised, the details of which are also given in scheme (v). Bromination of thienyl-2-aldehyde according to the method of Gronowitz[36] gave 5-bromothienyl-2-aldehyde (43). The p.m.r. spectrum of this compound exhibited an AB quartet (J = 4.0 Hz.) for the thiophene protons in accordance with the proposed structure. The action of phenyl hydrazine on (43) gave the hydrazone (44) which on treatment with three equivalents of bromine gave a compound with spectral properties and melting-point identical with (42).

SCHEME (v)

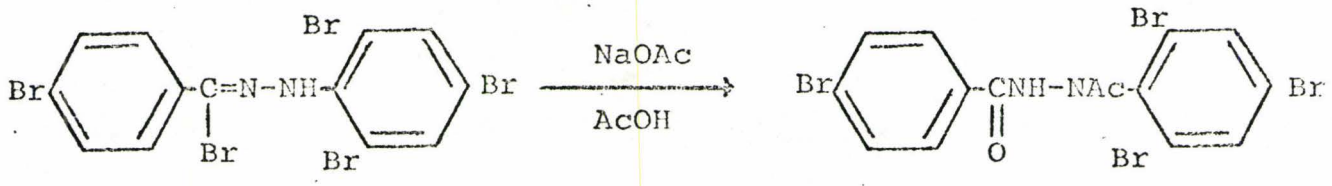


(43) (44)

I. REACTIONS OF THE HYDRAZIDIC HALIDES

i. With Acetate Ion

The reaction of (3) with sodium acetate in acetic acid has been shown to give (10)[2], and a more recent examination of the acetolysis reaction has provided a mechanism involving O→N acetyl migration in the intermediate inisolable acetoxy compound (9)[12]. Since (45) was also shown to give (46) under the same conditions it was concluded that steric factors were



(45) (46)

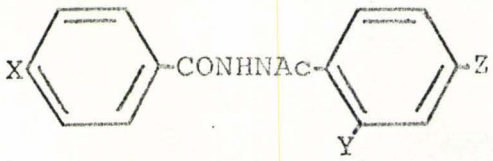
not critical in the acetyl transfer.

In the present study a series of hydrazidic halides was treated with five equivalents of anhydrous sodium acetate in refluxing acetic acid for two hours. The results are summarised in Table II. The products were characterised by analysis and their infrared spectra. Only N-α-bromobenzylidene-N'-(2-bromo-4-carboethoxyphenyl)hydrazine (48)[37] failed to give a high yield of acetylhydrazide but rather gave 59% of the unacetylated hydrazide (55). The electron-withdrawing ester function presumably decreased the nucleophilicity of the nitrogen sufficiently to prevent acetyl transfer in the intermediate acetoxycompound (56). Reaction of (56) with acetic acid or

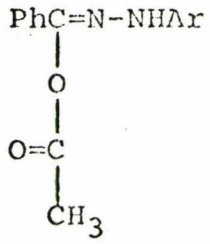
Table II. Preparation of the Acetylhydrazides

Hydrazidic Halide No.	SUBSTITUENTS			ACETYLHYDRAZIDE	
	X	Y	Z	No.	Yield%
3	H	Br	Br	50	87
41	Cl	Br	Br	51	86
47	OMe	Br	Br	52	88
48	H	Br	COOEt	53	0*
49	H	F	Br	54	86

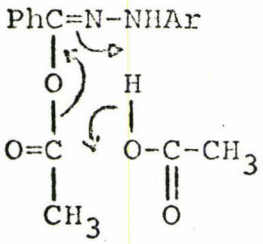
*59% of (unacetylated) hydrazide isolated



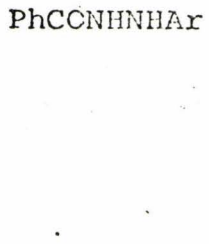
acetate ion would result in the formation of (55) through the transition state (57). Attempts to acetylate (55) with acetic



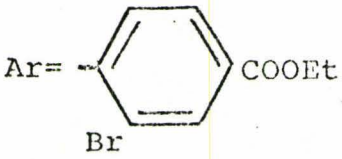
(56)



(57)

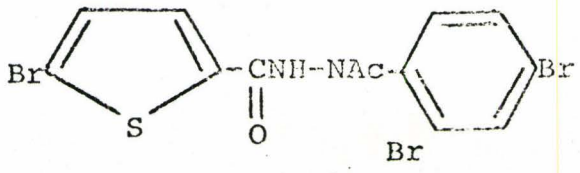


(55)

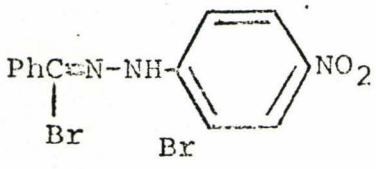


anhydride in either triethylamine or acetic acid were unsuccessful and served to emphasise the decreased nucleophilicity of the nitrogen in (56).

Sodium acetate and (42) under the standard reaction conditions yielded a compound with spectroscopic properties consistent with the acetylhydrazide structure (58). However analytical



(58)

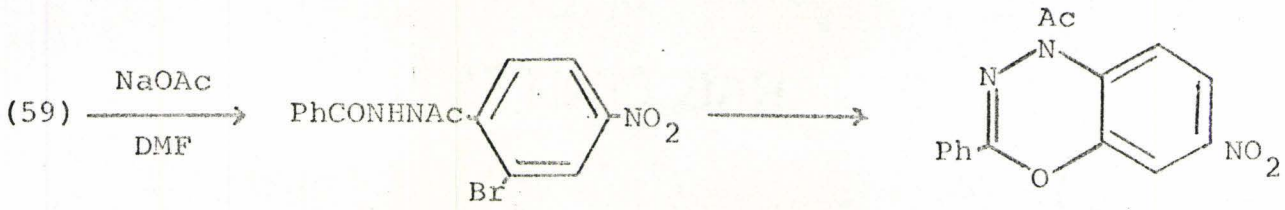


(59)

results were repeatedly inaccurate. The cyclisation of (58)

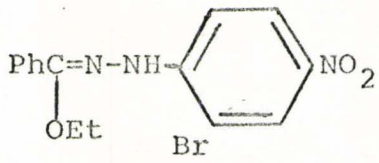
reported later in this thesis proceeded normally.

Dimethylformamide was chosen as the solvent for the reaction of N-α-bromobenzylidene-N'-(2-bromo-4-nitrophenyl)-hydrazine (59) with sodium acetate in order to increase the nucleophilicity of the nitrogen atom in question. When (59) and five equivalents of anhydrous sodium acetate were boiled together under reflux for twenty minutes, a 74% yield of 4-acetyl-7-nitro-2-phenyl-4H-benzo[1,3,4]oxadiazine (61) was produced, presumably via the acetylhydrazide (60). The cyclisation of similar acetylated hydrazides and the related thiohydrazides forms an important part of this thesis and will be discussed in more detail later.



(60) (61)

In an attempt to isolate (60), the reaction was repeated with a reflux time of only five minutes. The solution was immediately poured into dilute acetic acid solution and the yellow solid was filtered off. The crude product contained some of the benzoxadiazine (61) (t.l.c.). Crystallisation from ethanol-ethyl acetate however gave N-α-ethoxybenzylidene-N'-(2-bromo--4-nitrophenyl)hydrazine (62) in 74% yield. Since Aylward and Scott[38] had reported the preparation of (62) from the interaction



(62)

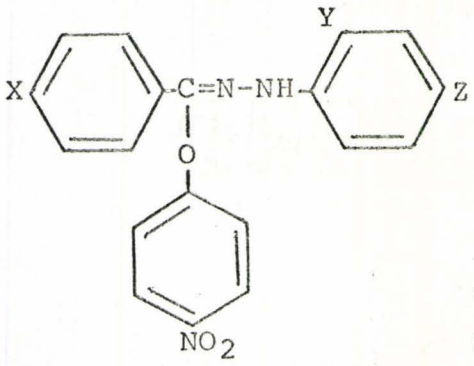
of sodium acetate and (59) in refluxing ethanol, it seemed likely that a similar reaction had occurred during the crystallisation procedure involving traces of sodium acetate and unreacted hydrazidic bromide. The presence of the benzoxadiazine (61) after only five minutes reaction time appeared to make the method unsuitable for the preparation of the acetylhydrazide (60).

ii. With Phenols

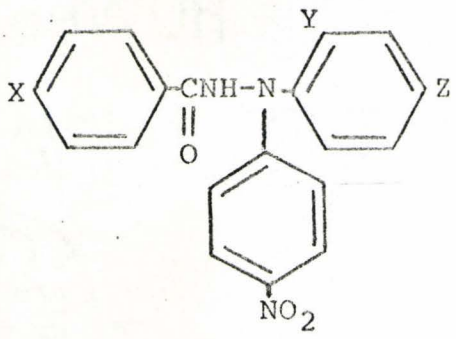
Since the O→N acetyl transfer in acetoxycompounds such as (9) was too fast for any general study of the reaction, a less labile migrating group was required. Phenol derivatives appeared an attractive alternative, since the electron-deficiency in the benzene ring, necessary for rearrangement, could be controlled by the choice of substituents. A rearrangement of this type, if it should occur, was recognised as an extension of the Smiles rearrangement (see Introduction).

For convenience the readily available nitrophenols were used in the preliminary study. Equivalent amounts of the hydrazidic bromide, p-nitrophenol and triethylamine were stirred

together in ethanol at room temperature for two hours. The results are summarised in Table III. In all cases studied, the initial product was the α-p-nitrophenoxy adduct of general structure (63). These adducts all rearranged to the corresponding hydrazides (64) in refluxing ethanol-triethylamine,

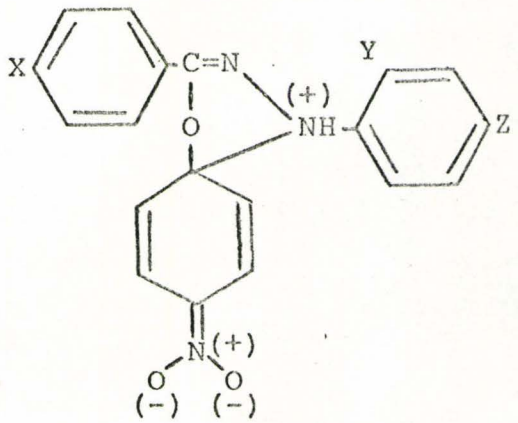


(63)



(64)

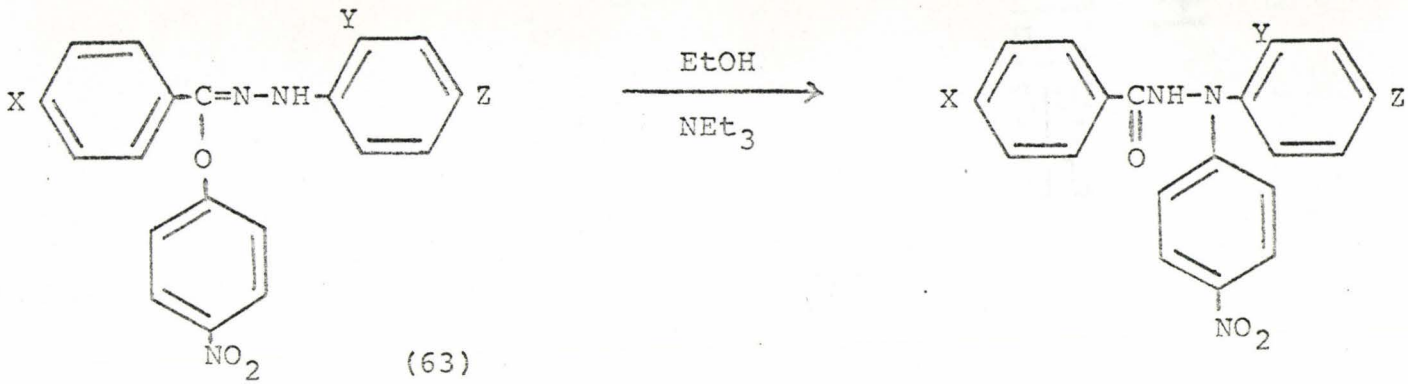
generally within a few minutes. The rearrangement presumably involves the five-membered transition-state (65). Compounds (63d) and (63f), which contained electron-attracting groups in



(65)

Table III. Reaction of Hydrazidic Halides with p-nitrophenol

Hydrazidic Halide No.	Substituents			p-Nitrophenoxy Adduct (63)		Hydrazide (64)		Time for Rearrangement hrs.
	X	Y	Z	No.	Yield%	No.	Yield%	
3	Br	Br	Br	63a	70	64a	69	0.25
47	OMe	Br	Br	63b	90	64b	82	0.25
41	Cl	Br	Br	63c	72	64c	64	0.25
48	H	Br	COOEt	63d	74	64d	62	2.0
49	H	F	Br	63e	90	64e	88	0.25
59	H	Br	NO_2	63f	83	64f	82	2.0



(63) (64)

the N-aryl ring, required longer reaction times for complete rearrangement, a fact which again reflected the decreased nucleophilicity of the nitrogen atoms in such compounds. Recent work has shown that these rearrangements were intramolecular[39]. The migration of the aryl group did not appear to be a thermal process since (63a) melted and solidified unchanged (t.l.c.).

The mass spectra of compounds (63a) and (64a), the main points of which are given in Table IV, proved interesting. Only the initial adduct (63a) lost the elements of p-nitrophenol on electron impact, a fact that is in agreement with the proposed structures. During later work with p-nitrothiophenoxy adducts and related compounds, this observation proved to be an invaluable aid in the assignment of structures.

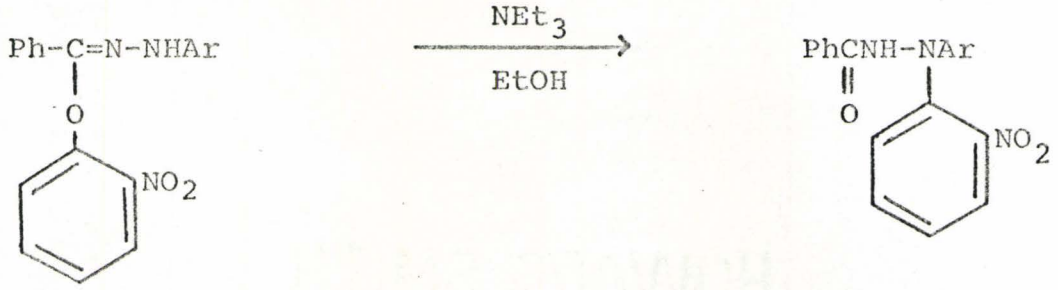
Examination of the breakdown of (63a) showed that the peaks at m/e values 384 and 370 were assignable only after allowing for an O→N aryl transfer. There was no evidence for reverse aryl migration in (64a).

For the first time these examples provided indirect evidence for the intermediate acetoxycompound (9) proposed by Burgess and Gibson. Presumably the heavier and less polar p-nitrophenoxy group provides the stabilisation necessary for the isolation of the intermediate aryloxy compounds.

Since a p-nitro substituent appeared to provide the necessary activation for the rearrangement, it remained to determine if other phenols would react similarly. o-Nitrophenol and (3) yielded initially the α-o-nitrophenoxycompound (66)

Table IV. Mass Spectral Data for (63a) and (64a)

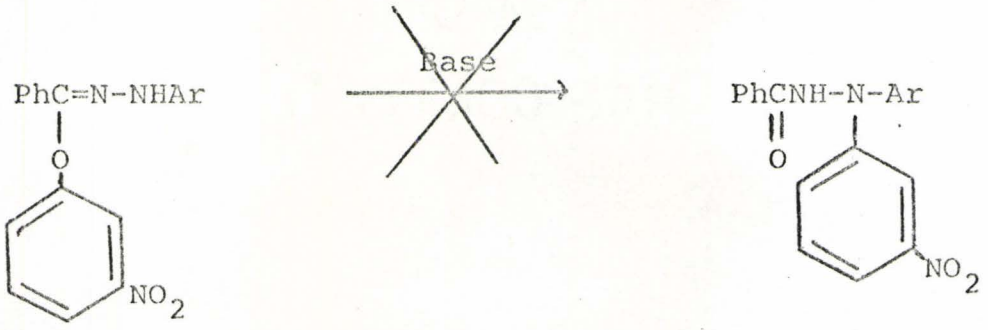
m/e	Structural Assignment	Intensity % (63a)	Intensity % (64a)
489	Parent ion	40.8	35.2
472	2 Br	1.8	5.9
410	P-Br	5.4	12
409	1 Br	2.7	-
384	P-PhCO	6.4	5.9
370	P-PhCON	4.5	65
354	2 Br	-	6
350	P-$NO_2C_6H_4OH$	3.2	-
340	2 Br	13.6	100
338	1 Br	8.1	23.6
324	2 Br	-	6
290	2 Br	-	6
272	1 Br	8.1	-
260	2 Br	-	35
249	$Br_2C_6H_3NH_2$	-	12
248	$Br_2C_6H_3NH$	100	-
245	1 Br	-	35



(66) (67)

Ar=2,4-$Br_2C_6H_3$-

which rearranged smoothly to give the hydrazide (67). However, the initial adduct (68) from the reaction of (3) and m-nitrophenol failed to rearrange when it was treated with base in the usual way.

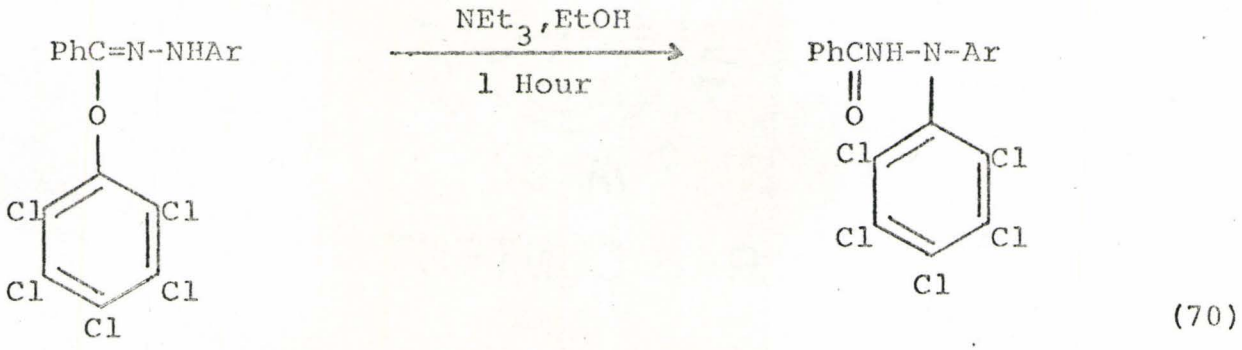


(68)

More drastic treatment using triethylamine in dimethylformamide gave only tarry material with no evidence of rearrangement. Thus the activation for the aryl transfer appeared critical, the reduced electron-withdrawing capabilities of a meta-nitro group[40] being insufficient to cause rearrangement.

The reaction of pentachlorophenol and (3) to give (69)

provided an opportunity to investigate the electron-deficiency of a polychlorinated phenyl ring. The initial adduct (69) rearranged on treatment with triethylamine in the usual way for one hour, but the product formulated as the hydrazide (70), could not be obtained analytically pure. However (70) exhibited spectral properties consistent with the proposed structure and a molecular weight determination by measurement of the vapour pressure of acetone gave a result well within experimental error.



(69)

(70)

Ar=2,4-$Br_2C_6H_3$-

Phenol, 2,4-dinitrophenol and 2,4,6-trinitrophenol all failed to give initial products with (3), in the presence of triethylamine. Phenol presumably does not form phenoxide ion under these conditions, whereas the anions from the polynitrophenols are not sufficiently nucleophilic since extensive delocalisation of the negative charge is possible.

During the latter part of this research it became important to determine if p-nitrophenoxy compounds could be hydrolysed under acidic conditions. Accordingly (63a) was

dissolved in benzene and concentrated hydrochloric acid was added to form a two-phase system. After heating the mixture for one hour on a steam-bath, no reaction was observed. The implication of this result is discussed in Section II(v).

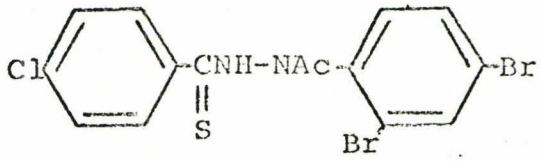
Initially the hydrolysis of hydrazides such as (64) looked promising as a method for the preparation of N,N-diarylhydrazines, since hot aqueous acid slowly hydrolyses hydrazides to carboxylic acids and hydrazine salts. Although such hydrolysis is usually successful with unsubstituted hydrazides, there was a report to suggest that substitution may greatly retard it[41]. In the event (67) remained unchanged by either ethanolic hydrochloric acid or ethanolic sodium ethoxide under conditions where (10) was hydrolysed completely[2].

iii. With Thioacetate Ion

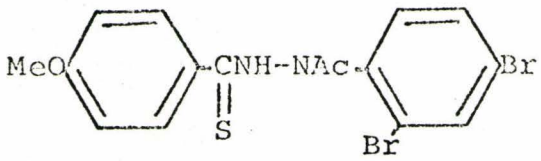
The conversion of hydrazidic halides into acetylthiohydrazides by reaction with thioacetate ion was recently realised by Callaghan and Gibson[17]. These workers assigned the structure of the major product of the reaction of (3) and two equivalents of potassium thioacetate at room temperature as (15) on the basis of spectroscopic evidence. The products was thought to result from S→N acetyl transfer in the intermediate thioacetoxy compound (17) in a manner analogous to the O→N acetyl transfer which occurs during the acetolysis of hydrazidic halides[12,42].

The formation of (15) by this method was shown to be accompanied by a small amount of the hydrazidic sulfide (16).

In order to eliminate this product in the present work, the hydrazidic halides employed were treated with only one equivalent of sodium thioacetate at room temperature in either ethanol or acetonitrile. Using this procedure (15) was obtained from the reaction of (3) and thioacetate ion in 75% yield (previously 58%). Similarly the hydrazidic bromide (41) gave the corresponding acetylthiohydrazide (71) in 84% yield. However



(71)



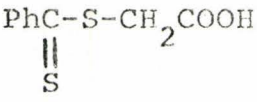
(72)

N-α-bromo-p-methoxybenzylidene-N'-(2,4-dibromophenyl)hydrazine (47) and thioacetate ion failed to react in either ethanol or acetonitrile. The thiohydrazide (72) was eventually isolated when dimethylformamide was used as solvent, but it appeared to be thermally unstable and analysis figures were repeatedly inaccurate. Callaghan and Gibson had noted that certain acetylthiohydrazides were unstable, and in an attempt to obtain molecular weights they had subjected their compounds to fragmentation in an M.S. 902 spectrometer. In all cases the weak parent ion lost water to give a strong radical-ion absorption. Examination of the mass spectrum of (72) showed the absence of a parent ion but the presenceof a strong radical-ion (m/e 434) corresponding

to loss of water. Further the breakdown pattern of (72) was consistent with the proposed structure.

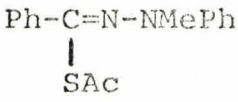
The decreased reactivity of hydrazidic bromide (47) towards thioacetate ion may be explained by electronic effects. The ease of addition of a nucleophile to the α-position of (47) would be reduced by the electron-donating capabilities of the p-methoxy substituent in the C-phenyl ring.

In order to investigate the properties of α-thioacetoxy compounds, it appeared necessary to block the nitrogen atom so that acetyl transfer could not take place. N-Thiobenzoyl-N'--methyl-N'-phenylhydrazine (74) was prepared by the reaction of carboxymethyldithiobenzoate[43] (73) with N-methyl-N-phenylhydrazine. Reaction of (74) with acetic anhydride in triethylamine was expected to give the corresponding thioacetoxy compound



(73)

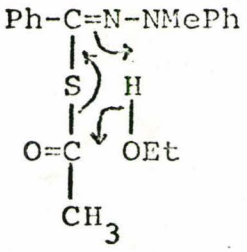
(74)



(75)

(75) and the infrared spectrum of the product was in agreement with this structure. Thus the carbonyl stretching frequency ($1710cm^{-1}$) was different from that in (15) ($1665cm^{-1}$). All attempts to obtain solid material from the yellow gummy product failed, although it appeared to be pure (t.l.c.). The addition of ethanol immediately produced a reaction, and the thiohydrazide (74) was recovered in a manner presumed to involve species such as

(76). Thus, just as had been observed with hydrazidic bromide (48) in the acetolysis reaction, the prevention of the intramolecular acetyl transfer had produced a compound which was



(76)

open to facile deacetylation by external nucleophiles.

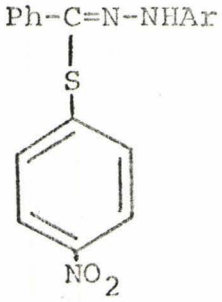
This was the first chemical evidence to suggest that Callaghan and Gibson had indeed assigned the correct structure to their product (15), since this compound did not undergo deacetylation in ethanol.

iv. With p-Nitrothiophenol

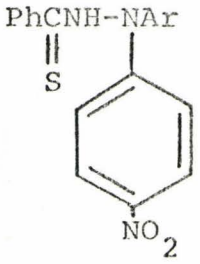
Since the reaction of hydrazidic halides with p-nitrophenol had been useful in the investigation of the O→N aryl migration, it was thought that the use of p-nitrothiophenol would permit a study of the analogous S→N aryl transfer. However identification of the products was seen at the outset to be a major problem, since there would be no carbonyl stretching frequency in their infrared spectra to denote the rearrangement. Recent evidence has suggested that thioamides and related compounds do not have an infrared absorption assignable to the

thiocarbonyl stretching frequency[44].

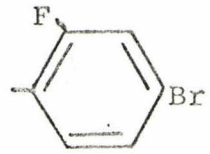
The reaction of N-α-bromobenzylidene-N'-(4-bromo-2--fluorophenyl)hydrazine (49), triethylamine, and two equivalents of p-nitrothiophenol has been reported to give (77) rather than the isomeric thiohydrazide (78)[17]. No hydrazidic sulfide was detected. The assignment of the structure was based almost entirely on ultra-violet data and was admitted to be speculative.



(77)



(78)

Ar = 

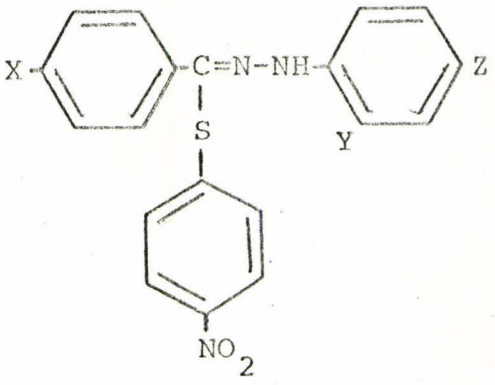
However prior to the present research the mass spectrum of (77) was examined and a peak (m/e 291) corresponding to loss of p-nitrothiophenol from the parent ion was found. This radical-ion must have arisen from (77) rather than (78), unless a reverse aryl migration in (78) is proposed. Such a process was shown later in the present work to be unlikely.

A series of hydrazidic halides was treated with equivalent amounts of p-nitrothiophenol and triethylamine. The results are summarised in Table V. Within the limits of the experiment the change of the α-halogen from bromine to chlorine in N-α-chloro-

Table V. Preparation of the p-Nitrothiophenoxy Adducts

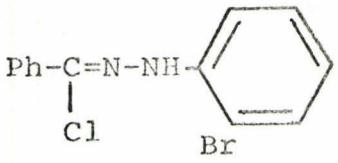
Hydrazidic Halide No.	Substituents			p-Nitrothiophenoxy Adduct	
	X	Y	Z	No.	Yield %
47	OMe	Br	Br	81a	57
41	Cl	Br	Br	81b	63
79	H	Br	H	81c	62
80	H	Br	SCN	81d	0*

*18% of (81c) isolated



(81)

benzylidene-N'-(2-bromophenyl)hydrazine[37] (79) did not affect the yield of the initial product. All of the compounds are



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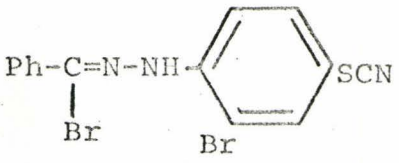
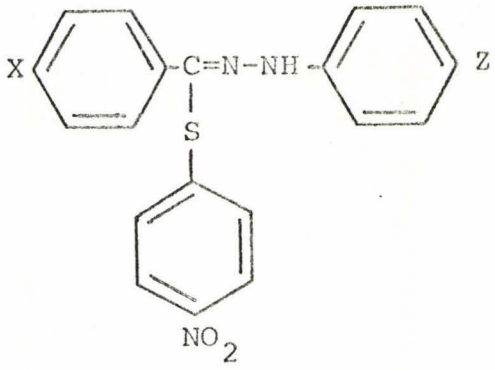


(80)

believed to be p-nitrothiophenoxy adducts of general structure (81). One curious reaction remains unexplained. When (80)[45]



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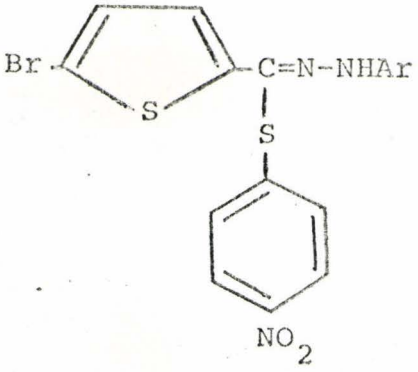


(82)

Ar = $2,4Br_2C_6H_3$-

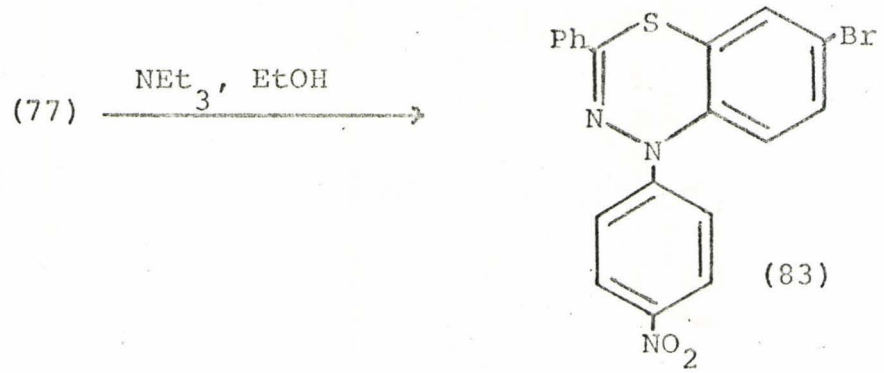
and p-nitrothiophenoxide ion were stirred together in ethanol there was evolved during the first hour of the reaction a gas with the smell of hydrogen cyanide. Work-up after two hours gave N-α-p-nitrothiophenoxybenzylidene-N'-(2-bromophenyl)-hydrazine (81c) (18%) as the only characterisable product. The identity of this product was in no doubt, since it was

identical in all respects with the product from the reaction of (79) and p-nitrothiophenoxide ion. Further the hydrazidic bromide (80) was analytically pure with spectral properties consistent with its structure. In some curious way p-nitrothiophenoxide ion had reduced the thiocyanato group to hydrogen.

An examination of the mass spectra of (81a) and (81c) showed that both compounds lost the elements of p-nitrothiophenol from the parent ion, in agreement with the proposed structures.

The hydrazidic bromide (42) and p-nitrothiophenoxide ion yielded an analogous compound, formulated as (82) in 55% yield. Once again, loss of p-nitrothiophenol from the parent ion was an important feature of the mass spectrum.

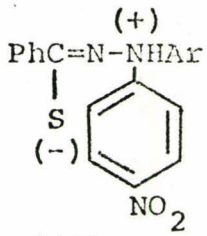
Treatment of (77) with triethylamine in refluxing ethanol had previously been reported to produce the benzothiadiazine (83) via an S→N transfer of the p-nitrophenyl group, followed by the displacement of the 2-fluorine substituent by sulfur[17]. As with the S→N acetyl transfer in thioacetoxy



(83)

compounds, the process could be synchronous or could occur via

the intermediate zwitterionic form of the thiohydrazide (84). In the event no evidence for (84) was found. Thus the treatment of the p-nitrothiophenoxy adducts prepared in the present



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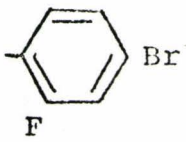
Ar = 

study was not expected to yield the corresponding thiohydrazides in base. However their conversion into benzothiadiazines was seen as evidence for an S→N aryl transfer and is described later in this thesis.

In connection with later work (81b) was dissolved in benzene and treated with concentrated hydrochloric acid in the same way as described earlier for (63a). After one hour there was no reaction and the implication of this result is discussed later.

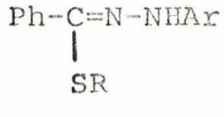
v. With Heterocyclic Thiols

Prior to this work there had been several reports of Smiles rearrangements involving activation by heteroaromatic ring systems. The majority of these reports were concerned with pyridine derivatives, although quinoline[31] and s-triazine[32] systems have been shown to undergo similar reactions.

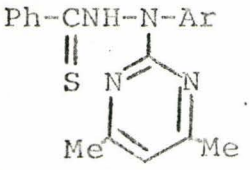
The use of heterocyclic thiols in the present work

appeared to be an attractive alternative to p-nitrothiophenol, since the S→N migration of the heterocyclic ring would presumably be both acid and base catalysed. Therefore under acidic conditions where benzothiadiazine formation presumably would not occur, the intermediate thiohydrazide might be isolated.

The thiols chosen for the study were 4,6-dimethyl-2--mercaptopyrimidine, 1-phenyl-5-mercapto-1H-tetrazole, 2-mercapto--5-nitropyridine, 4-methyl-2-mercaptoquinoline[46], 2-mercaptopyridine[46] and 2-mercaptoquinoxaline, and the results of the reactions of each of these with (3) at room temperature are summarised in Table VI. All of the compounds were assigned the unrearranged structure (85).



Ar = 2,4-$Br_2C_6H_3$-



(85) (86)

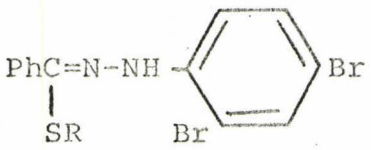
When the initial adducts (85) were dissolved in benzene and treated with concentrated hydrochloric acid at 100° only (85a) gave any rearranged product. The bright yellow N-thiobenzoyl-N'-(4,6-dimethyl-2-pyrimidyl)-N'-(2,4-dibromophenyl)-hydrazine (86) was obtained after one hour. For the first time both isomers involved in an S→N migration of an electron-deficient group had been isolated. An investigation of the spectral characteristics of (85a) and (86) was seen as a means

Table VI. Preparation of the Heterocyclic Thiol Adducts

Substituent R	Compound No.	Yield %	NH Position in p.m.r. Spectrum
4,6-dimethyl-2-mercapto-pyrimidyl	85a	75	9.15*δ
1-phenyl-5-mercapto-1H--tetrazolyl	85b	89	9.05δ
2-mercapto-5-nitropyridyl	85c	83	9.25**δ
2-mercaptoquinoxalyl	85d	63	9.18δ
2-mercaptopyridyl	85e	76	
2-mercapto-4-methyl-quinolyl	85f	73	

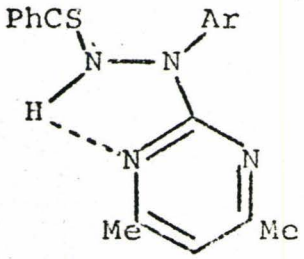
* NH signal of rearranged compound (86) at 9.7 δ

**NH signal of rearranged compound (93) at 9.9 δ

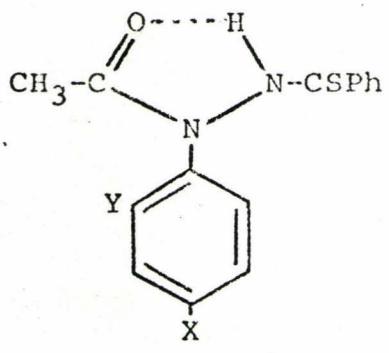


of identifying either initial or rearranged structures without any ambiguity.

The ultra-violet and infrared spectra of the compounds were complex and not very helpful. However the thioamide-type structure of (86) required a more acidic hydrogen bound to nitrogen. In fact a medium-strong band at 3340cm^{-1} was found in the infrared spectrum of (86), while a weak absorption at 3280cm^{-1} was present in the infrared spectrum of (85a). However the position of the proton bonded to nitrogen in the nuclear magnetic resonance spectra of the compounds appeared to be more promising. The signal for the N-H proton in (85a) occurred at 9.15δ whilst that in (86) had shifted to 9.7δ in accordance with the more acidic nature of the proton. The position of the N-H signal in (85a) was not expected to differ greatly from that in the p-nitrothiophenoxy compounds or in the other initial adducts of the heterocyclic thiols. This was found to be the case (Tables VI and VII). However in the thiohydrazide structure (86) the possibility of hydrogen bonding (87) was noted and thus the



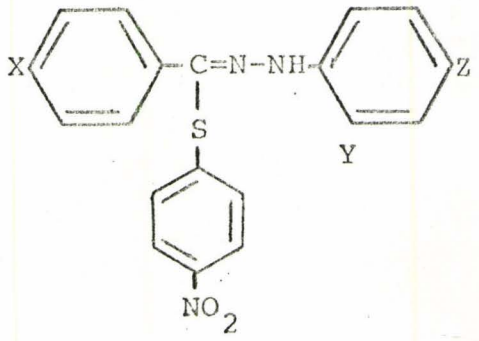
(87)



(88)

Table VII. Position of the N-H Proton Signal in the p.m.r. Spectra of the p-Nitrothiophenoxy Adducts (81)

Substituents			Position of N-H Signal (δ)	
X	Y	Z	p-nitrothiophenoxy Adduct	Hydrazidic Bromide
H	Br	Br	-	8.5
OMe	Br	Br	9.1	8.45
Cl	Br	Br	9.2	8.55
H	Br	H	9.25	-



(81)

position of the signal would depend on the nature of the heterocyclic ring.

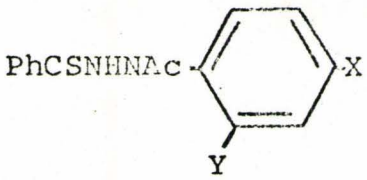
Similar hydrogen-bonding had been reported by Callaghan and Gibson[17] for a series of acetylated thiohydrazides. The results of their investigation, taken from the thesis presented by Callaghan are shown in Tables VIII and IX. To account for these observations, a strongly hydrogen-bonded structure was proposed, for which (88) seemed the most reasonable. Splitting of the methyl signal into a doublet can then be explained as due to hindered rotation about the Ar-N bond where bulky substituents such as Cl, Br or I occupy the 2-position. Each methyl peak would be associated with one or other of the N-H peaks in two major conformers. The 2-F appears to be the limiting case for free rotation at 35°, since the 2,4-difluoroacetylthiohydrazide showed splitting, while the 2-fluoro-4-iodo compound did not under the same conditions (a mesomeric effect may be involved to give some double-bond character to the Ar-N bond).

The 2,4-difluoroacetylthiohydrazide was studied in deuterochloroform at various temperatures in the range 35.5 to -70° (Table IX). The methyl doublet was observed to coalesce ar ca. -70° to a single sharp peak. The fact that neither of the peaks disappeared suggested that the single peak at -70° was not due to the more stable conformer, but more likely to different chemical shift variations with temperature of the two conformers, the shift values coinciding at that temperature.

In view of the uncertainty of the position of the N-H

Table VIII. ^{1}H Nuclear Magnetic Resonance Spectra in Deuterochloroform at 35.5°, 60Mc/S for Substituted Acetylthiohydrazides *

Substituents X	Y	N-H Proton (δ)	Aromatic Protons (δ)	Methyl Protons (δ)
H	H	7.9-7.21 (11)		2.01
I	F	7.85-7.1 (9)		2.1
F	F	?	7.93-6.64 (8)	2.22 and 2.02
I	Cl	9.9 and 9.54	7.93-7.26 (8)	2.29 and 1.95
Br	Br	9.94 and 9.56	8.19-7.25 (8)	2.30 and 1.94
Cl	I	9.96 and 9.53	8.25-7.24 (8)	2.31 and 1.92



*Taken from reference 17

Table IX. Variation of Methyl Absorption with Temperature for N-thiobenzoyl-N'--acetyl-N'-(2,4-fluorophenyl)hydrazine in Deuterochloroform*

Temperature (°C)	Methyl Proton Absorption (δ)		Separation (Hz.)
35.5	2.22	2.02	12
10	2.19	1.99	12
0	2.22	2.03	11.4
-10	2.21	2.04	10.2
-20	2.18	2.05	7.8
-40	2.14	2.05	5.4
-60	-		3.5
-70	-		ca.0

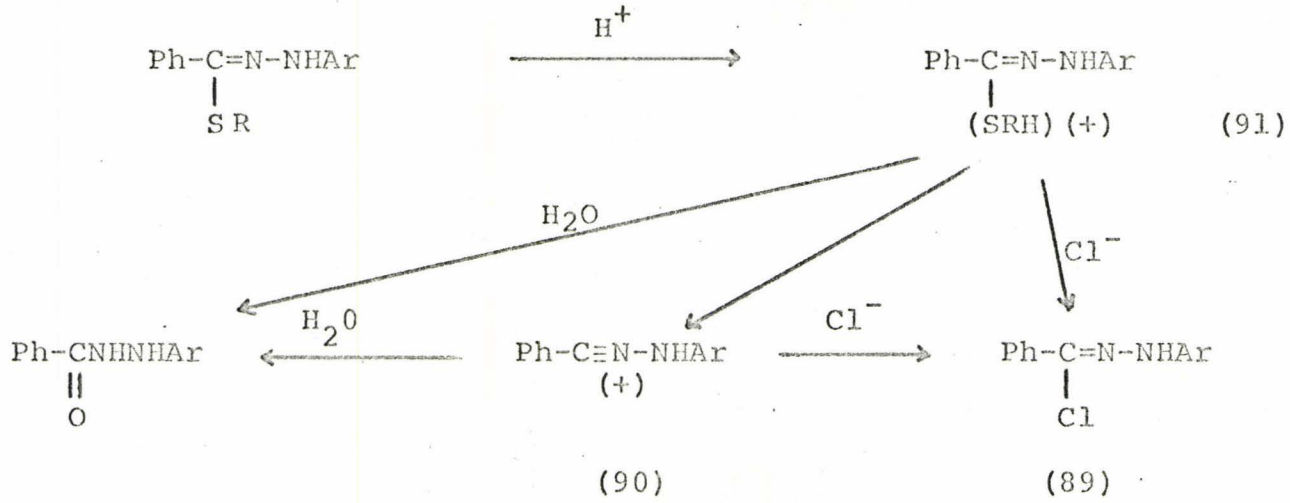
*Taken from reference 17

signal in thiohydrazides because of the possibility of hydrogen-bonding, it became clear that no unambiguous structural assignment could be made by this means alone. However the mass spectra of compounds (85a) and (86) provided more concrete evidence. Both compounds gave molecular ions but only (85a) gave a peak (m/e 350) corresponding to the loss of 4,6-dimethyl-2-mercapto-pyrimidine. The thiohydrazide (86) could only give such a peak if a reverse aryl migration occurred. Further the mass spectra of (85b,c,d) all exhibited a peak corresponding to loss of the heterocyclic thiol from the parent ion. It was thus concluded that the assignment of the unrearranged structures for these compounds was correct.

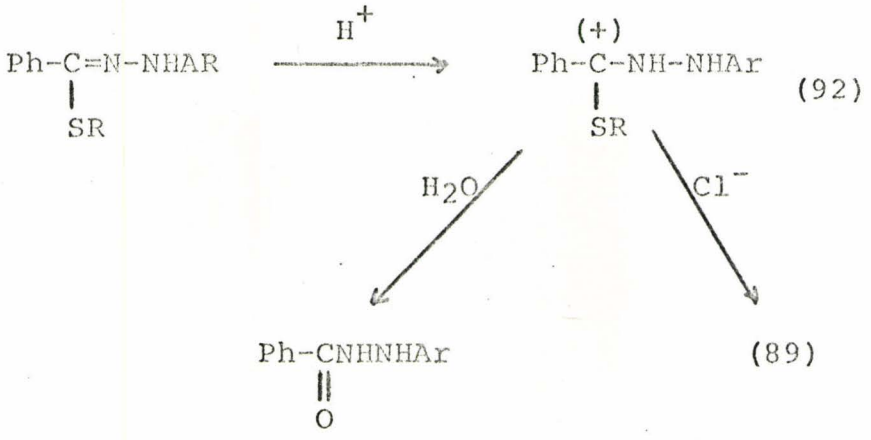
It was noted earlier that only (85a) gave any rearrangement product in acid. However three of the other compounds gave some reaction, whilst (85e) and (85f) were unaffected under the conditions employed.

The tetrazolyl adduct (85b) was dissolved in benzene and treated with concentrated hydrochloric acid for one hour in such a way as to keep the mixing of the two layers to a minimum. The free thiol, 1-phenyl-5-mercapto-1H-tetrazole (60%) and N-α-chlorobenzylidene-N'-(2,4-dibromophenyl)hydrazine (89) (41%) were isolated and N-benzoyl-N'-(2,4-dibromophenyl)hydrazine was detected. These products are thought to result from reaction scheme (vi). A similar reaction scheme was envisaged for the reaction of (85d) with acid, since (89) was obtained in 13% yield. No 2-mercaptoquinoxaline was isolated from this reaction. Unless

SCHEME (vi)



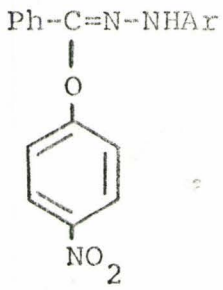
SCHEME (vii)



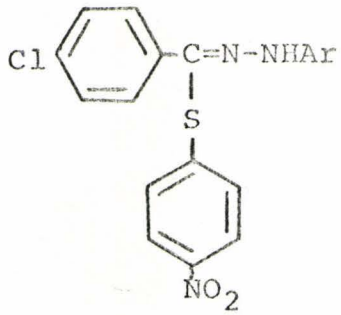
Ar = $2,4\text{-}Br_2C_6H_3^-$

an acid catalysed N→S shift of the aryl group is envisaged these products confirm the structural assignments of (85b) and (85d).

It should be noted that scheme (vi) represents a simplified version of the reaction, since reversible protonation will occur at all possible sites in the molecule. If steric factors are unimportant, the loss of (SRH) must be faster than the rearrangement step. The attack of an external nucleophile (i.e. Cl^- or H_2O) on the protonated species (91) would lead to products. Ionisation of (91) to give the relatively stable cation (90) (see Introduction) is also possible. Protonation of the benzylidene nitrogen to give (92) would also lead to products as shown in scheme (vii). However (63a) and (81b) were unaffected by acid under the same conditions, although if scheme (vii) were a major reaction pathway then some hydrolysis would be expected.



(63a)

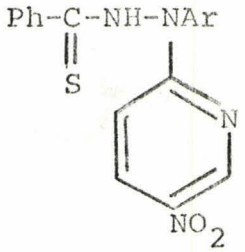


(81b)

Ar=2,4-$Br_2C_6H_3$

The competition between the two possible reaction modes, hydrolysis and rearrangement, must be controlled by the electron-

deficiency of the heterocyclic ring which makes the (SRH) species a good leaving group. In view of this, the action of acid on the nitropyridyl adduct (85c) was expected to give mostly (89) with little or no rearrangement. In the event, a yellow gum was obtained which appeared to contain at least eight components. However no (89) was found in the product and the p.m.r. spectrum favoured rearrangement. Thus the presence of an exchangeable proton at 9.9δ suggested that the thiohydrazide (93) was present. However no pure solid material could be obtained from the product.



Ar=2,4-$Br_2C_6H_3$-

(93)

The action of base on compounds (85a-f) is described later in this thesis.

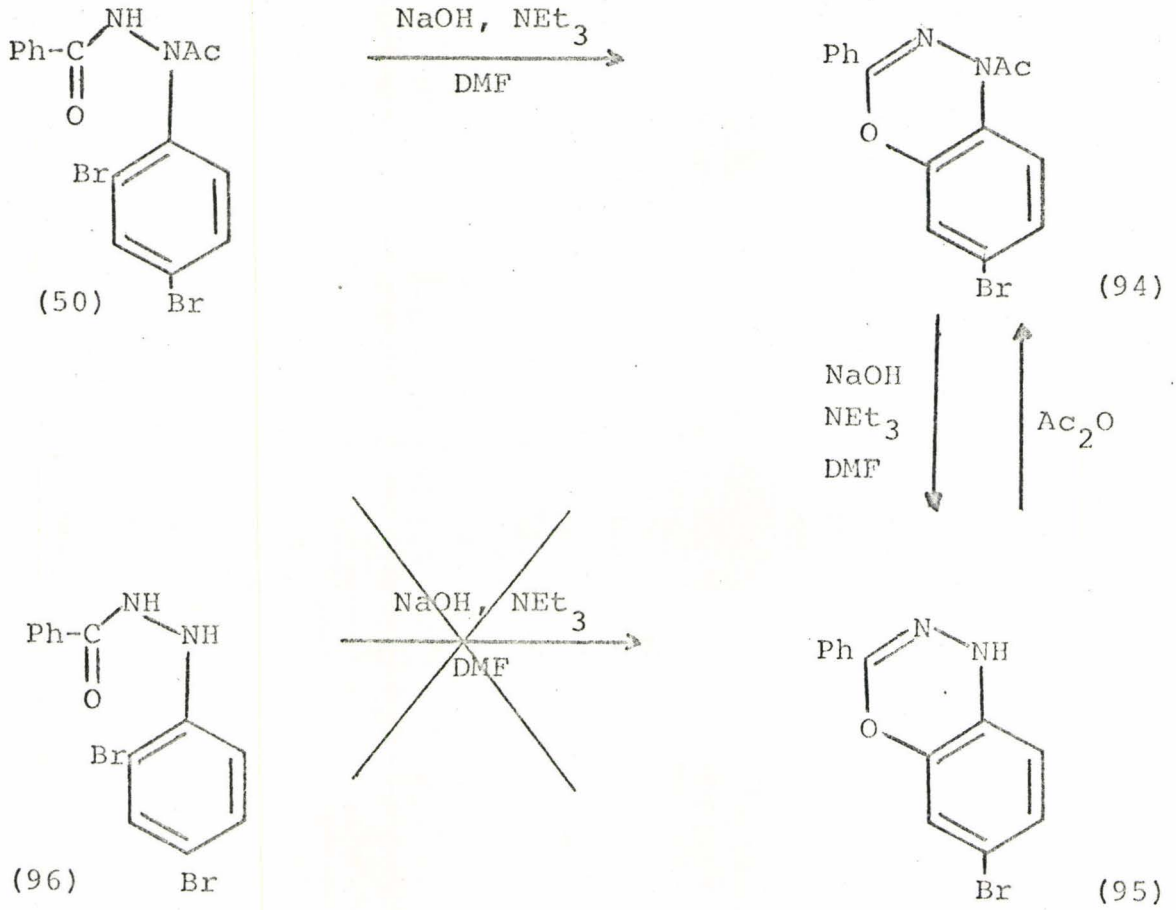
II. PREPARATION OF THE OXADIAZINES

i. Cyclisation of N-Aroyl-N'-acetyl-N'-arylhydrazines

The observation that the interaction of (59) with sodium acetate in dimethylformamide had yielded the benzoxadiazine (61) in reasonable yield, prompted an investigation into the reaction. Initially there appeared to be two possible mechanisms, one involving an intramolecular nucleophilic attack by oxygen on the 2-position of the halogenated ring, and the other via a benzyne-type intermediate. The former did not look too promising, since an m-nitro substituent is not a powerful activating group[40] and hydrazides are not normally nucleophilic through oxygen[47]. However, a mechanism of this type would be analogous to that proposed by Callaghan and Gibson for the cyclisation of acetyl-thiohydrazides discussed earlier. In order to present evidence for either mechanism, it was important to determine the effect of substituents in the halogenated phenyl ring and the influence of the leaving group on the reaction. Further, it was necessary to determine the exact nature of the product, since the structure of (61) had been assigned initially by analogy with the acetyl-thiohydrazide to benzothiadiazine conversions.

Using triethylamine as the base the cyclisation of N-benzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (50) was attempted in both ethanol and dimethylformamide with no success. However reaction in dimethylformamide using both triethylamine and an equivalent of solid sodium hydroxide gave 7-bromo-2-phenyl--4H-benzo[1,3,4]oxadiazine (95) in 39% yield (Scheme viii), the

SCHEME (viii)

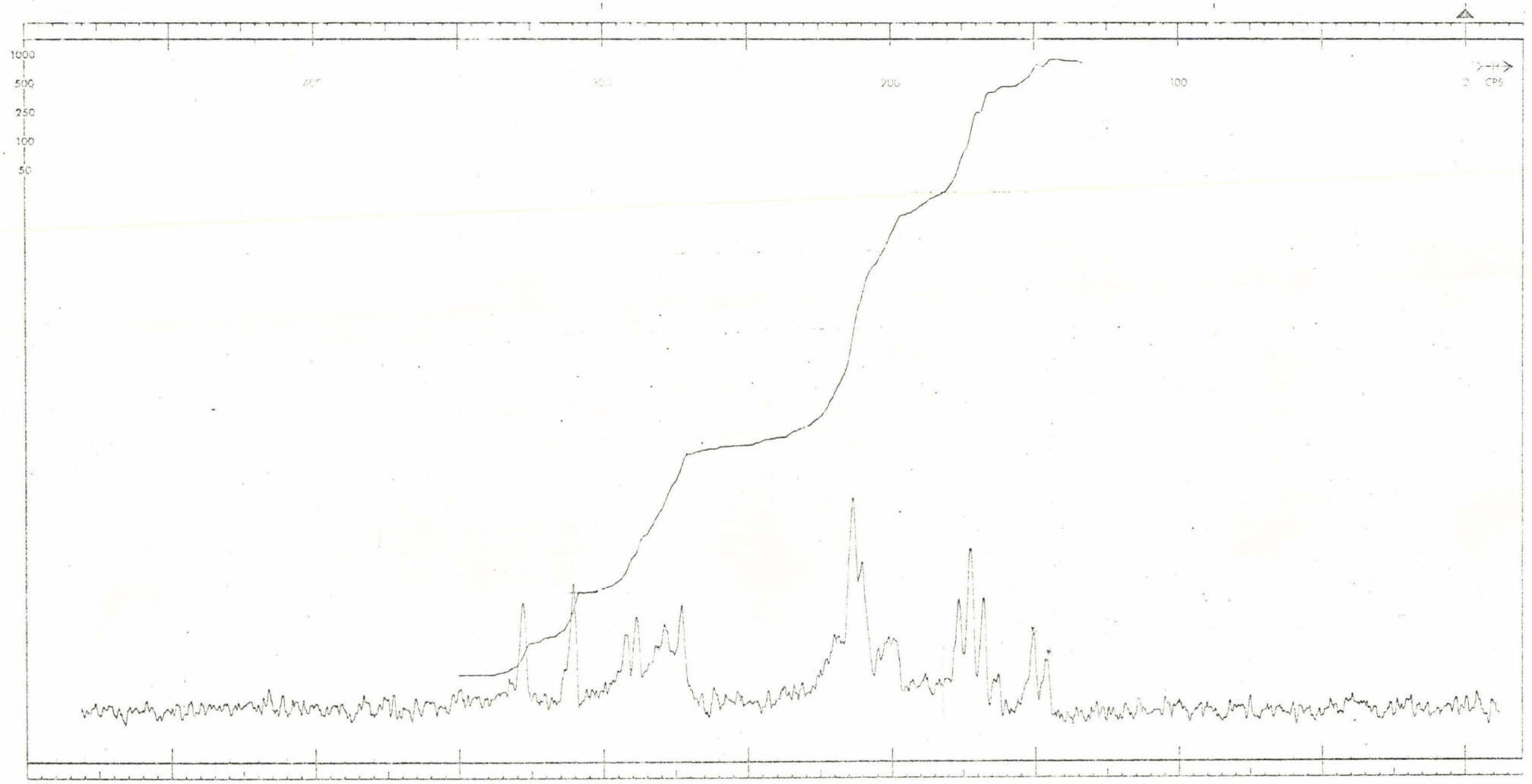


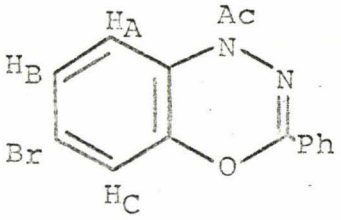
majority of the remaining material being unchanged (50). The reaction of (95) with acetic anhydride in acetic acid gave the acetyl derivative (94), which was shown to undergo deacetylation under the conditions of the cyclisation. Since N-benzoyl-N'--(2,4-dibromophenyl)hydrazine (96) did not cyclise under the same conditions, it was concluded that (94) was the initial product with deacetylation taking place after ring closure. Although no attempt was made to maximise the yield of (95) in this reaction, it was obvious that the reaction time was critical. After 2.5 hours at the reflux temperature 39% of (95) was obtained. After 6.0 hours the product was extremely tarry and only 11% was isolated. The product thus appeared to be destroyed on prolonged heating with base.

The aromatic region of the p.m.r. spectra of compounds (94) and (95) is reproduced in Figures (i) and (ii) respectively. Examination of these spectra shows that the structures assigned to these compounds are indeed correct. Thus in Figure (ii), the proton H_A is seen as the high field doublet as predicted by its position adjacent to nitrogen. In Figure (i), H_A has moved downfield considerably under the influence of the neighbouring acetyl group. Since H_A shows only ortho-coupling, the bromine substituent must occupy the 7-position as shown.

The cyclisation of N-benzoyl-N'-acetyl-N'-(4-bromo-2--fluorophenyl)hydrazine (54) was effected with triethylamine alone using dimethylformamide as the solvent. The acetyl group was not removed from the benzoxadiazine and (94) was obtained

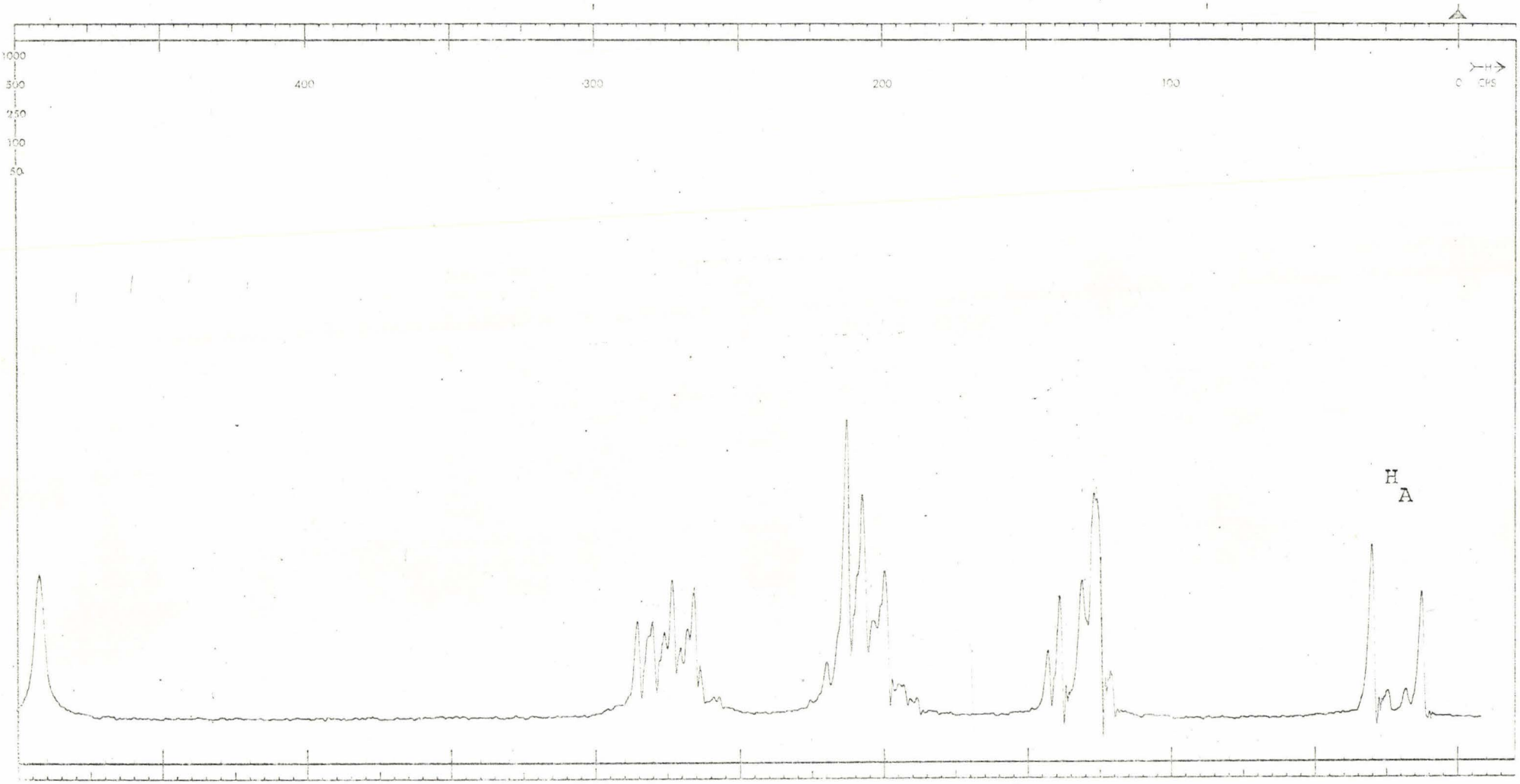
Figure (i): The Aromatic Region of the p.m.r. spectrum of (94)

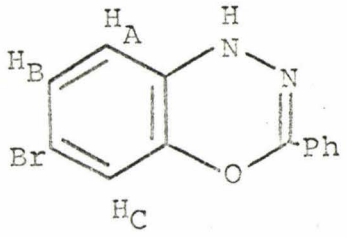




Solvent	DMSO d6
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	650 Hz.
Lock Signal	T.M.S.

Figure (ii): The Aromatic Region of the p.m.r. spectrum of (95)

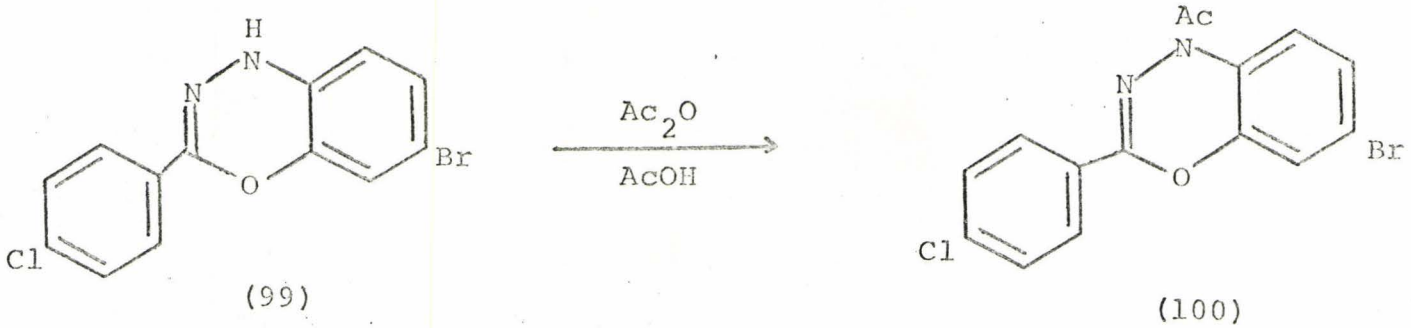




Solvent	DMSO d6
Frequency	100 MHz.
Sweep Width,	250 Hz.
Sweep Offset	640 Hz.
Lock Signal	T.M.S.

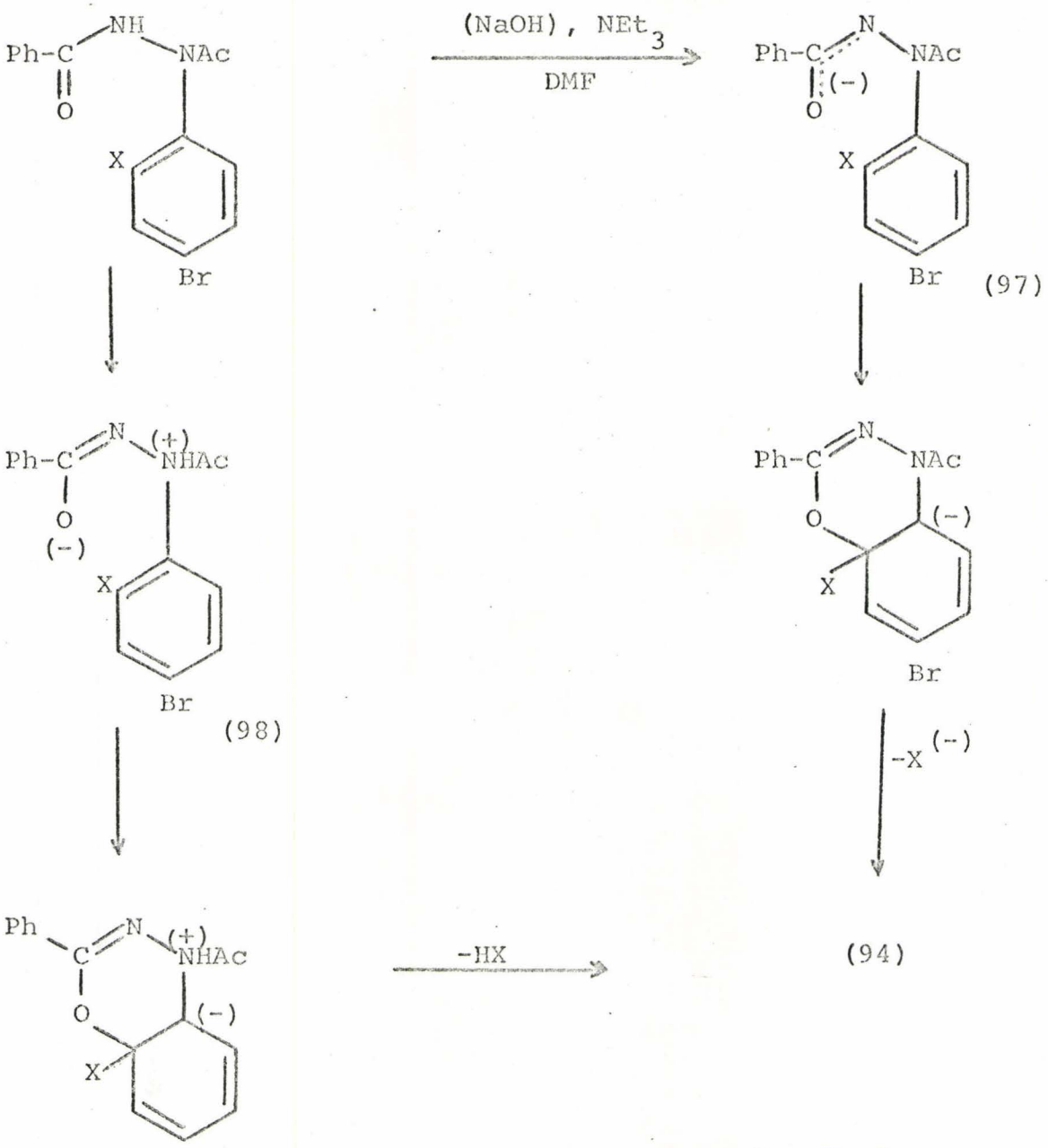
in 93% yield after 2.5 hours. This was the first indication that the cyclisation exhibited the characteristics of a nucleophilic aromatic substitution reaction, since fluorides are known to be converted to benzynes only with difficulty[48]. Further, the observation that fluorine is displaced more easily than bromine is usually made in nucleophilic aromatic substitution. Thus the cyclisation appeared to proceed via the anion (97) involving attack by negative oxygen on the 2-position of the halogenated ring as shown in Scheme (ix). Since the aromatic ring in (97) is not activated towards such an attack, it may be that the cyclisation proceeds through the zwitterionic form of the hydrazide (98). The concentration of such a species in the reaction medium would be very small, but the 2-halogen substituent in (98) would be activated towards nucleophilic attack.

The cyclisation of N-p-chlorobenzoyl-N'-acetyl-N'-(2,4--dibromophenyl)hydrazine (51) using both triethylamine and sodium hydroxide in dimethylformamide, gave the corresponding deacetylated benzoxadiazine (99) in 25% yield after 2.5 hours. The acetyl group was presumably lost after ring closure. Reaction of (99) with acetic anhydride gave the acetyl derivative (100).



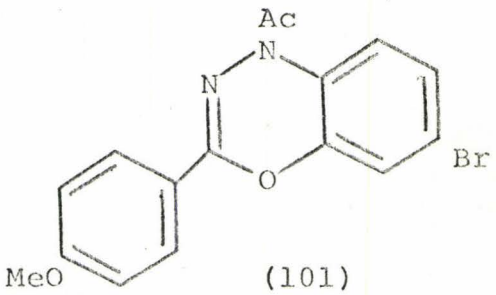
(99) (100)

SCHEME (ix)

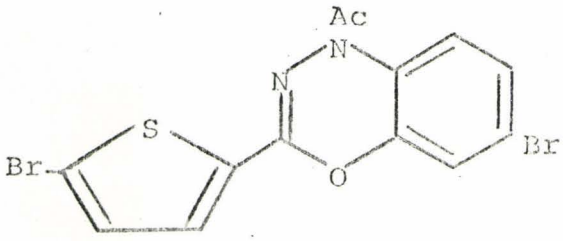


The cyclisation of (52) in the usual way gave a 45% yield of the acetylbenzoxadiazine (101). This compound resisted all attempts to deacetylate it under the basic conditions of the reaction. An attempted removal of the acetyl group in ethanolic hydrochloric acid gave only a dark brown oil. During later work it was found that all the benzoxadiazines prepared were sensitive to prolonged acidic treatment. Although the breakdown of these compounds in acid was not investigated in the present study, it is interesting to note that the corresponding thiadiazines were stable under the same conditions.

The cyclisation of (58) yielded a benzoxadiazine, formulated as (102) which also did not deacetylate under the basic reaction conditions. Since both (101) and (102) have



(101)



(102)

groups capable of electron-donation in the 2-position, it may be that in some curious way the acetyl group is less labile in such compounds. The low yield (6%) of (102) was attributed to the uncertain purity of the hydrazide (58), which could not be

obtained analytically pure.

Thus the reaction appears to be useful as a general synthesis for benzoxadiazines, although further work is required before removal of the acetyl group becomes a routine step for compounds where the cyclisation does not proceed with its loss. An examination of the literature shows only one other successful synthesis of the benzo[1,3,4]oxadiazine ring system.

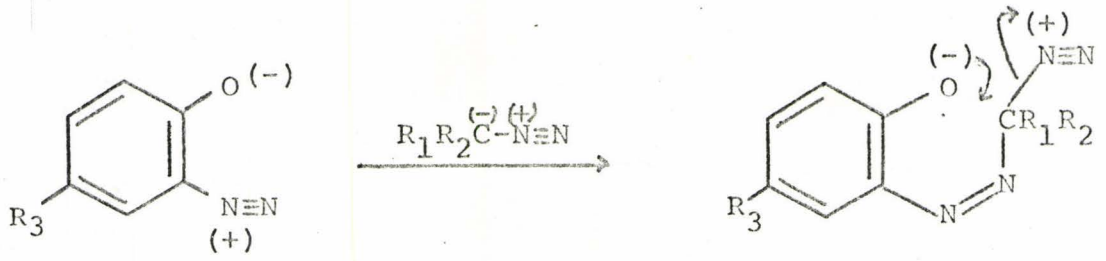
Huisgen et al[66] prepared the 2H-benzo[1,3,4]oxadiazine ring system by the reaction of substituted diazomethanes with diazonium compounds (Scheme x). When R_1 or R_2 was hydrogen, rearrangement to the isomeric 4H-benzo[1,3,4]oxadiazine was observed.

ii. Cyclisation of N-aroyl-N'-(p-nitrophenyl)-N'--arylhydrazines

The cyclisation of a series of hydrazides of general formula (64) was effected under standardised conditions which were as follows: the hydrazide and sodium hydroxide, in equivalent amounts, were dissolved in a mixture of dimethylformamide and triethylamine and the solution was boiled under reflux for 6 hours. The results are shown in Table X, and an examination of this table reveals several points.

The presence of electron-releasing groups in the C-phenyl ring or electron-withdrawing groups in the N-phenyl ring would be expected to aid the cyclisation. This appears to be the case, the only exception being that the carboethoxy group in (64d)

SCHEME (x)

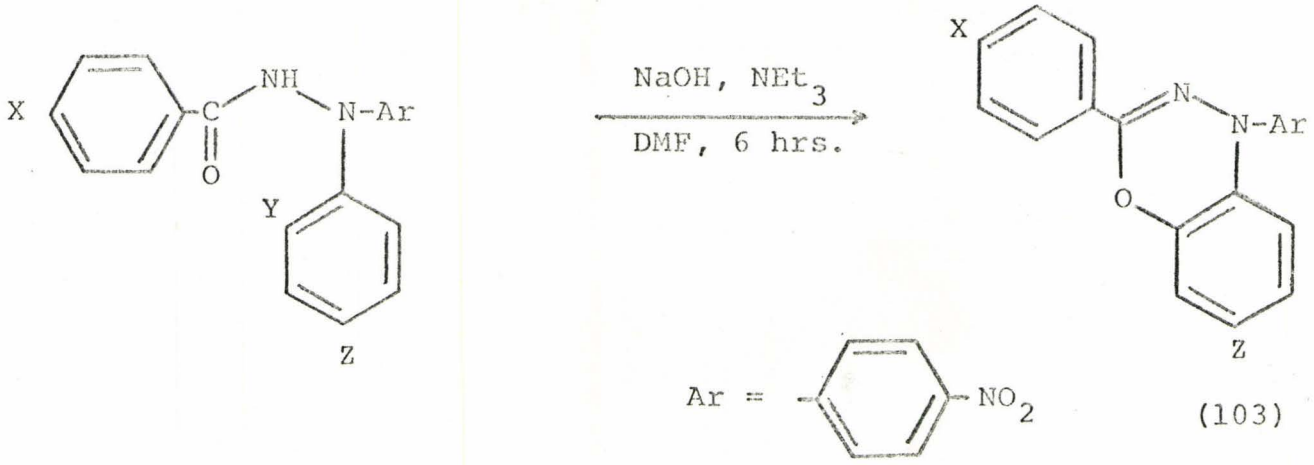


4H-Benzo[1,3,4]oxadiazine

2H-Benzo[1,3,4]oxadiazine

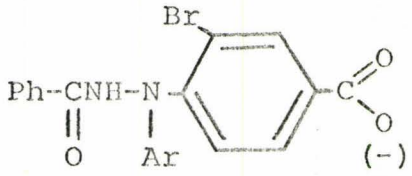
Table X. The Cyclisation of N-Aroyl-N'--p-Nitrophenyl-N'-Arylhydrazines

HYDRAZIDE				BENZOXADIAZINE	
	Substituents				
No.	X	Y	Z	No.	Yield %
64a	H	Br	Br	103a	29
64b	OMe	Br	Br	103b	61
64c	Cl	Br	Br	103c	36
64d	H	Br	$COOEt$	103d	25
64e	H	F	Br	103e	96
64f	H	Br	NO_2	103f	62



(103)

appears to lower the yield of cyclised product. However, hydrolysis of the hydrazide to give the species (104) would be a process occurring in competition with ring-closure since the electron-withdrawing capabilities of the ester function have been lost in (104) and cyclisation would not be expected to take place. It is perhaps surprising to note that the ester function



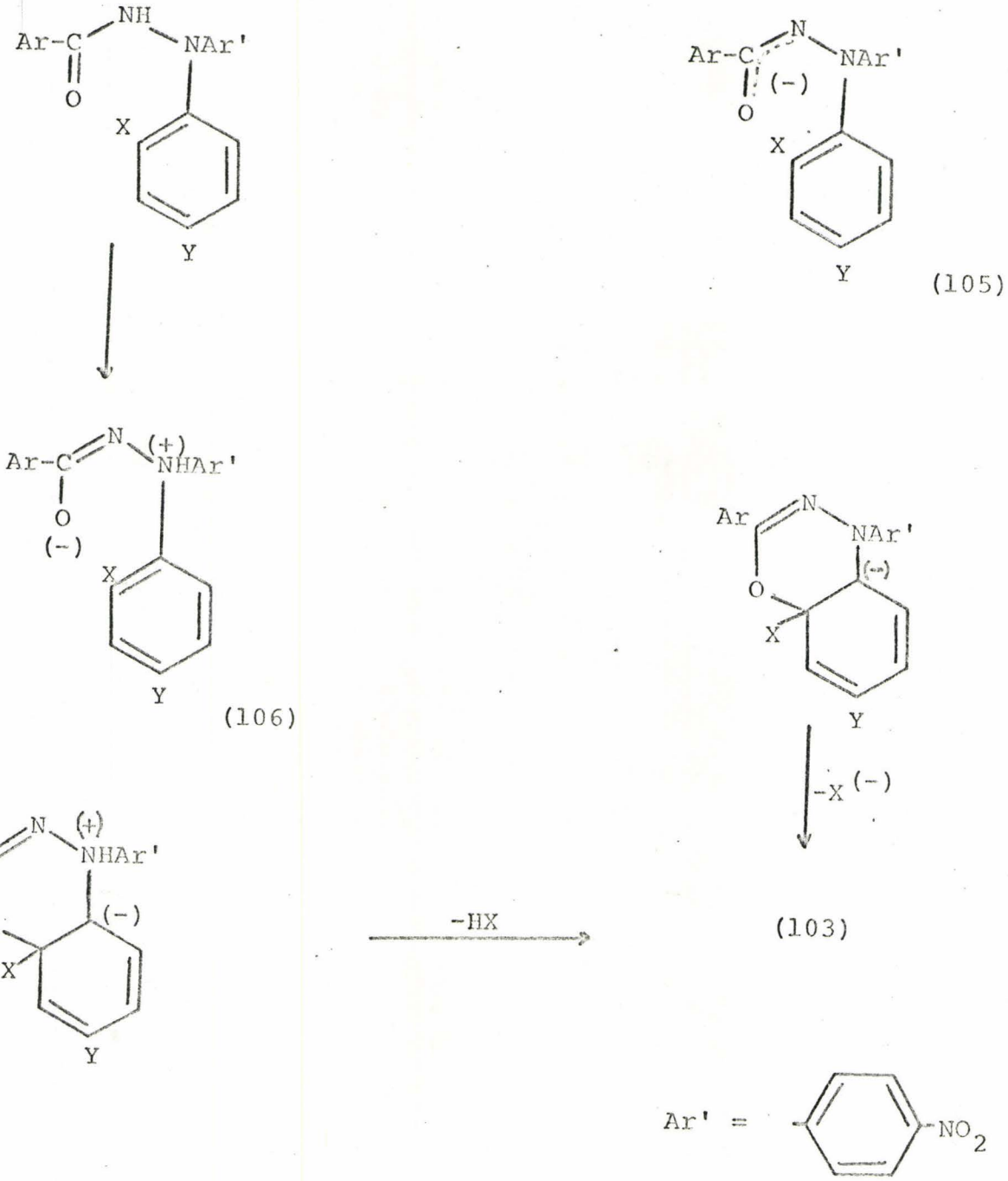
(104)

in the benzoxadiazine (103d) is unaffected under the reaction conditions.

The change in the leaving group from bromine to fluorine increases the yield of cyclised product markedly. In fact (64e) is converted entirely to the benzoxadiazine (t.l.c.) and the 96% yield represents the material obtained after work-up. In view of this the mechanism favoured for the reaction (Scheme xi) is analogous to that proposed earlier for the cyclisation of the acetylhydrazides. The anionic species (105) or the zwitterion (106) is thought to attack the 2-position of the N-phenyl ring in order to lead to products.

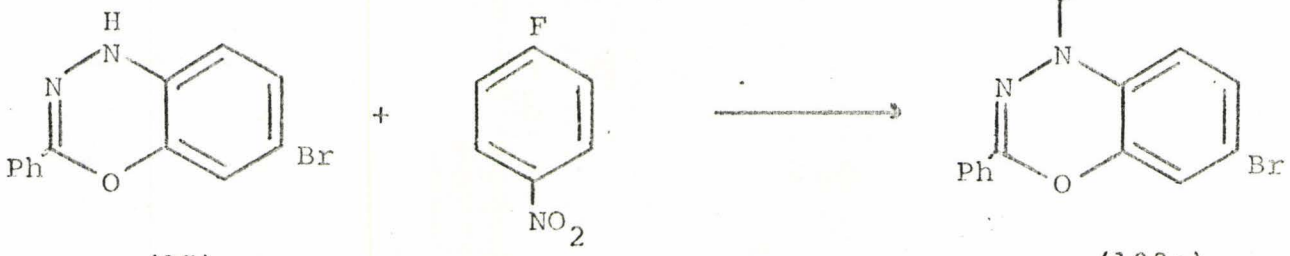
The p-nitrophenyl substituent is not as labile as an acetyl group, and is not removed under the reaction conditions.

SCHEME (xi)



Since (103) is stable to prolonged basic treatment (i.e. 6 hours) it appears that it is the NH oxadiazine which is sensitive to such conditions. Thus in these cases prolonged reaction times might be expected to increase the yields of cyclised products. Accordingly (64a) yielded (103a) in 79% after 10 hours (previously 29% after 6 hours).

The structure of (103a) was confirmed by an alternative synthesis. When 7-bromo-2-phenyl-4H-benzo[1,3,4]oxadiazine (95) and p-nitrofluorobenzene were boiled together in acetonitrile--triethylamine for 4 hours, (103a) was obtained in 66% yield



(95) (103a)

iii. Cyclisation of N-benzoyl-N'-(o-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine

N-Benzoyl-N'-(o-nitrophenyl)-N'-(2,4-dibromophenyl)-hydrazine (67) appeared to be an interesting compound, since

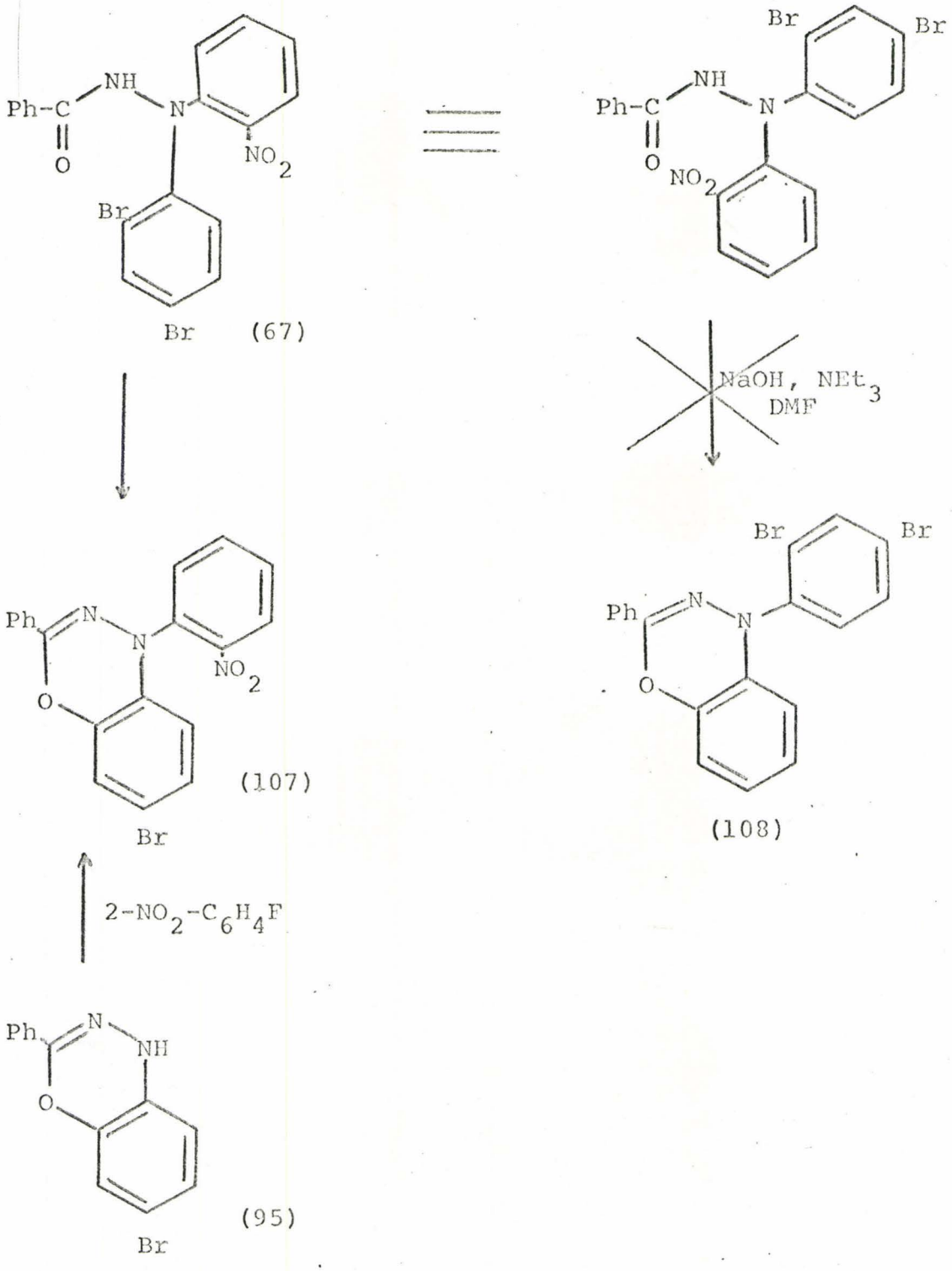
cyclisation might be expected to proceed in two ways (Scheme xii). Ring-closure in the usual way would give (107) but since the nitro group is sterically well placed, (108) might also be produced. When (67) was treated in the usual way for 6 hours, only (107) (27%) was obtained. There was no evidence of any other cyclised product (t.l.c.). The benzoxadiazine (95) and o-nitrofluorobenzene gave (107) in refluxing acetonitrile-triethylamine to confirm the proposed structure.

iv. Cyclisation of N-benzoyl-N'-pentachlorophenyl-N'--(2,4-dibromophenyl)hydrazine

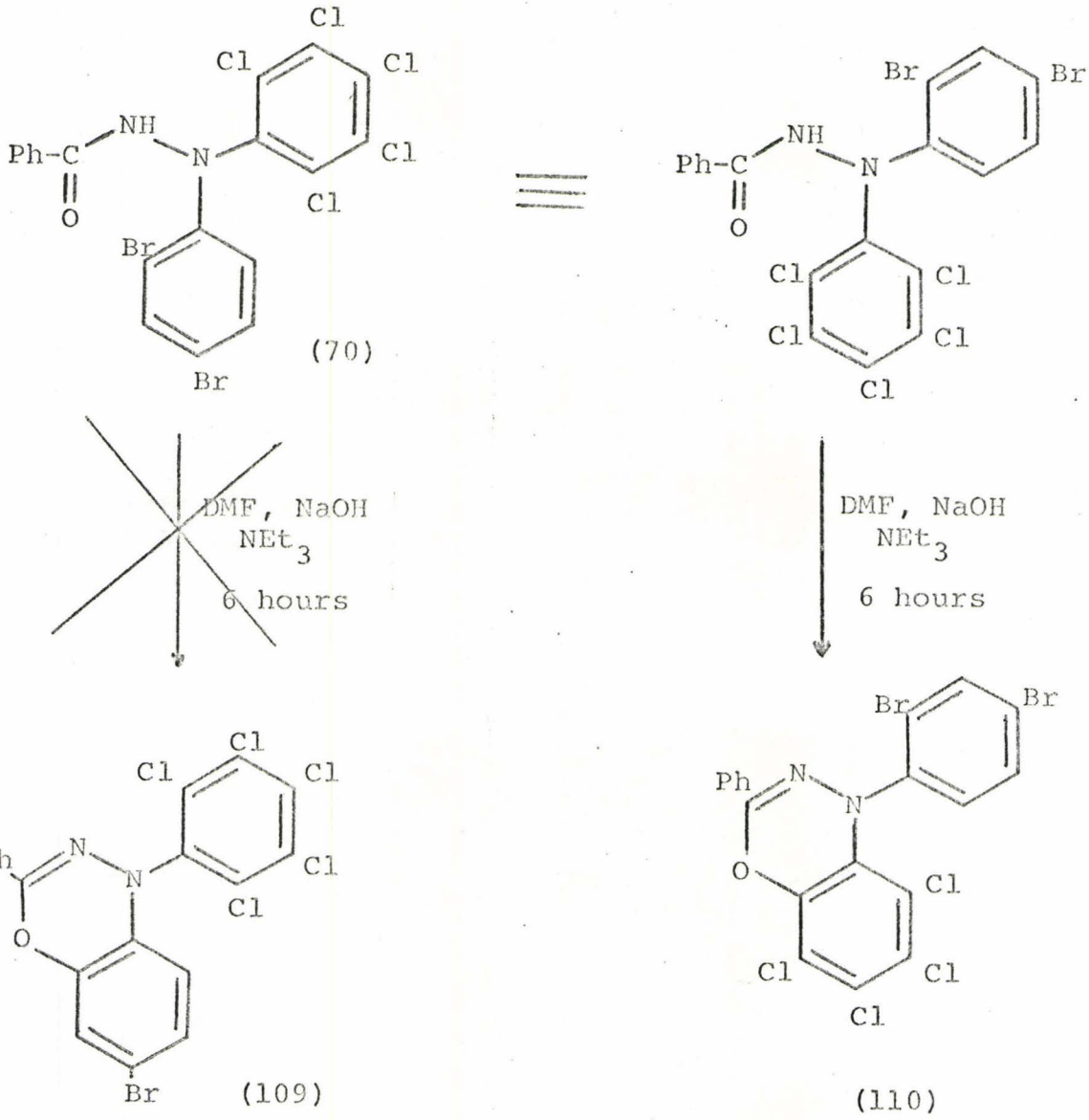
In their reactions with acetylthiohydrazides, Callaghan and Gibson had reported that a 2-chlorine substituent was not displaced under the conditions employed. In the present work the cyclisation of (70) was attempted under the standard reaction conditions and two modes of ring closure were seen to be possible. Cyclisation in the normal sense would give (109) as shown in Scheme (xiii). However, a 2-chlorine substituent might also be displaced and the benzoxadiazine (110) would result.

Rocklin has shown that hexachlorobenzene undergoes substitution under comparatively mild conditions [9], and more recent work by Suschitzky has shown the displacement of chlorine from polychloroaromatic rings to be a reaction of synthetic importance[11]. In the event 62% of (110) was obtained, with no evidence of any other cyclised product (t.l.c.).

SCHEME (xii)



SCHEME (xiii)


Cl
Cl
Cl
Cl
Cl
NH
Ph-C
N
O
Br
Br
(70)
≡
Br
Br
NH
Ph-C
N
O
Cl
Cl
Cl
Cl
Cl
DMF, NaOH
NEt3
6 hours
DMF, NaOH
NEt3
6 hours
Cl
Cl
Cl
Cl
Cl
Ph
N
N
O
Br
(109)
Br
Br
Ph
N
N
O
Cl
Cl
Cl
Cl
(110)

v. Cyclisation of N-benzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine

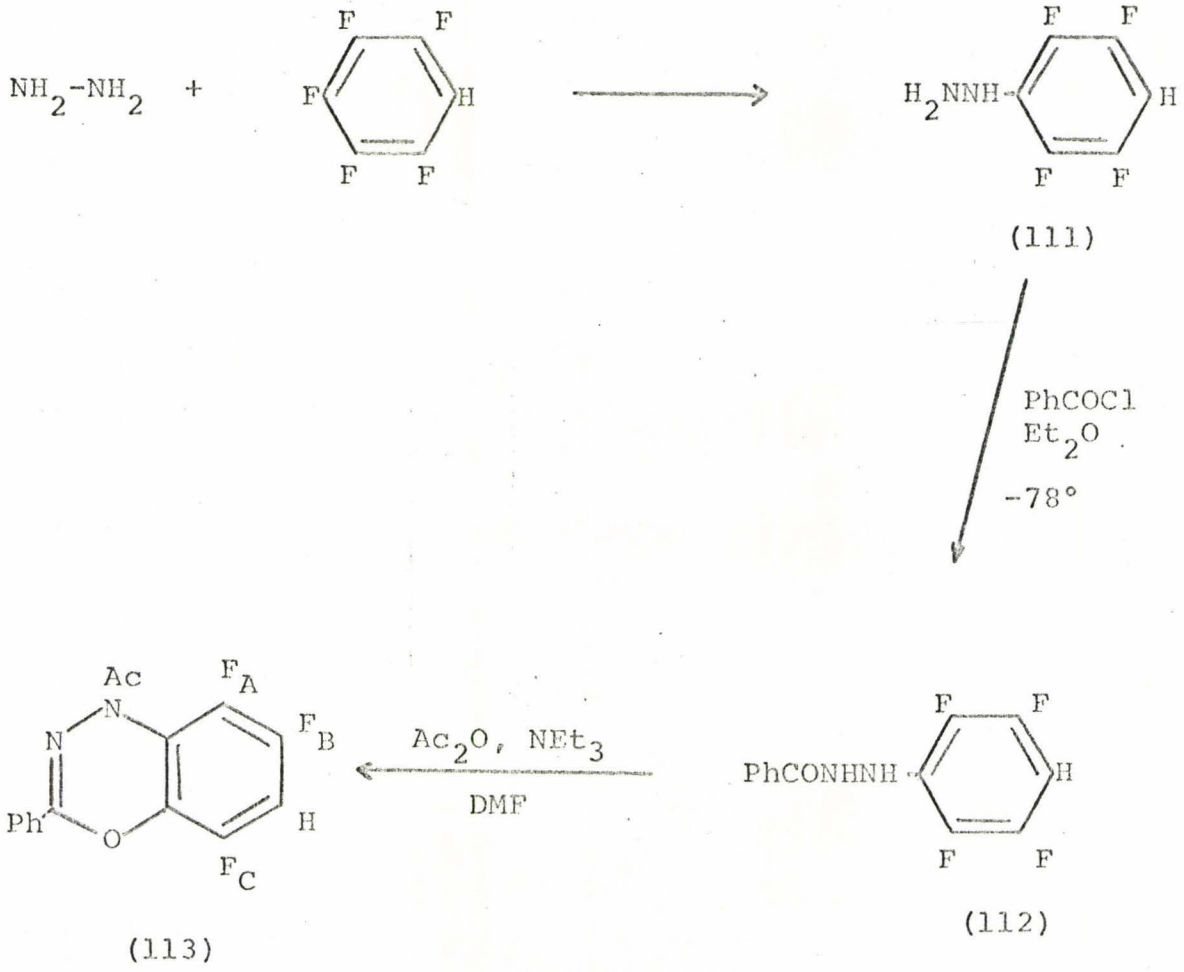
The preparation of the fluorinated benzoxadiazine (113) appeared useful in connection with other work in this department. Coincidently it provided an opportunity to examine the nuclear magnetic resonance spectrum of substituents (fluorine) attached to the benzoxadiazine ring system without the protons of the 2-phenyl ring interfering.

The reaction of hydrazine hydrate on pentafluorobenzene (Scheme xiv) gave the tetrafluorophenylhydrazine (111) which was benzoylated at -78° to give the hydrazide (112). Treatment of (112) with acetic anhydride, triethylamine and dimethylformamide for 4 hours at the reflux temperature, gave (113) in 65% yield. The cyclisation failed in the absence of acetic anhydride. An attempted removal of the acetyl group from (113) under basic conditions yielded only gummy material.

The fluorine nuclear magnetic resonance spectrum of (113) showed F_A at 52.84δ, F_B at 55.16δ and F_C at 57.06δ (upfield from CF_3CCl_3). These values, and the corresponding coupling constants, are in agreement with the proposed structure. The differences in the spectra of (113) and the corresponding fluorinated benzothiadiazine are discussed later.

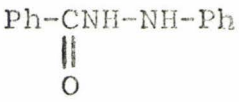
The nuclear Overhauser effects in (113) are presently under investigation[67].

SCHEME (xiv)

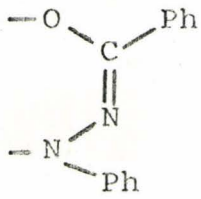

NH2-NH2 +
F
F
F
H
F
F
H2NNH
H
F
F
(111)
PhCOCl
Et2O
-78°
Ac
N
N
Ph
O
FA
FB
H
FC
Ac2O, NEt3
DMF
PhCONHNH
(113)
(112)

vi. Preparation of oxadiazines from N-benzoyl-N'--phenylhydrazine

At this stage of the research, the synthesis of benzoxadiazines via the cyclisation of suitably substituted hydrazides was well established. Since the ring-closure via oxygen appeared to proceed smoothly in favourable cases, it was thought that N-benzoyl-N'-phenylhydrazine (114) might behave as the bifunctional nucleophile represented as (115).



(114)

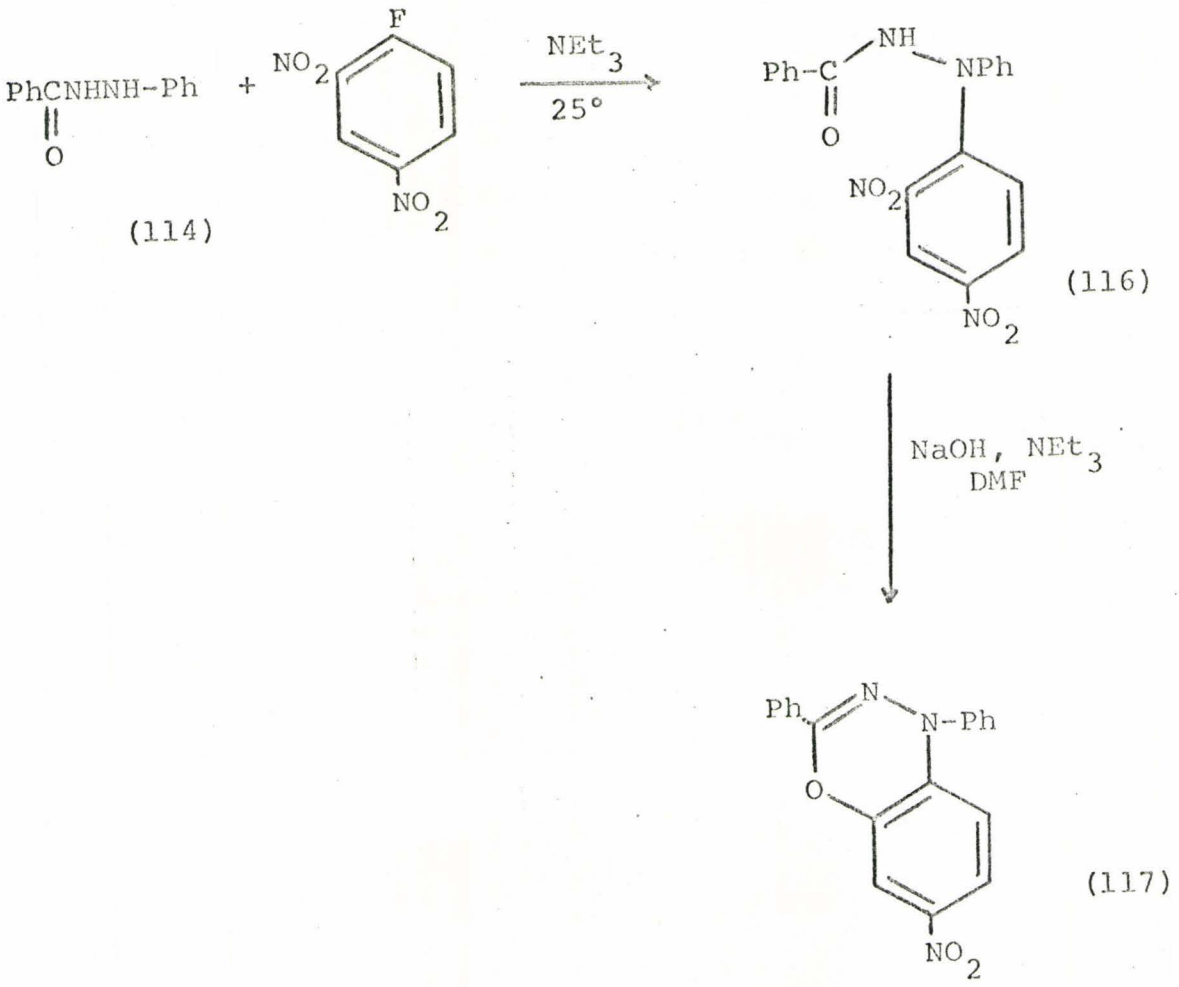


(115)

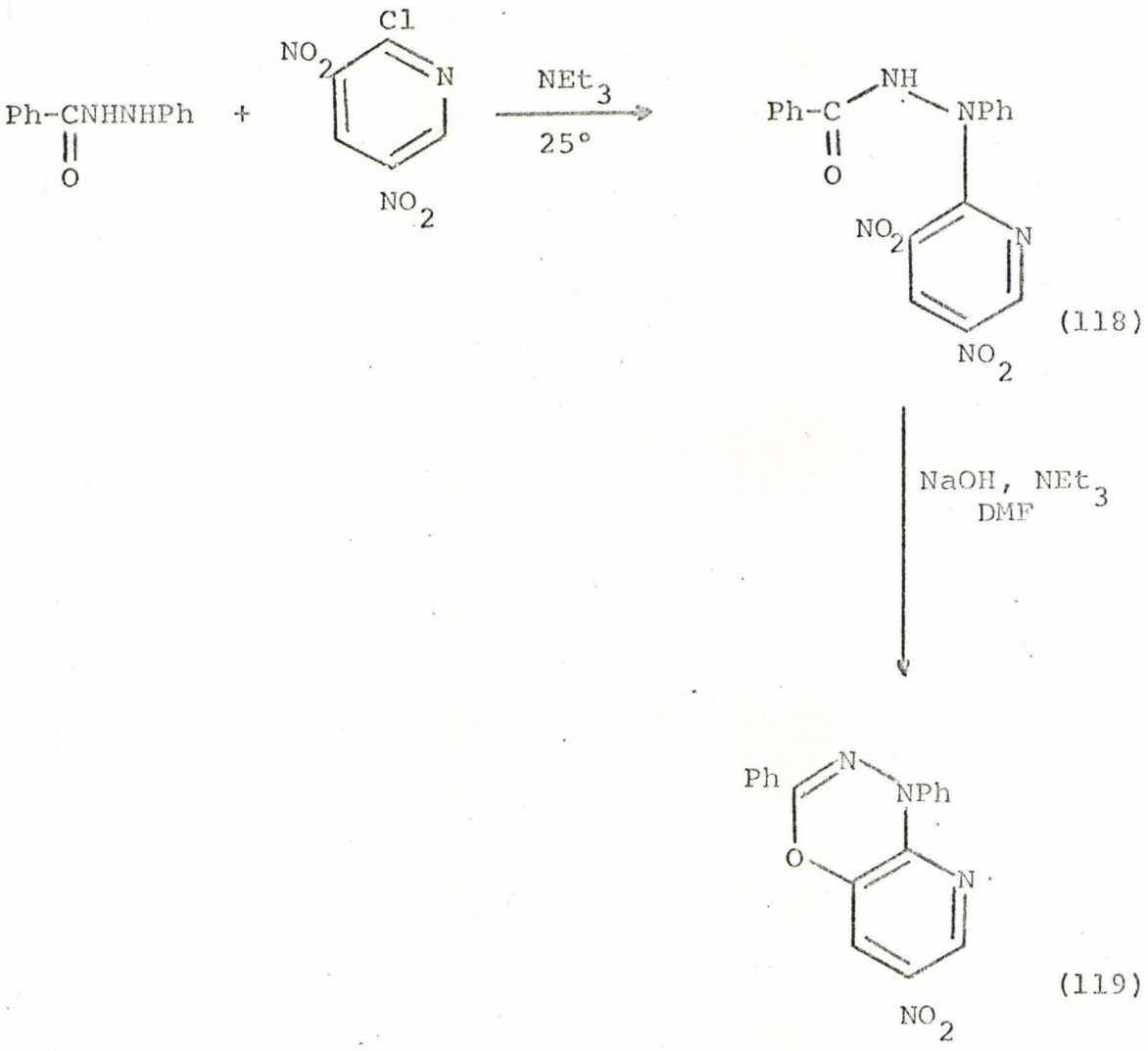
In order to test the method, the readily available and highly activated 2,4-dinitrofluorobenzene was condensed with (114). As expected the fluorine substituent was displaced by the nucleophilic nitrogen atom and N-benzoyl-N'-(2,4-dinitrophenyl)-N'--phenylhydrazine (116) was obtained in 74% yield (Scheme xv). The cyclisation of (116) was effected smoothly in the usual way, and the benzoxadiazine (117) was isolated in high yield. Thus it appeared that aromatic compounds with ortho substituents activated towards nucleophilic displacement might give the corresponding oxadiazine ring system with (114).

However (114) and 2-chloro-3-nitropyridine failed to

SCHEME (xv)

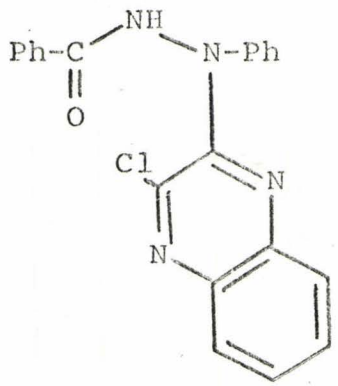

PhCNHNH-Ph
O
(114)
F
NO2
NO2
NEt3
25°
NH
NPh
Ph-C
O
NO2
NO2
(116)
NaOH, NEt3
DMF
Ph
N
N-Ph
O
NO2
(117)

SCHEME (xvi.)

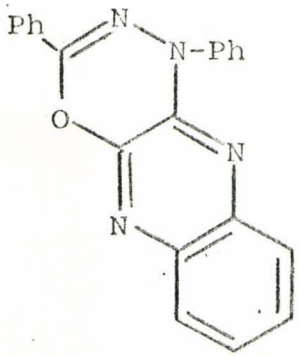

Ph-CNHNHPh
O
Cl
NO2
N
NO2
NEt3
25°
Ph-C
O
NH
NPh
NO2
N
NO2
(118)
NaOH, NEt3
DMF
Ph
N
NPh
O
N
NO2
(119)

condense together and the more powerfully activated 2-chloro--3,5-dinitropyridine was required before reaction would occur. In this way the hydrazide (118) was obtained in 71% yield, as outlined in Scheme (xvi). The cyclisation of this compound in the usual way gave the first example of the pyrido[3,2][1,3,4]-oxadiazine ring system (119) in 85% yield.

The hydrazide (114) also failed to condense with 2,3--dichloroquinoxaline when methanol-triethylamine was used as the solvent. The reaction proceeded smoothly when dimethylformamide was used as the co-solvent with triethylamine. The intermediate hydrazide (120) could not be isolated, but a reflux time of 12 hours gave the novel quinoxalino[2,3][1,3,4]oxadiazine ring system (121) in 82% yield.



(120)



(121)

vii. Summary

Under certain conditions hydrazides have been shown to be nucleophilic via oxygen and in favourable cases the benzo-

[1,3,4]oxadiazine ring system is produced. The cyclisation exhibits the characteristics of a nucleophilic aromatic substitution reaction and is unusual in that the aromatic ring which suffers attack is normally considered to be deactivated towards such substitution.

N-Benzoyl-N'-phenylhydrazine appears to contain two nucleophilic centres in its reactions with aromatic compounds containing ortho substituents activated towards nucleophilic attack. The initial displacement through nitrogen may be followed by cyclisation via oxygen in suitable cases to yield the corresponding oxadiazine ring-system.

III. PREPARATION OF THE THIADIAZINES

i. Cyclisation of N-Thioaroyl-N'-acetyl-N'-arylhydrazines

Since Callaghan and Gibson had effected the cyclisation of a series of acetylthiohydrazides earlier, no difficulties were expected in the present study. The conditions used by these workers (refluxing triethylamine-acetonitrile) were shown to be valid for the ring-closure of acetylthiohydrazides containing groups in the C-phenyl ring. Thus (72) yielded the benzothiadiazine (122) in 90% yield and removal of the acetyl group in ethanolic hydrochloric acid gave the corresponding NH compound (123) as shown in Scheme (xvii).

The aromatic region of the p.m.r. spectra of (122) and (123) are reproduced in Figures (iii) and (iv) respectively. Figure (v) shows the p.m.r. spectrum of (123) after the addition of deuterium oxide. In the p.m.r. of (95) (Figure (ii))discussed previously, the high-field doublet was assigned as the proton adjacent to nitrogen. Inspection of Figure (iv) shows that (123) exhibits a similar high-field doublet. Further, this doublet sharpens on the addition of deuterium oxide (Figure (v)) and thus the signal is attributed to H_A on the basis of long range coupling with the N-H. Upon acetylation of the nitrogen, H_A is seen to move downfield considerably (Figure (iii)) and is lost among the signals of the other aromatic protons. Since H_A shows only ortho-coupling, the bromine substituent must occupy the 7-position as indicated.

The occurrence of a high-field doublet (ortho-coupled)

SCHEME (xvii)

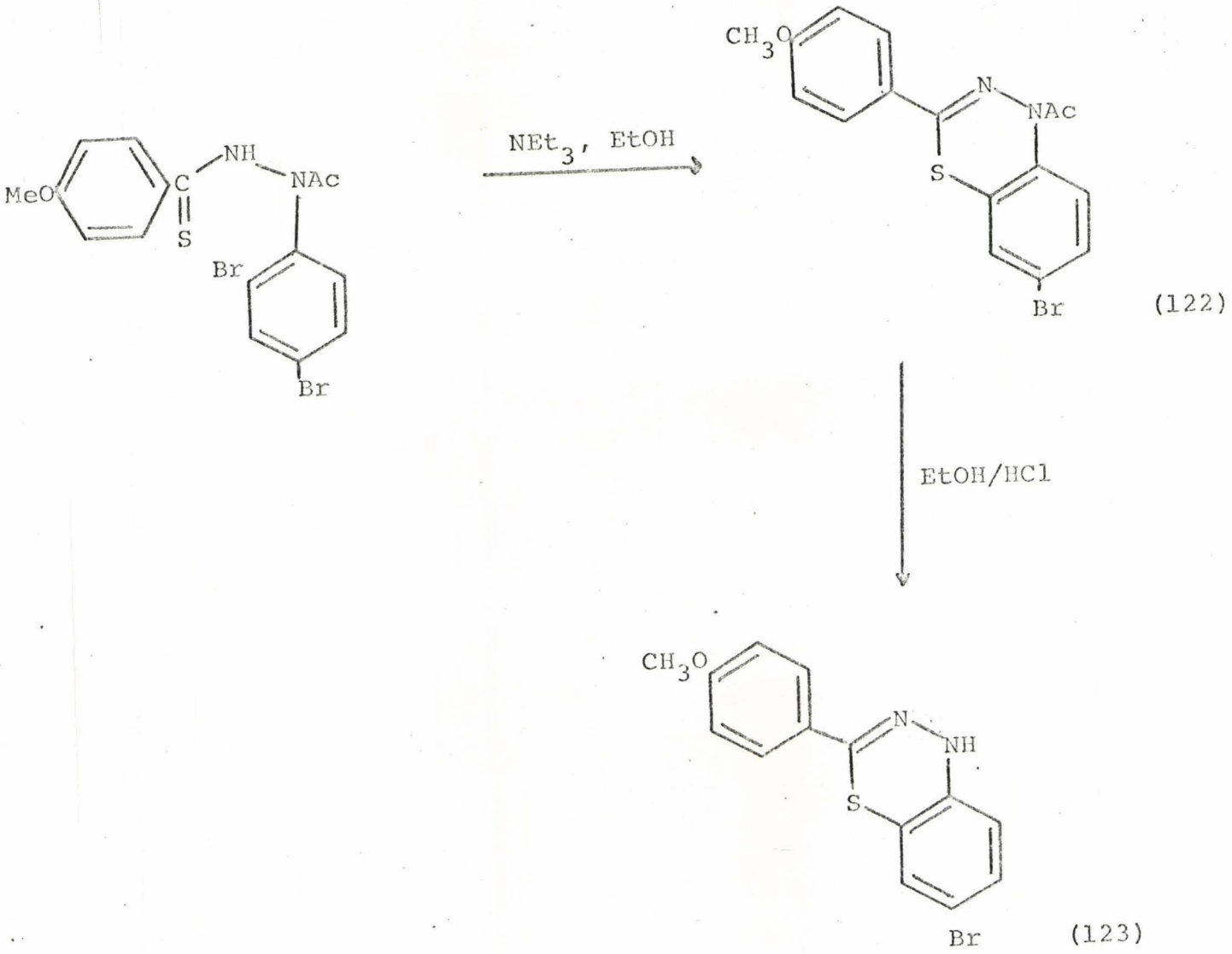
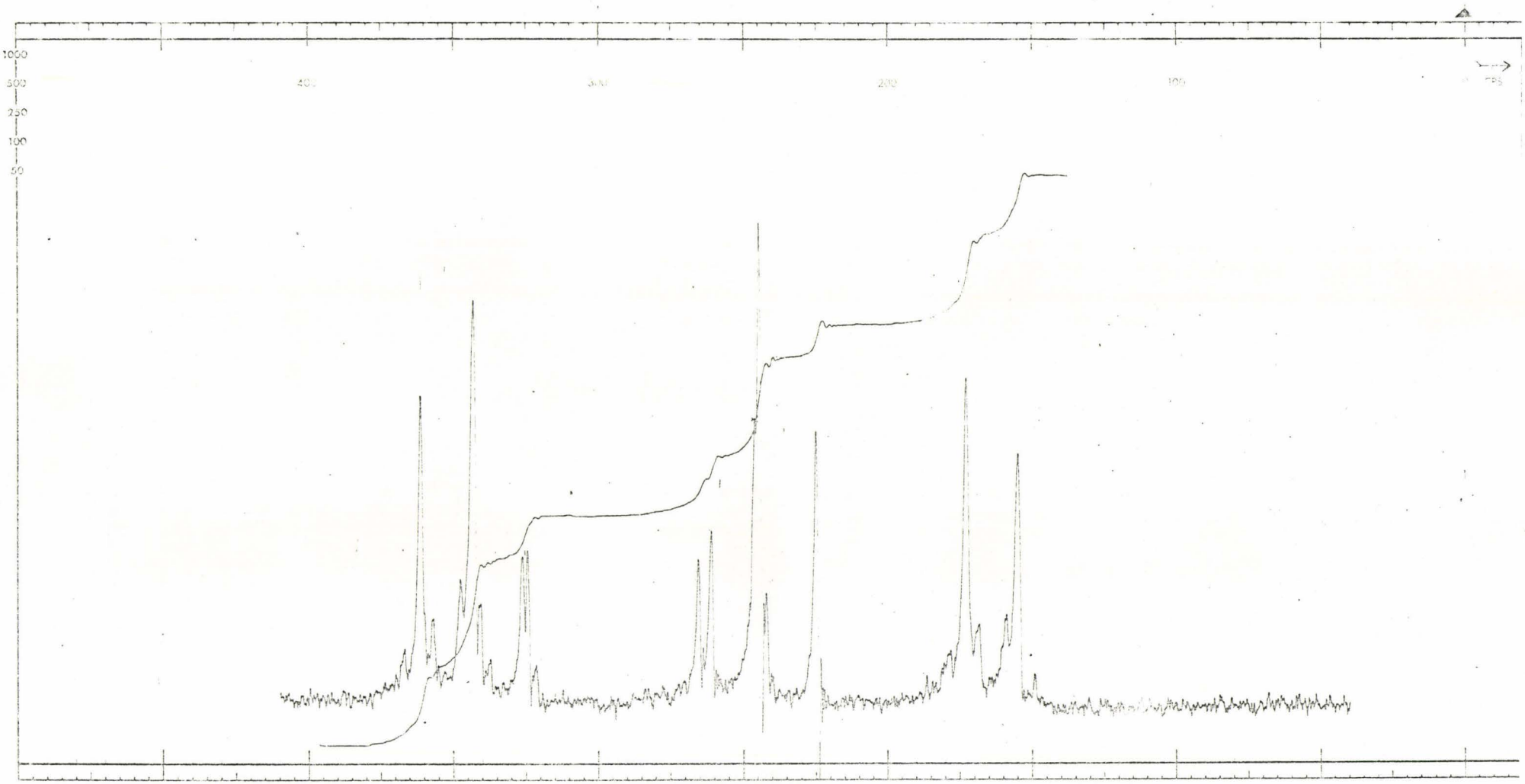
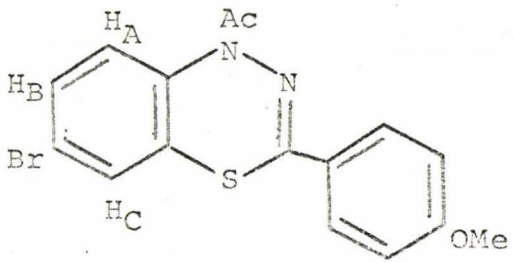

MeO
NH
NAc
C
S
Br
Br
NEt3, EtOH
CH3O
N
NAc
S
Br
(122)
EtOH/HCl
CH3O
N
NH
S
Br
(123)

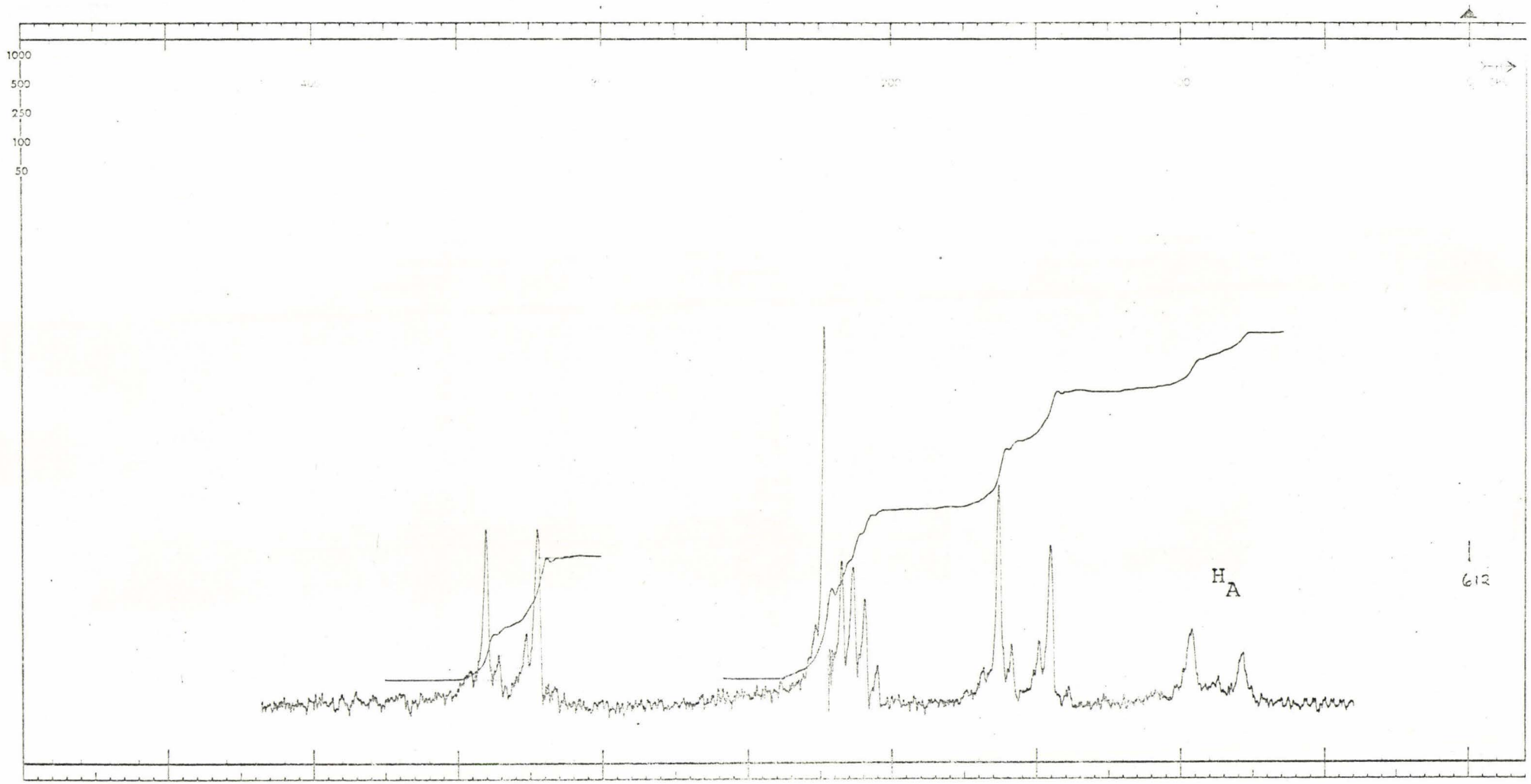
Figure (iii): The Aromatic Region of the p.m.r. Spectrum of (122)

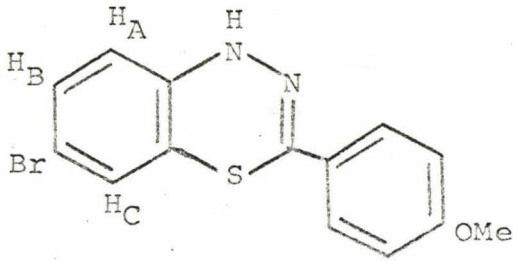




Solvent	$CDCl_3$
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	612 Hz.
Lock Signal	T.M.S.

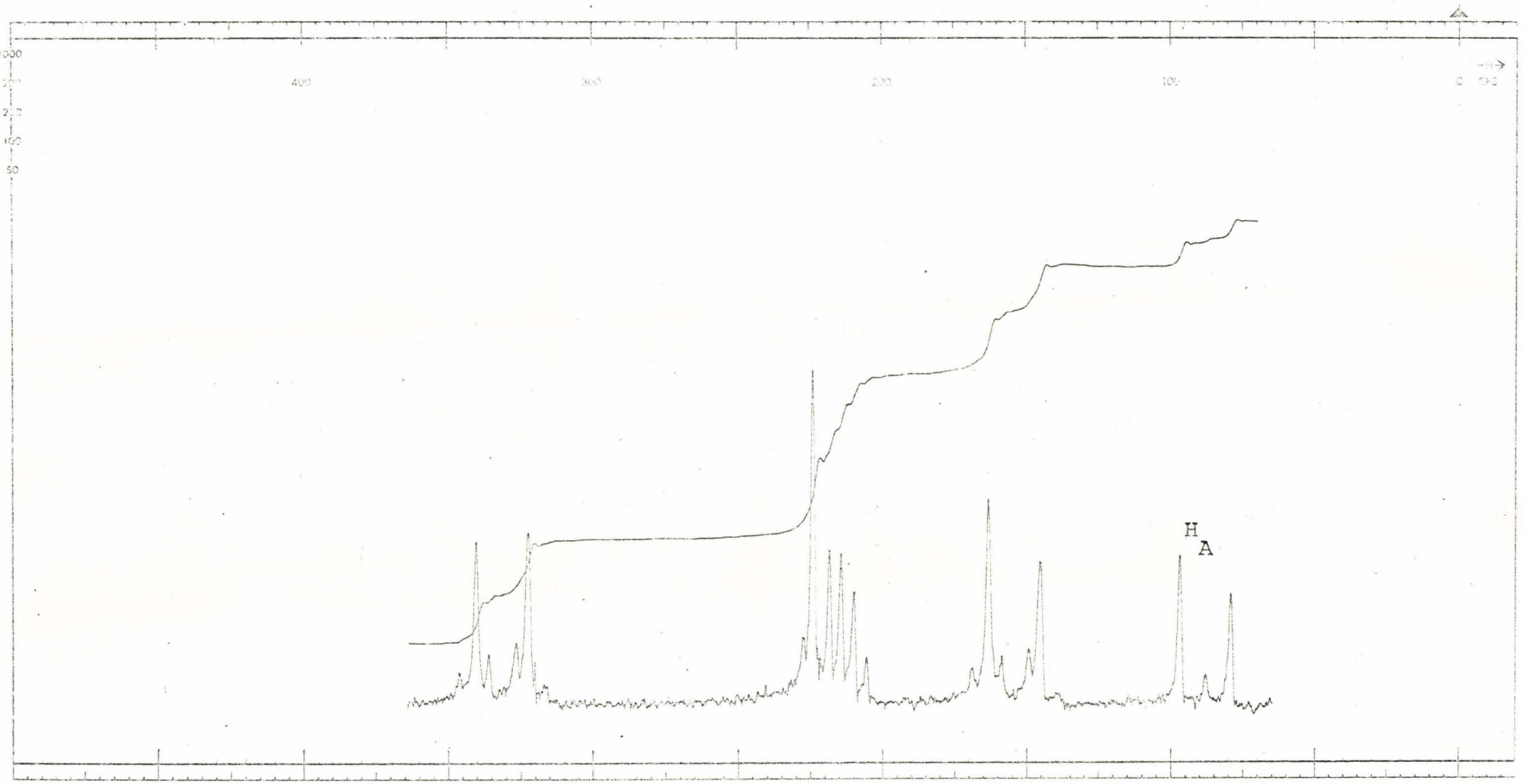
Figure (iv): The Aromatic Region of the p.m.r. Spectrum of (123)

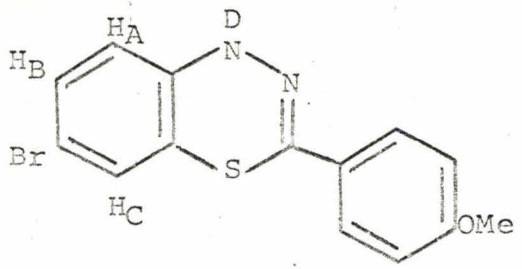




Solvent	$CDCl_3$
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	612 Hz.
Lock Signal	T.M.S.

Figure (v): The Aromatic Region of the p.m.r. Spectrum of (123) + D_2O





Solvent	$CDCl_3$
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	612 Hz.
Lock Signal	T.M.S.

was noted in all the p.m.r. spectra of the benzothiadiazines prepared in the present study. This observation was important in later work when the assignment of structure was more difficult.

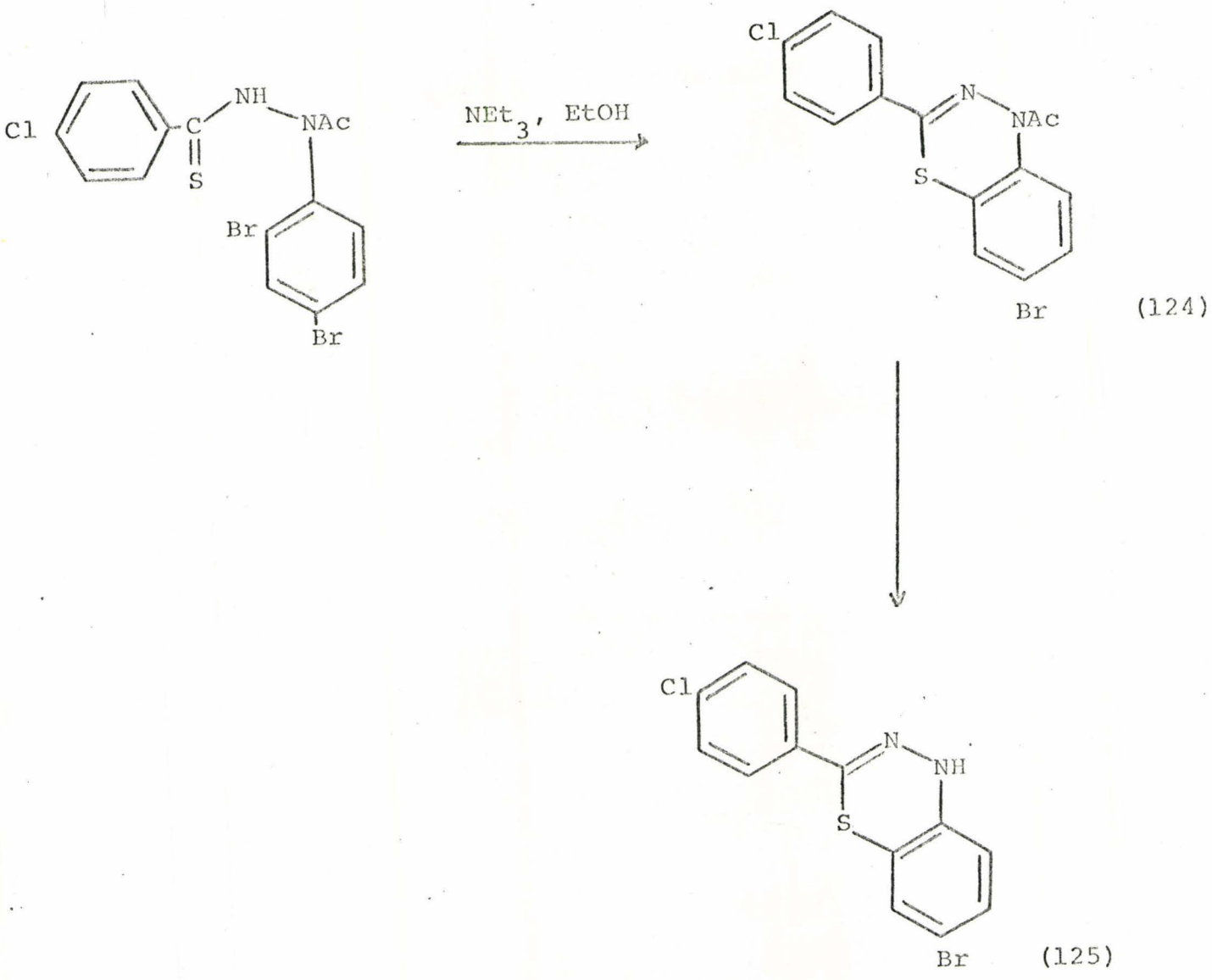
The cyclisation of (71) also proceeded smoothly, although the yield was only 66% of (124) as shown in Scheme (xviii). The product appeared to contain a yellow impurity which could not be removed by chromatography, although the analytical results were not affected. Removal of the acetyl group in the usual way gave the NH thiadiazine (125) which was shown not to be the impurity mentioned above (t.l.c.).

The mechanism favoured by Callaghan and Gibson for these reactions involved the zwitterionic form of the thiohydrazide (40). In this way the halogenated ring becomes activated towards nucleophilic attack by negative sulfur. Ring-closure via the anionic form of the thiohydrazide cannot be overlooked, however, since the sulfur atom in such a species would be extremely nucleophilic and attack at the relatively unactivated 2-position might occur.

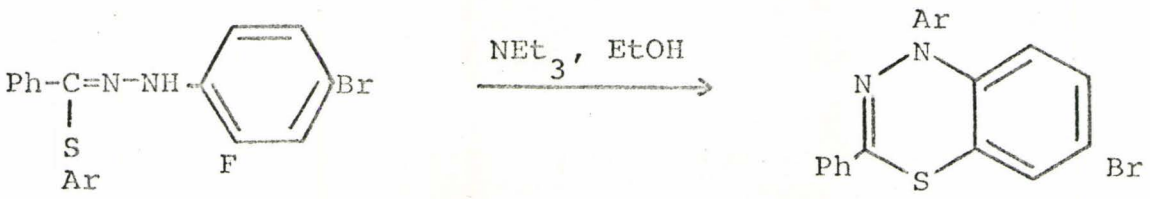
ii. Cyclisation of N-α-(p-nitrothiophenoxy)arylidene-N'--arylhydrazines

In Section I (iv) the preparation of the p-nitrothiophenoxy adducts was described. These compounds were all assigned the unrearranged structure (81). Treatment of these compounds with base was expected to give the corresponding benzothiadiazines

SCHEME (xviii)



via an S→N p-nitrophenyl migration followed by ring-closure through sulfur. Earlier, compound (77) had been shown to yield the benzothiadiazine (126) in refluxing ethanol-triethylamine[17].



(77) (126)

Ar = 4-NO_2-C_6H_4-

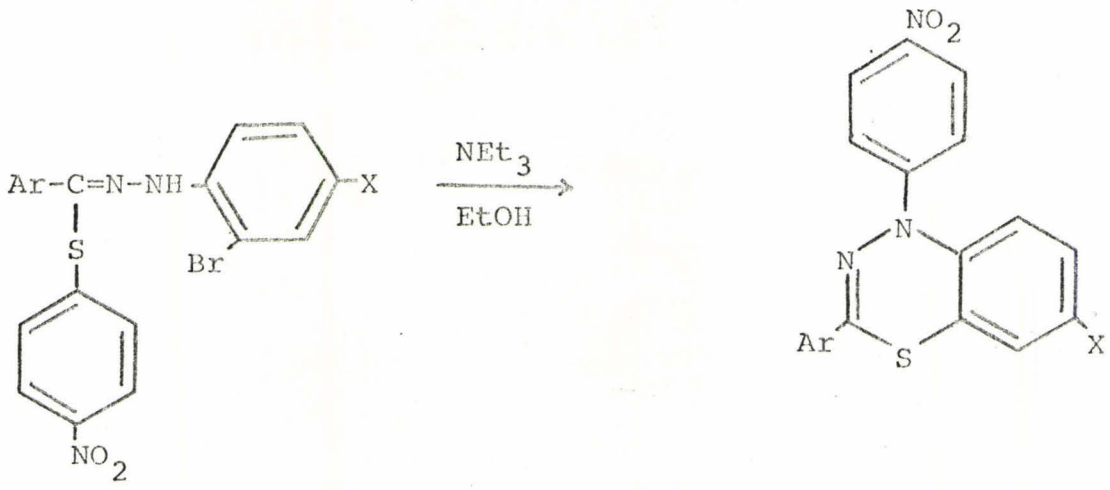
In the present study a series of p-nitrothiophenoxy compounds was treated in a similar manner. The results are summarised in Table XI. No attempt was made to isolate the (presumably) intermediate thiohydrazides.

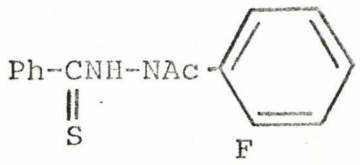
Only compound (81c) failed to yield a cyclised product. Since Callaghan and Gibson had earlier noted that (127) failed to yield any isolable benzothiadiazine under similar conditions[17], this result served to support the view of these workers that an electron-withdrawing group in the 4-position was essential for ring closure.

It might be expected that, since ring-closure had not taken place, the corresponding thiohydrazide (128) would be

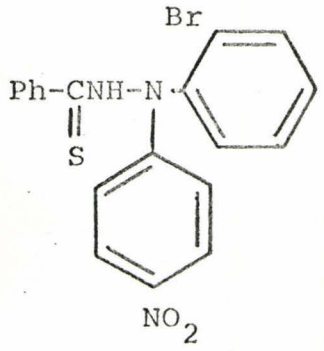
Table XI. Cyclisation of the p-Nitrothiophenoxy adducts

p-Nitrothiophenoxy Adduct			Benzothiadiazine
No.	Ar	X	Yield %
81a	4-methoxyphenyl	Br	74
81b	4-chlorophenyl	Br	40
81c	phenyl	H	0
82	5-bromo-2-thienyl	Br	64





(127)



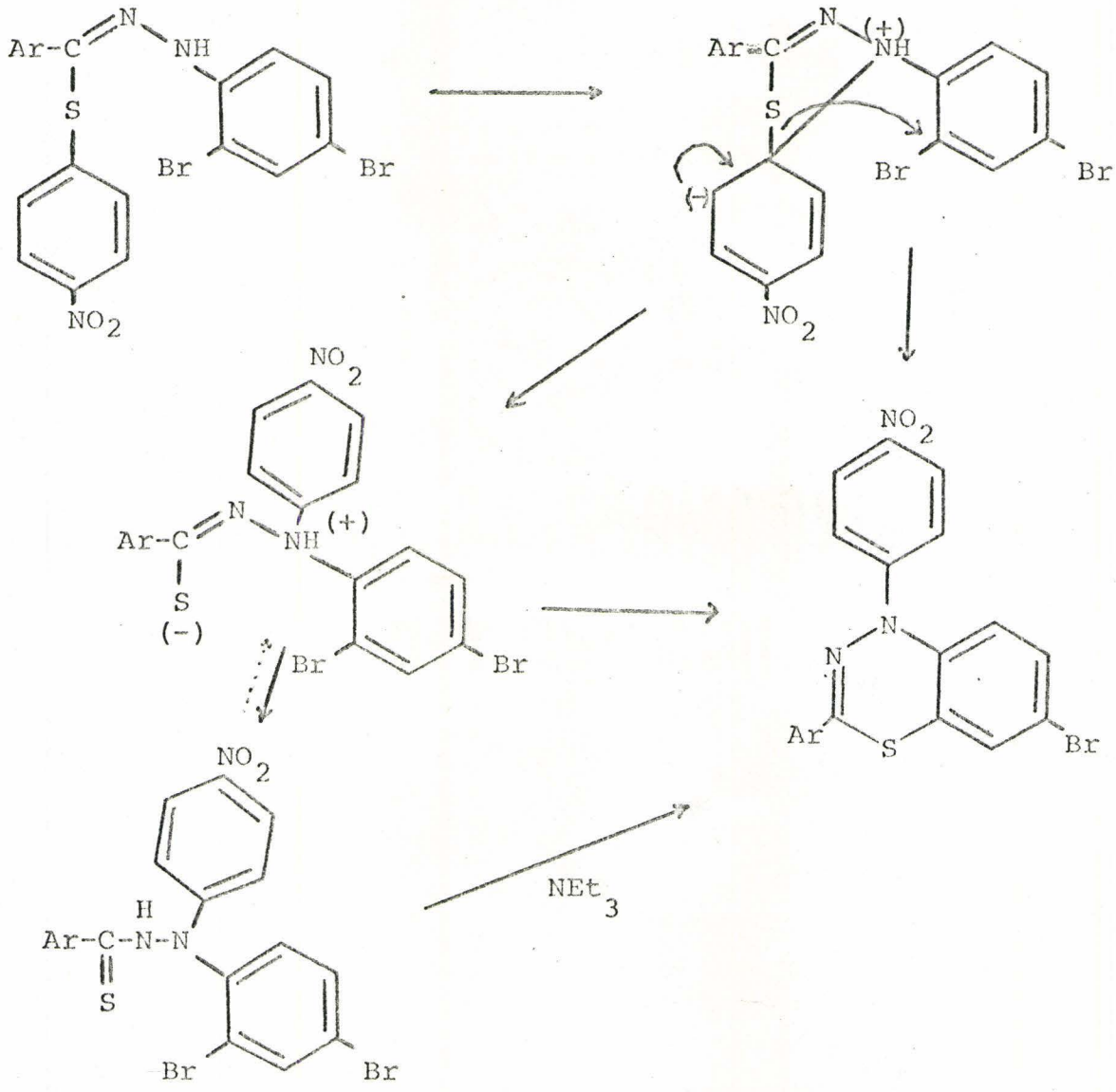
(128)

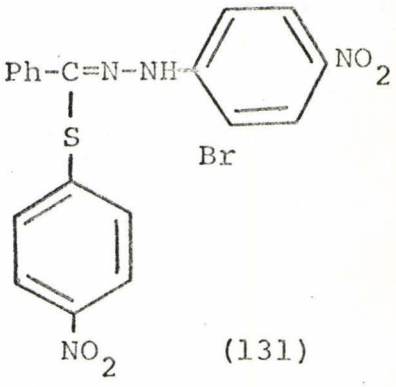
isolated. In fact only gummy material was obtained. Since some acetylthiohydrazides are known to be thermally unstable, it may be that (128) was destroyed during the reaction.

The isolation of the three other benzothiadiazines confirmed that the S→N aryl migration had taken place. Once again ring-closure could be synchronous or proceed via the thiohydrazide as shown in Scheme (xix).

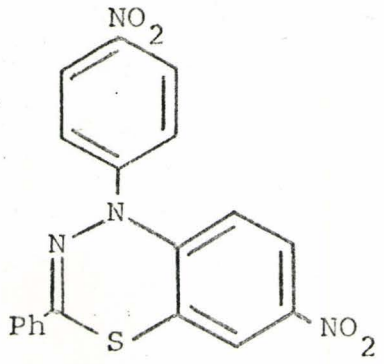
The reaction of the hydrazidic bromide (59) with p-nitrothiophenoxide ion at room temperature gave a yellow solid which was not characterised, but which was almost certainly (131). This compound gave the benzothiadiazine (132) in 45% yield, based on the hydrazidic bromide, on treatment with refluxing ethanol-triethylamine. Thus the S→N aryl migration appeared to proceed readily even when an electron-withdrawing nitro group is contained in the N-phenyl ring.

SCHEME (xix)





(131)



(132)

iii. Cyclisation of the hydrazidic thioethers derived from heterocyclic thiols

In Section I (v) the reaction of heterocyclic thiols with (3) was discussed, and all the products were assigned the unrearranged structure (85). The treatment of these compounds with refluxing ethanol-triethylamine was expected to yield benzothiadiazines of general structure (129) via an S→N migration of the electron-deficient heterocyclic ring.

The results of the study are shown in Table XII. Only in three cases was the expected product obtained. All the other compounds yielded tarry material, although in the case of (85a) the isomeric thiohydrazide (86) was detected (t.l.c.). The recovery of (85e) after 2 hours was notable. Compound (85b) survived similar treatment for 5 minutes, but a longer reflux time gave no characterisable product. It may be that the thermal stability of the thiohydrazide is important since (86) was destroyed in refluxing ethanol-triethylamine without giving any

Table XII. Cyclisation of the Hydrazidic Thioethers derived from the Heterocyclic Thiols

Hydrazidic Thioether		Benzothiadiazine	
No.	R	Yield %	No.
85a	4,6-dimethyl-2-pyrimidyl	0*	129a
85b	1-phenyl-1H-5-tetrazolyl	0**	129b
85c	5-nitro-2-pyridyl	79	129c
85d	2-quinoxalyl	94	129d
85e	2-pyridyl	0***	129e
85f	4-methyl-2-quinolyl	16	129f

* Starting material destroyed. Rearranged compound (86) detected

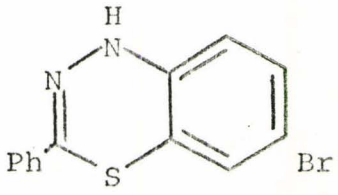
** Starting material destroyed

***Starting material recovered

(85) (129)

cyclised product (t.l.c.).

The structures of (129c) and (129d) were confirmed by an alternative synthesis. The reaction of 7-bromo-2-phenyl-4H--benzo[1,3,4]thiadiazine[18] (130) with each of 2-chloro-5-nitropyridine and 2-chloroquinoxaline in the presence of triethylamine gave (129c) and (129d) respectively. The unreactivity of 2-chloro-4,6-dimethylpyrimidine and 2-chloropyridine towards (130) under the same conditions was attributed to insufficient activity in the heterocyclic ring.



(130)

Thus only the quinoxaline and nitropyridine ring systems were seen to undergo a facile S→N migration under the influence of base. This result was important to later work and is discussed in Section III (vi).

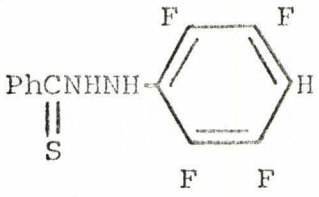
iv. Cyclisation of N-thiobenzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine

In Section II (v) the formation of the fluorinated benzoxadiazine (113) was described. The fluorine nuclear magnetic resonance spectrum of this compound was limited in its importance since the acetyl group could not be removed. However the corresponding fluorinated benzothiadiazine was thought to be more

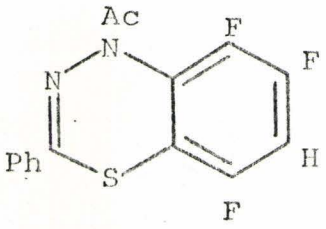
helpful since the acetyl group might be removed under acidic conditions. The effect of the acetylation of the nitrogen on the fluorine substituents could then be examined.

The action of 2,3,5,6-tetrafluorophenyl hydrazine on carboxymethyldithiobenzoate[43] in dilute potassium hydroxide solution gave N-thiobenzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine (133) which on treatment with acetic anhydride and triethylamine gave the benzothiadiazine, formulated as (134), in excellent yield. The cyclisation failed to proceed without the addition of acetic anhydride, but rather gave a compound which analysed for a 1:1 adduct of (133) and triethylamine.

The thiohydrazide (133) was regenerated on treatment of the adduct with ethanolic hydrochloric acid. If the product was a salt it was most unusual since it crystallised as needles from hexane-benzene. The p.m.r. spectrum was consistent with a



(133)

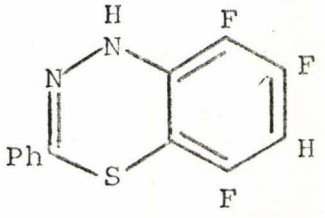


(134)

1:1 adduct, all the exchangeable protons being equivalent in the deuterochloroform solution. The exact nature of this product is unknown.

The benzothiadiazine (134) was deacetylated in ethanolic hydrochloric acid to give a product, formulated as (135) in good

yield.



(135)

The fluorine nuclear magnetic resonance spectra of (134) and (135) proved to be extremely interesting and useful. The details are listed in Table XIII together with those of the benzoxadiazine (113). An inspection of the table reveals three points:

(a) the coupling constants are consistent with the proposed structures[68]. The long-range couplings between the NH and F_A and F_B in (135) are of special interest, since a similar effect was observed in the p.m.r. spectrum of (123);

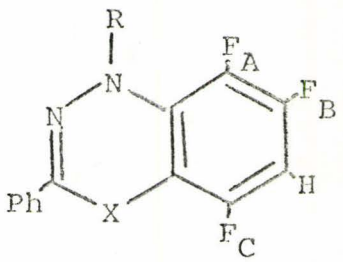
(b) the chemical shifts also support the structural assignments. Acetylation of the NH produces a shift downfield for F_A, while the other fluorines are almost unaffected. The higher field positions of F_B and F_C in the benzoxadiazine (113) are explained by the increased electron-density in the ring, since the smaller oxygen atom is capable of a greater resonance effect;

(c) irradiation of the NH signal of (135) produces a large nuclear Overhauser effect (N.O.E.) of F_A, whilst F_B and F_C are unaffected. Saturation of the methyl protons of (134) produces a smaller effect of F_A, whilst F_B and F_C are again unchanged. Saturation of the ring proton produces large N.O.E.'s of F_B

Table XIII. Fluorine Nuclear Magnetic Resonance Data for Fluorinated Benzothiadiazines and Benzoxadiazines

X	S	S	O
R	H	Ac	Ac
Chemical Shifts δ *			
F_A	82.25	54.08	52.84
F_B	54.27	50.92	55.16
F_C	36.54	36.28	57.06
Coupling Constants Hz.			
J_{AB}	21	20	22
J_{AC}	13	13	13
J_{BC}	2.5	2	0
J_{AH}	6	6	7
J_{BH}	10	9.5	10
J_{CH}	8.5	8	9
J_{AR}	3		
J_{BR}	1		
J_{CR}	0		
N.O.E.			
Irradiate R; Obs. F_A	32%	10%	
Irradiate H; Obs. F_A	0%	0%	
F_B	22%	21%	
F_C	33%	32%	

*Upfield from CF_3CCl_3



and F_C, whilst F_A is unaffected.

Only the structures (134) and (135) are consistent with the above data. By inference the proposed structure of the benzoxadiazine (113) is strongly favoured, although unequivocal evidence will come only from the measurement of the N.O.E.'s of this compound.

The shift of F_A from a high-field position in (135) to low-field upon acetylation is analogous to the shift of proton H_A in (95) and (123). The N.O.E.'s examined here thus provide more evidence for the structures of these compounds.

v. Preparation of benzothiadiazines from N-thiobenzoyl--N'-phenylhydrazine

In Section II (vi) the reaction of N-benzoyl-N'-phenylhydrazine with some ortho-disubstituted aromatic compounds was described. The initial substitution was shown to occur through the more nucleophilic nitrogen atom and ring-closure was effected via oxygen under more vigorous conditions.

The reaction of N-thiobenzoyl-N'-phenylhydrazine (136) with similar compounds appeared to be a pathway to the corresponding thiadiazines. However, thiohydrazides differ from hydrazides in that the initial nucleophilic attack is through sulfur under basic conditions[47].

When (136) and 2,4-dinitrofluorobenzene were stirred together in the presence of triethylamine, a cyclised product was obtained which could arise from one of two reaction pathways,

as shown in Scheme (xx). The initially formed 2,4-dinitrothiophenoxy compound (137) could cyclise directly via nitrogen attack at the 2-position to give (139). However, rearrangement of (137) through an S→N transfer of the 2,4-dinitrophenyl ring would yield (138) which could then cyclise via sulfur to give (140).

The product was eventually shown to be (140) in the following way. The aromatic region of the p.m.r. spectrum of (140), reproduced in Figure (vi), contained an ortho-coupled high-field doublet, a feature which had previously been attributed to benzothiadiazines with a substituent in the 7-position (Section III (i)). The oxidation of (140) with peracetic acid gave (141) in good yield, and the aromatic region of the p.m.r. spectrum of this compound is shown in Figure (vii). Under the influence of the neighbouring SO_2 group, H_C had moved downfield considerably and was seen as a doublet (meta-coupled). Proton H_B was also seen at slightly lower field and appeared as a quartet. These observations are consistent only with structure (140). There was no evidence for the formation of (139) in the reaction (t.l.c.).

Since (140) was formed at room temperature, the reaction was repeated at 0° in an attempt to isolate (137) or (138) or both. In the event, a yellow solid was obtained, together with some (140) (t.l.c.). Since the product was shown to undergo conversion to (140) when it was dissolved in ethanol-triethylamine, it was evident that it was either (137) or (138). The unrearranged

SCHEME (xx)

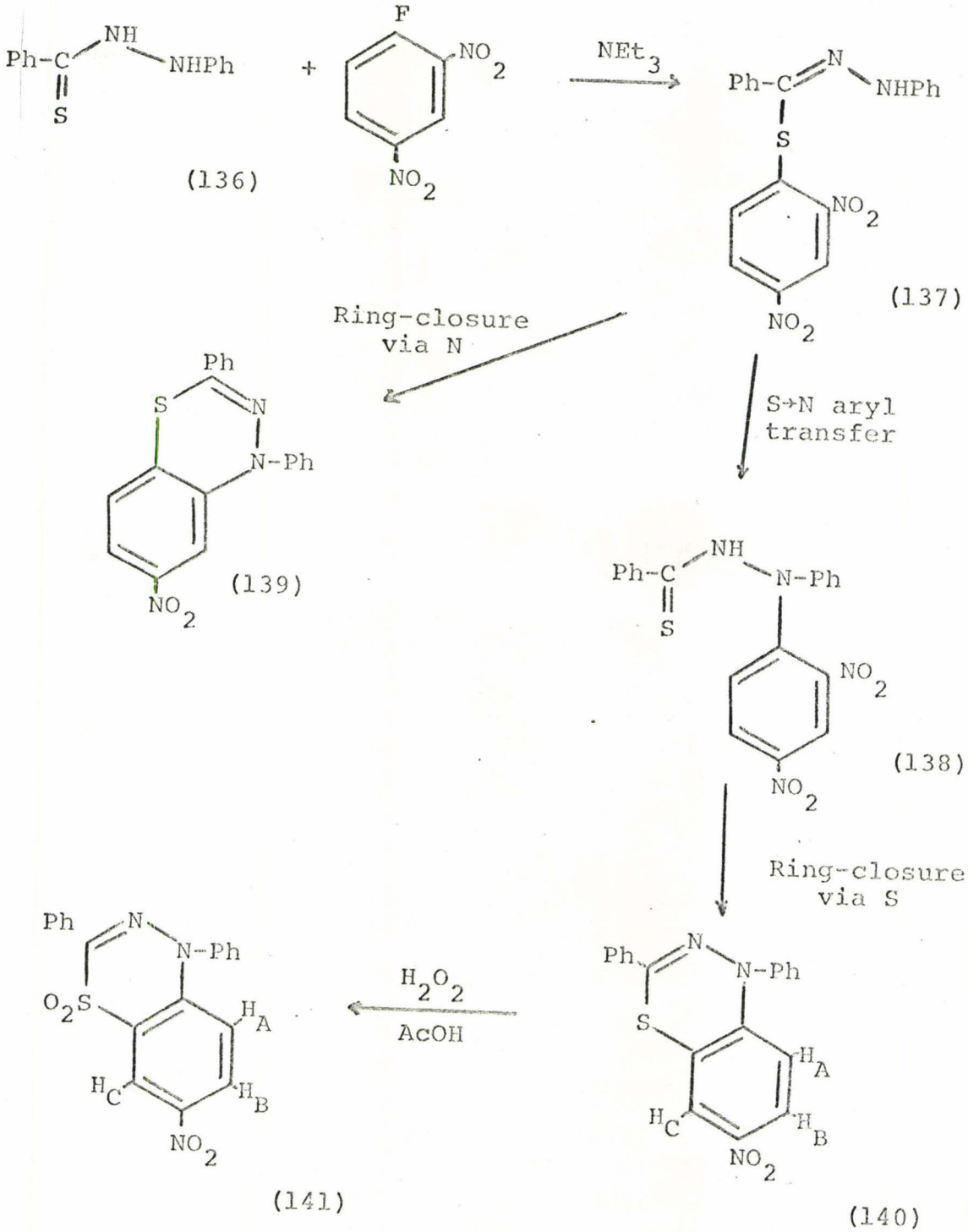
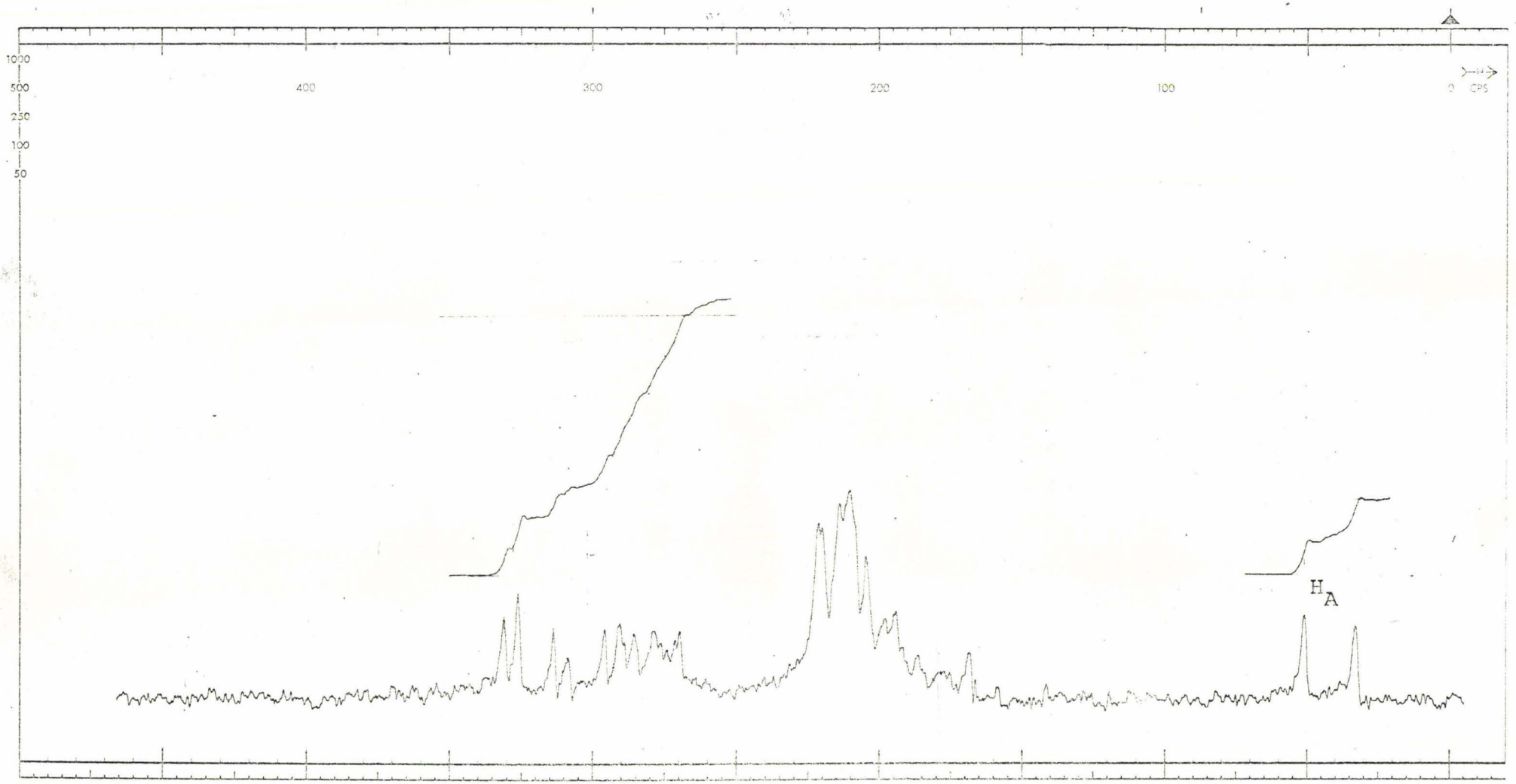
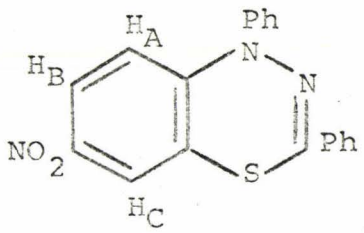

Ph-C(=S)-NH-NHPh
(136)
F
NO2
NO2
NEt3
Ph-C(=N-NHPh)-S
NO2
NO2
(137)
Ring-closure via N
S→N aryl transfer
Ph
S
N
N-Ph
NO2
(139)
Ph-C(=S)-NH-N-Ph
NO2
NO2
(138)
Ring-closure via S
Ph
N
N-Ph
S
HA
HB
HC
NO2
(140)
H2O2
AcOH
Ph
N
N-Ph
O2S
HA
HB
HC
NO2
(141)

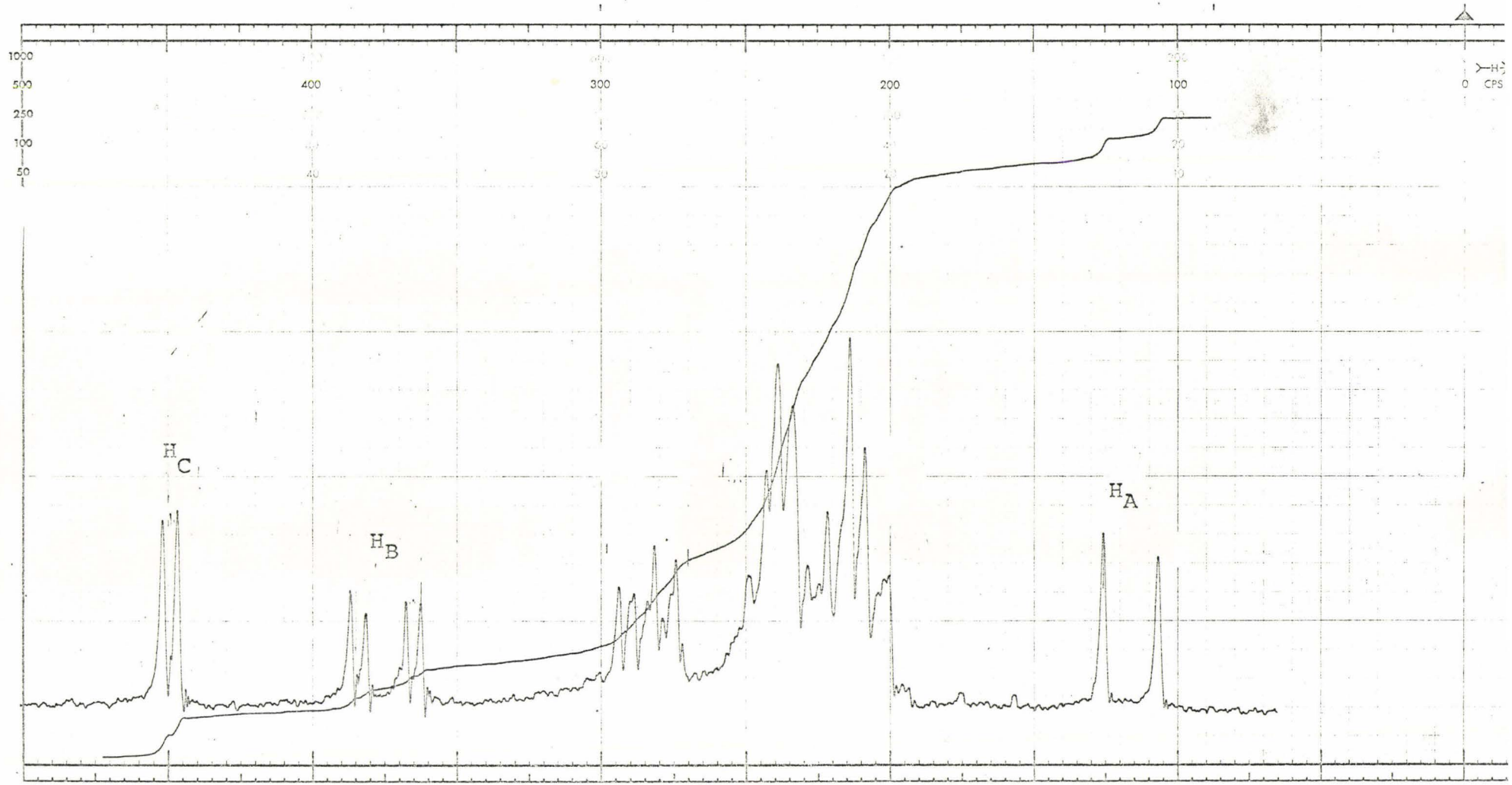
Figure (vi): The Aromatic Region of the p.m.r. Spectrum of (140)

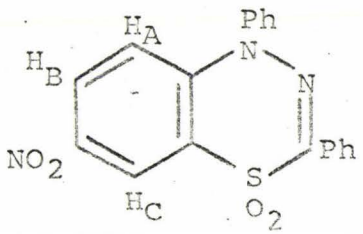




Solvent	DMSO d6
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	650 Hz.
Lock Signal	T.M.S.

Figure (vii): The Aromatic Region of the p.m.r. Spectrum of (141)

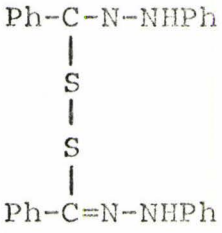




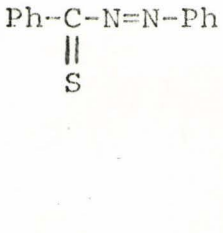
Solvent	DMSO d6
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	650 Hz.
Lock Signal	T.M.S.

structures of the p-nitrothiophenoxy compounds prepared previously were assigned on the evidence that their mass spectra contained a peak corresponding to loss of p-nitrothiophenol from the parent ion. The mass spectrum of the yellow product was identical with that of (140) and for this reason the rearranged structure (138) was favoured.

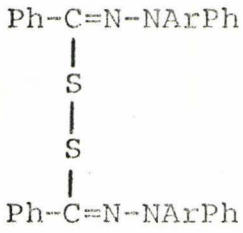
The oxidation of (136) was known to yield the disulfide (142)[58] and not the previously reported azo compound (143)[61]. The oxidation of the yellow product was undertaken in an attempt to isolate the corresponding disulfide (144). However no reaction



(142)



(143)



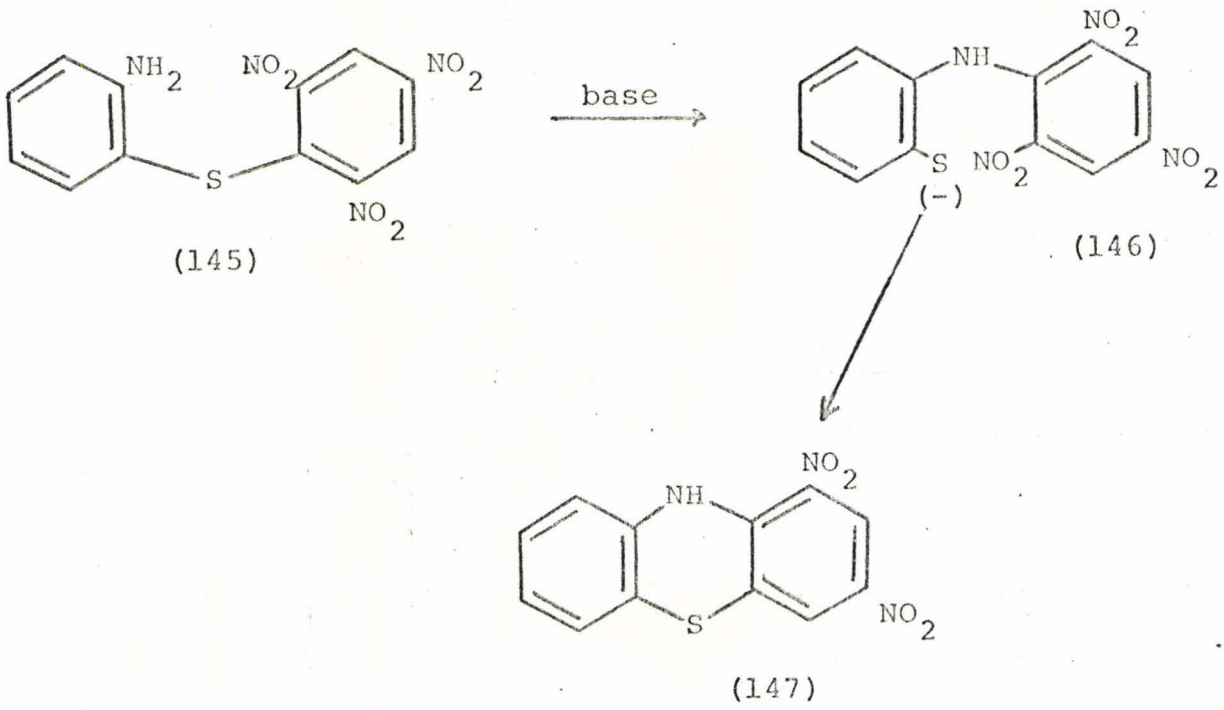
(144)

Ar = 2,4-$(NO_2)_2C_6H_3$-

was observed when peracetic acid was employed as the oxidant. The use of potassium ferricyanide under basic conditions (aqueous sodium bicarbonate) yielded only the cyclised product (140).

The S→N transfer of an aryl group prior to ring-closure through sulfur is well known in phenothiazine chemistry, an example being the conversion of (145) into (147) via the inter-

mediate (146)[69].



(145) (146) (147)

Similar migrations of p-nitrophenyl rings had already been shown to occur in the present work.

vi. Preparation of thiadiazines from dithizone

The use of diphenylthiocarbazone (dithizone) (148) in place of the thiohydrazide (136) was seen as a means of obtaining benzothiadiazines with a phenylazo substituent in the 2-position. Such compounds would be highly coloured and might be suitable intermediates for dyestuffs.

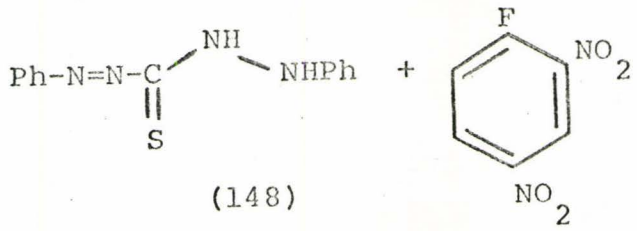
The reaction of dithizone with 2,4-dinitrofluorobenzene

in the presence of triethylamine (Scheme xxi) gave a purple cyclised product which was formulated as (151) on the basis of rearrangement prior to ring closure. The p.m.r. spectra of (151) and its oxidation product (152) were similar to those of (140) and (141) respectively. The aromatic portions of these spectra are reproduced in Figures (viii) and (ix) respectively. The presence of the high-field doublet (ortho-coupled) in Figure (viii) and the low-field doublet (meta-coupled) in Figure (ix) is consistent with the proposed structures (see Section III (v)).

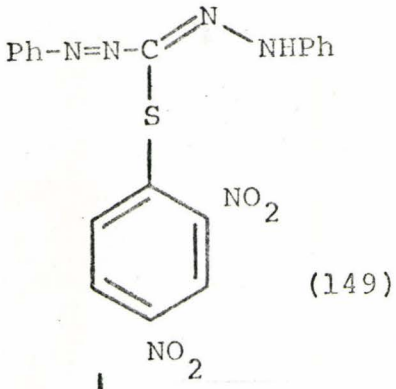
The reaction of dithizone with 2,4-dinitrofluorobenzene was repeated at 0° and the reaction was quenched after 5 minutes. A yellow solid was isolated which was thermally unstable and heating to ca.170° converted it to (151). The analysis figures were consistent with either (149) or (150) if this instability is taken into account. The mass spectrum was identical with the cyclised product (151) and therefore the rearranged structure (150) was favoured. However, since the inlet temperature was above 200° in the mass spectrometer, a thermal cyclisation cannot be dismissed. Attempted oxidation with peracetic acid resulted in the recovery of starting material (see Section III (v)) whilst the use of potassium ferricyanide as the oxidant yielded only (151).

Dithizone itself had previously been shown to undergo a facile oxidative ring-closure in refluxing acetic acid to give (153).[70,71] It was hoped that if the yellow product was indeed (150)

SCHEME (xxi)

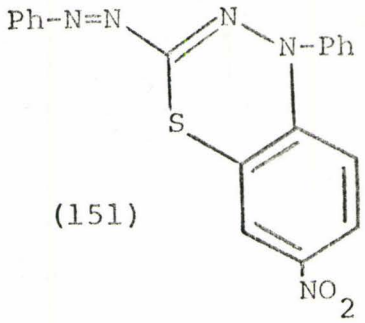


(148)



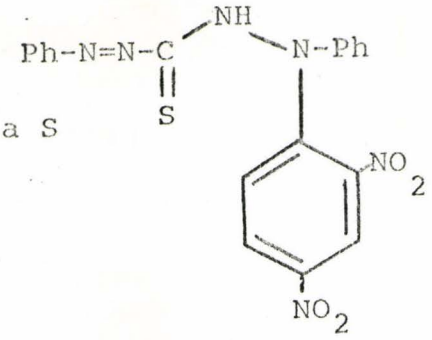
(149)

S→N aryl transfer



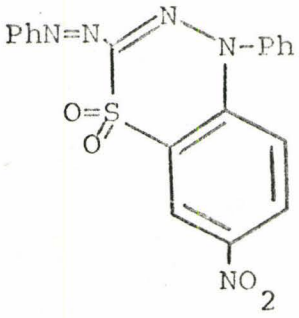
(151)

Ring closure via S



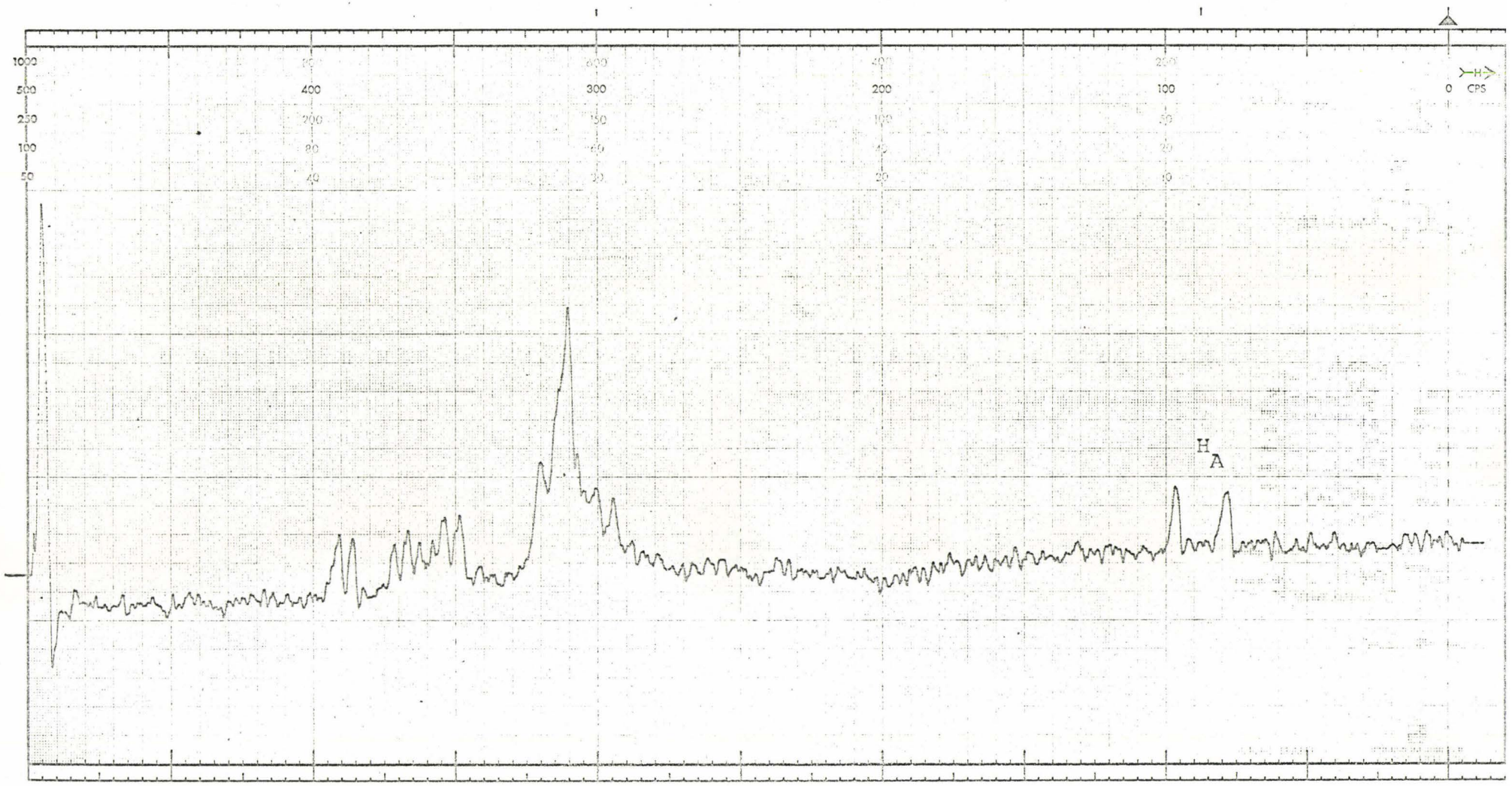
(150)

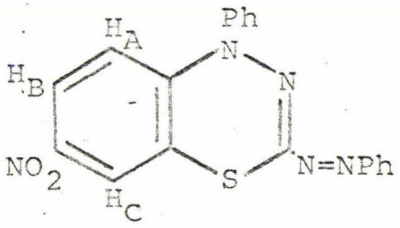
H_2O AcOH



(152)

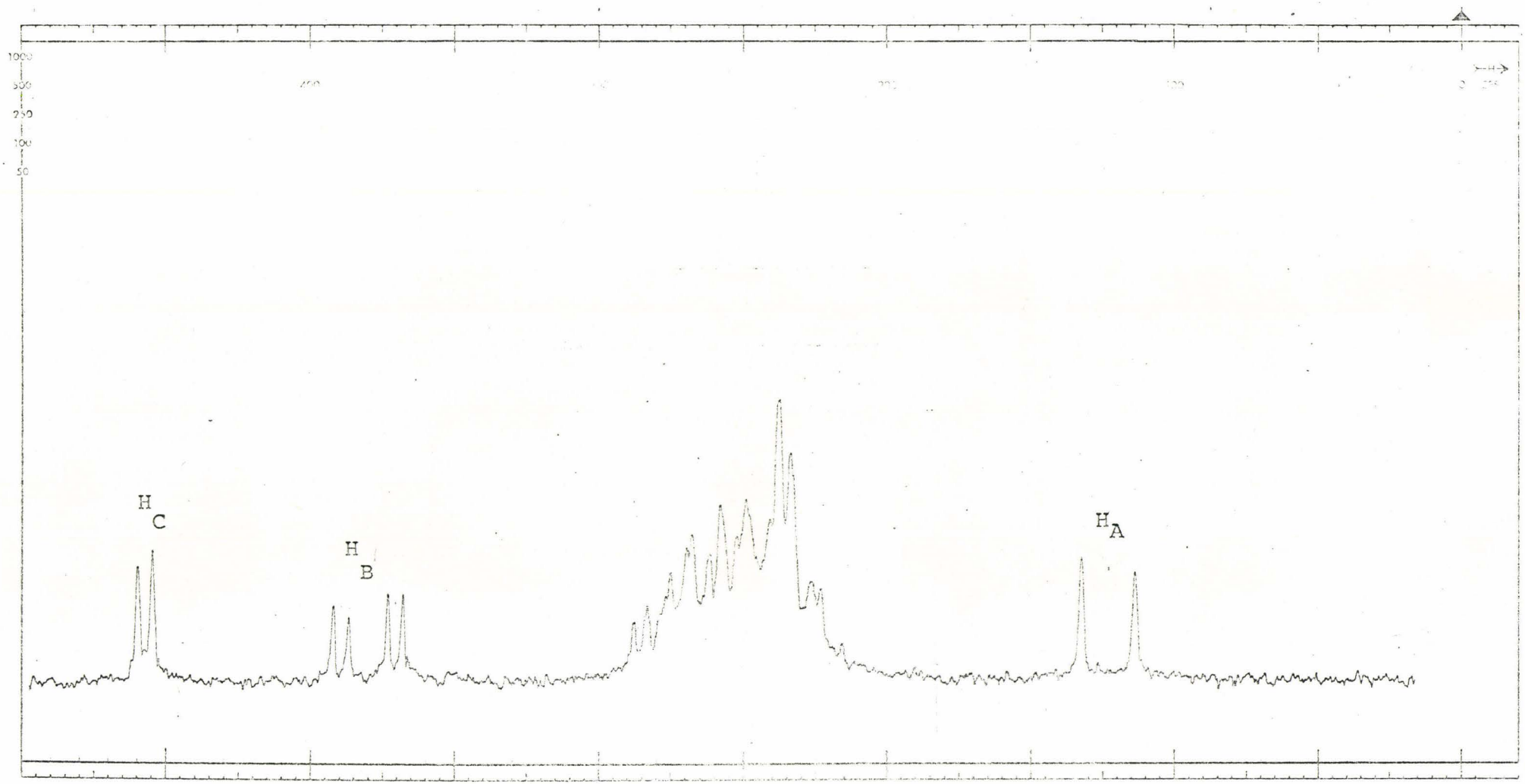
Figure (viii): The Aromatic Region of the p.m.r. Spectrum of (151)

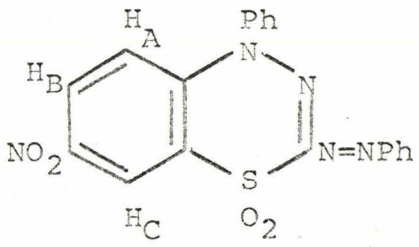




Solvent	DMSO d6
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	600 Hz.
Lock Signal	T.M.S.

Figure (ix): The Aromatic Region of the p.m.r. Spectrum of (152)

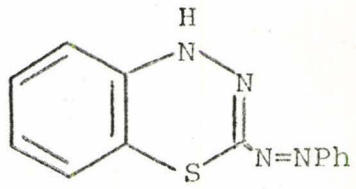




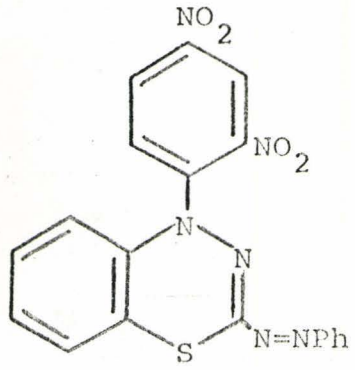
Solvent	DMSO d6
Frequency	100 MHz.
Sweep Width	250 Hz.
Sweep Offset	646 Hz.
Lock Signal	T.M.S.

an analogous oxidation would yield (154). However after 5 hours in refluxing acetic acid only (151) was obtained, presumably via the thermal cyclisation process.

Having established that dithizone would react with



(153)

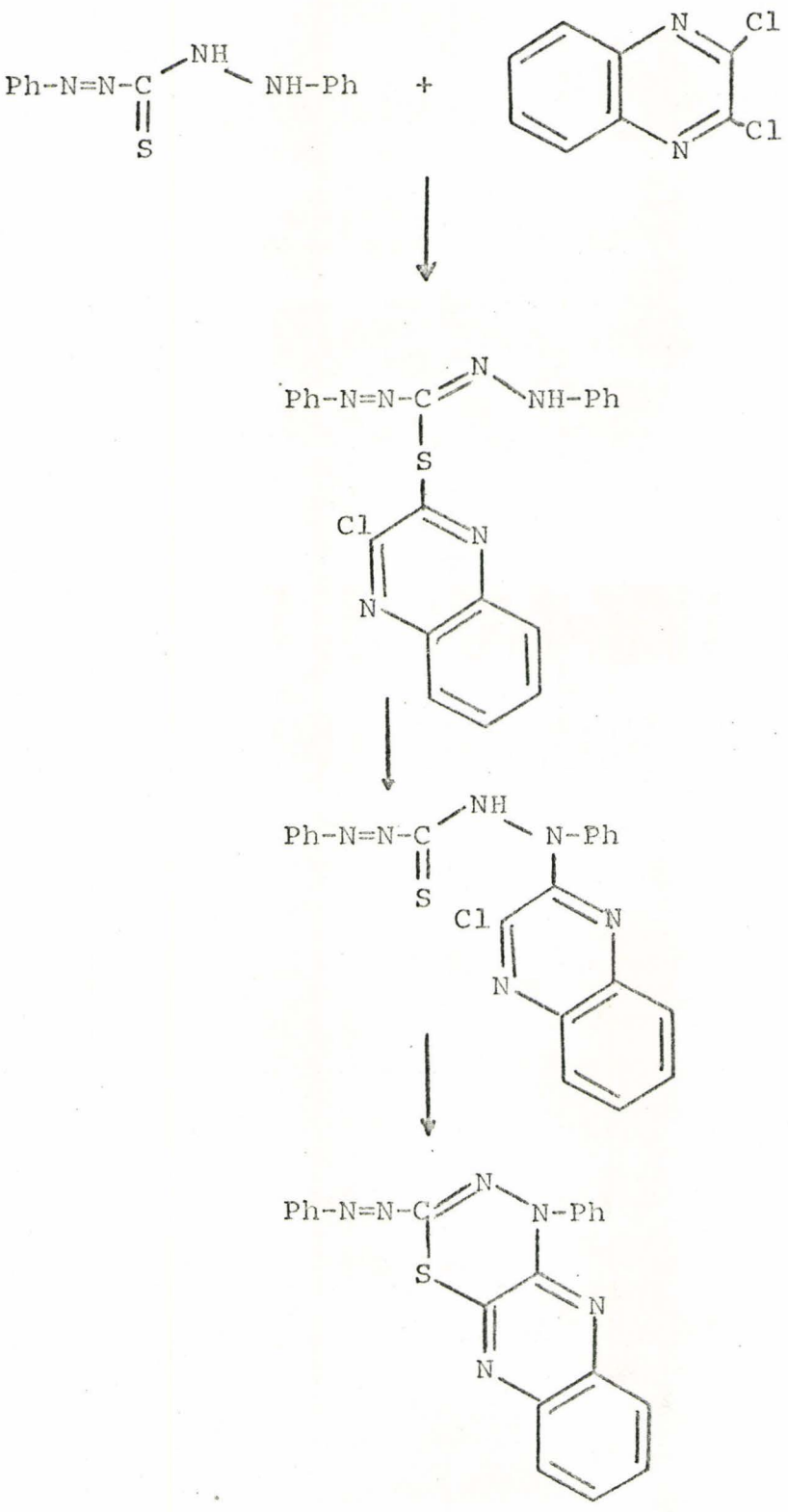


(154)

2,4-dinitrofluorobenzene in this manner, attention was focussed on the synthesis of heterocyclic analogues of 1,3,4-thiadiazines. The reaction of dithizone with 2,3-dichloroquinoxaline proceeded smoothly to yield the novel quinoxalino[2,3][1,3,4]thiadiazine ring system (155), presumably after S→N migration of the heterocyclic ring (Scheme xxii). A similar transfer of a quinoxaline ring had been observed earlier in the synthesis of (129d). It was not possible to isolate any intermediate uncyclised product.

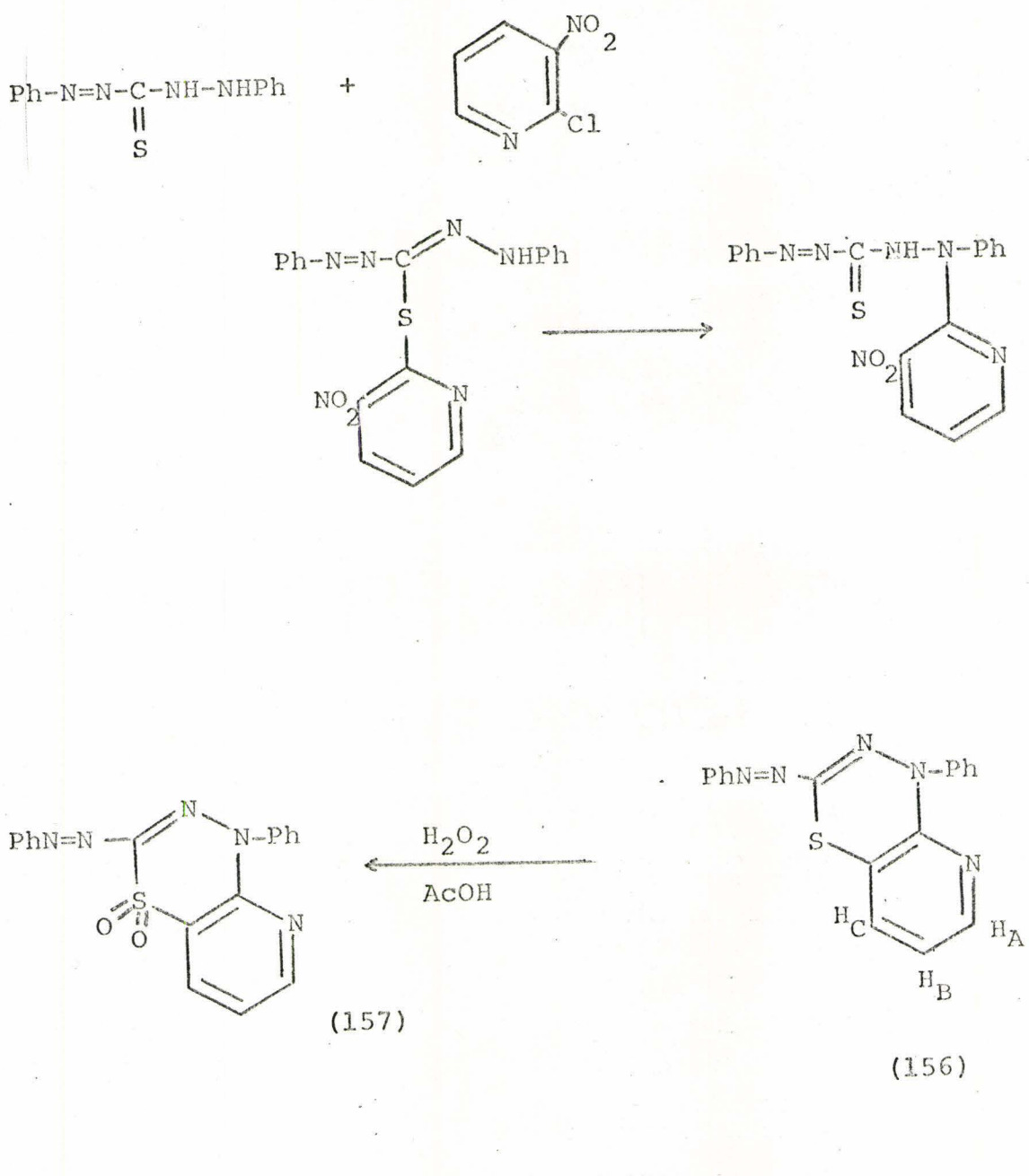
The reaction of dithizone with 2-chloro-3-nitropyridine yielded a purple, cyclised product which was formulated as (156) and is believed to be the first example of the pyrido[2,3][1,3,4]-thiadiazine ring system. The structure (156) requires the migration of the nitropyridine ring prior to ring-closure (Scheme xxiii). Earlier the nitropyridine ring in (85c) had been shown to undergo a similar transformation. The p.m.r. spectra of (156) and its

SCHEME (xxii)



(155)

SCHEME (xxiii)



(157)

(156)

oxidation product (157) were consistent with the proposed structures although they did not provide conclusive evidence. The high-field quartet in (156) was assigned as H_B on the basis of the coupling constants[62] and chemical shift[14]. Since H_B shows ortho-coupling to two protons, the pyridine nitrogen must be in the 5-position.

The formation of the three thiadiazines from dithizone and ortho disubstituted aromatic compounds all proceeded smoothly and in high yield. It is likely, therefore, that this method could be extended to the synthesis of other novel ring systems provided that suitably substituted heterocycles can be prepared.

EXPERIMENTAL

GENERAL

i. Outline of Experimental Section

The experimental section consists of four parts. In the first, the preparation of the hydrazidic halides is described. In the cases where these have already been described in the literature, detailed experimental procedures are not repeated.

The second part consists of the reactions of the hydrazidic halides with the nucleophiles chosen in the study. Where the products of these reactions are uncertain, the attempts to identify the compounds are also described.

The cyclisation of the hydrazides to give the oxadiazine ring system makes up the third part, while the synthesis of the thiadiazines is contained in part four. Also contained in part four is the oxidation of some of the thiadiazines.

ii. Drying of Solvents

Benzene and toluene were dried over sodium wire. Absolute ethanol and methanol were obtained by distillation from magnesium turnings containing a trace of iodine.

Acetonitrile was dried by distillation from phosphorus pentoxide. Dimethylformamide and triethylamine were stored over sodium hydroxide for at least four days prior to use.

iii. Chromatography

Microscope slides coated with Kieselgel GF (Merck) were used for thin layer chromatography (t.l.c.) and unless otherwise stated dry toluene was used as developer. The slides were dried and examined under ultra-violet light.

All chromatography columns were packed with Florisil (60-100 mesh) supplied by the Fisher Chemical Co.

iv. Spectroscopic Analysis

Proton magnetic resonance (p.m.r.) spectra were recorded on Varian Associates HA-100, A-60 and T-60 spectrometers using tetramethylsilane (T.M.S.) as internal standard. Unless otherwise stated the spectra refer to 60 MHz. All p.m.r. data are expressed as parts-per-million (δ) downfield from T.M.S., and the symbols s. = singlet, d. = doublet, t. = triplet, q. = quartet and m. = multiplet are used below in the recording of spectra. The presence of exchangeable protons, e.g. bonded to nitrogen, was confirmed by use of deuterium oxide.

Fluorine nuclear magnetic resonance spectra were recorded on a Varian Associates DP-60 IL spectrometer in deuterochloroform solution at 56.4 MHz. Results are given as parts-per-million (δ) upfield from 1,1,1-trichlorotrifluoroethane as internal standard.

Mass spectra were determined on an Hitachi Perkin-Elmer RMU-6A spectrometer and also on a C.E.C. 21-100 high resolution instrument. The results are quoted as m/e values for the

lowest isotopic species except where the sample contained bromine when values for ^{79}Br and ^{81}Br are given to denote the number of bromine atoms present in the fragment.

Infrared spectra were obtained on Beckmann IR-5 and Perkin-Elmer 337 infrared spectrophotometers as potassium bromide wafers, nujol mulls or in solution (solvent given). Abbreviations: v.s. = very strong, s. = strong, m. = medium, w. = weak and br. = broad.

v. Other Data

Microanalyses and molecular weight measurements were performed mainly by the Pascher Laboratories, 54 Buschstrasse, Bonn 53. Other analyses were obtained from the Chemistry Department, University of Manchester Institute of Science and Technology, Manchester 1.

Melting points were determined either on a Kofler block or on a Hoover "unimelt" capillary melting point apparatus and are given uncorrected in °C.

I PREPARATION OF THE HYDRAZIDIC HALIDES

N-α-Bromobenzylidene-N'-(2,4-dibromophenyl)hydrazine (3)

This was prepared by the method of Chattaway and Walker[2] in 63% yield and had m.p. 116-117° (lit.[2], 116-117°): $\nu_{max.}$ 1600, 1500, 815, 760, 692 cm^{-1} (s.); 1440, 1390, 1310, 1260, 1235, 1150, 1130, 1125, 1110, 1025, 938, 918, 862, 742 cm^{-1} (m.); 3250 cm^{-1} (w.): p.m.r., CCl_4, 8.5 δ (s., N-H), 7.7-7.95 δ (m., 2H), 7.54 δ (s., 1H), 7.2-7.4 δ (m., 5H).

N-α-Bromo-p-chlorobenzylidene-N'-(2,4-dibromophenyl)hydrazine (41)

p-Chlorobenzaldehyde (26g.) in ethanol (40 ml.) and phenylhydrazine (20 ml.) in ethanol (40 ml.) were swirled together and cooled in ice. The product was filtered off and sucked dry at the pump.

Bromine (27 ml.) in acetic acid (100 ml.) was added dropwise during one hour to a stirred suspension of the p-chlorobenzaldehyde phenylhydrazone in acetic acid (400 ml.) cooled in ice. When all the bromine had been added stirring was continued at room temperature for a further two hours. Water (25 ml.) was added and the precipitate was filtered off, washed well with water and dried *in vacuo*. Crystallisation (twice) from ethanol-ethyl acetate (charcoal) gave N-α-bromo-p-chlorobenzylidene-N'-(2,4-dibromophenyl)hydrazine (53g., 61%) as colourless needles, m.p. 145-146° (Found: C, 33.7; H, 1.7; N, 6.2. $C_{13}H_8Br_2ClN_2$ requires C, 33.4; H, 1.7; N, 6.0%): $\nu_{max.}$

1580, 1500, 1460, 1370, 1310, 1155, 1138, 832, 810 cm^{-1} (s.); 1440, 1237, 1096, 1014, 934, 868, 729, 711 cm^{-1} (m.); 3290 cm^{-1} (w.): p.m.r., CCl_4, 8.55 δ (s., N-H), 7.78 (A) and 7.32 (B) δ (A_2B_2q., J = 9Hz.), 7.60-7.26 δ (m., 3H).

N-α-Bromo-p-methoxybenzylidene-N'-(2,4-dibromophenyl)hydrazine (47)

This was prepared by the method outlined above using an equivalent amount (24ml.) of p-methoxybenzaldehyde. The product (48g., 55%) crystallised from ethyl acetate (charcoal) as colourless needles, m.p. 132° (lit.,[49] 135°) (Found: C, 36.6; H, 2.7. Calc. for $C_{14}H_{11}Br_3N_2O$: C, 36.3; H, 2.4%): $\nu_{max.}$ 1580, 1490, 1310, 1248, 1187, 1035, 834, 808 cm^{-1} (s.); 1370, 1320, 1239, 1120, 934, 868, 619 cm^{-1} (m.); 3300 cm^{-1} (w.): p.m.r., CCl_4, 8.45 δ (s., N-H), 7.75 (A) and 6.80 (B) δ (A_2B_2q., J = 9Hz.), 7.6-7.24 δ (m., 3H), 3.80 δ (s., 3H).

N-α-Bromobenzylidene-N'-(2-bromo-4-nitrophenyl)hydrazine (59)

The literature method gave the required product as yellow needles, m.p. 170-172° (lit.,[50] 171-172°).

N-α-Bromobenzylidene-N'-(4-bromo-2-fluorophenyl)hydrazine (49)

o-Fluorophenylhydrazine (from o-fluoroaniline)[51] was used in the literature preparation of this compound which crystallised from ethanol in 81% yield as light pink prisms, m.p. 83-87°, (lit.,[18] 87-88°).

N-α,5-Dibromo-2-thienylidene-N'-(2,4-dibromophenyl)hydrazine (42)

Method 1:

Thienyl-2-aldehyde (11.2g.) in ethanol (20ml.) was added with stirring to a solution of phenylhydrazine (10.8g.) in ethanol (20ml.). The mixture became solid and very hot. The dirty yellow solid was broken up and suspended in glacial acetic acid (250ml.) & cooled in an ice-bath. Bromine (72g., 23ml.) in glacial acetic acid (100ml.) was added dropwise during one hour to the stirred, cooled suspension. After the addition was complete the mixture, still cooled, was stirred for a further 1.5 hours. Water (50ml.) was added and the green solid filtered off. The product was washed in turn with a little acetic acid, much water and finally it was dried in vacuo. Crystallisation (twice) from ethanol-ethyl acetate gave N-α,5-dibromo-2-thienylidene-N'-(2,4-dibromophenyl)hydrazine (33.7g., 65%) as pale green needles, m.p. 147-8° (Found: C, 25.4; H, 1.3; Br, 61.9; N, 5.5; S, 6.3. $C_{14}H_6Br_4N_2S$ requires C, 25.5; H, 1.2; Br, 61.8; N, 5.4; S, 6.2%): $\nu_{max.}$ 1580, 1490, 1440, 1385, 1150, 1128, 804, 785, cm^{-1} (s.); 1300, 1248, 1033, 970, 858, 711, 696 cm^{-1} (m.); 3280 cm^{-1} (w.): p.m.r., T.H.F. (100 MHz.) 8.40 δ (s., N-H), 7.67-7.22 (m., 3H), 7.23 (A) and 7.07 (B) δ (ABq., J= 4.0Hz).

Method 2:

5-Bromothienyl-2-aldehyde was prepared from thienyl-2-aldehyde according to the literature method;[36] p.m.r., neat, 9.87 δ (s., 1H), 7.68 (A) and 7.26 (B) δ (ABq., J = 4.0Hz). The phenylhydrazone had m.p. 110-112° (lit.,[36] 111-112°).

The crude hydrazone (14.05g.) was suspended in glacial acetic acid (200ml.), cooled in ice. Bromine (9ml.) in glacial acetic acid (50ml.) was added dropwise during one hour to the stirred, cooled suspension, and after the addition was complete stirring was continued for a further 1.5 hours with cooling. Water (20ml.) was added and the green solid was filtered off. The product was washed in turn with acetic acid and water, and finally it was dried in vacuo. Crystallisation (three times) from ethanol-ethyl acetate gave N-α,5-dibromo-2-thienylidene--N'-(2,4-dibromophenyl)hydrazine (15.1g., 58%) as pale green needles, m.p. and mixed m.p. 147-8°. The i.r. spectrum was identical with that of the product from Method 1.

II REACTIONS OF THE HYDRAZIDIC HALIDES

i. Reaction with anhydrous sodium acetate

Sodium acetate trihydrate was fused in an evaporating dish immediately prior to use.

Typically, N-α-bromobenzylidene-N'-(2,4-dibromophenyl)-hydrazine, (3), (9.0g.) and anhydrous sodium acetate (9.0g., ca. 5 equiv.) were refluxed in glacial acetic acid for two hours. The mixture was cooled and poured into ice-water. The solid was filtered off and dried in vacuo to give the crude product. N-Benzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (7.25g., 87%) separated from benzene as colourless needles, m.p. 154-5°, (lit.,[2] 158-9).

Similarly (47) (4.64g.) gave N-p-methoxybenzoyl-N'--acetyl-N'-(2,4-dibromophenyl)hydrazine (3.9g., 88%) as colourless needles, m.p. 153-4° from hexane-toluene (Found: C, 43.61; H, 3.09; N, 6.50. $C_{16}H_{14}Br_2N_2O_3$ requires C, 43.44; H, 3.17; N, 6.33%): $\nu_{max.}$ 1670 cm^{-1} (s., br.); 3220, 1610, 1468, 1314, 1255, 1180, 679 cm^{-1} (s.); 1495, 1380, 1034, 847, 767 cm^{-1} (m.).

Compound (41) (4.67g.) gave N-p-chlorobenzoyl-N'-acetyl--N'-(2,4-dibromophenyl)hydrazine (3.7g., 86%) as colourless needles, m.p. 169.5-170.5°, from hexane-toluene (Found: C, 40.34; H, 2.51; N, 6.36. $C_{15}H_{11}Br_2ClN_2O_2$ requires C, 40.36; H, 2.47; N, 6.28%): $\nu_{max.}$ 1670 cm^{-1} (s., br.); 3190, 1480, 1460, 1380, 1342, 1265, 844, 751 cm^{-1} (s.); 1600, 1520, 1315, 1091, 1012, 983, 775 cm^{-1} (m.).

Compound (49) (3.72g.) yielded N-benzoyl-N'-acetyl-N'--(4-bromo-2-fluorophenyl)hydrazine (3.2g., 86%) as colourless matted needles, m.p. 174-5° (lit.,[17] 175.5-176°), from benzene (Found: C, 51.45; H, 3.48; N, 8.0. Calc. for $C_{15}H_{12}BrFN_2O_2$: C, 51.28; H, 3.42; N, 7.98%).

N-α-Bromobenzylidene-N'-(2-bromo-4-carbethoxyphenyl)-hydrazine[37] (2.13g.) however, gave N-benzoyl-N'-(2-bromo-4-carbethoxyphenyl)hydrazine (1.0g., 59%) as colourless needles, m.p. 134°, from hexane-toluene (Found: C, 53.15; H, 4.07; N, 7.57. $C_{16}H_{15}BrN_2O_3$ requires C, 52.89; H, 4.13; N, 7.71%): $\nu_{max.}$ 1700, 1650, 1590, 1270, 760 cm^{-1} (s.); 3200, 1500, 1305, 1110, 690, 662 cm^{-1} (m.); 3240 cm^{-1} (w.).

All attempts to acetylate this compound using acetic anhydride in both acidic (acetic acid) and basic media (triethylamine) resulted in the recovery of starting material.

Compound (42) (5.18g.) gave N-5-bromo-2-thienoyl-N'--acetyl-N'-(2,4-dibromophenyl)hydrazine (4.1g., 84%) as fawn coloured plates, m.p. 104.5-105°, from toluene (Found: C, 38.49; H, 2.74; N, 4.78. $C_{13}H_9Br_3N_2O_2S$ requires C, 31.39; H, 1.18; N, 5.63%): $\nu_{max.}$ 1670 cm^{-1} (s., br.); 1470, 1410, 1380, 1310, 1270, 1078, 740 cm^{-1} (s.); 3230, 988, 875, 805, 730, 579 cm^{-1} (m.): m.s. 500/498/496/494 (M^+), 458/456/454 / 452 ($M^+-CH_2=C=O$), 295/293/291 ($Br_2C_6H_3NHAc$), 267/265/263, 253/251/249 ($Br_2C_6H_3NH_2$), 235/233/231, 226/224/222, 207/205 ($BrC_4H_2SCONH_2$), 191/189, 170/168, 163/161, 156/154, 119, 117, 111, 92, 91, 82, 65, 63, 56, 43.

Reaction of (59) with anhydrous sodium acetate in dimethylformamide

Compound (59) (3.99g., 0.01 mole) and anhydrous sodium acetate (9g., Ca. 10 equiv.) were dissolved in dry dimethylformamide (30ml.) and the solution was boiled under reflux for 20 minutes. The solution was cooled and poured into water (750ml.) containing acetic acid (20ml.). The yellow solid was filtered off and dried in vacuo. Crystallisation from ethanol-ethyl acetate gave 4-acetyl-7-nitro-2-phenyl-4H-benzo[1,3,4]oxadiazine (2.2g., 74%) as yellow needles m.p. 204-5° (Found: C, 60.87; H, 4.07; $C_{15}H_{11}N_3O_4$ requires C, 60.61; H, 3.70%): $\nu_{max.}$ 1690, 1530, 1485, 1370, 1340, 1300, 742 cm^{-1} (s.); 1235, 1190, 1068, 940, 878, 817, 769, 684 cm^{-1} (m.).

An attempted removal of the acetyl group in methanolic sodium methoxide (reflux time, one hour) yielded a yellow gum which gave poorly defined spectra and was shown (t.l.c.) to contain at least four compounds, none of which was starting material.

The reaction was repeated as above, except that the solution was heated to reflux and then immediately poured into 10% acetic acid (750ml.). The yellow solid was filtered off and sucked partly dry at the pump. The presence of the oxadiazine was established (t.l.c., i.r.). Crystallisation from ethanol-ethyl acetate gave N-α-ethoxybenzylidene-N'-(2-bromo-4--nitrophenyl)hydrazine (2.7g., 74%) as yellow needles, m.p. 142.5-143.5° (lit.,[38] 149°) (Found: C, 49.27; H, 3.88; Br, 22.17.

Calc. for $C_{15}H_{14}BrN_3O_3$: C, 49.45; H, 3.85; Br, 21.98%): $\nu_{max.}$ 1580, 1500, 1325, 1282, 1120, 1105 cm^{-1} (s.); 1350, 1125, 1080, 1032, 1020, 898, 768, 746, 694 cm^{-1} (m.); 3350 cm^{-1} (w.): p.m.r., $CDCl_3$, 9.15 δ (s., N-H), 8.58-7.50 (m., 8H), 4.29 δ (q., 2H), 1.59 δ (t., 3H).

ii. With phenols

Reaction of (3) with p-nitrophenol

Compound (3) (4.33g., 0.01 mole), triethylamine (2ml., 0.02 mole) and p-nitrophenol (1.39g., 0.01 mole) were stirred together in ethanol (30 ml.) at room temperature for two hours. The precipitate was filtered off, washed well with water and crystallised from ethanol to give N-α-(p-nitrophenoxy)benzylidene--N'-(2,4-dibromophenyl) hydrazine (3.44g., 70%) as yellow prisms, m.p. 100-101° (Found: C, 46.5; H, 2.7; N, 8.6. $C_{19}H_{13}Br_2N_3O_3$ requires C, 46.5; H, 2.6; N, 8.6%): $\nu_{max.}$ 1580, 1510, 1470, 1450, 1365, 1340, 1320, 1145, 1105, 849 cm^{-1} (s.); 1595, 1220, 813, 765, 697 cm^{-1} (m.). 3380 cm^{-1} (w.): p.m.r., CCl_4, 8.25 δ (s., N-H), 8.3 (A) and 7.2 (B) δ ($A_2B_2q.$, J = 8Hz.), 7.9-7.35 δ (m., 8H): m.s. 493/491/489 (M^+), 476/474/472, 412/410 (M^+-Br), 411/409, 388/386/384 (M^+-PhCO), 372/370/368 (M^+-$PhCONH_2$), 354/352/350 (M^+-$NO_2C_6H_4OH$), 344/342/340, 274/272, 252/250/248 (base peak $Br_2C_6H_3NH$), 237/235/233, 225/223/221, 171/169, 106, 105, 77, 63.

The above product (0.5g., 0.001 mole) was dissolved in a warm mixture of triethylamine (5ml.) and ethanol (5ml.) and

the solution was boiled under reflux for 15 minutes. The solvent was removed *in vacuo* and the resulting solid crystallised from benzene to give *N-benzoyl-N'-(p-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine* (0.34g., 69%) as colourless prisms, m.p. 215-6° (Found: C, 46.3; H, 2.6; N, 8.4. $C_{19}H_{13}Br_2N_3O_3$ requires C, 46.5; H, 2.6; N, 8.6%): $\nu_{max.}$ 1645, 1580, 1490, 1455, 1320, 1290, 1275, 1105, 834 cm^{-1} (s.); 3220, 1530, 1370, 1249, 1040, 748, 687 cm^{-1} (m.): *m.s.* 493/491/489 (M^+), 476/474/472, 412/410, 411/409, 395/393, 388/386/384, 374/372/370 (M^+-PhCON), 372/370/368 (M^+-$PhCONH_2$), 344/342/340, 264/262/260, 253/251/249, 237/235/233, 182, 166, 121, 106, 105, 104, 103, 77, 76, 75, 63: *p.m.r.*, d_6 DMSO, 11.4 δ (s., N-H); 8.0 (A) and 6.65 (B) δ (A_2B_2 q., J = 9Hz.), 7.9-7.3 δ (m., 8H).

Reaction of (47) with p-nitrophenol

The hydrazidic bromide (4.64g., 0.01 mole), p-nitrophenol (1.39g., 0.01 mole) and triethylamine (2ml.) were stirred together in ethanol (25ml.) for two hours at room temperature. The solution was poured into water, the yellow solid filtered off and dried *in vacuo*. Crystallisation from ethanol-ethyl acetate gave *N-α-(p-nitrophenoxy)-p-methoxybenzylidene-N'-(2,4-dibromophenyl)hydrazine* (4.73g., 90%) as yellow needles, m.p. 143-144° (Found: C, 45.99; H, 2.88; N, 8.03. $C_{20}H_{15}Br_2N_3O_4$ requires C, 46.1; H, 2.9; N, 8.1%): $\nu_{max.}$ 1580, 1490, 1345, 1230, 1119 cm^{-1} (s.); 1610, 1520, 1250, 1150, 1050, 859 cm^{-1} (m.).

The above product (3g) was dissolved in a warm mixture of ethanol (15ml.) and triethylamine (15ml.) and the solution

was boiled under reflux for 15 minutes. The solvent was removed in vacuo and the orange solid crystallised from ethanol-ethyl acetate to give cream needles, m.p. 235°, of N-p-methoxybenzoyl--N'-(p-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine (2.5g., 82%) (Found: C, 46.04; H, 3.01; Br, 30.89. $C_{20}H_{15}Br_2N_3O_4$ requires C, 46.07; H, 2.88; Br, 30.71%): $\nu_{max.}$ 1322 cm^{-1} (s., br.); 1595, 1495, 1258 cm^{-1} (s.); 1655, 1465, 1112, 843, 751 cm^{-1} (m.); 3220 cm^{-1} (w.).

Reaction of (41) with p-nitrophenol

The hydrazidic bromide (4.67g., 0.01 mole), p-nitrophenol (1.39g.) and triethylamine (2ml.) were stirred in ethanol (30ml.) at room temperature for 2 hours. The yellow solid was filtered off, washed well with water and dried in vacuo. Crystallisation from a mixture of t-amyl alcohol and benzene gave N-α-(p-nitrophenoxy)-p-chlorobenzylidene-N'-(2,4-dibromophenyl)hydrazine (4.4g., 72%) as yellow needles, m.p. 151° (Found: C, 43.8; H, 2.5; N, 7.9. $C_{19}H_{12}Br_2ClN_3O_3$ requires C, 43.5; H, 2.3; N, 8.0%): $\nu_{max.}$ 1448, 1365, 1330 cm^{-1} (s.); 1580, 1220, 1140, 1090, 857, 804, 732, 718 cm^{-1} (m.); 3350 cm^{-1} (w.).

The above compound (0.5g., 0.001 mole) was dissolved in a warm mixture of ethanol (5ml.) and triethylamine(5ml.) and the solution refluxed for 15 minutes. Concentration and cooling of the reaction mixture gave cream needles, m.p. 235°, of N-p--chlorobenzoyl-N'-(p-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine (0.32g., 64%) (Found: C, 43.4; H, 2.4; N, 8.0. $C_{19}H_{12}Br_2ClN_3O_3$ requires C, 43.5; H, 2.3; N, 8.0%): $\nu_{max.}$ 1640, 1580, 1445,

1325, 1105, 832 cm^{-1} (s.); 3200, 1360, 1300, 1280, 1090, 1015, 748 cm^{-1} (m.).

Reaction of N-α-bromobenzylidene-N'-(2-bromo-4-carbethoxyphenyl)-hydrazine with p-nitrophenol

The hydrazidic bromide (2.13g., 0.005 mole), p-nitrophenol (0.69g., 0.005 mole) and triethylamine (0.5ml.) were stirred in ethanol (20ml.) for two hours. The solid was filtered off, washed well with water and crystallised from ethanol to give colourless needles, m.p. 145°, of N-α-(p-nitrophenoxy)-benzylidene-N'-(2-bromo-4-carbethoxyphenyl)hydrazine (1.49g.,74%) (Found: C, 54.5; H, 3.7, Br, 16.7; N, 8.7. $C_{22}H_{18}BrN_3O_5$ requires C, 54.6; H, 3.7; Br, 16.5; N, 8.7%): $\nu_{max.}$ 1590, 1340, 1255, 1145, 1120, 849, 760 cm^{-1} (s.); 1700, 1498, 1400, 1280, 1220, 1045, 747 cm^{-1} (m.); 3300 cm^{-1} (w.).

The above product (0.5g.), triethylamine (5ml.) and ethanol (5ml.) were boiled under reflux for two hours. The solvent was removed in vacuo and the orange oil crystallised from hexane-benzene to give N-benzoyl-N'-(p-nitrophenyl)-N'-(2-bromo--4-carbethoxyphenyl)hydrazine (0.31g., 62%) as pale yellow prisms, m.p. 119° (Found: C, 54.7; H, 3.9; Br, 16.5; N, 8.6. $C_{22}H_{18}BrN_3O_5$ requires C, 54.6; H, 3.7; Br, 16.5; N, 8.7%): $\nu_{max.}$ 1650, 1590, 1335, 1310, 1280, 1115, 846 cm^{-1} (s.); 3200, 1710, 1498, 1245, 1030, 908, 758, 722, 694 cm^{-1} (m.).

Reaction of (59) with p-nitrophenol

Compound (59) (3.99g., 0.01 mole), p-nitrophenol (1.39g., 0.01 mole), triethylamine (1ml.) and ethanol (30ml.) were stirred together at room temperature for two hours. The yellow solid was filtered off, washed well with water and dried *in vacuo*. Crystallisation from toluene (twice) gave yellow plates, m.p. 192°, of N-α-(p-nitrophenoxy)benzylidene-N'-(2-bromo-4--nitrophenyl)hydrazine (3.8g., 83%) (Found: C, 50.0; H, 3.0; Br, 17.3; N, 12.4. $C_{19}H_{13}BrN_4O_5$ requires C, 49.9; H, 2.8; Br, 17.5; N, 12.3%): $\nu_{max.}$ 1580, 1495, 1435, 1340, 1320, 1220, 1108 cm^{-1} (s.); 1400, 1265, 1142, 1050, 881, 849, 748, 740, 703 cm^{-1} (m.); 3300 cm^{-1} (w.).

The above product (0.5g.), triethylamine (5ml.) and ethanol (5ml.) were boiled under reflux for two hours. The product did not completely dissolve during this time. After cooling the solution was filtered and the pale yellow solid was collected. Trituration with a boiling mixture of toluene and hexane gave yellow prisms, m.p. 286°, of N-benzoyl-N'-(p-nitrophenyl)-N'-(2-bromo-4-nitrophenyl) hydrazine (0.41g., 82%) (Found: C, 50.2; H, 2.8; Br, 17.7; N, 12.35. $C_{19}H_{13}BrN_4O_5$ requires C, 49.9; H, 2.8; Br, 17.5; N, 12.3%): $\nu_{max.}$ 3190, 1645, 1580, 1495, 1448, 1345, 1320, 1285, 1115, 847, 742 cm^{-1} (s.); 1370, 1255, 1180, 1096, 1040, 1025, 931, 908, 869, 834, 748, 715, 704, 689, 678 cm^{-1} (m.).

Reaction of (49) with p-nitrophenol

The hydrazidic bromide (3.72., 0.01 mole), p-nitrophenol (1.39g.), triethylamine (1ml.) and acetonitrile (30ml.) were stirred together at room temperature for two hours. The reaction mixture was poured into water (500ml.), the yellow solid filtered off and dried *in vacuo*. Crystallisation from benzene-hexane gave bright yellow needles, m.p. 115°, of *N-α-(p-nitrophenoxy)-benzylidene-N'-(4-bromo-2-fluorophenyl)hydrazine* (3.85g., 90%) (Found: C, 53.22; H, 3.14; N, 9.68. $C_{19}H_{13}BrFN_3O_3$ requires C, 53.02; H, 3.02; N, 9.77%): $\nu_{max.}$ 1610, 1590, 1510, 1274, 1227, 1195, 1140, 1110 cm^{-1} (s.); 1445, 1410, 1380, 1340, 1067, 1044, 1023, 877, 862, 853, 762, 751, 708, 689 cm^{-1} (m.).

The above product (2.15g., 0.005 mole) was dissolved in a mixture of acetonitrile (15ml.) and triethylamine (15ml.) and the solution was boiled under reflux for 15 minutes. The solvent was removed *in vacuo* and the orange solid was crystallised from benzene to give colourless needles, m.p. 214-216°, of *N-benzoyl--N'-(p-nitrophenyl)-N'-(4-bromo-2-fluorophenyl)hydrazine* (1.9g., 88%) (Found: C, 53.15; H, 3.10. $C_{19}H_{13}BrFN_3O_3$ requires C, 53.02; H, 3.02%): $\nu_{max.}$ 1610, 1590, 1330, 1293, 1262, 1118, 870, 841, 692 cm^{-1} (s.); 1660, 1490, 1380, 1219, 1191, 754, 716, 632 cm^{-1} (m.); 3240 cm^{-1} (w.).

Reaction of (3) with o-nitrophenol

The hydrazidic bromide (4.33g., 0.01 mole), o-nitrophenol (1.39g.) and triethylamine (2ml.) were stirred in ethanol (25ml.)

at room temperature for two hours. The yellow solid was filtered off, washed well with water, and crystallised from ethanol to give N-α-(o-nitrophenoxy)benzylidene-N'-(2,4-dibromophenyl)-hydrazine (3.97g., 70%) as pale yellow prisms, m.p. 106° (Found: C, 46.6; H, 2.6; Br, 32.8; N, 8.6; $C_{19}H_{13}Br_2N_3O_3$ requires C, 46.5; H, 2.6; Br, 32.6, N, 8.6%): $\nu_{max.}$ 1595, 1490, 1385, 1345, 1325, 817, 741 cm^{-1} (s.); 1540, 1305, 1270, 1240, 1170, 1152, 1140, 1035, 863, 778, 762, 702, 687 cm^{-1} (m.); 3290 cm^{-1} (w.).

The above compound (0.5g., 0.001 mole) was dissolved in a mixture of ethanol (5ml.) and triethylamine (5ml.) and the solution was boiled under reflux for 15 minutes. The solvent was evaporated *in vacuo* and the solid was crystallised from hexane-benzene to give N-benzoyl-N'-(o-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine (0.32g., 64%) as bright yellow needles, m.p. 200-1° (Found: C, 46.4; H, 2.9; Br, 32.8; N, 8.8. $C_{19}H_{13}Br_2N_3O_3$ requires C, 46.5; H, 2.6; Br, 32.6, N, 8.6%): $\nu_{max.}$ 3180, 1645, 1597, 1520, 1455, 1298, 1280, 831, 690 cm^{-1} (s.); 1570, 1370, 1240, 1080, 1045, 933, 900, 871, 850, 802, 778, 769, 758, 728 cm^{-1} (m.).

Reaction of (3) with m-nitrophenol

The hydrazidic bromide (2.0g., 0.0046 mole), m-nitrophenol (0.64g., 0.0046 mole), triethylamine (1ml.) and ethanol (25ml.) were stirred together at room temperature for two hours. Filtration yielded a yellow solid which, after washing well with

water, was crystallised from ethanol to give N-α-(m-nitrophenoxy)-benzylidene-N'-(2,4-dibromophenyl)hydrazine (1.24g., 71%) as yellow prisms, m.p. 117-8° (Found: C, 46.5; H, 2.9; Br, 32.5; N, 8.5. $C_{19}H_{13}Br_2N_3O_3$ requires C, 46.5; H, 2.6; Br, 32.6; N, 8.6%): $\nu_{max.}$ 1580, 1530, 1480, 1215, 1150, 1050, 810, 740 cm^{-1} (s.); 1490, 1348, 1325, 1265, 1240, 1125, 1020, 884, 870, 828, 802, 793, 772, 719, 692 cm^{-1} (m.); 3380 cm^{-1} (w.).

The above product (0.5g., 0.001 mole)was dissolved in a mixture of triethylamine (5 ml.) and ethanol (5 ml.) and the solution was boiled under reflux for two hours. The solvent was removed in vacuo and the resulting solid crystallised from ethanol to give starting material (0.38g.) (t.l.c., i.r.). This was dissolved in 2,6-lutidine (10ml.) and refluxed for one hour. There was no reaction (t.l.c.).

An attempted rearrangement of the compound (0.5g.) in dimethylformamide (10ml.) and triethylamine (5ml.) at the reflux temperature for one hour gave only tarry material with no evidence of rearrangement (i.r.).

Reaction of (3) with pentachlorophenol

The hydrazidic bromide (4.33g., 0.01 mole), pentachlorophenol (2.66g., 0.01 mole), triethylamine(1ml.) and ethanol (30ml.) were stirred together at room temperature for two hours. The solid was filtered off, washed well with water and crystallised from ethanol to give N-α-(pentachlorophenoxy)benzylidene-N'--(2,4-dibromophenyl)hydrazine (5.2g., 84%) as colourless needles,

m.p. 165° (Found: C, 37.1; H, 1.7; N, 4.7. $C_{19}H_9Br_2Cl_5N_2O$ requires C, 36.9; H, 1.5; N, 4.5%): $\nu_{max.}$ 1485, 1380, 1352, 1320, 1270, 1046, 817, 761, 694 cm^{-1} (s.); 1590, 1235, 1148, 1115, 1020, 924, 868, 723, 703 cm^{-1} (m.); 3300 cm^{-1} (w.).

The above solid (0.5g.) was dissolved in ethanol (5ml.) and triethylamine (5ml.) and refluxed for one hour. The solvent was evaporated in vacuo and the white solid crystallised from hexane to give colourless needles, m.p. 248-9°, of N-benzoyl-N'-(pentachlorophenyl)-N'-(2,4-dibromophenyl)hydrazine (0.4g., 80%) (Found: C, 39.2; H, 1.9; N, 4.5. $C_{19}H_9Br_2Cl_5N_2O$ requires C, 36.9; H, 1.5; N, 4.5%). Molecular weight determination by measurement of vapour pressure (acetone) gave 620; $C_{19}H_9Br_2Cl_5N_2O$ requires 618.5: $\nu_{max.}$ 1650, 1460, 1392, 1364, 1350, 1284, 706, 691 cm^{-1} (s.); 3180, 1575, 1500, 1268, 1240, 1084, 1063, 1041, 1025, 909, 869, 842, 811, 763, 743, 658 cm^{-1} (m.).

Attempted reaction of (3) with phenol, 2,4-dinitrophenol and 2,4,6-trinitrophenol

Equivalent amounts of (3) triethylamine and each of the three phenols were stirred together in ethanol under nitrogen for two hours. In each case unchanged (3) was recovered and in one case (trinitrophenol) the phenol was recovered.

Attempted reaction of N-α-(p-nitrophenoxy)benzylidene-N'-(2,4-dibromophenyl)hydrazine with hydrochloric acid

The hydrazine (1g.) was dissolved in warm benzene (30ml.)

and hydrochloric acid (10ml., d 1.18) was added to form a two-phase system. The mixture was heated on a steam-bath for one hour in such a way as to keep unnecessary mixing of the two layers to a minimum. Examination of the benzene layer (t.l.c.) indicated that no reaction had taken place.

Attempted hydrolysis of N-benzoyl-N'-(o-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine

Method A:

The hydrazine (1g.) was dissolved in warm ethanol (20ml.) and hydrochloric acid (20ml., d 1.18) was added. The solution was boiled under reflux for 24 hours and the solvent removed in vacuo. Starting material (t.l.c., m.p. 200-1°) was recovered quantitatively.

Method B:

Sodium (0.5g.) was added to ethanol (25ml.) and the hydrazine (2g.) was added. The solution was refluxed for 12 hours and carefully poured into a mixture of ice-water (20ml.) and hydrochloric acid (20ml., d 1.18). The yellow solid was filtered off and washed with water. Starting material (1.7g.) was recovered (t.l.c., m.p. 199-201°).

iii. With Sodium Thioacetate

Preparation of sodium thioacetate

Thioacetic acid (50ml., 53.3g.) was added portionwise to sodium bircarbonate (55g.) in water (150ml.) with stirring. The solution was stirred for a further 30 minutes. The resulting dark oily solution was extracted with ether (100ml.) to remove impurities and the aqueous layer reduced to dryness *in vacuo*. Ether (200ml.) was added to the dry residue in the flask and the solid was filtered off at the pump to yield sodium thioacetate (49g.). This was stored *in vacuo* over sodium hydroxide.

Reaction of (3) with sodium thioacetate

The hydrazidic bromide (4.33g., 0.01 mole) and sodium thioacetate (0.98g., 0.01 mole) were stirred together in acetonitrile at room temperature for 2 hours. The yellow solid was filtered off, washed well with water and dried. Crystallisation from toluene gave N-thiobenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)-hydrazine (3.2g., 75%) as yellow needles, m.p. 161-162° (reported m.p.,[17] 161-162°): $\nu_{max.}$ 3210, 1665, 1460, 1375, 1345, 1320, 1260, 765 cm^{-1} (s.); 1580, 1480, 1305, 1140, 1115, 1080, 1000, 923, 968, 812, 793, 727 cm^{-1} (m.).

Reaction of (41) with sodium thioacetate

The hydrazidic bromide (4.67g., 0.01 mole), sodium thioacetate (0.98g., 0.01 mole) and ethanol (30ml.) were stirred together at room temperature for 2 hours. The bright yellow

solid was filtered off, washed with water, dried and crystallised from benzene to give N-p-chlorothiobenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (3.9g., 84%) as yellow needles, m.p. 168° (Found: C, 39.0; H, 2.6; N, 5.9. $C_{15}H_{11}Br_2ClN_2OS$ requires C, 39.0; H, 2.4; N, 6.1%): $\nu_{max.}$ (CCl_4) 1685, 1455, 1355, 1325, 1010, 960, 831, 807 cm^{-1} (s.); 1580, 1255, 1240, 1205, 1095, 1090, 997, 908, 860, 819, 719, 680 cm^{-1} (m.); 3230 cm^{-1} (w.). m.s. 446/444/442 (M^+-H_2O), 363 (M^+-Br), 308/306/304, 295/293/291 ($Br_2C_6H_3NHAc$), 253/251/249 ($Br_2C_6H_3NH_2$), 229/227, 216/214/212, 172/170/168, 149, 140/138 (ClC_6H_4CN), 133, 111, 102, 75.

Reaction of (47) with sodium thioacetate

The hydrazidic bromide (4.6g., 0.01 mole) and sodium thioacetate (0.98g., 0.01 mole) were dissolved in dimethylformamide (30ml.) at room temperature and the solution was stirred for 30 minutes. The solution was poured into 5% acetic acid (750ml.) and the yellow solid was filtered off. After drying in vacuo the product was crystallised from benzene to give yellow prisms, m.p. 160-161° (with reddening above 120°) of N-p-methoxythiobenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (4.0g., 87%). Microanalysis figures were repeatedly inaccurate. $\nu_{max.}$ 1600, 1460, 1380, 1255, 1180, 1034, 840 cm^{-1} (s.); 1680, 1485, 1310, 1116, 1081, 1053, 991, 777, 699, 568 cm^{-1} (m.); 3220 cm^{-1} (w.): m.s. 438/436/434 (M^+-H_2O), 379/377 (M^+-Br), 361/359 (M^+-Br-H_2O), 337/335 ($377-CH_2=C=O$), 295/293/291 ($Br_2C_6H_3NHAc$), 280 ($359-Br$), 268/266/264, 253/251/249 ($Br_2C_6H_3NH_2$), 230/228/226,

214/212, 203/201, 191, 151, 149, 133 ($CH_3OC_6H_4CN$), 122, 103, 90, 78, 63, 52, 51, 50.

Preparation of N-thiobenzoyl-N'-methyl-N'-phenylhydrazine

Carboxymethyldithiobenzoate[43] (10.6g., 0.05 mole) was dissolved in potassium hydroxide solution (1N, 75ml.) and the pH was found to be 10. N-Methyl-N-phenylhydrazine (6.1g., 0.05 mole) was added portionwise to the stirred solution during ten minutes. Potassium hydroxide solution (1N) was added during this time to keep the pH about 10. When all the hydrazine had been added, the solution was warmed to 70°. The solution was allowed to cool to room temperature with stirring and dilute acetic acid was added until the pH reached 6. The solution was extracted with ether and the ethereal solution was washed successively with water, sodium bicarbonate solution, and water, and then dried over sodium sulfate. The ether was removed *in vacuo* and the resulting yellow oil crystallised twice from hexane to give the required product (6.1g., 50%) as bright yellow needles, m.p. 94-95° (Found: C, 69.55; H, 5.91. $C_{14}H_{14}N_2S$ requires C, 69.42; H, 5.79%): $\nu_{max.}$ 3260, 1600, 1505, 1450, 1380, 760, 696 cm^{-1} (s.); 1505, 1355, 1257, 1192, 1158, 1120, 887, 779, 729, 584 cm^{-1} (m.). p.m.r., $CDCl_3$, 9.14 δ (s., N-H), 7.7-6.5 δ (m., 10H) 2.98 δ (s., 3H).

Reaction of N-thiobenzoyl-N'-methyl-N'-phenylhydrazine with acetic anhydride

The hydrazine (1g.), triethylamine (15ml.) and acetic anhydride (15ml.) were boiled under reflux for 10 minutes. The reaction mixture was cooled and poured onto ice. Acetic acid (20ml.) was added and the gummy solid was taken up in ether. The ethereal solution was washed with sodium bicarbonate solution until evolution of carbon dioxide ceased. The ethereal solution was then dried over sodium sulfate and split into two portions.

The first portion was evaporated to dryness and recrystallisation of the gummy yellow-orange product was attempted without success from a variety of hydrocarbon solvents. The addition of warm ethanol immediately discharged the orange colour and t.l.c. indicated the presence of starting material.

The second portion was evaporated to dryness and the product taken up in chloroform. The solution showed $\nu_{max.}$ 1710, 1595, 1485, 1460, 1445, 1372, 1355, 1079, 894 indicating the product is α-thioacetoxybenzylidene-N'-methyl-N'-phenylhydrazine.

iv. With p-Nitrothiophenol

Reaction of (47) with p-nitrothiophenol

The hydrazidic bromide (4.63g.), p-nitrothiophenol (1.55g.) and triethylamine (1ml.) were stirred together in ethanol (25ml.) at room temperature for 2 hours. The yellow solid was filtered off, washed with warm water and crystallised from ethanol to afford N-α-(p-nitrothiophenoxy)-p-methoxybenzylidene--N'-(2,4-dibromophenyl)hydrazine (3.1g., 57%) as yellow needles, m.p. 164° (Found: C, 44.52; H, 2.68; Br, 29.83. $C_{20}H_{15}Br_2N_3O_3S$

requires C, 44.53; H, 2.78; Br, 29.69%): $\nu_{max.}$ 1605, 1590, 1520, 1495, 1340, 1308, 1248, 1176, 842 cm^{-1} (s.); 1390, 1160, 1103, 1087, 1032, 947, 854, 810, 742 cm^{-1} (m.); 3280 cm^{-1} (w.): p.m.r., $CDCl_3$, 9.1 δ (s., N-H), 8.0 (A) and 7.0 (B) δ (A_2B_2q., J = 9Hz.), 8.25-7.3 δ (m., 7H), 3.9 δ (s., 3H): m.s. 539/537/535 (M^+), 457/455 (M^+-HBr), 384/382/380 (M^+-$NO_2C_6H_4SH$), 304/302, 278/276, 277/275, 252/250/248 ($Br_2C_6H_3NH$), 225/223/221, 198/196, 171/169, 170/168. 155, 151, 133, 90, 63.

Reaction of (41) with p-nitrothiophenol

The hydrazidic bromide (4.67g., 0.01 mole), p-nitrothiophenol (1.55g., 0.01 mole) and triethylamine (1ml.) were stirred together in ethanol (25ml.) for 2 hours. The yellow solid was filtered off, washed with water and dried. Crystallisation from hexane-benzene gave yellow needles, m.p. 158-160°, of N-α-(p--nitrothiophenoxy)-p-chlorobenzylidene-N'-(2,4-dibromophenyl)-hydrazine (3.4g., 63%) (Found: C, 42.27; H, 2.25; N, 7.69. $C_{19}H_{12}Br_2ClN_3O_2S$ requires C, 42.14; H, 2.22; N, 7.76%): $\nu_{max.}$ 1520, 1500, 1482, 1340, 830 cm^{-1} (s.); 1580, 1392, 1304, 1270, 1240, 1164, 1083, 1012, 952, 852, 808, 739, 697 cm^{-1} (m.); 3250 cm^{-1} (w.): p.m.r., $CDCl_3$, 9.2 δ (s., N-H), 8.1-7.25 δ (m., 11H).

Reaction of (42) with p-nitrothiophenol

The hydrazidic bromide (5.18g., 0.01 mole), p-nitrothiophenol (1.55g., 0.01 mole) and triethylamine (1ml.) were stirred

together in ethanol (25ml.) for 2 hours. The yellow solid was filtered off, washed with warm water and crystallised from ethanol to give N-α-(p-nitrothiophenoxy)-5-bromo-2-thienylidene--N'-(2,4-dibromophenyl)hydrazine (2.8g., 55%) as yellow needles, m.p. 170° (Found: C, 34.68; H, 1.74; Br. 40.51; N, 6.99. $C_{17}H_{10}Br_3N_3O_2S_2$ requires C, 34.46; H, 1.69; Br, 40.54; N, 7.10%). $\nu_{max.}$ 1585, 1515, 1490, 1440, 1338, 852, 738 cm^{-1} (s.); 1385, 1315, 1300, 1268, 1242, 1162, 1184, 1134, 968, 842, 796 cm^{-1} (m.); 3270 cm^{-1} (w.): m.s. 595/593/591/589 (M^+), 513/511/509 (M^+-HBr), 440/438/436/434 (M^+-$NO_2C_6H_4SH$), 281/279/277, 252/250/248 ($Br_2C_6H_3NH$), 225/223/221, 207/205, 189/187, 171/169, 155, 108, 90, 82, 69, 63.

Reaction of N-α-chlorobenzylidene-N'-(2-bromophenyl)hydrazine with p-nitrothiophenol

The hydrazidic chloride[37] (3.09g., 0.01 mole), p-nitrothiophenol (1.55g., 0.01 mole) and triethylamine (1ml.) were stirred in ethanol (30ml.) for 2 hours. The yellow solid was filtered off, washed well with water and crystallised from ethanol to give N-α-(p-nitrothiophenoxy)benzylidene-N'-(2-bromophenyl)hydrazine (2.62g., 62%) as yellow needles, m.p. 159° (Found: C, 53.7; H, 3.4; N, 10.0. $C_{19}H_{14}BrN_3O_2S$ requires C, 53.4; H, 3.3; N, 9.8%): $\nu_{max.}$ 1585, 1505, 1345, 1092, 857, 838, 767, 749, 738 cm^{-1} (s.); 1450, 1390, 1253, 1175, 1118, 1050, 1029, 1018, 956, 718, 690, 670 cm^{-1} (m.); 3270 cm^{-1} (w.): p.m.r., CCl_4, 9.25 δ (s., N-H), 8.25-7.88 δ (m., 3H), 7.75-7.15 δ (m., 7H), 6.95-6.70 δ (m., 1H).

Reaction of N-α-bromobenzylidene-N'-(2-bromo-4-thiocyanatophenyl)-hydrazine with p-nitrothiophenol

The hydrazidic bromide[45] (2.09g., 0.005 mole), p-nitrothiophenol (0.77g., 0.005 mole) and triethylamine (0.5ml.) were stirred in ethanol (15ml.) at room temperature for 2 hours. Hydrogen cyanide was evolved during the initial hour. The orange-yellow solid was filtered off, washed with water and dried *in vacuo*. The product was chromatographed and two fractions were obtained. The first fraction (hexane:ether, 4:1) provided a solid which crystallised from ethanol as yellow needles, m.p. 159°, identified (t.l.c., i.r., p.m.r.) as N-α-(p-nitrothiophenoxy)benzylidene-N'-(2-bromophenyl)hydrazine (0.4g., 18%): m.s. 429/427 (M^+), 347 (M^+-HBr), 274/272 (M^+-$NO_2C_6H_4SH$), 211, 194, 173/171, 172.170 (BrC_6H_4NH), 171/169, 155, 145/143, 121, 103, 91, 90, 77, 69.

The second fraction (ether) yielded a yellow tarry material from which no solid product was obtained.

Attempted reaction of N-α-(p-nitrothiophenoxy)-p-chlorobenzylidene-N-(2,4-dibromophenyl)hydrazine with hydrochloric acid

The hydrazine (1g.) was dissolved in warm benzene (30ml.) and hydrochloric acid (*d* 1.18, 10ml.) was added to form a two-phase system. The mixture was heated on a steam-bath for one hour in such a way as to keep unnecessary mixing of the two layers to a minimum. Examination of the benzene layer (t.l.c.) indicated that no reaction had taken place.

v. With Heterocyclic Thiols

4,6-Dimethyl-2-mercaptopyrimidine[52], 2-mercaptoquinoxaline[53] (from 2-chloroquinoxaline[54]), and 2-mercapto-5-nitropyridine[55,56] (from 2-chloro-5-nitropyridine[57]) were prepared by literature methods.

Sodium salts of the thiols

Where appropriate the addition of one equivalent of sodium to ethanolic solutions of the thiols produced the sodium salts which were precipitated by the addition of sodium-dried ether. These were collected and stored *in vacuo*.

Reaction of (3) with the sodium salt of 4,6-dimethyl-2-mercaptopyrimidine

The hydrazidic bromide (4.33g., 0.01 mole) and the sodium salt of 4,6-dimethyl-2-mercaptopyrimidine (1.62g., 0.01 mole) were stirred together in dry acetonitrile (30ml.) at room temperature for 2 hours. The solid was filtered off, washed with water and dried *in vacuo*. Crystallisation from hexane gave colourless needles, m.p. 118°, of N-α-(4,6-dimethyl-2-mercaptopyrimidyl)benzylidene-N'-(2,4-dibromophenyl)hydrazine (3.7g., 75%) (Found: C, 46.4; H, 3.4; Br, 32.6; N, 11.7. $C_{19}H_{16}Br_2N_4S$ requires C, 46.5; H, 3.3; Br, 32.6; N, 11.4%): $\nu_{max.}$ 1580, 1530, 1485, 1440, 1285, 1255, 1235, 1155, 764, 696 cm^{-1} (s.); 1380, 1330, 1130, 1065, 1030, 883, 824, 737, 685 cm^{-1} (m.); 3280 cm^{-1} (w.). *p.m.r.*, $CDCl_3$, 9.15 δ (s., N-H), 8.1-7.95 δ (m., 2H),

7.55-7.1 δ (m., 6H), 6.62 δ (s., 1H), 2.32 δ (s., 6H). m.s. 494/492/490 (M^+), 461/459.457, 413/411 (M^+-Br), 359/357/355, 354/352/350 (M^+-$C_6H_7N_2SH$), 310/308, 278/276, 251/249/247 ($Br_2C_6H_3N$), 225, 170, 168, 140, 121, 103, 82, 77, 67.

The above product (1g., 0.002 mole) was dissolved in warm benzene (30ml.) and hydrochloric acid (d 1.18, 10ml.) was added to form a two-phase system. The mixture was heated on a steam-bath for one hour. In this way there was no unnecessary mixing of the two layers and the water layer did not boil. The mixture was cooled and the organic layer was separated. After washing with sodium bicarbonate solution and water, the benzene solution was dried over sodium sulfate. The solvent was evaporated in vacuo and the resulting yellow solid was crystallised from hexane-toluene to give N-thiobenzoyl-N'-(4,6-dimethyl-2-pyrimidyl)--N'-(2,4-dibromophenyl)hydrazine (0.55g., 55%) as bright yellow prisms, m.p. 142° (Found: C, 46.4; H, 3.2; Br, 32.5; N, 11.6. $C_{19}H_{16}Br_2N_4S$ requires C, 46.5; H, 3.3; Br, 32.6; N, 11.4%): $\nu_{max.}$ 1590, 1550, 1390, 1370, 1328, 1247, 845, 763, 772, 734, 698, 598 cm^{-1} (s.); 3340, 1470, 1450, 1420, 1271, 1176, 1080, 1040, 987, 948, 927, 868, 824, 753, 632 cm^{-1} (m.): p.m.r., $CDCl_3$, 9.7 δ (s., N-H), 8.1-7.15 δ (m., 8H), 6.47 δ (s., 1H), 2.3 δ (s., 6H): m.s. 494/492/490 (M^+), 461/459/457, 413/411, 359/357/355, 310/308, 278/276, 251/249/247 ($Br_2C_6H_3N$), 225, 197, 170, 168, 121, 103, 77, 67.

Reaction of (3) with the sodium salt of 1-phenyl-5-mercapto-1H--tetrazole

The hydrazidic bromide (4.33g., 0.01 mole) and the sodium salt of 1-phenyl-5-mercapto-1H-tetrazole[58] (2.0g., 0.01 mole) were stirred together in ethanol (30ml.) at room temperature for 2 hours, after which time the mixture was poured into water (500ml.). The white solid was filtered off and dried *in vacuo*. Crystallisation from hexane-toluene gave fawn coloured needles, m.p. 171-172° (dec.), of N-α-(1-phenyl-5-mercapto-1H--tetrazolyl)benzylidene-N'-(2,4-dibromophenyl)hydrazine (4.7g., 89%) (Found: C, 45.53; H, 2.61; N, 15.75. $C_{20}H_{14}Br_2N_6S$ requires C, 45.28; H, 2.64; N, 15.85%): $\nu_{max.}$ 1590, 1530, 1480, 1380, 1310, 1232, 1155, 813, 765, 868 cm^{-1} (s.); 1560, 1440, 1270, 1135, 1080, 1037, 1019, 948, 868, 740 cm^{-1} (m.); 3255 cm^{-1} (w.): *p.m.r.*, $CDCl_3$, 9.05 δ (s., N-H), 7.9-7.25 δ (m., 13H). *m.s.* 532/530/528 (M^+), 489/487/485, 457/455/453, 434/432, 408/406, 397/395/393 ($Br_2C_6H_3NHC_7H_5N_4$), 354/352/350 ($M^+-C_7H_5N_4SH$), 305/303, 288/286, 251/249/247 ($Br_2C_6H_3N$), 207, 178, 160, 158, 135, 121, 118, 103, 91.

The above product (2g.) was dissolved in warm benzene (50ml.) and treated with hydrochloric acid (*d* 1.18, 20ml.) in the usual way. The benzene layer was washed with sodium hydroxide (2N, 50ml.) and the aqueous extract acidified with concentrated hydrochloric acid to precipitate a white solid. This was filtered off and dried *in vacuo*. Crystallisation from toluene gave 1-phenyl-5-mercapto-1H-tetrazole (0.4g., 60%) as colourless

needles, m.p. 157° (dec.) (lit.[59], 150°) (Found: C, 47.38; H, 3.24; N, 30.98; S, 17.98. Calc. for $C_7H_6N_4S$: C, 47.19; H, 3.37; N, 31.46; S, 17.98%).

The benzene solution was concentrated *in vacuo* and then chromatographed using toluene as eluant. The fraction corresponding to the greatest Rf. (t.l.c.) was collected and crystallised from hexane to give N-α-chlorobenzylidene-N'-(2,4-dibromophenyl)hydrazine (0.6g., 41%) as colourless needles, m.p. 105-8° (lit.[34], 109°): *p.m.r.*, $CDCl_3$, 8.05 δ (s., N-H), 7.6-7.4 δ (m., 2H), 7.2-6.85 δ (m., 6H): *m.s.* 390/388/386 (M^+), 354/352/350 (M^+-HCl), 273/271, 251/249/247 ($Br_2C_6H_3N$), 237/235/233 ($Br_2C_6H_3$), 225/223/221, 171/169, 170/168, 143/141, 119/117, 103 89, 77, 76, 63, 50.

The only other product from the reaction was almost certainly N-benzoyl-N'-(2,4-dibromophenyl)hydrazine (t.l.c.).

The hydrazidic chloride from above (0.38g., 0.001 mole), 1-phenyl-5-mercapto-1H-tetrazole (0.18g., 0.001 mole, isolated from the reaction above) and triethylamine (0.2 ml.) were stirred together in ethanol (5ml.) for 2 hours at room temperature. The mixture was poured into water (100ml.) and the mixture was extracted with ether (2x25ml.). The ether layer was dried over sodium sulfate and then evaporated *in vacuo*. The product was crystallised from toluene (twice) to give N-α-(1-phenyl-5--mercapto-1H-tetrazolyl)benzylidene-N'-(2,4-dibromophenyl)hydrazine (*ca.* 0.05g.), m.p. and mixed m.p. 171-172° (dec.).

Reaction of (3) with 2-mercapto-5-nitropyridine

The hydrazidic bromide (4.33g., 0.01 mole), 2-mercapto--5-nitropyridine (1.56g., 0.01 mole) and triethylamine (1ml.) were stirred together in ethanol (30ml.) at room temperature for 2 hours. The mixture was poured into water, the solid was filtered off and dried in vacuo. Crystallisation from ethanol-ethyl acetate gave N-α-(2-mercapto-5-nitropyridyl)benzylidene--N'-(2,4-dibromophenyl)hydrazine (3.4g., 83%) as yellow plates, m.p. 144-5°. Analysis figures were repeatedly inaccurate. $\nu_{max.}$ 1580, 1380, 1340, 1158, 1129, 1104, 858, 771 cm^{-1} (s.); 1560, 1510, 1480, 1445, 1300, 1270, 1240, 1037, 948, 841, 818, 752, 696 cm^{-1} (m.);3260 cm^{-1} (w.): p.m.r., $CDCl_3$, 9.25 δ (s., N-H), 9.25 δ (d., 1H, J = 2.5Hz.), 8.4-7.98 δ (m., 3H), 7.65-7.3 δ (m., 7H): m.s. 510/508/506 (M^+), 477/475/473, 429/427 (M^+-Br), 428/426, 376/374/372 ($Br_2C_6H_3NC_5NH_3NO_2$), 354/352/350 (M^+-$NO_2C_6H_3NSH$), 347, 309/307/305, 305/303, 295/293/291, 251/249/247 ($Br_2C_6H_3N$), 241, 198, 170/168, 155, 121, 103, 76.

The above product (2.0g.) was treated with hydrochloric acid in the usual manner. The benzene layer was washed with sodium hydroxide solution (2N, 50ml.) and the aqueous extract acidified with concentrated hydrochloric acid. No solid separated. The benzene solution was dried over sodium sulfate and the solvent was removed in vacuo. The resulting yellow gum contained at least 8 components (t.l.c.) and all attempts at separation and crystallisation were unsuccessful. The product had the following

spectral characteristics: $\nu_{max.}$, CCl_4, 1590, 1475, 1332, 1282 cm^{-1}(s., br.); 1401, 1118, 1079, 853, 690 cm^{-1}(s.); 3320, 1725, 1155, 1047, 979, 945, 07, 865 cm^{-1} (m.): p.m.r., $CDCl_3$, 9.9 δ (s., N-H), 9.02 δ (d., 1H, J = 2.5Hz.), 8.4-7.25 δ (m., ca. 10H), 6.7 δ (d., 1H, J = 9Hz.).

Reaction of (3) with 2-mercaptoquinoxaline

The hydrazidic bromide (4.33g., 0.01 mole), 2-mercaptoquinoxaline (1.62g., 0.01 mole) and triethylamine (1ml.) were stirred together in ethanol (30ml.) for 2 hours at room temperature. The solid was filtered off, washed well with water and dried in vacuo. Crystallisation from hexane-toluene gave N-α-(2-mercaptoquinoxalyl)benzylidene-N'-(2,4-dibromophenyl)hydrazine (3.2g., 63%) as yellow prisms, m.p. 142-3° (Found: C, 49.01; H, 2.63; Br, 31.35. $C_{21}H_{14}Br_2N_4S$ requires C, 49.03; H, 2.72; Br, 31.13%): $\nu_{max.}$ 1590, 1500, 1390, 1310, 1154, 1079, 768, 761 cm^{-1} (s.); 1530, 1485, 1440, 1267, 1248, 1128, 961, 949, 872, 811, 691 cm^{-1} (m.); 3260 cm^{-1} (w.); p.m.r., $CDCl_3$, 9.18 δ (s., N-H), 8.52 δ (s., 1H), 8.1-7.1 δ (m., 12H): m.s. 516/514/512 (M^+), 435/433 (M^+-Br), 434/432, 381/379/377, 354/352/350 (M^+-$C_8H_5N_2SH$), 300/298, 251/249/247 ($Br_2C_6H_3N$), 219, 170, 168, 162, 129, 121, 118, 103, 91.

The above product (2.0g.) was dissolved in warm benzene (50ml.) and treated with hydrochloric acid (20ml.) in the usual way. The benzene solution was evaporated in vacuo and the residue chromatographed using toluene:hexane (1:1) as the eluting

agent. The first (colourless) fraction was collected and after crystallisation from hexane gave colourless needles, m.p. 104-8°, (lit.[34], 109°) of N-α-chlorobenzylidene-N'-(2,4-dibromophenyl)-hydrazine (0.2g., 13%). The i.r. spectrum was identical with that of an authentic sample. The other fractions appeared to be difficulty separable oils or gums (7 components on t.l.c.).

Reaction of (3) with 2-mercaptopyridine

The hydrazidic bromide (4.33g., 0.01 mole) and the sodium salt of 2-mercaptopyridine (1.33g., 0.01 mole) were stirred together in acetonitrile (30ml.) for 2 hours at room temperature. The white solid was filtered off, washed well with water and dried in vacuo. Crystallisation from hexane-toluene gave N-α-(2--mercaptopyridyl)benzylidene-N'-(2,4-dibromophenyl)hydrazine (3.5g., 76%) as colourless needles, m.p. 131° (Found: C, 47.0; H, 3.1; Br, 34.8; N, 8.8. $C_{18}H_{13}Br_2N_3S$ requires C, 46.7, H, 2.8; Br, 34.6; N, 9.1%): $\nu_{max.}$ 1520, 1485, 1380, 1290, 1145, 806, 760 cm^{-1} (s.); 1565, 1440, 1410, 1252, 1110, 1025, 868 cm^{-1} (m.); 3220 cm^{-1} (w.): m.s. 465/463/461 (M^+), 433/431/429, 384/382 (M^+-Br), 354/352/350 (M^+-C_5NH_4SH), 330/328/326 ($Br_2C_6H_3NHC_5H_4N$), 281/279, 274/272, 273/271, 262, 252/250/248 ($Br_2C_6H_3NH$), 251/249/247 ($Br_2C_6H_3N$), 225/223/221, 213, 196, 170, 168, 121, 111, 103.

Reaction of (3) with 2-mercapto-4-methylquinoline

Compound (3) (4.33g., 0.01 mole) and the sodium salt of

2-mercapto-4-methylquinoline[4,6] (1.97g., 0.01 mole) were stirred together in acetonitrile (30ml.) at room temperature for 2 hours. The pale yellow solid was filtered off, washed well with water and dried *in vacuo*. Crystallisation from hexane-toluene gave pale yellow prisms, m.p. 117-8°, of N-α-(2-mercapto-4-methylquinolyl)benzylidene-N'-(2,4-dibromophenyl)hydrazine (3.8g., 73%) (Found: C, 52.3; H, 3.4; Br, 30.3; N, 7.9. $C_{23}H_{17}Br_2N_3S$ requires C, 52.5; H, 3.2; Br, 30.4; N, 8.0%): $\nu_{max.}$ CCl_4, 1575, 1500, 1295, 1155, 1140 cm^{-1} (s.); 1375, 1255, 1225, 1030, 948, 899, 857, 813, 686 cm^{-1} (m.); 3220 cm^{-1} (w.).

III PREPARATION OF OXADIAZINES

i. From N-Aroyl-N'-acetyl-N'-arylhydrazines

Cyclisation of N-benzoyl-N'-acetyl-N'-2,4-(dibromophenyl)hydrazine (50)

a. Compound (50) (4.12g., 0.01 mole), dimethylformamide (25ml.), triethylamine (5ml.) and sodium hydroxide (0.4g., 0.01 mole) were boiled under reflux for 2.5 hours. The reaction mixture was cooled and poured into 5% acetic acid solution (450ml.). The green solid was filtered off, washed well with water and dried *in vacuo*. The crude solid was chromatographed using benzene as eluant. The fraction containing the yellow fluorescent product was collected and evaporated. Crystallisation from hexane-benzene gave 7-bromo-2-phenyl-4H-benzo[1,3,4]oxadiazine (1.3g., 39%) as yellow needles, m.p. 151-2° (Found: C, 53.89; H, 2.98; Br, 27.73. $C_{13}H_9BrN_2O$ requires C, 53.98; H, 3.11; Br, 27.68%): $\nu_{max.}$ 1490, 1450, 1314, 1286, 1068, 1020, 808, 691 cm^{-1} (s.); 3280, 1380, 1261, 1250, 1190, 944, 888, 856, 772, 727, 653 cm^{-1} (m.): p.m.r., 100 MHz., d_6 dmso, 8.86 δ (s., N-H), 7.84-7.70 δ (m., 2H), 7.52-7.34 δ (m., 3H), 7.13-7.00 δ (m., 2H), 6.51 δ (d., 1H, J = 8.8Hz.).

The other materials present in the crude product were N-benzoyl-N'-(2,4-dibromophenyl)hydrazine, starting material, and two other minor products (t.l.c.) which remained unidentified.

b. The reaction was repeated with a reflux time of 6 hours. The crude product was a green tarry material which on chromatography yielded the oxadiazine (0.4g., 11%), identified by its i.r. spectrum and its m.p. 151-2°.

c. Compound (50) (2.06g., 0.005 mole), dimethylformamide (15ml.) and triethylamine (5ml.) were boiled together under reflux for 4 hours. There was no reaction (t.l.c.).

Reaction of 7-bromo-2-phenyl-4H-benzo[1,3,4]oxadiazine with acetic anhydride

The oxadiazine (0.4g.) was dissolved in a warm mixture of acetic anhydride (10ml.) and acetic acid (10ml.) and the solution was boiled under reflux for 15 minutes. After cooling, the solution was poured into water (250ml.) when a white solid quickly precipitated. This was collected and dried in vacuo. Crystallisation from hexane gave 4-acetyl-7-bromo-2-phenyl-4H--benzo[1,3,4]oxadiazine (0.3g., 63%) as colourless needles, m.p. 138° (Found: C, 54.32; H, 3.35; N, 8.54. $C_{15}H_{11}BrN_2O_2$ requires C, 54.38; H, 3.32; N, 8.46%): $\nu_{max.}$ 1680, 1480, 1365, 1335, 1308, 1285, 1230, 1067, 810, 688 cm^{-1} (s.); 1575, 1446, 1255, 1184, 1119, 1030, 938, 893, 871, 852, 768, 653 cm^{-1} (m.): p.m.r., 100MHz., d_6 dmso, 8.09 δ (d., 1H, J = 8.8Hz.), 7.98-7.85 δ (m., 2H), 7.65-7.48 δ (m., 3H), 7.40-7.22 δ (m., 2H), 2.42 δ (s., 3H).

Attempted cyclisation of N-benzoyl-N'-(2,4-dibromophenyl) hydrazine

N-Benzoyl-N'-2,4-(dibromophenyl)hydrazine (1.76g., 0.005 mole) was dissolved in a warm mixture of dimethylformamide (15ml.) and triethylamine (5ml.) and sodium hydroxide (0.2g., 0.005 mole) was added. The mixture was refluxed for 3 hours, cooled and poured into 5% acetic acid solution (250ml.). The white solid was filtered off and dried to give starting material, m.p. 169-171° (lit.[2], 172°), identified by its i.r. spectrum and t.l.c.

Removal of the acetyl group from 4-acetyl-7-bromo-2-phenyl-4H--benzo[1,3,4]oxadiazine under standard conditions for oxadiazine formation

The acetyloxadiazine (1.1g.), sodium hydroxide (0.2g.), dimethylformamide (15ml.) and triethylamine (5ml.) were boiled under reflux for one hour. The solution was cooled and poured into water (400ml.) containing acetic acid (20ml.). The yellow solid was filtered off and dried *in vacuo*. Crystallisation from benzene-hexane gave yellow needles, m.p. and mixed m.p. 151-2°, of 7-bromo-2-phenyl-4H-benzo[1,3,4]oxadiazine (0.65g., 68%).

Cyclisation of N-benzoyl-N'-(4-bromo-2-fluorophenyl)hydrazine (54)

Compound (54) (1.75g., 0.005 mole), dimethylformamide (25ml.) and triethylamine (5ml.) were boiled under reflux for 2.5 hours. The solution was cooled and poured into 5% acetic

acid solution (700ml.). The colourless solid was filtered off and dried in vacuo to give 4-acetyl-7-bromo-2-phenyl-4H-benzo-[1,3,4]oxadiazine (1.50g., 93%). Crystallisation from hexane gave colourless needles, m.p. and mixed m.p. 138°.

Cyclisation of N-p-chlorobenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)-hydrazine (51)

Compound (51) (2.23g., 0.005 mole), dimethylformamide (25ml.), triethylamine (5ml.) and sodium hydroxide (0.2g., 0.005 mole) were boiled under reflux for 2.5 hours. The solution was cooled and poured into 5% acetic acid solution (600ml.). The yellow solid was collected, washed well with water and dried. The crude product was chromatographed using toluene as eluant. The fraction containing the yellow fluorescent product was collected, evaporated and the residue crystallised from toluene-hexane to give light green prisms, m.p. 185-6° of 7-bromo-2--(p-chlorophenyl)-4H-benzo[1,3,4]oxadiazine (0.5g., 25%) (Found: C, 48.50; H, 2.47; N, 8.58. $C_{13}H_8BrClN_2O$ requires C, 48.30; H, 2.48; N, 8.67): $\nu_{max.}$ 3300, 1498, 1380, 1318, 1097, 1014, 829, 808 cm^{-1} (s.); 1610, 1460, 1288, 1264, 1073, 889, 874, 753, 693, 649 cm^{-1} (m.).

The crude product also contained starting material (t.l.c.).

Reaction of 7-bromo-2-(p-chlorophenyl)-4H-benzo[1,3,4]oxadiazine with acetic anhydride

The oxadiazine (0.2g.), acetic anhydride (5ml.) and glacial acetic acid (5ml.) were boiled under reflux for ten minutes. The solution was cooled and poured into water (200ml.). The pale yellow solid was filtered off, washed with water and dried. Crystallisation from hexane gave 4-acetyl-7-bromo-2-(p-chlorophenyl)-4H-benzo[1,3,4]oxadiazine (0.18g., 75%) as colourless needles, m.p. 180-1° (Found: C, 49.22; H, 2.70. $C_{15}H_{10}BrClN_2O_2$ requires C, 49.32, H, 2.74%): $\nu_{max.}$ 1680, 1482, 1368, 1338, 1292 cm^{-1} (s.); 1580, 1400, 1305, 1230, 1108, 1092, 1063, 1013, 939, 895, 858, 830, 714 cm^{-1} (m.).

Cyclisation of N-p-methoxybenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (52)

Compound (52) (2.21g., 0.005 mole), dimethylformamide (25ml.), triethylamine (5ml.) and sodium hydroxide (0.2g.) were boiled under reflux for 2.5 hours, cooled and poured into 5% acetic acid solution (800ml.). The white solid was filtered off and dried *in vacuo*. Crystallisation (twice) from ethanol-ethyl acetate gave 4-acetyl-7-bromo-2-(p-methoxyphenyl)-4H-benzo[1,3,4]oxadiazine (0.8g., 44.5%) as colourless, spongy needles, m.p. 148-9° (Found: C, 53.06; H, 3.55; Br, 22.28. $C_{16}H_{13}BrN_2O_3$ requires C, 53.19; H, 3.60; Br, 22.16%): $\nu_{max.}$ 1680, 1620, 1492, 1377, 1348, 1319, 1264, 1239 cm^{-1} (s.); 1580, 1520, 1430, 1180, 1116, 1071, 1028, 938, 897, 864, 833,

818, 806, 655 cm^{-1} (m.).

Acidic hydrolysis of 4-acetyl-7-bromo-2-(p-methoxyphenyl)-4H--benzo[1,3,4]oxadiazine

The oxadiazine (0.5g.) was dissolved in a warm mixture of ethanol (15ml.) and hydrochloric acid (d 1.18, 20ml.) and the solution was boiled under reflux for 4 hours. The solution was diluted with water (300ml.) and extracted with ether (2x100 ml.). The ethereal solutions were combined and dried over magnesium sulfate. The ether was removed *in vacuo* and a dark brown viscous oil was obtained. Trituration with various solvents gave no solid material and the product contained at least 4 components (t.l.c.).

Cyclisation of N-5-bromo-2-thienoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (58)

Compound (58) (2.0g., 0.004 mole), sodium hydroxide (0.16g., 0.004 mole), dimethylformamide (20ml.) and triethylamine (5ml.) were boiled under reflux for 2.5 hours, cooled and poured into 5% acetic acid (520ml.). The white solid was filtered off, washed with water and dried *in vacuo*. The product was separated from starting material by chromatography (toluene). Crystallisation from hexane-benzene gave cream coloured needles of 4-acetyl-7-bromo-2-(5-bromo-2-thienyl)-4H-benzo[1,3,4]oxadiazine (0.1g., 6%). The crystals melted at 184° and immediately solidified. The compound did not melt again below 260°. (Found:

C, 37.35; H, 1.97; Br, 38.48. $C_{13}H_8Br_2N_2O_2S$ requires C, 37.50; H, 1.92; Br, 38.46%): $\nu_{max.}$ 1690, 1490, 1380, 1375, 1031, 805 cm^{-1} (s.); 1449, 1425, 1348, 1303, 1292, 1234, 1073, 940, 852 cm^{-1} (m.).

ii. From N-Aroyl-N'-(p-Nitrophenyl)-N'-Arylhydrazines

The cyclisations of N-aroyl-N'-(p-nitrophenyl)-N'-aryl-hydrazines were effected under standardised conditions, which were as follows:

The hydrazine and sodium hydroxide in equivalent amounts were dissolved in a mixture of dimethylformamide and triethylamine, and were boiled under reflux for 6 hours. The reaction solution was cooled and poured into excess 5% acetic acid solution. The solid was filtered off, washed well with water and dried *in vacuo*. With two exceptions the crude compounds were chromatographed (toluene) and the fraction containing the fluorescent product was collected.

Cyclisation of N-benzoyl-N'-(p-nitrophenyl)-N'-(2,4-dibromophenyl)-hydrazine (64a)

Compound (64a) (4.91g., 0.01 mole), sodium hydroxide (0.4g., 0.01 mole), dimethylformamide (25ml.) and triethylamine (5ml.) yielded 7-bromo-4-(p-nitrophenyl)-2-phenyl-4H-benzo[1,3,4]-oxadiazine (1.2g., 29%) as yellow-orange needles, m.p. 221-2°, from benzene (Found: C, 54.97; H, 2.90; N, 10.09. $C_{19}H_{12}BrN_3O_3$ requires C, 55.61; H, 2.93; N, 10.24%): $\nu_{max.}$ 1500, 1390, 1330,

1300, 1233, 1118, 858, 690 cm^{-1} (s.); 1590, 1177, 1090, 1072, 1054, 1029, 891, 822, 769 cm^{-1} (m.).

The experiment was repeated as above, except that the reflux time was extended to 10 hours. The crude compound was found to be almost entirely oxadiazine (t.l.c.) and two crystallisations from benzene gave the oxadiazine (3.3g., 79%) as orange needles, m.p. 220-2°.

Cyclisation of N-benzoyl-N'-(p-nitrophenyl)-N'-(4-bromo-2-fluorophenyl)hydrazine (64e)

Compound (64e) (2.15g., 0.005 mole), sodium hydroxide (0.2g., 0.005 mole), dimethylformamide (25ml.) and triethylamine (5ml.) yielded 7-bromo-4-(p-nitrophenyl)-2-phenyl-4H-benzo-[1,3,4]oxadiazine (2.0g., 95.5%). The crude compound appeared to be pure oxadiazine (t.l.c.) and one crystallisation from benzene gave orange needles, m.p. and mixed m.p. 221-2°.

Cyclisation of N-p-methoxybenzoyl-N'-(p-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine (64b)

Compound (64b) (1.3g., 0.0025 mole) sodium hydroxide (0.1g., 0.0025 mole), dimethylformamide (15ml.)and triethylamine (5ml.) yielded 7-bromo-2-(p-methoxyphenyl)-4-(p-nitrophenyl)-4H-benzo[1,3,4]oxadiazine (0.8g., 61%) as orange needles, m.p. 179-80°, from ethanol-ethyl acetate (Found: C, 54.26; H, 3.35; Br, 18.48. $C_{20}H_{14}BrN_3O_4$ requires C, 54.55; H, 3.18; Br, 18.18%): $\nu_{max.}$ 1585, 1500, 1340, 1297, 1269, 1231, 1112, 1078 cm^{-1} (s.);

1610, 1390, 1173, 1049, 1034, 1010, 889, 852, 843, 820, 754 cm^{-1} (m.).

Cyclisation of N-p-chlorobenzoyl-N'-(p-nitrophenyl)-N'-(2,4-dibromophenyl)hydrazine (64c)

Compound (64c) (2.6g., 0.005 mole), sodium hydroxide (0.2g., 0.005 mole), dimethylformamide (25ml.) and triethylamine (5ml.) yielded 7-bromo-2-(p-chlorophenyl)-4-(p-nitrophenyl)-4H-benzo[1,3,4]oxadiazine (0.8g., 36%) as yellow needles, m.p. 267-8°, from benzene (Found: C, 51.29; H, 2.54; N, 9.80. $C_{19}H_{11}BrClN_3O_3$ requires C, 51.35; H, 2.48; N, 9.46%): $\nu_{max.}$ 1495, 1340, 1300, 1229, 1117, 1084, 861 cm^{-1} (s.); 1602, 1505, 1495, 1390, 1176, 1097, 1045, 1018, 830, 807, 748, 645 cm^{-1} (m.).

Cyclisation of N-benzoyl-N'-(p-nitrophenyl)-N'-(2-bromo-4-carbethoxyphenyl)hydrazine (64d)

Compound (64d) (1.21g., 0.0025 mole), sodium hydroxide (0.1g., 0.0025 mole), dimethylformamide (15ml.) and triethylamine (2ml.) yielded 7-carbethoxy-4-p-nitrophenyl-2-phenyl-4H-benzo-[1,3,4]oxadiazine (0.25g., 25%) as yellow-orange prisms, m.p. 217°, from toluene (Found: C, 65.66; H, 4.14; N, 10.31. $C_{22}H_{17}N_3O_5$ requires C, 65.61, H, 4.22; N, 10.42%): $\nu_{max.}$ 1710, 1590, 1505, 1332, 1287, 1265, 1220 cm^{-1} (s.); 1620, 1367, 1188, 1134, 1111, 1095, 1068, 1043, 1026, 895, 855, 838, 778, 765, 755, 697 cm^{-1} (m.).

Cyclisation of N-benzoyl-N'-(p-nitrophenyl)-N'-(2-bromo-4-nitrophenyl)hydrazine (64f)

Compound (64f) (4.57g., 0.01 mole), sodium hydroxide (0.4g., 0.01 mole), dimethylformamide (25ml.) and triethylamine (5ml.) yielded 7-nitro-4-(p-nitrophenyl-2-phenyl-4H-benzo[1,3,4]-oxadiazine (2.3g., 62%). The crude compound was crystallised without chromatography from dimethylformamide to give red prisms, m.p. 288° (Found: C, 60.56; H, 3.31; N, 14.73. $C_{19}H_{12}N_4O_5$ requires C, 60.64; H, 3.19; N, 14.89%): $\nu_{max.}$ 1320 cm^{-1} (s., br.); 1590, 1500, 1320, 1263, 1236, 1113, 1069 cm^{-1} (s.); 1605, 1385, 1178, 1024, 940, 858, 812, 769, 741, 693, 657 cm^{-1} (m.): m.s. 376 (M^+), 346, 330, 300, 284, 256, 226, 215, 199, 197, 169, 154, 153, 141, 126, 103, 76.

Reaction of 7-bromo-2-phenyl-4H-benzo[1,3,4]oxadiazine with p-nitrofluorobenzene

The oxadiazine (0.3g.), p-nitrofluorobenzene (0.14g.), triethylamine (5ml.) and acetonitrile (15ml.) were boiled together under reflux for four hours, cooled and the solvent was removed in vacuo. The yellow solid was washed with water and dried. Crystallisation from benzene gave 7-bromo-4-(p-nitrophenyl)-2--phenyl-4H-benzo[1,3,4]oxadiazine (0.24g., 66%), m.p. and mixed m.p. 221-2°.

iii. From N-Benzoyl-N'-(o-Nitrophenyl)-N'-(2,4-Dibromophenyl)Hydrazine

N-Benzoyl-N'-(o-nitrophenyl)-N'-(2,4-dibromophenyl)-hydrazine (4.91g., 0.01 mole), sodium hydroxide (0.4g., 0.01 mole), dimethylformamide (25ml.) and triethylamine (5ml.) were boiled under reflux for 6 hours, cooled and poured into 5% acetic acid solution (500ml.). The red solid was filtered off and dried *in vacuo*. The crude product (2.3g.) was chromatographed (benzene) and the fraction containing the red fluorescent product was collected. Crystallisation from benzene-hexane gave 7-bromo--4-(o-nitrophenyl)-2-phenyl-4H-benzo[1,3,4]oxadiazine (1.1g., 27%) as red needles, m.p. 163° (Found: C, 55.49; H, 2.84; Br, 19.58. $C_{19}H_{12}BrN_3O_3$ requires C, 55.61; H, 2.93; Br, 19.51%): $\nu_{max.}$ 1575, 1530, 1483, 1365, 1292, 1212, 1069, 772, 692 cm^{-1} (s.); 1605, 1450, 1342, 1177, 1090, 1050, 1024, 972, 925, 890, 871, 858, 831, 805, 758, 713 cm^{-1} (m.).

Reaction of 7-bromo-2-phenyl-4H-benzo[1,3,4]oxadiazine with o-nitrofluorobenzene

The oxadiazine (0.3g.) o-nitrofluorobenzene (0.14g.), triethylamine (5ml.) and acetonitrile (15ml.) were boiled under reflux for 4 hours, cooled and the solvent was removed *in vacuo*. The red solid was washed with water and dried. Crystallisation from a toluene-hexane mixture gave 7-bromo-4-(o-nitrophenyl)-2--phenyl-4H-benzo[1,3,4]oxadiazine (0.20g., 66%) m.p. and mixed m.p. 162-3°.

iv. From N-Benzoyl-N'-Pentachlorophenyl-N'-(2,4-Dibromophenyl)Hydrazine

N-Benzoyl-N'-pentachlorophenyl-N'-(2,4-dibromophenyl)-hydrazine (3.09g., 0.005 mole), sodium hydroxide (0.2g., 0.005 mole), dimethylformamide (15ml.) and triethylamine (5ml.) were boiled under reflux for 6 hours. The solution was cooled, the yellow solid filtered off, washed well with water and dried. The filtrate was poured into 5% acetic acid solution (800ml.). This produced a brown oily solid which was filtered off and dried in vacuo. The brown gum was chromatographed (benzene) and the fraction containing the yellow fluorescent product was collected and evaporated. This was combined with the yellow solid filtered off earlier and crystallisation from benzene-hexane then gave 4-(2,4-dibromophenyl)-5,6,7,8-tetrachloro-2-phenyl-4H-benzo[1,3,4]-oxadiazine (1.8g., 62%) as yellow needles, m.p. 215-6° (Found: C, 39.45; H, 1.45; N, 4.82. $C_{19}H_8Br_2Cl_4N_2O$ requires C, 39.18; H, 1.38; N, 4.81%): Molecular weight determination by measurement of vapour pressure (benzene) gave 577; $C_{19}H_8Br_2Cl_4N_2O$ requires 582; $\nu_{max.}$ 1473, 1440, 1380, 1317, 1303, 1059, 1047, 1025, 756m 687 cm^{-1} (s.); 1640, 1575, 1240, 1182, 1085, 1008, 907, 869, 835, 818, 792, 767, 648 cm^{-1} (m.).

v. From N-Benzoyl-N'-(2,3,5,6-Tetrafluorophenyl)Hydrazine

2,3,5,6-Tetrafluorophenylhydrazine

Pentafluorobenzene (82.5g.), hydrazine hydrate (100%,

74ml.) and freshly distilled dioxan (350ml.) were boiled under reflux for 4.5 hours. The solvent was removed in vacuo below 40° and water (250ml.) was added. The orange solid was filtered off and dried. The filtrate was extracted with n-butanol and the solvent removed in vacuo, to yield more product. The combined crops (62.7g., 71%) were crystallised from hexane to give the required product as biscuit coloured leaves, m.p. 89-91° (lit.[64], 90-91.5°).

N-Benzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine

Benzoyl chloride (2.8g.) was added dropwise to a stirred solution of 2,3,5,6-tetrafluorophenylhydrazine (3.6g.) in a mixture of dry ether (50ml.) and dry triethylamine (5ml.) at -78°. After the addition was complete, the stirring was continued for a further two hours at -78° and the mixture was then allowed to warm to room temperature. The solvent was removed in vacuo and the white solid washed with ice-cold water. The product was crystallised from aqueous methanol to give colourless needles, m.p. 176°, of N-benzoyl-N'-(2,3,5,6-tetrafluorophenyl)-hydrazine (4.2g., 75%) (Found: C, 54.80; H, 2.87; N, 9.83. $C_{13}H_8F_4N_2O$ requires C, 54.93; H, 2.82; N, 9.86%): $\nu_{max.}$ 1645, 1530, 1485, 1175, 946, 696 cm^{-1} (s.); 3260, 1580, 1380, 1328, 1268, 1100, 903, 821, 758, 717 cm^{-1} (m.).

Attempted cyclisation of N-benzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine

The hydrazine (1.0g.), dimethylformamide (20ml.), triethylamine (2ml.) and sodium hydroxide (0.4g.) were boiled under reflux for 4 hours, cooled and poured into 10% acetic acid solution (250ml.). A light yellow gum separated, which contained at least 5 compounds, including starting material, but no fluorescent material (t.l.c.).

Cyclisation of N-benzoyl-N'-acetyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine

N-Benzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine (1g.), dimethylformamide (15ml.), acetic anydride (5ml.) and triethylamine (5ml.) were boiled together under reflux for 4 hours, cooled and poured into 10% acetic acid solution (350ml.). The white solid was filtered off and dried. Crystallisation from hexane gave 4-acetyl-2-phenyl-5,6,8-trifluoro-4H-benzo[1,3,4]-oxadiazine (0.6g., 65%) as colourless needles, m.p. 144-5°. (Found: C, 58.62; H, 2.85. $C_{15}H_9F_3N_2O_2$ requires C, 58.82, H, 2.94%): $\nu_{max.}$ 1700, 1505, 1460, 1360, 1330, 1289, 1251, 1064, 690 cm^{-1} (s.); 3065, 1635, 1445, 1179, 1148, 1030,948, 892, 865, 770, 739, 594 cm^{-1} (m.): ^{19}F n.m.r. 52.84 δ (m., F_A), 55.16 δ (m., F_B), 57.06 δ (m., F_C), J_{AB}=22Hz., J_{AC}=13Hz., J_{BC}=0, J_{AH}=7Hz., J_{BH}=10Hz., J_{CH}=9Hz.

Removal of the acetyl group was attempted as follows: The acetyloxadiazine (0.4g.), dimethylformamide (10ml.),

triethylamine (2ml.) and sodium hydroxide (0.2g.) were boiled together under reflux for one hour, cooled and poured into 10% acetic acid solution. A dark brown gum was obtained from which no solid could be obtained by crystallisation.

v. From N-Benzoyl-N'-Phenyl Hydrazine

N-Benzoyl-N'-(2,4-dinitrophenyl)-N'-phenylhydrazine

N-Benzoyl-N'-phenylhydrazine[60] (4.24g., 0.02 mole), 2,4--dinitrofluorobenzene (3.72g., 0.02 mole) and acetonitrile (35 ml.) were stirred together at room temperature. Triethylamine (5ml.) was added and the mixture was stirred for 2 hours. The solvent was removed in vacuo and the resulting yellow solid was washed with water before being dried. The product was crystallised from benzene (twice) to give the required product (5.8g., 74%) as yellow needles, m.p. 159-60° (Found: C, 60.31; H, 3.59; N, 14.74. $C_{19}H_{14}N_4O_5$ requires C, 60.32; H, 3.70; N, 14.82%): $\nu_{max.}$ 1660, 1605, 1635, 1385, 1340, 694 cm^{-1} (s.); 3210, 1490, 1260, 1145, 1069, 1027, 907, 830, 749, 739 cm^{-1} (w.).

Cyclisation of N-benzoyl-N'-(2,4-dinitrophenyl)-N'-phenylhydrazine

N-Benzoyl-N'-(2,4-dinitrophenyl)-N'-phenylhydrazine (3.78g., 0.01 mole), dimethylformamide (25ml.), sodium hydroxide (0.4g., 0.01 mole) and triethylamine (5ml.) were boiled under reflux for 4 hours, cooled and poured into 5% acetic acid solution (500ml.). The red solid was filtered off, washed with water, and dried in vacuo. Crystallisation from benzene gave

2,4-diphenyl-7-nitro-4H-benzo[1,3,4]oxadiazine (2.7g., 82%) as red needles, m.p. 178-9° (Found: C, 68.72; H, 3.85; N, 12.89. $C_{19}H_{13}N_3O_3$ requires C, 68.89; H, 3.93; N, 12.69%): $\nu_{max.}$ 1505, 1430, 1320, 1300, 763, 689 cm^{-1} (s.); 1580, 1445, 1258, 1226, 1182, 1021, 938, 875, 811, 738, 651 cm^{-1} (m.): p.m.r., 100MHz., d_6 dmso, 7.96-7.75 δ (m., 4H), 7.59-7.40 δ (m., 8H), 6.60 δ (d., J = 9.5Hz., 1H): m.s. 331 (M^+), 301, 285, 198, 170, 155, 154, 128, 127, 103, 77, 76, 51.

N-Benzoyl-N'-(3,5-dinitro-2-pyridyl)-N'-phenylhydrazine

N-Benzoyl-N'-phenylhydrazine[60] (2.12g., 0.01 mole), 2-chloro-3,5-dinitropyridine (2.03g., 0.01 mole) and methanol (30ml.) were stirred together at room temperature. Triethylamine (5ml.) was added and the solution was stirred for 2 hours. The reaction solution was poured into ice-cold water (500ml.) containing acetic acid (20ml.), and the yellow solid was filtered off, washed well with water and dried in vacuo. The product was crystallised from toluene to give N-benzoyl-N'-(3,5-dinitro-2-pyridyl)-N'-phenylhydrazine (2.7g., 71%) as yellow needles, m.p. 231-2° (Found: C, 57.25; H, 3.26; N, 18.43. $C_{18}H_{13}N_5O_5$ requires C, 56.99; H, 3.43; N, 18.47%): $\nu_{max.}$ 1665, 1590, 1530, 1340, 1271, 1142, 831, 768, 728, 624 cm^{-1} (s.); 3260, 1490, 1470, 1415, 1390, 1092, 1031, 933, 831, 802, 753, 624 cm^{-1} (m.).

Cyclisation of N-benzoyl-N'-(3,5-dinitro-2-pyridyl)-N'-phenylhydrazine

N-Benzoyl-N'-(3,5-dinitro-2-pyridyl)-N'-phenylhydrazine (3.80g., 0.01 mole), sodium hydroxide (0.4g., 0.01 mole), dimethylformamide (25ml.) and triethylamine (5ml.) were boiled under reflux for 4 hours, cooled and poured into 5% acetic acid solution (500ml.). The red solid was filtered off, washed well with water and dried *in vacuo*. Crystallisation from toluene gave 2,4-diphenyl-7-nitro-4H-pyrido[3,2][1,3,4]oxadiazine (2.8g. 85%) as red matted needles, 180° (Found: C, 65.31; H, 3.60; N, 18.82. $C_{18}H_{12}N_4O_3$ requires C, 65.06; H, 3.61; N, 16.87%: $\nu_{max.}$ 1515, 1455, 1440, 1345, 1308, 746, 690 cm^{-1} (s.); 1600, 1498, 1475, 1385, 1228, 1157, 1091, 1050, 1023, 891, 807, 771, 760, 650, 601 cm^{-1} (m.): m.s. 332 (M^+), 302, 287, 286, 258, 209, 184, 171, 155, 144, 131, 119, 118, 104, 103, 91, 77, 76, 75, 74.

Attempted reaction of N-benzoyl-N'-phenylhydrazine with 2-chloro--3-nitropyridine

The hydrazine[60] (2.12g., 0.01 mole), 2-chloro-3-nitropyridine (1.59g., 0.01 mole), triethylamine (5ml.) and acetonitrile (25ml.) were boiled under reflux for 4 hours. No reaction was observed (t.l.c.).

Reaction in dimethylformamide with reflux times varying from 0.5-12.0 hours gave only dark gummy materials with complex t.l.c. characteristics and no fluorescent material.

Attempted reaction of N-benzoyl-N'-phenylhydrazine with 2,3--dichloroquinoxaline in methanol

The hydrazine[60] (1.06g., 0.005 mole), 2,3-dichloroquinoxaline (1.0g., 0.005 mole), triethylamine (20ml.) and methanol (20ml.) were boiled under reflux for one hour. No reaction was observed (t.l.c.).

Reaction of N-benzoyl-N'-phenylhydrazine with 2,3-dichloroquinoxaline in dimethylformamide

N-Benzoyl-N'-phenylhydrazine[60] (2.12g., 0.01 mole), 2,3-dichloroquinoxaline (1.99g., 0.01 mole), triethylamine (10ml.) and dimethylformamide (50ml.) were boiled under reflux for 12 hours, cooled and poured into 5% acetic acid solution (750ml.). The yellow solid was filtered off, washed well with water and dried *in vacuo*. The crude compound was chromatographed (toluene) and the fraction containing the yellow fluorescent product was collected and evaporated. Crystallisation from toluene gave 2,4-diphenyl-4H-quinoxalino[2,3][1,3,4]oxadiazine (2.8g., 82%) as yellow needles, m.p. 241-2° (Found: C, 74.43; H, 4.16; N, 16.58. $C_{21}H_{14}N_4O$ requires C, 74.56; H, 4.14; N, 16.57%): $\nu_{max.}$ 1495, 1448, 1380, 1304, 1148, 762, 699 cm^{-1} (s.); 1332, 1280, 1229, 1127, 1070, 1021, 883 cm^{-1} (m.): m.s. 338 (M^+), 310, 261, 235, 219, 218, 207, 206, 103, 91, 77, 65, 64, 63.

IV PREPARATION OF THIADIAZINES

i. From N-Thioaroyl-N'-Acetyl-N'-Arylhydrazines

Cyclisation of N-p-methoxythiobenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (72)

Compound (72) (2.3g., 0.005 mole), triethylamine (15ml.) and acetonitrile (15ml.) were boiled under reflux for 2 hours, cooled and poured into 5% acetic acid solution (500ml.). The white gelatinous solid was filtered off, washed well with water and dried *in vacuo*. Crystallisation from acetonitrile gave 4-acetyl-7-bromo-2-(p-methoxyphenyl)-4H-benzo[1,3,4]thiadiazine (1.7g., 90%) as colourless matted needles, m.p. 199-200° (Found: C, 51.03; H, 3.44; Br, 21.21. $C_{16}H_{13}BrN_2O_2S$ requires C, 50.93; H, 3.45; Br, 21.22%): $\nu_{max.}$ 1680, 1605, 1465, 1367, 1181 cm^{-1} (s.); 1585, 1510, 1338, 1310, 1211, 1030, 953, 864, 835, 807 cm^{-1} (m.): p.m.r., 100 MHz., $CDCl_3$, 7.88 and 6.93 δ (A_2B_2q., J = 8.7Hz.), 7.68-7.74 δ (m., 1H), 7.44 δ (d., 1H, J= 2.3Hz.), 7.30 δ (d., 1H, J = 10.5Hz.), 1.73 δ (s., 3H), 0.37 δ (s., 3H).

Hydrolysis of 4-acetyl-7-bromo-2-(p-methoxyphenyl)-4H-benzo[1,3,4]-thiadiazine

The acetylthiadiazine (3.77g., 0.01 mole), ethanol (100 ml.) and hydrochloric acid (d 1.18, 50ml.) were boiled under reflux for 2 hours, cooled and poured into water (750ml.). The green solid was filtered off and dried. Crystallisation from hexane-toluene gave 7-bromo-2-(p-methoxyphenyl)-4H-benzo[1,3,4]-

thiadiazine (1.4g., 42%) as yellow plates, m.p. 157° (Found: C, 50.39; H, 3.29. $C_{14}H_{11}BrN_2OS$ requires C, 50.15; H, 3.28%): $\nu_{max.}$ 1600, 1505, 1450, 1380, 1246, 1180, 1032, 838, 811 cm^{-1} (s.); 3360, 1570, 1480, 1410, 1313, 1284, 1274, 957, 878, 820, 689, 650, 620 cm^{-1} (m.): p.m.r., 100MHz., $CDCl_3$, 7.78 and 6.89 δ ($A_2B_2q.$, J = 8.7Hz.), 7.63 δ (s., N-H), 7.27-7.15 δ (m., 2H), 6.56 δ (d., 1H, J = 9.0Hz.), 1.70 δ (s., 3H).

Cyclisation of N-p-chlorothiobenzoyl-N'-acetyl-N'-(2,4-dibromophenyl)hydrazine (71)

Compound (71) (4.62g., 0.01 mole), triethylamine (15ml.) and acetonitrile (15ml.) were boiled under reflux for 2 hours, cooled and poured into 5% acetic acid solution (500ml.). The yellow solid was filtered off and dried. The product could not be obtained in a pure condition (t.l.c.) either by column chromatography or crystallisation. A yellow impurity, which appeared to be a decomposition product, was always present. Crystallisation from either ethanol-ethyl acetate or hexane-toluene gave 4-acetyl-7-Bromo-2-(p-chlorophenyl)-4H-benzo[1,3,4]-thiadiazine (2.5g., 66%) as a pale yellow amorphous solid, m.p. 176-9° (Found: C, 47.24; H, 2.58; N, 7.34. $C_{15}H_{10}BrClN_2OS$ requires C, 47.24; H, 2.63; N, 7.35%): $\nu_{max.}$ 1685, 1470, 1367, 1332, 1098, 957 cm^{-1} (s.); 1595, 1485, 1470, 1400, 1265, 1250, 1210, 1015, 911, 832, 812, 790, 741 cm^{-1} (m.).

Hydrolysis of 4-acetyl-7-bromo-2-(p-chlorophenyl)-4H-benzo[1,3,4]-thiadiazine

The acetylthiadiazine (1.9g., 0.005 mole), ethanol (25ml.) and hydrochloric acid (25ml.) were boiled under reflux for 2 hours. On cooling light green needles, m.p. 145-7° were deposited which needed no further purification and the product was identified as 7-bromo-2-(p-chlorophenyl)-4H-benzo[1,3,4]-thiadiazine (0.8g., 48%) (Found: C, 46.63; H, 2.46; N, 8.54. $C_{13}H_8BrClN_2S$ requires C, 46.02; H, 2.36; N, 8.26%): $\nu_{max.}$ 1455, 1385, 1271, 1098, 827 cm^{-1} (s.); 1490, 1241, 1036, 1029, 970, 883, 870, 802, 701 cm^{-1} (m.): m.s. 338 (M^+), 306, 259, 201, 174, 155, 137, 122, 111, 102, 95, 78, 69.

ii. From N-α-(p-Nitrothiophenoxy)Arylidene-N'-Arylhydrazines

Cyclisation of N-α-(p-nitrothiophenoxy)-p-methoxybenzylidene-N'--(2,4-dibromophenyl)hydrazine (81a)

Compound (81a) (2g.), ethanol (20ml.) and triethylamine (20ml.) were boiled under reflux for 2 hours, cooled and the solution was concentrated in vacuo. The orange solid was filtered off, washed well with water and dried. Crystallisation from benzene afforded 7-bromo-2-(p-methoxyphenyl)-4-(p-nitrophenyl)-4H-benzo[1,3,4]thiadiazine (1.2g., 74%) as orange prisms, m.p. 217° (dec.) (Found: C, 52.54; H, 2.97; Br, 17.65. $C_{20}H_{14}BrN_3O_3S$ requires C, 52.63; H, 3.07; Br, 17.54%): $\nu_{max.}$ 1595, 1500, 1324, 1250, 1115, 832 cm^{-1} (s.); 1465, 1350, 1205,

1174, 1035, 967, 901, 852, 777, 751 cm^{-1} (m.).

Cyclisation of N-α-(p-nitrothiophenoxy)-p-chlorobenzylidene--N'-(2,4-dibromophenyl)hydrazine (81b)

Compound (81b) (2g.), ethanol (20ml.) and triethylamine (20ml.) were boiled under reflux for 2 hours, cooled and the solution was concentrated in vacuo. The yellow-orange solid was filtered off, washed well with water and dried. Crystallisation from benzene gave 7-bromo-2-(p-chlorophenyl)-4-(p-nitrophenyl)--4H-benzo[1,3,4]thiadiazine (0.7g., 40%) as yellow-orange needles, m.p. 253-4° (dec.) (Found: C, 49.47; H, 2.41; N, 8.96. $C_{19}H_{11}BrClN_3O_2S$ requires C, 49.57; H, 2.39; N, 9.13%): $\nu_{max.}$ 1698, 1515, 1345, 1317, 698 cm^{-1} (s.); 1498, 1470, 1263, 1204, 1116, 1098, 1035, 968, 856, 833, 809, 756 cm^{-1} (m.).

Cyclisation of N-α-(p-nitrothiophenoxy)-5-bromo-2-thienylidene--N'-(2,4-dibromophenyl)hydrazine (82)

Compound (82) (1.5g.), ethanol (15ml.) and triethylamine (15ml.) were boiled under reflux for 4 hours, cooled and the orange solid was filtered off. The product was washed with water and, after drying, was crystallised from benzene-hexane to give 7-bromo-2-(5-bromo-2-thienyl)-4-(p-nitrophenyl)-4H-benzo[1,3,4]-thiadiazine (0.8g., 64%) as orange-brown prisms, m.p. 213° (Found: C, 38.62; H, 1.75; Br, 31.50; S, 12.65. $C_{17}H_9Br_2N_3O_2S_2$ requires C, 38.92; H, 1.76; Br, 31.31; S, 12.52%): $\nu_{max.}$ 1315, 854 cm^{-1} (s., br.); 1580, 1492, 1463, 1110 cm^{-1} (s.,); 1428, 1262,

1238, 1205, 1174, 1040, 974, 941, 810, 790, 779, 749, 692 cm^{-1} (m.).

Attempted cyclisation of N-α-(p-nitrothiophenoxy)benzylidene-N'--(2-bromophenyl)hydrazine (81c)

Compound (81c) (0.5g.), ethanol (5ml.) and triethylamine (5ml.) were boiled under reflux for 2 hours. The solvent was removed in vacuo to yield a yellow gummy material which contained (t.l.c.) at least 4 compounds, none of which were starting material or were fluorescent. All attempts at crystallisation were unsuccessful.

Reaction of (59) with p-nitrothiophenol and cyclisation of the product

The hydrazidic bromide (3.10g.), p-nitrothiophenol (1.2g.) and ethanol (25ml.) were stirred together at room temperature. Triethylamine (1ml.) was added and the solution was stirred for 2 hours. The yellow solid was filtered off, washed well with water and dried.

Without further characterisation the above product (1g.) was dissolved in a warm mixture of ethanol (10ml.) and triethylamine (10ml.) and the solution was boiled under reflux for 4 hours. The solution was concentrated, the red solid was filtered off, washed well with water and dried in vacuo. The product was triturated with boiling acetone and benzene and then crystallised from dioxan to give 7-nitro-4-(p-nitrophenyl)-2-phenyl-4H-benzo-

[1,3,4]thiadiazine (0.37g., 45% based on the hydrazidic bromide) as red prisms, m.p. 274° (dec.) (Found: C, 58.6; H, 3.1; N, 14.0. $C_{19}H_{12}N_4O_4S$ requires C, 58.2; H, 3.1; N, 14.3%): $\nu_{max.}$ 1385, 1348, 1315, 1257, 1113, 744 cm^{-1} (s.); 1595, 1572, 1510, 1460, 1203, 1174, 1148, 1128, 1027, 968, 917, 852, 760, 688 cm^{-1} (m.).

iii. From Hydrazidic Thioethers Derived From Heterocyclic Thiols

Cyclisation of N-α-(5-nitro-2-mercaptopyridyl)benzylidene-N'--(2,4-dibromophenyl)hydrazine

The hydrazine (2g., 0.005 mole), ethanol (10ml.) and triethylamine (10ml.) were boiled under reflux for 2 hours, cooled and the yellow solid was filtered off. After washing with water, drying and crystallisation from benzene 7-bromo-4--(5-nitro-2-pyridyl)-2-phenyl-4H-benzo[1,3,4]thiadiazine (1.31g., 79%) was obtained as yellow needles, m.p. 223° (Found: C, 50.8; H, 2.8; N, 12.9. $C_{18}H_{11}BrN_4O_2S$ requires C, 50.5; H, 2.6; N, 13.1%): $\nu_{max.}$ 1590, 1455, 1400, 1320, 1280, 1115, 850, 800, 757 cm^{-1} (s.); 1500, 1425, 1250, 1195, 1145, 1048, 998, 965, 913, 858, 830, 784, 692, 678 cm^{-1} (m.).

Cyclisation of N-α-(2-mercaptoquinoxalyl)benzylidene-N'-(2,4--dibromophenyl)hydrazine

The hydrazine (2.57g., 0.005 mole), ethanol (20ml.) and triethylamine (20ml.) were boiled under reflux for 2 hours. The solution was cooled and poured into 5% acetic acid solution

(700ml.). The product was filtered off, washed well with water and dried *in vacuo*. Crystallisation from benzene gave *7-bromo--2-phenyl-4-(2-quinoxalyl)-4H-benzo[1,3,4]thiadiazine* (2.03g., 94%) as yellow needles, m.p. 211-2° (Found: C, 58.05; H, 2.92; Br, 18.66. $C_{21}H_{13}BrN_4S$ requires C, 58.20; H, 3.00; Br, 18.48%): $\nu_{max.}$ 1560, 1480, 1420, 1385, 1352, 1241, 1197, 1142, 987, 955, 759, 689 cm^{-1} (s.); 1550, 1445, 1312, 1290, 1268, 1137, 1096, 1074, 803, 728, 703, 605, 589 cm^{-1} (m.).

Cyclisation of N-α-(4-methyl-2-mercaptoquinolyl)benzylidene-N'--(2,4-dibromophenyl)hydrazine

The hydrazine (2g.), ethanol (10ml.) and triethylamine (10ml.) were boiled under reflux for 2 hours. On filtration a brown solid was isolated, which after being washed with water was dried *in vacuo*. The product was chromatographed (chloroform) and the fraction containing the yellow fluorescent product was collected and evaporated. Crystallisation from benzene gave *7-bromo-4-(4-methyl-2-quinolyl)-2-phenyl-4H-benzo[1,3,4]thiadiazine* (0.2g., 16%) as yellow needles, m.p. 204° (Found C, 61.6; 59.0; H, 4.2, 3.6; Br, 17.8, 18.0; N, 8.5. $C_{23}H_{15}BrN_3S$ requires C, 61.7; H, 3.6; Br, 17.8; N, 9.4%): $\nu_{max.}$ 1600, 1460, 1380, 756, 681 cm^{-1} (s.); 1355, 1260, 1142, 1178, 1137, 1092, 1029, 980, 937, 852, 800, 725, 632, 580, 561 cm^{-1} (m.): *m.s.* 447/445 (M^+), 348, 315, 284, 283, 278, 263, 223, 177/175, 176/174, 159, 149, 142, 140, 130, 115, 103, 89, 79.

Attempted cyclisation of N-α-(2-mercaptopyridyl)benzylidene-N'--(2,4-dibromophenyl)hydrazine

The hydrazine (2g.), ethanol (15ml.) and triethylamine (15ml.) were boiled under reflux for 2 hours. The mixture was cooled and poured into water (500ml.). A white solid was precipitated which was collected and dried *in vacuo*. Crystallisation from hexane-toluene gave starting material (t.l.c.), m.p. 129°.

Attempted cyclisation of N-α-(1-phenyl-5-mercapto-1H-tetrazolyl)-benzylidene-N'-(2,4-dibromophenyl)hydrazine

The hydrazine (2g.), ethanol (20ml.) and triethylamine (10ml.) were boiled under reflux for 5 minutes. There was no change (t.l.c.). The solution was boiled under reflux for a further 2 hours. The solvent was removed *in vacuo* and a dark brown sticky solid remained, which contained at least 6 components (t.l.c.). All attempts to obtain a solid product were unsuccessful.

Attempted cyclisation of N-α-(4,6-dimethyl-2-mercaptopyrimidyl)-benzylidene-N'-(2,4-dibromophenyl)hydrazine

The hydrazine (1g.), ethanol (10ml.) and triethylamine (10ml.) were boiled under reflux for 2 hours. After 0.5 hours the starting material had been converted to N-thiobenzoyl-N'--(4,6-dimethyl-2-pyrimidyl)-N'-(2,4-dibromophenyl)hydrazine (t.l.c.). After 2 hours the solvent was removed *in vacuo* and the green solid which remained consisted mainly of the thiohydrazide,

together with at least 3 other products (t.l.c.). All attempts to separate the new products from the thiohydrazide were unsuccessful.

Reaction of 7-bromo-2-phenyl-4H-benzo[1,3,4]thiadiazine with 2-chloroquinoxaline

The thiadiazine (1.02g.), 2-chloroquinoxaline[54] (0.54g.), acetonitrile (20ml.) and triethylamine (3ml.) were boiled under reflux for 4 hours. The solvent was removed in vacuo, the yellow solid washed well with water and dried. Crystallisation from benzene gave 7-bromo-2-phenyl-4-(2-quinoxalyl)-4H-benzo[1,3,4]-thiadiazine (0.9g., 62%) as yellow needles, m.p. and mixed m.p. 211-2°, identical (t.l.c.) with the sample prepared previously.

Reaction of 7-bromo-2-phenyl-4H-benzo[1,3,4]thiadiazine with 2-chloro-5-nitropyridine

The thiadiazine (1.02g.) and 2-chloro-5-nitropyridine[57] (0.53g.) were treated as above. Crystallisation from benzene gave 7-bromo-4-(5-nitro-2-pyridyl)-2-phenyl-4H-benzo[1,3,4]-thiadiazine (1.1g., 76%) as yellow needles, m.p. and mixed m.p. 223°, identical (t.l.c.) with the sample prepared previously.

Attempted reaction of 7-bromo-2-phenyl-4H-benzo[1,3,4]thiadiazine with (a) 2-chloro-4,6-dimethylpyrimidine and (b) 2-chloropyridine

a. The thiadiazine (0.51g.) and 2-chloro-4,6-dimethylpyrimidine[63] (0.28g.) were treated in the usual way. There was no

reaction (t.l.c.).

b. The thiadiazine (1.02g.) and 2-chloropyridine[58] (0.38g.) were treated in the usual way. There was no reaction (t.l.c.).

iv. From N-Thiobenzoyl-N'-(2,3,5,6-Tetrafluorophenyl)-Hydrazine

N-Thiobenzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine

Carboxymethyldithiobenzoate[43] (21.2g., 0.1 mole) was dissolved in potassium hydroxide solution (1N, 100ml.) and the pH was found to be 10. 2,3,5,6-Tetrafluorophenyhydrazine (18g., 0.1 mole) was added portionwise to the stirred solution during 10 minutes and potassium hydroxide solution (1N) was added from time to time to keep the pH at 10. The solution was then heated on a steam-bath to 70° and was allowed to cool to room temperature during one hour. Dilute acetic acid was added until the pH reached 6. The yellow solid was collected, washed well with water and dried in vacuo. Crystallisation from hexane gave the required product (17.1g., 57%) as long yellow needles, m.p. 90-2° (Found: C, 51.97; H, 2.68; N, 9.28. $C_{13}H_8F_4N_2S$ requires C, 52.00; H, 2.67; N, 9.33%): $\nu_{max.}$ 3230, 1530, 1510, 1482, 1460, 1176, 985, 756, 692 cm^{-1} (s.); 1648, 1370, 1257, 1240, 1068, 1032, 1002, 919, 823, 737, 715, 705 cm^{-1} (m.): p.m.r., $CDCl_3$, 9.35 δ (s., br., N-H), 7.92 δ (s., br., N-H), 7.81-7.61 δ (m., 2H), 7.50-7.18 δ (m., 3H), 7.00-6.25 δ (m., 1H).

Reaction of N-thiobenzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine with acetic anhydride in triethylamine

The thiohydrazide (3.0g., 0.01 mole), triethylamine (20ml.) and acetic anhydride (20ml.) were boiled under reflux for 2 hours, cooled and poured into water (500ml.). The product was filtered off, washed with water and dried *in vacuo*. Crystallisation from ethanol or hexane gave 4-acetyl-2-phenyl-5,6,8-trifluoro-4H-benzo[1,3,4]thiadiazine (3.1g., 91%) as buff-coloured needles, m.p. 127-8° (Found: C, 5605; H, 2.84; F, 17.68. $C_{15}H_9F_3N_2OS$ requires C, 55.90; H, 2.80; F, 17.70%): $\nu_{max.}$ 1710, 1492, 1465, 1382, 1362, 1305, 1230, 951, 879, 762, 687 cm^{-1} (s.); 3040, 1620, 1560, 1255, 1189, 1168, 1137, 1075, 1059, 1033, 1003, 978, 825, 722, 696 cm^{-1} (m.): p.m.r., $CDCl_3$, 8.13-7.92 δ (m., 2H), 7.62-7.43 δ (m., 3H), 7.33-6.77 δ (m., 1H), 2.50 δ (s., 3H): ^{19}F n.m.r., 54.08 δ (m., F_A), 50.92 δ (m., F_B), 36.28 (m., F_C), J_{AB}= 20Hz., J_{AC}= 13Hz., J_{BC}= 2Hz., J_{AH}= 6Hz., J_{BH}= 9.5Hz., J_{CH}= 8.0Hz.

Hydrolysis of 4-acetyl-2-phenyl-5,6,8-trifluoro-4H-benzo[1,3,4]-thiadiazine

The acetylthiadiazine (2g.), ethanol (30ml.) and hydrochloric acid (d 1.18, 20ml.) were boiled under reflux for one hour. The solution was cooled and the solid filtered off. Crystallisation from ethanol afforded 2-phenyl-5,6,8-trifluoro--4H-benzo[1,3,4]thiadiazine (1.4g., 80%) as long yellow needles, m.p. 107-8° (Found: C, 55.77; H, 2.53. $C_{13}H_7F_3N_2S$ requires

C, 55.71; H, 2.50%): $\nu_{max.}$ 3300, 1502, 1440, 1229, 1088, 961, 815, 756m 682 cm^{-1} (s.); 1630, 1452, 1380, 1260, 1153, 1062, 1030, 911, 885, 797, 719, 669, 652 cm^{-1} (m.): ^{19}F n.m.r., 82.25 δ (m., F_A), 54.27 δ (m., F_B), 36.54 (m., F_C), J_{AB}= 21Hz., J_{AC}=13Hz., J_{BC}= 2.5Hz., J_{AH}= 6Hz., J_{BH}= 10Hz., J_{CH}= 8.5Hz., $J_{C,NH}$= 1Hz., $J_{A,NH}$= 3Hz.

Reaction of N-thiobenzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine with triethylamine

The thiohydrazide (2g.), triethylamine (15ml.) and ethanol (15ml.) were boiled under reflux for 5 hours. The solvent was removed in vacuo, the solid was washed well with water, and dried. Crystallisation from benzene-hexane gave the 1:1 adduct as buff-coloured needles, m.p. 106-8° (Found: C, 56.77; H, 5.85; N, 10.47. $C_{19}H_{23}F_4N_3S$ requires C, 56.86; H, 5.74; N, 10.47%): $\nu_{max.}$ 1650, 1520, 1385, 1163, 949, 771 cm^{-1} (s.); 2565, 2460, 1480, 1305, 1238, 1131, 1031, 926, 783, 698, 679 cm^{-1} (m.): p.m.r., $CDCl_3$, 9.64 δ (s., br., 2N-H), 8.24-8.00 δ (m., 2H), 7.41-7.17 δ (m., 3H), 6.75-6.10 δ (m., 1H), 2.72 δ (q., 6H), 1.05 δ (t., 9H).

Action of the acid on the 1:1 adduct

The 1:1 adduct (1g.), ethanol (10ml.) and hydrochloric acid (d 1.18, 10ml.) were boiled under reflux for 0.5 hours, cooled and poured into water (150ml.). The yellow solid was filtered off, washed with water and dried. Crystallisation from

hexane gave N-thiobenzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine (0.4g.) as yellow needles, m.p. and mixed m.p. 90-1°. The product was further characterised by its i.r. spectrum, which was identical with that of the thiohydrazide.

v. From N-Thiobenzoyl-N'-Phenylhydrazine

N-Thiobenzoyl-N'-phenylhydrazine

Carboxymethyldithiobenzoate[43] (10.6g., 0.05 mole) was dissolved in potassium hydroxide solution (1N, 75ml.) and the pH was found to be 10. Phenylhydrazine (5.4g., 0.05 mole) was added portionwise to the stirred solution during 10 minutes, and during this time the pH was kept at 10 by the addition of potassium hydroxide solution (1N). When all the phenylhydrazine had been added, the solution was warmed to 70° and then left to cool at room temperature during one hour. Acetic acid was added until the pH was 6, the yellow solid was filtered off, washed well with water and dried *in vacuo*. Crystallisation from hexane-benzene gave the required product (6.7g., 59%) as yellow needles, m.p. 87-9° (lit.[65] dimorphous solid, m.p. 69.5-70° and 90-91°): $\nu_{max.}$ 1600, 1448, 1380, 1260, 1155, 855, 751, 725, 689 cm^{-1} (s.); 1520, 1490, 1485, 1355, 1310, 1230, 1180, 1078, 1030, 966, 928, 886, 842, 771, 656 cm^{-1} (m.): the i.r. spectrum of the lower melting form was identical.

Reaction of N-thiobenzoyl-N'-phenylhydrazine with 2,4-dinitrofluorobenzene

The hydrazine (2.28g., 0.01 mole), 2,4-dinitrofluorobenzene (1.86g., 0.01 mole) and acetonitrile (30ml.) were stirred together at 0°. Triethylamine (5ml.) was added and the solution was stirred for ten minutes at 0° before being poured into ice-water (500ml.) containing acetic acid (20ml.) The yellow solid (X) was filtered off, washed well with water and dried *in vacuo*. The yield was 3.7g. consisting of a yellow major product and a yellow fluorescent minor product (t.l.c.). $\nu_{max.}$ 1600, 1530, 1380, 1340, 1264, 1051, 692 cm^{-1} (s.); 1485, 1445, 1310, 1175, 1158, 1141, 1098, 1078, 951, 922, 837, 758, 749 cm^{-1} (m.); 3280 cm^{-1} (w.).

The product (X) was divided into three portions and treated as follows:

a. The product (X) (1.9g.), ethanol (15ml.) and triethylamine (15ml.) were boiled under reflux for 0.5 hours, cooled and the solvent was evaporated *in vacuo*. The red solid was washed well with water and crystallised from dimethylformamide to give *2,4-diphenyl-7-nitro-4H-benzo[1,3,4]thiadiazine* (1.4g., 82% based on the thiohydrazide) as red needles, m.p. 158-9° (Found: C, 65.49; H, 3.73; N, 11.90. $C_{19}H_{13}N_3O_2S$ requires C, 65.71; H, 3.75; N, 12.10%): $\nu_{max.}$ 1490, 1390, 1340, 1314, 1300, 1259, 1147, 1130, 769, 757, 739, 687 cm^{-1} (s.); 1580, 1515, 1199, 1171, 1042, 922, 884, 820, 717, 698, 619, 578 cm^{-1} (m.): *p.m.r.*, 100 MHz., d_6 dmso, 8.14 δ (d., 1H, J = 2.4Hz.), 8.01 δ (q., 1H, J_{ORTHO} = 8.7Hz., J_{META} = 2.4Hz.), 7.95-7.84 δ (m., 2H), 7.64-7.32 δ (m., 8H), 6.71 δ (d., 1H, J = 8.7Hz.).

b. The product (X) (1g.) was dissolved in acetic acid (25ml.) and hydrogen peroxide solution (6%, 10ml.) was added. The solution was boiled under reflux for 0.5 hours. There was no reaction (t.l.c.).

c. The product (X) (1g.) was dissolved in chloroform (30ml.) and a solution of potassium ferricyanide (4g.) and sodium bicarbonate (4g.) in water (100ml.) was added to form a two-phase system. The mixture was stirred at room temperature for one hour and the chloroform layer was separated. The only product was 2,4-diphenyl-7-nitro-4H-benzo[1,3,4]thiadiazine (t.l.c.).

Oxidation of 2,4-diphenyl-7-nitro-4H-benzo[1,3,4]thiadiazine

The thiadiazine (0.7g.) was dissolved in a warm mixture of acetic acid (30ml.) and hydrogen peroxide solution (6%, 10ml.) and the solution was boiled under reflux for 15 minutes. Water (10ml.) was added and the solution was allowed to cool. The yellow solid was filtered off, washed well with water and dried *in vacuo*. Crystallisation from ethanol-ethyl acetate gave 1,1-dioxo-2,4-diphenyl-7-nitro-4H-benzo[1,3,4]thiadiazine (0.5g., 69%) as yellow needles, m.p. 202-4°, going black at *ca.* 195° (Found: C, 59.97; H, 3.45; N, 11.22. $C_{19}H_{13}N_3O_4S$ requires C, 60.16; H, 3.43; N, 11.08%): $\nu_{max.}$ 1520, 1470, 1340, 1309, 1295, 1159, 1116, 768, 697, 530 cm^{-1} (s.); 1600, 1580, 1495, 1380, 1261, 1245, 984, 934, 916, 890, 823, 786, 743, 689, 611 530 cm^{-1} (m.): *p.m.r.*, 100 MHz., d_6 dmso, 8.75 δ (d., 1H, J = 2.5Hz), 8.37 δ (q., 1H, J_{ORTHO}= 9.5Hz., J_{META}= 2.5Hz.),

7.99-7.85 δ (m., 2H), 7.79-7.49 δ (m., 8H), 7.08 δ (d., 1H, J = 9.5Hz.): m.s. 379 (M^+), 315, 269, 268, 192, 182, 166, 154, 140, 139, 103, 89, 77, 63, 51.

vi. From 1,5,-Diphenylthiocarbazone (Dithizone)

Reaction of dithizone with 2,4-dinitrofluorobenzene at room temperature

Dithizone (5.12g., 0.02 mole) was suspended in acetonitrile (40ml.) and 2,4-dinitrofluorobenzene (3.72g., 0.02 mole) was added. Triethylamine (10ml.) was added and the mixture was stirred at room temperature for 2 hours. The precipitate was filtered off and the dark metallic-looking solid was washed with water. The reaction solution was poured into water (200ml.) and more solid was filtered off. The recovered solids were combined and dried in vacuo. Crystallisation from benzene gave 7-nitro-4-phenyl-2-phenylazo-4H-benzo[1,3,4]thiadiazine (6.8g., 79% as dark purple needles, m.p. 259-60° (Found: C, 60.65; H, 3.54; N, 18.50. $C_{19}H_{13}N_5O_2S$ requires C, 60.80; H, 3.47; N, 18.67%): $\nu_{max.}$ 1560, 1500, 1335, 1270, 1090, 772 cm^{-1} (s.); 1468, 1385, 1305, 1205, 1156, 1003, 951, 891, 822, 795, 740, 717, 691, 680 cm^{-1} (m.): p.m.r., 100 MHz., d_6 dmso, 51 SCANS C.A.T., 7.94 δ (d., J = 2.5Hz.), 7.87-7.73 δ (m.,), 7.65-7.40 δ (m.), 6.44 δ (d., J = 9.25Hz.): m.s. 375 (M^+), 345, 300, 270, 243, 224, 223, 222, 198, 197, 196, 166, 165, 154, 153, 140, 139, 128, 120, 105, 103, 95, 77, 69, 63.

Reaction of dithizone with 2,4-dinitrofluorobenzene at 0°

Dithizone (1.28g., 0.005 mole), 2,4-dinitrofluorobenzene (0.93g., 0.005 mole) and acetonitrile (20ml.) were stirred together at 0° (ice-bath) and triethylamine (5ml.) was added. The mixture was stirred for 5 minutes and then poured into ice-water (400ml.) containing acetic acid (20ml.). The yellow solid was filtered off, washed with water and dried *in vacuo*. Crystallisation (twice) from chloroform-hexane gave a 1:1-condensation product (1.6g., 80%) as yellow needles which decompose *ca.* 170° without melting to 7-nitro-4-phenyl-2-phenylazo-4H-benzo[1,3,4]-thiadiazine (t.l.c.) (Found: C, 53.02; H, 3.39; N, 19.46. $C_{19}H_{14}N_6O_4S$ requires C, 54.03; H, 3.32; N, 19.91%): $\nu_{max.}$ 1590, 1520, 1380, 1340, 1262, 1154, 1132, 747, 735, 689 cm^{-1} (s.); 3245, 1480, 1450, 1305, 1186, 1091, 1073, 1050, 920, 883, 836, 635, 600, 584 cm^{-1} (m.): the mass spectrum of the product was identical with that of 7-nitro-4-phenyl-2-phenylazo-4H-benzo-[1,3,4]thiadiazine.

Attempted oxidation of the 1:1 condensation product

a. The 1:1 condensation product (1g.) was dissolved in acetic acid (25ml.) and hydrogen peroxide solution (6%, 10ml.) was added. The solution was boiled under reflux for 0.5 hours. There was no reaction.

b. The 1:1 condensation product (1g.) was dissolved in chloroform (30ml.) and the solution was introduced into a flask containing potassium ferricyanide (4g.) and sodium bicarbonate (4g.) in

water (100ml.) at 0°. The two-phase mixture was stirred for one hour and investigation (t.l.c.) of the chloroform solution indicated no reaction. The solution was allowed to warm to room temperature with stirring during 2 hours. The only product (t.l.c.) was 7-nitro-4-phenyl-2-phenylazo-4H-benzo-[1,3,4]thiadiazine.

c. The 1:1 condensation product (0.1g.) and acetic acid (10ml.) were boiled under reflux for 4 hours, cooled and poured into ice-water (200ml.). The product was filtered off and was identified (i.r., t.l.c.) as 7-nitro-4-phenyl-2-phenylazo-4H--benzo[1,3,4]thiadiazine, m.p. 257-9°.

Oxidation of 7-nitro-4-phenyl-2-phenylazo-4H-benzo[1,3,4]-thiadiazine

The thiadiazine (2g.), acetic acid (50ml.) and hydrogen peroxide solution (6%, 10ml.) were boiled under reflux for 20 minutes. The reaction solution was allowed to cool and the precipitate was filtered off. Crystallisation from acetic acid gave 1,1-dioxo-7-nitro-4-phenyl-2-phenylazo-4H-benzo[1,3,4]thia-diazine (1.7g., 78%) as orange needles, m.p. 243-7° after darkening at 225° (Found: C, 56.06; H, 3.16; N, 17.32. $C_{19}H_{13}N_5O_4S$ requires C, 56.02; H, 3.19; N, 17.20%): $\nu_{max.}$ 1520, 1380, 1345, 1302, 1155, 1121, 688 cm^{-1} (s.); 1600, 1490, 1470, 1217, 951, 887, 829, 775, 741, 713, 644, 599 cm^{-1} (m.): p.m.r., 100 MHz., d_6 dmso, 8.75 δ (d., 1H, J = 2.5Hz.), 8.35 δ (q., 1H, J_{ORTHO}= 9.5Hz., J_{META}= 2.5Hz.), 7.92-7.51 δ (m., 10H), 7.08 δ

(d., 1H, J = 9.5Hz.): m.s. 423 ($C_{19}H_{13}N_5O_5S$), 407 (M^+), 345, 343, 269, 268, 254, 214, 212, 192, 166, 154, 140, 139, 131, 105, 77, 53.

Reaction of dithizone with 2,3-dichloroquinoxaline

Dithizone (2.56g., 0.01 mole), 2,3-dichloroquinoxaline (1.99g., 0.01 mole), dimethylformamide (50ml.) and triethylamine (10ml.) were boiled under reflux for 4 hours. The reaction mixture was cooled, and the crystalline red solid was filtered off and washed well with water. The product was dried in vacuo to give 4-phenyl-2-phenylazo-4H-quinoxalino[2,3][1,3,4]thiadiazine (2.7g., 71%) as red needles, m.p. 313°, which needed no further purification (Found: C, 66.12; H, 3.85; N, 22.04; S, 8.54. $C_{21}H_{14}N_6S$ requires C, 65.97; H, 3.67; N, 21.99; S, 8.38%): $\nu_{max.}$ 1570, 1395, 1380, 1360, 1242, 1133, 688 cm^{-1} (s.); 1485, 1455, 1325, 1262, 1206, 1153, 1073, 817, 774, 762, 720, 600, 554 cm^{-1} (m.): m.s. 382 (M^+), 353, 293, 277, 250, 219, 218, 191, 166, 105, 102, 91, 90, 78, 77.

Reaction of dithizone and 2-chloro-3-nitropyridine

Dithizone (2.56g., 0.01 mole) and 2-chloro-3-nitropyridine (1.58g., 0.01 mole) were dissolved in a warm mixture of acetonitrile (20ml.) and triethylamine (10ml.) and the solution was boiled under reflux for 4 hours. The solution was cooled and poured into water (700ml.) containing acetic acid (20ml.). The purple solid was filtered off and dried in vacuo. Crystallisation

from ethanol gave 4-phenyl-2-phenylazo-4H-pyrido[3,2][1,3,4]-thiadiazine (2.5g., 75%) as purple needles, m.p. 164° (Found: C, 65.44; H, 3.81; N, 21.08; S, 9.76. $C_{18}H_{13}N_5S$ requires C, 65.26; H, 3.93; N, 21.15; S, 9.67%): $\nu_{max.}$ 1585, 1415, 1380, 1259, 1127, 1120, 686 cm^{-1} (s.); 1552, 1495, 1455, 1294, 1208, 1143, 1075, 803, 789, 762, 741, 739, 711, 530: p.m.r., 100 MHz., d_6 dmso, 7.91-7.77 δ (m., 3H), 7.65-7.45 δ (m., 9H), 6.99 δ (q., 1H, J = 7.5Hz., J' = 4.7Hz.): m.s. 331 (M^+), 302, 243, 242, 226, 199, 168, 155, 140, 129, 115, 105, 96, 82, 78, 77, 70, 64.

Oxidation of 4-phenyl-2-phenylazo-4H-pyrido[3,2][1,3,4]thiadiazine

The thiadiazine (1.65g., 0.005 mole) was dissolved in warm acetic acid (60ml.) and hydrogen peroxide solution (6%, 10ml.) was added. The mixture was boiled under reflux for 0.5 hours, and allowed to cool. The orange solid was filtered off, washed well with water and dried. Crystallisation from acetic acid gave 1,1-dioxo-4-phenyl-2-phenylazo-4H-pyrido[3,2][1,3,4]thiadiazine (1.1g., 61%) as orange needles, m.p. 227-9° after darkening ca. 220° (Found: C, 58.93; H, 3.60; N, 19.18. $C_{18}H_{13}N_5O_2S$ requires C, 59.50, H, 3.58; N, 19.28%): $\nu_{max.}$ 1575, 1540, 1425, 1310, 1161, 1139, 1073, 751, 683 cm^{-1} (s.); 1495, 1385, 1260, 1200, 1004, 956, 812, 770, 711, 657, 645, 592, 521 cm^{-1} (m.): p.m.r., 100MHz., d_6 dmso, 8.69 δ (s., 1H), 8.63 δ (q., 1H, J = 4Hz., J' = 1.5Hz.), 7.93-7.81 δ (m., 2H), 7.78-7.52 δ (m., ca. 11H): m.s. 379 ($C_{18}H_{13}N_5O_3S$), 363 (M^+), 301, 286, 270, 261, 258, 243, 225, 210, 194, 193, 169, 168, 140, 131, 115, 105, 93, 77, 64, 51.

SUMMARY

Methods have been developed for (1) a new synthesis of the 1,3,4-benzoxadiazine ring system and (2) syntheses of new 1,3,4-benzothiadiazines from hydrazides and thiohydrazides respectively.

Extensions of these reactions involving the use of aromatic heterocyclic compounds bearing substituents 1,2 with respect to each other have led to four new ring systems.

The course of the cyclisation reactions has been confirmed by the use of n.m.r. and mass spectroscopy.

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