THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

ENTITLED

"EXTRUSION OF SULPHUR"

Submitted to the University of Glasgow

by L. B. Young B.Sc.

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Summary

Some 3,6-diaryl-2,7-dihydrothiadiazepines are prepared and converted into 3,6-diarylpyridazines either thermally or by means of N-bromosuccinimide in carbon tetrachloride. A dichloro derivative of 2,7-dihydro-3,6-diphenylthiadiazepine, obtained by the action of sulphuryl chloride on the dihydrothiadiazepine, affords 3,6-diphenylpyridazine by treatment with sodium iodide in acetone. The S-dioxides of the dihydrothiadiazepines are more easily converted into pyridazines by thermal means, and in this series of compounds, the oxidised is more easily eliminated than the unoxidised sulphur atom.

Oxidation of 3,6-diaryl-2,7-dihydrothiadiazepines with hydrogen peroxide in ethanol gave 3,5-diarylpyrazoles. The S-monoxides of the dihydrothiadiazepines are shown to be intermediates in the reaction, and other methods are also described for their conversion into 3,5-diarylpyrazoles. 3,5-Diphenylpyrazole is found to be readily degraded by hydrogen peroxide in acetic acid affording 2,5-diphenyl-1,3,4-oxadiazole, dibenzoyl hydrazine

and benzoic acid.

Attempts to prepare 2,7-dihydro-2,3,6,7-tetraphenylthiadiazepine by reaction of desyl sulphide with hydrazine gave instead benzylphenyl ketazine and benzil monohydrazone. Desyl sulphone was similarly hydrolysed by hydrazine in ethanol to dibenzyl sulphone.

2,7-Dihydro-3,6-diphenylthiadiazepine-S-dioxide dissolves in cold ethanolic sodium ethoxide and gives, on acidification, an unstable solid which forms 3,6-diphenylpyridazine on attempted crystallisation from ethanol. Acidification of the solution obtained by treatment of the S-dioxide with hot ethanolic sodium ethoxide gives a stable solid, Compound A, which is thermally converted into 3-methyl-4,5-diphenylpyrazole with loss of sulphur dioxide. Compound A also affords a methyl sulphone, and structures are suggested for both of these compounds.

Repetition of the literature preparation of bis-cyclohexanonyl sulphide gave only "bis-cyclohexanonyl disulphide". This compound is shown to be perhydro-4a,9a-dihydroxythianthren. Dehydration of this diol affords octahydrothianthren which is oxidised to a disulphone. Dehydrogenation of octahydrothianthren gives thianthren, but octahydrothianthren disulphone resists dehydrogenation under similar conditions. Octahydrothianthren extrudes sulphur to give octahydrodibenzothiophen in high yield. Oxidation of octahydrodibenzothiophen gives tetrahydrodibenzo-

thiophen sulphone, which is reduced to tetrahydrodibenzothiophen by lithium aluminium hydride. Octahydrodibenzothiophen is readily dehydrogenated to dibenzothiophen, but tetrahydrodibenzothiophen sulphone resists similar dehydrogenation conditions.

Cleavage of perhydro-4a,9a-dihydroxythianthren by potassium hydroxide in dimethylformamide, and reaction with phenacyl bromide gives cyclohexanonylphenacyl sulphide. By reaction with hydrazine, this sulphide condenses to the corresponding dihydrothiadiazepine, which decomposes, in boiling ethylene glycol, to 3-phenyltetrahydrocinnoline.

The major peaks in the infrared spectra of a number of pyrazoles and their N-acetyl derivatives are recorded, similarities are observed, and the existence of a characteristic frequency of absorption of the pyrazole nucleus is suggested.

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C O N T E N T S

CHAPTER 1

"RING CONTRACTIONS OF SEVEN- TO SIX-MEMBERED SYSTEMS"

INTRODUCTION

Extrusion of sulphur may be defined as the elimination of a sulphur atom from a molecule with the simultaneous formation of a bond between the two atoms to which the sulphur was originally attached. This is not to be confused with the normal Mozingo reaction in which sulphur is removed from a sulphide R-S-R by means of Raney nickel. Such hydrogenolytic desulphurizations may however be accompanied by combination of two radicals R since the Mozingo reaction is regarded as a free radical process.

In 1886, Ris[1] prepared a dibenzophenothiazine (probably 1) by heating di-β-naphthylamine with sulphur, and found that slow distillation of (1) in a carbon dioxide atmosphere afforded a dibenzocarbazole (probably 2). In the following year, Goske[2] obtained the carbazole (4) by boiling phenothiazine (3) with copper in an atmosphere of coal gas for two hours. The series was completed by Kym[3] in 1890 who prepared 1,2-benzocarbazole (6) from 1,2-benzophenothiazine (5). Ferrario[4] subsequently reported the conversion of phenoxathiin (7) to dibenzofuran (8) by treatment with copper at 250° but later workers[5,6,7] were unable to repeat this observation or even effect the conversion by changing the reaction conditions. In a

further variant of Ferrario's conditions during the present investigation, the S-monoxide and the S-dioxide of phenoxathiin were separately boiled with copper. The S-dioxide was recovered unchanged, but the S-monoxide was reduced to phenoxathiin (7), no dibenzofuran (8) being detected in either case.

Thianthren (9) however can[8] be converted into dibenzothiophen (10) by boiling with copper. Similarly dibenzo--o-dithiin (11) on treatment with copper at 250° for two hours affords[9] dibenzothiophen (10). Armarego and Turner[10] have extended this to various methyl derivatives of dibenzo--o-dithiin (11) and have in addition shown[11] that dibenzo--o-dithiin-5,5-dioxide (12) can lose sulphur dioxide to give dibenzothiophen (10).

Parham and his co-workers have studied[12] the possibilities of extrusion of sulphur from 1,4-dithiadiene (13, R = R' = H) and some of its 2,5-disubstituted derivatives. 1,4-Dithiadiene (13, R = R' = H) shows good thermal stability, and can be refluxed and distilled at atmospheric pressure[13], but 2,5-dimethyldithiadiene (13, R = R' = CH_3) decomposes at its boiling point[14] to give a mixture which contains some 2,4-dimethylthiophen (14, R = R' = CH_3). 2,5-Diaryldithiadienes (13, R = R' = Aryl; or R = Aryl; R' = Aryl') are thermally even less stable, extruding a sulphur atom to

give[15,16,17,18] 2,4-diarylthiophens (14, R=R'= Aryl; or R= Aryl; R'= Aryl'). Negatively substituted 2,5-diaryldithiadienes (15, R=CHO; or R=NO_2) decompose at rather lower temperatures and give predominantly one of two possible thiophens i.e. (16, R=CHO[15]; or R=NO_2[16]) and not (17, R=CHO; or R=NO_2).

To interpret these facts, Parham suggests that extrusion of sulphur from the diaryldithiadienes (15) proceeds via the episulphide structures (15a and 15b) which he considers to be two of the possible resonance hybrids of (15). The predominant formation of (16, R=CHO; or R=NO_2) can therefore be explained by observing that the contribution of structures (15a, R=CHO; or R=NO_2), where the negative charge can be delocalised by the aldehydo or nitro group, should be greater than the contribution of (15b, R=CHO; or R=NO_2). In a similar fashion, it has been suggested[14] that since 2,5-disubstituted dithiadienes (13, R=R'=CH_3; or R=R'=Aryl) extrude a sulphur atom but the parent heterocycle, 1,4-dithiadiene (13, R=R'=H) does not, the role of the 2- and 5-substituents is to increase the resonance stabilization in an intermediate such as (18), decreasing the thermal stability of the ring system and so promoting decomposition to thiophens.

The postulation of episulphide intermediates in these

and related cases of sulphur extrusion has its basis in the decomposition of aryl or alkyl substituted episulphides. Delépine[19] has reported the preparation of ethylene sulphide (20), the parent compound of the series, by the action of sodium sulphide on β-chloroethylthiocyanate (19). The product was a colourless liquid which readily polymerised, but there is no mention of any tendency to form ethylene by extrusion of sulphur. At the same time, Staudinger and Siegwart[20] prepared tetraphenylethylene sulphide (21) as shown, and found that when heated to 175° it lost the sulphur atom forming tetraphenylethylene (22). Schonberg[21] likewise showed that treatment of the episulphide (23) with copper bronze in boiling benzene gave the tetra-substituted ethylene (24), and the same author has more recently published[22] various extensions of this type of reaction.

Culvenor, Davies et al[23,24,25,26] discovered a convenient method of preparing episulphides by treatment of an epoxide with thiourea or various other thio-compounds, but no mention is made of any tendency of the aliphatic episulphides they prepared to extrude sulphur. It was observed[24] however, that tervalent phosphorus compounds abstracted the sulphur atom, but no attempt was made to identify the organic products of the reaction.

Recently two groups of workers have repeated Culvenor and Davies experiments on the reaction of episulphides with tervalent phosphorus compounds, and have shown that triethylphosphite[27,28] (26, R" = C_2H_5O) or triphenylphosphine[29] (26, R" = Ph) react with episulphides (25) to give olefins and the corresponding thionophosphorus-V-derivative (27, R" = C_2H_5O or R" = Ph). Scott has observed[30] the reaction of triethylphosphite (26, R" = C_2H_5O) with epoxides forming the corresponding olefin and triethylphosphate, but the reaction conditions were much more severe than those needed for the episulphides (25). In a similar fashion, Bordwell[31] has obtained good yields of cyclohexene by treatment of an etheral solution of cyclohexene sulphide with butyl lithium or phenyl magnesium bromide. It is also interesting to observe that stilbene oxide (28) on treatment with thiourea in ethanol for six days afforded[24] an 80% yield of stilbene (29). No episulphide was detected but the high recovery of sulphur (65% of the theoretical amount) supports the view that such an intermediate episulphide had been formed. It can be seen from these examples that the tendency of an episulphide to extrude sulphur forming an olefin, either thermally or under the accelerating influence of an additive, provides some justification for the postulation of episulphide

intermediates in other cases of extrusion of sulphur.

Episulphones (ethylene sulphones) are at least as unstable as episulphides; in fact relatively few are known. Hesse, Reichold and Majmudar[32] have reported the isolation of the parent compound, ethylene sulphone (30), by reaction of sulphur dioxide with diazomethane at -45°, and part of the evidence for the structure (30) is its thermal decomposition to ethylene and sulphur dioxide. Tetraphenylethylene sulphone (31), prepared as shown, is readily converted[33] into tetraphenylethylene (32), and Vargha and Kovacs[34] have prepared diethylstilboestrol (34) from the episulphone (33). From these few examples, it can be seen that extrusion of sulphur can also occur with the oxidised sulphur atom, a theme which will be developed later in this thesis, and this has been demonstrated in ring systems other than three-membered. Thus Parham[15-18], Szmant[35] and their respective co-workers have shown that 2,5-diaryl-1,4-dithiadienes (15) are readily converted into thiophenes (16) by oxidation with peroxides, and it has been shown that mono-sulphoxides are intermediates, and that the oxidised sulphur atom is preferentially extruded.

Various groups of workers have been concerned with the "dimerisation" of thiophen sulphones, thus thiophen

sulphone[36], 3,4-dichlorothiophen sulphone[37], benzothiophen sulphone[38,39] and related compounds[40] all dimerise via a Diels-Alder reaction followed by loss of the bridge sulphonyl group. In illustrating this theme, one recent example[41], the dimerisation of 3,4-diphenylthiophen sulphone (35) to form (36) will suffice. In a similar fashion, thiophen sulphones react with acetylenic dienophiles[36,42] and form aromatic products by extrusion of sulphur dioxide.

From these observations recorded in the literature, it is apparent that extrusion of sulphur is now a well established phenomena, and in a recent review, Loudon[43], has suggested "that a thia atom is more or less readily extruded from a heterocycle if the ring contraction involved leads to an aromatic structure". This theme is especially demonstrated by extrusion of sulphur from a seven-membered heterocycle to give the corresponding six-membered aromatic ring.

The monocyclic thiepin (37) is unknown, but the condensate (38) formed by reaction of o-phthaldehyde with diethyl thiodiacetate in an alkaline medium readily forms naphthalene-2,3-dicarboxylic acid (39) on mild heating or in boiling aqueous ethanol[44,45]. Perhaps the condensate (38) undergoes bond rearrangement to an

intermediate of structure (40) prior to the formation of the acid (39). In an extension of this type of reaction, Sloan[46] found that condensation between diphenacyl sulphide (41) and o-phthaldehyde in alkali gave 2,3-dibenzoyl-naphthalene (42), no intermediate thiepin being isolated. By using naphthalene-2,3-dialdehyde instead of o-phthaldehyde, a good yield of 2,7-dibenzoyl(2',3'-4,5)thiepin (43, R=Ph) was obtained, which decomposed to dibenzoyl-anthracene (44, R=Ph) at 180°. The reaction between naphthalene-2,3-dialdehyde and diethyl thiodiacetate proved to be more complicated, a mixture of the mono and diethyl esters of the thiepin (43, R=OH) being obtained. The diethyl ester gave the anhydride of anthracene-2,3-dicarboxylic acid (44, R=OH) at 180°.

Parham, after observing[47] that halocarbenes react with dihydropyran (45) to give cyclopropyl adducts (46) which afford dihydrooxepins (47) by susequent ring expansion and elimination of hydrogen chloride, tried to develop a method for the synthesis of seven-membered heterocycles. Reaction[48] of 4H-1-benzothiopyran (48) with dichlorocarbene gave the cyclopropyl adduct (49), which could be recovered unchanged after prolonged reflux in pyridine, but decomposed when heated in quinoline at 210° with evolution of some hydrogen sulphide and formation of

2-chloronaphthalene (50). It is possible that the benzothiepin (51) may be an intermediate in this transformation.

The benzothiepin sulphone (52) has also been shown to extrude sulphur dioxide to form naphthalene[49].

Loudon, Sloan and Summers[50] investigated dibenzothiepins of type (53) and found that the sulphur atom could be extruded yielding phenanthrenes(54). Similarly dibenzothiazepines (55) have been shown[51,52,53] to extrude the sulphur atom affording phenanthridines (57) with an episulphide (56) being a postulated intermediate. Galt, Loudon and Sloan[54] provided a further demonstration of this type of ring contraction in the conversion of polycyclic thiazepines such as (58) into polycyclic diaza compounds (59).

It would therefore be of interest to prepare dibenzothiadiazepine (60), or derivatives of this structure, and to study their extrusion of sulphur in relation to the systems already mentioned. Allinger and Youngdale[55] have recently reported the synthesis of dibenzothiadiazepine (60) in 6% yield by reduction of 2,2'-dinitrodiphenyl sulphide (61), but a general synthesis of dibenzothiadiazepines is still lacking despite many attempts.

Because of this, we tried to prepare 3,6-diarylthiadiazepines (62) with a view to extruding the sulphur atom to form 3,6-diarylpyridazines (63). There are no 3,6-

diarylthiadiazepines (62) known in the literature, however Fromm and Erhardt[56] had prepared 2,7-dihydro-3, 6-diphenylthiadiazepine (64, R=H), and we therefore set out to devise a method for oxidation of the dihydrothiadiazepine (64, R=H) to the thiadiazepine (62, R=H), which we could then attempt to convert to 3,6-diphenylpyridazine (63, R=H) by extrusion of sulphur.

DISCUSSION.

The essential starting material for this investigation, 2,7-dihydro-3,6-diphenylthiadiazepine (64, R=H) was prepared by the reaction scheme indicated. The conversion of phenacyl bromide (65, R=H) to diphenacyl sulphide (66, R=H) was initially[57] accomplished using ethanolic sodium hydrogen sulphide. During the present investigation, it was found that crystalline sodium sulphide nonahydrate readily dissolved in hot moist dimethyl formamide, and that if such a solution were added to a solution of phenacyl bromide (65, R=H) in the same solvent, excellent yields of diphenacyl sulphide (66, R=H) were obtained by simply diluting the reaction mixture with water. This method is in fact much cleaner and simpler than that previously used.

The second stage of the scheme, the reaction of diphenacyl sulphide (66, R=H) with hydrazine was first accomplished by Fromm and Erhardt[56], although in poor yield. This was improved by Begg[58] whose method involved addition of excess hydrazine hydrate to a solution of diphenacyl sulphide (66, R=H) in hot ethanol. Subsequent dilution with dilute acetic acid gave a white precipitate, m.p. below 70°, rising on recrystallisation

to 175°.

The method now adopted is simply to introduce an excess of hydrazine hydrate to a warm solution of diphenacyl sulphide (66, R=H) in glacial acetic acid, and the desired 2,7-dihydro-3,6-diphenylthiadiazepine (64, R=H) crystallises in high yield within a short time.

The reaction could also afford a monohydrazone or a dihydrazone, however elemental analysis in conjunction with infrared spectral evidence shows that the compound produced by the reaction is the required dihydrothiadiazepine (64, R=H). The compound analyses for $C_{16}H_{14}N_2S$ (see table 1). The infrared spectra, (nujol or KCl disc) do not show any absorption attributable to either an >NH or a carbonyl group in the molecule. Hence both a monohydrazone and a dihydrazone structure for the compound can be excluded.

TABLE 1.

Found %	$C_{16}H_{14}N_2S$ (64, R=H)	$C_{16}H_{16}N_2OS$ Monohydrazone	$C_{16}H_{18}N_4S$ Dihydrazone
C 71.75	72.15	67.6	64.4.
H 5.35	5.3	5.65	6.1

The 2,7-dihydro-3,6-diphenylthiadiazepine (64, R=H) can possibly tautomerise to either a 2,6-dihydro form (67, R=H) or a 4,5-dihydroform (68, R=H). As already mentioned, the solid state infrared spectra of the dihydrothiadiazepine (64, R=H) show no absorption attributable to an >NH group, but in dilute carbon tetrachloride solution, absorption at 3418cm.$^{-1}$ could only be assigned to an >NH group. Therefore in dilute carbon tetrachloride solution, the dihydrothiadiazepine (64, R=H) may tautomerise to some extent, possibly to the 2,5-dihydro tautomer (67, R=H).

However attempts to acetylate the compound were unsuccessful, as were oxidative experiments with mercuric oxide, and if there is an equilibrium between the forms (64), (67) and (68), then this equilibrium must normally lie well to the side of the 2,7-dihydrothiadiazepine tautomer (64, R=H).

The 2,7-dihydro-3,6-diphenylthiadiazepine (64, R=H) was treated with a variety of oxidising agents in an attempt to obtain 3,6-diphenylthiadiazepine (63, R=H), but was recovered unchanged after treatment with the following reagents, chloramine-T, chloranil, mercuric chloride and mercuric oxide, (both in alcohol and the higher boiling toluene). However the use of N-bromosuccinimide in carbon tetrachloride, a reagent known to effect

aromatisation or mild bromination/dehydrobromination[59,60,61] did meet with some measure of success. The reaction of N-bromosuccinimide in carbon tetrachloride on the dihydrothiadiazepine (64, R=H), using a lamp heater as a source of heat and photons, was initially carried out by Begg[58], who obtained the expected product 3,6-diphenyl-pyridazine[62] (63, R=H). This result has been confirmed by the writer, and the reaction extended to two new dihydrothiadiazepines (64, R=Br; R=CH_3), which respectively afforded the known[63] pyridazines (63, R=Br; R=CH_3). The two new dihydrothiadiazepines (64, R=Br; R=CH_3) were prepared by the method adopted for the parent compound (64, R=H).

Groebel[64] has shown that phenyl phenacyl sulphide (69) reacts with N-bromosuccinimide in carbon tetrachloride affording the 2-bromosulphide (70), and he has subsequently extended this reaction to a series of substituted phenyl phenacyl sulphides[65].

By analogy with this work, one would expect N-bromosuccinimide to react with the dihydrothiadiazepine (64) to give a 2-bromo compound which could spontaneously eliminate hydrogen bromide to form the episulphide (71). This episulphide (71) could then extrude sulphur as shown, affording the 3,6-diarylpyridazine (63).

In this connection it is extremely interesting to observe the recent report of Maier[66] who assigns the bisaza-norcaradiene structure (73) to the initial product obtained by reaction of trans-1,2,4-tribenzoylcyclopropane (72) with hydrazine. The compound rearranges to 3,6-diphenyl-4-phenacylpyridazine (74) on treatment with conc. hydrochloric acid.

Thus although the N-bromosuccinimide method does not produce 3,6-diarylthiadiazepines (62), the structure of the postulated episulphide intermediate is intimately related to that of the thiadiazepines (62), and the products obtained are those expected by extrusion of sulphur from the thiadiazepines (62).

The conversion of the dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) into the pyridazines (63, R=H; R=Br; R=CH_3) using N-bromosuccinimide proceeded in high yield, and experiments were tried on the parent dihydrothiadiazepine (64, R=H), to see if bromine alone could effect the change. The reaction proved to be complex. Addition of a solution of bromine in acetic acid to one of the dihydrothiadiazepine (64, R=H) in the same solvent, gave a brown solid precipitate, perhaps a perbromide addition complex, which could not be characterised. It was converted, however, into 3,6-diphenylpyridazine (63, R=H) when refluxed in the reaction

mixture or in acetic acid. In either case the yield was much inferior to that obtained using N-bromosuccinimide, which is the preferred method.

Since the reaction of N-bromosuccinimide with the dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) is thought to proceed via a 2-bromo compound, the independent preparation of such a 2-halo derivative could provide more information on the exact mechanism whereby the formation of the pyridazines (63, R=H; R=Br; R=CH_3) occurs.

Bordwell and Pitt[67] have shown that 2-chloro sulphides can be formed by treatment of a suitable sulphide with sulphuryl chloride in methylene chloride. Consequently the dihydrothiadiazepine (64, R=H) was treated with this reagent in the hope of obtaining a 2-chlorodihydrothiadiazepine. The product obtained was dimorphic, crystallising either as colourless prisms m.p. 158° (dec.) or as soft white needles m.p. 179° (dec.). The compound gave a positive test for halogen, and gave an analysis in accordance with the presence of two chlorine atoms.

Oxidation of the compound with 30% hydrogen peroxide in alcohol (see p.57) gave a small amount of 3,6-diphenylpyridazine (63, R=H) and a 75% yield of benzoic acid. Therefore the chlorine atoms have not substituted in either of the benzene rings.

Infrared spectra of the dichloro compound (nujol and KCl disc) showed no absorption attributable to an >NH group but it was not possible to say whether the compound still possessed a methylene group or not. The spectrum was therefore recorded in dilute carbon tetrachloride solution and compared with a similar spectrum of the starting dihydrothiadiazepine (64, R=H). Both spectra showed identical maxima in the 3200-2700cm.$^{-1}$ region of the spectrum but in the dichloro compound, the absorption maxima associated with methylene groups were reduced in intensity relative to that for maxima associated with the aromatic groups. Since the compound contains two chlorine atoms, as analyses show, then the infrared spectrum would suggest that the compound is a 2,2-dichloro (75, X=Y=Cl), and not a 2,7-dichloro derivative (76, X=Y=Cl) of the dihydrothiadiazepine (64, R=H). In this connection, Truce, Birum and McBee[68], in a study of the chlorination of dimethyl sulphide, found that the methyl group on which the first chlorine atom is substituted is completely chlorinated before there is any chlorination of the second methyl group. By analogy, one would expect the dichloro derivative of the dihydrothiadiazepine (64, R=H) to be a 2,2-dichloro derivative (75, X=Y=Cl).

It was also interesting to note in the dilute solution

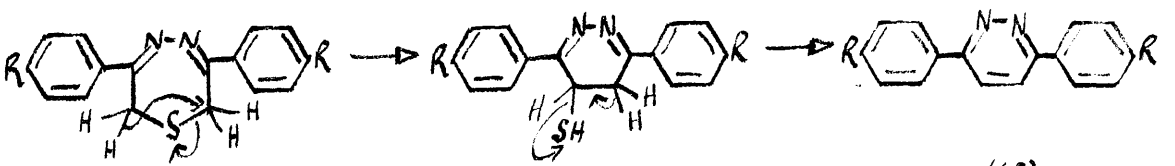
spectrum of the dichloro compound a peak at 3418cm.$^{-1}$ which must be due to >NH absorption. Since this is not present in the solid state spectra, the dichloro compound, like the parent dihydrothiadiazepine (64, R=H), may be capable of tautomerism.

A well known method for conversion of vic-dihalides into ethylenic compounds employs sodium iodide in acetone or alcohol, and the same process can be used to convert a suitable 1,3-dihalogeno compound into a cyclopropane derivative. Since the dichloro compound could have been a 2,7-dichloro derivative (76, X=Y=Cl) of the dihydro-thiadiazepine (64, R=H), treatment of the dichloro compound with sodium iodide in acetone could give the episulphide (71, R=H) which should then extrude the sulphur atom affording 3,6-diphenylpyridazine (63, R=H).

At room temperature no reaction occurred, although after four hours, the acetone became pale yellow in colour and slightly cloudy. Refluxing for three hours produced a yellow orange colour in the acetone and a small amount of inorganic precipitate, but again a high recovery of starting material was obtained. However after refluxing for 24hrs. the acetone had become red brown in colour, and there was a definite precipitate of sodium chloride. Dilution with water and crystallisation of the product

gave a 69% yield of 3,6-diphenylpyridazine (63, R=H). Since the infrared spectral evidence suggests that the dichloro compound is a 2,2-dichloro derivative (75, X=Y=Cl) and not a 2,7-dichloro derivative (76, X=Y=Cl), it is difficult to see how treatment with sodium iodide in acetone effects conversion into 3,6-diphenylpyridazine (63, R=H). Perhaps since the treatment with sodium iodide in acetone has to be prolonged, the 2,2-dichloro compound (75, X=Y=Cl) may rearrange via a 2,2-dihalogeno derivative (75, X≠Y) to the 2,7-dihalogeno isomer (76, X≠Y) which may then be the final reactant molecule.

The dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) when heated above their melting points effervesce, the evolved gases blackening lead acetate paper, and attempts were therefore made to isolate the organic products of these decompositions. In every case, the corresponding pyridazine was obtained, but the yields were poor. By refluxing the dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) in ethylene glycol however, high yields of the corresponding pyridazines (63, R=H; R=Br; R=CH_3) were obtained. A possible mechanism for the reaction can be written as shown.



Alternatively the reaction may proceed through an initial oxidation to the thiadiazepine (62) followed by a simple extrusion of sulphur.

The temperature required for this reaction is fairly moderate, about 200°, in comparison with other systems such as dibenzothiepins (53) or dibenzothiazepines (55) which require a reaction temperature of about 300° [51,52,53,54]. Presumably in these structures the two benzene rings fused to the central thiepin or thiazepine ring confer a higher degree of stability, and this may similarly be found for dibenzothiadiazepines (60). It is nevertheless apparent that the thermal instability of the dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) provides an easy method for their conversion into the corresponding pyridazines (63, R=H; R=Br; R=CH_3).

Extrusion of sulphur is not confined simply to the bivalent sulphur atom; some examples of extrusion of an oxidised sulphur atom have already been described, and a few more examples will now be given. Galt, Loudon and Sloan[54] found thattreatment of the thiazepine (77) with hydrogen peroxide in acetic acid gave the acridine (78), and it is suggested that the sulphur atom is oxidised to an intermediate S-monoxide which can then eliminate sulphur monoxide. Under similar conditions, Bradsher and

McDonald[69] converted derivatives of the pyrido(2,1-b)-benzo(f)(1,3)thiazepinium system (79) into the benzo(a)-quinolizium system (80), and again an intermediate is probably an oxidised form of the sulphur atom. It is also of interest to observe that Gilman and Swayampati[70] found a preferential extrusion of the oxidised sulphur atom in thianthren-5-oxide (81) similar to that observed with 1,4-dithiadiene-S-monoxides (82)[15,16,17,18,35]. Sultones[71,72] such as (83) and sultams[73] such as (84) also extrude the oxidised sulphur atom to give aromatic products. In a similar fashion, thiophen sulphones and acetylenic dienophiles react to give adducts (85) which yield aromatic products by extruding sulphur dioxide[36,42].

We therefore decided to prepare the 2,7-dihydro-3,6-diphenylthiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3) and to compare the ease of their expected conversion into the corresponding pyridazines (63, R=H; R=Br; R=CH_3) with the ease of conversion of the unoxidised dihydro-thiadiazepines (64, R=H; R=Br; R=CH_3).

One route to the dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3) was by reaction of hydrazine hydrate with the bis phenacyl sulphones (86, R=H[56]; R=Br[74]; R=CH_3). The keto-sulphones (86, R=H; R=Br; R=CH_3) were easily prepared by oxidation of the keto-sulphides

(66, R=H; R=Br; R=CH_3) with potassium permanganate in acetic acid.

The reaction of diphenacyl sulphone (86, R=H) with hydrazine hydrate has been previously reported[56] to yield the dihydrothiadiazepine-S-dioxide (87, R=H) m.p. 206° and a monohydrazone m.p. 185°. In our hands, addition of hydrazine hydrate to a warm solution of diphenacyl sulphone (86, R=H) in acetic acid gave, on immediate cooling, a quantitative yield of soft white needles m.p. 196°. The compound effervesced as it melted, resolidified, then melted at the m.p. of 3,6-diphenylpyridazine (63, R=H). The compound analysed for the dihydrothiadiazepine-S-dioxide (87, R=H) and not for a monohydrazone or a dihydrazone (see table 2).

TABLE 2

Found%	$C_{16}H_{14}N_2O_2S$ (87)	$C_{16}H_{16}N_2O_3S$ Monohydrazone	$C_{16}H_{18}N_4O_2S$ Dihydrazone
C 64.3	64.4	60.75	58.15
H 4.4	4.7	5.1	5.5
N 9.45	9.4	8.9	16.95

The infrared spectrum (nujol) showed no absorption attributable to an >NH or a carbonyl group, but did retain

peaks associated with the sulphone group at 1324 and 1142, 1118cm.$^{-1}$. The compound is therefore the required dihydrothiadiazepine-S-dioxide (87, R=H).

Similar treatment of the keto-sulphone (86, R=CH_3) with hydrazine hydrate in warm acetic acid gave the dihydrothiadiazepine-S-dioxide (87, R=CH_3), but under the same conditions, the keto-sulphone (86, R=Br) gave only the pyridazine (63, R=Br). Presumably the dihydrothiadiazepine-S-dioxide (87, R=Br) is too unstable for isolation under these conditions. However all three dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3) could be obtained by oxidation of the corresponding dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) with potassium permanganate in acetic acid.

In contrast to the dihydrothiadiazepine (64, R=H), the dihydrothiadiazepine-S-dioxide (87, R=H) could be recovered unchanged after treatment with N-bromosuccinimide in carbon tetrachloride.

The dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3) were easily converted into the corresponding pyridazines (63, R=H; R=Br; R=CH_3) however, simply by melting, or short reflux in either acetic acid or ethylene glycol. The dihydrothiadiazepine-S-dioxide (87, R=H) also afforded 3,6-diphenylpyridazine (63, R=H) by longer

reflux in ethanol. These facile thermal reactions show that in this series of compounds, the oxidised sulphur atom is more easily eliminated by thermal means than is the unoxidised sulphur atom. The dihydrothiadiazepines (64, R=H; R=Br; R=CH_3) are recovered from boiling acetic acid or toluene, conditions under which the dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3) are smoothly converted into the corresponding pyridazines (63, R=H; R=Br; R=CH_3).

The gases which could be detected in the thermal decompositions of the dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3) proved to contain both sulphur dioxide and hydrogen sulphide.

Previous publications on the pyrolysis of sulphones have not been concerned with seven-membered cyclic sulphones, but have mostly dealt with either five-membered cyclic sulphones or acyclic sulphones. For example, it is wellknown[75] that the reaction between butadiene and sulphur dioxide to give 2,5-dihydrothiophen sulphone (88) is reversible, the five-membered cyclic sulphone reforming the starting components on being heated. Cava and his co-workers have extended this process to the synthesis of benzocyclobutene[76] (89); naphtho(b)cyclobutene[77] (90) and naphtho(a)cyclobutene[78] (91) by pyrolysis of the

appropriate dihydrothiophen sulphone (92); (93) and (94). In each case the orthoquinodimethane (95); (96) and (97) was formed and could be trapped by reaction with N-phenylmaleimide.

La Combe and Stewart[79] have found that certain allylic sulphones lose sulphur dioxide on pyrolysis, affording olefinic products. Thus allyl benzyl sulphone (98) may be converted into 4-phenyl-1-butene (99), and to accomodate their observations, they propose an intramolecular cyclic mechanism as shown. They further suggest that a comparable mechanism could account for the products obtained in the pyrolysis of the dihydrothiophen sulphones.

If such a scheme were applied to the dihydrothiadiazepine-S-dioxide (87), then an intermediate of structure (100) could be obtained, which might form the dihydropyridazine (103), via either an open chain intermediate (101) or an episulphone of type (102). The dihydropyridazine (103), if formed, should immediately oxidise to the pyridazine (63). In none of the other examples of pyrolysis of sulphones was such a final oxidation step, (103) ⟶ (63) probable or even possible, and perhaps the joint formation of hydrogen sulphide and sulphur dioxide arises from the nature of this final step.

It is perhaps pertinent here to note that Hesse and

Reichold[80], on treatment of diazocyclohexylethylmethane (104, $R=C_2H_5$; $R'=C_6H_{11}$) with sulphur dioxide, obtained two stereoisomers of molecular formula $C_{18}H_{32}N_2O_2S$. When either isomer is passed through neutral alumina, the ketazine (105, $R=C_2H_5$; $R'=C_6H_{11}$) is produced; and at 200° both decomposed to give the ethylene (106, $R=C_2H_5$; $R'=C_6H_{11}$). The authors prefer the structure (107, $R=C_2H_5$; $R'=C_6H_{11}$) for the isomers, and cyclic intermediates can be written, (108) and (109), for the formation of the ketazine (105, $R=C_2H_5$; $R'=C_6H_{11}$) respectively.

In our case, a mechanism similar to that suggested for the thermal conversion of the dihydrothiadiazepine (64) into the pyridazine (63) can also be envisaged. In this case, the intermediate would have a structure such as (110) and the fragments eliminated would correspond to the unknown sulphoxylic acid, whose decomposition is known to involve dismutation, but otherwise is a matter of conjecture. It is clear however that none of these suggestions satisfactorily explains the conversion of the dihydrothiadiazepine-S-dioxide (87) into the pyridazine (63) and perhaps the true mechanism may yet become clear.

The initial objective of this chapter was the preparation of 3,6-diarylthiadiazepines (62) by the oxidation of the corresponding dihydrothiadiazepines (64).

This has not been achieved, possibly because the conditions necessary to effect oxidation of the relatively stable dihydrothiadiazepines (64) would be sufficient to effect extrusion of sulphur from the thiadiazepines (62). Methods for the conversion of the dihydrothiadiazepines (64) into pyridazines (63), both thermal and chemical, have been devised however, and it has been shown that in this series of compounds, the oxidised sulphur atom is more easily eliminated than the unoxidised sulphur atom.

EXPERIMENTAL

Infrared absorption maxima are quoted for samples run on a Perkin Elmer Model No. 13 unless otherwise stated. Where hydrazine hydrate is used in this and other chapters, this refers to 100% hydrazine hydrate. Similarly hydrogen peroxide refers to 30% hydrogen peroxide. Petrol refers to light petroleum (b.p. 60-80°) unless otherwise stated.

Diphenacyl Sulphide (66, R=H).

This was prepared by the method of Fromm and Flaschen[57] or by the following method.

Sodium sulphide nonahydrate (20g.) was dissolved in hot moist dimethylformamide (200cc.). The cooled solution was added slowly at room temperature with stirring to a solution of phenacyl bromide[81] (20g.) in dimethylformamide (100cc.). The mixture was stirred 30mins. after complete addition, then diluted with water, and the precipitate crystallised from ethanol affording diphenacyl sulphide as white prismatic needles (10.8g.) m.p. 77-78°.

2,7-Dihydro-3,6-diphenylthiadiazepine (64, R=H).

Excess hydrazine hydrate was introduced into a solution of diphenacyl sulphide (10g.) in hot glacial acetic acid (30cc.). After shaking the hot solution for a few mins., cooling induced the dihydrothiadiazepine to crystallise as

white needles (8.2g.) m.p. 174-175°. (Found: C, 71.75; H,5.35. Calc. for $C_{16}H_{14}N_2S$: C,72.15; H,5.3%).

νmax (0.005mol. in CCl_4) 3418cm.$^{-1}$.

N-bromosuccinimide Oxidation[58].

2,7-Dihydro-3,6-diphenylthiadiazepine (1.33g.); N-bromosuccinimide (0.89g.) were refluxed in carbon tetrachloride (50cc.) for 1hr. by means of a 250watt lamp heater. On heating, the solution changed colour from colourless, through yellow and orange to red, and luminesced brightly for a few minutes. The blackish solid (ca. 1.8g.) which separated out from the hot carbon tetrachloride was recrystallised from ethanol with charcoaling, affording 3,6-diphenylpyridazine (63, R=H) as silvery leaflets (1g.) m.p. and mixed m.p. with an authentic[62] sample 220-221°.

Bis-(p-bromophenacyl)-sulphide[82](66, R=Br).

This was prepared from p-bromophenacyl bromide[83] (65, R=Br) by reaction with ethanolic sodium hydrogen sulphide, and was obtained as yellowish plates (ethanol) m.p. 141-143°.

2,7-Dihydro-3,6-di-(p-bromophenyl)-thiadiazepine (64, R=Br).

This compound was obtained in 80% yield by the method adopted for the parent dihydrothiadiazepine (64, R=H), as colourless needles (benzene-petrol) m.p. 201-202°. (Found: C,45.75; H,2.95; N,6.85. $C_{16}H_{12}Br_2N_2S$ requires C,45.3; H,2.85; N,6.6%).

N-bromosuccinimide on the Dihydrothiadiazepine (64, R=Br). Using the technique adopted for the parent dihydrothiadiazepine (64, R=H), the dihydrothiadiazepine (64, R=Br) was converted in 78% yield by N-bromosuccinimide into the pyridazine (63, R=Br) which was obtained as colourless rods (ethanol) m.p. 286-288° (lit.[63] 285°). (Found: N,7.5. Calc. for $C_{16}H_{10}Br_2N_2$: N,7.2%).

Bis-(p-methylphenacyl)-sulphide[82](66, R=CH_3). This sulphide was obtained from p-methylphenacyl bromide[84] (65, R=CH_3), by reaction with ethanolic sodium hydrogen sulphide, as colourless prisms (ethanol) m.p. 88-89°.

2,7-Dihydro-3,6-di-(p-tolyl)-thiadiazepine (64, R=CH_3). This compound was prepared in 80% yield, by the method adopted for the parent dihydrothiadiazepine (64, R=H), as colourless rods (ethyl acetate) m.p. 214-215°. (Found: C,73.2; H,5.9; N,9.6. $C_{18}H_{18}N_2S$ requires C,73.45; H,6.15; N,9.5%).

N-bromosuccinimide on the Dihydrothiadiazepine (64, R=CH_3). Using the technique adopted for the parent compound (64, R=H), the dihydrothiadiazepine (64, R=CH_3) was converted in 60% yield, by N-bromosuccinimide, into the pyridazine (63, R=CH_3), obtained as colourless needles (ethanol) m.p. 235-236° (lit.[63] 231-232°). (Found: N,10.85. Calc. for $C_{18}H_{16}N_2$: N,10.75%).

Action of Bromine on the Dihydrothiadiazepine (64, R=H).

Aliquots (1cc.) of a solution of bromine (0.12cc.) in glacial acetic acid (5cc.) were added every 30mins. at room temperature to a solution of 2,7-dihydro-3,6-diphenylthiadiazepine (0.5g.) in glacial acetic acid (25cc.). A brown solid precipitate gradually separated out. The mixture was refluxed for 4hrs., cooled, diluted with water, extracted with ether and the combined ether extracts washed several times with saturated sodium bicarbonate, then water, and dried. After removing the solvent, the red solid product was crystallised from ethanol with charcoaling affording 3,6-diphenylpyridazine as colourless plates (0.18g.), m.p. and mixed m.p. with an authentic sample[62] 221-222°.

2,7-Dihydro-3,6-diphenylthiadiazepine (64, R=H) with Sulphuryl Chloride[67].

A solution of sulphuryl chloride (2.5g.) in dry methylene chloride (15cc.) was carefully dripped into a solution of 2,7-dihydro-3,6-diphenylthiadiazepine (4g.) in dry methylene chloride (40cc.). The mixture was then gently refluxed for 1hr., some of the solvent was removed in vacuo, and the solid material which separated out was filtered off and dried giving a pinkish solid (1.7g.) m.p. 155° (dec.). Evaporation of the filtrate gave a black tarry residue

from which no crystalline material could be obtained.

The pinkish solid crystallised from ethyl acetate either as colourless prisms m.p. 158° or as soft white needles m.p. 179° (dec.). The infrared spectra of both samples were identical however, and the compound appears to be dimorphic. Elements tests showed the presence of chlorine, nitrogen and sulphur. (Found : C,57.45; H,4.1; N,8.45. $C_{16}H_{12}N_2Cl_2S$ requires C,57.3; H,3.6; N,8.35%. $C_{16}H_{13}N_2ClS$ requires C,63.85; H,4.35; N,9.3%). ν max (0.005m. in CCl_4) 3418cm.$^{-1}$.

Oxidation of the Dichloro Compound.

The dichloro compound (223mg.) was suspended in ethanol (25cc.), hydrogen peroxide (4cc.) was added and the mixture was refluxed 1.5hr.. After evaporating some of the ethanol, dilution with water gave a white precipitate which crystallised from ethanol as colourless plates (13mg.) m.p. and mixed m.p. with 3,6-diphenylpyridazine 219-220°

The filtrate was saturated with sodium chloride and extracted with chloroform. Working up in the usual way gave a white solid (114mg.), sublimed as colourless crystals m.p. and mixed m.p. with benzoic acid 118-120° The infrared spectra of the two samples were identical.

Sodium Iodide in Acetone on the Dichloro Compound.

a) Room Temperature.

A solution of sodium iodide (101mg.) in acetone (2.5cc.) was added to a solution of the dichloro compound (104mg.) in acetone (15cc.), and the mixture was allowed to stand 4hrs. at room temperature with occasional shaking. Dilution with water gave a white precipitate (91mg.) whose infrared spectrum was identical to that of the starting material.

b) 3hr. Reflux.

A solution of sodium iodide (103mg.) in acetone (2.5cc.) was added to the dichloro compound (105mg.) in acetone (15cc.) and the mixture was refluxed 3hrs. The solution became yellow-orange in colour, and a slight amount of inorganic material was precipitated. Cooling and dilution with water gave a white precipitate (94mg.) whose infrared spectrum was identical to that of the starting material.

c) 24hr. Reflux.

The dichloro compound (200mg.) and sodium iodide (800mg.) were refluxed in acetone (30cc.) for 24hrs. The solution became red-brown in colour and there was a definite precipitate of sodium chloride. The solution was cooled, diluted with water, and the precipitate obtained crystallised from ethanol as colourless plates (90mg.), m.p. and mixed m.p. with 3,6-diphenylpyridazine 219-221°.

The mother liquors of the crystallisation contained

more solid material, but its infrared spectrum suggested that it might be the starting dichloro compound.

Ethylene Glycol Decompositions.

a) 2,7-Dihydro-3,6-diphenylthiadiazepine (0.2g.) was refluxed in ethylene glycol (25cc.) for 4hrs.. There was vigorous evolution of hydrogen sulphide, detected by smell and blackening of lead acetate paper. The solution was cooled, diluted with water, and the precipitate crystallised from ethanol as colourless plates (0.14g.) m.p. and mixed m.p. with 3,6-diphenylpyridazine 219-221°.

b) Using the same technique, 2,7-dihydro-3,6-di(p-bromophenyl)-thiadiazepine (64, R=Br) was converted in 76% yield into 3,6-di(p-bromophenyl)-pyridazine (63, R=Br).

c) Similarly 2,7-dihydro-3,6-di(p-tolyl)-thiadiazepine (64, $R=CH_3$) was converted in 78% yield into 3,6-di(p-tolyl)-pyridazine (63, $R=CH_3$).

Preparation of the Bis-phenacyl Sulphones (86, R=H; R=Br; $R=CH_3$).

a) Diphenacyl Sulphone (86, R=H).

A solution of potassium permanganate (8g.) in water (240cc.) was added to a solution of diphenacyl sulphide (8g.) in acetic acid (50cc.) and the mixture allowed to stand 1hr. with occasional mild warming and shaking. After decolourising with sulphur dioxide, the yellow precipitate was

crystallised from ethanol giving diphenacyl sulphone as white plates (6.9g.) m.p. 119-120° (lit.[56] 120°).

b) Bis-(p-bromophenacyl) Sulphone (86, R=Br).

Bis-(p-bromophenacyl) sulphide (1.5g.) was refluxed 1hr. in glacial acetic acid (30cc.) with hydrogen peroxide (10cc.). The precipitate, obtained after cooling and diluting with water, crystallised from ethanol affording bis-(p-bromophenacyl) sulphone as soft white needles (1.1g.) m.p. 205-206° (lit.[74] 201-202°). (Found: C,41.45; H,2.8. Calc. for $C_{16}H_{12}Br_2O_4S$: C,41.75; H,2.65%).

This sulphone could also be prepared as in (a) above.

c) Bis-(p-methylphenacyl) Sulphone (86, R=CH_3).

Oxidation of bis-(p-methylphenacyl) sulphide by the method described in (a) above gave bis-(p-methylphenacyl) sulphone as colourless needles (ethanol) m.p. 147-148°. (Found: C,65.35; H,5.35. $C_{18}H_{18}O_4S$ requires C,65.45; H,5.5%).

Preparation of the Dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3).

a) 2,7-Dihydro-3,6-diphenylthiadiazepine-S-dioxide (87, R=H).

(i) Excess hydrazine hydrate was introduced into a solution of diphenacyl sulphone (1.4g.) in warm glacial acetic acid (25cc.). The mixture was shaken briskly, then immediately cooled and diluted with water. The resulting precipitate crystallised from benzene, affording

the dihydrothiadiazepine-S-dioxide (87, R=H) as soft white needles m.p. 196° (with effervescence). (Found: C,64.3; H,4.4; N,9.45. Calc. for $C_{16}H_{14}N_2O_2S$: C,64.4; H,4.7; N,9.4%). νmax (nujol) 1324; 1142, 1118cm.$^{-1}$.

(ii) A solution of potassium permanganate (0.5g.) in water (20cc.) was added to a solution of 2,7-dihydro-3,6-diphenylthiadiazepine (0.5g.) in acetic acid (30cc.) and the mixture was allowed to stand 1hr. at room temperature with occasional shaking. After decolourising with sulphur dioxide, the precipitate was crystallised from benzene giving the dihydrothiadiazepine-S-dioxide (87, R=H) as soft white needles m.p. 196°, identical in every respect to the material obtained by the previous method.

b) The Dihydrothiadiazepine-S-dioxide (87, R=Br). Attempts to prepare the dihydrothiadiazepine-S-dioxide (87, R=Br) by the method (a)(i) above were unsuccessful, no reaction occuring in the cold, and on heating, only the pyridazine (63, R=Br) was isolated. The dihydrothiadiazepine-S-dioxide (87, R=Br) was however obtained, using the technique (a)(ii) above, as colourless prisms (chloroform) m.p. 224-225°. (Found: C,42.1; H,2.85; N,5.95. $C_{16}H_{12}Br_2N_2O_2S$ requires C,42.1; H, 2.65; N,6.15%). νmax (nujol) 1324; 1142, 1131cm.$^{-1}$.

c) The Dihydrothiadiazepine-S-dioxide (87, R=CH_3).
This compound could be obtained either from p-methylphenacyl sulphone (86, R=CH_3) by method (a)(i) above, or from the dihydrothiadiazepine (64, R=CH_3) by the method (a)(ii) above, and crystallised as tiny colourless prisms (chloroform) m.p. 207-208°. (Found: C,66.1; H,6.0; N,8.5. $C_{18}H_{18}N_2O_2S$ requires C,66.25; H,5.6; N,8.6%). νmax (nujol) 1328, 1309; 1130cm.$^{-1}$.

Decomposition of the Dihydrothiadiazepine-S-dioxides (87, R=H; R=Br; R=CH_3).

a) 2,7-Dihydro-3,6-diphenylthiadiazepine-S-dioxide (87, R=H).
(i) The dihydrothiadiazepine-S-dioxide (87, R=H) was converted into 3,6-diphenylpyridazine in 90% yield simply by melting, cooling, and crystallisation of the product. The gases evolved turned acid dichromate paper green, and blackened lead acetate paper.
(ii) The dihydrothiadiazepine-S-dioxide (56mg.) was refluxed in ethanol (20cc.) for 8hrs.. On cooling, colourless plates (36mg.) were deposited m.p. and mixed m.p. with 3,6-diphenylpyridazine 220-221°. The infrared spectra of the two samples were superimposable.
(iii) The dihydrothiadiazepine-S-dioxide (0.2g.) was refluxed in acetic acid (10cc.) for 1hr. . Cooling, dilution with water, and crystallisation of the precipitate

from ethanol gave 3,6-diphenylpyridazine as colourless plates (o.13g.) identical in every respect to an authentic sample (mixed m.p. and infrared spectra).

(iv) The dihydrothiadiazepine-S-dioxide (0.3g.) was refluxed in ethylene glycol for 30mins., the evolved gases blackening lead acetate paper and turning acid dichromate paper green. Cooling, dilution with water and crystallisation of the precipitate from ethanol gave 3,6-diphenylpyridazine as colourless plates (0.2g.) identical in every respect (mixed m.p. and infrared spectra) to an authentic sample.

b) The dihydrothiadiazepine-S-dioxide (87, R=Br) was converted into the pyridazine (63, R=Br) in 75% yield by method (a)(iii) above.

c) The dihydrothiadiazepine-S-dioxide (87, R=CH_3) was converted into the pyridazine (63, R=CH_3) in 78% yield by method (a)(iii) above.

Attempted Decomposition of Phenoxathiin-S-monoxide.

Phenoxathiin-S-monoxide[85] (0.2g.) was heated with copper bronze (0.4g.) to 340° (in a metal bath) for 1hr.. After cooling, the mixture was extracted with hot acetone, and the product obtained crystallised from methanol as colourless rods (0.13g.) m.p. and mixed m.p. with phenoxathiin 54-56°. The infrared spectra of the two samples were identical.

Attempted Decomposition of Phenoxathiin-S-dioxide.

Phenoxathiin-S-dioxide[85] (0.2g.) was heated with copper bronze (0.4g.) at 340° (in a metal bath) for 1hr.. After cooling, the mixture was extracted with hot acetone, and the product crystallised from ethanol as colourless needles (0.15g.) m.p. and mixed m.p. with starting material 144-146°. The infrared spectra of the two samples were superimposable.

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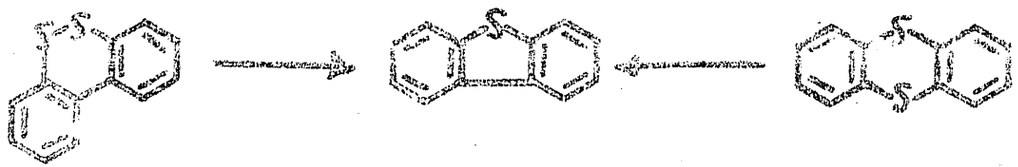

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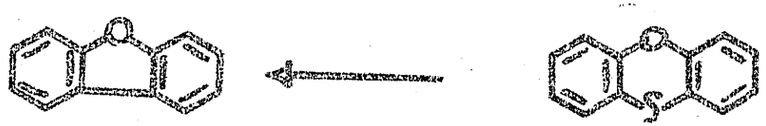

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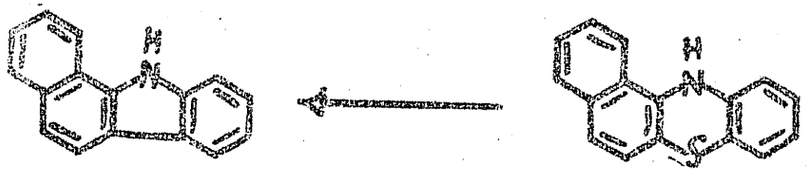

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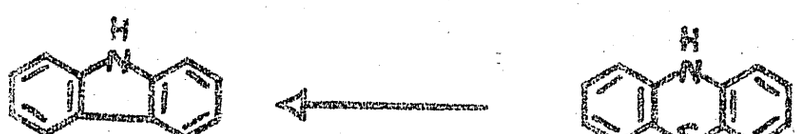

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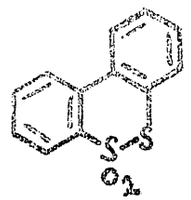

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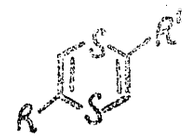

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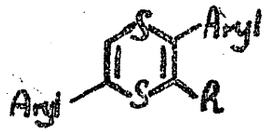

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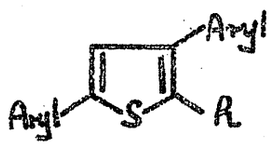

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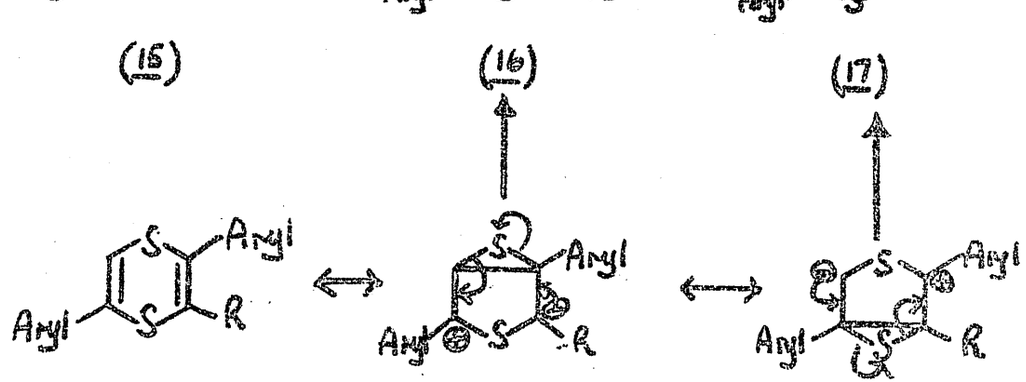

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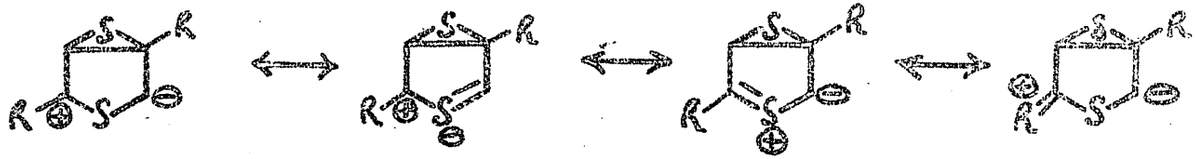

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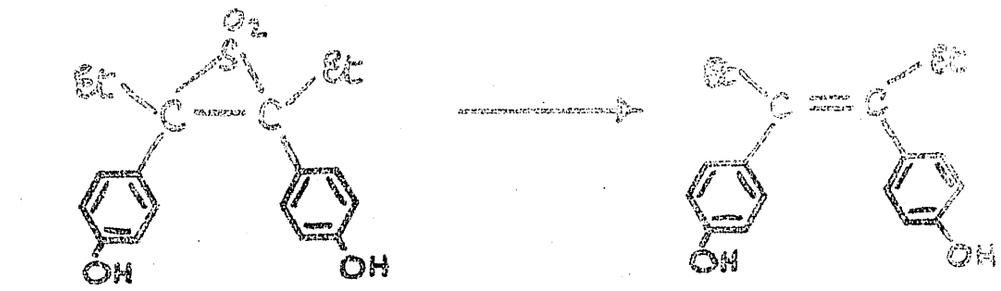

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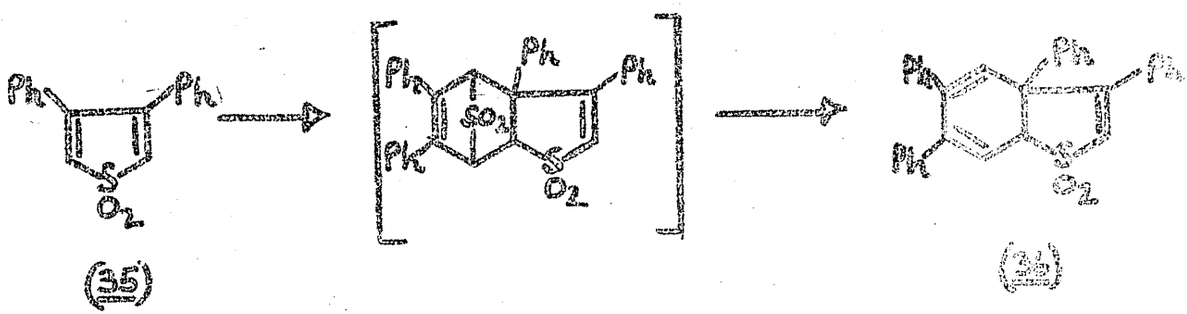

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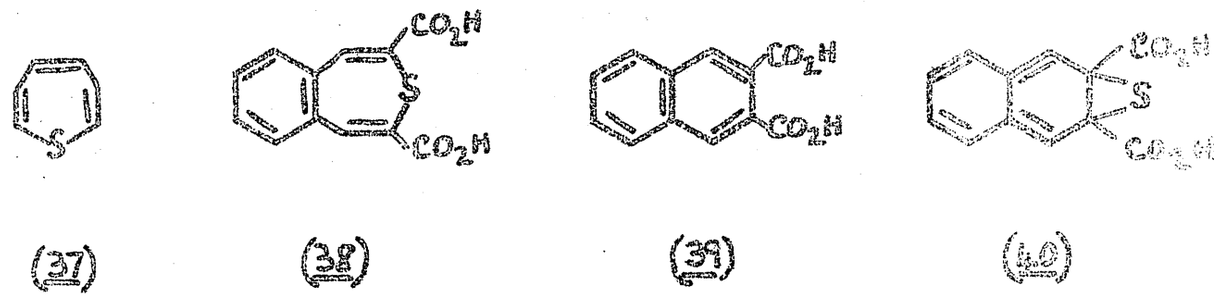

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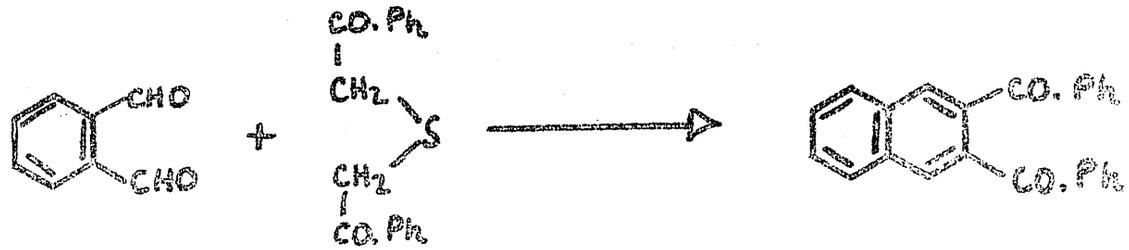

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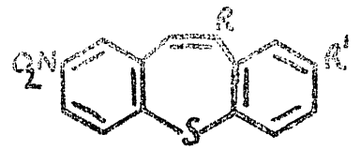

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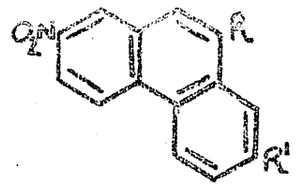

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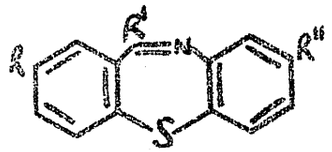

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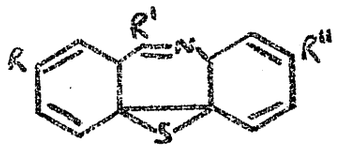

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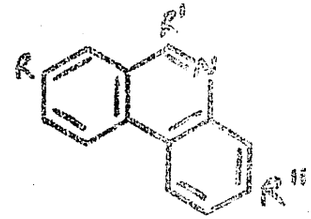

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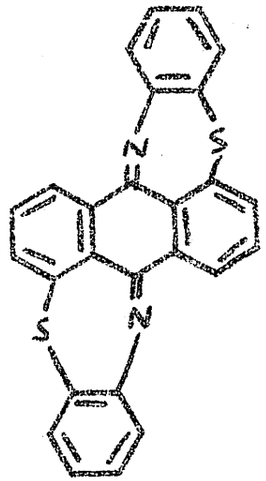

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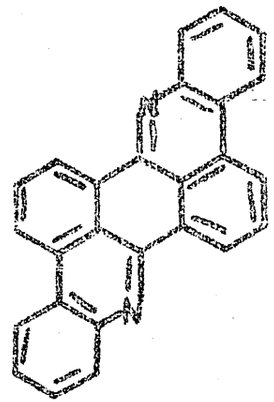

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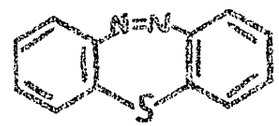

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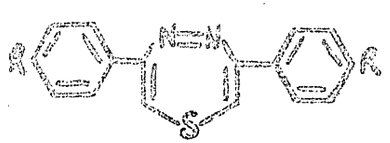

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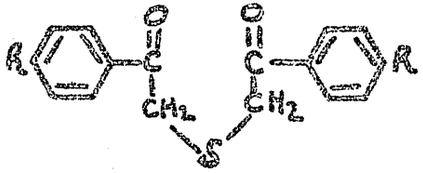

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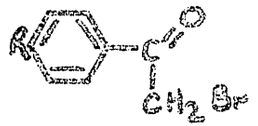

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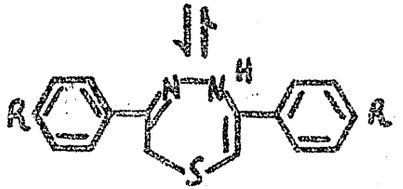

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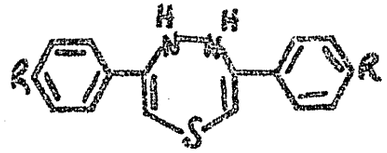

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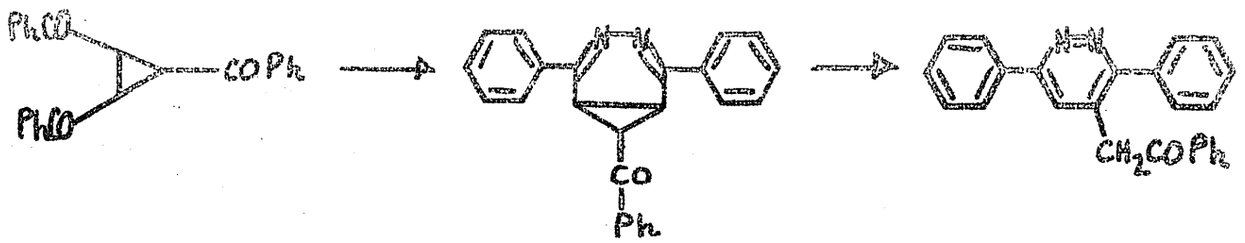

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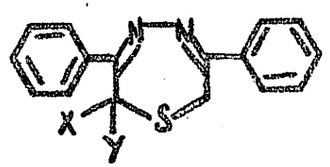

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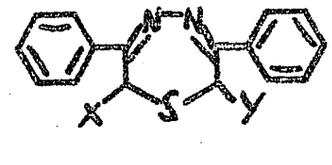

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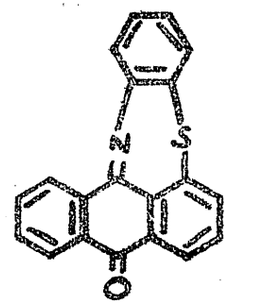

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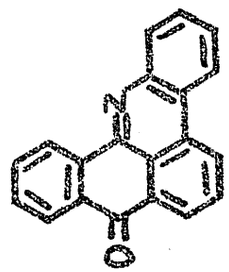

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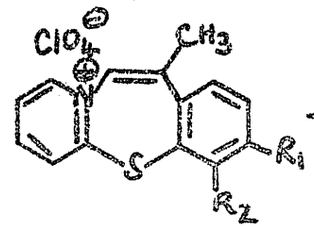

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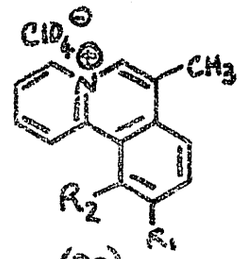

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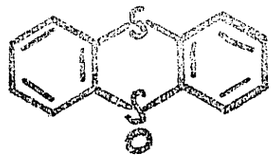

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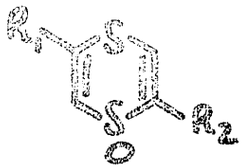

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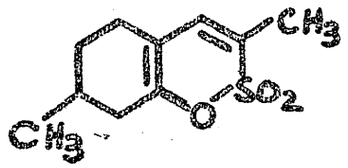

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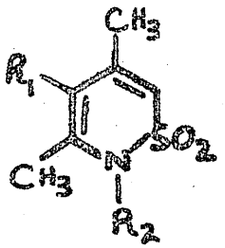

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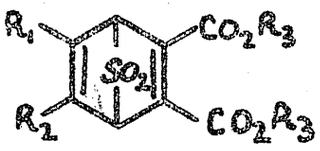

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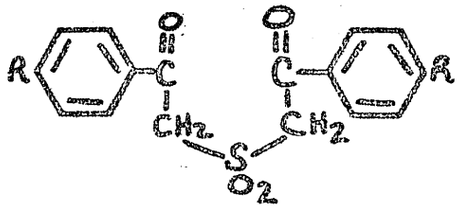

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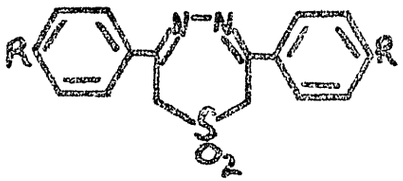

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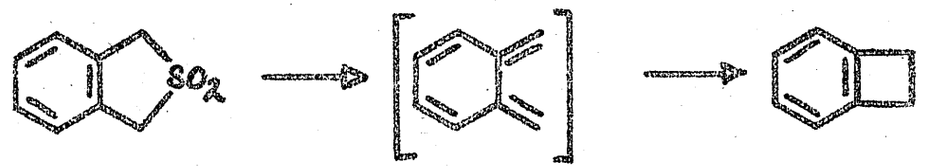

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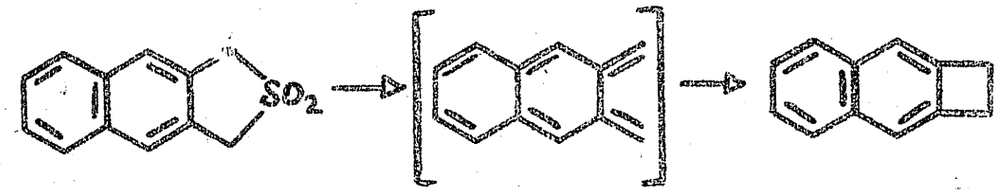

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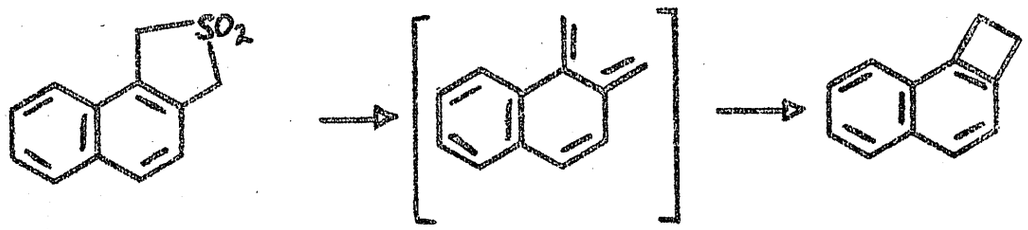

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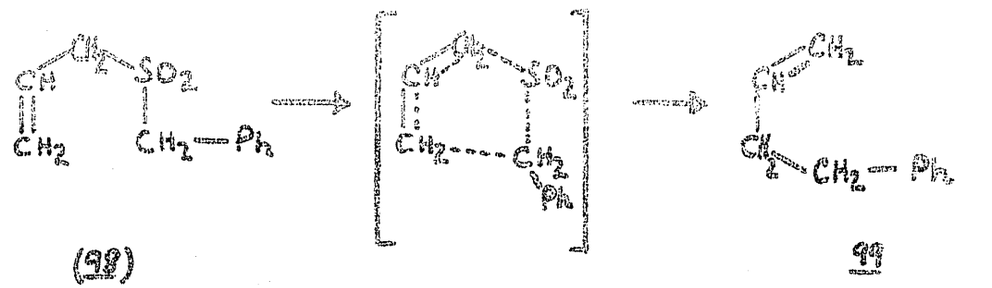

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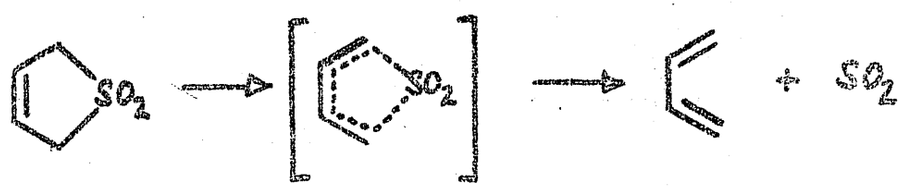

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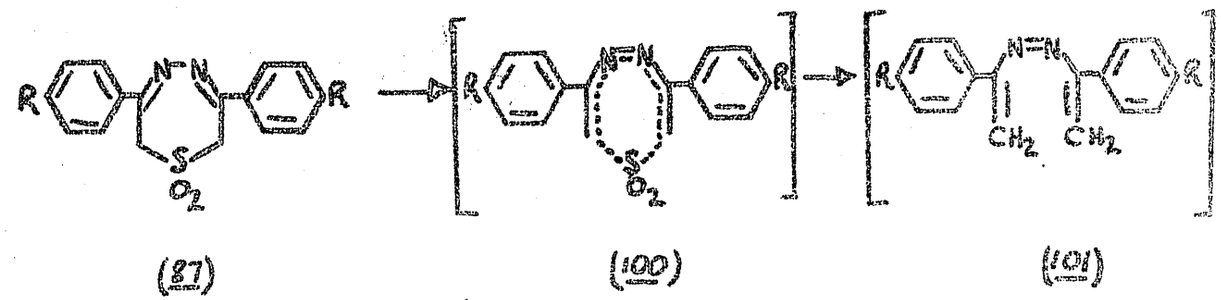

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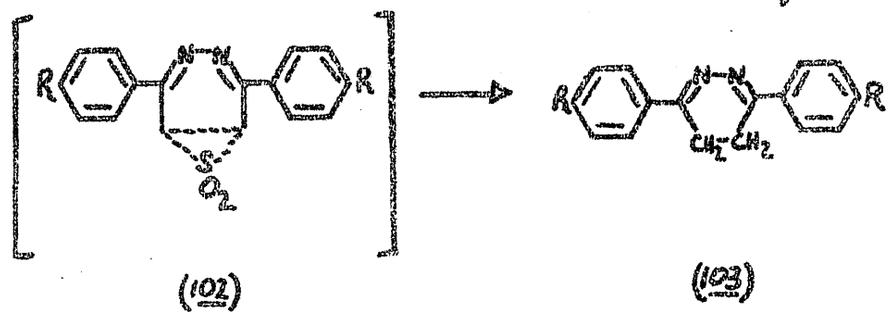

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CHAPTER 2

"RING CONTRACTIONS OF SEVEN- TO FIVE-MEMBERED SYSTEMS TYPE A"

INTRODUCTION

A variety of reagents can be used for the oxidation of sulphides to sulphones[1]. As noted in the previous chapter, the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) for example, were oxidised to the dihydrothiadiazepine-S-dioxides (2, R=H; R=Br; R=CH_3) by potassium permanganate in acetic acid. Another well known method for the oxidation of sulphides to sulphones employs 30% hydrogen peroxide in acetic acid. This reagent has also caused[2] extrusion of sulphur from the thiazepine (3) giving the acridine (4); and the pyrido(2,1-b)benzo(f)(1,3)-thiazepinium system (5) being converted into benzo(a)-quinolizium salts (6)[3].

Since the dihydrothiadiazepine-S-dioxides (2, R=H; R=Br; R=CH_3) could readily be obtained by oxidation of the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) with potassium permanganate in acetic acid, it seemed probable that hydrogen peroxide in acetic acid would effect similar oxidation with or without extrusion of sulphur, and we therefore investigated these possibilities.

PART 1.

DISCUSSION.

Initial experiments on oxidation of the dihydrothiadiazepine (1, R=H) with 30% hydrogen peroxide in acetic acid at 95° for one hour gave no water insoluble products, a remarkable result in the circumstances. However when the dihydrothiadiazepine (1, R=H) was refluxed in ethanol with 30% hydrogen peroxide, dilution with water gave a solid product, crystallising from benzene as colourless prisms m.p. 198-199° . This compound was found to be free of sulphur. Infared spectra and mixed melting point showed that it was quite distinct from 3,6-diphenylpyridazine (7, R=H), the expected product of extrusion of sulphur from the dihydrothiadiazepine (1, R=H).

The compound was a weak base, affording a bright yellow picrate, m.p. 160°, and with dry hydrogen chloride in anhydrous ether, forming an unstable hydrochloride m.p. 231°, although in aqueous mineral acid there was no evidence of salt formation. The compound, with acetic anhydride, gave a mono-acetyl derivative m.p. 84-85° and the problem presented at this stage by the analytical results is shown in table 1.

TABLE 1.

	Base			Acetyl			Picrate		
	C	H	N	C	H	N	C	H	N
Found	82.2	5.4	12.5	78.2	5.3	10.4	56.85	3.3	15.2
$C_{16}H_{14}N_2$	82.0	6.0	12.0	78.2	5.85	10.15	57.0	3.7	15.1
$C_{16}H_{12}N_2$	82.7	5.2	12.1	78.8	5.15	10.2	57.25	3.3	15.2
$C_{15}H_{12}N_2$	81.8	5.5	12.7	77.8	5.4	10.7	56.1	3.35	15.6

A C_{16} formula seemed by far the more probable. The presenee of an acetylatable hydrogen atom excluded all purely aromatic, six-membered diaza-systems. Moreover the infrared spectrum (KCl disc) of the base showed strong absorption at 2850 and 1464cm.$^{-1}$ indicative of the presence of a methylene group.

Vigorous oxidation of the base with potassium permanganate in t-butanol gave benzoic acid in over 50% yield, thereby providing assurance that both phenyl groups were still attached to carbon. The compound was resistant not only to catalytic hydrogenation, but also to dehydrogenation (yellow mercuric oxide, chloranil, nitrous acid[4,5] and alkaline hydrogen peroxide[6] were tried without success) indicating an aromatic nucleus. The instability of

dihydropyridazines appears to be fairly well established[4,5,6] and this was confirmed by experience when 3,6-diphenyl-pyridazine (7, R=H) and not its dihydride was obtained from diphenacyl and hydrazine hydrate under mild conditions. Therefore structures such as (8) could be excluded, and similar arguments lead to the exclusion of structures such as (9) which are likewise unstable[7]. Hence a five-membered heterocycle with either a pyrrole or a pyrazole system was indicated.

Aminated pyrrole structures such as (10) are untenable since there is no evidence of an $-NH_2$ group in the infrared spectrum. Such a compound would also be expected to react with nitrous acid, and this compound did not.

A pyrazole structure on the other hand is consistent with the observed facts, the feeble basicity; mono-acetylation to a neutral tertiary amide and the ease of hydrolysis of this acetyl derivative. Furthermore the infrared spectra of the acetyl derivative (nujol and KCl disc) show an abnormally high amide carbonyl frequency at 1735cm.$^{-1}$. Otting[8] has shown that in the series pyrrole, iminazole, 1,3,4-triazole and 1,2,3,4-tetrazole, the frequency of the carbonyl absorption of the N-acetyl derivatives changes as shown in table 2.

TABLE 2.

Compound $R = COCH_3$				
$\nu(C=O)$	1732	1747	1765	1779 cm^{-1} (KCl disc)

Hence carbonyl absorption at 1735cm^{-1} could possibly fit an N-acetyl pyrazole.

In terms of a C_{16} formula, the base should therefore be a methyldiphenylpyrazole (11) or a benzylphenylpyrazole (12).

It was at this point that the probability of a C_{16} formula came seriously into question. Conceivably in the infrared spectrum of the base, strong absorption at 2850 and 1464cm^{-1} can be due to a methylene or a methyl group. In the spectrum of the acetyl derivative however, the strong absorption at 2850cm^{-1} disappears, and even the methyl group absorption (appropriate to the acetyl group) is not evident. Moreover, comparison with the recorded infrared spectra of pyrazole[9], iminazole and 1,3,4-triazole[10] shows that the absorption at 2850and 1464cm^{-1} are in fact characteristic of the >NH and >C=N- groupings in the heterocyclic nucleus. There is therefore no evidence for a methylene or a methyl group in the base, and the C_{16}

formula had to be abandoned.

With attention now directed to the C_{15} formula, the problem was immediately solved, the compound being recognised as the known 3,5-diphenylpyrazole (13, R=H). This was fully confirmed by a known synthesis[11] (from chalcone dibromide by reaction with hydrazine) and direct comparison of the samples, their infrared spectra, and the derivatives from the two sources. Ironically too, renewed analysis of the base gave results in better accord with its structure, although the low value for nitrogen, a factor in the original preference for a C_{16} formula, still persisted.

The reaction has been successfully extended to two other dihydrothiadiazepines (1, R=Br; R=CH_3) giving similar yields (@ 75%) of the respective pyrazoles (13, R=Br; R=CH_3). Neither of these pyrazoles has been described before. They have m.p.'s 262° and 236-237° respectively, and show the characteristic pyrazole infrared spectra (KCl discs) of νmax 2855 and 1444cm.$^{-1}$ (13, R=Br); and 2850 and 1462cm.$^{-1}$ (13, R=CH_3).

Similarly their acetyl derivatives show the high amide carbonyl peak at 1735 and 1730cm.$^{-1}$ respectively.

Therefore by this method of oxidation, the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) are converted into the 3,5-diarylpyrazoles (13, R=H; R=Br; R=CH_3) with

the loss of the sulphur atom and the methylene group.

In order to suggest a mechanism for the reaction, it was necessary to define how the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) lost the sulphur atom and the methylene group. Since during the reaction, a gas is evolved which blackens lead acetate paper, but does not smell exactly like hydrogen sulphide, it was hoped that the fragments of the reaction could be deduced from a knowledge of this evolved gas. This gas, when passed in a stream of nitrogen through (a) dimedone solution to detect formaldehyde; (b) 4% mercuric cyanide solution to detect methyl mercaptan[12]; (c) 3% mercuric chloride solution to detect dimethyl sulphide[12], produced no change in solutions (a) or (c) but gave a black colloidal precipitate in solution (b). Mercury dimethyl mercaptide should be a white precipitate m.p. 174-175° [12] so the precipitate obtained could be this compound only if contaminated with mercuric sulphide, or simply mercuric sulphide if a component of the evolved gas is indeed hydrogen sulphide. This problem has not been satisfactorily solved as yet.

In looking for an intermediate in the conversion of the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) to the pyrazoles (13, R=H; R=Br; R=CH_3), it seems probable that the action of hydrogen peroxide on the dihydrothiadiazepines

would be to effect oxidation of the sulphur atom. The products of such an oxidation would therefore be the dihydrothiadiazepine-S-monoxides (14, R=H; R=Br; R=CH_3) or the S-dioxides (2, R=H; R=Br; R=CH_3).

Since the dihydrothiadiazepine-S-dioxide (2, R=H) can be converted into 3,6-diphenylpyridazine (7, R=H) by reflux in alcohol, the S-dioxides (2, R=H; R=Br; R=CH_3) cannot be intermediates in the conversion of the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) into the pyrazoles (13, R=H; R=Br; R=CH_3). Attention therefore turned to the preparation of the dihydrothiadiazepine-S-monoxide (14, R=H).

The S-monoxide (14, R=H) was prepared by oxidation of the dihydrothiadiazepine (1, R=H) with hydrogen peroxide in acetic acid at room temperature for one hour. It was later found that brief treatment of the dihydrothiadiazepine (1, R=H) with hydrogen peroxide in hot acetic acid produces immediate oxidation to the S-monoxide (14, R=H), which can be isolated in good yield by prompt dilution with water. This is the preferred operation since it overcomes the disadvantage of having to use large volumes of cold acetic acid to dissolve small amounts of the dihydrothiadiazepine (1, R=H).

The products of these oxidations were identical, crystallising from ethanol as soft white needles m.p. 181°

(dec.). Elemental analysis fitted the S-monoxide structure (14, R=H). The infrared spectrum (nujol) showed absorption at 1056cm.$^{-1}$ characteristic of the sulphoxide group. The compound could also be oxidised to the dihydrothiadiazepine-S-dioxide (2, R=H) by potassium permanganate in acetic acid.

When the S-monoxide (14, R=H) was refluxed with hydrogen peroxide in alcohol for one hour, the product obtained was 3,5-diphenylpyrazole (13, R=H), and the reaction proceeded with evolution of a gas which blackened lead acetate paper.

The dihydrothiadiazepine-S-monoxide (14, R=H) could also be converted into 3,5-diphenylpyrazole (13, R=H) by one hour's reflux in either aqueous ethanol or ethanol containing a little mineral acid. In neither case was the yield comparable to that obtained in the presence of hydrogen peroxide. In all of these experiments, a control experiment, refluxing a sample of the S-monoxide (14, R=H) in alcohol was run side-by-side with the actual experiment, and in every case was recovered unchanged at the end of the reflux.

Since hydrogen peroxide in acetic acid at room temperature oxidises the dihydrothiadiazepine (1, R=H) to the S-monoxide (14, R=H), it was thought that if such an experiment were taken to this stage, when the S-monoxide

(14, R=H) was known to be present, then a short period of heating should produce the dihydrothiadiazepine-S-dioxide (2, R=H). This was not the case, the product isolated was not the S-dioxide (2, R=H) but 3,5-diphenylpyrazole (13, R=H). It was then found that short heating of the S-monoxide (14, R=H) in acetic acid alone afforded 3,5-diphenylpyrazole (13, R=H).

In view of these results, it seemed necessary to look at the reaction of the dihydrothiadiazepine (1, R=H) with hydrogen peroxide in acetic acid more closely. It was found that if hydrogen peroxide was added to a solution of the dihydrothiadiazepine (1, R=H) in acetic acid at 95°, then a crystalline precipitate of the dihydrothiadiazepine (1, R=H) resulted. If heating was continued until the precipitate just dissolved, and the reaction stopped at this point by cooling and dilution with water, then the product obtained was the S-monoxide (14, R=H). This oxidation is therefore virtually instantaneous under these conditions. Further experiments in this manner showed that by stopping both the heating and the reaction 5mins. after the addition of the hydrogen peroxide, 3,5-diphenylpyrazole (13, R=H) is obtained. Thus the action of hydrogen peroxide in acetic acid on the dihydrothiadiazepine (1, R=H) is to produce immediate oxidation to the

S-monoxide (14, R=H) which is rapidly converted into 3,5-diphenylpyrazole (13, R=H).

Thus under a variety of conditions, the dihydrothiadiazepine (1, R=H) is convertible into 3,5-diphenylpyrazole (13, R=H) with the S-monoxide (14, R=H) as intermediate.

Several mechanisms can be offered for the conversion of the dihydrothiadiazepine-S-monoxide (14, R=H) into 3,5-diphenylpyrazole (13, R=H), none of which however can be selected as representing the precise reaction course. For example, sulphoxides such as (15) are known[13,14] to cleave to a mercaptan (16) and an aldehyde (17) or some derived product of hemimercaptal formation[15], under mildly acid conditions. Such a cleavage (scheme A) of the S-monoxide (14, R=H) affords the mercaptoaldehyde (18, R=H) which, by addition of the thiol group across one of the >C=N- bonds, might give the dihydro-1,3,4-thiadiazine aldehyde (19, R=H). By rearrangement as shown, this aldehyde could eliminate thioformic acid and form 3,5-diphenylpyrazole (13, R=H). This scheme does not explain why the yield of 3,5-diphenylpyrazole (13, R=H) should decrease in the absence of hydrogen peroxide i.e. when the S-monoxide (14, R=H) is refluxed in ethanol containing mineral acid. The value of hydrogen peroxide might be explained by a sequence of reactions such as scheme B.

Here the aldehyde (19) rearranges as shown to form the thioaldehyde (20), which could undergo oxidation to a thioacid of type (21), decarboxylation then producing 3,5-diphenylpyrazole (13, R=H) and carbonyl sulphide.

It is of interest to note that the mechanism of the oxidation of sulphoxides to sulphones by peracids is thought to involve a nucleophilic attack by the peracid upon the sulphoxide[14,15]. In scheme C, such a nucleophilic attack on the S-monoxide (14, R=H) could achieve bond rearrangement with formation of 3,5-diphenylpyrazole (13, R=H) as shown. This scheme should not be acid catalysed, and so the conversion of the S-monoxide (14, R=H) into 3,5-diphenylpyrazole by refluxing in ethanol containing some mineral acid, or by heating in acetic acid, cannot be explained by this route. A more complete knowledge of the fate of the methylene group and the sulphur atom that are lost could possibly solve these problems.

Initial experiments on oxidation of the dihydrothiadiazepine (1, R=H) with hydrogen peroxide in acetic acid had given only water soluble products, but it has now been shown that one can in fact isolate the dihydrothiadiazepine-S-monoxide (14, R=H) and then 3,5-diphenylpyrazole (13, R=H) from such an oxidation. These products are water insoluble and their conversion into water soluble products on longer

treatment must involve destruction of the 3,5-diphenylpyrazole. Consequently a series of such hydrogen peroxide/acetic acid oxidation experiments were conducted on 3,5-diphenylpyrazole (13, R=H). Fractions were removed at definite time intervals, and the products at these stages isolated by cooling and diluting the portions with water. Examination of the products showed that after 45mins. treatment, only a small amount of water insoluble material survived, and that this was not the starting pyrazole (13, R=H), but was identified as 2,5-diphenyl-1,3,4-oxadiazole (22). Isolation of the water soluble products showed that these were dibenzoyl hydrazine (23) and benzoic acid. The yields of the oxadiazole (22) and dibenzoyl hydrazine (23) were small, 8% and 11% respectively, the major product being benzoic acid. Repetition of the oxidation of the dihydrothiadiazepine (1, R=H) with hydrogen peroxide in acetic acid for one hour, gave a small amount of water insoluble oxadiazole (22), and dibenzoyl hydrazine and benzoic acid as water soluble fragments.

This easy oxidation of the pyrazole system is quite surprising. Pyrazole is normally regarded as a highly aromatic compound, and as such, strongly resistant to oxidation[17,18,19]. In our own experience, 3,5-diphenyl-

pyrazole (13, R=H) was not completely oxidised to benzoic acid by refluxing with a large excess of potassium permanganate in t-butanol for six hours. We have not attempted to find whether this easy oxidation with hydrogen peroxide in acetic acid is a general reaction or one which is peculiar to 3,5-diarylpyrazoles (13), nor have we examined the precise course of this particular oxidation.

Dibenzoyl hydrazine (23) is known to yield 2,5-diphenyl-1,3,4-oxadiazole (22) by dehydration, but if here the two compounds are products of a single oxidation pathway, then hydration (ring opening) of the oxadiazole (22) would appear to be the more acceptable course. Hydrogen peroxide oxidises a hetero-sulphur atom more readily than a hetero-nitrogen atom (e.g. formation of the S-monoxide (14, R=H) from the dihydrothiadiazepine (1, R=H)), but both for the pyrazole (13, R=H) and for the oxadiazole (22) degradations, the intervention of N-oxides is possible and unexplored.

PART 2.

It has already been noted that in the conversion of a dihydrothiadiazepine (1, R=H; R=Br; R=CH_3) into a 3,5-diarylpyrazole (13, R=H; R=Br; R=CH_3), a gas is evolved, the nature of which has not been determined. With this in mind, the synthesis of the dihydrothiadiazepine (24) was attempted, for if this compound could be converted into a pyrazole, it should provide a fragment analogous to the volatile fragments in the previous cases, but of higher molecular weight, hence facilitating detection.

The appropriate keto-sulphide, desyl sulphide (25), did not react with hydrazine in acetic acid at room temperature, and at higher temperatures, reacted with evolution of hydrogen sulphide giving a yellow oil which retained a carbonyl peak in the infrared, but could not be crystallised.

The sulphide (25) reacted with hydrazine in alcohol to give a mixture of two compounds, in variable yield, again accompanied by evolution of hydrogen sulphide. The two products were generally separated by fractional crystallisation, although some experiments afforded one of the products almost free of the other. One compound crystallised from ethanol as bright yellow prisms m.p. 164° and was quickly identified as benzylphenyl ketazine (26) by

comparison with an authentic sample.

The identification of the other product proved more difficult. It contained nitrogen but no sulphur, and had m.p. 152-153°. The infrared spectra (nujol and KCl disc) had νmax at 3400, 3300 and 3200cm^{-1} perhaps due to some type of >NH or $-NH_2$ group in the molecule; νmax at 1640cm^{-1}, possibly due to a carbonyl group, the νmax being lowered by some feature in the molecule other than aromatic conjugation; and νmax at 1550cm^{-1}, possibly a >C=N- linkage. The compound was only feebly basic, forming a picrate which dissociated on recrystallisation. A molecular weight of 224 (mass spectrum) in conjunction with analytical data, suggested a molecular formula $C_{14}H_{12}N_2O$. Consideration of possible structures suggested that the compound was benzil monohydrazone (27), and this was confirmed by comparison with an authentic sample. The low carbonyl frequency is therefore due to hydrogen bonding. Thus treatment of desyl sulphide (25) with hydrazine in alcohol affords a mixture of benzylphenyl ketazine (26) and benzil monohydrazone (27).

Schonberg and Iskander[20] have shown that treatment of desyl sulphide (25) with base gives desoxybenzoin and benzilic acid. It is therefore conceivable that hydrazine could similarly hydrolyse desyl sulphide (25) and that the

desoxybenzoin formed could then react with hydrazine to give benzylphenyl ketazine (26). Furthermore, since the benzilic acid detected by Schonberg and Iskander must be derived from benzil as intermediate, then in the present reaction, the benzil would be trapped by reaction with hydrazine as benzil monohydrazone (27). Alternatively benzil monohydrazone (27) may be formed without prior formation of benzil by the mechanism shown.

The reactivity of the dihydrothiadiazepine-S-dioxides (2) also prompted an attempt to prepare the dihydrothiadiazepine-S-dioxide (28), by reaction of hydrazine with desyl sulphone (29). Desyl sulphone (29) was quantitatively recovered after treatment with hydrazine in acetic acid at room or reflux temperature for a period of hours. However on introduction of hydrazine to a suspension of desyl sulphone (29) in boiling alcohol, the sulphone rapidly dissolved. After a one hour reflux, dilution with water gave a white crystalline compound m.p. 149-150°, identical in every respect to an authentic sample of dibenzyl sulphone (30). Repetition of the experiment using dilute potassium hydroxide instead of hydrazine gave the same product. The reaction is therefore a simple basic hydrolysis of the β-keto-sulphone, desyl sulphone (29), and no dihydrothiadiazepine-S-dioxide was obtained.

In concluding this chapter, a short account will be made of an attempt to prepare unsymmetrical diaryl sulphides (31), from which we hoped to obtain unsymmetrical 3,6-diaryldihydrothiadiazepines. This scheme involved preparation of an α-mercapto ketone such as phenacyl mercaptan (32). The best method[21] of obtaining phenacyl mercaptan (32) is by reaction of phenacyl chloride with sodium thiosulphate, and hydrolysis of the derived Bunte salt with hydrochloric acid affording, amongst other products, the mercaptan (32) as a smelly yellow oil. Groth[22] could not obtain phenacyl mercaptan (32) by the standard method of hydrolysis of the corresponding xanthate, and here, attempts to hydrolyse phenacyl xanthate or phenacyl benzylxanthate to the mercaptan (32), also failed.

Using phenacyl mercaptan (32) obtained by the Bunte salt method, reaction in ethanolic sodium ethoxide with p-bromophenacyl bromide gave a white crystalline product m.p. 135-136° having a single carbonyl peak in the infrared at 1670cm.$^{-1}$. The compound analysed for the disulphide (33) and so was not investigated any further.

A similar reaction with desyl chloride yielded a small amount of a white crystalline compound which did not contain sulphur, and is of unknown constitution.

Schonberg and Iskander[20] have shown that desyl

mercaptan can be hydrolysed in alcohol with 10% sodium hydroxide to desoxybenzoin and sulphur. Similar alkali lability with other α-mercapto ketones such as phenacyl mercaptan (32) could therefore be a hindrance to the formation of unsymmetrical sulphides.

EXPERIMENTAL.

Oxidation of 2,7-dihydro-3,6-diphenylthiadiazepine (1, R=H).

Hydrogen peroxide (50cc.) was added to a solution of the dihydrothiadiazepine (8.6g.) in hot ethanol (450cc.), and the mixture was refluxed for six hours. The gases evolved during the reflux blackened lead acetate paper. The solution was evaporated to smaller bulk, diluted with water, and the resulting precipitate crystallised from benzene as colourless prisms (4.4g.) m.p. 198-199°. (Found; (1) C,82.2; H,5.4; N,12.5%. (2) C,81.55; H,5.2; N,12.65%. See Table 1, p. 47.). νmax (KCl disc) 2850 and 1464cm.$^{-1}$.

Derivatives of the Oxidation Product.

The picrate crystallised from benzene as canary yellow needles m.p. 159-160°. (See Table 1, p. 47 for analysis data). The compound was acetylated by boiling with acetic anhydride for a few mins., the product crystallising from petrol as white plates m.p. 83-84°. (See Table 1, p. 47 for analysis). νmax (KCl disc) 1735cm.$^{-1}$.

The acetyl derivative was insoluble in dilute sodium hydroxide or dilute hydrochloric acid, but was rapidly hydrolysed with either warm dilute or cold conc. hydrochloric acid.

A hydrochloride m.p. 231° was obtained by passing dry hydrogen chloride into an ethereal solution of the base.

The hydrochloride was hydrolysed to the starting base by rubbing with water.

Oxidation of the Unknown Base with Potassium Permanganate.

A mixture of the base (0.28g.); potassium permanganate (2g.); water (10cc.) and t-butanol (10cc.) was refluxed for 6hrs.. After decolourisation with sulphur dioxide, the t-butanol was evaporated down, and the mixture allowed to cool. The solid obtained was crystallised from benzene as colourless prisms (60mg.) m.p. and mixed m.p. with starting material 197-199°.

The filtrate was acidified and the solid obtained, after standing overnight, sublimed, giving a white crystalline solid (95mg.) m.p. and mixed m.p. with benzoic acid 118-120°.

Attempted Dehydrogenations of the Unknown Base.

Attempts were made using standard literature procedure to dehydrogenate the unknown base with mercuric oxide; nitrous acid[4,5]; chloranil; and alkaline hydrogen peroxide[6], but in all cases the starting base was recovered in high yield.

Hydrogenation in acetic acid with 10% palladium charcoal as catalyst was also unsuccessful.

Reaction of Diphenacyl with Hydrazine Hydrate.

Excess hydrazine hydrate was added to a solution of diphenacyl[23] (120mg.) in glacial acetic acid (6cc.). After brief heating, dilution with water gave a yellow precipitate

which crystallised from ethanol as colourless plates (80mg.) m.p. and mixed m.p. with 3,6-diphenylpyridazine 219-221°.

3,5-Diphenylpyrazole (13, R=H).

3,5-Diphenylpyrazole (13, R=H) was obtained, by the method of Freudenberg and Stoll[11], as colourless prisms m.p. 198-199°. A mixed m.p. of this sample and the base obtained by hydrogen peroxide oxidation of the dihydrothiadiazepine (1, R=H), was also 198-199°, and their respective infrared spectra were superimposable.

Oxidation of the Dihydrothiadiazepine (1, R=Br).

Oxidation of the dihydrothiadiazepine (1, R=Br) under the conditions described for the parent dihydrothiadiazepine (1, R=H) gave the pyrazole (13, R=Br) as soft white needles (benzene) m.p. 262° in 75% yield. (Found: C,47.75; H,2.45; N,7.15. $C_{15}H_{10}Br_2N_2$ requires C,47.6; H,2.65; N,7.4%). ν max (KCl disc) 2855 and 1444cm^{-1}.

The acetyl derivative of the pyrazole (13, R=Br) crystallised from petrol as fine white needles m.p. 175-176°. (Found: C,48.65; H,2.9; N,6.95. $C_{17}H_{12}Br_2N_2O$ requires C,48.6; H,2.9; N,6.7%). ν max (KCl disc) 1735cm^{-1}.

Oxidation of the Dihydrothiadiazepine (1, R=CH_3).

Oxidation of the dihydrothiadiazepine (1, R=CH_3) under the conditions described for the parent dihydrothiadiazepine (1, R=H) gave the pyrazole (13, R=CH_3) as white needles

(benzene) m.p. 236-237° in 70% yield. (Found: C,82.15; H,6.3; N,11.4. $C_{17}H_{16}N_2$ requires C,82.2; H,6.5; N,11.3%). νmax (KCl disc) 2850 and 1462cm.$^{-1}$.

The acetyl derivative of the pyrazole (13, R=CH_3) crystallised from petrol as rosettes of white needles m.p. 83-84°. (Found: C,78.3; H,6.05; N,9.55. $C_{19}H_{18}N_2O$ requires C,78.6; H,6.25; N,9.65%). ν max (KCl disc) 1730cm.$^{-1}$.

2,7-Dihydro-3,6-diphenylthiadiazepine-S-monoxide (14, R=H). The dihydrothiadiazepine (1, R=H) (2g.) was dissolved in hot acetic acid (150cc.), then cooled to room temperature. Hydrogen peroxide (20cc.) was added, the mixture became cloudy and some solid crystallised out, and this mixture was allowed to stand 1hr. at room temperature with occasional shaking. Dilution with water gave a white precipitate (1.6g.)which, after complete drying, crystallised from ethanol affording the S-monoxide (14, R=H) as white needles m.p. 181° (dec.). (Found: C,68.05; H,4.85. $C_{16}H_{14}N_2OS$ requires C,68.05; H,5.0%). ν max (nujol) 1056cm.$^{-1}$.

Oxidation of the S-monoxide (14, R=H).

A solution of potassium permanganate (0.4g.) in water was added to a solution of the S-monoxide (14, R=H) (0.2g.) in acetic acid (10cc.), and the mixture was allowed to stand at room temperature 30mins. with occasional shaking. After decolourising with sulphur dioxide, the precipitate

obtained by dilution with water was crystallised from benzene as white needles (0.17g.) m.p. and mixed m.p. with the S-dioxide (2, R=H) 195°. The infrared spectra of the two samples were superimposable.

S-monoxide (14, R=H) to 3,5-diphenylpyrazole (13, R=H).

a) The S-monoxide (14, R=H) (100mg.) was refluxed in ethanol (5cc.) with hydrogen peroxide (0.25cc.) for 1hr.. The gases evolved blackened lead acetate paper. The pale yellow solution was diluted with water, the resulting precipitate crystallised from benzene as colourless prisms (65mg.) m.p. and mixed m.p. with 3,5-diphenylpyrazole 198-199°. The infrared spectra were superimposable.

b) The S-monoxide (14, R=H) (104mg.) was refluxed in ethanol (5cc.) containing water (1cc.) for 1hr. The gases evolved blackened lead acetate paper. Dilution with water gave a white precipitate which crystallised from benzene as colourless prisms (32mg.) m.p. and mixed m.p. with 3,5-diphenylpyrazole 198-200°. The infrared spectra were superimposable.

c) The S-monoxide (14, R=H) (96mg.) was refluxed in ethanol (5cc.) containing dilute hydrochloric acid (5 drops) for 1hr.. The solution became yellow-brown in colour, and the gases evolved blackened lead acetate paper. Dilution with water and crystallisation of the precipitate from

benzene gave colourless prisms (18mg.) m.p. and mixed m.p. with 3,5-diphenylpyrazole 195-198°. The infrared spectra were superimposable.

d) The S-monoxide (14, R=H) (85mg.) was heated in glacial acetic acid (4cc.) on the steam bath for 10mins., the solution rapidly developing a red colour. Dilution with wa ter and crystallisation of the precipitate from benzene gave colourless prisms (38mg.) m.p. and mixed m.p. with 3,5-diphenylpyrazole 198-199°. The infrared spectra were superimposable.

The Dihydrothiadiazepine (1, R=H) with Hydrogen Peroxide in Acetic Acid.

a) The dihydrothiadiazepine (1, R=H) (0.5g.) was dissolved in warm acetic acid (40cc.), the solution cooled to room temperature, and hydrogen peroxide (5cc.) added, and the mixture stood 1hr. with occasional shaking. The mixture was then heated on the steam bath for 15mins., (an orange-red colour developed), diluted with water, and the precipitate crystallised from benzene as colourless prisms (0.25g.) identical in every respect, m.p. and mixed m.p. (198-199°) and infrared spectra, to 3,5-diphenylpyrazole.

b) 1min.'s Heating.

The dihydrothiadiazepine (1, R=H) (100mg.) was dissolved in hot acetic acid (2.5cc.) and hydrogen peroxide (1cc.)

added, giving a white precipitate of starting material. The mixture was heated until this precipitate just dissolved (@ 1min.), and the solution then diluted with cold water. The precipitate obtained was dried and crystallised from ethanol as soft white needles (82mg.) m.p. and mixed m.p. with the dihydrothiadiazepine-S-monoxide (14, R=H) 181° (dec.). The infrared spectra were identical.

c) 5mins. Heating.

The dihydrothiadiazepine (1, R=H) (86mg.) was dissolved in hot acetic acid (2.5cc.), hydrogen peroxide (0.8cc.) added, and the mixture was heated on the steam bath 5mins.. Dilution with water and crystallisation of the precipitate from benzene gave colourless prisms (46mg.) identical in every respect, infrared spectra, m.p. and mixed m.p. (196-198°), to 3,5-diphenylpyrazole.

3,5-Diphenylpyrazole (13, R=H) with Hydrogen Peroxide in Acetic Acid.

3,5-Diphenylpyrazole (0.25g.) was heated on the steam bath for 45mins. in acetic acid (7.5cc.) with hydrogen peroxide (4cc.). The solution developed a yellow-orange colour, most intense after @ 20mins., but lightened to almost colourless at the end of the period of heating. Dilution with water gave a white solid (20mg.) which crystallised from ethanol as colourless plates m.p. 136-138°. This

compound was identified as 2,5-diphenyl-1,3,4-oxadiazole (22) by direct comparison with an authentic[24] sample, using m.p., mixed m.p. and infrared spectra.

The filtrate was treated with just less than the amount of solid sodium carbonate required to react with the acetic acid present, then extracted several times with chloroform. The extracts were washed several times with aqueous sodium carbonate, water and dried. Removal of the solvent gave a white solid (32mg.) which crystallised from chloroform as white needles m.p. 238-241°. This was identified as N,N'-dibenzoyl hydrazine (23) by direct comparison with an authentic[25] sample (infrared spectra and mixed m.p.).

The sodium carbonate washings were acidified, and the aqueous solution continuously extracted for 24hrs. with chloroform. Work up in the usual way gave a white solid (132mg.) identified by infrared spectra and mixed m.p. (118-120°) as benzoic acid.

Complete Oxidation of the Dihydrothiadiazepine (1, R=H). The dihydrothiadiazepine (1, R=H) (0.3g.) was heated on the steam bath in acetic acid (10cc.) with hydrogen peroxide (4cc.) for 1.5hrs.. Dilution with water and standing overnight gave a white precipitate (8mg.), m.p. 128-131°, whose infrared spectrum was identical to that of 2,5-

diphenyl-1,3,4-oxadiazole (22).

Work up of the water soluble material as in the last experiment gave, as the carbonate insoluble material, white needles (19mg.) m.p. and mixed m.p. with N,N'-dibenzoyl hydrazine (23) 237-240°. The infrared spectra were identical.

From the carbonate soluble portion was obtained a white solid (104mg.) identified as benzoic acid by direct comparison with an authentic sample.

Desyl Sulphide (25).

Desyl sulphide was obtained by the method of Schonberg and Iskander[20] as colourless rods (benzene) m.p. 168° (blue melt). (Found: C,79.65; H,5.6. Calc. for $C_{28}H_{22}O_2S$: C,79.6; H,5.25%).

Desyl Sulphide with Hydrazine Hydrate in Acetic Acid.

a) Room Temperature.

Desyl sulphide (0.2g.) was suspended in acetic acid (50cc.), excess hydrazine hydrate added, and the mixture stirred at room temperature overnight. The undissolved material was filtered off (0.13g.), and shown to be starting material by mixed m.p.. Dilution of the filtrate with water gave a further quantity (0.05g.) of starting material.

b) 70° for 1hr..

Excess hydrazine hydrate was added to a solution of desyl sulphide (0.2g.) in acetic acid (40cc.) at 70°, and the

mixture heated at this temperature 1hr.. The solution became yellow in colour, and the gases evolved blackened lead acetate paper. Dilution with water and standing in the 'fridge overnight gave a yellow oil which crystallised from ethyl acetate/petrol as colourless prisms (0.09g.) m.p. 165-167° (blue melt). The infrared spectrum was identical to that of the starting material.

The mother liquors of the crystallisation gave a small amount of yellow oil which retained a carbonyl peak in the infrared, but showed no >NH or $-NH_2$ absorption.

Similar reactions in hot acetic acid for longer periods proceeded with evolution of hydrogen sulphide and the formation of yellow oils which could not be crystallised.

Desyl Sulphide with Hydrazine Hydrate in Alcohol.

Desyl sulphide (1g.) was refluxed in alcohol (100cc.) with hydrazine hydrate (0.2cc.) for 1.5hr.. Hydrogen sulphide was evolved, detected by lead acetate paper. After cooling, the solution was neutralised with a little dilute acetic acid, diluted with water till cloudy white, and on standing several hours, a yellowish precipitate (0.5g.) separated out. This proved to be a mixture of two compounds.

a) Crystallised from benzene as bright yellow needles m.p. 164°. (Found: C,86.9; H,6.3; N,7.1. Calc. for $C_{28}H_{24}N_2$:

C,86.6; H,6.2; N,7.2%). Direct comparison, infrared, m.p. and mixed m.p. with an authentic[26] sample of benzylphenyl ketazine (26) proved the identity of this compound.

b) Crystallised from benzene/petrol as white rods m.p. 152-153°. (Found: C,74.65; H,5.2. Calc. for $C_{14}H_{12}N_2O$: C,75.0; H,5.4%). Molecular weight 224 (mass spectrum). νmax (nujol and KCl disc, Infracord) 3400; 3300; 3200; 1640; 1550cm^{-1}. Direct comparison, infrared, m.p. and mixed m.p., with an authentic[27] sample of benzil monohydrazone (27) established the identity of this compound.

Desyl Sulphone (29).

Desyl sulphide (0.5g.) was refluxed in glacial acetic acid (7cc.) with hydrogen peroxide (2cc.) for 2hrs.. Cooling and filtering gave soft white needles (0.4g.) of desyl sulphone m.p. 226-228°, crystallised from chloroform/petrol as white needles m.p. 230-231°. (Found: C,73.65; H,5.05. $C_{28}H_{22}O_4S$ requires C,74.0; H,4.9%).

Desyl Sulphone with Hydrazine Hydrate.

a) In Acetic Acid.

Desyl sulphone could be quantitatively recovered after treatment with hydrazine hydrate in acetic acid either at room temperature, at 95°, or after prolonged reflux.

b) In Alcohol.

Excess hydrazine hydrate was added to a suspension of desyl

sulphone (0.2g.) in boiling ethanol (50cc.). The sulphone rapidly dissolved, and the solution was refluxed 1hr.. After evaporating some of the ethanol, dilution with water gave a white precipitate which crystallised from ethanol as white plates (0.09g.) m.p. 150-151°. (Found: C,68.3; H,5.4. Calc. for $C_{14}H_{14}O_2S$: C,68.3; H,5.75%).

The compound proved identical in every respect, infrared m.p. and mixed m.p. (149-151°), to an authentic sample of dibenzyl sulphone (30).

Desyl Sulphone with Ethanolic Potassium Hydroxide.

4n-potassium hydroxide (0.5cc.) was added to a suspension of desyl sulphone (0.1g.) in boiling ethanol (25cc.), the sulphone rapidly dissolved and the solution was then boiled 30mins.. After evaporating some of the ethanol, dilution with water gave a white solid which crystallised from ethanol as colourless plates (0.04g.) m.p. and mixed m.p. with dibenzyl sulphone 148-151°.

Phenacyl Mercaptan with p-Bromophenacyl Bromide.

Phenacyl mercaptan[21] (4g.); p-bromophenacyl bromide[28] (8g.) were refluxed for 1hr. in a solution of sodium (0.6g.) in ethanol (100cc.). Cooling and dilution with water gave a red oil which was extracted with ether. After removal of solvent, trituration with benzene/petrol gave some solid material (0.5g.) which crystallised from ethanol as

colourless plates m.p. 135-136°. (Found: C,41.85; H,2.75. $C_{16}H_{12}Br_2O_2S_2$ requires C,41.75; H,2.65%). ν_{max} (nujol) 1670cm.$^{-1}$.

Phenacyl Mercaptan with Desyl Chloride.

Phenacyl mercaptan (4g.) and desyl chloride[29] (7g.) were refluxed for 1hr. in a solution of sodium (0.6g.) in ethanol (100cc.). Dilution with water and extraction with ether gave a dark red oil. Trituration with benzene/petrol gave some solid material (0.3g.) which crystallised from benzene/petrol as colourless prisms m.p. 234-236°. (Found: C,87.4; H,5.6%). Elements tests did not detect either halogen or sulphur present.

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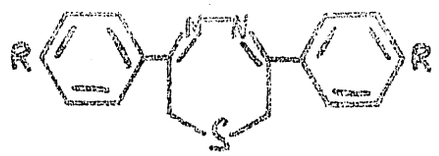

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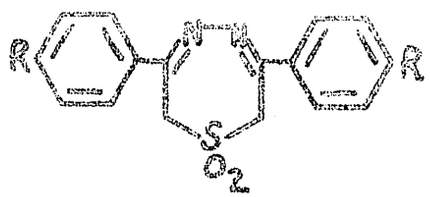

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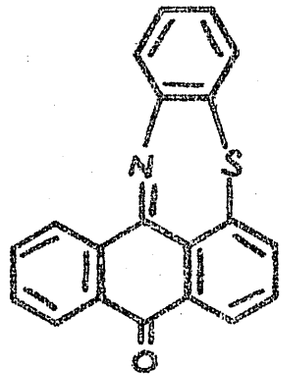

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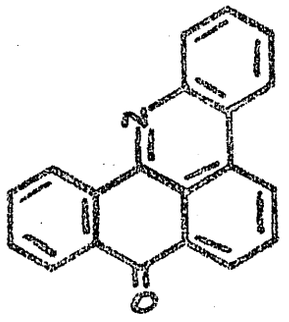

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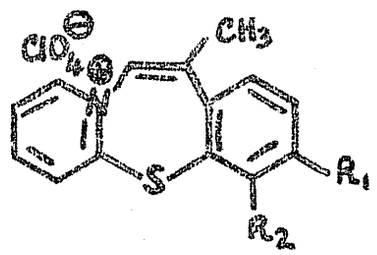

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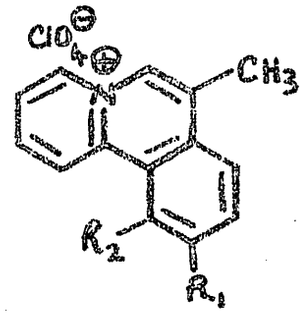

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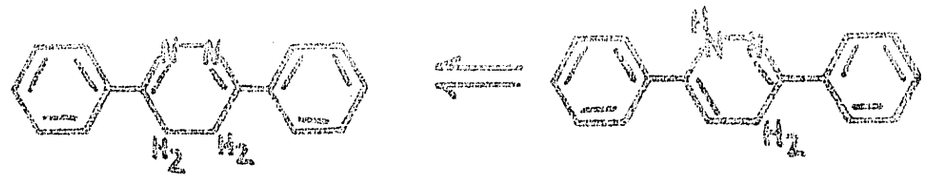

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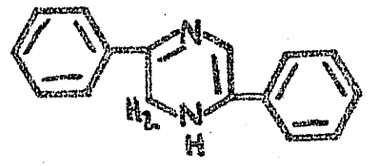

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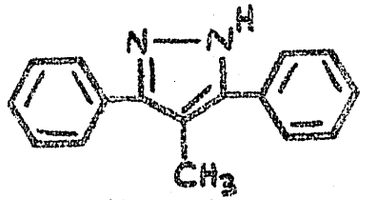

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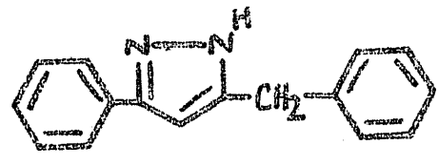

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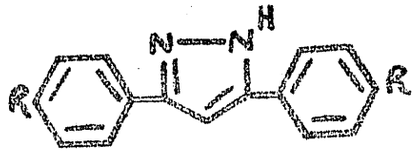

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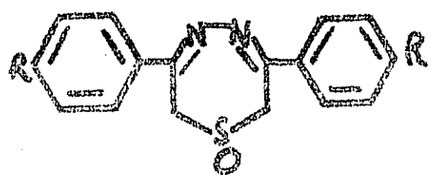

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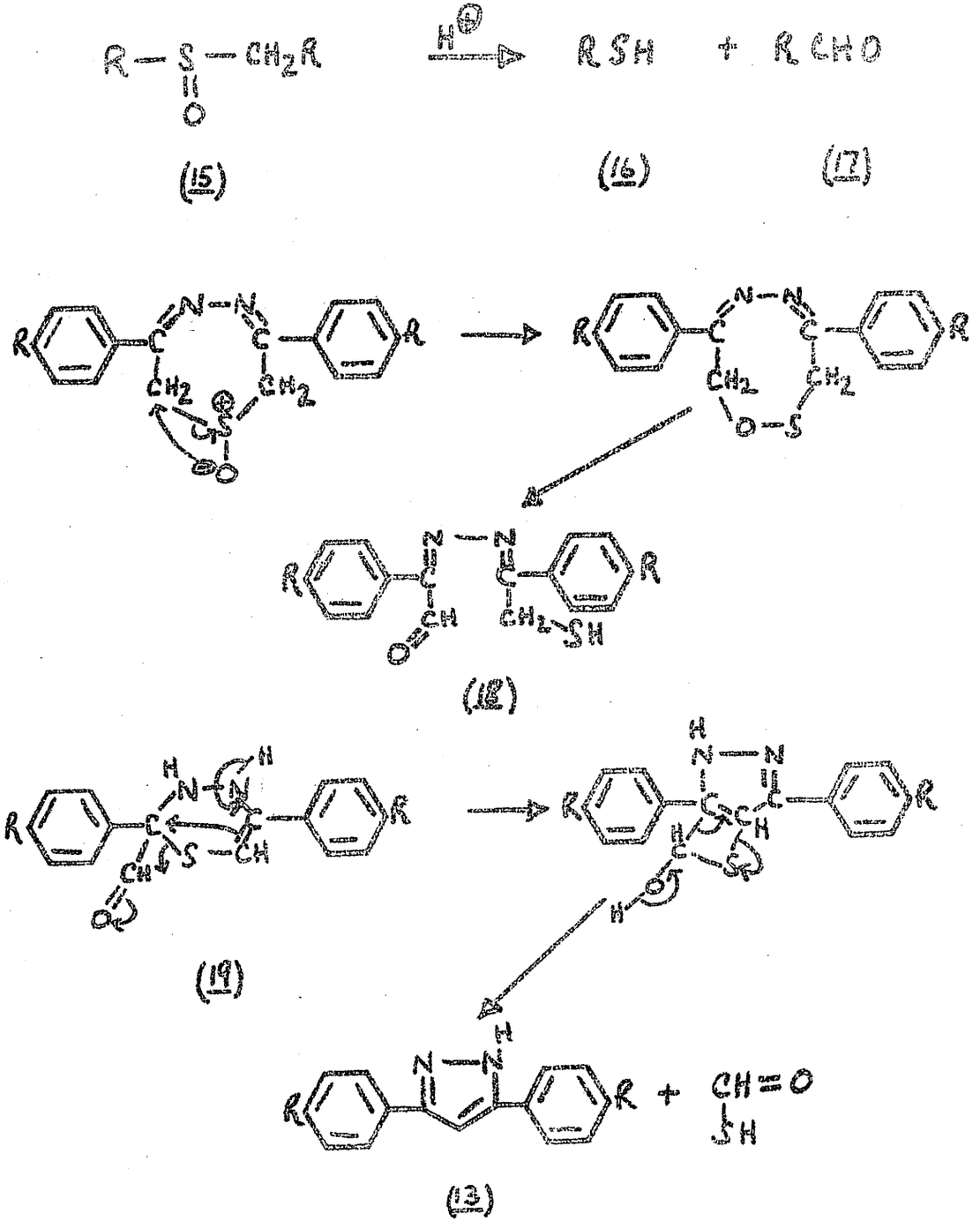

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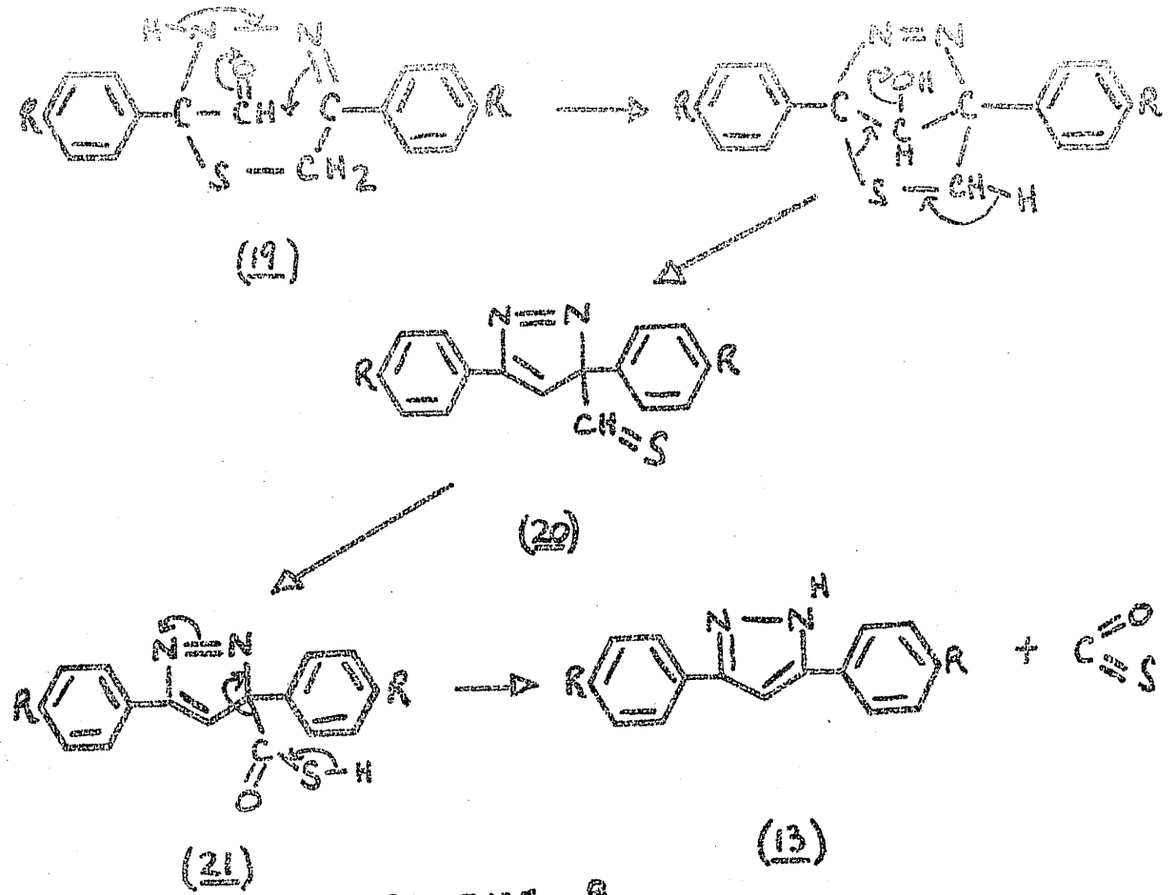

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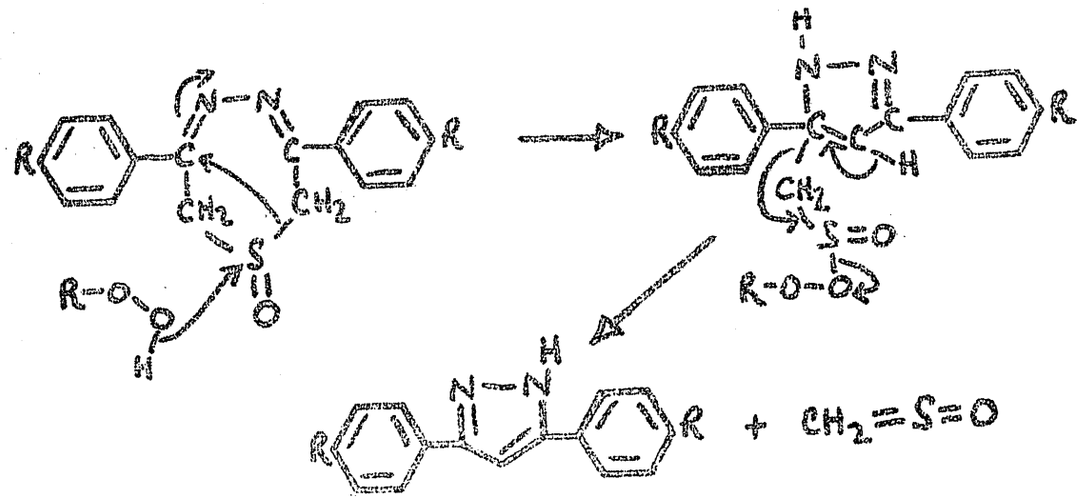

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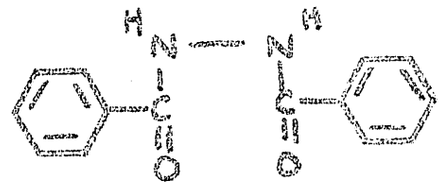

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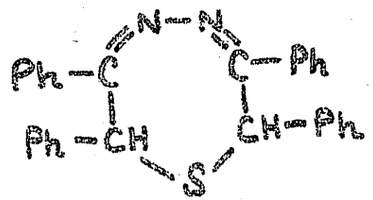

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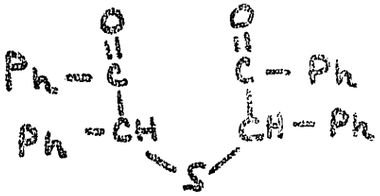

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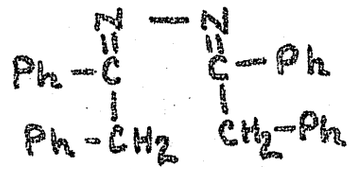

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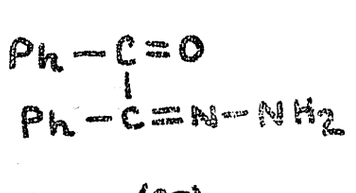

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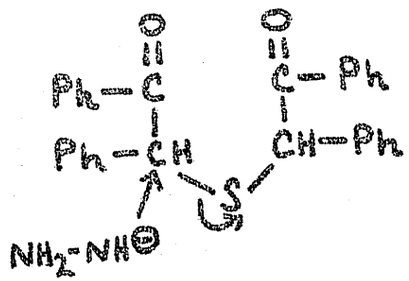

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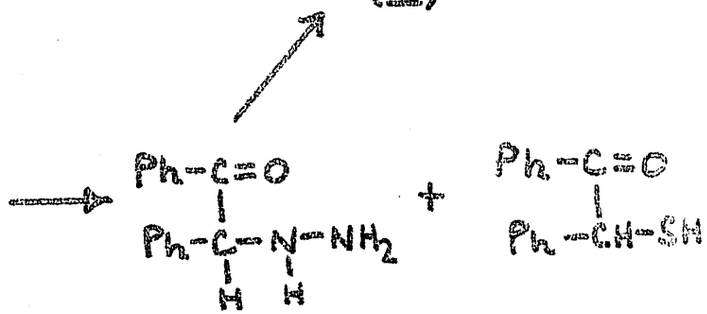

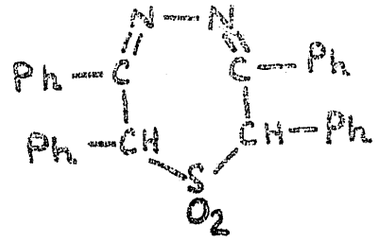

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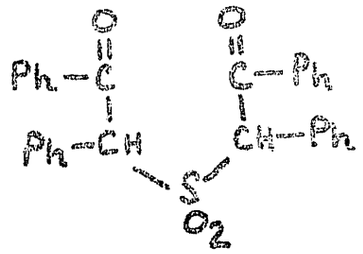

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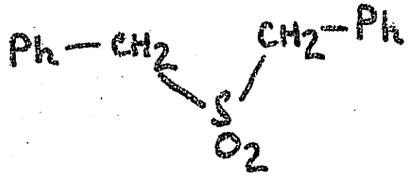

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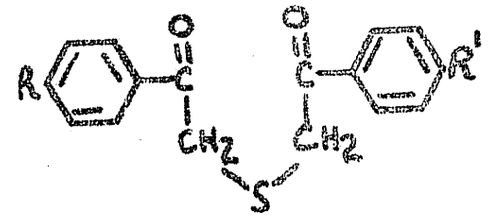

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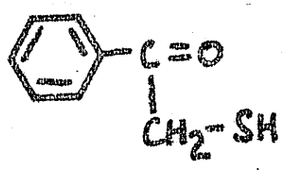

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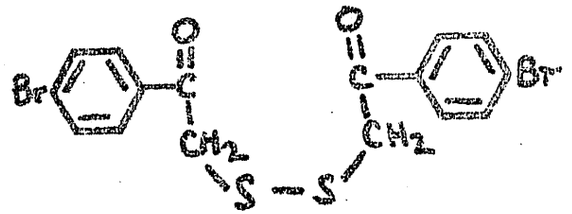

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CHAPTER 3

"RING CONTRACTIONS OF SEVEN- TO FIVE-MEMBERED SYSTEMS TYPE B"

INTRODUCTION

In Chapter 1, various methods were described for the conversion of the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3) and their S-dioxides (2, R=H; R=Br; R=CH_3) into the pyridazines (3, R=H; R=Br; R=CH_3). The action of base on the dihydrothiadiazepines (1, R=H; R=Br; R=CH_3), or more especially their S-dioxides (2, R=H; R=Br; R=CH_3) might effect a similar type of ring contraction, and we therefore investigated this possibility.

DISCUSSION

As expected, diphenacyl sulphide (4) and the derived dihydrothiadiazepine (1, R=H) are insoluble in base, and the dihydrothiadiazepine (1, R=H) can be recovered after an overnight reflux in ethanolic sodium ethoxide. However diphenacyl sulphone (5) dissolved readily in cold aqueous alkali, and was precipitated on acidification. Diphenacyl sulphone (5) was in fact recovered by acidification after a 2hr.'s reflux in ethanolic sodium ethoxide.

The dihydrothiadiazepine-S-dioxide (2, R=H) did not dissolve in cold aqueous alkali, but did however dissolve in cold ethanolic sodium ethoxide when a suspension therein was shaken overnight, approximately 1 mole of base being required for complete solution. Dilution of the almost neutral solution with water did not produce any precipitate or even cloudiness, but acidification precipitated a white compound m.p. 106-112°. This product effervesced as it melted, crystallised, then remelted at 180-200°. The infrared spectrum of the compound did not show any sulphone absorption, but had ν_{max} at 3300cm.$^{-1}$ in the >NH or -OH region. Attempts to purify the compound by crystallisation resulted only in the formation of 3,6-diphenylpyridazine (3, R=H), and the precise effects of

cold ethanolic sodium ethoxide on the dihydrothiadiazepine-S-dioxide (2, R=H) have yet to be determined.

Treatment of the dihydrothiadiazepine-S-dioxide (2, R=H) with boiling ethanolic sodium ethoxide for 1.5hrs. also afforded water soluble products, but acidification did not provide the unstable solid isolated from the cold ethanolic sodium ethoxide experiments. In this case, the precipitate obtained could be crystallised unchanged from ethanol, having m.p. 165-167°, again effervescing when it melted. Analysis data were in accordance with the formula $C_{16}H_{14}N_2O_2S$, and the compound (designated Compound A) is therefore isomeric with the starting S-dioxide (2, R=H). Compound A did not however show any sulphone absorption in the infrared, the spectrum otherwise providing no useful information. Although apparently only slightly soluble in cold water and in cold sodium carbonate solution, Compound A dissolved in cold sodium hydroxide or in warm sodium carbonate solution, and could be recovered on acidification.

Since Compound A effervesced on melting, we investigated the decomposition products in the hope that they might help in the elucidation of the structure of Compound A. By melting, or better, in boiling ethylene glycol, Compound A decomposed with evolution of sulphur dioxide to

give a white crystalline product, Compound B, m.p. 181-182°. This product analysed in accordance with the molecular formula $C_{16}H_{14}N_2$, and a molecular weight (mass spectrum) of 234 supported this conclusion. Compound B was however quite distinct from 3,6-diphenylpyridazine (3, R=H) or even 3,5-diphenylpyrazole (6). Unlike Compound A, Compound B was insoluble in alkali. It was weakly basic, and afforded a mono-acetyl derivative which could be readily hydrolysed back to Compound B with warm dilute hydrochloric acid.

Our experience with the infrared spectra of pyrazoles now proved invaluable. Compound B showed νmax (KCl disc) at 3120; 1444 and 970cm.$^{-1}$. The N-acetyl derivative had νmax (KCl disc) at 1730; 1460 and 954cm.$^{-1}$, and in view of the infrared results we had obtained from other pyrazoles (see Appendix) we concluded that Compound B contained a pyrazole ring.

Assuming that the two benzene rings had remained intact, Compound B could therefore be a benzylphenylpyrazole such as (7), or 4-methyl-3,5-diphenylpyrazole (8) or 3-methyl-4,5-diphenylpyrazole (9). Only compounds (8) and (9) had m.p.'s in the same region as Compound B, and synthesis[1] of 4-methyl-3,5-diphenylpyrazole (8) and direct comparison with Compound B proved that Compound B did not

have the structure (8). The mass spectrum of Compound B, in addition to the large parent peak at 234 mass units, had an intense peak at 165 mass units, which could possibly originate from a molecule in which two phenyl groups were attached to the same or adjacent carbon atoms, indicating that Compound B might have the structure (9). 3-methyl-4,5-diphenylpyrazole (9) is a known[2] compound, m.p. 185-186°, obtained by acid-catalysed rearrangement of the nitropyrazoline (10) (prepared as shown). Synthesis[2] of this pyrazole (9) and direct comparison of the synthetic sample with Compound B, using mixed m.p., infrared and mass spectra, proved that Compound B was indeed 3-methyl-4,5-diphenylpyrazole (9).

Parham and Hasek[2] prepared 3-methyl-4,5-diphenylpyrazole (9) by treatment of the nitropyrazoline (10) with conc. hydrochloric acid in ethanol. Under similar conditions, our Compound A was converted in good yield into 3-methyl-4,5-diphenylpyrazole (9) with evolution of sulphur dioxide. Compound A could also be converted into this pyrazole (9) by short heating in acetic acid.

It was previously mentioned that Compound A dissolves in cold sodium hydroxide solution. By suitably adjusting the concentration of the alkali, a water soluble sodium salt crystallised from the alkaline solution, and reaction

of this sodium salt with methyl iodide in ethanol afforded a crystalline product which analysed for $C_{17}H_{16}N_2O_2S$. The infrared spectrum of the compound had ν_{max} (KCl disc) at 1306 and 1130cm^{-1}, and the compound is probably a methyl sulphone.

The reactions of Compound A can be explained in terms of structure (11). Rearrangement via (12) provides 3-methyl-4,5-diphenylpyrazole (9) by loss of sulphur dioxide from the intermediate sulphinic acid (12). This scheme may be compared to the conversion of the nitropyrazoline (10) into 3-methyl-4,5-diphenylpyrazole (9), and Parham has effected similar decompositions of simpler pyrazolines into pyrazoles[3,4]. The lactone type of structure (11) might also be expected to be insoluble in cold aqueous sodium carbonate, but soluble in cold aqueous sodium hydroxide or warm aqueous sodium carbonate or in ethanolic sodium ethoxide, the lactone ring opening under these conditions to the pyrazolenine (13), which could recyclise on acidification. The methyl sulphone could therefore have either the structure (14) (formed from the ion (12)), or the structure (15), formed from the pyrazolenine (13). Infrared evidence suggests that the methyl sulphone probably does not possess a pyrazole ring, and the structure (15) is therefore favoured at the moment.

It is interesting to note that the mass spectrum of Compound A does not have a peak corresponding to the molecular weight expected for the structure (11). A peak at 234 mass units corresponds to the loss of sulphur dioxide, which was in fact detected by a peak at 64 mass units. The spectrum does exhibit most of the peaks shown in the mass spectrum of 3-methyl-4,5-diphenylpyrazole (9), and it would seem that Compound A rearranges in the electron beam to this pyrazole (9).

The formation of the compound of structure (11) by the action of base on the dihydrothiadiazepine-S-dioxide (2, R=H) can be rationalised by a mechanism as in the scheme shown.

This ring contraction of the seven-membered S-dioxide (2, R=H) into the five-membered 3-methyl-4,5-diphenyl-pyrazole (9) is quite surprising and has as yet unexplored potential.

EXPERIMENTAL

Sodium ethoxide refers to a solution of sodium (0.57g.) in ethanol (250cc.).

The Dihydrothiadiazepine (1, R=H) in Sodium Ethoxide.

The dihydrothiadiazepine (1, R=H) (0·3g.) was refluxed in sodium ethoxide (20cc.) overnight. After filtering and evaporating some of the ethanol, cooling gave white needles (0.25g.) m.p. and mixed m.p. with starting material 173-175°. The infrared spectra of the two samples were superimposable.

Diphenacyl Sulphone (5) in Sodium Ethoxide.

Diphenacyl sulphone (0.2g.) was refluxed in sodium ethoxide (7.5cc.) for 2hrs., the solution becoming red in colour. After evaporating some of the ethanol, dilution with water and acidification gave a cream precipitate which crystallised from ethanol as colourless plates (0.15g.) m.p. and mixed m.p. with diphenacyl sulphone 118-120°; a mixed m.p. with trans-dibenzoyl ethylene was 87-103°.

The Dihydrothiadiazepine-S-dioxide (2, R=H) in Aqueous Alkali.

The dihydrothiadiazepine-S-dioxide (2, R=H) (0.1g.) was shaken overnight as a suspension in 1n sodium hydroxide (10cc.). The undissolved solid was filtered off (0.09g.)

m.p. and mixed m.p. with starting material 196°. No precipitation occurred on acidification of the filtrate.

The Dihydrothiadiazepine-S-dioxide (2, R=H) in Cold Sodium Ethoxide.

The dihydrothiadiazepine-S-dioxide (2, R=H) (0.4g.) was shaken with sodium ethoxide (13.6cc.) overnight at room temperature. Dilution with water did not cause any precipitation from the yellow solution, but acidification of the aqueous ethanolic solution afforded a white precipitate (0.3g.) m.p. 106-112° (with effervescence). Two crystallisations of this solid from ethanol gave colourless plates m.p. and mixed m.p. with 3,6-diphenylpyridazine 220-222°. The infrared spectra of the two samples were identical.

The Dihydrothiadiazepine-S-dioxide (2, R=H) with Hot Sodium Ethoxide.

The dihydrothiadiazepine-S-dioxide (2, R=H) (1g.) was refluxed in sodium ethoxide (34cc.) for 1.5hrs., the S-dioxide dissolving almost immediately on heating. The solution was diluted with water (25cc.), the ethanol evaporated off, and the aqueous solution cooled and acidified with dilute mineral acid. The white precipitate (0.9g.) obtained crystallised from ethanol affording Compound A as colourless prisms m.p. 165-167° (with effervescence). (Found: C,64.6; H,4.85; N,9.25. $C_{16}H_{14}N_2O_2S$

requires C,64.4; H,4.7; N,9.4%).

Decomposition of Compound A.

a) Melting.

Compound A (0.1g.) was melted in a test tube, the evolved gases turning acid dichromate paper green. The cooled melt was crystallised from ethanol (charcoal) affording Compound B as a matte of soft white needles (0.04g.) m.p. 181-182°. Sublimed for analysis m.p. 181-182°. (Found: C,82.3; H,6.0; N,11.95. Calc. for $C_{16}H_{14}N_2$: C,82.0; H, 6.0; N,11.95%). νmax (KCl disc) 3120; 1444 and 970cm.$^{-1}$. Molecular weight (mass spectrum) 234.

b) In Ethylene Glycol.

Compound A (1.25g.) was refluxed in ethylene glycol (20cc.) for 30mins., the evolved gases turning acid dichromate paper green. Cooling, dilution with water and crystallisation of the resulting precipitate from ethanol gave Compound B as soft white needles (0.95g.) m.p. 181-182°, identical to the material obtained in the previous experiment.

N-Acetyl Derivative of Compound B.

The N-acetyl derivative of Compound B (prepared by reflux in acetic anhydride) crystallised from petrol (40-60°) as colourless prisms m.p. 77-78°. (Found: C,78.05; H,5.90; N,10.0. $C_{18}H_{16}N_2O$ requires C,78.25; H,5.85; N,10.15%).

νmax (KCl disc) 1730; 1460 and 954cm.$^{-1}$.

This acetyl derivative was hydrolysed back to the starting base by treatment with dilute hydrochloric acid in warm ethanol.

4-Methyl-3,5-diphenylpyrazole (8).

This compound was obtained by the method of Abell[1] as colourless plates m.p. 228-229° (lit. 222-223°) (Found: C,82.1; H,5.85; N,11.95. Calc. for $C_{16}H_{14}N_2$: C,82.0; H,6.0; N,11.95%).

A comparison of the infrared and mass spectra of this pyrazole with those of Compound B, in conjunction with a mixed m.p. (158-170°) proved that this pyrazole (8) was not identical to Compound B.

3-Methyl-4,5-diphenylpyrazole (9).

This compound was obtained from the nitropyrazoline (10) by the method of Parham and Hasek[2] and crystallised from ethanol as soft white needles m.p. 181-182° (lit. 185-186°). Sublimation did not raise the melting point. A mixed m.p. of this sample and Compound B was 181-182°. The infrared and mass spectra of the two samples were respectively identical.

Compound A with Conc. Hydrochloric Acid in Ethanol.

Compound A (0.3g.) was refluxed in ethanol (15cc.) with conc. hydrochloric acid (0.6cc.) for 3hrs., the evolved

gases turning acid dichromate paper green. After cooling, neutralisation with dilute sodium hydroxide and dilution with water, the resulting precipitate was crystallised from ethanol as soft white needles (0.14g.) m.p. and mixed m.p. with 3-methyl-4,5-diphenylpyrazole (9) 180-182°. The infrared spectra of the two samples were identical.

Compound A in Hot Acetic Acid.

Compound A (0.2g.) was heated in acetic acid (10cc.) at 95° for 30mins.. Dilution with water and crystallisation of the product from ethanol gave soft white needles (0.11g.) m.p. and mixed m.p. with 3-methyl-4,5-diphenylpyrazole (9) 179-182°. The infrared spectra of the two samples were superimposable.

Methyl Sulphone.

Compound A (0.3g.) was shaken with 1n sodium hydroxide (3cc.) at room temperature until all the solid dissolved (@ 3mins.), and the solution then set aside to crystallise. The sodium salt obtained was dissolved in a little hot aqueous ethanol, and the hot solution shaken vigorously with excess methyl iodide for 15mins.. After boiling off the excess methyl iodide, dilution with water gave a white precipitate which crystallised from ethanol as colourless needles m.p. 144-146°. (Found: C,65.6; H,5.15; N,9.0. $C_{17}H_{16}N_2O_2S$ requires C,65.35; H,5.15; N, 8.95%) νmax (KCl disc) 1306; 1130cm.$^{-1}$.

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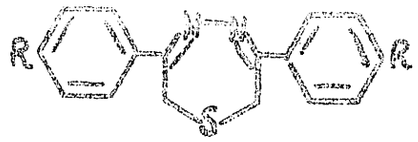

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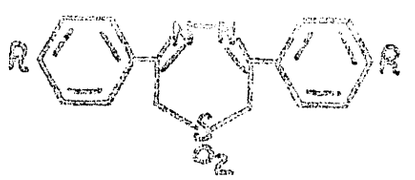

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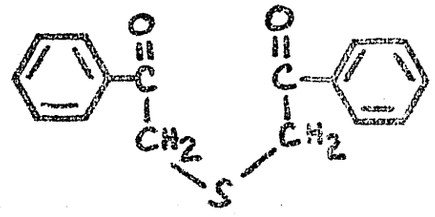

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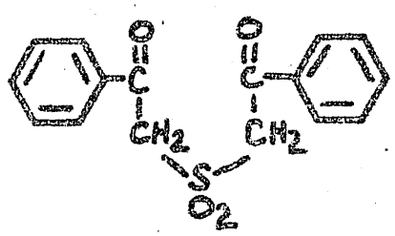

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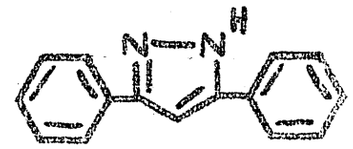

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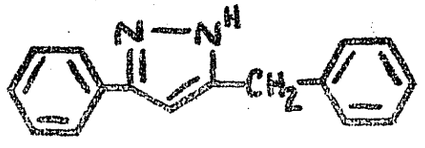

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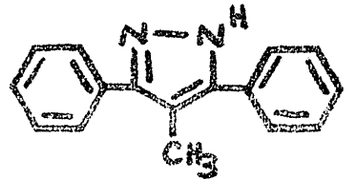

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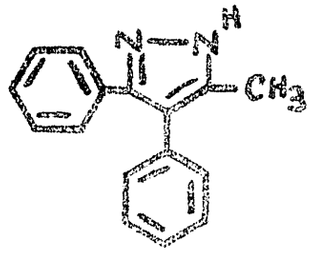

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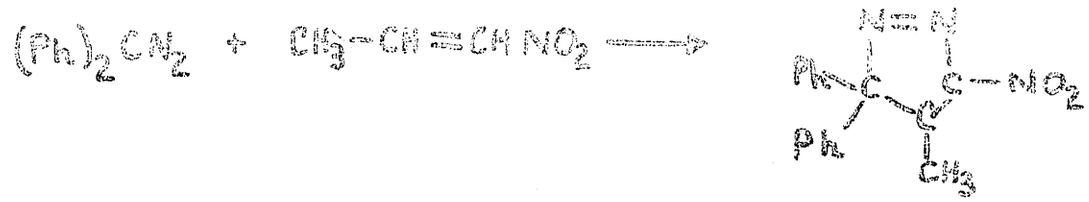

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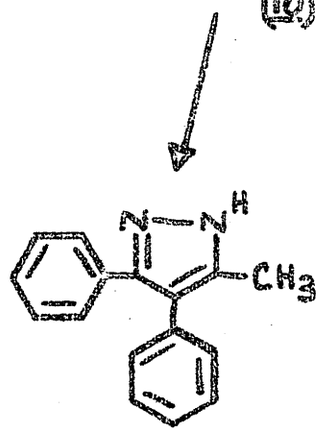

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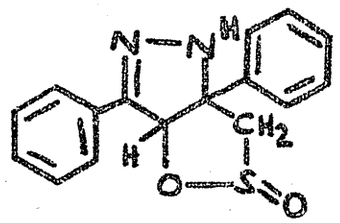

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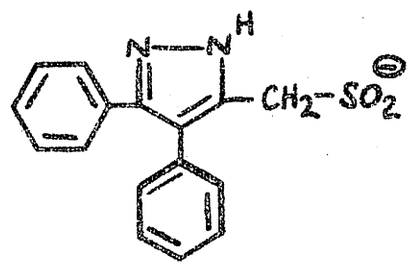

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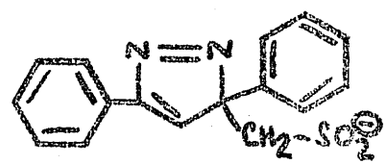

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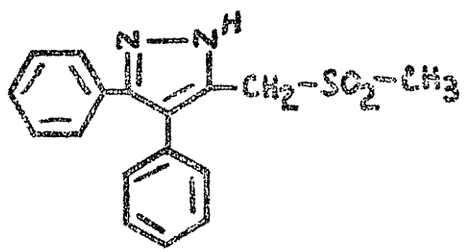

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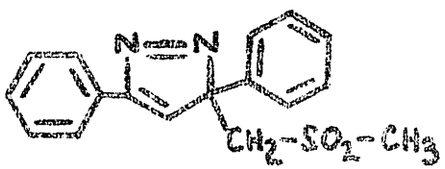

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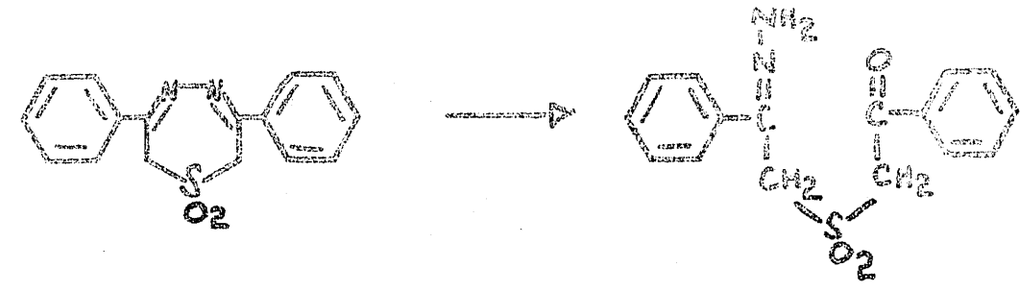

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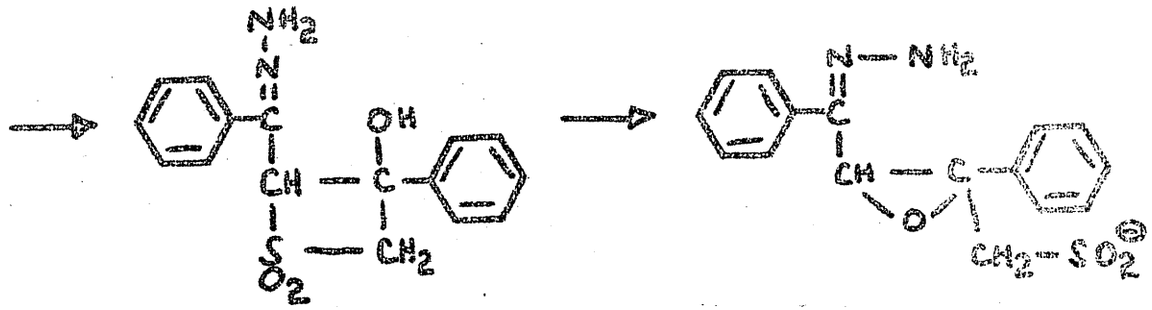

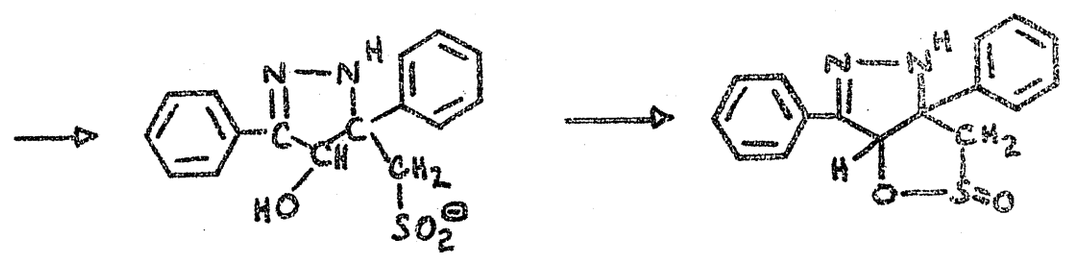

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CHAPTER 4

"VARIOUS RING CONTRACTIONS"

INTRODUCTION.

In Chapter 1, interest was expressed in the synthesis[1] of dibenzothiadiazepine (1), since a study of the extrusion of sulphur from this and related compounds would be of obvious value in view of the previous work of Loudon and his colleagues[2,3,4,5] on the extrusion of sulphur from dibenzothiepins (2) and dibenzothiazepines (3).

The inaccessibility of dibenzothiadiazepines prompted us to prepare 2,7-dihydro-3,6-diarylthiadiazepines (4), and the conversion of these compounds (4) into both 3,6-diarylpyridazines (5) and 3,5-diarylpyrazoles (6) has been described in previous chapters.

It was therefore of interest to prepare octahydrodibenzothiadiazepine (7) by a similar reaction to that used for the preparation of the dihydrothiadiazepines (4, R=H; R=Br; R=CH_3), i.e. by the reaction of hydrazine hydrate on bis-cyclohexanonyl sulphide (8). The dihydrothiadiazepine (7) might then provide some useful extension of the type of reactions described earlier.

DISCUSSION.

Bis-cyclohexanonyl sulphide (8) is a known compound, having been obtained by Backer, Strating and Huisman[6] by treatment of 2-chlorocyclohexanone with ethanolic sodium hydrogen sulphide. To their initial precipitate, a white crystalline compound m.p. 150-151.5° they assigned the structure (9), bis-cyclohexanonyl disulphide, and from the filtrate they obtained bis-cyclohexanonyl sulphide (8).

Repeating their experiments gave the product m.p. 151-152°, but no crystalline material could be obtained from the filtrate. An infrared spectrum of Backer's disulphide (9) showed no absorption in the carbonyl region of the spectrum, but showed $\tilde{\nu}$ max at 3280cm.$^{-1}$ appropriate to a hydroxyl group. In view of this, Backer's bis-cyclohexanonyl disulphide structure (9) became untenable, the most obvious alternative being the diol (10), formed by self-condensation of 2-mercaptocyclohexanone (11).

A mass spectrum gave anaccurate molecular weight of 260, (the disulphide (9) requires 258), and a splitting pattern which fitted the diol structure (10) but not the disulphide (9). Attempts to form an acetyl, 3,5-dinitrobenzoyl and p-toluene sulphonyl derivative were unsuccessful. However dehydration of the compound, best effected in

benzene with p-toluene sulphonic acid, gave a white crystalline product m.p. 97°, which analysed for the diol (10) minus two molecules of water i.e. an octahydrothianthren. An infrared spectrum of this dehydrated compound had ν max 1620cm.$^{-1}$ corresponding to double bond absorption. An ultraviolet spectrum of the compound showed λmax 254mμ, ε 4385; and λmax 265mμ, ε 3162. Parham, Gadsby and Mikulec[7] describe the ultraviolet spectrum of 1,4-dithiadiene (12, R=H) as having λmax 262mμ, ε 5400; and λmax 266-270mμ, ε 5280; and of 2,5-dimethyl-1,4-dithiadiene (12, R=CH_3) as λmax 262mμ, ε 4131; and λmax 269mμ, ε 4102. Hence the product is [illegible], ε 4131; and λmax 269mμ, ε [illegible]diene (13), i.e. octahydrothianthren. If dehydration of the diol (10) had not taken place in the central 1,4-dithiin ring, the double bonds formed would be expected to move into conjugation with both sulphur atoms, so structure (13) can reasonably be assigned to the octahydrothianthren.

The molecular formula of the compound was confirmed by oxidation with hydrogen peroxide in acetic acid to a product, m.p. 261-262°, which analysed for a disulphone of (13) and had νmax in the infrared at 1320 and 1142cm.$^{-1}$. Confirmation of the overall structure (13) was obtained by dehydrogenating the octahydride (13) with chloranil in

phenetole to a compound identical in every respect to an authentic sample of thianthren (14).

When this work was completed, it was found that Asinger and co-workers[8,9] have recently prepared the diol (10) in 80% yield by Backer's method, and have demonstrated the structure of the diol (10) by dehydration to octahydrothianthren (13) m.p. 97°, which was oxidised to a disulphone m.p. 249-258°. They have also prepared the authentic disulphide (9) m.p. 78.5°.

Milligan and Swann[10], without reference to Asinger's work, have recently prepared the thiosulphate salt (15) by reaction of 2-chlorocyclohexanone with sodium thiosulphate, and have converted this salt (15) either by oxidation or by reaction with sodium sulphide, into the disulphide (9) m.p. 80°. They have also prepared the diol (10) m.p. 150° by Backer's method, but although the compound analysed correctly Rast molecular weight determinations were inconsistent and rather low. Their product showed ν_{max} in the infrared at 3455 (in CCl_4) or 3332cm.$^{-1}$ (KBr disc), but after standing 3 months, the compound had a m.p. 133° and showed a weak carbonyl absorption in the infrared at 1720cm.$^{-1}$.

By reaction of disodium sulphide with 2-chlorocyclohexanone, they obtained a second diol, isomeric with their other product, m.p. 143-144° or 168-170° depending on the

solvent. Their Rast molecular weight determinations were again low and inconsistent. To explain these observations, Milligan and Swann suggest that their two compounds are isomers or mixtures of isomers of the diol (10), for which six geometrical isomers are possible. They further suggest that the diol (10) partially decomposes to 2-mercaptocyclohexanone (11) and that this is the reason for their inconsistent molecular weight determinations and for the appearance of a weak carbonyl absorption in the infrared spectrum.

They have also prepared octahydrothianthren (13) m.p. 97°, by treatment of the salt (15) with ethanolic hydrogen chloride (c.f. references 11 and 12) or treatment of the diol (10) with anhydrous hydrogen chloride in dioxan.

The results obtained in the present investigation are therefore consistent with those of Asinger and co-workers, and Milligan and Swann, though it may be remarked that like Asinger, we did not encounter the troubles of Milligan and Swann. In fact the infrared spectrum of a sample of the diol (10) was unchanged after six months, no trace of carbonyl absorption appearing. The diol (10) can also be obtained by treatment of 2-chlorocyclohexanone with a solution of sodium sulphide in dimethylformamide or by treatment of 2-chlorocyclohexanone with a methanolic solution of sodium hydrogen sulphide prepared by the method

of Hodgson and Ward[13].

Thianthren (14) is known[14] to extrude sulphur giving dibenzothiophen (16). We therefore decided to examine the possibility of extrusion from octahydrothianthren (13), expecting to obtain octahydrodibenzothiophen (17), this being a known[15,16] compound m.p. 31-32°, best obtained[16] by reaction of 2-cyclohexenylcyclohexanone with sulphur.

Initial experiments conducted in refluxing ethylene glycol, with or without the presence of copper , gave only a high recovery of starting material. However treatment of octahydrothianthren (13) with copper in diethyl phthalate at @ 310° for a few minutes, produced immediate blackening of the copper. After removal of the copper, the solution was diluted with phenetole and treated with chloranil to dehydrogenate the products. Working up in the usual way, followed by chromatography, gave white crystalline material which proved to be a mixture of thianthren (14) and dibenzothiophen (16). Thus although extrusion of sulphur had taken place, the isolation of thianthren (14) shows that some of the octahydrothianthren (13) survived, and indicates a fairly high degree of stability for the compound.

Using the same conditions, but extending the period of heating to 15mins. gave, after chromatography of the product

an 80% yield of a colourless oil which crystallised as colourless plates m.p. 29-30° (lit.[15,16] 31-32°). This product had an infrared spectrum identical with that of a synthetic sample and with the spectrum recorded by the original worker[16], hence confirming its identity as octahydrodibenzothiophen (17).

Parham and his co-workers[17] have studied the extrusion of sulphur from 1,4-dithiadienes (12) quite extensively. They have shown[18] that 1,4-dithiadiene (12, R=H) shows good thermal stability and can in fact be refluxed and distilled at atmospheric pressure, no thiophen ever being detected. 2,5-Dimethyl-1,4-dithiadiene (12, R=CH_3) is however thermally somewhat less stable[19] and decomposes at its boiling point, @ 204°, to give a mixture which contains some 2,4-dimethylthiophen. 2,5-Diaryl-1,4-dithiadienes (12, R=Aryl) are thermally much less stable[20,21,22,23] and readily extrude sulphur to give thiophens. The extrusion of sulphur from octahydrothianthren (13) stands in contrast to this, since (13) can be regarded as a 2,3,5,6-tetraalkyll-1,4-dithiadiene. As such, it would be expected to extrude sulphur with approximately the same ease as 2,5-dimethyl-1,4-dithiadiene (12, R=CH_3) and this is not the case. The difference in ease of extrusion between octahydrothianthren (13) and 2,5-diaryl-1,4-dithiadienes (12,

R=Aryl) is striking, the aromatic rings evidently assisting thermal instability.

The fact that octahydrodibenzothiophen (17) had such a low melting point, 32°, had prompted experiments to obtain a higher melting derivative to facilitate its' detection in the extrusion products. Cagniant and Cagniant[15] could not obtain a crystalline picrate, and this was confirmed here, though evidence for picrate formation was apparent in the appearance of a bright red solution when octahydrodibenzothiophen (17) was added to a solution of picric acid in ethanol or benzene. Similar attempts to form a trinitrobenzene or trinitrofluorenone derivative were also unsuccessful. Since dibenzothiophen (16) can be oxidised to a stable, higher melting sulphone, a similar oxidation was tried with octahydrodibenzothiophen (17). The product crystallised as colourless plates m.p. 185-186°, but analysed for $C_{12}H_{12}O_2S$ and not $C_{12}H_{16}O_2S$. A mass spectrum gave a molecular weight of 220 in accordance with a $C_{12}H_{12}O_2S$ formula. An infrared spectrum had ν_{max} at 1290 and 1146cm.$^{-1}$ corresponding to the presence of a sulphone group, and also peaks in the regions associated with aromatic double bond absorption. These results all pointed to the structure (18), making the compound tetrahydrodibenzothiophen sulphone.

Cagniant and Cagniant[15] have described the synthesis of tetrahydrodibenzothiophen (19), an oil which forms a red picrate m.p. 106°, and a lemon-yellow trinitrobenzene derivative m.p. 137°, but they do not describe oxidation to a sulphone. The reduction of dibenzothiophen sulphones to dibenzothiophens is known[24,25] to proceed in good yield, and this was therefore a convenient method for proving the identity of the oxidation product of octahydrodibenzothiophen (17).

Treatment of the oxidation product with lithium aluminium hydride in ether gave a colourless oil which formed a red picrate m.p. 104-105° and a lemon-yellow trinitrobenzene derivative m.p. 136-137°, in good agreement with the quoted figures, and so the oil was tetrahydrodibenzothiophen (19). The oil could be oxidised back to the same product obtained by oxidation of octahydrodibenzothiophen (17), and the product is therefore tetrahydrodibenzothiophen sulphone (18).

Whether oxidation of the sulphur atom precedes oxidation of the ring is not known, but evidently the thianaphthen sulphone system thus formed is sufficiently stable to resist further oxidation under these conditions to dibenzothiophen sulphone. In fact tetrahydrodibenzothiophen sulphone (18) resisted oxidation with chloranil in phenetole, conditions which promoted easy oxidation of octahydrodibenzothiophen

(17) to dibenzothiophen (16). In this respect tetrahydrodibenzothiophen sulphone (18) resembles the disulphone of octahydrothianthren (13), which resists oxidation with chloranil in phenetole, whereas octahydrothianthren (13) is easily oxidised under the same conditions to thianthren (14). Evidently conversion of the sulphur atoms to the electron-withdrawing sulphone state places tetrahydrodibenzothiophen sulphone (18) and octahydrothianthren disulphone outwith the oxidising power of chloranil, although perhaps quinones of higher redox potential could effect oxidation.

The diol (10) is formed from 2-mercaptocyclohexanone (11) by hemimercaptal formation, and it should therefore be possible to cleave the diol (10) with alkali, and to trap the 2-mercaptocyclohexanone (11) formed by reaction with a suitable electrophile. In fact the diol (10) on treatment with ethanolic potassium hydroxide gave the water soluble potassium salt of 2-mercaptocyclohexanone (11) which regenerated the diol (10) on acidification. However attempts to prepare a 2,4-dinitrophenyl sulphide derivative (20) by reaction of 2,4-dinitrochlorobenzene with a solution of the potassium salt of 2-mercaptocyclohexanone (11) in either ethanol or dimethylformamide were unsuccessful. The only crystalline product isolated in any of the experiments was tetranitrodiphenyl sulphide (21), the rapid formation of

red coloured solutions indicating reduction of the nitro groups.

The use of phenacyl bromide as electrophile did meet with success. Treatment of a solution of the diol (10) and phenacyl bromide in dimethylformamide with potassium hydroxide affording a white crystalline solid m.p. 68-69°, which analysed for the diketo-sulphide (22). The infrared spectrum (KCl disc), apart from showing both aromatic and methylene group absorption, had carbonyl peaks at 1690 and 1666cm^{-1}. The reaction of this diketo-sulphide (22) in hot acetic acid with hydrazine hydrate gave a good yield of the dihydrothiadiazepine (23). The compound analysed in accordance with this structure, and the infrared spectra, both solid state and dilute solution, showed no evidence of any carbonyl or >NH absorption.

In view of the results in Chapters 1 and 2 of this thesis, it was obviously of interest to see whether the dihydrothiadiazepine (23) could afford 3-phenyltetrahydrocinnoline (24) and 3-phenyltetrahydroindazole (25) since such transformations would provide novel methods of synthesising these compounds.

Refluxing the dihydrothiadiazepine (23) in ethylene glycol for 15mins. and dilution with water gave, after extraction with chloroform, an oily product which showed

some signs of crystallising. This oil was however immediately converted into a picrate m.p. 169-172° which analysed for the picrate of 3-phenyltetrahydrocinnoline (24). Chromatography of the picrate on Grade 1 alumina gave the free base as a colourless crystalline solid m.p. 87-88° which analysed in accordance with the structure (24).

Baumgarten, Creger and Villars[26] have prepared 3-phenyltetrahydrocinnoline (24) by the reaction scheme shown, and give m.p.'s of the base and the derived picrate as 86-87.5° and 174-175° respectively. Hence there seems no doubt that the product obtained here is 3-phenyltetrahydrocinnoline (24), and the thermal instability of dihydrothiadiazepines such as (23) provides a new method for the synthesis of tetrahydrocinnolines of the type (24).

The conversion of the dihydrothiadiazepine (23) into 3-phenyltetrahydroindazole (25) however, has not yet been achieved. Initial experiments using either hydrogen peroxide in alcohol or acetic acid, have proceeded with evolution of a gas which blackens lead acetate paper, but in neither case has any material resembling a pyrazole or indazole been isolated. The infrared spectra of the products show at least one, and probably two carbonyl peaks, and, it would seem at the moment, that either the dihydrothiadiazepine (23) or 3-phenyltetrahydroindazole (25) is

susceptible to hydrolysis or to oxidative degradation. This problem is therefore still under investigation.

EXPERIMENTAL

Chlorocyclohexanone with Ethanolic Sodium Hydrogen Sulphide[6].
A solution of sodium (0.45g.) in ethanol (15cc.) was saturated with hydrogen sulphide with ice-cooling. This solution was added slowly with stirring to a solution of chlorocyclohexanone[27] (2.6g.) in ethanol (10cc.) in an ice-bath. After complete addition, the mixture was stirred 1hr., the precipitate filtered off, washed with water, and dried. Crystallisation from ethanol gave a white solid (0.8g.) m.p. 151-152°. (Found: C,55.4; H,7.35. Calc. for $C_{12}H_{20}O_2S_2$: C,55.35; H, 7.75%). Molecular weight (mass spectrum)260. νmax (nujol) 3280cm.$^{-1}$.

The filtrate was evaporated to dryness, neutralised with dilute hydrochloric acid, diluted with water and extracted with chloroform giving an oil (0.1g.) which could not be crystallised.

Chlorocyclohexanone with Methanolic Sodium Hydrogen Sulphide.
A methanolic solution of sodium hydrogen sulphide[13], prepared from crystalline sodium sulphide (64g.); sodium bicarbonate (22.4g.) and methanol (160cc.), was added slowly with stirring to a solution of chlorocyclohexanone (8.8g.) in methanol (50cc.) in an ice-bath. After complete addition, the mixture was stirred 30mins., then water (300cc.) added. The precip-

iuate was filtered off, washed with water and crystallised from ethanol giving a white solid (5-6g.) identical to the material obtained above.

Chlorocyclohexanone with Sodium Sulphide in Dimethylformamide.

A solution of sodium sulphide (20g.) in moist dimethylformamide (200cc.) was added slowly with stirring to a solution of chlorocyclohexanone (10g.) in dimethylformamide (15cc.) at ice-bath temperature. After complete addition, the mixture was stirred 1hr., then diluted with water and allowed to crystallise. The solid obtained was washed with water, dried, and crystallised from ethanol affording a white solid (5-6g.) m.p. and infrared spectra identical to those of the material obtained above.

Dehydration of the Diol (10).

a) Conc. Hydrochloric Acid[11].

The diol (0.25g.) was refluxed in ethanol (10cc.) with conc. hydrochloric acid (5cc.) for 2hr.. Cooling and dilution with water gave octahydrothianthren as white needles (0.13g.) m.p. 91-94°, recrystallised from ethanol as colourless plates m.p. 97°. (Found: C,64.2; H,7.1. Calc. for $C_{12}H_{16}S_2$: C,64.25; H,7.2%). νmax (nujol) 1620cm^{-1}. λmax (95% ethanol) 254mμ, ε 4385; 265mμ, ε 3162.

b) Toluene Sulphonic Acid.

The diol (1g.) was refluxed in dry benzene (30cc.) with p-

toluene sulphonic acid (0.2g.) for 2hrs.. The mixture was cooled, diluted with ether, washed several times with dilute sodium hydroxide, then water, and dried. After removing the solvents, the solid obtained was crystallised from ethanol as colourless plates m.p. 97° (0.82g.), identical to the material obtained in the previous experiment.

Oxidation of Octahydrothianthren[19].

Octahydrothianthren (58mg.) was heated in acetic acid (3cc.) to 70°, hydrogen peroxide (0.6cc.) added, and the mixture maintained at 70° overnight. Cooling gave octahydrothianthren disulphone as colourless prisms (40mg.) which crystallised from ethanol as tiny colourless prisms m.p. 261-262°. (Found: C,50.3; H,5.7. Calc. for $C_{12}H_{16}O_4S_2$: C,50.0. H, 5.6%) νmax (nujol) 1320 and 1142cm.$^{-1}$.

Dehydrogenation of Octahydrothianthren.

Octahydrothianthren (0.5g.) was refluxed in phenetole (25cc.) with chloranil (2.5g.) for 3hrs.. The cooled mixture was diluted with ether, washed several times with dilute sodium hydroxide, then water, and dried. After removing the solvents, the brownish solid was crystallised from ethanol (charcoal) as white needles m.p. and mixed m.p. with an authentic sample of thianthren 152-153°. Both the ultraviolet and infrared spectra of the two samples

were respectively identical.

Octahydrodibenzothiophen (17).

This compound was prepared from 2-cyclohexenylcyclohexanone[28] by the method of Cooper[16] and had b.p. 84-87°/0.03mm. (lit. 120°/1mm.) and a m.p. 28-30° (lit. 32°). λmax 240mμ, ε 7737 (lit. λmax 240mμ, ε 7560).

Octahydrothianthren (13) in Ethylene Glycol.

a) Octahydrothianthren (148mg.) was refluxed in ethylene glycol (5cc.) for 3hrs.. On cooling, a white crystalline solid was deposited (98mg.), identical in every respect to the starting material (infrared and mixed m.p.). Dilution of the filtrate with water and extraction with ether gave a further quantity (28mg.) of starting material.

b) Octahydrothianthren (162mg.) and copper bronze (200mg.) were refluxed in ethylene glycol (7.5cc.) for 3hrs.. After filtering, the cooled solution deposited a white crystalline solid (80mg.) identical to starting material. Dilution of the filtrate with water and extraction with ether gave a further quantity (65mg.) of starting material.

c) In an experiment similar to (b), an 80% recovery of starting material was obtained after an 8hr. reflux.

Octahydrothianthren (13) in Diethyl Phthalate.

a) Octahydrothianthren (200mg.) and copper bronze (200mg.)

in diethyl phthalate (1.5cc.) were immersed in a metal bath regulated at 310°. The copper became black almost immediately, and the mixture was heated at @ 310° for 5mins.. After cooling, the mixture was filtered, and the copper sulphide extracted with hot benzene and filtered again. Phenetole (5cc.) and chloranil (700mg.) were added to the combined filtrates, and the mixture was refluxed for 2hrs.. After working up (see p.107) and removing the phenetole in vacuo, the residue was chromatographed on Grade 1 neutral alumina (Woelm), eluting with petrol. Crystallisation of the resulting solid from ethanol gave a white crystalline solid (48mg.) m.p. 149-151°, identical in every respect to thianthren (14). The mother-liquors of the crystallisation gave white needles (35mg.) m.p. 82-86°, whose infrared spectrum was almost identical to that of dibenzothiophen (16).

b) Octahydrothianthren (500mg.) and copper bronze (500mg.) in diethyl phthalate (3cc.) were immersed in a metal bath heated to @310°. The copper was rapidly blackened, and the mixture was heated at @ 310° for 20mins., cooled and filtered, using hot benzene as a further solvent. After concentration, the residue was chromatographed on Grade 1 neutral alumina (Woelm), eluting with petrol. The first fraction gave a colourless oil (235mg.) whose infrared spectrum was identical to that of octahydrodibenzothiophen

(17). The oil crystallised from ethanol as colourless plates m.p. 29-30° (lit. 31-32°).

Succeeding fractions showed progressively more ester content, so they were hydrolysed with 4n potassium hydroxide and the ether soluble material chromatographed as before. The colourless oil (175mg.) obtained crystallised from ethanol as colourless plates (140mg.) m.p. 29-31°, whose infrared spectrum was identical to that of authentic octahydrodibenzothiophen (17).

Oxidation of Octahydrodibenzothiophen (17).

Hydrogen peroxide (4cc.) was added to a solution of octahydrodibenzothiophen (1g.) in acetic acid (10cc.) over a period of 15mins.. The mixture was heated at the same temperature (95°) for a further 15mins., cooled, diluted with water, and the resulting precipitate crystallised from ethanol as colourless leaflets (0.75g.) m.p. 184-185°. (Found: C,65.65; H,5.45. $C_{12}H_{12}O_2S$ requires C,65.45; H,5.5%) Molecular weight (mass spectrum) 220. νmax (nujol) 1592; 1580; 772;731cm.$^{-1}$. νmax (nujol) 1290; 1146cm.$^{-1}$.

Reduction of Tetrahydrodibenzothiophen Sulphone (18)[24,25].

Tetrahydrodibenzothiophen sulphone (0.4g.) and lithium aluminium hydride (0.32g.) were weighed into a dry flask, ether (120cc.) was run in, and the mixture refluxed 2hrs..

The mixture was cooled, ethyl acetate and then dilute mineral acid added. The ether layer was separated, and the aqueous layer extracted several times with ether. The combined ether extracts were washed with water, dried, and the ether removed, leaving tetrahydrodibenzothiophen (19) as a colourless oil (0.32g.) which showed no sulphone absorption in the infrared. The oil gave a picrate as red needles (ethanol) m.p. 104-105° (lit.[15] 106°) and a bright yellow trinitrobenzene derivative as yellow needles (benzene) m.p. 136-137° (lit.[15] 137°).

Oxidation of Tetrahydrodibenzothiophen (19).

Hydrogen peroxide (0.5cc.) was added to a solution of tetrahydrodibenzothiophen (245mg.) in hot acetic acid (3cc.), and the mixture was heated at 95° for 15mins.. Dilution with water and crystallisation of the precipitate from ethanol gave tetrahydrodibenzothiophen sulphone (18) as colourless plates (190mg.) m.p. 183-185°. The infrared spectrum of this sample was identical to that of the sample obtained by oxidation of octahydrodibenzothiophen (17). A mixed m.p. of the two samples was 183-185°.

Hydrolysis of the Diol (10).

The diol (130mg.) was shaken in ethanol (5cc.) with solid potassium hydroxide (90mg.). Dilution of the cloudy yellow mixture with water gave a clear solution, and on

acidification, a white crystalline solid (70mg.) was precipitated, m.p. and mixed m.p. with starting material, 147-150°.

Reaction of the Diol (10) with Phenacyl Bromide.

4n potassium hydroxide (2cc.) was dropped into a solution of the diol (10) (10g.) and phenacyl bromide[29] (16g.) in dimethylformamide (400cc.) at room temperature with stirring. After stirring 30mins., the yellow mixture was stirred 30 mins. at 95°, then diluted with water, and allowed to crystallise in the 'fridge. Cyclohexanonylphenacyl sulphide (22) was obtained as a yellow sticky solid which crystallised from ethanol as colourless needles (10.6g.) m.p. 68-69°. (Found: C,67.4; H,6.7. $C_{14}H_{16}O_2S$ requires C,67.7; H,6.5%). ν_{max} (KCl disc) 1690; 1666cm.$^{-1}$.

Cyclohexanonylphenacyl Sulphide (22) with Hydrazine.

Excess hydrazine hydrate was introduced into a solution of cyclohexanonylphenacyl sulphide (5g.) in hot acetic acid (30cc.). The hot solution was shaken for a few minutes, then diluted with water, and the yellow precipitate of the dihydrothiadiazepine (23) crystallised from ethanol as colourless needles (4.1g.) m.p. 116-117°. (Found: C,69.1; H,6.85; N,11.6. $C_{14}H_{16}N_2S$ requires C,68.85; H,6.6; N,11.45%)

Decomposition of the Dihydrothiadiazepine (23).

The dihydrothiadiazepine (400mg.) was added to refluxing

ethylene glycol (12cc.) and the solution refluxed for 15mins., during which time there was vigorous evolution of hydrogen sulphide. The dark red solution was cooled, diluted with water and extracted several times with chloroform. The extracts were washed with water, dried and charcoaled. Removal of the chloroform gave a yellow oil which afforded a picrate which crystallised as yellow prisms (ethanol) m.p. 169-172° (Found: C,54.85; H,4.4; N,15.8. Calc. for $C_{20}H_{17}N_5O_7$: C,54.65; H,3.9; N,15.95%). (Lit.[26] m.p. 174-175°).

The picrate was dissolved in chloroform, and chromatographed on Grade 1 neutral alumina (Woelm). Elution with chloroform gave 3-phenyltetrahydrocinnoline (24) as an oil which crystallised from petrol as colourless leaflets (150mg.) m.p. 87-88° (lit.[26] 86-87.5°). (Found: C,79.95; H,6.45; N,13.1. Calc. for $C_{14}H_{14}N_2$: C,79.95; H,6.7; N,13.3%).

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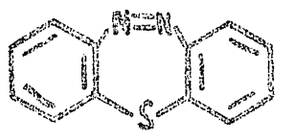

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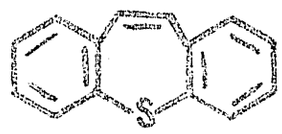

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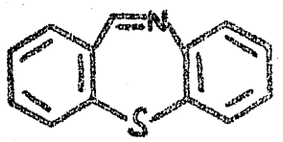

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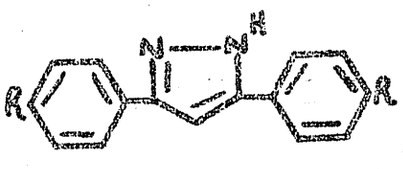

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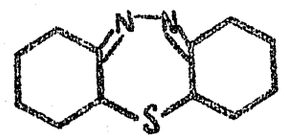

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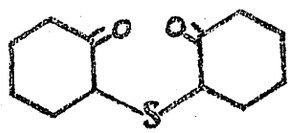

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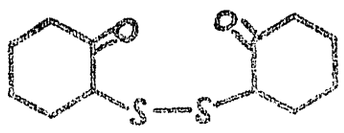

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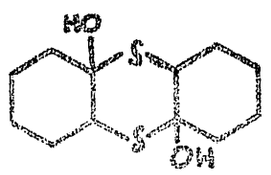

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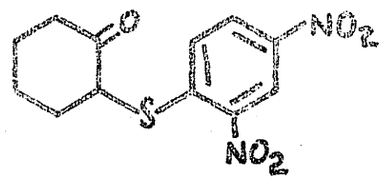

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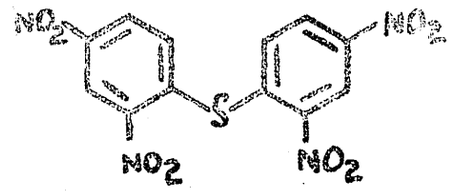

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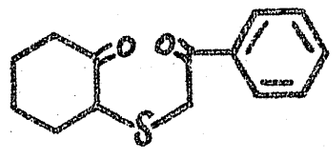

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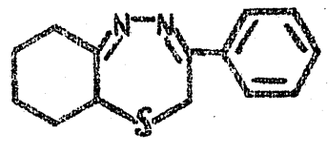

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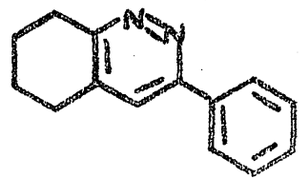

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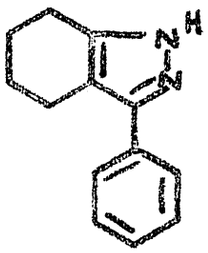

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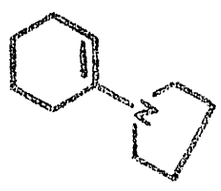
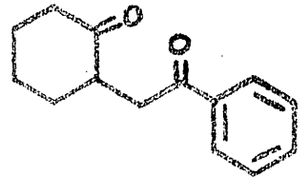




APPENDIX

"THE INFRARED SPECTRA OF SOME PYRAZOLES AND THEIR N-ACETYL DERIVATIVES"

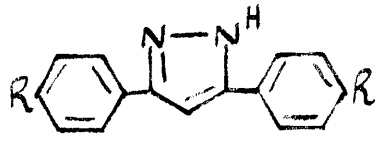
PAGE

DISCUSSION

In Chapter 2 of this thesis, the pyrazoles (1, R=H; R=Br; R=CH_3) were described, information from the literature[1,2] on the characteristic infrared absorption properties of the >NH and >C=N- groupings of the pyrazole ring assisting in the structural determinations. The N-acetyl derivatives of the pyrazoles (1, R=H; R=Br; R=CH_3) had abnormally high amide carbonyl absorption, and this was related to other types of azole systems[3].

When studying these spectra, it was observed that the pyrazoles (1, R=H; R=Br; R=CH_3) all showed an intense absorption in the fingerprint region at @ 974cm^{-1}, and that on acetylation, this absorption remained just as intense, but at a slightly lower frequency, @ 942cm^{-1}.

The pyrazoles (2, R=Br; R=CH_3) showed similar characteristics, and this information was collectively used in the determination of the structure of the pyrazole (3) in Chapter 3. The results of these studies are assembled in Table 1 (the pyrazoles), and Table 2 (the N-acetylpyrazoles) all the spectra being recorded in the form of KCl discs.



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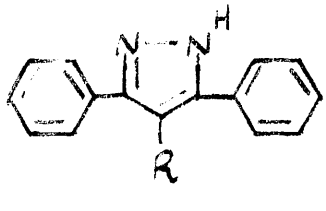

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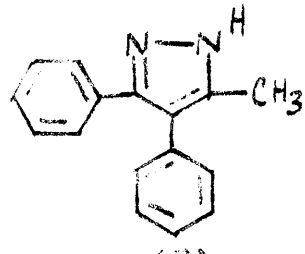

(3)

TABLE 1.

Pyrazole	>NH	>C=N-	Fingerprint
(1, R=H)	2850	1464	976
(1, R=Br)	2855	1444	973
(1, R=CH_3)	2850	1462	974
(2, R=Br)	3150	1462	956
(2, R=CH_3)	3165	1460	946
(3)	3120	1444	970

The physical properties of pyrazoles, high b.p., association etc., have led to the suggestion[4] that pyrazoles exist as hydrogen-bonded dimers, hence the compounds (1, R=H; R=Br; R=CH_3) have a low >NH absorption frequency. Since the pyrazoles (2, R=Br; R=CH_3) and (3) exhibit their >NH absorption at rather higher frequencies, this may indicate that 3,4,5-trisubstituted pyrazoles have difficulty in forming hydrogen-bonded dimers.

TABLE 2.

Pyrazole	>C=O	>C=N-	Fingerprint
(1, R=H)	1735	1462	944
(1, R=Br)	1735	1448	942
(1, R=CH_3)	1730	1448	941
(2, R=Br)	1730	1440	940
(2, R=CH_3)	1720	1442	935
(3)	1730	1460	954

Very recently, Zerbi and Alberti[5] have discussed the infrared spectra of 3(5)-alkyl; 4-alkyl and N-alkylpyrazoles and they have observed intense peaks in the fingerprint region of the spectrum corresponding to those reported here. It would therefore seem that such an absorption is a characteristic property of the pyrazole ring.

EXPERIMENTAL

4-Bromo-3,5-diphenylpyrazole[6] (2, R=Br).

Bromine was dropped into a solution of 3,5-diphenylpyrazole (0.25g.) in chloroform (8cc.) until the solution no longer decolourised the bromine. The solution was washed with sodium carbonate, water then dried. Removal of the solvent gave a yellow solid which crystallised from ethanol, affording 4-bromo-3,5-diphenylpyrazole as colourless prisms (0.22g.) m.p. 201-202° (lit.[6] 198-199°) (Found: C,60.15; H,3.85; N,9.4. Calc. for $C_{15}H_{11}BrN_2$: C,60.2; H,3.75; N,9.35%).

The acetyl derivative crystallised from petrol as colourless rods m.p. 92-93°. (Found: C,60.05; H,3.75; N,8.2. $C_{17}H_{13}BrN_2O$ requires C,59.85; H,3.8; N,8.2%).

1-Acetyl-4-methyl-3,5-diphenylpyrazole.

This compound was obtained by acetylation of 4-methyl-3,5-diphenylpyrazole (2, R=CH_3) with boiling acetic anhydride and crystallised from petrol (40-60°) as colourless prisms m.p. 72-73°. (Found: C,77.95; H,5.95; N,10.05. $C_{18}H_{16}N_2O$ requires C,78.25; H,5.85; N,10.15%).

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2. Otting, Ber., 1956, 89, 2887.

3. Otting, Ber., 1956, 89, 1940.

4. Hunter, J. Chem. Soc., 1945, 806.

5. Zerbi and Alberti, Spectrochim. Acta, 1962, 18, 407.

6. Keller and von Halban, Helv. Chim. Acta, 1944, 27, 1253.

Leslie B. Young

Thesis: 'Extrusion of Sulphur'

A copy of the thesis has now been sent to the External Examiner who is Dr. E. J. Forbes of the University of Birmingham.

Your Special Committee is Professor Raphael (Convener)
Dr. Loudon
Dr. McCorkindale