SOME REACTIONS OF THIOHYDRAZIDES
AND RELATED COMPOUNDS

a thesis presented by

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ABSTRACT

The reactions of several aromatic thiohydrazides, especially N-phenyl-N'-benzothiohydrazide, were studied. Air and iodine oxidations were found to be of particular interest and gave formation of bis-hydrazonodisulphides or, in one case, a 1,3,4-benzothiodiazine. Further oxidation of these bis-hydrazonodisulphides was found to give 5,6-dihydro-1,2,4,5-dithiadiazines or 4,5-dihydro-1,3,4-thiadiazoles. The reactions of the bis-hydrazonodisulphides were also extensively studied.

ACKNOWLEDGEMENTS

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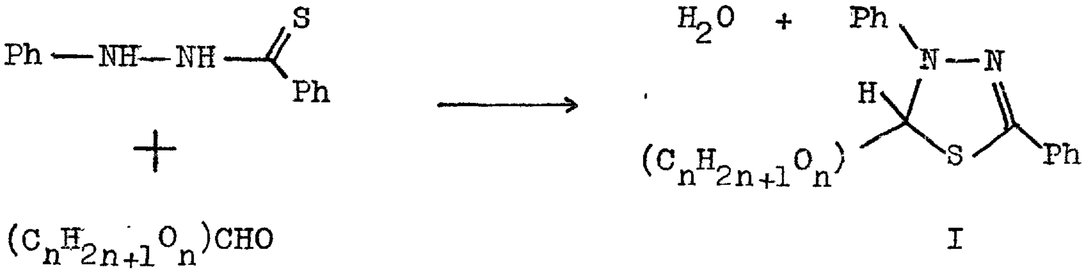
CONTENTS

DISCUSSION

REVIEW

The chemistry of thiohydrazides is of particular interest for the variety of unusual heterocyclic systems which can be formed from them.

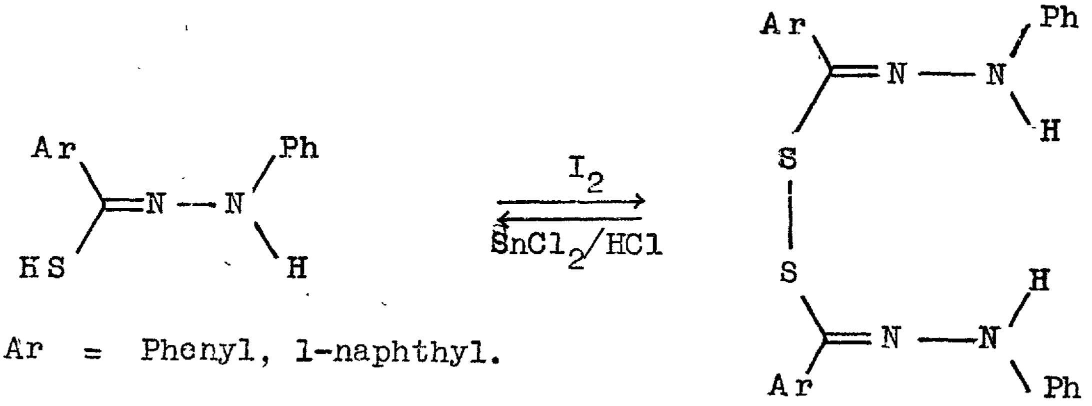
The first such systems to be studied were the sugar derivatives, the glycothiadiazolines (I) first prepared by Wuyts[1,2,3,4] :-



I

These derivatives readily formed by warming together the sugar and the thiohydrazide in the presence of ethanol saturated with hydrogen chloride were found to contain optical isomers with high optical rotations, the fraction of the mixture not very soluble in methanol-benzene mixtures being found to be dextrorotatory and the more soluble fraction levorotatory. Wuyts and Verstraeten[2] recorded an optical rotation of +1406° from the less soluble fraction of the glycothiadiazoline obtained from galactose and N-phenyl-N'-benzothiohydrazide. This reaction may also be used to prepare thiadiazoles from aldehydes or ketones and thiohydrazides, several such reactions being reported by Wuyts and Verstraeten.[2]

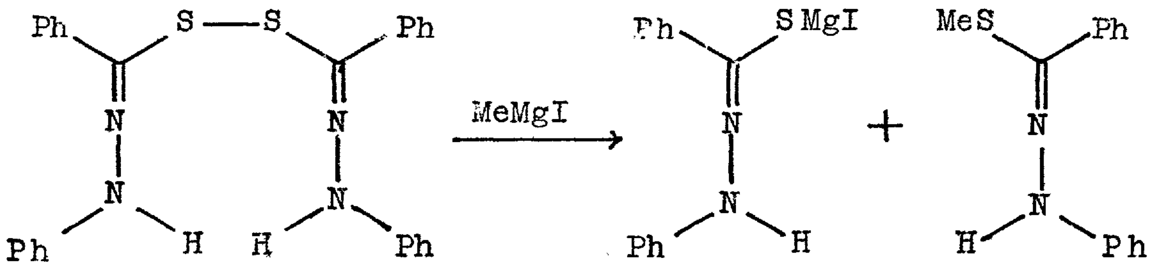
Wuyts and Lacourt also studied the iodine oxidation products of some thiohydrazides[5] and found formation of symmetrical disulphides from what they concluded to be the tautomeric thio-enol form of the thiohydrazides:-



Ar = Phenyl, 1-naphthyl.

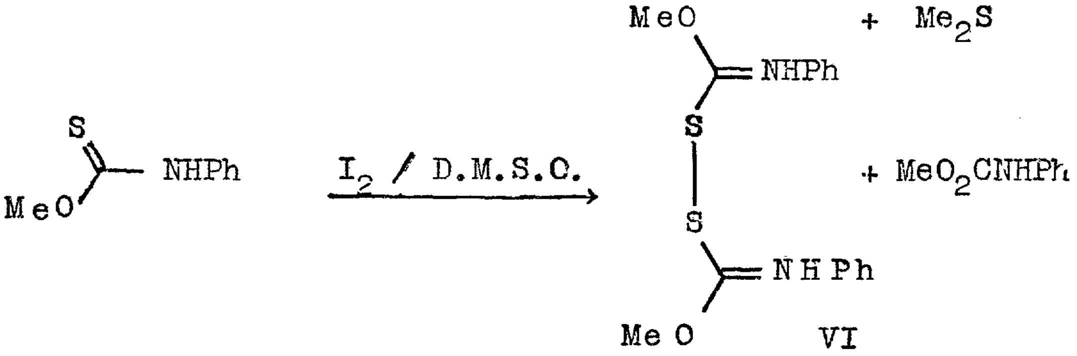
II

The structure of these disulphides was demonstrated by molecular weight determination, by attempted oxidation of the S-methylated derivative of N-phenyl-N'-benzothiohydrazide (no reaction) and by oxidation of N-cyclohexylcarbothioyl-N'-phenyl-N'-methyl hydrazine to give formation of an oxidation product which it was not found possible to purify. The disulphides formed could be reduced to the thiohydrazides in almost quantitative yield by stannous chloride. Treatment with methyl magnesium iodide yielded a half-molar amount of thiohydrazide and an oily uncharacterised compound supposed to be the S-methyl derivative of the thiohydrazide (V) :-

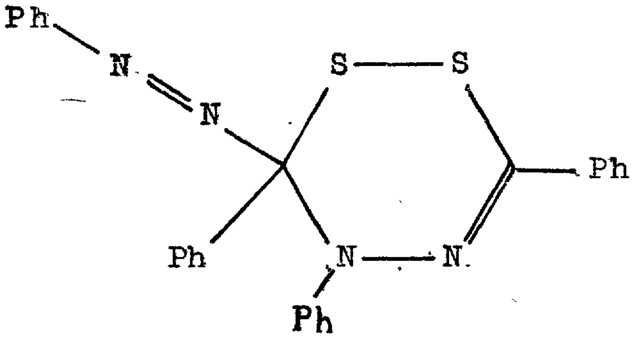


III IV V

An analogous iodine oxidation in which thiocarbamates are converted to corresponding disulphides (e.g.VI) is reported by Kinoshita et al.[6]:-

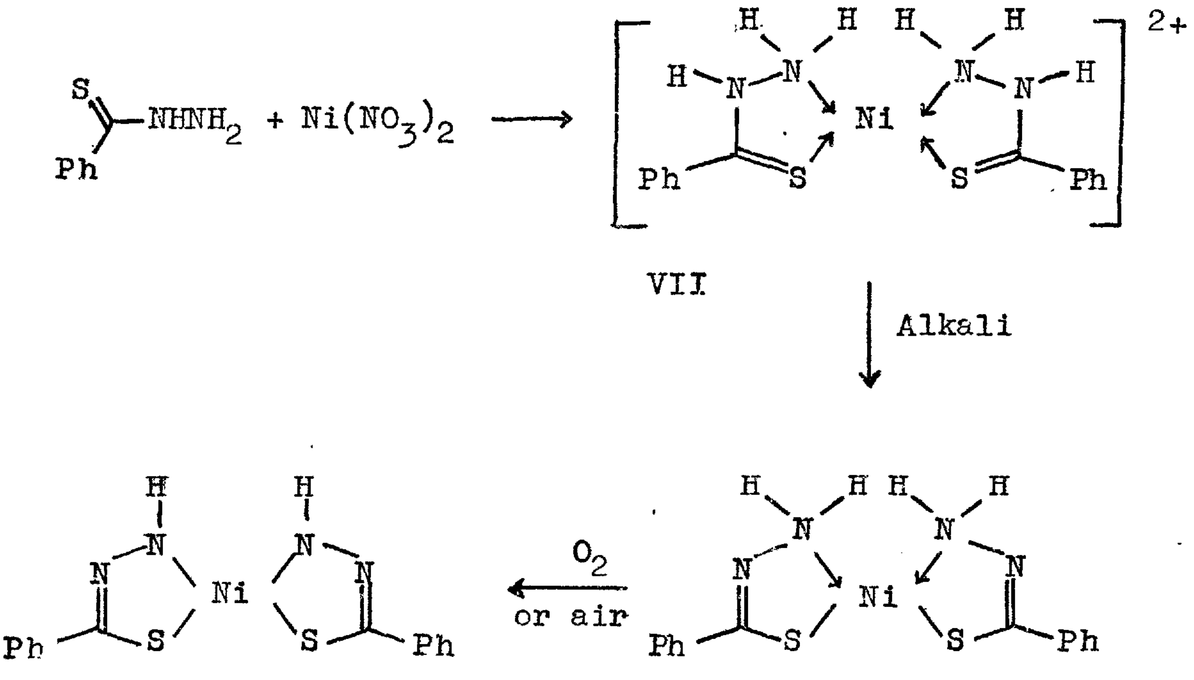


Another thiohydrazide oxidation, that of N-phenyl-N'-benzothiohydrazide by N-bromo-succinimide, has been shown by Bock et al.[7] to give a dimer of α-phenylazo-thiobenzaldehyde, this compound being identical with 5,6-dihydro-3,5,6-triphenyl-1,2,4,5-dithiadiazine (XIX) prepared in this project



XIX

Formation of brown, air-stable complexes (VII) of thiohydrazides with nickel salts is reported by K.A. Jensen and J.F. Miquel[8]. These give air-sensitive divalent nickel complexes (VIII) on treatment with alkali which are readily oxidised by oxygen or air to give blue, tetravalent nickel complexes (IX) e.g. :-

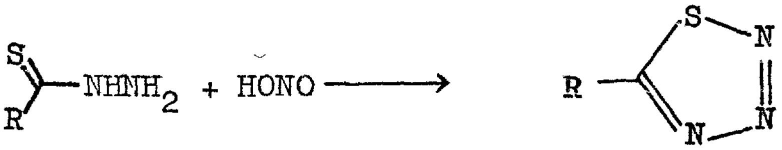


VII

IX

VIII

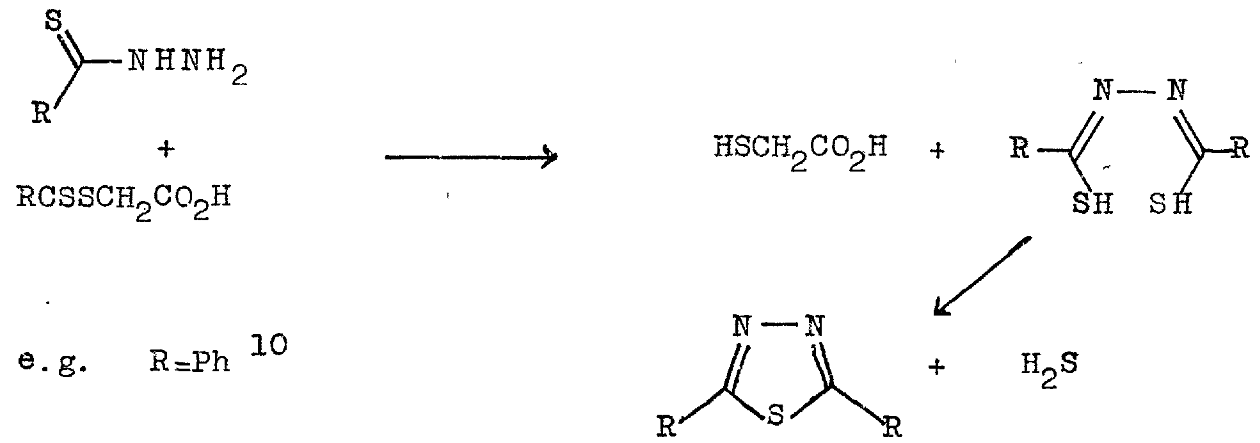
Jensen and Pedersen[9] have synthesised several 1,2,3.4-thiatriazoles (X) from thiohydrazides and nitrous acid:-



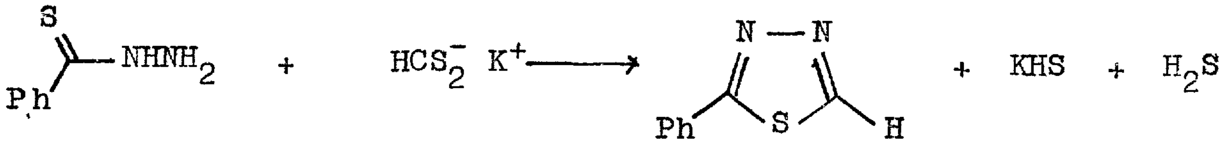
X

R= Phenyl (65%), p-hydroxyphenyl (88%), α-naphthyl (75%) β-naphthyl (70%), 2-furyl (83%), 2-thienyl (95%) 2-pyrryl (83%), 3-indolyl (83%).

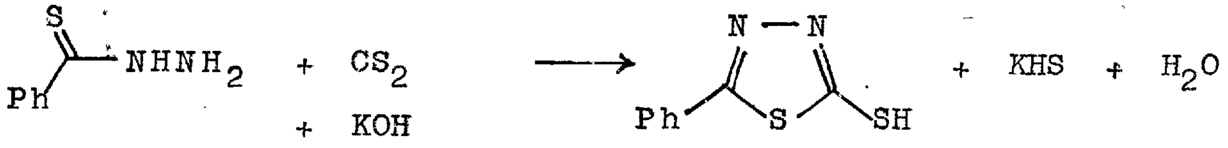
Thiohydrazides also provide a convenient means of synthesising many 1,3,4-thiadiazoles[1,10-13] (XI, XII, XIII)



XI



XII



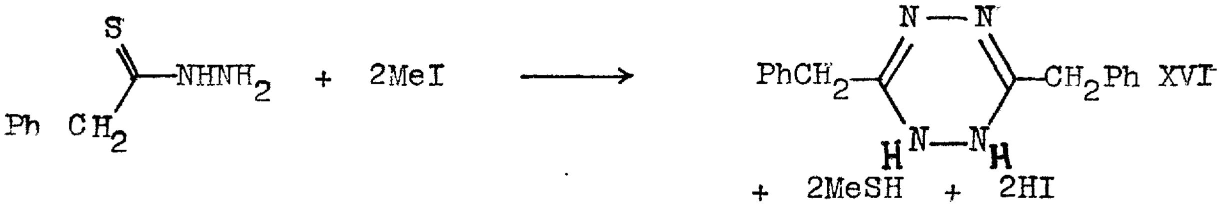
XIII

Some thiadiazoles (XIV, XV) may be prepared directly and in good yields by treatment of hydrazine with carboxydithioates :-

XIV

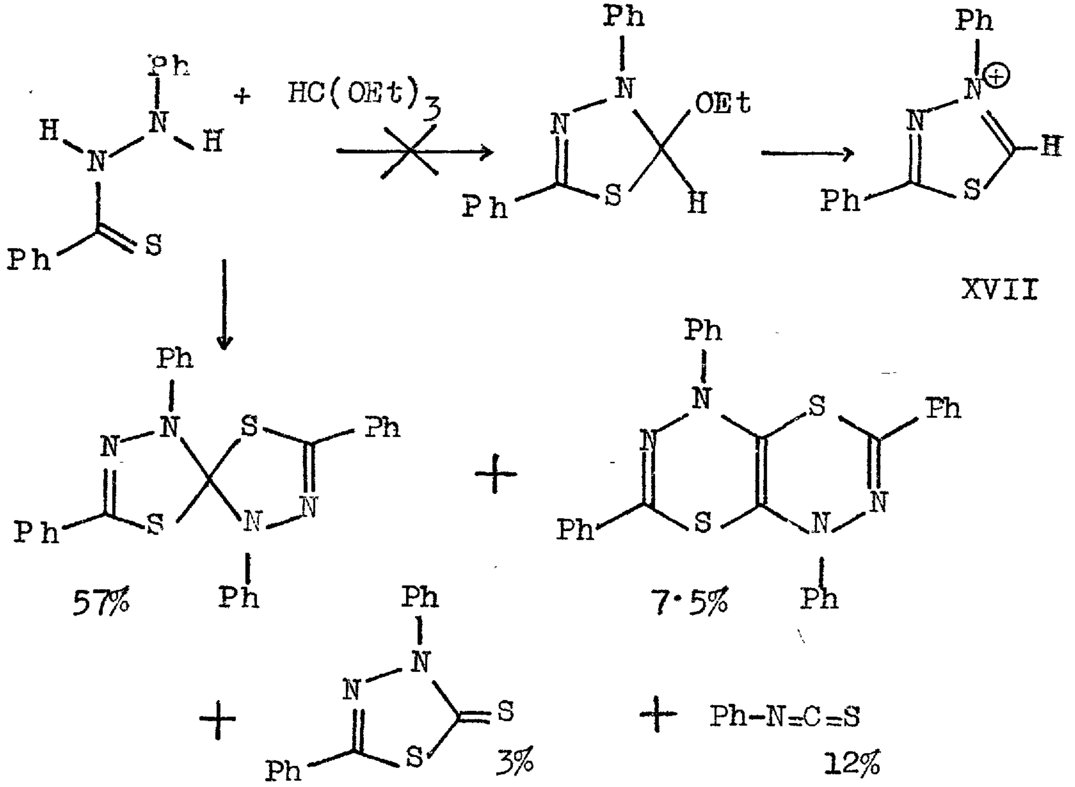
XV

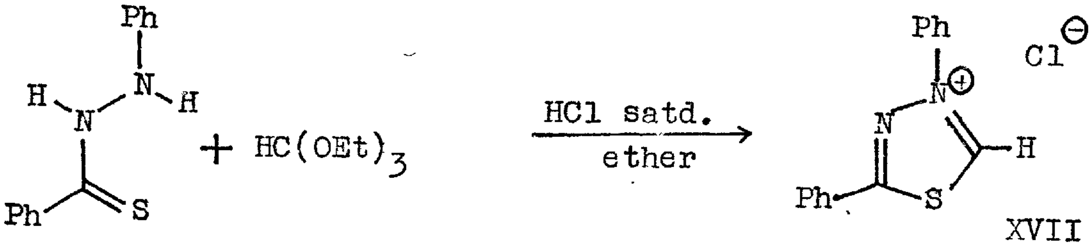
Treatment of some thiohydrazides with methyl iodide gives formation of dihydrotetrazines (XVI) :-



XVI

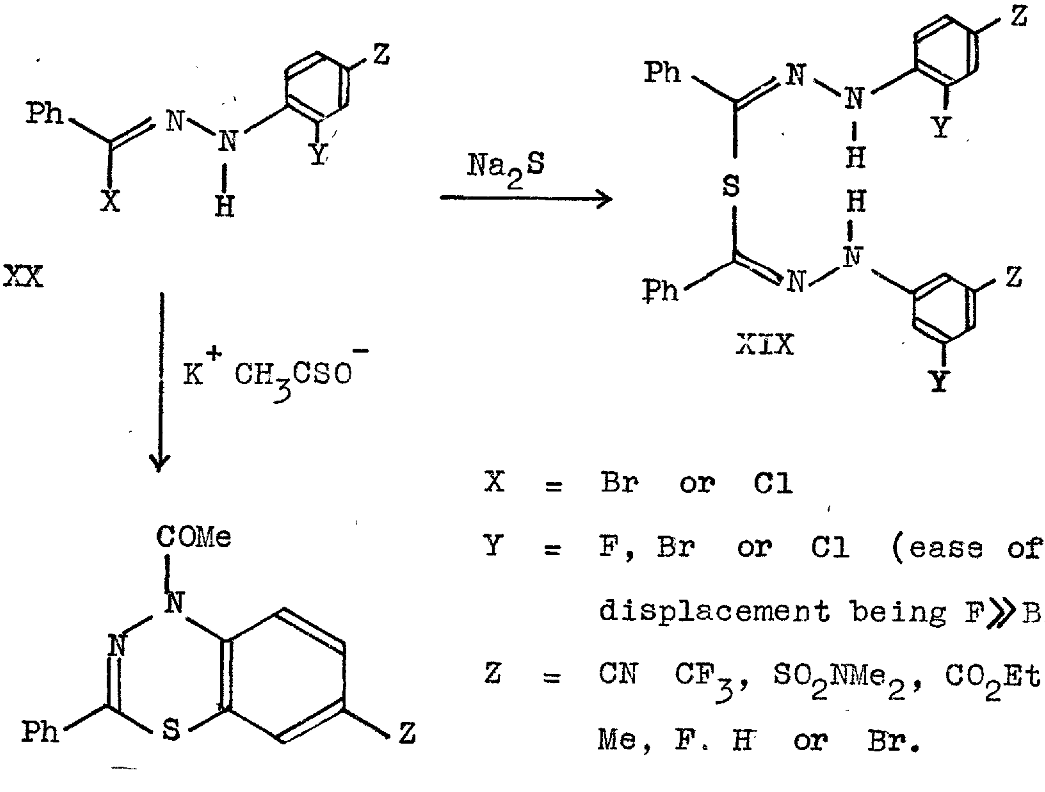
Scherowsky[16]. in an attempt to synthesise 2,4-diaryl-1,3,4-thiadiazolium salts (XVII). isolated several interesting products from the reaction of N-phenyl-N'-benzothiohydrazide and ethyl orthoformate at 90° :-





Synthesis of several thiadiazolium salts by this method is reported by Scherowsky.

Gibson et al.[17.18.19] have reported the synthesis of two classes of compounds also studied in this thesis, the hydrazonyl sulphides (XIX), prepared by reaction of α-halogeno-benzaldehyde phenyl-hydrazones (XX) and sodium sulphide, and 4H -1,3,4-benzothiadiazines (XXI) prepared from the reaction of α-halogeno-benzaldehyde phenylhydrazones and potassium thioacetate in boiling acetonitrile :-



XX

XIX

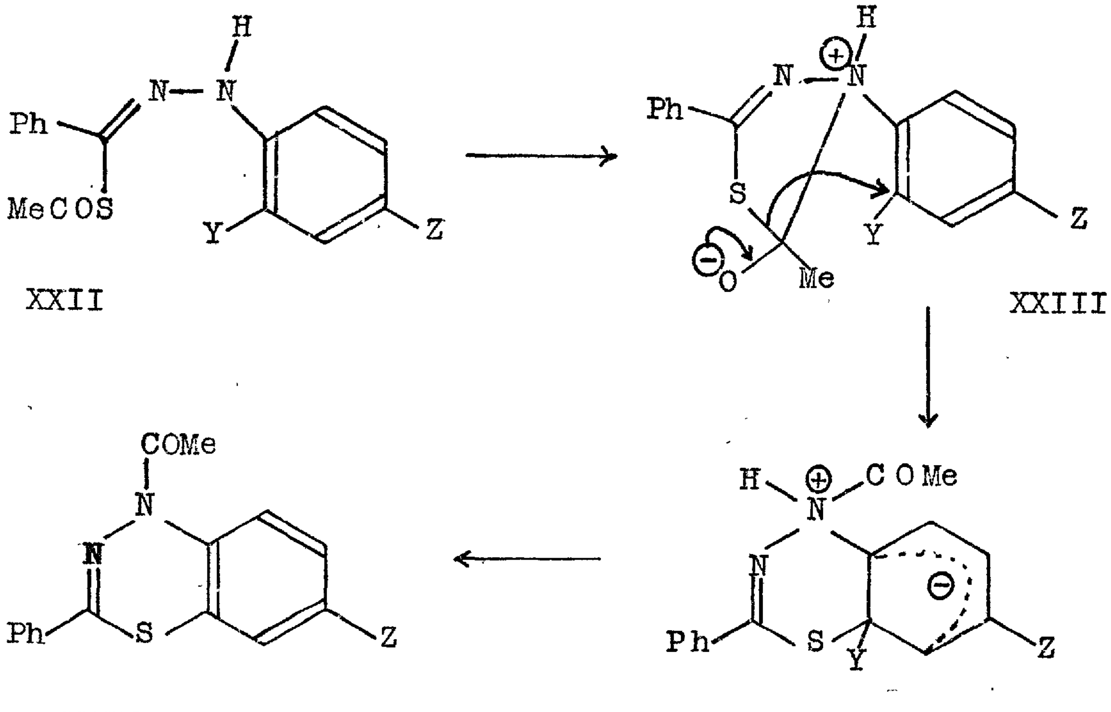
XXI

X = Br or Cl

Y = F, Br or Cl (ease of displacement being F≫Br> Cl)

Z = CN CF_3, SO_2NMe_2, CO_2Et, SCN, Me, F. H or Br.

Barnish and Gibson[17] suggest a mechanism for thiadiazine formation in which a protonated species (XXIII) is formed, the positive charge on nitrogen facilitating the stage leading to XXIV. Thus in the species XXIII, derived from the α-thioacetate, they suggest the move towards completion of S –– N acetyl transfer is accompanied by addition of incipiently negative S to the ortho-position of the halogenated benzene ring in a synchronous process :-



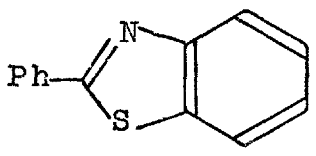
XXII

XXIII

XXIV

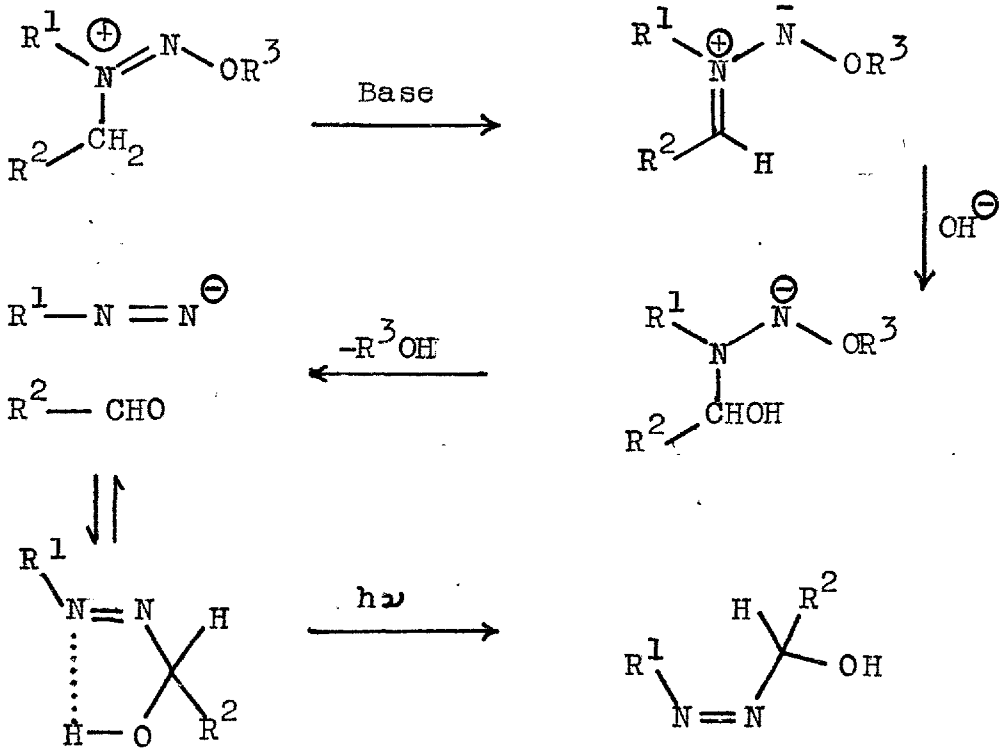
They also suggest an alternative mechanism in which completion of acetyl transfer is followed by addition of negative sulphur to the ortho-position of the halogenated benzene ring as a discrete process.

A reported synthesis of 2-phenyl-4H-benzo-1,3,4-thiadiazine by Guha and Ghosh[20] from N-phenyl-N'-benzhydrazide and sulphur has been shown by Corsi [21] and Barnish and Gibson [17] not to give this product, 2-phenylbenzothiazole (XXV) being the product obtained.

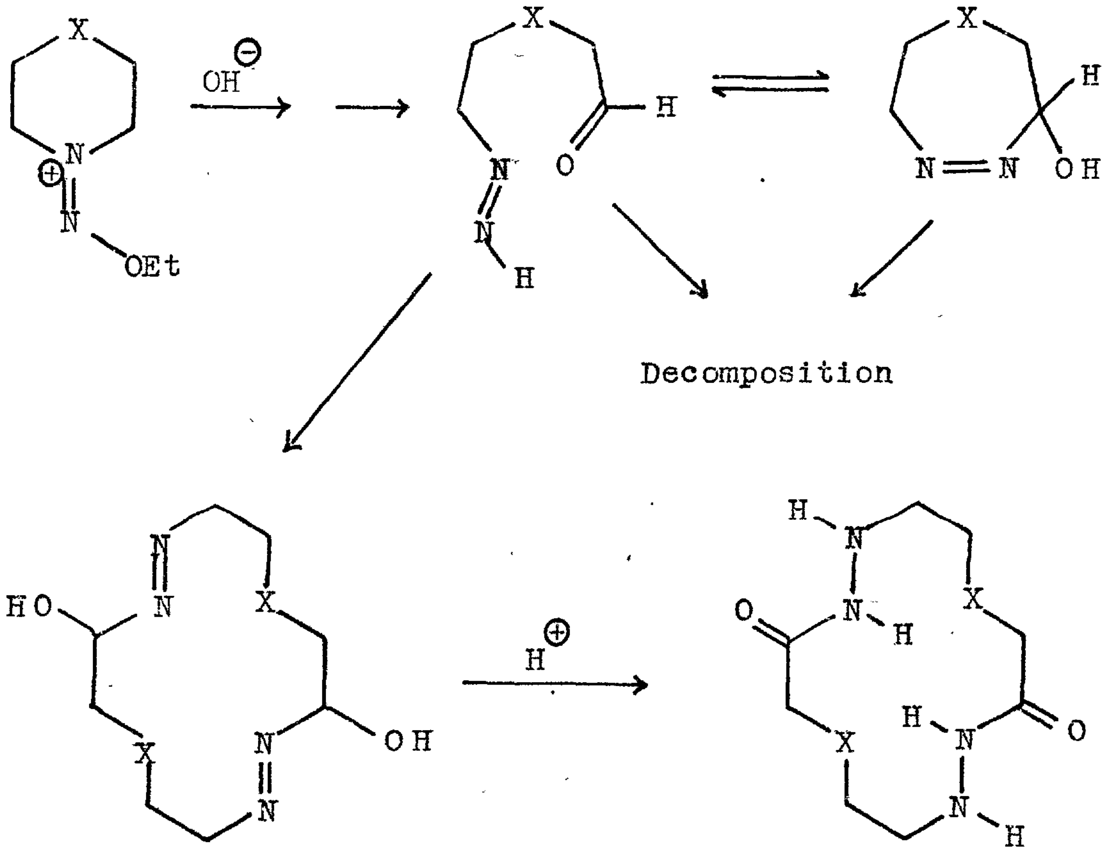


XXV

The azo-thiol system, at one time thought to be present in some of the compounds studied in this thesis, is not known in the literature but oxygen analogues have been studied [22, 23, 24, 25] and are stable at room temperature. The trans- forms of these compounds are usually obtained, being more stable than the corresponding cis-compounds in which no stabilization by hydrogen bonding can take place. (The trans forms are often distillable at low temperatures.)



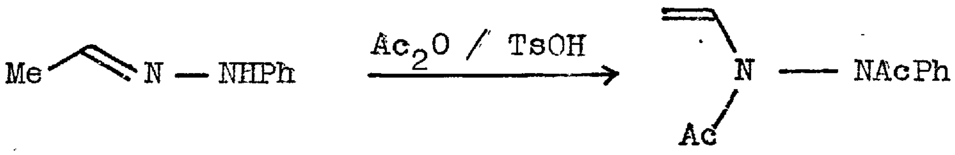
In another interesting example of this type of reaction cyclic starting materials give rise to dimeric products, which, although they are formed in good optical yield (c.90%), could only be isolated in poor yield (22% for $X=CH_2$, 11% for $X=O$) because of difficult separation from resinous by-products.



The azo-hydrazide isomerization was effected using hydrogen chloride. Structures of the dimers were proved by X-ray crystallography and thorough studies of n.m.r., u.v. and i.r. spectra.

The existence of azo- and ene-hydrazine tautomers of aryl hydrazones lends further support to the possible existence of thiohydrazide-azo thiol isomerization. Formaldehyde phenylhydrazone was found by Ioffe and Stopskii [26] to yield phenylazomethane on distillation from alkali and acetylation of several arylhydrazones with acetic anhydride in the presence of p-toluenesulphonic acid was found by Suvorov and

Sorokina[27] to give N,N'-diacetyl-β-arylhydrazonoalkenes e.g.:-



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DISCUSSION

Preparation of Thiohydrazides

Several methods for the preparation of thiohydrazides exist in the literature [1], the most successful ones involving formation of a carboxymethyl dithioate (I) followed by reaction with a hydrazine.

The carboxymethyl dithioate synthesis most generally used is that involving preparation of a Grignard reagent followed by reaction with carbon disulphide and chloracetic acid [2,3] :-

$$\mathrm{RMgX} + \mathrm{CS_2} \longrightarrow \mathrm{RCSSMgX} \xrightarrow{\mathrm{ClCH_2CO_2Na}} \underset{\mathrm{I}}{\mathrm{RCSSCH_2COONa}}$$

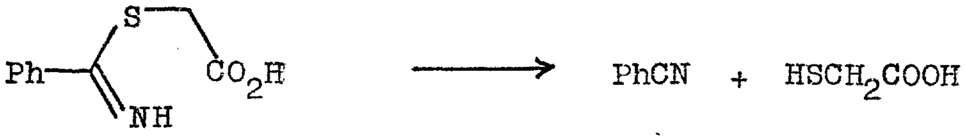
However, this scheme is poor for R= alkyl due to poor reaction of the Grignard reagent with carbon disulphide and cannot be used for R= halogenated or nitrated aryl. (Holmberg [4] used this method for preparation of carboxymethyl dithiobenzoate from benzotrichloride).

Reaction of ammonium polysulphide with aldehydes [5] gives a fast and convenient method for preparation of dithioacids but yields tend to be low, separation from resinous by-products being necessary. Yields are also very dependent on the structure of the aldehyde used.

Preparation of the imine of acyl and aryl derivatives (II) of thioglycollic acid followed by treatment of a solution of its salt in pyridine with hydrogen sulphide gives generally poor yields [6,7]:-

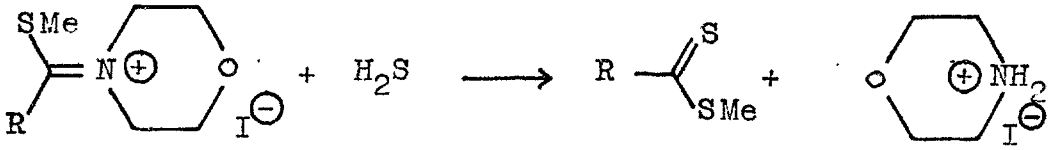
II

For R=methyl, this method gives a crude yield of 24% of thioacetyl thioglycollic acid. Poor yields may be due to the decomposition of the thioimidoester on being liberated from its salt on dissolution in pyridine. An analogous decomposition has been observed in aqueous solutions [8]:-

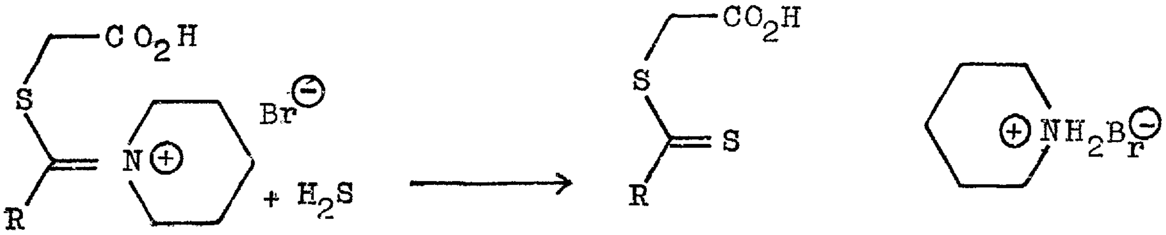


Peak and Stansfield [9] obtained good yields of dithiocarboxylic esters by thiohydrolysis of S-methyl thiomorpholidium iodides (III) in absolute ethanol.

III



Similary, Doyle et al.[10] prepared methyl indole-3-dithiocarboxylate by thiohydolysis of the corresponding S-methyl thiomorpholidium iodide. Jensen and Pedersen [1] investigated the analagous thiohydrolysis of several S-carboxymethyl-thiopiperidinium bromides (IV) in absolute ethanol:-

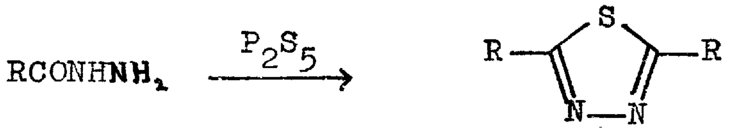


IV

These reactions give good yields, thiopiperidides having definite advantages over thiomorpholides. Thiopiperidides may be prepared by the Willgerodt-Kindler method or from piperidides by treatment with phosphorous pentasulphide. The bromide salts may be prepared from thiopiperidides and bromoacetic acid in benzene, this method being used by Holmberg [11] for the preparation of S-carboxymethyl thiobenzpiperididium bromide.

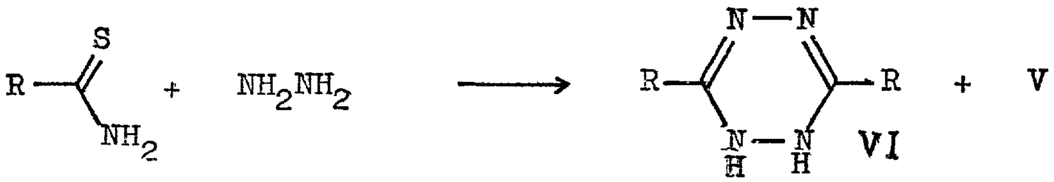
Synthesis of many thiohydrazides has been achieved by Jensen and Pedersen [12] by the reaction of hydrazines and carboxymethyl dithioates. Reaction with monoalkyl hydrazines gave N-alkyl-N'-thiohydrazides in all cases studied except for methyl hydrazine which with thiobenzoyl thioglycollic acid was found to give a 5-10% yield of N,N-methylbenzothiohydrazide. Jensen and Pedersen found symmetric di-secondary alkyl hydrazines to be unreactive towards carboxymethyl dithioates.

Other methods for synthesising thiohydrazides were attempted by Jensen and Pedersen with little success. Reaction of hydrazides with phosphorus pentasulphide generally gave formation of 1,3,4-thiadiazoles (V) although they obtained a 6% yield of benzothiohydrazide by this method.



V

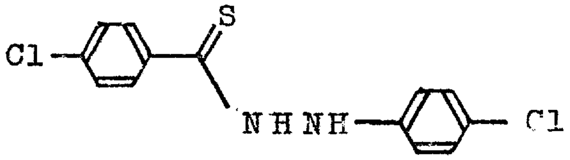
Thioamides were found to react with hydrazine to give hydrogen sulphide and dihydrotetrazines (VI) or 1,3,4-thiadiazoles and thioesters gave α-alkoxy hydrazones (VII) and hydrogen sulphide with hydrazine.



VI

VII

In this project, use of carboxymethyl dithioates prepared from Grignard reagents was found to give generally excellent results. The thiopiperidide route was used in the synthesis of N-4-chlorophenyl-N'-4-chlorobenzothiohydrazide (VIII) with good results.

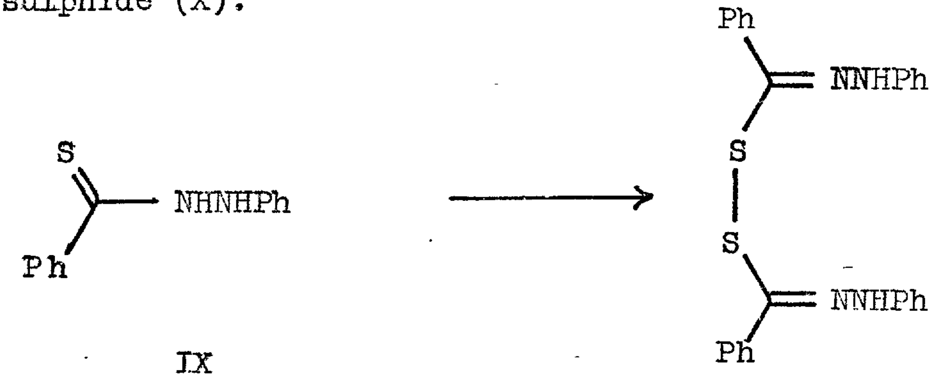


VIII

The method used for preparing thiobenzoyl thioglycollic acid due to Kjaer[3] was not found to give such good yields as those quoted by Kjaer (50%) and yields more in line with those quoted by Jensen and Pedersen [1] for the same method (36-40%) were obtained.

Oxidation products of N-phenyl-N'-benzothiohydrazide.

N-phenyl-N'-benzothiohydrazide (IX) was found to form a new compound on standing in the presence of triethylamine or alumina in benzene solution. This compound was later found to be bis-(α-phenylhydrazonobenzyl)-disulphide (X).

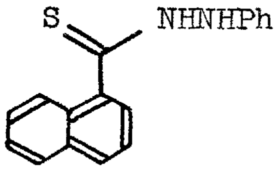


IX

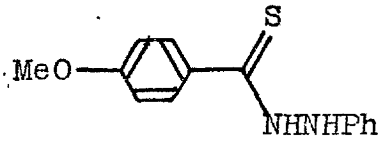
X

All the spectral properties of this compound originally examined indicated it to be an isomer of the thiohydrazide, phenylazo-benzyl-mercaptan (Ph·CHSH·N:N·Ph) (XI) and for some time work on it continued to give results in accordance with this: mass spectroscopy indicated what appeared to be the molecular ion at m/e 228; the infra-red spectrum showed little evidence of any bands due to N-H and gave no conclusive proof of either the proposed isomeric structure or the actual structure; the n.m.r. spectrum showed only a wide band of aromatic protons and D_2O exchange and integration of the signals gave no definite proof of exchangeable protons, the N-H protons probably giving a band too wide to be easily recognisable; the u.v. spectrum proved to be totally different from that of either the thiohydrazide or what was expected for a hydrazono disulphide, having a strong band at λ 400mμ (ε =13,000). Analysis was also ambiguous, being correct for either an isomer or the actual disulphide structure. Active hydrogen determination showed presence of one atom of active hydrogen per molecule for a monomer (two for a dimer) a result in accordance with both structures.

The analogous products from N-phenyl-N'-α-napthothiohydrazide (XII), N-phenyl-N'-4-methoxybenzothiohydrazide (XIII) and N-4-chlorophenyl-N'-4-chlorobenzothiohydrazide (VIII) were also prepared and gave similarly ambiguous spectral and analytical data.



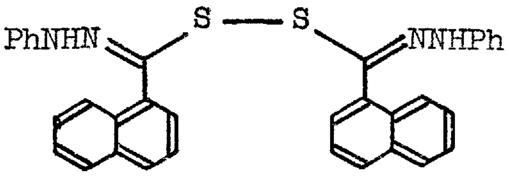
XII



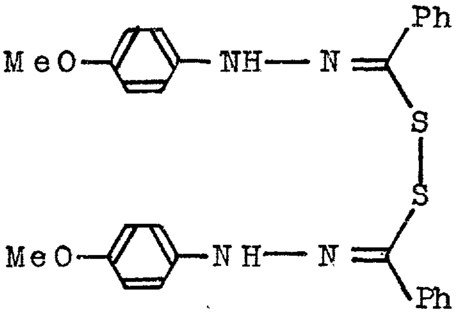
XIII

Thus, for some time bis-(α-phenylhydrazonobenzyl) disulphide (X) was held to be α-phenylazo benzyl mercaptan (XI) and reactions characteristic of this system were sought. However, a thorough literature search on reactions of thiohydrazides revealed the paper by Wuyts and Lacourt [13] in which iodine oxidation of N-phenyl-N'-benzothiohydrazide (IX) had given apparently the same compound. Repetition of this preparation and mixed melting point of the product with the supposed isomer gave no depression of melting point.

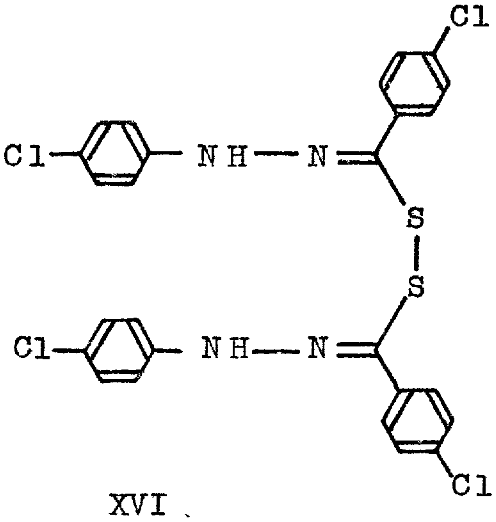
Care was taken to show that improved oxidation results with alumina and triethylamine were not merely due to an accidentally increased availability of air. A blank experiment without either triethylamine or alumina under a current of oxygen gave no apparent conversion to disulphide after four hours. Using a stream of oxygen, conversion to disulphide with alumina was complete after 1½ hours and with triethylamine after 4 hours. Furthermore, alumina catalysed oxidation was found to be strongly dependent on the grade of alumina used, grade V alumina giving excellent results whereas grade I alumina gave little conversion to disulphide. Molecular weight determinations on those products obtained from thiohydrazides by treatment with alumina showed that all were disulphides.



XIV



XV

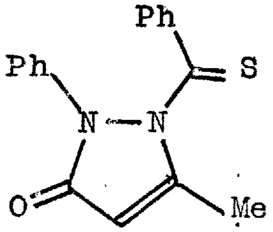


XVI

Before the structure of these compounds (X,XIV,XV,XVI) was certain, their formation was thought to be due to a base (triethylamine) or surface (alumina) catalysed isomerisation, the latter giving excellent yields. Those hydrogenations which gave back the thiohydrazide starting material were held to be reverse isomerisations which took place because of the greater stability of the polar hydrazide system in polar solvents (e.g. ethanol, tetrahydrofuran) and the less polar azothiol system in less polar solvents (e.g. petroleum ether, benzene).

Addition reactions with bis-(α-phenylhydrazonobenzyl)-disulphide (X) were attempted, those with diphenyl nitrone and diazomethane both giving mixtures of products, attempted isolation of which was unsuccessful, and that with tetraphenyl-cyclopentadienone giving no reaction.

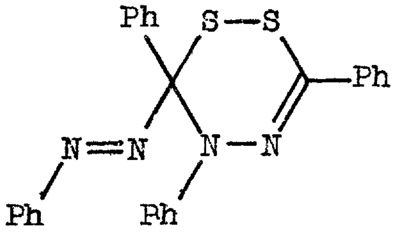
Several attempts were made to form thiol derivatives of the disulphide. Attempted acetylations and benzoylations by standard procedures failed to give clean reactions, and the only product isolated was a product of attempted acetylation, 1-phenyl-2-thiobenzoyl-3-methyl-5-pyrazolone (XVII) (18%).



XVII

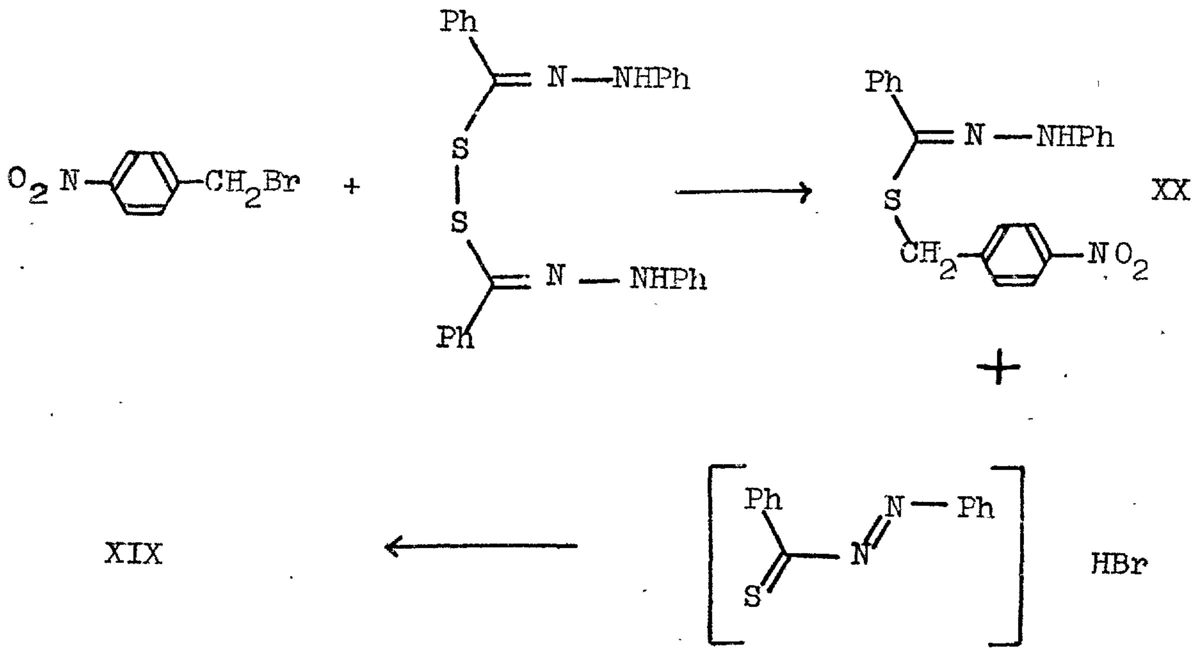
This was later synthesised in improved yield by acetylation of N-phenyl-N'-benzothiohydrazide (60%).

Reaction with triethyl oxonium fluoroborate in dry dichloromethane under reflux gave a red gum which mass spectroscopy showed to be a polymer with peaks at m/e 523 and above. Reactions with trityl chloride, benzyl bromide, tosyl chloride, p-nitrobenzyldiazonium fluoroborate and sulphenyl chloride all gave complex reactions, no products being isolated except in the case of the reaction with tosyl chloride from which a 25% yield of the oxidation product of the disulphide, 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine was obtained (XIX) 30% of the starting material being recovered. (This indicates that a disproportionation of the disulphide probably took place to give a tosylated thiol derivative and the oxidation product obtained.)



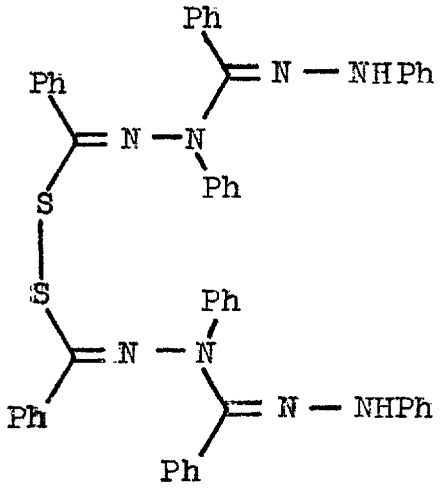
XIX

The disulphide was found to react with p-nitrobenzyl bromide to give p-nitrobenzyl-(α-phenylhydrazonobenzyl)-sulphide (XX) (64%) and 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (48%), another disproportionation to give thiol derivative and oxidation product.

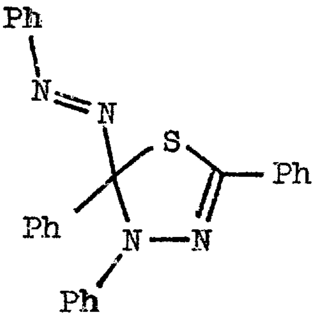


Attempted borohydride reduction of the sulphide product gave no reaction and synthesis of this product by reaction of p-nitrobenzyl bromide and N-phenyl-N'-benzothiohydrazide (IX) (60%) established that the structure was the hydrazono form and not the azo form, u.v., i.r. and n.m.r. spectroscopy once again not giving proof of structure.

Reaction of the disulphide with N-phenyl benzenecarbohydrazonoyl chloride gave bis(α-phenyl hydrazono (α-phenyl, benzyl-hydrazonobenzyl)) disulphide (XXI) (30%), the proposed structure of the product being confirmed by u.v. spectroscopy, λ_{max} 344 and 300mμ (ε= 80,000 and 40,000 respectively) . benzaldehyde phenylhydrazone, λ_{max} 355 and 303mμ, ε =20,000 and 10,000 respectively. A by-product of this reaction was another oxidation product of the disulphide, 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (30%).



XXI

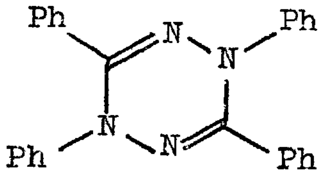


XXII

Reaction of the disulphide with sodium nitroprusside gave a positive thiol test and a purple complex was formed, which. although partial hydrolysis of cyanide groups had taken place, indicated on analysis an original composition of four nitroprusside complexes to one α-phenylhydrazonobenzyl sulphide moiety. The complex gave no n.m.r. spectrum indicating it to be a free radical. This reaction was repeated on a small sample of N-phenyl-N'-benzothiohydrazide at a later date and what appeared to be the same complex (T.L.C. on silica/methanol, same Rf, colour.) was obtained. although the formation of the complex had for some time given the impression that the disulphide was an azothiol.

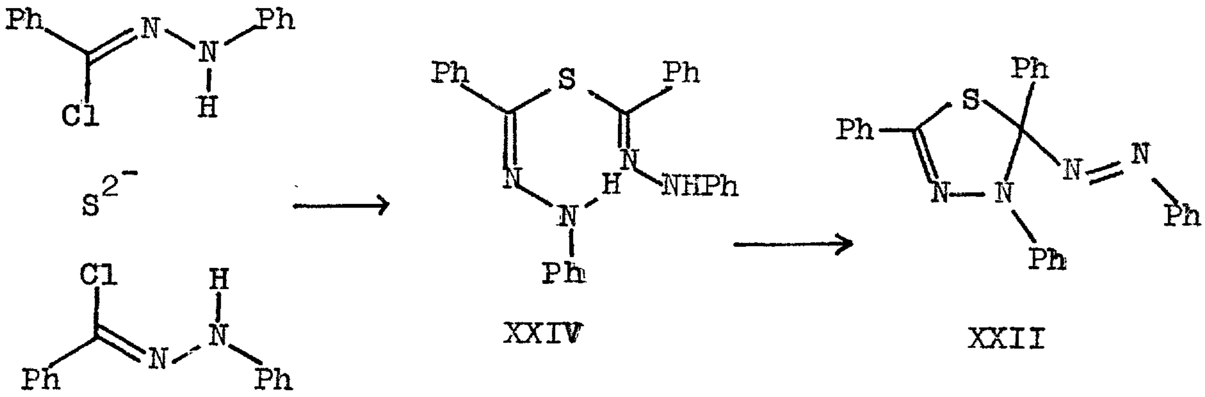
Many attempts were made to oxidise the disulphide in the hope that if it were an azothiol, a disulphide would be formed. Naturally, no such compound was formed, but the two oxidation products 4,5-dihydro-2,4,5-triphenyl-5 phenylazo-1,3,4-thiadiazole (XXII) and 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) were formed as products from several reactions.

Attempted silver oxide/methyl iodide methylation of the disulphide gave the dihydrothiadiazole (XXII) (26%) and 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5 tetrazine (XXIII) (19%).



XXIII

The dihydrothiadiazole (XXII) was synthesised by reaction of N-phenyl benzenecarbohydrazonoyl chloride with sodium sulphide to give bis-(α-phenylhydrazonobenzyl)-sulphide (XXIV), potassium ferricyanide oxidation of which gave the thiadiazole (XXII).



XXIV

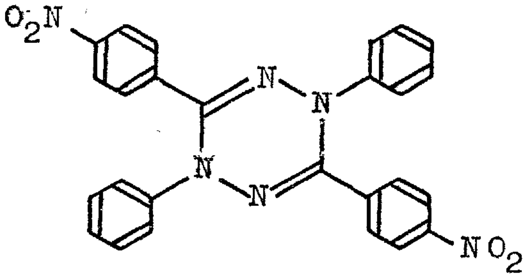
XXII

The dihydrotetrazine (XXIII) was synthesised by fusion of N-phenyl benzenecarbohydrazonoyl chloride at 190° for 30 minutes (25%). (It is interesting to note that Saxena et al.[14], to whom this method is due, quote their poorer yield of this product (10%) as proof of the minor role played by the zwitterion $Ph-\overset{-}{N}-\overset{+}{N}\equiv C-Ph \longleftrightarrow Ph-N=\overset{+}{N}=\overset{-}{C}-Ph$ in reactions of N-phenyl benzenecarbohydrazonoyl chloride

The yield obtained here perhaps indicates a larger participation of this zwitterion.)

Reaction of the disulphide with silver oxide alone gives little improvement in the yield of the thiadiazole (XXII) (33%) although this was the only product isolated. It is assumed that silver oxide adsorbed the remainder of the product, although continuous extraction with diethyl ether gave little improvement in yield.

Reaction of the disulphide with iodine gave a complex mixture of products, as did the reaction of the disulphide with tetranitromethane, although the latter gave 1,4-bis (4-nitrophenyl)-3,6-dihydro-1,2,4,5-tetrazine (XXV) (20%).



XXV

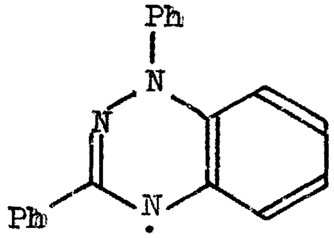
Reaction of the disulphide with hydrogen peroxide alone gave no reaction but in the presence of ferric chloride at 0° many products were formed, the major one of which, the dihydrotetrazine (XXIII) was the only one isolated.

Reaction of the disulphide with potassium ferricyanide was found to give good yields of the dihydrodithiadiazine (XIX) although on several occasions the dihydrothiadiazole (XXII) and sulphur were isolated in comparable yields. The reason for this elimination of sulphur is difficult to understand since the dithiadiazine (XIX) appears to be completely stable at the temperatures at which it was handled and in the presence of all solvents and reagents used. However, it was found that the dithiadiazine (XIX) gave reasonably good conversion to the thiadiazole(XXII) (70%) on refluxing for 2h. in analar acetone (the solvent used for recrystallisation of the dithiadiazine) although this time is obviously very much longer than that during which the dithiadiazine was exposed to acetone during recrystallisation.

The reaction of the disulphide with potassium ferricyanide was later used as a means of determining the stoichiometry of the oxidation, the dihydrodithiadiazine (XIX) being a known oxidation product of N-phenyl-N'-benzothiohydrazide[16] (IX) (although its structure had not been determined). Structure determination of the dihydrodithiadiazine (XIX) had proved less ambiguous than that of the disulphide (X) and addition of a known excessive amount of standard ferricyanide solution to a solution of the disulphide in benzene under nitrogen followed by addition of excess potassium iodide and back-titration with sodium thiosulphate gave yet another proof of the stoichiometry of this reaction and of the structure of the disulphide(X).

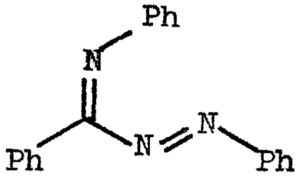
Reaction of dicyano-dichloro-benzoquinone (D.D.Q.) with the disulphide gave one product only, the dihydrodithiadiazine (XIX) (91%).

Attempted nitrosobenzene oxidation of the disulphide gave a surprising product, the 1,3-diphenyl-1,2,4-benzotriazinyl free radical (XXVI) (24%) [17,18]:-



XXVI

Identification of this product was found to be difficult and for some time it was thought to be either phenyl (phenylimino) (benzeneazo) methane (XXVII) or an isomer of it, e.g. an azo isomer.



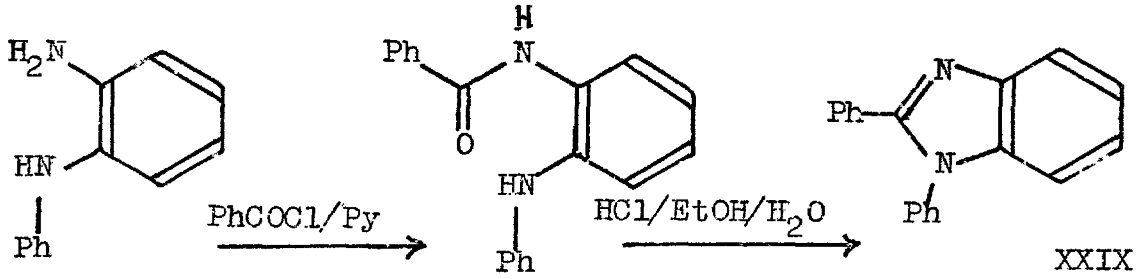
XXVII

No reference to the former was found in the literature for some time, there being no mention of it in Beilstein's Organische Chemie or the Chemical Abstracts formula indices. No n.m.r. of the free radical was taken because it was believed that only aromatic protons would show and no information would be gained.

Analysis and mass spectroscopy gave results in accordance with both the actual structure and the theory that the product might be an isomer of phenyl (phenylimino) (benzeneazo) methane (XXVII).

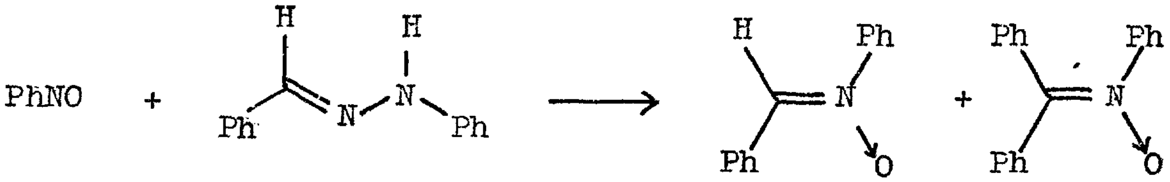
Reductive acetylation gave what appeared to be a remarkable result: the major product isolated was

1,2-diphenyl benzimidazole (XXIX) (39%). This was verified by preparation of an authentic sample by the method of Wolff [19] and mixed melting point:-



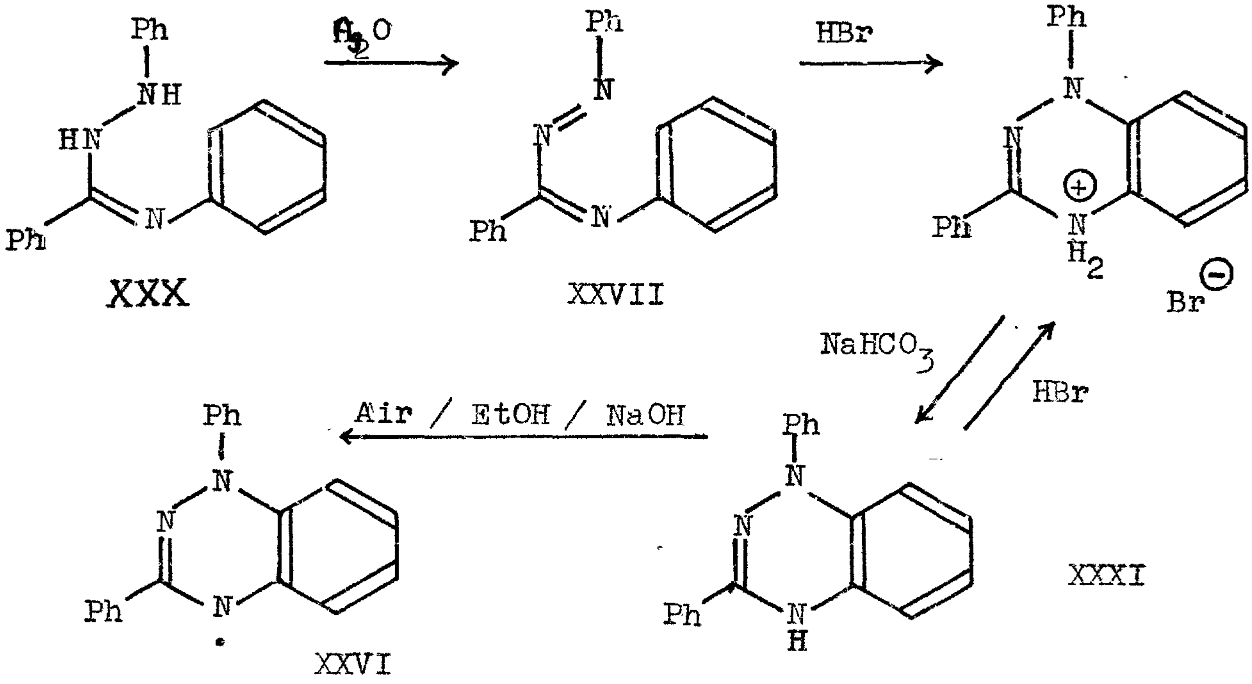
Reduction of the free radical (XXVI) with sodium dithionite gave a yellow air sensitive compound which it was not found possible to crystallise in the small quantities obtained.

Reaction of nitrosobenzene with N-phenyl-N'-benzothiohydrazide (IX) was attempted; T.L.C. indicated formation of a complex mixture of products including some benzotriazinyl free radical (XXVI) but this was not isolated. Reactions of nitrosobenzene with other compounds having the same carbon and nitrogen skeleton were also attempted in the hope that another synthesis of the free radical in better yield might be found: reaction with N-phenyl-N'-benzhydrazide did not proceed so readily as with the thiohydrazide (IX) or disulphide (X) and a complex mixture of products was obtained which did not appear to contain the benzotriazinyl free radical; reaction with benzaldehyde phenylhydrazone also failed to give any formation of the free radical but diphenyl nitrone was formed as the major product (50%) with triphenyl nitrone (5%) as the major by-product.



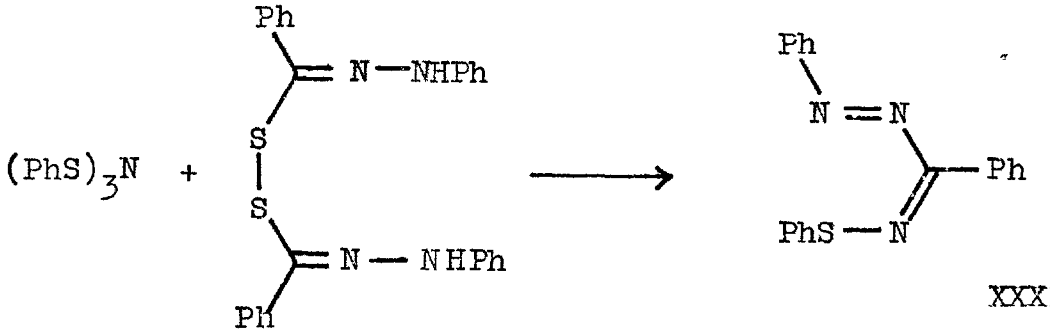
Benzanilide phenylhydrazone was prepared, by an adaptation of the literature method [20] using N-phenyl benzenecarbohydrazonoyl chloride and aniline, the chloride being fused with excess aniline at 130° for 30 minutes (81%). A literature reference [21] to preparation of phenyl (phenylimino) (benzeneazo) methane by reaction of benzanilide phenylhydrazone and mercuric oxide was found showing it to be different from the free radical. Phenyl (phenylimino) (benzeneazo) methane (XXVII) was synthesised by treatment of benzanilide phenylhydrazone (XXX) with excess silver oxide (91%) and solutions of this product were observed to become dark brown on standing, due to formation of the free radical by air oxidation, indicating the close connection between the two compounds.

At this point a literature search covering all isomers of phenyl (phenylimino) (benzeneazo) methane, including previously unexpected cyclic ones, was carried out and revealed the amine 1,3-diphenyl-1,4-dihydro-1,2,4-benzotriazine (XXXI) [17] a yellow compound identical with the dithionite reduction product and a precursor of the benzotriazinyl free radical (XXVI) which is formed by air oxidation of an alkaline alcoholic solution of this amine. The literature method for the preparation of the free radical was followed and mixed melting point with the nitrosobenzene product showed them to be identical.



A more direct synthesis of the free radical, and one giving a considerably better overall yield than the above literature procedure, was achieved by treatment of benzanilide phenylhydrazone (XXX) (which is tautomeric with its imine-hydrazine form) with N-bromo-succinimide. This method, analogous to that of Bock et al.[16] for preparation of azo compounds from hydrazides, gave the free radical in one step in 74% yield.

Reaction of the disulphide with tris (benzenesulphenyl) nitride[22] yielded α-phenylazobenzaldehyde phenylthioxime (XXXII) (42%) as the major product, this also being prepared from N-phenyl-N'-benzothiohydrazide and tris (benzenesulphenyl) nitride (40%).



XXXII

It was found possible to reduce the disulphide back to the thiohydrazide using sodium dithionite (83%), zinc dust/glacial acetic acid (60%), zinc/copper couple (67%) and sodium borohydride (67%).

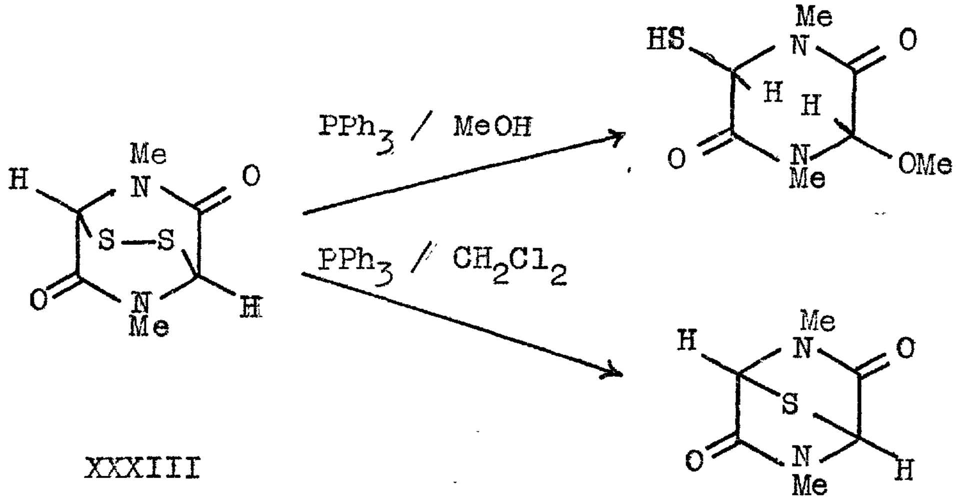
Reactions of the dihydrodithiadiazine (XIX) and the dihydrothiadiazole (XXII).

The structures of these two compounds and their close structural similarity were proved by a series of reductions and desulphurisations and by synthesis of the dihydrothiadiazole (XXII).

Zinc/ammonium chloride reduction gave the dihydrotetrazine (XXIII) as the major product from both compounds (40% in both cases).

Desulphurisation attempted with tri-ethyl phosphite gave complex mixtures of products in both cases, the dihydro tetrazine (XXIII) once again being formed as the major product (13% from the dihydrothiadiazole, 24% from the dihydrodithiadiazine).

Desulphurisation of the dihydrodithiazine with triphenyl phosphine under T.H.F. reflux was found to give a complex mixture of products. However, reaction of triphenyl phosphine with the dithiadiazine in methanol at room temperature gave a slow reaction which yielded the thiadiazole as the only isolated product (70%). (Machin [23] reports formation of a methoxy product (XXXIV) using this solvent, triphenyl phosphine in dichloromethane giving straightforward formation of a monosulphide (XXXV):-



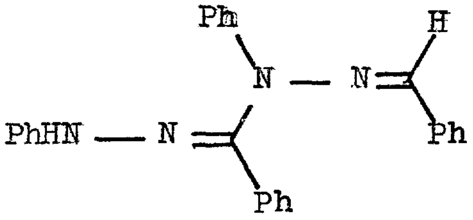
XXXIII

XXXIV

XXXV

Reduction of the dithiadiazine by sodium borohydride also gave the thiadiazole (63%).

Raney nickel desulphurisation of the thiadiazole was found to give the phenylhydrazone of benzaldehyde phenyl-benzoyl-hydrazone (XXXVI) (40%) as the only product isolated.



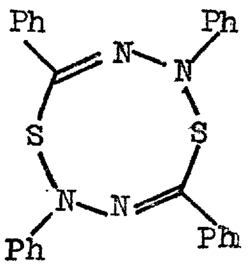
XXXVI

This product was also obtained by reaction of Raney nickel with the dihydrodithiadiazine (XIX) (12%), the poor yields probably being due to adsorption to the Raney nickel. Continuous ether extraction of the Raney nickel residues was found to give little improvement in yield.

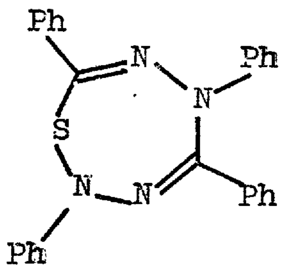
It was hoped that the structure of XXXVI could be proved by oxidative cyclisation to give the dihydrotetrazine (XXIII). Attempted cyclisation using lead dioxide gave a complex mixture of products. The reaction was not followed further.

(Benzaldehyde phenyl-benzoyl-hydrazone) phenylhydrazone (XXXVI) was synthesised by fusion of benzaldehyde phenylhydrazone and N-phenyl benzenecarbohydrazonoyl chloride at 130^{o} for 10 mins. to give the required product (40%).

The evidence so far assembled, coupled with i.r. and u.v. spectral data, is still not sufficient to determine whether the correct structures are those suggested or the two shown below, which would also fit all the experimental data so far described.



XXXVII



XXXVIII

However, the synthesis of the dihydrothiadiazole (XXII) by the reaction of N-phenyl benzenecarbohydrazonoyl chloride and excess sodium sulphide followed by oxidation by potassium ferricyanide proves the structure to be as suggested.

Attempted formation of the dihydrodithiadiazine by reaction of N-phenyl benzenecarbohydrazonoyl chloride and sodium disulphide (formed by solution of equimolar quantities of sodium sulphide and sulphur in a little hot water and crystallising out the product) gave bis-(α-phenylhydrazonobenzyl)-sulphide as the only product.

Formation of a tetrasulphide analogue of the dihydrodithiadiazine (XIX) was also attempted [24] by dissolving the dithiadiazine in pyridine and adding 2 mole equivalents of sulphur. After 24 hours at room temperature no tetrasulphide formation could be detected and the dihydrothiadiazole (XXII) was isolated (40%). (The formation of tetrasulphides reported in the literature [24] involves diketopiperazines with a disulphide bridge. This system, having a rigid molecular framework after pyridine cleavage of the S-S bond probably favours formation of a tetrasulphide more than the dithiadiazine system).

A synthesis of α-phenylazo-thiobenzaldehyde was attempted by reaction of phosphorus pentasulphide with α-phenylazo-benzaldehyde, prepared by the method of Bock et al. [16] (this method giving the dihydrodithiadiazine (XIX) when applied N-phenyl-N'-benzothiohydrazide). T.L.C. showed formation of a complex mixture of products. The reaction was not studied further. (It would appear that if α-phenylazo-thiobenzaldehyde does exist, it dimerises at a temperature below room temperature to give the dihydrodithiadiazine.)

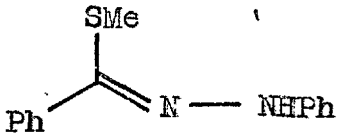
Thiohydrazides - their preparation and reactions.

Most thiohydrazides studied in this project were prepared from carboxymethyl dithioates, prepared from Grignard reagents, and hydrazines. However, one, N-4-chlorophenyl-N'-4-chlorobenzothiohydrazide was synthesised from a carboxymethyl dithioate prepared by the thiopiperidide route, this being found to give clean reactions and good yields.

Attempted preparation of N-phenyl-N'-benzothiohydrazide by passing hydrogen sulphide through a solution of N-phenyl benzenecarbohydrazonoyl chloride in pyridine failed to give appreciable product formation.

Oxidation of N-phenyl-N'-benzothiohydrazide with potassium ferricyanide proceeded considerably less readily than oxidation of the disulphide (X) with potassium ferricyanide; an incomplete reaction was found to take place giving a complex mixture of products from which benzaldehyde phenylhydrazone was the only product isolated (13%). The same thiohydrazide was found to react with hydrogen peroxide to give the disulphide (X) in high yield (95%). (This reaction was studied in the hope of forming an S-oxide, a known product from the oxidation of some thioamides [15].) D.D.Q. oxidation of N-phenyl-N'-benzothiohydrazide was found to give a mixture of two products, the dihydrodithiadiazine (XIX) and the dihydrothiadiazole (XXII). It was not found possible to separate these since both have identical Rf. values on T.L.C. in all solvent systems tested.

Methylation of N-phenyl-N'-benzothiohydrazide with excess diazomethane was found to give the S-methyl derivative, methyl-(α-phenylhydrazonobenzyl)-sulphide (XXXIX).

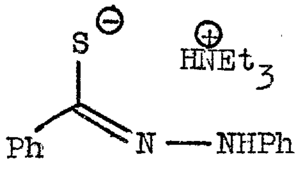


XXXIX

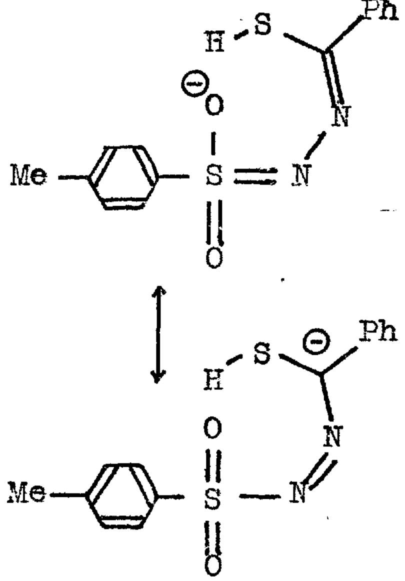
Treatment of the same thiohydrazide with acetic anhydride/pyridine gave formation of 1-phenyl-2-thiobenzyl-3-methyl-5-pyrazolone (XVII) (60%). (This compound was first isolated from an attempted acetylation of the corresponding disulphide in 18% yield.)

N-phenyl-N'-benzothiohydrazide (IX) and N-tosyl-N'-benzothiohydrazide were both found to form salts with triethylamine. On addition of large amounts of triethylamine to concentrated solutions of N-phenyl-N'-benzothiohydrazide in benzene, a pale yellow oil separated out which was found to crystallise below room temperature. Attempts to separate these crystals consistently met with failure, possibly due to the weak association of the triethylamine and the thiohydrazide and the ready dissociation of the salt in the absence of a large excess of triethylamine.

However, it was found possible to take a u.v. spectrum of a solution of this salt which proved it to be different from the thiohydrazide starting material and probably a thiol salt of the structure shown (XXXX). Spectroscopic evidence (e.g. the i.r. spectrum, which shows no N-H bands) indicates the triethylamine/N-tosyl-N'-benzothiohydrazide salt to be very different and probably the unusual resonance-stabilised form shown below (XXXXI) :-



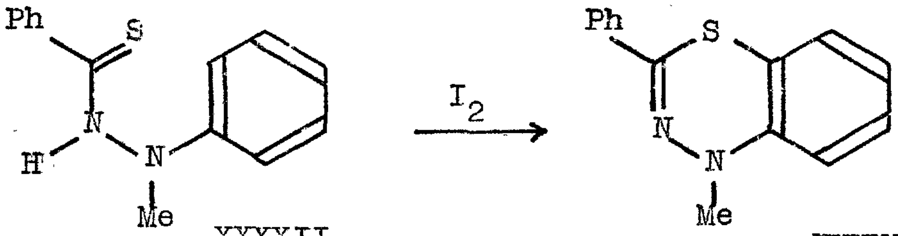
XXXX



XXXXI

Oxidation of several thiohydrazides was found to give the corresponding bis-hydrazono disulphides. (N-phenyl-N'-benzo-, N'-4-methoxybenzo- and N'-1-naphthothiohydrazides and N-4-chlorophenyl-N'-4-chlorobenzothiohydrazide were all found to give bis-hydrazono disulphides on air/alumina oxidation. (X, XV, XIV, XVI) Iodine oxidation of N-phenyl-N'-1-naphthothiohydrazide is also known to give the corresponding disulphide (XIV)[13] and T.L.C. scale tests for iodine oxidation of the other two thiohydrazides converted by air oxidation to disulphides also indicated clean formation of identical products. However, oxidation of thiohydrazides to disulphides does not appear to be a general reaction. Thiobenzhydrazide and N-tosyl-N'-benzothiohydrazide reacted with iodine to give complex mixtures of products and attempted alumina/air and triethylamine/air oxidations gave no formation of disulphides.

The reaction of N-methyl, phenyl-N'-benzothiohydrazide (XXXXII) with iodine was found to give 2-phenyl-4-methyl-1,3,4-benzothiadiazine (XXXXIII) in good yield (80%).



XXXXII XXXXIII

This unexpected cyclisation to give an interesting and hitherto little studied [25,26,27] heterocyclic system is all the more unsuspected since no cyclised products are observed on oxidation of any other N-phenyl-N'-thiohydrazides studied. It would appear that activation energies for both processes are similar but for the reactions studied give a significantly faster rate of disulphide formation in all cases except that of the N-methyl thiohydrazide (XXXXII).

(This reaction was studied in the hope of forming a disulphide having spectral properties similar to those of the disulphides already prepared, thus ruling out the possibility of the disulphide having an azo structure, a possibility later ruled out by ^{13}C n.m.r.) One point of interest in this reaction is the high yield. It is felt that the yield obtained (80%) could be bettered considerably by working on a larger scale and by using a more efficient solvent system for recrystallisation. (T.L.C. shows no trace of by-products or unreacted starting material.) (The yield obtained is considerably better than those quoted by Gibson et al. [25,26,27] for similar systems).

Assignment of structures from spectral data.

I. U.V. Spectroscopy.

As can be seen from the accompanying tables, for the disulphides, u.v. spectra show little similarity with compounds containing apparently similar chromophores. The bis-(α-phenylhydrazonobenzyl),-(α-phenylhydrazono-4-methoxybenzyl) and -(α-4-chlorophenylhydrazono-4-chlorobenzyl)- disulphides all give peaks at about 400mμ, a peak not observed in either benzaldehyde phenylhydrazone or phenyl-(α-hydrazonobenzyl)disulphide, although both these models, and all three of the aforementioned disulphides, have peaks at about 300mμ. It is not therefore possible to draw any conclusions about structure from u.v. spectra.

Comparison of u.v. spectra of compounds believed to contain the α-phenylhydrazonobenzyl moiety showed considerable similarities and can be regarded as good evidence for the structures proposed. It must be mentioned, however, that neither the dihydrothiadiazole(XXII) nor the dihydrodithiadiazine (XIX) shows any band corresponding to the phenylazo group. The two alternative structures (XXXVII) and (XXXVIII) may be ruled out on the evidence of synthesis of the dihydrothiadiazole (XXII).

2. I.R. Spectroscopy.

All i.r. spectra of disulphides show strong similarities with the spectra of the thiohydrazides from which they are formed. The most striking differences between spectra of thiohydrazides and those of their corresponding disulphides are:-

1). Virtual disappearance of amide bands at c. 3200 $cm.^{-1}$

2). In the cases of N-phenyl-N'-benzothiohydrazide and N-phenyl-N'-4-methoxybenzothiohydrazide, multiplet bands at 1230-1270 $cm.^{-1}$ in the thiohydrazides are replaced by single bands for the disulphide.

3). N-phenyl-N'-benzothiohydrazide, N-phenyl-N'-4-methoxy-benzothiohydrazide and N-4-chlorophenyl-N'-4-chlorobenzothiohydrazide all show bands at c. 960 cm. in their disulphide oxidation products.

4). Assignation of C=S bands at c. 1200 $cm.^{-1}$ is not possible several bands occurring in this region. However, N-phenyl-N'-benzothiohydrazide and N-phenyl-N'-1-naphthothiohydrazide show loss of bands at 1150 $cm.^{-1}$ and 1190 $cm.^{-1}$ respectively on oxidation.

I.r. spectroscopy is not therefore a great help in structure proof of the disulphides nor for structure proof of most other products in which all possible structures contain similar bonds.

3. N.M.R.

This too proves to be generally of limited usefulness since many of the compounds studied have only aromatic protons and many contain secondary amine protons giving broad peaks which are sometimes difficult to observe.

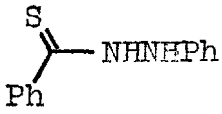
^{13}C n.m.r., used in the case of bis-(α-phenylhydrazonobenzyl) disulphide (X), gives another conclusive proof of structure. The proton spin-decoupled spectrum shows eight peaks corresponding to nine different carbon atom environments (two of which coincidentally overlap). Removal of the spin decoupling causes all but three of these peaks to be split into doublets, indicating that only three carbon atom environments exist in the molecule in which the carbon atom is not bonded to a proton.

Coupled with the evidence of molecular weight determination, this conclusively establishes the structure as being (X).

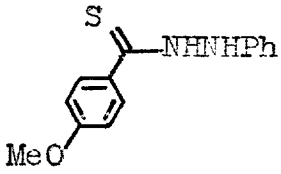
Table of λ_{max} and ε for thiohydrazides, disulphides and related compounds.

	λ [redacted] ([redacted]μ)	i	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	x	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	E	[redacted]
		[redacted]								[redacted]	[redacted]	
	[redacted]			[redacted]								
	[redacted]											[redacted]
	[redacted]											
	[redacted]		[redacted]								[redacted]	
	[redacted]									[redacted]		
[redacted]	[redacted]				[redacted]	[redacted]		[redacted]				
	[redacted]								[redacted]			
	[redacted]					[redacted]						
	[redacted]	14							[redacted]		[redacted]	
	[redacted]											
	[redacted]				[redacted]		[redacted]					
	[redacted]			[redacted]								
	[redacted]											
	[redacted]									[redacted]		
	[redacted]											
	[redacted]					[redacted]		[redacted]	[redacted]			[redacted]

Solvents, E = ethanol, C = chloroform.



i



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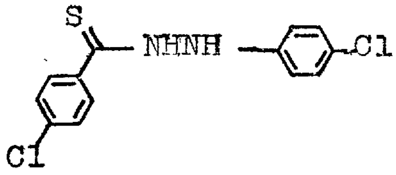

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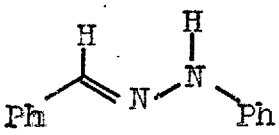

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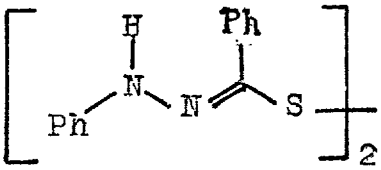

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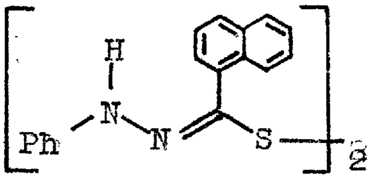

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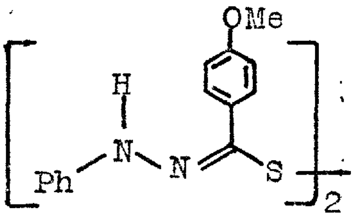

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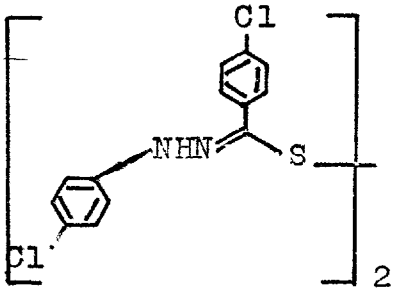

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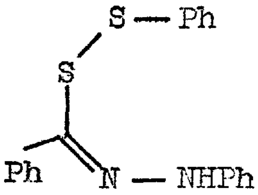

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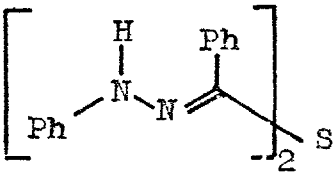


x

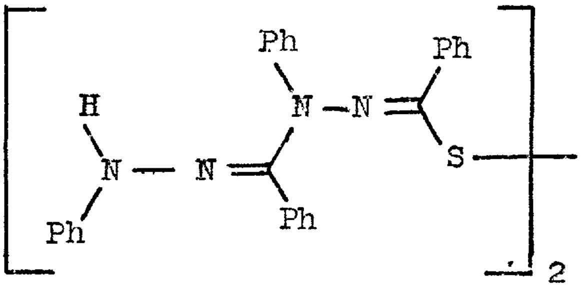
$Ph - N = N - Me$

xi

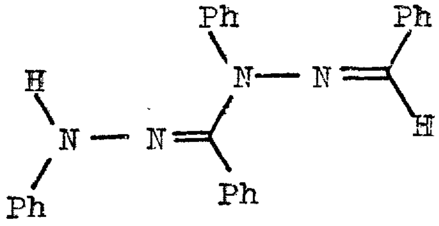
Table of λ_{max} and $\mathcal{E}$ for compounds containing the benzaldehyde phenylhydrazone moiety.

	[redacted]	[redacted]	X	V	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]i
[redacted]		[redacted]		[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		[redacted]T
	[redacted]										[redacted]	
	[redacted]		[redacted]0		[redacted]			[redacted]				
	[redacted]											
	[redacted]										2[redacted]	
	[redacted]											
[redacted]	[redacted]		[redacted]						[redacted]	[redacted]		
	[redacted]				[redacted]							
	[redacted]	[redacted]		[redacted]		[redacted]0	[redacted]	[redacted]3.				
	[redacted]										[redacted]	
	[redacted]	[redacted]		[redacted]								
	[redacted]	[redacted]										
	[redacted]		[redacted]			[redacted]	[redacted]			S		
	[redacted]							[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]										
	[redacted]											16
	[redacted]				[redacted]						[redacted]	
	[redacted]											
				[redacted]3								

Solvent D/T = 50% CH_2CL_2 / Et_3N. S = Shoulder.



xii



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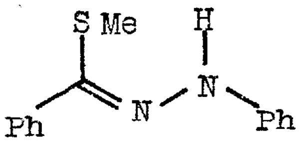

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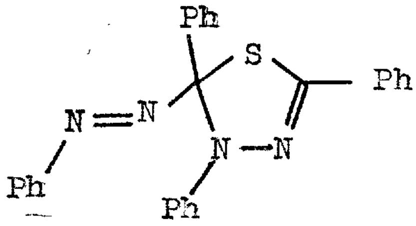

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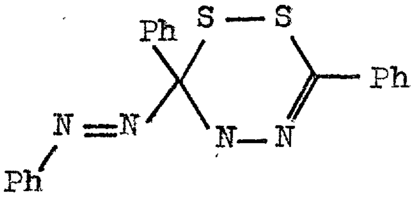
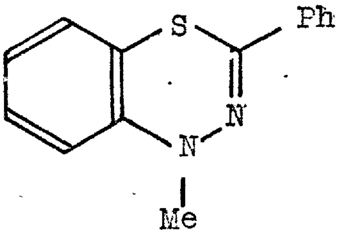
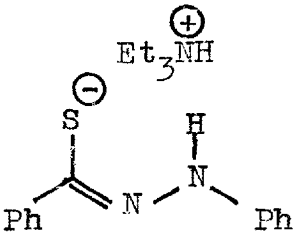


xvi



xvii



xviii

EXPERIMENTAL

Unless otherwise stated, the following data apply to experiments described in this section.

Melting points were measured on a Kofler block and are uncorrected.

Infra-red spectra were taken on Unicam SP 200 or Perkin-Elmer P.E.157 spectrometers as nujol mulls. N.m.r. spectra were recorded in deuterochloroform solution with Varian A-60 or T-60 spectrometers using **tetra**methyl silane as the internal standard. U.v. spectra were recorded using a Unicam SP 800 spectrometer.

Solvents were dried where necessary by standard techniques. Organic solutions from extractions were dried using anhydrous sodium sulphate.

The silica gel used for thin and preparative layer chromatography was Merck GF 254.

Bis-(α-phenylhydrazonobenzyl)-disulphide. (X)

N-phenyl-N'-benzothiohydrazide (1g) was dissolved in benzene and stirred for 12 h. with the following amounts of alumina and triethylamine. No precautions were taken to exclude air.

Volume of Benzene (ml.)	Weight of Et_3N (g.)	Alumina		Yield (%)
		Weight (g.)	Grade	
100	0	0		15
100	5	0		55
100	0	45	I	15
100	0	45	II	20
100	0	45	III	28
100	0	45	IV	51
100	0	45	V	64
200	0	45	V & 12% H_2O	77
100	0	15	V	55
200	0	30	V	91
200	0	60	V	74
200	5	30	V	86

Product-containing solutions were concentrated and filtered through alumina to remove starting material and polar by-products. (This was not found to be necessary in the case of the higher yield reactions.) Bis-(α-phenylhydrazonobenzyl) disulphide (X) was obtained by crystallisation from benzene/ethanol as orange-red needles (optimum yield 91%).

M.p. 140-142°

ν_{max}^{nujol}, 1602, 1518, 1262, 762, 745, 690cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 324, 304, and 400mμ (ε =21,800, 19,100 and 13,100 respectively).

τ 1·9-3·2 (m)

^{13}C n.m.r. (^{1}H spin decoupled) singlets at offset 3596·2, 3428·7, 3325·0, 3250·0, 3234·7, 3197·3, 3057·5 and 2864·8 Hz. All but first three peaks form doublets on removal of ^{1}H spin decoupling, indicating three carbon atoms not bonded to hydrogen.

Found: C, 68·30; H, 5·03; N, 12·24; S, 13·88%

$C_{26}H_{22}N_4S_2$ requires: C, 68·41; H, 5·30; N, 12·27; S, 14·02%.

Mass spectroscopy indicates M^{+} at m/e 228 and peaks at m/e 194 ($Ph_2CN_2^{+}$), 180 (Ph-C≡$\overset{+}{N}$-Ph), 121 (Ph-C≡$\overset{+}{S}$).103 (PhCN^{+}) and 91 (PhN^{+}).

Osmometric molecular weight determination gives M.W. = 436·0.

To check that this product was the same as that reported by Wuyts and Lacourt [13], their method of iodine oxidation of N-phenyl-N'-benzothiohydrazide was repeated to give a product identical with the thiohydrazide/alumina/benzene/air product. However, their melting point (149°) could not be repeated, m.p. 140-142° again being obtained. Mixed melting point gave no depression of melting point.

Formation of the disulphide (X) using optimum alumina/benzene/thiohydrazide conditions was attempted under nitrogen. No product had been formed after one day.

Alumina and triethylamine catalysed formations of the disulphide (X) were attempted under oxygen under the following conditions:-

1). N-Phenyl-N'-benzothiohydrazide (IX) (200 mg.) was dissolved in benzene (40 ml.) and the solution was stirred with alumina (6 g. grade V). Oxygen was passed into the mixture until T.L.C. showed complete reaction ($1\frac{1}{2}$ h.). The solution was filtered off, evaporated to dryness, and the product recrystallised from benzene /ethanol to give <u>bis-(α-phenylhydrazonobenzyl)-disulphide (X)</u> (180 mg., 90%).

2). As in (1), except triethylamine (1 g.) was used in place of alumina. T.L.C. showed disappearance of starting material after 4 h. Work-up as before yielded the disulphide (X) (140 mg., 70%).

3). As in (1) without any catalyst. T.L.C. showed negligible product formation after 4 h.

Estimation of Active Hydrogen in the Disulphide (X).

The number of active hydrogen atoms per molecule of disulphide was determined by the method of Elvidge and Sammes[26].

2·14 mg. X gave 0·210 mls. hydrogen at room temperature and pressure. (Equivalent to one active hydrogen atom to 228 atomic mass units).

2·835 mg. X gave 0·242 ml. hydrogen at room temperature and pressure. (Equivalent to one active hydrogen atom to 196 atomic mass units).

ADDITION REACTIONS OF THE DISULPHIDE (X).

Reaction with phenyl-N-phenyl nitrone.

Phenyl-N-phenyl nitrone (92 mg.) and the disulphide (106 mg.) were dissolved in dry dichloromethane (20 ml.) and the mixture left at room temperature in the dark for 6 hours. T.L.C. showed one major product and three minor products. Attempts to isolate products by T.L.C. and by direct crystallisation failed to yield pure or crystalline products. The products were not investigated further.

Reaction with diazomethane.

The disulphide (X) (120 mg.) was treated with an approximately tenfold excess of diazomethane solution in ether (30 ml.) and left for 15 mins. at room temperature. No effervescence was observed and the colour of the solution was discharged; T.L.C. showed three products, all more polar than starting material. Attempts to isolate these were unsuccessful and the reaction was not studied further.

Reaction with tetraphenyl cyclopentadienone.

Tetraphenyl cyclopentadienone (40 mg.) and the disulphide (X) (20 mg.) were dissolved in dichloromethane (15 ml.) and stood at room temperature for a day. No reaction was visible on T.L.C. after that time and the reaction was then refluxed for a day. The reaction still showed no change and was therefore repeated under benzene (15 ml.) reflux. After 3 hours T.L.C. showed a complex mixture of products. The reaction was not studied further.

ATTEMPTED FORMATION OF DERIVATIVES OF THE DISULPHIDE (X).

Attempted acetylation of the disulphide (X).

In collaboration with Dr. J. W. Ducker.

Acetylation of the disulphide was attempted under the following conditions:-

1). The disulphide (X) (100 mg.) and sodium acetate (300 mg.) were dissolved in acetic anhydride (5 ml.) and the solution was left at room temperature for 1 day. T.L.C. showed partial conversion to a complex mixture of products. The reaction was not studied further.

2). The disulphide (X) (50 mg.) was dissolved in a mixture of pyridine (1 ml.) and acetic anhydride (5 ml.) and the solution left at room temperature for 1 day. Once again, T.L.C. showed an incomplete, unclean reaction which was not studied further.

3). The disulphide (20 mg.) was dissolved in acetic anhydride (2 ml.) and pyridine (1 ml.) and the solution was heated at 100° for 2 hours. The mixture was poured into water and extracted into chloroform (3 x 10 ml.). T.L.C. of the chloroform solution indicated complete conversion to a mixture of products, the major one of which was isolated (T.L.C. on silica, chloroform eluant) to give 1-phenyl-2-thiobenzoyl-3-methyl-5-pyrazolone (XVII) (2 mg., 18%.)

M.p. 152-3°.

1-Phenyl-2-thiobenzoyl-3-methyl-5-pyrazolone (XVII).

A solution of N-phenyl-N'-benzothiohydrazide (400 mg.)

in acetic anhydride (10 ml.) and pyridine (10 ml.) was heated at 100° for 2 hours. The mixture was cooled, poured into water and the precipitate of white crystals filtered off and washed with water. Recrystallisation from ethanol gave <u>1-phenyl-2-thiobenzoyl-3-methyl-5-pyrazolone (XVII)</u> (300 mg., 60%).

M.p. 152-3°.

ν_{max}^{nujol}, 1590 cm.$^{-1}$ (C=O).

τ ($CDCl_3$) 7·82 (s,3H) 3·98 (s,1H).

λ_{max}^{EtOH}, 356 mμ (ε =17,600).

Mass spectroscopy gives peaks at m/e 294 (M^+), 251, 144, 121 ($Ph-C\equiv\overset{+}{S}$)

Found: C, 69·4; H, 5·1; N, 9·4; S, 11·2%

$C_{17}H_{14}N_2OS$ requires: C, 69·4; H, 4·8; N, 9·4; S, 10·9%.

Mixed melting point with the acetylation product of the disulphide (X) gave no depression of melting point.

<u>Attempted benzoylation of the disulphide (X).</u>

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (110 mg.) was dissolved in pyridine (5 ml.) and benzoyl chloride (100 mg.) was added dropwise. The mixture was left at room temperature for one day. after which a small sample was acidified (HCl) and a T.L.C. taken, which showed partial conversion to a mixture of products. The reaction was not followed further.

Reaction of the disulphide (X) with triethyl oxonium fluoroborate.

The disulphide (114 mg.) and triethyloxonium fluoroborate (100 mg.) were dissolved in dichloromethane (15 ml.) and the mixture allowed to stand at room temperature for 12 h. T.L.C. showed no reaction. The reaction was then refluxed for 3 hours to give a complex mixture of products, the major one of which was an orange-red compound shown by T.L.C. to be more polar than the disulphide. Isolation of this afforded a gum shown by mass spectroscopy to be a polymer (peaks at m/e 523 and above). This reaction was not studied further.

Reaction of the disulphide (X) and trityl chloride.

The disulphide (114 mg.), trityl chloride (140 mg.) and pyridine (0·5 ml.) were dissolved in dichloromethane and allowed to stand at room temperature for 2 days. T.L.C. still showed no reaction and the reaction was repeated under benzene reflux for 4 hours. A complex mixture was obtained and the reaction was studied no further.

Reaction of the disulphide (X) and p-nitrobenzyl bromide.

The disulphide (250 mg.) and p-nitrobenzylbromide (250 mg.), dissolved in acetone (10 ml.) were stirred with sodium bicarbonate (1 g.) for 2 days. The reaction was shown by T.L.C. to have given several products, two of which were major. Separation of these by preparative T.L.C. (carbon tetrachloride as eluant) gave p-nitrobenzyl-(α-phenylhydrazonobenzyl)-sulphide (XX) (125 mg., 64%) as the major product, obtained as yellow-brown prisms from benzene/60-80° petroleum ether.

M.p. 90-91°.

ν_{max}^{nujol}, 1602, 1520, 1345, 690 cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 348mμ (ε =19,400).

τ 6·1 (s,2H), 4·5-1·6 (m,15H).

Found: C, 66·37; H, 4·84; N, 11·53; S, 8·81%.

$C_{20}H_{17}N_3O_2S$ requires: C, 66·11; H, 4·72; N, 11·57; S, 8·81%

Mass spectroscopy gives M^+ at m/e 363 (as required for $C_{20}H_{17}N_3O_2S$).

A secondary product, 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (60 mg., 48%) was also obtained from this reaction as orange granular crystals.

M.p. 119-121° (from dichloromethane/acetone)

ν_{max}^{nujol}, 1495, 1300, 1230, 990, 790 and 710cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 286mμ (ε =20,000).

τ 2·0-3·1 (m,20H).

Found: C, 68·79; H, 4·55; N, 12·22; S, 13·89%.

$C_{26}H_{20}N_4S_2$ requires: C, 69·01; H, 4·46; N, 12·38; S, 14·14%.

Treatment of the major product of this reaction with a large excess of sodium borohydride in tetrahydrofuran at room temperature failed to give any reaction after 3 days.

4-Nitrobenzyl-(α-phenylhydrazonobenzyl)-sulphide (XX).

N-phenyl-N'-benzothiohydrazide (250 mg.) and 4-nitrobenzyl bromide (250 mg.) were dissolved in acetone (10 ml.) and the mixture stirred with sodium bicarbonate (500 mg.) for 2 days. The products were separated by preparative T.L.C. to give 4-nitrobenzyl-(α-phenylhydrazonobenzyl)-sulphide (XX) (240 mg., 60%).

M.p. 90-91°. (Recrystallised from benzene/80-100° petroleum ether).

Mixed melting point with a sample from the previous reaction gave no depression of melting point.

Reaction of the disulphide (X) with benzyl bromide.

The disulphide (250 mg.) and benzyl bromide (200 mg.) were dissolved in acetone (10 ml.) and the solution was stirred with sodium bicarbonate (1 g.) at room temperature for 3 days. T.L.C. showed a complex mixture of products from which no product could be isolated.

Reaction of the disulphide (X) with tosyl chloride.

The disulphide (250 mg.) and tosyl chloride (400 mg.) were dissolved in dry pyridine (7 ml.) and allowed to stand at room temperature for one week. Pyridine was removed by pouring the mixture into dilute hydrochloric acid and extracting the products into benzene (3 x 20 ml.). Separation of the products by preparative T.L.C. yielded 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dihydrodithiadiazine (XIX) (63 mg., 25%) and unreacted disulphide (75 mg., 30%), the remainder of the reaction products being a complex mixture.

Reaction of the disulphide (X) and 4-nitrobenzyl diazonium fluoroborate.

4-Nitrobenzyl diazonium fluoroborate (120 mg.) was dissolved in acetone (5 ml.) and the minimum volume of water and the disulphide (110 mg.) were added. A large number of coloured products was rapidly formed, none of which was deemed to be in sufficient quentity to be of interest.

Reaction of the disulphide (X) and sulphenyl chloride.

Sulphenyl chloride was prepared by passing chlorine into a solution of thiophenol (110 mg.) in dry dichloromethane (10 ml.) until no further darkening of the colour was observed. Nitrogen was passed through the solution until the issuing gas was shown to contain no chlorine (starch-iodide paper). To this solution was added a solution of the disulphide (228 mg.) in dry dichloromethane (10 ml.) and the mixture was allowed to stand at room temperature for 30 mins. T.L.C. after this time showed formation of a complex mixture of products. The reaction was not studied further.

Reaction of the disulphide (X) and N-phenyl benzenecarbohydrazonoyl chloride.

The disulphide (120 mg.) and N-phenyl benzenecarbohydrazonoyl chloride (120 mg.) were dissolved in dry dichloromethane (15 ml.), triethylamine (1 ml.) added and the mixture refluxed for 2 hours. The products were separated by T.L.C. and the major product recrystallised from ethanol to give pale yellow needles of bis-(α-phenylhydrazono-(α-phenylbenzyl hydrazonobenzyl)) disulphide (XXI) (67 mg., 30%).

M.p 175-7°

ν_{max}^{nujol}, 1580, 1515, 1490, 1250, 760, 750 and 690cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 344 and 300mμ (ϵ=80,000 and 40,000 respectively).

Mass spectroscopy shows peaks at m/e 470, 408, 315, 297, 287, 180 ($Ph-\overset{+}{N}\equiv C-Ph$), 121 ($Ph-C\equiv\overset{+}{S}$)

Found: C, 73·91; H, 5·25; N, 13·26; S, 7·57%.

$C_{52}H_{42}N_8S_2$ requires: C, 74·08; H, 5·03; N, 13·30; S, 7·59%.

A by-product of this reaction was a red gum later found to be 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (35 mg., 30%).

Reaction of the disulphide (X) and sodium nitroprusside.

The disulphide (X) (100 mg.) was dissolved in a 1:1 mixture of dilute aqueous ammonium hydroxide solution and tetrahydrofuran (20 ml.) To this mixture an excess of 5% sodium nitroprusside solution was added and the mixture heated under reflux until T.L.C. showed all the disulphide to have reacted. Organic by-products were removed by extraction into diethyl ether and the remaining purple aqueous solution was evaporated at room temperature overnight in a crystallising dish in a vacuum desiccator. The resulting solid was dissolved in methanol and the solution filtered to remove sodium salts. The methanol was removed under reduced pressure to give a purple black solid (210 mg., 30%).

ν_{max}^{nujol}, 2150, 1950, 1620, 1270cm.$^{-1}$.

The solid gave no n.m.r. spectrum showing it to be a free radical. The complex was found to be unstable and smelled of hydrogen cyanide. Analysis showed this to be a complex of probably four nitroprusside complexes to one α-phenylhydrazonobenzyl sulphide moiety and indicated partial hydrolysis of cyano groups by low carbon and nitrogen percentages.

Found: C, 25·93; H, 2·38; N, 23·82; S, 2·80%
341·8 μg. of sample gave 150·4 μg. residue.

$(Na_2Fe(CN)_5NO)_4\ C_{13}H_{12}N_2S$ requires: C, 30·84; H, 1·01;
N, 28·35; S, 2·49%.
139·0 μg. residue from 341·8 μg. of sample.

Treatment of N-phenyl-N'-benzothiohydrazide with sodium nitroprusside under the same conditions gave what appeared to be the same complex (T.L.C. on silica methanol eluant.)

OXIDATIONS OF BIS-(α-PHENYLHYDRAZONOBENZYL)-DISULPHIDE (X).

Attempted methylation of the disulphide (X).

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (240 mg.)

and methyl iodide (500 mg.) in benzene (10 ml.) were stirred with excess silver oxide (400 mg.) at room temperature for 3 days. T.L.C. showed formation of several products of which the major two, both oxidation products, were isolated. The major product was found to be the red 4,5-dihydro-2,4,5-triphenyl-5-phenylazo 1,3,4-thiadiazole (XXII) (58 mg., 26%) which was isolated as a gum which crystallised after standing for 3 months at 0° to give dark red, granular crystals. These were recrystallised from benzene/ethanol.

M.p. 106-8°.

ν_{max}^{nujol}, 1590, 1490, 1345, 1130, 980, 770, 750, 695cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 347mμ ($\mathcal{E}$ =15,700).

Mass spectroscopy gives peaks at m/e 392 (M^+-N_2), 388(M^+-S).

Found: C, 74·27; H, 4·79; N, 13·33; S, 7·61%.

$C_{26}H_{20}N_4S$ requires: C, 74·35; H, 4·70; N, 13·25;
S, 7·57%.

The secondary product also isolated was recrystallised from benzene/80-100° petroleum ether to give yellow crystals of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII) (44 mg., 19%).

M.p. 204-5° (Literature m.p.[14] 204-5°)

1,3,4,6-Tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII).

A satisfactory synthesis of the dihydrotetrazine was achieved by an adaptation of the method of Saxena et al.[14] N-phenyl benzenecarbohydrazonoyl chloride (115 mg.) was heated in an open tube in an oil bath at 190° for 30 mins. and the product separated by preparative T.L.C. The product was recrystallised from benzene/80-100° petroleum ether to give 1,3,4,6-tetraphenyl-1,4,-dihydro-1,2,4,5-tetrazine (XXIII) (24 mg., 25%).

M.p. 204-5°

Mixed melting point of this product with the secondary product of the disulphide/silver oxide reaction gave no depression of melting point.

Reaction of the disulphide (X) with silver oxide.

The disulphide (200 mg.) was dissolved in benzene (15 ml.) and stirred with excess silver oxide (1 g.) for 2 days. T.L.C. showed only one spot, the red dihydrothiadiazole (XXII) obtained as the major product in the presence of methyl iodide. Evaporation of solvent and crystallisation gave 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (56 mg., 33%). Continuous Soxhlet extraction of the silver residues with diethyl ether gave no significant increase in yields, nor did a reduction in the amount of silver oxide used.

Reaction of the disulphide (X) and iodine.

A solution of the disulphide (30 mg.) in chloroform (5 ml.) was shaken with iodine (18 mg.) and saturated sodium hydrogen carbonate solution (5 ml.) for 5 mins. T.L.C. showed a complex mixture of products. The reaction was not studied further.

Reaction of the disulphide (X) with tetranitromethane.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) was dissolved in dichloromethane (20 ml.) and tetranitromethane (600 mg.) was added. The solution darkened in colour and gas was evolved. After 1 h. the solution had lightened somewhat and reaction appeared to have stopped. T.L.C. showed the reaction to have given a complex mixture with one major product which was separated by preparative T.L.C. and recrystallised from dichloromethane/diethyl ether to give 44 mg. (20%) of dark red granular crystals of 1,4,-bis-(4-nitrophenyl)-3,6-dihydro-1,2,4,5-tetrazine (XXV).

M.p. 308-313° (with decomposition).
(Literature ^{27} m.p. 305°).

$\nu_{\max}^{\text{nujol}}$, 1590, 1500, 1308, 1110, 1000. 852, 700cm.$^{-1}$.

Mass spectroscopy gives M^+ at m/e 478 and peaks at m/e225 ($O_2N{\cdot}C_6H_4\overset{+}{N}{:}C{\cdot}Ph$), 179 (225-$NO_2$), 103 ($PhC\overset{+}{N}$).

Reaction of the disulphide (X) and hydrogen peroxide.

The disulphide (100 mg.) was dissolved in acetone (15 ml.) and hydrogen peroxide (1 ml. 30%) was added. The mixture was left for 1 day after which time T.L.C. showed no reaction had occurred. Ferric chloride (10 mg.) was added and the mixture left at 0° for 12 h. T.L.C. showed formation of many products the major one of which was recrystallised from benzene/80-100° petroleum ether to give 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII) (20 mg., 25%).

M.p. 204-5°.

Mixed melting point with an authentic sample gave no depression in melting point.

Reaction of the disulphide (X) with potassium ferricyanide.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (1 g.) was dissolved in benzene (40 ml.) and ethanol (40 ml.) was added. A solution of potassium ferricyanide (1·65 g.) and sodium hydroxide (400 mg.) in water (10 ml.) was prepared and the two solutions were shaken together. The colour of the disulphide solution changed from red to orange and the benzene layer was separated, washed with water (3 x 20 ml.), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The resulting gum was crystallised from dichloromethane/acetone to give orange granular crystals of 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-

dithiadiazine (XIX) (870 mg., 86%).

M.p. 119-121°.

On several occasions, this synthesis failed to give the above product, the product solution changing from orange to red on evaporation or recrystallisation. This red solution was found to contain sulphur and the red 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (600 mg., 71% from 1 g. of disulphide). 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) was heated in benzene solution and in acetone solution in the presence of each of the reagents used (separately) for 5 mins. No formation of thiadiazole was observed in any case. However, on refluxing the dihydrothiadiazine (100 mg.) in acetone (25 ml.) for 2 h., evaporating the resulting solution and recrystallising the product from ethanol, the dihydrothiadiazole (XXII) (60 mg., 70%) was obtained.

Determination of stoichiometry of the oxidation of the disulphide (X).

Nitrogen flushed alkaline 0·1N potassium ferricyanide solution (10 ml.) was pipetted into a stirred solution od bis-(α-phenylhydrazonobenzyl)-disulphide (X) (114 mg.) in benzene (10 ml.) and ethanol (10 ml.) under nitrogen. The mixture was stirred for 10 mins., the mixture neutralised with dilute hydrochloric acid and excess potassium iodide solution added. Starch solution (5 drops) was added and the mixture titrated with 0·1N sodium thiosulphate. The titration was repeated twice.

Volumes of O 0·01N thiosulphate used = 48·6, 48·9, 50.1 ml.

Average volume of 0·01N thiosulphate used = 49·2 ml.

∴ Excess of 0·1N ferricyanide solution = 4·92 ml.

Volume 0·1N ferricyanide used = 5·08 ml.

Equivalent weight of disulphide $= \frac{114 \times 10}{5\cdot 08} = 222\cdot 4$

This value is in reasonable agreement with the theoretical equivalent weight (227) for the proposed structure of the disulphide (X).

Reaction of the disulphide (X) and dicyano-dichlorobenzoquinone (D.D.Q).

The disulphide (114 mg.) was dissolved in benzene (10 ml.) and D.D.Q. (103 mg.) was added. T.L.C. showed only one product spot. The solution was filtered through alumina to remove D.D.Q. residues, evaporated to dryness and the resulting gum crystallised from dichloromethane/acetone to give the dihydrodithiadiazine (XIX) (103 mg., 91 %).

M.p. 119-121°.

Reaction of the disulphide (X) with nitrosobenzene.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (120 mg.) was dissolved in dichloromethane (25 ml.) and the solution cooled to 0°. Nitrosobenzene (500 mg.) was added and the mixture allowed to stand at 0° for 2 days. The products were separated by T.L.C. to give a complex mixture from which only one product was isolated. This was recrystallised from benzene/ethanol to give 1,3-diphenyl-1,2,4-benzotriazinyl radical (XXVI)(37 mg., 24%).

M.p. 109-11° (Literature melting point[17] 113-115°).

Mixed melting point with a sample prepared by the method of Blatter and Lukaszewski [17] (m.p. 110-111°) gave m.p. 109-111°.

Reaction of nitrosobenzene and N-phenyl-N'-benzothiohydrazide (IX).

The thichydrazide (IX) (120 mg.) was dissolved in ether (25 ml.) and the solution cooled to 0°. Nitrosobenzene (500 mg.) was added and the mixture allowed to stand at 0° for 4 h. T.L.C. showed formation of a complex mixture of products one of which had the same Rf. and colour as the benzotriazinyl free radical (XXVI). No products were isolated.

Reaction of nitrosobenzene with N-phenyl-N'-benzhydrazide.

The hydrazide (105 mg.) was dissolved in ether (25 ml.) and nitrosobenzene (500 mg.) was added. The mixture was allowed to stand at room temperature for 2 days. T.L.C. showed little reaction. The reaction mixture was refluxed for 1 day. T.L.C. showed partial conversion to a complex mixture of products, none of which corresponded to the benzotriazinyl free radical (XXVI).

Reaction of nitrosobenzene with benzaldehyde phenylhydrazone.

The hydrazone (200 mg.) was dissolved in ether (25 ml.) and nitrosobenzene (100 mg.) was added. The mixture was allowed to stand at room temperature for 5 h. Separation of the two main products by preparative T.L.C. and recrystallisation from benzene/80-100° petroleum ether yielded phenyl-N-phenyl nitrone (100 mg., 50%) m.p. 115-6° as the major product. Mixed melting point with an authentic sample of phenyl-N-phenyl nitrone (m.p. 116°) gave no depression of melting point. Triphenyl nitrone (14 mg., 5%) was also obtained.

M.p. 216-8° (Literature [28] m.p. 218-20°).

Reaction of the 1,3-diphenyl-1,2,4-benzotriazinyl radical (XXVI) and sodium dithionite.

1,3-diphenyl-1,2,4-benzotriazinyl radical (100 mg.)

and finely powdered sodium dithionite (200 mg.) were added to ethanol (5 ml.) and stirred together for 6 h. at room temperature. The colour of the solution changed from brown to yellow. The solution was filtered off and evaporated to give a yellow gum which resisted all attempts at crystallisation. This yellow product (later found to be 1,3-diphenyl-1,2,4-benzotriazine (XXXI) was found to undergo air oxidation to give back the free radical XXVI. This reaction was not studied further.

Reductive acetylation of the 1,3-diphenyl-1,2,4-benzotriazinyl free radical (XXVI).

1,3-diphenyl-1,2,4-benzotriazinyl radical (100 mg.) was dissolved in acetic anhydride (5 ml.) and glacial acetic acid (5 drops) and zinc dust (200 mg.) were added. The mixture was stirred at room temperature for 8 h. The solution was filtered and the solvent removed under reduced pressure. The products were separated by preparative T.L.C. to give 1,2-diphenyl-benzimidazole (XXIX) (36 mg., 39%).

M.p. 110-111°.

An authentic sample of this was prepared by the method of Wolff [19] (m.p. 112-113°). Mixed melting point gave m.p. 110-111°.

Benzanilide phenylhydrazone (XXX).

N-phenyl benzenecarbohydrazonoyl chloride (500 mg.) and aniline (1 g.) were heated together in an open tube in an oil bath at 130° for 30 minutes. The hot melt was poured into benzene (40 ml.) and filtered to remove precipitated aniline hydrochloride. The resulting solution was concentrated to 5 ml., ethanol (10 ml.) was added and the solution allowed to stand at 0° for 12 h. Cream coloured needles of benzanilide phenylhydrazone (XXX) (500 mg., 81%) were obtained.

M.p. 173-5° (Literature [20] m.p. 175-6°).

Phenyl (phenylimino) (benzeneazo) methane (XXVII).

Benzanilide phenylhydrazone (XXX) (200 mg.) was dissolved in benzene (5 ml.) and stirred with silver oxide (500 mg.) for 2 h. The resulting red solution was filtered off, the benzene evaporated and the product recrystallised from benzene/ethanol to give phenyl (phenylimino) (benzeneazo) methane (XXX) (180 mg.,91%).

M.p. 101-2° (Literature [21] m.p. 101-2°)

1,3-diphenyl-1,2,4-benzotriazinyl radical (XXVI).

Benzanilide phenylhydrazone (XXX) (287 mg.) was dissolved in methylene chloride (30 ml.) and pyridine

(3 ml.) added. The solution was stirred and N-bromosuccinimide (2 38 g.) was added over 10 minutes. The solution turned red and then became very dark brown as the free radical was formed. After 30 min. the solution was washed with dilute aqueous sodium thiosulphate solution (3 x 20 ml.) water (3 x 20 ml.) dilute hydrochloric acid (3 x 20 ml.), saturated sodium bicarbonate solution (3 x 20 ml.) and water (3 x 20 ml.) and dried over anhydrous sodium sulphate. The solution was evaporated down and the product recrystallised from benzene/ethanol to give 1,3-diphenyl-1,2,4-benzotriazinyl radical (XXVI) (210 mg., 74%).

M.p. 110-111°.

OTHER REACTIONS OF BIS-(α-PHENYLHYDRAZONOBENZYL) DISULPHIDE (X).

Reaction of the disulphide (X) with tris (benzenesulphenyl) nitride.

In collaboration with Dr. R. K. Norris.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (114 mg.) and the nitride (340 mg.) were dissolved in dichloroethane (20 ml.) (dried over anhydrous potassium carbonate) and the solution was refluxed for 2 h. Evaporation of the solvent followed by separation of the product by preparative T.L.C. gave dark brown crystals of α-phenylazobenzaldehyde phenylthiooxime (XXXII) (67 mg., 42%).

M.p. 119-120° (from 40-60° petroleum ether).

ν_{max}^{nujol}, 1580, 1260, 770, 745, 700cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 292mμ (ε=22,000), 453mμ (ε=10,600).

Mass spectroscopy gives peaks at m/e 317 (M^{+}), 212 (M^{+} - PhN_2), 109 (PhS^{+}), 105 (PhN_2^{+}), 104, 103 ($PhCN^{+}$) and 77 (Ph^{+}).

Found: C, 71·8; H, 5·0; N, 13·25; S, 10·0%.

$C_{19}H_{15}N_3S$ requires: C, 71·9; H, 4·8; N, 13·25; S, 10·1%.

The reaction was repeated with N-phenyl-N'-benzothiohydrazide (IX) (57 mg.) to give the same product (30 mg., 40%).

Reduction of the disulphide (X) with sodium dithionite.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (120 mg.) and sodium dithionite (300 mg.) were stirred together in ethanol (5 ml.) for 6 hours. The colour of the solution changed from orange-red to yellow. The solution was filtered off, evaporated and the product recrystallised from benzene/80-100° petroleum ether to give N-phenyl-N'-benzothiohydrazide (IX) (100 mg., 83%).

M.p. 89-90°.

Reduction of the disulphide (X) with zinc/acetic acid.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (25) mg.) and zinc dust (600 mg.) were stirred together in glacial acetic acid (15 ml.) until the orange-red colour of the disulphide had changed to yellow. The solution was filtered off and the acetic acid distilled off under reduced pressure. T.L.C. separation of the products showed an unclean reaction from which N-phenyl-N'-benzothiohydrazide (IX) (150 mg., 60%) was the only product isolated.

M.p. 89-90°.

Reduction of the disulphide (X) with zinc/copper couple.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (240 mg.) and zinc/copper couple[29] (1 g.) were stirred together in methanol (25 ml.) at room temperature for 10 h. T.L.C. separation of the products again showed an unclean reaction from which N-phenyl-N'-benzothiohydrazide (IX) (160 mg., 67%) was obtained.

M.p. 89-90°

Reduction of the disulphide (X) with sodium borohydride.

Bis-(α-phenylhydrazonobenzyl)-disulphide (X) (200 mg.) was dissolved in dry tetrahydrofuran (10 ml.) and sodium hydroxide (70 mg.) added. After 10 min. the orange-red colour of the solution had been discharged and T.L.C. showed formation of a single product. Water (10 ml.) was added to the solution and the product was extracted into benzene (3 x 10 ml.). The benzene extract was washed with water (2 x 10 ml.), dried (anhydrous sodium sulphate) and evaporated and the product crystallised from benzene/80-100° petroleum ether to give N-phenyl-N'-benzothiohydrazide (IX) (165 mg., 82%).

M.p. 89-90°.

REACTIONS OF 5,6-DIHYDRO-3,5,6-TRIPHENYL-6-PHENYLAZO-1,2,4,5-DITHIADIAZINE (XIX) AND 4,5-DIHYDRO-2,4,5-TRIPHENYL-5-PHENYLAZO-1,3,4-THIADIAZOLE (XXII).

Zinc/ammonium chloride reduction of the dihydrothiadiazole (XXII).

4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (84 mg.), zinc dust (100 mg.) and ammonium chloride (100 mg.) were stirred in ethanol (10 ml.) for 6 hours. T.L.C. separation of the products gave, from a complex mixture of products, 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII) as the major product (26·5 mg., 40%).

M.p. 204-5°.

Mixed melting point with an authentic sample gave no depression of melting point. Starting material (12 mg., 15%) was also recovered.

Zinc/ammonium chloride reduction of the dihydrodithiadiazine (XIX).

5,6-Dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (25 mg.), zinc dust (30 mg.) and ammonium chloride (30 mg.) were stirred together in ethanol for 10 hours to give a complex mixture of products from which 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII) (7 mg., 40%), 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (2 mg., 10%) and starting material (4 mg., 16%) were recovered. Mixed melting points with authentic samples gave no depression of melting point for any product.

Reaction of the dihydrothiadiazole (XXII) with triethyl phosphite.

Triethyl phosphite (300 mg.) and 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (100 mg.) were refluxed in benzene (15 ml.) for 2 hours. At the end of 2 h. the red colour of the dihydrothiadiazole had disappeared and T.L.C. showed formation of many products, only one of which, 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII) was isolated (T.L.C.) (12 mg., 13%).

Reaction of the dihydrodithiadiazine (XIX) with triethyl phosphite.

Triethyl phosphite (400 mg.) and the 5,6-dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (120 mg. were refluxed in benzene (15 ml.) until the orange colour of the starting material had disappeared (4 h.) Only one of the many products formed was separated (T.L.C.), 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (XXIII) (24 mg., 24%). Mixed melting point with an authentic sample gave no reduction of melting point.

Reaction of the dihydrothiadiazine (XIX) with triphenyl phosphine.

5 ,6-Dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (120 mg.) and triphenyl phosphine (200 mg.) were refluxed in dry tetrahydrofuran for 1 h. during which time the colour of the solution changed from orange to red. Attempts to isolate the products by T.L.C. gave a complex mixture of products and the experiment was not studied further.

Reaction of the dihydrodithiadiazine (XIX) with triphenyl phosphine in methanol.

5,6-Dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (120 mg.) and triphenyl phosphine

(200 mg.) were added to methanol and left at room temperature for 2 days, after which time dark red crystals of 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (75 mg., 70%) had separated.

M.p. 115-117° with decomposition.

Raney nickel desulphurisation of the dihydrothiadiazole (XXII).

4,5-Dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (120 mg.) and Raney nickel (1 g.) were stirred together in a mixture of benzene (5 ml.) and ethanol (5 ml.) at room temperature until the solution became colourless (3 hours). The solution was filtered off, evaporated to dryness and the major product separated by T.L.C. Recrystallisation from benzene/ethanol gave (benzaldehyde phenyl benzoyl hydrazone) phenylhydrazone (XXXVI) (45 mg., 40%).

M.p. 207-9° with decomposition.

ν_{max}^{nujol}, 1600, 1485, 1450, 1380, 1250, 1130, 755cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 336, 300mμ (ε =42,000 and 15,000 respectively).

Found: C, 80·18; H, 5·45; N, 14·38%.

$C_{26}H_{22}N_4$ requires: C, 79·97; H, 5·68; N, 14·38%.

Mass spectroscopy gives peaks at m/e 390 (M^+), 313 (M^+-Ph), 298 (M^+-PhNH), 286 (M^+-PhCHN) and 195 ($PhNH\overset{+}{N}{\equiv}CPh$).

Raney nickel desulphurisation of the dihydrodithiadiazine (XIX).

5,6-Dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (120 mg.) and Raney nickel (1 g.) were stirred together in a mixture of benzene (5 ml.) and ethanol (5 ml.) until the solution had become colourless (3 hours). Isolation of the product by T.L.C. and recrystallisation from benzene/ethanol gave (benzaldehyde phenyl benzoyl hydrazone) phenylhydrazone (XXXVI), (13 mg., 12%). (Weighing of the crude sample before chromatography showed the loss of product to have taken place before chromatography, but continuous diethyl ether extraction of the Raney nickel residues failed to give any improvement in yield.)

(Benzaldehyde phenyl benzoyl hydrazone) phenylhydrazone (XXXVI).

N-phenyl benzenecarbohydrazonoyl chloride (200 mg.) and benzaldehyde phenylhydrazone (1 g.) were ground together in a mortar and then heated in an open tube in an oil bath at 130° for 10 minutes. The resulting melt was cooled, dissolved in acetone and the product, the least polar major compound, was separated by preparative scale T.L.C. Recrystallisation from benzene/ethanol gave (benzaldehyde phenyl benzoyl hydrazone) phenylhydrazone (XXXVI) (135 mg., 40%).

M.p. 207-9° .

A mixed melting point of this product with the Raney nickel desulphurisation products gave no depression of melting point.

Attempted cyclisation of (benzaldehyde phenyl benzoyl hydrazone) phenylhydrazone (XXXVI).

(Benzaldehyde phenyl benzoyl hydrazone) phenylhydrazone (XXXVI) (15 mg.) was stirred with lead dioxide (20 mg.) in benzene (2 ml.) at room temperature for 48 h. T.L.C. showed formation of many products including a yellow product having the same Rf as the dihydrotetrazine (XXIII). The experiment was not studied further.

Attempted reaction of the dihydrodithiadiazine (XIX) with sulphur to give a tetrasulphide.

5,6-Dihydro-3,5,6-triphenyl-6-phenylazo-1,2,4,5-dithiadiazine (XIX) (120 mg.) was dissolved in pyridine (5 ml.) and sulphur (50 mg.) added. The mixture was left at room temperature for 24 hours after which T.L.C. of the crude reaction mixture showed formation of a complex mixture of products from which the major product, 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) was isolated (T.L.C. (40 mg., 40%) as dark red crystals.

M.p. 106-108°.

4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII).

a). Bis-(α-phenylhydrazonobenzyl) sulphide.

N-phenyl-benzenecarbohydrazonoyl chloride (60 mg.) was dissolved in acetone (5 ml.) and the solution stirred with powdered sodium sulphide nonohydride (10 mg.) for 3 h. The resulting yellow solution was filtered off, evaporated down and the product separated by T.L.C. Recrystallisation from benzene/ 80-100° petroleum ether gave yellow granular crystals of bis-(α-phenylhydrazonobenzyl)-sulphide (45 mg., 81%).

M.p. 151-2°.

ν_{max}^{nujol}, 1580, 1480, 1440, 1330, 1250, 760, 600cm.$^{-1}$.

λ_{max}^{EtOH}, 242, 284 and 335mμ (ε=30,000, 17,600 and 15,200 respectively).

Mass spectroscopy shows M$^+$ at m/e 422

Found: C, 74·30; H, 5·35; N, 13·82; S, 7·72%.

$C_{26}H_{22}N_4S$ requires: C, 73·91; H, 5·25; N, 13·26; S, 7·57%.

b). Oxidation of bis-(α-phenylhydrazonobenzyl) sulphide.

A solution of the sulphide in acetone was prepared as above using N-phenyl benzenecarbohydrazonoyl chloride

(1 g.), sodium sulphide nonohydrate (1·5 g.) and acetone (25 ml.). The solution was extracted using benzene/water (50 ml. of each). The benzene layer was washed with water (3 x 50 ml.) and ethanol (50 ml.) and excess alkaline aqueous potassium ferricyanide solution were added. The mixture was shaken vigorously and the colour of the benzene layer changed from yellow to red. The benzene layer was separated, washed with water (3 x 50 ml.), dried over anhydrous sodium sulphate, condensed to 5 ml. and ethanol (10 ml.) added. Red crystals of 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) separated (0·64 g., 70%).

M.p. 106-8° (with decomposition).

Three further recrystallisations (benzene/ethanol) improved the melting point to 114-116° with decomposition. Mixed melting points with samples from other oxidations (bis-(α-phenylhydrazonobenzyl)-disulphide (X) and silver oxide, disulphide (X) and potassium ferricyanide) gave no depression of melting point.

Attempted formation of the dihydrodithiadiazine (XIX).

N-phenyl benzenecarbohydrazonoyl chloride (120 mg.) was dissolved in acetone (10 ml.) and powdered sodium disulphide hydrate (200 mg.) was added. (This was prepared by solution of equimolar amounts of sulphur and sodium sulphide nonohydrate in a little hot water and crystallisation of the product). The mixture was stirred for 3 hours and the resulting solution treated as in the previous reaction with alkaline potassium ferricyanide solution. Work-up of the product as before gave 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII) (80 mg., 75%).

M.p. 106-8°.

Attempted formation of α-phenylazo-thiobenzaldehyde.

α-phenylazobenzaldehyde (1·05 g.) (prepared by the method of Bock et al.[16]) was dissolved in benzene (25 ml.) and phosphorus pentasulphide (300 mg.) was added. The mixture was left at room temperature for 24 hours. T.L.C. showed formation of a complex mixture of products and the reaction was not studied further.

SYNTHESIS AND REACTIONS OF THIOHYDRAZIDES.

Attempted synthesis of N-phenyl-N'-benzothiohydrazide.

N-phenyl benzenecarbohydrazonoyl chloride (240 mg.) was dissolved in pyridine (5 ml.) and hydrogen sulphide was passed through the solution for 24 h. T.L.C. showed slight formation of a yellow product having the same Rf as bis-(α-phenylhydrazonobenzyl) sulphide and polar by-products. The reaction was not studied further.

Reaction of N-phenyl-N'-benzothiohydrazide (IX) with potassium ferricyanide.

N-Phenyl-N'-benzothiohydrazide (IX) (100 mg.) was dissolved in benzene (10 ml.) and ethanol (10 ml.) was added. To this mixture was added a solution of potassium ferricyanide (170 mg.) and sodium hydroxide (50 mg.) in water (10 ml.). The mixture was stirred vigorously for 36 hours. T.L.C. showed incomplete reaction to give a complex mixture of products, the major one, isolated by T.L.C. and recrystallised from ethanol, being benzaldehyde phenylhydrazone (15 mg., 13%).

M.p. 158-9° (Literature [30] m.p. 157-8°), mixed melting point with an authentic sample 158-9°.

Reaction of N-phenyl-N'-benzothiohydrazide (IX) with hydrogen peroxide.

N-Phenyl-N'-benzothiohydrazide (IX) (200 mg.) was dissolved in tetrahydrofuran (5 ml.) and a large excess of hydrogen peroxide (3 ml., 30%) was added. The mixture was left for 30 min., separated by addition of water (30 ml.) and extraction into benzene (3 x 30 ml.), the benzene solution dried (anhydrous sodium sulphate) and evaporated under reduced pressure to a small volume (c. 3 ml.). Ethanol (10 ml.) was added and the resulting orange crystals filtered and dried to give bis-(α-phenylhydrazonobenzyl)-

disulphide (X) (190 mg., 95%).

M.p. 140-142°. Mixed melting point with an authentic sample gave no depression of melting point.

Reaction of N-phenyl-N'-benzothiohydrazide (IX) and dicyano-dichloro-benzoquinone (D.D.Q.).

N-Phenyl-N'-benzothiohydrazide (IX) (112 mg.) was dissolved in benzene (10 ml.) and D.D.Q. (103 mg.) was added. T.L.C. showed complete disappearance of the thiohydrazide and fromation of two overlapping product spots at Rf corresponding to the dithiadiazine (XIX) and 4,5-dihydro-2,4,5-triphenyl-5-phenylazo-1,3,4-thiadiazole (XXII). It was not found possible to isolate these by T.L.C. and the experiment was abandoned.

Methyl-(α-phenylhydrazonobenzyl) sulphide (XXXIX).

N-Phenyl-N'-benzothiohydrazide (IX) (100 mg.) was dissolved in benzene (10 ml.) and a large excess of diazomethane solution in diethyl ether was added. The colour of the solution changed from bright yellow to pale yellow and nitrogen was evolved. T.L.C. separation of the products gave only one major product, methyl-(α-phenylhydrazonobenzyl) sulphide (XXXIX), a pale yellow gum which resisted all attempts at crystallisation (90 mg., 85%).

ν_{max}^{film}, 1595, 1505, 1445, 1255, 1145, 1070, 955, 795, 755cm.$^{-1}$.

λ_{max}^{EtOH}, 238, 301 and 346mμ (ε =15,000, 7,300 and 17,000).

τ 7·9 (s, 3H), 2·0–3·3 (m, 13H, 1H D_2O exchangeable).

Found: C, 69·57; H, 5·86; N, 11·40; S, 13·14%.

$C_{14}H_{14}N_2S$ requires: C, 69·40; H, 5·83; N, 11·56; S, 13·21%.

Phenyl-(α-phenylhydrazonobenzyl)-disulphide.

A solution of sulphenyl chloride was prepared by passing chlorine through a solution of diphenyl disulphide (109 mg.) in dry dichloromethane (10 ml.) until no further colour change occurred. Excess chlorine was removed by flushing with nitrogen until no chlorine was shown to be in the issuing gases (starch-iodine paper). To the sulphenyl chloride solution was added a solution of N-phenyl-N'-benzothiohydrazide (IX) (228 mg.) in dry dichloromethane (5 ml.). The resulting orange-yellow solution was evaporated down at room temperature and the products separated by preparative T.L.C. on silica with 40-60° petroleum ether as eluant to remove bis-(α-phenylhydrazonobenzyl)-disulphide (X). Recrystallisation from dichloromethane/40-60° petroleum ether gave fine yellow crystals of phenyl-(α-phenylhydrazonobenzyl)-disulphide (300 mg., 90%).

M.p. 88-89°.

ν_{max}^{nujol}, 1600, 1500, 1440, 1260, 1165, 755, 695cm.$^{-1}$.

λ_{max}^{EtOH}, 243, 294 and 380mμ (ϵ =15,800, 8,200 and 7,730 respectively).

Attempted preparation of analytical samples gave some disproportionation of the disulphide and separation of crystals of the less soluble bis-(α-phenylhydrazono-benzyl)-disulphide.

Reaction of N-phenyl-N'-benzothiohydrazide (IX) and triethylamine.

N-Phenyl-N'-benzothiohydrazide (IX) (200 mg.) was dissolved in benzene (10 ml.) and triethylamine (15 ml.) added. The solution went cloudy and a pale yellow oil separated which crystallised on cooling to 0°. T.L.C. of the oil showed one spot corresponding to N-phenyl-N'-benzothiohydrazide. All attempts to separate the crystals gave immediate conversion to the oil and dissociation of the salt to triethylamine and the deeper yellow thiohydrazide. It appears that this is the salt of the tautomeric thiol form and that it is only stable in the presence of excess triethylamine. Treatment of the oil with acids gave an immediate return of the yellow thiohydrazide colouration. A u.v. spectrum of the salt taken in 50% triethylamine/dichloromethane gave:

λ_{max}, 371mμ ($\mathcal{E}$=15,000) (cf. the thiohydrazide λ_{max}, 242 and 334mμ ($\mathcal{E}$=34,000 and 14,000 respectively))

I.R. of the oil gave:

ν_{max}^{film}, 2,950, 2,600, 1,470, 1,350, 1,170, 1,035cm.$^{-1}$. (cf. the thiohydrazide ν_{max}^{nujol}, 3,200, 1,590, 1,255, 970cm.$^{-1}$.)

N-Phenyl-N'-1-naphthothiohydrazide (XII).

1-Thionaphthoyl thioglycollic acid (1 g.) was dissolved in 1N sodium hydroxide solution (4 ml.) and phenyl hydrazine (0.5 g.) was added. The mixture was warmed on a steam bath until the colour of the acid had been discharged and an oil had separated. Water (20 ml.) was added, the oil extracted into benzene (3 x 20 ml.), the benzene extract washed with water (2 x 50 ml.), dried (anhydrous sodium sulphate) and the solution evaporated to dryness. The product was recrystallised from benzene/ 80-100° petroleum ether to give fine pale yellow needles of N-phenyl-N'-1-naphthothiohydrazide (XII) (0.79 g., 74%).

M.p. 168-70° (Literature [13] m.p. 164°)

Bis-(α-phenylhydrazono-1-naphthyl)-disulphide (XIV).

N-Phenyl-N'-1-naphthothiohydrazide (350 mg.) was dissolved in benzene (60 ml.) and alumina (15 g., grade V) added. The mixture was stirred at room temperature for 12 hours, no precautions being taken to exclude air. Bis-(α-phenylhydrazono-1-naphthyl)-disulphide (XIV) was isolated by preparative T.L.C. followed by recrystallisation from benzene/ethanol as fine orange-yellow needles (0·20 g., 57%).

M.p. 165-166° (Literature [12] m.p. 165°).

N-Phenyl-N'-4-methoxybenzothiohydrazide (XIII).

4-Methoxythiobenzoylthioglycollic acid (1 g.) was dissolved in 1N sodium hydroxide solution (4 ml.) and phenyl hydrazine (0·5 g.) was added. The mixture was warmed on a steam bath until disappearance of the red colour of the acid indicated completion of the reaction and a yellow oil had separated. Water (20 ml.) was added and the oil extracted into benzene (3 x 20 ml.). The benzene extract was washed with water (2 x 50 ml.), dried (anhydrous sodium sulphate) and the solution evaporated to dryness. The product was recrystallised from benzene/80-100° petroleum ether to give yellow granular crystals of N-phenyl-N'-4-methoxybenzothiohydrazide (XIII) (0·84 g., 80%).

M.p. 95·5-96·5°.

ν_{max}^{nujol}, 3,200, 1605, 1500, 1267, 1190, 960, 835cm.$^{-1}$.

λ_{max}^{EtOH}, 282mμ (ε =12,000).

Mass spectroscopy gives peaks at m/e 258 (M^+),
224 (M^+- MeOH or S), 151 ($p\text{-MeO}\cdot C_6H_4\cdot C\!:\!S^+$ and
$Ph\cdot NH\cdot NH\cdot C\!:\!S^+$)

Found: C, 65·08; H, 5·44; N, 10·90: S, 12·66%

$C_{14}H_{14}N_2OS$ requires: C, 65·10; H, 5·46; N, 10·85:
S, 12·60%.

Bis-(α-phenylhydrazono-4-methoxybenzyl)-disulphide (XV).

N-Phenyl-N'-4-methoxybenzothiohydrazide (1 g.) was dissolved in benzene (200 ml.) and alumina (45 g. grade V) added. The mixture was stirred at room temperature for 16 h., the product solution filtered off, evaporated to dryness and the product recrystallised from benzene/ethanol to give dark red granular crystals of bis-(α-phenylhydrazono-4-methoxybenzyl)-disulphide (XV) (0·56 g., 57%).

M.p. 114-116°

ν_{max}^{nujol}, 1605, 1505, 1250, 1175, 1030 and 685cm.$^{-1}$.

λ_{max}^{EtOH}, 302 and 407mμ (ε =30,400 and 15,200 respectively)

Mass spectroscopy gives peaks at m/e 258
($MeOC_6H_4CSNHNHPh^+$), 224 (258-H_2S), 151 ($MeOC_6H_4C{\equiv}S^+$,
$PhNHNHC{\equiv}S^+$) and 133.

Osmometric molecular weight determination gives:

M.W. = 522·4

$C_{28}H_{26}N_4O_2S_2$ requires M.W. = 514

Found: C, 65·41; H, 5·17; N, 10·78; S, 12·60%.

$C_{28}H_{26}N_4O_2S_2$ requires: C, 65.34; H, 5.10; N, 10.89; S, 12·44%.

N-4-Chlorophenyl-N'-4-chlorobenzhydrazide (VIII).

4-Chlorobenzoyl chloride (525 mg.) (prepared by refluxing 4-chlorobenzoic acid (470 mg.) with excess thionyl chloride and distilling off unreacted thionyl chloride under reduced pressure) was dissolved in dry ether (25 ml.) and 4-chlorophenylhydrazine (430 mg.) and pyridine (250 mg.) were added. A vigorous reaction followed and pyridinium chloride and the comparatively insoluble product were precipitated out. The product was taken up in a large excess of ether, the ether evaporated off and the product recrystallised from benzene/ 80-100° petroleum ether to give N-4-chlorophenyl-N'-4-chlorobenzhydrazide (590 mg., 70%).

M.p. 184-5°

ν_{max}^{nujol}, 3,200 (N-H), 1645 (C=O), 1100, 905, 855, 820.

λ_{max}^{EtOH}, 246mμ (ε =22,500).

Found: C, 55·47; H, 3·56; N, 9·94; Cl, 25·39%.

$C_{13}H_{16}N_2OCl_2$ requires: C, 55·43; H, 3·58; N, 9·97; Cl, 25·22%.

Reaction of phosphorus pentasulphide and N-4-chlorophenyl-N'-4-chlorobenzhydrazide.

N-4-Chlorophenyl-N'-4-chlorobenzhydrazide (100 mg.) was treated with excess phosphorus pentasulphide (200 mg.) under the following conditions:

1). In acetonitrile at room temperature, sodium bicarbonate as a base.

2). In benzene at room temperature.

3). In pyridine at room temperature.

4). In pyridine under reflux.

None of these gave product formation and synthesis by this method was abandoned in favour of the following route.

N-4-Chlorophenyl-N'-4-chlorobenzothiohydrazide (VIII).

4-Chlorothiobenzoylthioglycollic acid (1 g.) (prepared by the method of Jensen and Pedersen [1]) was dissolved in 1N sodium hydroxide solution (4 ml.) and 4-chlorophenylhydrazine (0·57 g.) added. The mixture was warmed on a steam bath until disappearance of the red colour of the acid indicated completion of reaction. Water (20 ml.) was added and the semi-solid product extracted into benzene (3 x 20 ml.). The benzene extract was washed with water (2 x 50 ml.), dried (anhydrous sodium sulphate) and the solution evaporated to dryness. The product was recrystallised from benzene/ 80-100° petroleum ether to give yellow granular crystals of <u>N-4-chlorophenyl-N'-4-chlorobenzothiohydrazide (VIII)</u> (0·95 g., 80%).

M.p. 132-3°.

ν_{max}^{nujol}, 3280 (N-H), 1595, 1490, 1250, 1095, 820cm.$^{-1}$.

λ_{max}^{EtOH}, 248 and 362mμ (ε =34,000 and 20,000 respectively)

Mass spectroscopy gives peaks at m/e 296 (M^+) 262, 238 192, 155 ($Cl \cdot C_6H_4 \cdot C{\equiv}\overset{+}{S}$), 142, 127.

Found: C, 52·46; H, 3·60; N, 9·37; S, 10·65%.

$C_{13}H_{10}N_2Cl_2S$ requires: C, 52·54; H, 3·29; N, 9·43; S, 10·79%.

<u>Bis-(α-(4-chlorophenylhydrazono)4-chlorobenzyl)-disulphide (XVI)</u>.

N-4-Chlorophenyl-N'-4-chlorobenzothiohydrazide (250 mg.) was dissolved in benzene (40 ml.) and alumina (6 g. grade V) added. The mixture was stirred for 14 hours and the product solution filtered off and evaporation to dryness. recrystallisation from benzene/ethanol (four times) gave orange-red needles of <u>bis-(α-(4-chlorophenylhydrazono)-4-chlorobenzyl)-disulphide (XVI)</u> (125 mg., 50%).

M.p. 146-147°.

ν_{max}^{nujol}, 1590, 1255, 1150, 1090 and 825cm.$^{-1}$.

$\lambda_{max}^{CHCl_3}$, 332, 313 and 406mμ (ε =42,000, 40,000 and 29,000 respectively).

Mass spectroscopy shows peaks at m/e 296 ($ClC_6H_4CSNHNHC_6H_4Cl^+$), 262, 248, 192.

Osmometric molecular weight determination gives:

M.W. = 579 ($C_{26}H_{18}N_4Cl_4S_2$ requires 594)

Found: C, 52·38; H, 3·20; N, 9·32; S, 10·56%.

$C_{26}H_{18}N_4Cl_4S_2$ requires: C, 52·71; H, 3·06; N, 9·46: S, 10·82%.

Treatment of N-phenyl-N'-benzhydrazide with alumina.

N-Phenyl-N'-benzhydrazide (100 mg.) was dissolved in benzene (20 ml.), alumina (3 g., grade V) added and the mixture stirred for 2 days. No precautions were taken to exclude air. T.L.C. showed partial decomposition to polar by-products and a small amount of non-polar product. The reaction was not studied further.

Reaction of N-phenyl-N'-benzhydrazide in the presence of triethylamine.

N-Phenyl-N'-benzhydrazide (100 mg.) was dissolved in benzene (20 ml.) and triethylamine (500 mg.) was added. The mixture was left at room temperature for 2 days. No precautions were taken to exclude air. T.L.C. showed no reaction to have taken place.

Reaction of N-tosyl-N'-benzhydrazide in the presence of alumina.

N-Tosyl-N'-benzhydrazide (100 mg.) was dissolved in benzene (20 ml.) and alumina (3 g., grade V) was added. The mixture was stirred for 2 days, no precautions being taken to exclude air. T.L.C. showed no reaction to have taken place.

Reaction of N-tosyl-N'-benzhydrazide in the presence of triethylamine.

N-Tosyl-N'-benzhydrazide (100 mg.) was dissolved in benzene (20 ml.) and triethylamine (500 mg.) added. The mixture was left for 2 days, no precautions being taken to exclude air. T.L.C. showed some formation of polar by-products, the bulk of the starting material remaining unchanged. The reaction was not studied further.

N-Tosyl-N'-benzothiohydrazide.

Thiobenzoyl thioglycollic acid (2 g.) was dissolved in 1N sodium hydroxide solution (8 ml.) and a solution of tosyl hydrazide (2 g.) in tetrahydrofuran (10 ml.) was added. The tetrahydrofuran was boiled off on a steam bath and heating continued until disappearance of the red colour indicated completion of the reaction. Water (20 ml.) was added and the product extracted into benzene (3 x 20 ml.) The benzene extract was washed with water (2 x 50 ml.), dried (anhydrous sodium sulphate), the solvent evaporated off and the product carefully recrystallised from benzene/80-100° petroleum ether. (Rapid recrystallisation caused precipitation of unchanged tosyl hydrazide along with the product). The product was obtained as yellow granular crystals (1·0 g., 33%).

M.p. 130-131°.

ν_{max}^{nujol}, 3300(N-H), 1600, 1350, 1175, 1095, 1035, 920, 815, 780 and 715cm.$^{-1}$.

λ_{max}^{EtOH}, 262mμ (ε=12,200).

Found: C, 54·70; H, 4·47; N, 9·15; S, 20·63%.

$C_{14}H_{14}N_2O_2S_2$ requires: C, 54·90; H, 4·61; N, 9·15; S, 20·90%.

<u>Attempted formation of N-tosyl-N'-benzothiohydrazide from N-tosyl-N'-benzhydrazide</u>.

N-Tosyl-N'-benzhydrazide (100 mg.) was treated with phosphorus pentasulphide (200 mg.) under the following conditions:-

1). Benzene (20 ml.), room temperature, 2 days.

2). Benzene (20 ml.), reflux, 1 day.

3). Toluene (20 ml.), reflux, 1 day.

4). Pyridine (15 ml.), reflux, 14 h.

T.L.C. showed negligible product formation from any of these reactions, although reactions (3) and (4) showed some formation of polar by-products. The reaction was not studied further.

Reaction of N-tosyl-N'-benzothiohydrazide and triethylamine.

N-Tosyl-N'-benzothiohydrazide (200 mg.) was dissolved in benzene (10 ml.) and triethylamine was added dropwise until the yellow colour of the hydrazide solution had been discharged and no further precipitation of product occurred. Pale yellow crystals of the triethyl ammonium salt of the N-anionic thiol imine form of the hydrazide was obtained (quantitative yield).

M.p. 101-105° (with decomposition).

ν_{max}^{nujol}, 2650, 1170, 1045, 745cm.$^{-1}$.

λ_{max}^{EtOH}, 221 and 292mμ (ϵ =21,000 and 8,000).

Found: C, 59·04; H, 7·03; N, 10·34; S, 15·39%.

$C_{20}H_{29}N_3O_2S_2$ requires: C, 58 95; H, 7 17; N, 10 31;
S, 15 71%.

Mass spectroscopy shows peaks as for N-tosyl-N'-benzothiohydrazide, also peaks due to triethylamine (M^+ at m/e 101).

Reaction of dithizone with alumina.

Dithizone (100 mg.) was dissolved in benzene (20 ml.) and alumina (3 g., grade V) was added to the solution. The mixture was stirred for 2 days, no precautions being taken to exclude air. T.L.C. showed no reaction to have taken place.

Reaction of dithizone with triethylamine.

Dithizone (100 mg.) was dissolved in benzene (20 ml.) and triethylamine (500 mg.) was added. The mixture was left for 2 days, no precautions being taken to exclude air. T.L.C. showed no reaction.

Reaction of dithizone with silica.

Dithizone (30 mg.) was applied to silica T.L.C. plates (8 x (20cm. x 20cm.)) and the plates were continuously eluted for 14 hours (5% ethyl acetate/40-60° petroleum ether). An intensely red product was formed which on removal from the plates and crystallisation (chloroform/60-80° petroleum ether) gave black granular crystals with

with a gold sheen.

M.p. 244-5°. (with decomposition).

ν_{max}^{nujol}, 1525, 1345, 1315, 1280, broad band 1170 - 1020cm^{-1}

$\lambda_{max}^{CHCl_3}$ 276, 357 and 528mμ (ε = 50,000, 20,000 and 160,000)

Found: C, 53·98; H, 3·90; N, 19·11; S, 10·72,
residue 12·29%.

Mass spectroscopy shows peaks at m/e 574, 377, 245, 169 and 150, also minor peaks up to m/e 894. The complex is therefore probably one of three molecules of dithizone and a residue of approximately 126 atomic mass units;

this requires: C, 52·34; H, 4·03; N, 18·79; S, 10·74;
residue 14·10%.

Presence of a carbon atom in the non-dithizone moiety of the complex, perhaps as a carbonate of a metal, would explain the high percentage of carbon found. Iron is a relatively abundant impurity in the silica used.

Iodine Oxidation of Benzothiohydrazide.

Benzothiohydrazide (150 mg.) was dissolved in benzene (10 ml.) and a solution of iodine (130 mg.) in benzene (10 ml.) was added. The solution was shaken with saturated sodium bicarbonate solution until the brown colouration of the iodine had disappeared. The benzene layer was separated, dried over anhydrous sodium sulphate, evaporated under reduced pressure and the products separated by preparative T.L.C. A complex mixture of products was formed from which 2,5-diphenyl-1,3,4-thiadiazole (40 mg., 33%) was the only product isolated.

M.p. 139-140° (Literature [31] m.p. 141-2°)

Iodine Oxidation of N-tosyl-N'-benzothiohydrazide.

The oxidation was carried out as for benzothiohydrazide using 150 mg. of thiohydrazide and 70 mg. of iodine. A complex mixture of products was obtained. The reaction was not studied further.

Iodine Oxidation of N-methyl, phenyl-N'-benzothiohydrazide.

N-Methyl, phenyl-N'-benzothiohydrazide (XXXXII) (116 mg.) prepared in the usual way from N-methyl, phenyl-hydrazine and thiobenzoylthioglycollic acid was dissolved in benzene (10 ml.) was added. The resulting benzene solution was shaken with saturated sodium becarbonate solution until the brown colouration of the iodine had disappeared, separated, dried over anhydrous sodium sulphate, evaporated and the products separated by preparative T.L.C. Two products were obtained. the major being a non-polar yellow compound which crystallised from ethanol as large platelets, 2-phenyl-4-methyl-1,3,4-benzothiadiazine (XXXXIII) (30 mg., 26%).

M.p. 53-4°.

ν_{max}^{nujol}, 1570, 1550, 1440, 1180, 1115, 990, 920, 755, 700cm.$^{-1}$.

λ_{max}^{EtOH}, 229, 265, 316 and 380m (ϵ =15,800, 20,600; 3,600 and 3,400 respectively)

τ 6·5 (5,3H), 2·5-3·2 (m, 7H), 2-2·2 (m. 2H).

Mass spectroscopy gives peaks at m/e 240 (M^+), 225 (M^+- Me), 208 (M^+- S), 136, 103 (PhCN).

Found: C, 70·05; H, 5·28; N, 11·83; S, 13·80%.

$C_{14}H_{12}N_5$ requires: C, 69·99; H, 5·03; N, 11·66; S, 13·32%.

The minor product was a more polar yellow compound which on isolation gave a yellow gum. This product was not studied further.

Starting material (40 mg., 35%) was also recovered.

The experiment was repeated using 100 mg. of the thiohydrazide and 120 mg. iodine. T.L.C. showed conversion to the benzothiadiazine only and this product was obtained direct from the reaction solution without chromatography (80%).

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