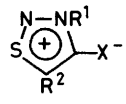
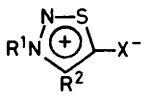
Cyclic Meso-ionic Compounds. Part 23.[1] Novel Chemistry of 1,2,4-Thiadiazoles and Their Transformation into Meso-ionic 1,2,4-Thiadiazolium Derivatives

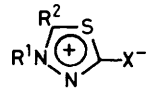
Christopher G. Newton and W. David Ollis *
Department of Chemistry, The University, Sheffield S3 7HF
Derek E. Wright
The Research Laboratories, May and Baker Ltd., Dagenham, Essex RM10 7XS

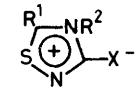
Representatives of two new classes of meso-ionic heterocycles have been synthesised, the 1,2,4-thiadiazolium-3-olate (8) and the 1,2,4-thiadiazolium-3-tosylaminide (25). The reactions of 1,2,4-thiadiazoles and nucleophiles follow two general pathways: (i) reductive transformation to *N*-thiobenzoyl derivatives and (ii) elimination of elemental sulphur and the formation of *N*-benzoyl derivatives. A mechanistic rationale is proposed for the operation of pathways (i) and (ii). Earlier views on the oxidative formation of certain 1,2,4-thiadiazoles are corrected. A novel synthetic route to heterocycles containing sulphur–nitrogen bonds is described. 1,2,4-Thiadiazoles are formed by oxidation of *N*-thiobenzoylureas and *N*-thiobenzoylguanidines by bis(4-methoxyphenyl) telluroxide.

Four types of meso-ionic thiadiazoles can in principle exist as possible members of the type-A class of meso-ionic heterocycles.[2] These are the conjugated mesomeric betaine[3] derivatives of 1,2,3-thiadiazoles [(1) and (2)], 1,3,4-thiadiazoles (3), and 1,2,4-thiadiazoles (4). Meso-ionic heterocycles of the types (1), (2), and (3) have been extensively investigated.[2] Known representatives include the 1,2,3-thiadiazolium-4-olates (1; X = O), 1,2,3-thiadiazolium-5-olates (2; X = O), 1,2,3-thiadiazolium-5-aminides (2; X = NR^3), 1,2,3-thiadiazolium-5-thiolates (2; X = S), 1,2,3-thiadiazolium-5-methylides (2; X = CYZ), 1,3,4-thiadiazolium-2-olates (3; X = O), 1,3,4-thiadiazolium-2-aminides (3; X = NR^3), 1,3,4-thiadiazolium-2-thiolates (3; X = S), and 1,3,4-thiadiazolium-2-methylides (3; X = CYZ). It is interesting to note that the pioneering investigations on the 1,3,4-thiadiazolium-2-thiolates (3; X = S) were carried out by Busch (1865—1941), long before it was recognised that these compounds could be appropriately formulated with monocyclic meso-ionic structures.


(1)


(2)


(3)

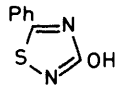

(4)

The claim[4] to have prepared the first example of a meso-ionic 1,2,4-thiadiazole (4; R^1 = Ph, R^2 = Me, X = NH) was subsequently withdrawn:[5] our present re-investigation has confirmed this decision. Thus, at the commencement of our studies, no meso-ionic 1,2,4-thiadiazole derivative (4) was known. We now report upon the synthesis and the chemistry of two new classes of meso-ionic heterocycles (4; X = O) and [4; X = $NSO_2C_6H_4Me$-*p*]. These compounds thus become the first authentic examples of meso-ionic 1,2,4-thiadiazoles.

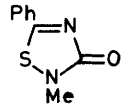
Our approach to the 1,2,4-thiadiazolium-3-olate (8) was based upon the methylation of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (5).[6] It was appreciated that, in principle, *O*- and *N*-methylation could lead to three products, (6), (7), and (8): these three products were obtained using two different methods. Methylation using dimethyl sulphate and aqueous sodium hydroxide at room temperature gave 2-methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-one (6) (yield 16%), 3-methoxy-5-phenyl-1,2,4-thiadiazole (7) (yield 8%), and recovered starting material. The desired result was obtained by heating (100 °C; 3 h) 3-hydroxy-5-phenyl-1,2,4-thiadiazole (5) with methyl toluene-4-sulphonate followed by aqueous work-up. This gave 2-methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-one (6) (yield 23%), 4-methyl-5-phenyl-1,2,4-thiadiazolium-3-olate (8) (yield 10%), and *N*-benzoyl-*NN'*-dimethylurea (9) (yield 19%). It is proposed that *N*-benzoyl-*NN'*-dimethylurea (9) is formed by alkaline hydrolytic desulphurisation (see below) during the work-up of the 2,4-di-*N*-methyl derivative (12) produced during the methylation.

The constitutions (6), (7), and (8) were assigned to the isomeric monomethyl derivatives on the basis of the following evidence. Mass spectrometry established their molecular formula, $C_9H_8N_2OS$. The compound, m.p. 45—47 °C, showed the absence of a carbonyl band in its i.r. spectrum and its ^{1}H n.m.r. spectrum showed a singlet (δ 4.14) assignable to an *O*-methyl group. These spectral properties, its u.v. spectrum ($\lambda_{max.}$ 248 and 293 nm) and direct comparison established that this compound was identical with 3-methoxy-5-phenyl-1,2,4-thiadiazole (7) which had been previously obtained from 3-chloro-5-phenyl-1,2,4-thiadiazole and sodium methoxide by Kurzer and Taylor.[6] The second methylation product, m.p. 184—185 °C, showed a carbonyl band ($\nu_{max.}$ 1 682 cm^{-1}) in its i.r. spectrum, an *N*-methyl singlet (δ 3.42) in its ^{1}H n.m.r. spectrum, and long wavelength absorption ($\lambda_{max.}$ 262, 300, and 325 nm) compatible with its constitution as the *N*-methyl derivative (6). This constitution (6) was confirmed by its alkaline hydrolysis yielding *N*-benzoyl-*N'*-methylurea (10), and *N*-methyl-*N'*-thiobenzoylurea (13). The transformation (6) ⟶ (10) is an alkaline hydrolytic desulphurisation (see below). The transformation (6) ⟶ (13) involved a base catalysed reduction the mechanism of which is considered later.

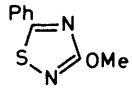
Having settled the constitutions of the *N*-methyl derivative (6) and the *O*-methyl derivative (7), it followed by exclusion that the meso-ionic structure (8) should be considered for the



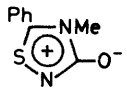
(5)



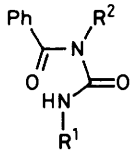
(6)



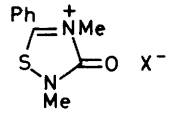
(7)



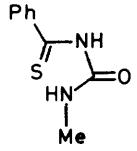
(8)



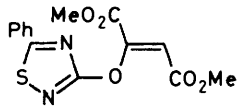
(9) $R^1 = R^2 = Me$
(10) $R^1 = Me$, $R^2 = H$
(11) $R^1 = H$, $R^2 = Me$



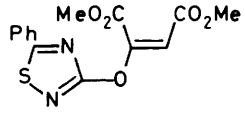
(12) X = Toluene–4–sulphonate



(13)



(14)



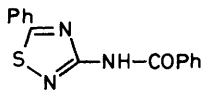
(15)

third isomer, m.p. 173—178 °C. Comparison of the spectroscopic properties of the *N*-methyl isomers (6) and (8) was informative. The formulation (8) was supported by (i) the extent of single-bond character indicated for its carbonyl group by its i.r. spectrum ($\nu_{max.}$ 1 660 cm^{-1}), (ii) the ^1H n.m.r. chemical shift of the *N*-methyl group (δ 3.68) indicating its association with a partially positively charged system, and (iii) its absorption spectrum ($\lambda_{max.}$ 254 and 335 nm). The location of the *N*-methyl substituent was demonstrated by the presence of a fragment ion ($PhC{\equiv}\overset{+}{N}Me$) defined by high resolution in the mass spectrum of the compound (8). This fragmentation is characteristic of similarly constituted meso-ionic heterocycles.[7]

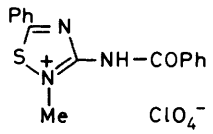
Alkaline hydrolysis of 4-methyl-5-phenyl-1,2,4-thiadiazolium-3-olate (8) yielded *N*-methylbenzamide and *N*-benzoyl-*N*-methylurea (11). These two products are formed by reactions which provide a further example of alkaline hydrolytic desulphurisation (see below). *N*-Benzoyl-*N*-methylurea (11) has not been described previously. Benzoylation of *N*-methylurea yielded *N*-benzoyl-*N'*-methylurea (10) and *N*-benzoyl-*N*-methylurea (11).

In principle, 3-hydroxy-5-phenyl-1,2,4-thiadiazole (5) could equilibrate with its 4*H* meso-ionic tautomer [*cf.* (8)]. However, attempts to trap this 4*H* tautomer by cycloaddition with dimethyl acetylenedicarboxylate were not successful. Instead this reaction yielded the fumarate (14) and the maleate (15) derivatives formed by nucleophilic addition. These diastereoisomers were distinguished by comparison of the chemical shift of their vinyl protons [(14) δ 7.11)] and [(15) δ 6.02] with the ^1H n.m.r. spectra of appropriate model compounds.[8]

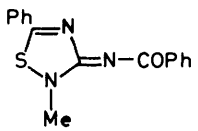
The synthesis of the meso-ionic heterocycle (4; R^1 = Ph, R^2 = Me, X = NBz) was not successfully completed, but the results of some experiments directed towards this objective are briefly reported. Methylation of 3-benzamido-5-phenyl-1,2,4-thiadiazole (16) [9] with methyl fluorosulphonate followed by treatment with perchloric acid yielded the salt (17). The site of *N*-methylation in the formation of the salt (17) was established by treatment of the salt with aqueous sodium carbonate which yielded *N*-benzoyl-2-methyl-5-phenyl-1,2,4-thiadiazol-3-(2*H*)-imine (18). The constitution (18)



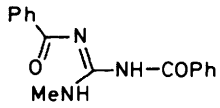
(16)



(17)



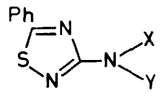
(18)



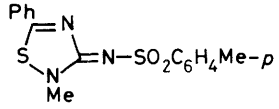
(19)

was based upon (i) its mass spectrum which showed the absence of a fragment ion at *m/z* 118 ($PhC{\equiv}\overset{+}{N}Me$) and the presence of a fragment ion at *m/z* 103 ($PhC{\equiv}N^{+\cdot}$) and (ii) its ready hydrolysis on silica gel yielding *NN'*-dibenzoyl-*N''*-methylguanidine (19).

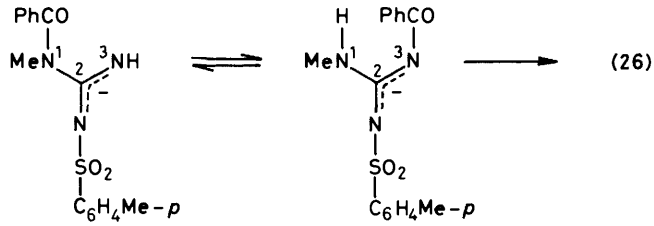
The synthesis of the meso-ionic 1,2,4-thiadiazole (25), in which the exocyclic anionoid residue is a toluene-*p*-sulphonaminide group, has been successfully achieved by the following transformations. Methylation of the *N*-toluene-4-sulphonyl derivative (21) [9] with methyl fluorosulphonate followed by treatment with aqueous sodium carbonate yielded three isomeric products, m.p. 130—131 °C, m.p. 238—241 °C, and m.p. 230—232 °C. Three possible sites of *N*-methylation were available in the precursor (21) so three constitutions (23), (24), and (25) could be considered for the three isomeric products, $C_{16}H_{15}N_3O_2S$. Structural assignments could be initially considered on the basis of mass spectral fragmentation patterns.[7] The compounds, m.p. 130—131 °C and m.p. 238—241 °C, both showed fragment ions at *m/z* 103 ($PhC{\equiv}N^{+\cdot}$) which could be associated with the constitutions (23) and (24). In contrast, the mass spectrum of the isomer, m.p. 230—232 °C,



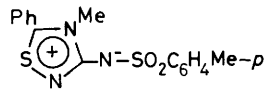
(20) X = Me, Y = H
(21) X = H, Y = $SO_2C_6H_4Me$-*p*
(22) X = Y = $SO_2C_6H_4Me$-*p*
(23) X = Me, Y = $SO_2C_6H_4Me$-*p*



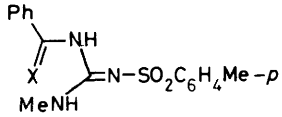
(24)



Scheme 1.



(25)



(26) X = O
(27) X = S

showed a fragment ion at *m/z* 118 ($PhC\equiv\overset{+}{N}Me$) indicating this isomer had the meso-ionic structure (25). Tosylation of 3-methylamino-5-phenyl-1,2,4-thiadiazole (20)[5] gave the isomer, m.p. 130—131 °C, thus establishing that this isomer had the constitution (23). It followed that the isomer, m.p. 238—241 °C, had the constitution (24) and this assignment provided an interpretation of the results of its hydrolysis. Acidic hydrolysis yielded 3-methylamino-5-phenyl-1,2,4-thiadiazole (20) and *N*-benzoyl-*N'*-methyl-*N''*-(*p*-tolylsulphonyl) guanidine (26). The formation of 3-methylamino-5-phenyl-1,2,4-thiadiazole (20) by hydrolysis of the 2-methyl derivative (24) presumably involved hydrolysis of the *N*-tosyl group followed by a Dimroth rearrangement of 2-methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-imine to 3-methylamino-5-phenyl-1,2,4-thiadiazole (20) as previously reported by Goerdeler and Mertens.[5] Alkaline hydrolysis of the 2-methyl derivative (24) yielded a mixture of the *N*-benzoyl and *N*-thiobenzoyl derivatives (26) and (27). The transformation (24) ⟶ (27) is another example of a base catalysed reduction with retention of sulphur in the product (see below). This result contrasts with the alkaline hydrolysis of the 4-methyl derivative (25) which surprisingly yielded the *N*-benzoyl derivative (26) with no trace of the *N*-thiobenzoyl derivative (27). The mechanism of the transformation (25) ⟶ (26) clearly involves a 1,3-migration of the *N*-benzoyl group which has ample precedent.[10] The course of this base catalysed isomerisation could well be determined by the relative thermodynamic stabilities of the anions leading to the observed product (26) (Scheme 1).

Possible Mechanisms for the Hydrolysis of 1,2,4-*Thiadiazoles and Meso-ionic* 1,2,4-*Thiadiazolium Derivatives.*—The products obtained by the alkaline hydrolysis of various 1,2,4-thiadiazoles are reported in this paper. These results may be summarised as follows: (6) ⟶ (10) + (13); (8) ⟶ (11); (24) ⟶ (26) + (27); (25) ⟶ (26).

The products (10), (11), and (26) are *N*-benzoyl derivatives and their formation involves the loss of ring sulphur from the precursors. The products (13) and (27) are *N*-thiobenzoyl derivatives and their formation involves retention of ring sulphur and a process which is the equivalent of a formal reduction of the precursor: thus (6) + 2H ⟶ (13) and (24) + 2H ⟶ (27). The possibility that this reduction involved the use of aqueous ethanol as solvent (see Experimental section) has been firmly excluded. The same results were obtained when aqueous tetrahydrofuran or aqueous dimethylformeride was used as solvent.

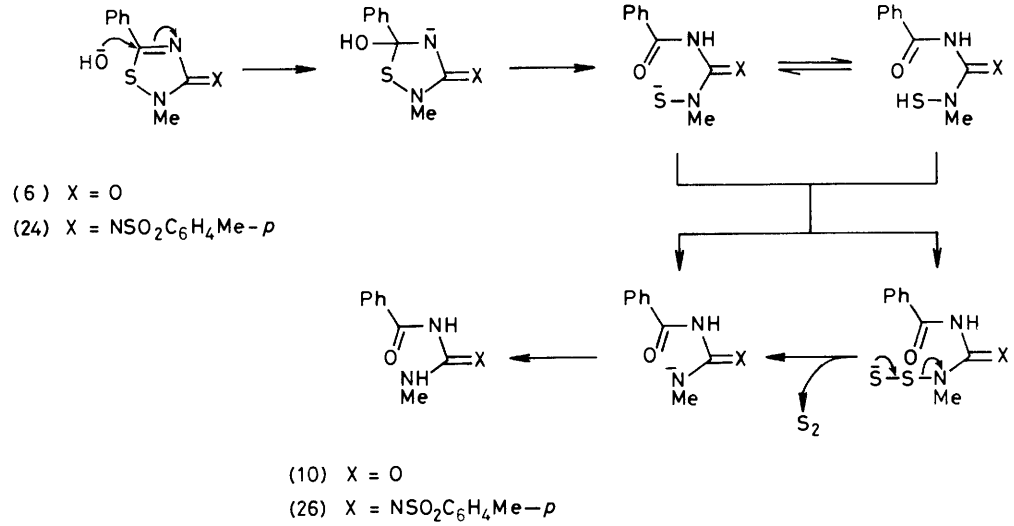
These base catalysed transformations pose interesting mechanistic problems. The possibility that the *N*-benzoyl derivatives were formed by hydrolysis of the corresponding *N*-thiobenzoyl derivatives is excluded by the following experimental result. The *N*-thiobenzoyl derivative (13) was not hydrolysed to the *N*-benzoyl derivative (10) under the conditions used to achieve the hydrolysis (6) ⟶ (10) + (13). Two pathways which could be involved in two transformations, (6) ⟶ (10) + (13) and (24) ⟶ (26) + (27), are given in Scheme 2 and Scheme 3.

Mechanisms for the formation of the *N*-benzoyl derivatives (Scheme 2) and the *N*-thiobenzoyl derivatives (Scheme 3) are depicted only in general terms. Scheme 2 indicates how the formation of the *N*-benzoyl derivatives could be accompanied by the elimination of elemental sulphur, as S_2 or its equivalent, in accord with current opinion regarding this type of reaction.[11] Organic reactions resulting in the extrusion of sulphur are usually depicted in mechanistic terms as involving the elimination of atomic sulphur. This elimination of atomic sulphur is, of course, unacceptable and the elimination of sulphur as S_2 molecules, or their equivalent, is much more reasonable.

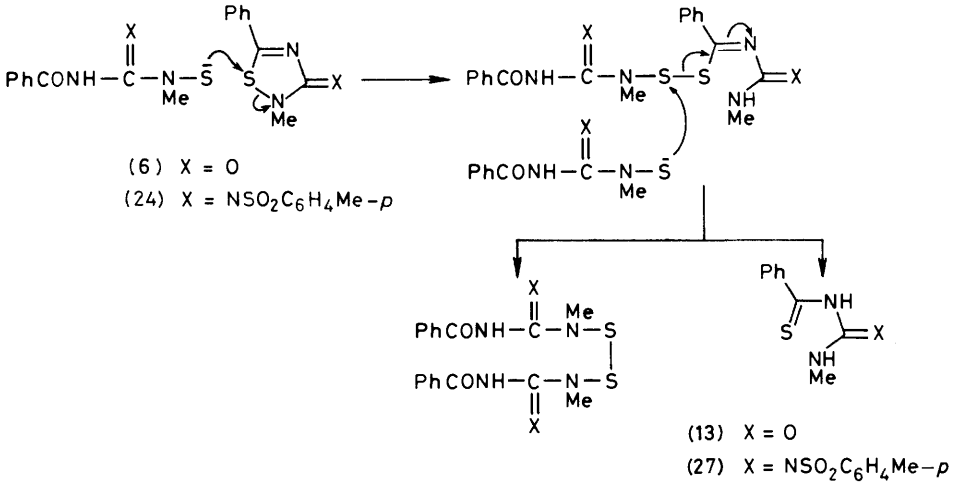
The formation of *N*-thiobenzoyl derivatives (13) and (27) involves reduction. The thiohydroxamate anion generated in Scheme 2 is the postulated reducing agent (Scheme 3) and this leads to a postulated disulphide and the observed *N*-thiobenzoyl derivatives (13) and (27). The disulphide was not detected but it would not be expected to survive and its transformation into other substances could be expected. The reaction between the thiohydroxamate anion and 1,2,4-thiadiazoles (6) and (24) can be regarded either as an electron transfer process or as a nucleophilic attack at sulphur by the thiohydroxamate anion (Scheme 3). Nucleophilic attack at sulphur with cleavage of S–N bonds is well known in the reactions of nucleophilic reagents towards isothiazoles,[12–14] 1,2,3-thiadiazoles,[15] and 1,2,4-thiadiazoles.[16–18]

In contrast, alkaline hydrolysis of the meso-ionic heterocycles (8) and (25) yield the *N*-benzoyl derivatives (11) and (26); the corresponding *N*-thiobenzoyl derivatives were not detected. This difference in reactivity between the 1,2,4-thiadiazoles (6) and (24) and the meso-ionic 1,2,4-thiadiazolium derivatives (8) and (25) can be rationalised on the basis of reaction mechanisms related to those given in Schemes 2 and 3. It is proposed that the meso-ionic 1,2,4-thiadiazolium derivatives (8) and (25) react with hydroxide anion exclusively by nucleophilic attack at C-5 (compare Scheme 2). Nucleophilic attack at sulphur with S–N bond cleavage (compare Scheme 3) is not observed in the alkaline hydrolysis of the meso-ionic heterocycles (8) and (25) because nucleophilic attack at sulphur is mechanistically unacceptable for the meso-ionic heterocycles (8) and (25).

Crook and Sykes [18] have made a detailed examination of the reaction between the 2-methyl-3,5-diphenyl-1,2,4-thiadiazolium cation and many nucleophiles. The consequences



Scheme 2.



Scheme 3.

of nucleophilic attack at C-3, C-5, and S-1 are all observed in association with two major pathways (i) loss of sulphur and the formation of *N*-benzoyl derivatives and (ii) retention of sulphur and the reductive formation of *N*-thiobenzoyl derivatives. There is clearly a reassuring correspondence between our results on the alkaline hydrolysis of 2- and 4-substituted 1,2,4-thiadiazoles and the complementary results obtained by Crook and Sykes [18] on the reaction of 1,2,4-thiadiazolium cations with nucleophiles. Crook and Sykes [18] have observed that the sulphur nucleophiles (benzenethiolate, sodium sulphide, and sodium thiosulphate) and sodium borohydride all yield the *N*-thiobenzoyl derivative exclusively and in good yields. The formation of diphenyl disulphide from benzene thiolate anion provides excellent support for the proposal given in Scheme 3.

Crook and Sykes [18] observe these reactions but do not comment on the mechanism of the reductive formation of *N*-thiobenzoyl derivatives by reaction of the 2-methyl-3,5-diphenyl-1,2,4-thiadiazolium cation with alkali. We believe that the mechanisms now proposed (Schemes 2 and 3) may be of general significance in many reactions of sulphur–nitrogen heterocycles with nucleophiles. The general mechanisms given in Schemes 2 and 3 provide satisfying rationalisations for all the results obtained by Crook and Sykes.[18]

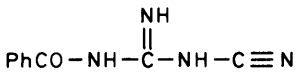
Reinterpretation of Earlier Work on the Oxidative Formation of 1,2,4-*Thiadiazoles.*—The reaction of *N*-benzoyl-*N'*-cyanoguanidine (28) with hydrogen sulphide in ethanolic solution at room temperature has been reported to yield the corresponding thioamide (29).[19] Kurzer [9] subsequently discovered two interesting transformations of this thioamide (29) by its oxidation with hydrogen peroxide. Under neutral conditions, oxidation with aqueous hydrogen peroxide in boiling ethanol yielded compound A ($C_8H_7N_3S$, m.p. 132—134 °C, yield 75—82%). Under acidic conditions, oxidation with aqueous hydrogen peroxide in boiling ethanol plus concentrated hydrochloric acid yielded compound B ($C_9H_8N_4OS$, m.p. 215—217 °C, yield 60%). Kurzer [9] recognised that compound A was identical with 3-amino-5-phenyl-1,2,4-thiadiazole (30), previously obtained by Goerdeler and Fincke [20] by oxidation of *N*-thiobenzoylguanidine with bromine and sodium carbonate in methanol.

Kurzer [9] formulated compound B as 5-amino-3-benzamido-1,2,4-thiadiazole (31). He believed that the oxidative transformation (29) ⟶ (31) was straightforward, but he was clearly perplexed by the formation of the known compound (30) by the oxidative transformation (29) ⟶ (30). Careful consideration of possible mechanisms did not provide a solution.[21]

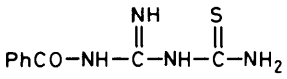
We repeated this reaction under neutral conditions and found that oxidation of the putative thioamide (29) with hydrogen peroxide in boiling ethanol gave compound A (m.p. 139—141 °C, yield 65%) (30) and compound B (m.p. 215—217 °C, yield 11%). The compounds (28) and (30) were obviously correctly formulated so the constitution (29) was re-examined.

The 'thioamide' was yellow and its electronic spectrum ($\lambda_{max.}$ 281, 338, and 440 nm) suggested that it was an *N*-thiobenzoyl derivative. The reaction of *N*-benzoyl-*N'*-cyanoguanidine (28) with hydrogen sulphide could be interpreted (Scheme 4) in terms of the equilibrium (28a) ⇌ (28b) and this suggested that the constitution (29) for the 'thioamide' should be replaced by (32).

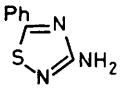
The constitution (32), or a tautomeric equivalent, is fully supported by its mass spectral fragmentation pattern (Scheme 5).



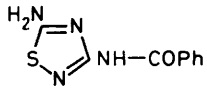
(28)



(29)

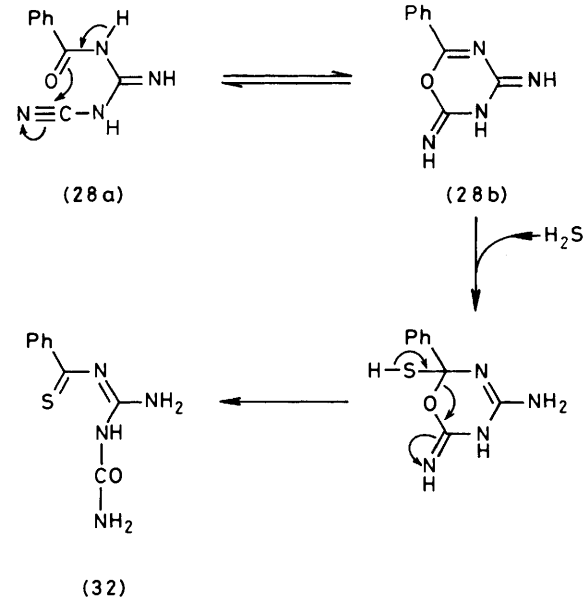


(30)



(31)

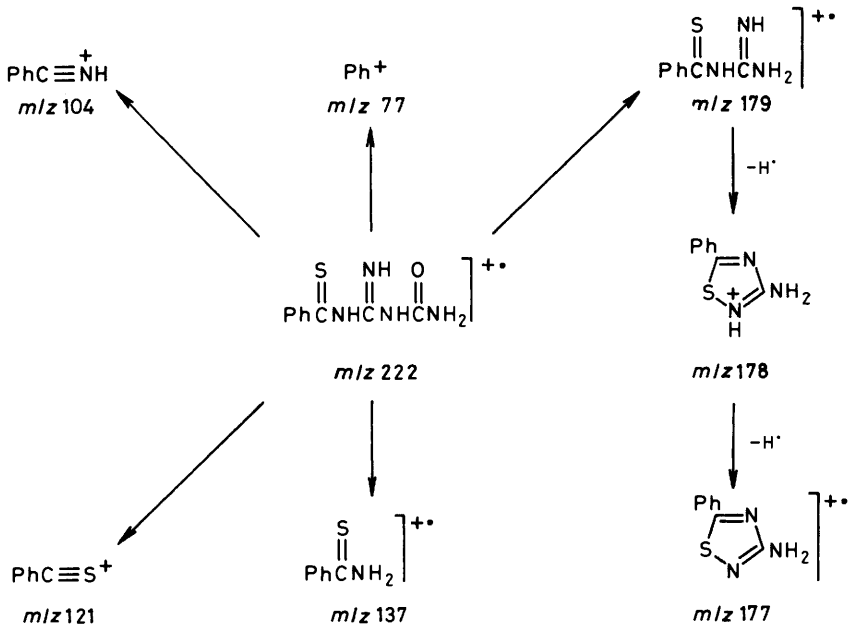
Oxidative cyclisation (Scheme 6) involving the conformational equilibrium (32a) ⇌ (32b) could yield the two products (30) and (33). Replacement of the constitution (31) by the constitution (33) for compound B follows. A mechanism is proposed (Scheme 6) for the oxidative cyclisation (32a) ⟶ (30) which also accounts satisfactorily for the loss of the carboxamido group by an oxidative process. The new constitution (33) for compound B is confirmed by its mass spectral fragmentation pattern (Scheme 7).



Scheme 4.

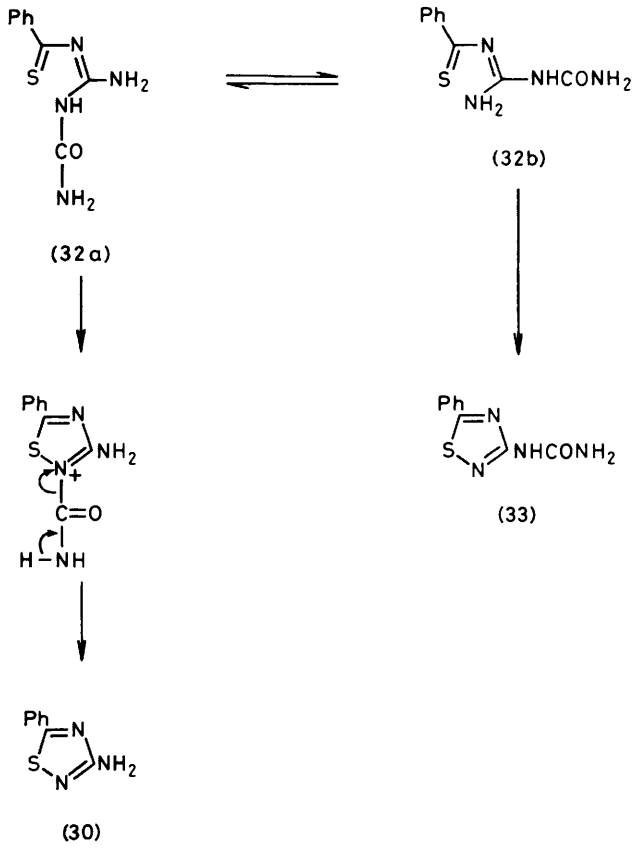
Bis(4-methoxyphenyl) telluroxide has been shown to be a very selective reagent for the conversion of thiocarbonyl into carbonyl groups.[22] Intramolecular participation by nitrogen occurred when the *N*-thiobenzoyl derivative (32) was oxidised with bis(4-methoxyphenyl) telluroxide. This reaction yielded compound A (30) (yield 76%) and compound B (33) (yield 22%). Nitrogen–sulphur bond formation also occurred in the oxidation of *N*-thiobenzoyl-*N'*-methylurea with bis(4-methoxyphenyl) telluroxide yielding the 1,2,4-thiadiazol-3-one (6).

The replacement of the old constitution (29) by the new constitution (32) also solves another problem.[19] Base catalysed cyclisation of a compound with the constitution (29) was expected to yield 2-amino-4-mercapto-6-phenyl-1,3,5-triazine.[19] The product was, in fact, 2-amino-4-hydroxy-6-phenyl-1,3,5-triazine.[19] This result could not be explained by the original



Scheme 5. Mass spectral fragmentation pattern of *N*-carbamoyl-*N'*-thiobenzoylguanidine (32). The composition of all fragment ions was established by high resolution measurements

constitution (29), but is in full accord with the new constitution (32).



Scheme 6.

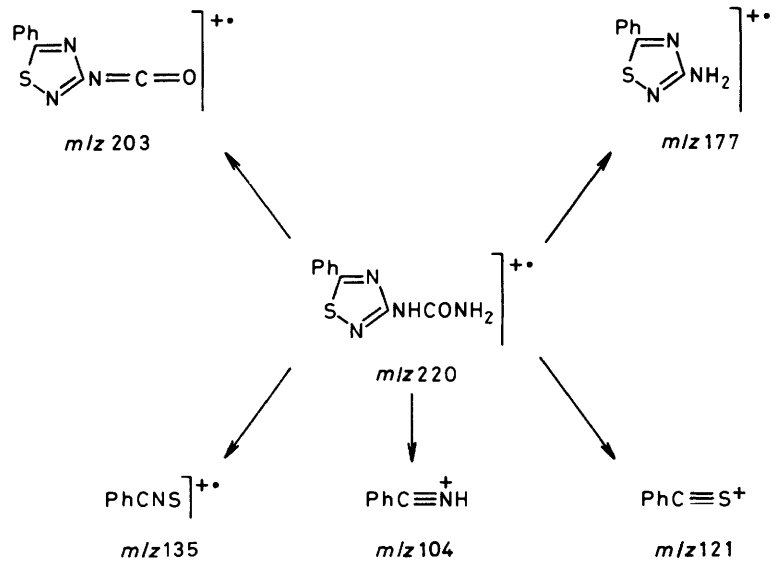
The creation of nitrogen–sulphur bonds, by oxidation of suitable precursors with the reagent, bis(4-methoxyphenyl) telluroxide, could well be a general reaction for the synthesis of 1,2,4-thiadiazoles and related heterocycles containing N–S bonds. Oxidation of thiocarbonyl derivatives by bis(4-methoxyphenyl) telluroxide with retention of sulphur in the product is a new type of reaction for this reagent. However, the mechanism for the creation of S–N bonds obviously parallels that proposed [22] for the transformation of thiocarbonyl to carbonyl groups.

Experimental

General experimental directions are given in Part 21.[23]

3-Hydroxy-5-phenyl-1,2,4-thiadiazole (5).—This compound was prepared (70%) as previously described [6] by diazotisation of 3-amino-5-phenyl-1,2,4-thiadiazole. Its ^{13}C n.m.r. spectrum is recorded for comparison with the ^{13}C n.m.r. spectra of related heterocycles: δ_C [$(CD_3)_2SO$] 126.5 (2,6- or 3,5-phenyl-C), 129.5 (3,5- or 2,6-phenyl-C), 130.0 (1-phenyl-C), 132.3 (4-phenyl-C), 171.7 (C-3), and 186.9 (C-5).

Methylation of 3-Hydroxy-5-phenyl-1,2,4-thiadiazole (5): *Formation of 2-Methyl-5-phenyl-1,2,4-thiadiazol-3(2H)-one* (6), *3-Methoxy-5-phenyl-1,2,4-thiadiazole* (7), *4-Methyl-5-phenyl-1.2,4-thiadiazolium-3-olate* (8), *and N-Benzoyl-NN'-dimethylurea* (9).—*Method A.* A solution of 3-hydroxy-5-phenyl-1,2,4-thiadiazole [6] (376 mg) in aqueous sodium hydroxide (20 ml; 0.45% w/v) was treated with dimethyl sulphate (0.1 ml) and the mixture stirred (48 h) at room temperature. Extraction with methylene dichloride, evaporation, and fractionation by preparative t.l.c. (methylene dichloride–ethyl acetate, 9 : 1) gave two fractions. Fraction 1 yielded *2-methyl-5-phenyl-1,2,4-thiadiazol-3(2H)-one* (R_F 0.15) (66 mg, 16%), colourless crystals, m.p. 184—185 °C from ethyl acetate (Found: C, 56.5; H, 4.4; N, 14.7; S, 16.6%; $M^{+\cdot}$, 192. $C_9H_8N_2OS$ requires C, 56.2; H, 4.2; N, 14.6; S, 16.7%; *M*, 192); $\lambda_{max.}$ 225sh, 262, 300sh, and 325 nm (ε 17 100, 21 850, 5 100, and 5 650); $\nu_{max.}$ 1 682 cm^{-1}; δ_H 3.42 (3 H, s, NCH_3), 7.50 (2 H, t, *J* 8.5 Hz, 3,5-phenyl-H), 7.60 (1 H, t, *J* 8.5 Hz, 4-phenyl-H), and 7.88 (2 H, d, *J* 8.5 Hz, 2,6-phenyl-H); δ_C 30.0 (CH_3), 126.3 (2,6- or 3,5-phenyl-*C*), 129.3 (3,5- or 2,6-phenyl-*C*), 129.5 (1-phenyl-C), 133.4 (4-phenyl-C), 165.8 (C-3), and 177.0 (C-5). Fraction 2 yielded 3-methoxy-5-phenyl-1,2,4-thiadiazole (R_F 0.85) (30 mg, 8%) m.p. 45—47 °C (lit.,[6] m.p. 50—51 °C) (Found: $M^{+\cdot}$, 192. Calc. for $C_9H_8N_2OS$: *M*, 192); $\lambda_{max.}$ 248 and 293 nm (ε 12 100



Scheme 7. Mass spectral fragmentation pattern of *N*-(5-phenyl-1,2,4-thiadiazol-3-yl)urea (33). The composition of all fragment ions was established by high resolution measurements

and 9 500); $\nu_{max.}$ 2 920, 1 600, and 1 500 cm^{-1}; δ_H 4.14 (3 H, s, OCH_3), 7.42—7.55 (3 H, m, 3,5- and 4-phenyl-H), and 7.93 (2 H, dd, *J* 8.5 and 2 Hz, 2,6-phenyl-H). Acidification of the aqueous phase after methylene dichloride extraction yielded starting material (159 mg, 42%).

Method B. A mixture of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (1 g) and methyl toluene-4-sulphonate (1 g) was heated (3 h) at 100 °C, cooled, and shaken with a mixture of aqueous sodium hydrogen carbonate and methylene dichloride. The organic layer was then washed with aqueous sodium hydroxide solution (10% w/v), then with water, and finally evaporated. The residual oil was purified by medium pressure column chromatography (methylene dichloride followed by acetone–methylene dichloride–ethyl acetate–methanol, 1 : 1 : 1 : 1), giving the following fractions. Fraction 1 yielded N-*benzoyl*-NN′-*dimethylurea* (203 mg, 19%) as colourless crystals, m.p. 98—99 °C from ethanol (Found: C, 62.7; H, 6.4; N, 14.5%; $M^{+\cdot}$, 192. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 14.6%; *M*, 192); $\nu_{max.}$ 3 320, 1 705, and 1 650 cm^{-1}; δ_H 2.88 (3 H, d, *J* 6 Hz, $NHCH_3$), 3.14 (3 H, s, NCH_3), 7.43 (5 H, s, phenyl-H), and 9.02 (1 H, br q, NH); δ_C 27.0 (q, $NHCH_3$), 35.7 (q, $PhCONCH_3$), 126.4 (d, 2,6- or 3,5-phenyl-C), 128.6 (d, 3,5- or 2,6-phenyl-C), 130.6 (d, 4-phenyl-C), 136.1 (s, 1-phenyl-C), 155.9 (s, $CONHCH_3$), and 174.4 (s, PhCO). Fraction 2 yielded 2-methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-one (250 mg, 23%) as colourless crystals, m.p. 184—185 °C, identical with the product obtained by Method A. Fraction 3 yielded 4-*methyl*-5-*phenyl*-1,2,4-*thiadiazolium*-3-*olate* (101 mg, 10%) as colourless crystals, m.p. 173—178 °C from ethyl acetate (Found: C, 56.0; H, 4.4; N, 14.4; S, 16.7%; $M^{+\cdot}$, 192.0361. $C_9H_8N_2OS$ requires C, 56.2; H, 4.2; N, 14.6; S, 16.7%; *M*, 192.0357); $\lambda_{max.}$ 225, 238, 254, and 335 nm (ε 8 050, 7 500, 7 600, and 6 100); $\nu_{max.}$ 1 660 cm^{-1}; δ_H 3.68 (3 H, s, NCH_3) and 7.55—7.75 (5 H, m, phenyl-H); δ_C 33.8 (CH_3), 125.9 (1-phenyl-C), 128.0 (2,6- or 3,5-phenyl-C), 129.6 (3,5- or 2,6-phenyl-C), 132.7 (4-phenyl-C), 163.0 (C-3), and 179.7 (C-5).

Alkaline Hydrolysis of 2-*Methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*one* (6): *Formation of* N-*Benzoyl*-N′-*methylurea* (10) *and* N-*Methyl*-N′-*thiobenzoylurea* (13).—A solution of 2-methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-one (161 mg) and sodium hydroxide (50 mg) in a mixture of ethanol (5 ml) and water (4 ml) was heated (2 min) at 100 °C with stirring, and kept (30 min) at room temperature. The solution was acidified with concentrated hydrochloric acid, evaporated, and the residue was shaken with a mixture of chloroform and water. The chloroform extract was evaporated and the residue was fractionated by preparative t.l.c. (methylene chloride–ethyl acetate, 9 : 1), giving two fractions. Fraction 1 yielded *N*-benzoyl-*N*′-methylurea (R_F 0.35) (74 mg, 50%) as colourless crystals, m.p. 172—174 °C from ethanol (lit.,[24] m.p. 170—171 °C) (Found: C, 60.6; H, 5.9; N, 15.8%; $M^{+\cdot}$, 178. Calc. for $C_9H_{10}N_2O_2$: C, 60.7; H, 5.7; N, 15.7%; *M*, 178); $\nu_{max.}$ (KBr) 1 700 and 1 670 cm^{-1}; δ_H 2.90 (3 H, d, *J* 5.5 Hz, $NHCH_3$), 7.42 (2 H, t, *J* 7 Hz, 3,5-phenyl-H), 7.53 (1 H, t, *J* 7 Hz, 4-phenyl-H), 8.02 (2 H, d, *J* 7 Hz, 2,6-phenyl-H), 8.79 (1 H, br q, $NHCH_3$), and 10.15 (1 *H*, br s, PhCONH); δ_C 26.3 (NCH_3), 127.7 (2,6- or 3,5-phenyl-C), 128.7 (3,5- or 2,6-phenyl-C), 132.5 (1-phenyl-C), 133.0 (4-phenyl-C), 154.8 (CH_3NHCO), and 168.1 (PhCO). Fraction 2 yielded *N*-methyl-*N*′-thiobenzoylurea (R_F 0.6) (43 mg, 26%) as yellow crystals, m.p. 165—167 °C from ethanol (lit.,[25] m.p. 143.5 °C) (Found: C, 55.7; H, 5.4; N, 14.4; S, 16.4%; $M^{+\cdot}$, 194. Calc. for $C_9H_{10}N_2OS$: C, 55.6; H, 5.2; N, 14.4; S, 16.5%; *M*, 194); $\lambda_{max.}$ 260 and 412 nm (ε 13 300 and 300); $\nu_{max.}$ (KBr) 1 705 cm^{-1}; δ_H 2.92 (3 H, d, *J* 5 Hz, $NHCH_3$), 7.41 (2 H, t, *J* 7 Hz, 3,5-phenyl-H), 7.51 (1 H, t, *J* 7 Hz, 4-phenyl-H), 7.78 (2 H, d, *J* 7 Hz, 2,6-phenyl-H), 9.70 (1 H, br s, PhCSN*H*), and 9.85 (1 H, br q, N*H*CH_3); δ_C 26.2 (NCH_3), 127.1 (2,6- or 3,5-phenyl-C), 128.4 (3,5- or 2,6-phenyl-C), 132.1 (4-phenyl-C), 141.8 (1-phenyl-C), 154.7 (CO), and 200.6 (CS).

Alkaline Hydrolysis of 4-*Methyl*-5-*phenyl*-1,2,4-*thiadiazolium*-3-*olate* (8): *Formation of* N-*Methylbenzamide and* N-*Benzoyl*-N-*methylurea* (11).—4-Methyl-5-phenyl-1,2,4-thiadiazolium-3-olate (78 mg), ethanol (5 ml), and aqueous potassium carbonate solution (1 ml, 10% w/v) were heated (10 min) at 100 °C, kept (3 h) at room temperature, and then shaken with dilute hydrochloric acid (20 ml; 2M) and chloroform (10 ml). Chloroform extraction, evaporation, and fractionation by preparative t.l.c. (ethyl acetate) yielded three fractions. Fraction 1 yielded starting material (R_F 0.1) (13 mg, 17%) as a colourless solid, m.p. 173—178 °C. Fraction 2 yielded *N*-methylbenzamide (R_F 0.47) (13 mg, 24%) as a colourless solid, m.p. 80—82 °C. Fraction 3 yielded N-*benzoyl*-N-*methylurea* (R_F 0.53) (8.5 mg, 12%) as colourless crystals, m.p. 125—127 °C from ethanol (Found: $M^{+\cdot}$, 178.0724. $C_9H_{10}N_2O_2$ requires *M*, 178.0741); $\nu_{max.}$ 3 500, 3 310, 1 710, and 1 665 cm^{-1}; δ_H 3.18 (3 H, s, NCH_3), 5.42 (1 H, br s, NH), 7.48 (5 H, s, phenyl-H), and 8.78 (1 H, br s, NH).

N-*Benzoyl*-N′-*methylurea* (10) *and* N-*Benzoyl*-N-*methylurea* (11).—*N*-Methylurea (740 mg), benzoyl chloride (1.6 g), and pyridine (15 ml) were heated (3 h) at 100 °C and then added to hydrochloric acid (100 ml; 1M) and ice. The precipitate yielded *N*-benzoyl-*N*′-methylurea (0.96 g, 54%) as colourless crystals, m.p. 166—170 °C. Chloroform extraction of the filtrate, washing with hydrochloric acid (2M), and evaporation yielded a residue (0.59 g, 33%) which consisted of *N*-benzoyl-*N*′-methylurea and *N*-benzoyl-*N*-methylurea only in the ratio 5 : 4 by ^1H n.m.r. Fractionation by h.p.l.c. (Spherisorb 11μ column, ethyl acetate–light petroleum, 1 : 3, flow rate 5.0 ml/min, u.v. detector at 280 nm) gave *N*-benzoyl-*N*-methylurea as colourless crystals, m.p. 125—127 °C, identical with an authentic sample.

Reaction of 3-*Hydroxy*-5-*phenyl*-1,2,4-*thiadiazole* (5) *with Dimethyl Acetylenedicarboxylate.*—3-Hydroxy-5-phenyl-1,2,4-thiadiazole (121 mg) and dimethyl acetylenedicarboxylate (110 mg) in nitromethane 10 ml) were heated (50 h) under reflux. Further portions (0.1 ml and 0.3 ml) of dimethyl acetylenedicarboxylate were added (at 7.5 and 22 h respectively) during the heating period. Evaporation and preparative t.l.c. (methylene dichloride–ethyl acetate, 9 : 1) gave two fractions. Fraction 1 yielded the *maleate derivative* (15) (R_F 0.55) (70 mg, 32%) as colourless crystals, m.p. 167—169 °C from ethanol (Found: C, 52.7; H, 3.9; N, 8.9; S, 10.1%; $M^{+\cdot}$, 320. $C_{14}H_{12}N_2O_5S$ requires C, 52.5; H, 3.8; N, 8.8; S, 10.0%; *M*, 320); $\nu_{max.}$ 1 735 and 1 720 cm^{-1}; δ_H 3.76 (3 H, s, OCH_3), 4.00 (3 H, s, OCH_3), 6.02 (1 H, s, $CHCO_2CH_3$), 7.56 (2 H, t, *J* 7 Hz, 3,5-phenyl-*H*), 7.70 (1 H, t, *J* 7 Hz, 4-phenyl-H), and 7.92 (2 H, d, *J* 7 Hz, 2,6-phenyl-H). Fraction 2 yielded the *fumarate derivative* (14) (R_F 0.4) (38 mg, 17%) as colourless crystals, m.p. 109—110 °C from ethanol (Found: $M^{+\cdot}$, 320.0455. $C_{14}H_{12}N_2O_5S$ requires *M*, 320.0464); $\nu_{max.}$ 1 730 and 1 710 cm^{-1}; δ_H 3.78 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.11 (1 H, s, $CHCO_2CH_3$), 7.52 (2 H, t, *J* 7.5 Hz, 3,5-phenyl-H), 7.63 (1 H, t, *J* 7.5 Hz, 4-phenyl-H), and 7.94 (2 H, d, *J* 7.5 Hz, 2,6-phenyl-H).

Methylation of 3-*Benzamido*-5-*phenyl*-1,2,4-*thiadiazole* (16): *Formation of* 3-*Benzamido*-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazolium Perchlorate* (17).—A mixture of 3-benzamido-5-phenyl-1,2,4-thiadiazole [9] (910 mg), chloroform (50 ml), and methyl fluorosulphonate (4 ml) was heated (48 h) under reflux. Fur-

ther portions (2 ml) of methyl fluorosulphonate were added (2.5 h, 28.5 h) during this heating period. The residue obtained from evaporation of the reaction mixture was dissolved in a mixture of glacial acetic acid (5 ml) and aqueous perchloric acid (3 ml; 60% w/v). The solution was diluted with ether (250 ml) and kept (18 h) at −30 °C when 3-*benzamido*-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazolium perchlorate* was obtained (546 mg, 43%) as colourless crystals, m.p. 165—175 °C from acetonitrile–ether (Found: C, 48.6; H, 3.8; Cl, 8.7; N, 10.5; S, 8.2%. $C_{16}H_{14}ClN_3O_5S$ requires C, 48.6; H, 3.6; Cl, 9.0; N, 10.6; S, 8.1%); $\nu_{max.}$ (KBr) 1 720 and 1 110—1 070 cm^{-1}; δ_H (CF_3CO_2H) 4.22 (3 H, s, NCH_3), 7.62 (2 H, t, *J* 7 Hz, 3,5-phenyl-H), 7.65 (2 H, t, *J* 7 Hz, 3,5-phenyl-H), 7.79 (1 H, t, *J* 7 Hz, 4-phenyl-H), 7.83 (1 H, t, *J* 7 Hz, 4-phenyl-H), 8.06 (2 H, d, *J* 7 Hz, 2,6-phenyl-H), and 8.13 (2*H*, d, *J* 7 Hz, 2,6-phenyl-H).

N-*Benzoyl*-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*imine* (18) *and* NN′-*Dibenzoyl*-N″-*methylguanidine* (19).—3-Benzamido-2-methyl-5-phenyl-1,2,4-thiadiazolium perchlorate (178 mg) was added to a solution of sodium carbonate (300 mg) in water (10 ml) and the mixture was immediately extracted with chloroform. Evaporation of the chloroform extract and fractionation by preparative t.l.c. (chloroform) gave two fractions. Fraction 1 yielded N-*benzoyl*-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*imine* (R_F 0.25) (102 mg, 77%) as pale yellow crystals, m.p. 120—130 °C from ethyl acetate (Found: C, 65.1; H, 4.3; N, 14.1; S, 10.6%; $M^{+\cdot}$, 295. $C_{16}H_{13}N_3OS$ requires C, 65.1; H, 4.4; N, 14.2; S, 10.9%; *M*, 295); $\nu_{max.}$ 1 630 and 1 590—1 560 cm^{-1}; δ_H 3.52 (3 H, s, NCH_3), 7.30—7.55 (6 H, m, 2 × 3,5-phenyl-H and 2 × 4-phenyl-H), 7.84 (2 H, d, *J* 7 Hz, 2,6-phenyl-H), and 8.32 (2 H, d, *J* 8 Hz, 2,6-phenyl-H). Fraction 2 yielded NN′-*dibenzoyl*-N″-*methylguanidine* (R_F 0.5) (3 mg, 2%) (the yield of this product was increased to 16% on allowing 24 h to elapse before elution of the t.l.c. plates) as colourless crystals, m.p. 120—122 °C from methanol (Found: C, 68.1; H, 5.5; N, 14.7%; $M^{+\cdot}$, 281. $C_{16}H_{15}N_3O_2$ requires C, 68.3; H, 5.4; N, 14.9%; *M*, 281); $\nu_{max.}$ 1 675 and 1 635 cm^{-1}; δ_H 3.15 (3 H, d, *J* 4.5 Hz, $NHCH_3$), 7.35—7.65 (6 H, m, 2 × 3,5-phenyl-H and 2 × 4-phenyl-H), 8.04 (2 H, d, *J* 7 Hz, 2,6-phenyl-H), 8.30 (2 H, d, *J* 7 Hz, 2,6-phenyl-H), 9.4 (1 H, br q, N*H*CH_3), and 14.48 (1 H br s, N*H*COPh).

5-*Phenyl*-3-(*toluene*-p-*sulphonamido*)-1,2,4-*thiadiazole* (21) *and* 5-*Phenyl*-3-[*bis*(p-*tolylsulphonyl*)*amino*]-1,2,4-*thiadiazole* (22).—3-Amino-5-phenyl-1,2,4-thiadiazole [9] (3.54 g), toluene-*p*-sulphonyl chloride (11.4 g) and pyridine (50 ml) were heated (4 h) at 100 °C and then added to dilute hydrochloric acid (300 ml; 1M) and ice. The precipitate was recrystallised from butan-2-one yielding 5-*phenyl*-3-[*bis*(p-*tolylsulphonyl*)*amino*]-1,2,4-*thiadiazole* (2.83 g, 28%) as colourless crystals, m.p. 218—220 °C (Found: C, 54.5; H, 3.9; N, 8.7; S, 20.1%; $M^{+\cdot}$, 485. $C_{22}H_{19}N_3O_4S_3$ requires C, 54.4; H, 3.9; N, 8.7; S, 19.8%; *M*, 485); $\nu_{max.}$ (KBr) 1 595 cm^{-1}; δ_H (CF_3CO_2H) 2.50 (6 H, s, 2 × tolyl-CH_3), 7.42 (4 H, d, *J* 9 Hz, 2 × 2,6-tolyl-H), 7.59 (2 H, t, *J* 7.5 Hz, 3,5-phenyl-H), 7.67 (1 H, t, *J* 7.5 Hz, 4-phenyl-H), 7.88 (4 H, d, *J* 9 Hz, 2 × 3,5-tolyl-H), and 7.92 (2 H, d, *J* 7.5 Hz, 2,6-phenyl-H). Concentration of the butan-2-one mother liquors gave 5-phenyl-3-(toluene-*p*-sulphonamido)-1,2,4-thiadiazole (3.27 g, 48%) as colourless crystals, m.p. 206—208 °C (lit.,[9] m.p. 206—208 °C) (Found: $M^{+\cdot}$, 331. Calc. for $C_{15}H_{13}N_3O_2S_2$: *M*, 331); δ_H [$(CD_3)_2CO$] 2.33 (3 H, s, tolyl-CH_3), 7.38 (2 H, d, *J* 9 Hz, 2,6-tolyl-H), 7.40—7.60 (3 H, m, 3,5-phenyl-H and 4-phenyl-H), 7.92 (2 H, d, *J* 7.5 Hz, 2,6-phenyl-H), 8.03 (2 H, d, *J* 9 Hz, 3,5-tolyl-H), and 10.71 (1 H, br s, NH).

3-[N-*Methyl*(p-*tolylsulphonyl*)*amino*]-5-*phenyl*-1,2,4-*thiadiazole* (23).—3-Methylamino-5-phenyl-1,2,4-thiadiazole (126 mg),[5] toluene-*p*-sulphonyl chloride (500 mg), and pyridine (5 ml) were heated (18.5 h) at 100 °C, and then added to dilute hydrochloric acid (15 ml; 1M) and ice. The precipitate was crystallised from ethanol giving 3-[N-*methyl*(p-*tolylsulphonyl*)*amino*]-5-*phenyl*-1,2,4-*thiadiazole* (212 mg, 93%) as colourless crystals, m.p. 130—131 °C (Found: C, 55.7; H, 4.6; N, 12.2; S, 18.7%; $M^{+\cdot}$, 345. $C_{16}H_{15}N_3O_2S_2$ requires C, 55.6; H, 4.4; N, 12.2; S, 18.6%; *M*, 345); $\nu_{max.}$ 1 600 cm^{-1}; δ_H 2.39 (3 H, s, tolyl-CH_3), 3.70 (3 H, s, NCH_3), 7.28 (2 H, d, *J* 8 Hz, 2,6-tolyl-H), 7.45—7.55 (3 H, m, 3,5-phenyl-H and 4-phenyl-H), 7.87 (2 H, d, *J* 8 Hz, 2,6-phenyl-H), and 8.02 (2 H, d, *J* 8 Hz, 3,5-tolyl-H).

Methylation of 5-*Phenyl*-3-(*toluene*-p-*sulphonamido*)-1,2,4-*thiadiazole* (21)*: Formation of* 3-[N-*Methyl*-N-(p-*tolylsulphonyl*)*amino*]-5-*phenyl*-1,2,4-*thiadiazole* (23), N-(p-*Tolylsulphonyl*)-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*imine* (24), and N-(p-*Tolylsulphonyl*)-4-*methyl*-5-*phenyl*-1,2,4-*thiadiazolium*-3-*aminide* (25).—5-Phenyl-3-(toluene-*p*-sulphonamido)-1,2,4-thiadiazole (330 mg), sodium carbonate (112 mg), and methyl fluorosulphonate (0.1 ml) in chloroform (10 ml) were heated (28 h) under reflux. Further portions (1 ml, 0.5 ml) of methyl fluorosulphonate were added (7 h, 24 h) during the heating period. The mixture was treated with a solution of sodium carbonate (2 g) in water (15 ml). Chloroform extraction and fractionation by preparative t.l.c. (chloroform–ethyl acetate, 7 : 3) gave three fractions. Fraction 1 yielded N-(p-*tolylsulphonyl*)-4-*methyl*-5-*phenyl*-1,2,4-*thiadiazolium*-3-*aminide* (R_F 0.05) (64 mg, 18.5%) as colourless crystals, m.p. 230—232 °C from ethanol (Found: C, 55.9; H, 4.6; N, 12.0; S, 18.6%; $M^{+\cdot}$, 345.0612. $C_{16}H_{15}N_3O_2S_2$ requires C, 55.6; H, 4.4; N, 12.2; S, 18.6%; *M*, 345.0606); $\nu_{max.}$ (KBr) 1 550 cm^{-1}; δ_H 2.32 (3 H, s, tolyl-CH_3), 3.82 (3 H, s, NCH_3), 7.18 (2 H, d, *J* 9 Hz, 2,6-tolyl-H), 7.55—7.71 (5 H, m, phenyl-H), and 7.98 (2 H, d, *J* 9 Hz, 3,5-tolyl-H). Fraction 2 yielded N-(*p-tolylsulphonyl*)-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*imine* (R_F 0.15) (140 mg, 41%) as colourless crystals, m.p. 238—241 °C from ethanol (Found: C, 55.8; H, 4.5; N, 12.1; S, 18.5%; $M^{+\cdot}$, 345. $C_{16}H_{15}N_3O_2S_2$ requires C, 55.6; H, 4.4; N, 12.2; S, 18.6%; *M*, 345); $\nu_{max.}$ (KBr) 1 600 and 1 550 cm^{-1}; δ_H ([$^2H_5$]-pyridine) 2.15 (3 H, s, tolyl-CH_3), 3.38 (3 H, s, NCH_3), 7.26 (2 H, d, *J* 9 Hz, 2,6-tolyl-H), 7.42 (2 H, t, *J* 9 Hz, 3,5-phenyl-H), 7.50 (1 H, t, *J* 9 Hz, 4-phenyl-H), 7.78 (2 H, d, *J* 9 Hz, 2,6-phenyl-H), and 8.47 (2 H, d, *J* 9 Hz, 3,5-tolyl-H); δ_H (100 MHz) 2.37 (3 H, s, tolyl-CH_3), 3.56 (3 H, s, NCH_3), 7.25 (2 H, d, *J* 9 Hz, 2,6-tolyl-H), 7.45—7.85 (5 H, m, phenyl-H), and 8.10 (2 H, d, *J* 9 Hz, 3,5-tolyl-H). Fraction 3 (R_F 0.95) was further purified by preparative t.l.c. (chloroform) giving 3-[*N*-methyl-*N*-(*p*-tolylsulphonyl)amino]-5-phenyl-1,2,4-thiadiazole (R_F 0.35) obtained (35 mg, 10%) as a colourless solid, m.p. 130—131 °C, identical with an authentic sample.

Acid Hydrolysis of N-(p-*Tolylsulphonyl*)-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*imine* (24) *Formation of* 3-*Methylamino*-5-*phenyl*-1,2,4-*thiadiazole* (20) *and* N-*Benzoyl*-N′-*methyl*-N″-(p-*tolylsulphonyl*)*guanidine* (26).—*N*-(*p*-Tolylsulphonyl)-2-methyl-5-phenyl-1,2,4-thiadiazol-3(2H)-imine (160 mg), dilute hydrochloric acid (1 ml; 2M), and ethanol (20 ml) were heated (77 h) under reflux, concentrated, and shaken with dilute aqueous sodium carbonate and chloroform. Chloroform extraction, evaporation, and fractionation by preparative t.l.c. (chloroform–ethyl acetate, 19 : 1) yielded three fractions. Fraction 1 yielded starting material (R_F 0.05) (28 mg, 18%) as colourless crystals, m.p. 238—241 °C, identical with an authentic sample. Fraction 2 yielded 3-methylamino-5-phenyl-1,2,4-thiadiazole (R_F 0.4) (16 mg, 19%) as colourless crystals, m.p. 99—100 °C (lit.,[5] 101 °C)

(Found: $M^{+\cdot}$, 191. Calc. for $C_9H_9N_3S$: M, 191); δ_H 3.04 (3 H, d, J 6 Hz, $NHCH_3$), 5.42 (1 H, br q, $NHCH_3$), 7.20—7.60 (3 H, m, 3,4,5-phenyl-H), and 7.86 (2 H, dd, J 8, 2 Hz, 2,6-phenyl-H). Fraction 3 yielded N-*benzoyl*-N′-*methyl*-N″-(p-*tolylsulphonyl*)*guanidine* (R_F 0.6) (28 mg, 18%) as colourless crystals, m.p. 195—197 °C from ethanol (Found: C, 58.2; H, 5.4; N, 12.4%; $M^{+\cdot}$, 331.0996. $C_{16}H_{17}N_3O_3S$ requires C, 58.0; H, 5.2; N, 12.7%; M, 331.0991); $\nu_{max.}$ 1 690 and 1 640 cm^{-1}; δ_H 2.31 (3 H, s, tolyl-CH_3), 2.87 (3 H, d, J 5 Hz, $NHCH_3$), 7.20 (2 H, d, J 8.5 Hz, 2,6-tolyl-H), 7.46 (2 H, t, J 8.0 Hz, 3,5-phenyl-H), 7.58 (1 H, t, J 8.0 Hz, 4-phenyl-H), 7.78 (2 H, d, J 8.5 Hz, 3,5-tolyl-H), 7.92 (2 H, d, J 8.0 Hz, 2,6-phenyl-H), 9.92 (1 H, br q, $NHCH_3$), and 11.81 (1 H, br s, NH).

Alkaline Hydrolysis of N-(p-*Tolylsulphonyl*)-2-*methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*imine* (24): *Formation of* N-*Benzoyl*-N′-*methyl*-N″-(p-*Tolylsulphonyl*)*guanidine* (26), *and* N-*Methyl*-N′-*thiobenzoyl*-N″-(p-*tolylsulphonyl*)*guanidine* (27).—*N*-(*p*-Tolylsulphonyl)-2-methyl-5-phenyl-1,2,4-thiadiazol-3(2H)-imine (246 mg), potassium carbonate (500 mg), ethanol (30 ml), and water (3.5 ml) were heated (2.5 min) at 100 °C, concentrated, and shaken with dilute hydrochloric acid (2M) and chloroform. Chloroform extraction and fractionation by preparative t.l.c. (chloroform–ethyl acetate, 1 : 1) gave three fractions. Fraction 1 yielded N-*methyl*-N′-*thiobenzoyl*-N″-(p-*tolylsulphonyl*)*guanidine* (R_F 0.85) (38 mg, 15%) as yellow crystals, m.p. 166—168 °C from ethanol (Found: C, 55.2; H, 4.9; N, 12.1; S, 18.3%; $M^{+\cdot}$, 347. $C_{16}H_{17}N_3O_2S_2$ requires C, 55.3; H, 4.9; N, 12.1; S, 18.5%; M, 347); $\lambda_{max.}$ 227, 275, and 424 nm (ε 21 300, 17 600, and 360); $\nu_{max.}$ 1650 cm^{-1}; δ_H 2.39 (3 H, s, tolyl-CH_3), 2.97 (3 H, d, J 4.5 Hz, $NHCH_3$), 7.26 (2 H, d, J 8 Hz, 2,6-tolyl-H), 7.48 (2 H, t, J 7 Hz, 3,5-phenyl-H), 7.59 (1 H, t, J 7 Hz, 4-phenyl-H), 7.83 (2 H, d, J 8 Hz, 3,5-tolyl-H), and 7.96 (2 H, d, J 7 Hz, 2,6-phenyl-H). Fraction 2 (R_F 0.3) yielded a colourless solid (171 mg) which consisted of essentially two components which both contained one ethoxy group (^{1}H n.m.r.). This solid was dissolved in a mixture of ethanol (5 ml), water (1 ml), and sodium hydroxide (100 mg). The solution was heated (4 min) at 100 °C and, after concentration, was acidified (pH 1) with concentrated hydrochloric acid. Chloroform extraction yielded a residue (92 mg) which was shown (^{1}H n.m.r.) to consist of a mixture (3.5 : 1) of benzoic acid and *N*-benzoyl-*N*′-methyl-*N*″-(*p*-tolylsulphonyl)guanidine, m.p. 195—197 °C, identical with an authentic sample. Fraction 3 yielded starting material (R_F 0.1) (13 mg, 5%), m.p. 238—241 °C, identical with an authentic sample.

Alkaline Hydrolysis of N-(p-*Tolylsulphonyl*)-4-*methyl*-5-*phenyl*-1,2,4-*thiadiazolium*-3-*aminide* (25). *Formation of* N-*Benzoyl*-N′-*methyl*-N″-(p-*tolylsulphonyl*)*guanidine* (26).—*N*-(*p*-Tolylsulphonyl)-4-methyl-5-phenyl-1,2,4-thiadiazolium-3-aminide (120 mg), potassium carbonate (200 mg), ethanol (5 ml), and water (2 ml) were heated (1 min) at 100 °C with stirring. Acidification with dilute hydrochloric acid (2M) and chloroform extraction yielded a residual oil (70 mg) [which contained ethyl benzoate (^{1}H n.m.r.)]. Fractionation by preparative t.l.c. (chloroform–ethyl acetate, 4 : 1) yielded *N*-benzoyl-*N*′-methyl-*N*″-(*p*-tolylsulphonyl)guanidine (R_F 0.75) (20 mg, 17%), m.p. 195—197 °C, identical with an authentic sample.

Reaction of N-*Benzoyl*-N′-*cyanoguanidine* (28) *with Hydrogen Sulphide: Formation of* N-*Carbamoyl*-N′-*thiobenzoylguanidine* (32).—Treatment of *N*-benzoyl-*N*′-cyanoguanidine [19] with hydrogen sulphide as previously described [19] yielded N-*carbamoyl*-N′-*thiobenzoylguanidine* obtained (72%) as yellow crystals, m.p. 170—171 °C from ethanol (Found: C, 48.6; H, 4.5; N, 25.6; S, 14.2%; $M^{+\cdot}$, 222.0573. $C_9H_{10}N_4OS$ requires C, 48.6; H, 4.5; N, 25.3; S, 14.4%; M, 222.0576); $\lambda_{max.}$ 219, 281, 338, and 440 nm (ε 15 700, 16 700, 10 200, and 152); $\nu_{max.}$ (Nujol) 3 460, 3 330, and 1 715—1 690 cm^{-1}; δ_H [$(CD_3)_2CO$] 6.53 (2 H, br s, NH_2), 7.32 (2 H, t, J 7.5 Hz, 3,5-phenyl-H), 7.42 (1 H, t, J 7.5 Hz, 4-phenyl-H), 8.27 (2 H, d, J 7.5 Hz, 2,6-phenyl-H), 9.60 (1 H, br s, NH), 9.82 (1 H, br s, NH), and 11.73 (1 H, br s, NH).

Oxidation of N-*Carbamoyl*-N′-*thiobenzoylguanidine* (32): *Formation of* 3-*Amino*-5-*phenyl*-1,2,4-*thiadiazole* (30) *and* N-(5-*Phenyl*-1,2,4-*thiadiazol*-3-*yl*)*urea* (33).—A boiling solution of *N*-carbamoyl-*N*′-thiobenzoylguanidine (20 g) in ethanol (156 ml) was treated with 6% aqueous hydrogen peroxide (3 × 48 ml) at 2 min intervals. The solution was cooled, concentrated to half volume, and stored (12 h) at 0 °C. The precipitate was fractionated by medium pressure column chromatography (chloroform) yielding two fractions. Fraction 1 yielded 3-amino-5-phenyl-1,2,4-thiadiazole (10.5 g, 65%) as colourless needles, m.p. 139—141 °C from 50% aqueous ethanol (lit.,[9] 132—134 °C); $\nu_{max.}$ 3 520, 3 420, and 1 609 cm^{-1}; δ_H 5.25 (2 H, br s, NH_2), 7.45—7.50 (3 H, m, 3,4,5-phenyl-H), and 7.88 (2 H, dd, 2,6-phenyl-H). Fraction 2 yielded N-(5-*phenyl*-1,2,4-*thiadiazol*-3-*yl*)*urea* (2.2 g, 11%) as colourless crystals, m.p. 215—217 °C from 50% aqueous ethanol (Found: $M^{+\cdot}$, 220.0430. $C_9H_8N_4OS$ requires M, 220.0419); $\nu_{max.}$ (KBr) 3 400, 3 300—2 900, and 1 690 cm^{-1}; δ_H ([$^2H_5$]pyridine) 7.40—7.50 (3 H, m, 3,4,5-phenyl-H), 8.00 (2 H, dd, J 7, 2 Hz, 2,6-phenyl-H), and 8.40 (2 H, br s, NH_2).

Reaction of N-*Carbamoyl*-N′-*thiobenzoylguanidine* (32) *with Bis*(4-*methoxyphenyl*) *Telluroxide: Formation of* 3-*Amino*-5-*phenyl*-1,2,4-*thiadiazole* (30) *and* N-(5-*Phenyl*-1,2,4-*thiadiazol*-3-*yl*)*urea* (33).—*N*-Carbamoyl-*N*′-thiobenzoylguanidine (222 mg), ethanol (15 ml), and bis(4-methoxyphenyl) telluroxide [26] (358 mg) was stirred (1 h) at room temperature. The colourless solid which separated was filtered off and *N*-(5-phenyl-1,2,4-thiadiazol-3-yl)urea was obtained (49 mg, 22%) as colourless crystals, m.p. 205—210 °C, identical with an authentic sample. Evaporation of the filtrate and fractionation of the residue by preparative t.l.c. (methylene chloride–ethyl acetate, 9 : 1) gave two fractions. Fraction 1 yielded bis(4-methoxyphenyl) teiluride (R_F 1.0) (300 mg, 88%) as a colourless solid, m.p. 50—53 °C (lit.,[27] m.p. 53—54 °C) (Found: $M^{+\cdot}$, 344. Calc. for $C_{14}H_{14}O_2Te$: M, 344); $\nu_{max.}$ 1 585 and 1 480 cm^{-1}; δ_H 3.66 (6 H, s, 2 × OCH_3), 6.66 (4 H, d, J 9 Hz, 2 × 2,6-ArOCH_3-*H*), 7.58 (4 H, d, J 9 Hz, 2 × 3,5-ArOCH_3-*H*). Fraction 2 yielded 3-amino-5-phenyl-1,2,4-thiadiazole (R_F 0.7) (135 mg, 76%), m.p. 139—141 °C, identical with an authentic sample.

Reaction of N-*Methyl*-N′-*thiobenzoylurea* (13) *with Bis*(4-*methoxyphenyl*) *Telluroxide: Formation of* 2-*Methyl*-5-*phenyl*-1,2,4-*thiadiazol*-3(2H)-*one* (6).—A solution of *N*-methyl-*N*′-thiobenzoylurea (83 mg) in ethanol (9 ml) was treated with bis(4-methoxyphenyl) telluroxide (168 mg) and the mixture was stirred (30 min) at room temperature. Evaporation and fractionation of the residue by preparative t.l.c. gave two fractions. Fraction 1 yielded 2-methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-one (R_F 0.3) (69 mg, 84%) as colourless cystals, m.p. 184—185 °C, identical with an authentic sample. Fraction 2 (R_F 1.0) yielded bis(4-methoxyphenyl) telluride, identical with an authentic sample.

Acknowledgements

We warmly thank the S.E.R.C. and May and Baker Ltd. for the award of a CASE Studentship (to C. G. N.).

References

1 Part 22, C. G. Newton, W. D. Ollis, and D. E. Wright, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
2 W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.*, 1976, **19**, 1; C. G. Newton and C. A. Ramsden, *Tetrahedron*, 1982, **38**, 2965.
3 W. D. Ollis, C. A. Ramsden, and S. P. Stanforth, *Tetrahedron*, in press.
4 J. Goerdeler and W. Roth, *Chem. Ber.*, 1963, **96**, 534.
5 J. Goerdeler and P. Mertens, *Chem. Ber.*, 1970, **103**, 1805.
6 F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 1960, 3234.
7 Part 13, W. D. Ollis and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1974, 645; Part 20, R. N. Hanley, W. D. Ollis, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1979, 747.
8 M. N. Gudi, J. G. Hiriyakkanavar, and M. V. George, *Indian J. Chem.*, 1969, **7**, 971.
9 F. Kurzer, *J. Chem. Soc.*, 1956, 4524.
10 P. S. Landis in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, 1969, p. 43.
11 R. F. Hudson and H. Dj.-Forudian, *Phosphorus Sulphur*, 1978, **4**, 9; K. J. Miller, K. F. Moschner, and K. T. Potts, *J. Am. Chem. Soc.*, 1983, **105**, 1705.
12 W. R. Hatchard, *J. Org. Chem.*, 1964, **29**, 660.
13 M. Winn, *J. Org. Chem.*, 1975, **40**, 955.
14 T. Nishiwaki, E. Kawamura, N. Abe, and M. Iori, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2693.
15 S. Auricchio, S. Brückner, L. M. Giunchi, and V. A. Kozinsky, *Heterocycles*, 1980, **14**, 1757; S. Auricchio, S. Brückner, L. M. Giunchi, V. A. Kozinsky, and O. V. Zelenskaja, *J. Heterocycl. Chem.*, 1980, **17**, 1217.
16 A. R. Butler, C. Glidewell, and D. C. Liles, *Acta Crystallogr., Ser. B*, 1978, **34**, 2570.
17 A. R. Butler and I. Hussain, *J. Chem. Res. (S)*, 1980, 266.
18 S. Crook and P. Sykes, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1791.
19 P. Adams, D. W. Kaiser, D. E. Nagy, G. A. Peters, R. L. Sperry, and J. T. Thurston, *J. Org. Chem.*, 1952, **17**, 1162.
20 J. Goerdeler and A. Fincke, *Chem. Ber.*, 1956, **89**, 1033.
21 F. Kurzer, *Adv. Heterocycl. Chem.*, 1965, **5**, 146.
22 D. H. R. Barton, S. V. Ley, and C. A. Meerholz, *J. Chem. Soc., Chem. Commun.*, 1979, 755; S. V. Ley, C. A. Meerholz, and D. H. R. Barton, *Tetrahedron Lett.*, 1980, **21**, 1785; *Tetrahedron Supplement*, 1981, **37**, 213.
23 Part 21, C. G. Newton, W. D. Ollis, M. L. Podmore, and D. E. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1984, 63.
24 A. E. Dixon, *J. Chem. Soc.*, 1899, **75**, 375.
25 K. Itoh, I. Matsuda, T. Katsuura, and Y. Ishii, *J. Organomet. Chem.*, 1969, **19**, 347.
26 K. Lederer, *Ber.*, 1916, **49**, 1076.
27 F. H. Burstall and S. Sugden, *J. Chem. Soc.*, 1930, 229.

Received 10*th June* 1983; *Paper* 3/973