The Oxidation of 1-Thioaroylsemicarbazides

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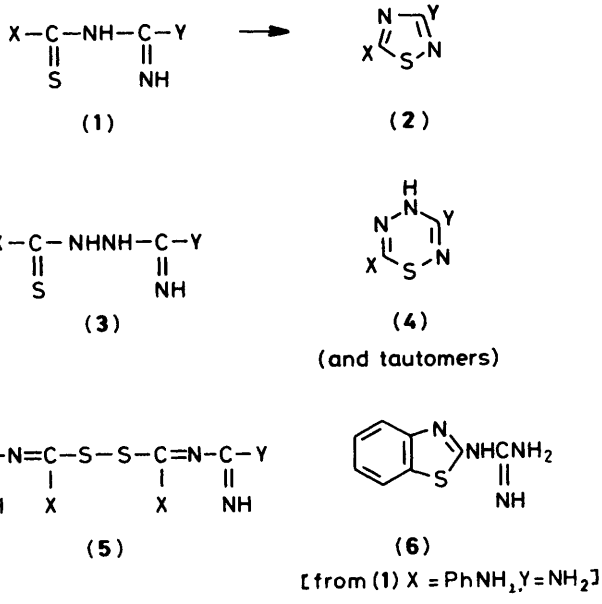
Oxidation of 1-thioaroylsemicarbazides by bromine or hydrogen peroxide yields bis(*C*-aryl-*N*-ureido)formimidoyl disulphides. As a novel class of the generally labile di-imidoyl disulphides, such products display unusual stability; however, upon acylation, methylation, and acid or alkaline hydrolysis they are cleaved at their disulphide bond, to give the same products as their thioaroyl precursors.

The oxidative cyclisation of structures (**1**) incorporating the 'CS·NH·C(:NH)' grouping is the basis of a versatile general synthesis of 1,2,4-thiadiazoles (**2**).[1] Numerous variants of the linear starting materials (**1**) are readily obtainable and provide access to a correspondingly wide range of 3,5-disubstituted 1,2,4-thiadiazoles (**2**; X, Y = R, RO, RS, RR'N, etc., where R = H, Alk, Ar). Ring closure to 1,2,4-thiadiazoles appears to be the preferred course of the reaction, even when the formation of alternative structures, *e.g.*, disulphides (**5**) or substituted benzothiazoles (**6**) is also possible.[1] Compounds (**3**) containing



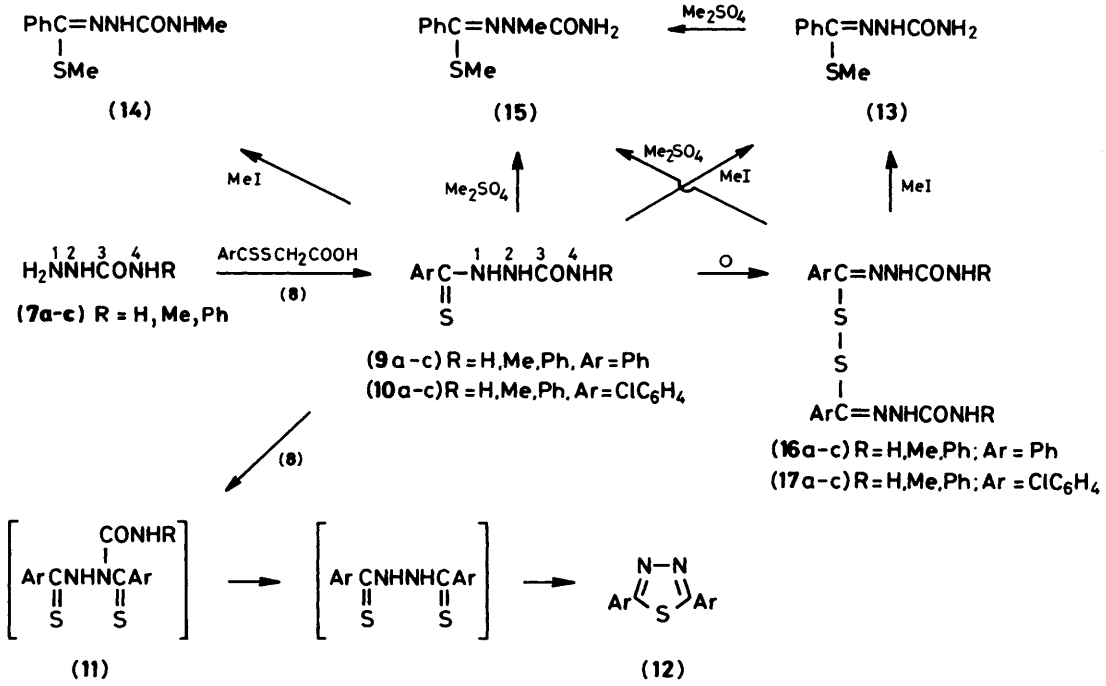
the 'CS·NHNH·C(:NH)' group are potentially accessible in the same diversity as their ·CS·NH·C(:NH)· analogues, but have been less extensively studied. Their oxidative cyclisation, involving the intramolecular linking of their imino and (tautomerised) thioxo group would result in compounds of the as yet unknown 1,2,4,5-thiatriazine ring system (**4**). Exploratory experiments employing several CS·NHNH·C(:NH) variants have shown, however, that other reaction paths are preferred. The oxidation of 1-thioaroylsemicarbazides (**3**; X = Ar, Y = OH), to compounds possessing a novel disulphide structure, forms the main subject of this paper.

Production.—1-Thioaroylsemicarbazides (**9**) and (**10**) were obtained by the action of thioaroylthioacetic acids (**8**) with the appropriate semicarbazide (**7**).[2–5] Small amounts of 2,5-diaryl-1,3,4-thiadiazoles (**12**) (up to 15%), formed in some examples as by-products, are thought to arise, in spite of a large excess of the semicarbazide (**7**), by dithiobenzoylation at the adjacent 1- and 2-nitrogen atoms of the hydrazino grouping, followed by hydrolytic cleaving and cyclisation of the intermediate (**11**). This mechanism, implying an enhanced reactivity of the *N*-2-hydrazino-moiety once reaction has occurred at N-1, accounts also for the promotion of the same side-reaction in the thiobenzoylation of aminoguanidine,[5] 1,2-diaminoguanidine,[6] and more generally in comparable addition processes of heterocumulenes to hydrazine derivatives.[7]

Methylation.—Methylated 1-thiobenzoylsemicarbazides were required as reference compounds for identifying products arising in the methylation of their oxidation products (see below). 1-Thiobenzoylsemicarbazide (**9a**) and its 4-methyl homologue (**9b**) gave the *S*-methyl derivatives (**13**) and (**14**) on treatment with sodium methoxide (1 mol) and an excess of iodomethane. *S*-Methylation was also effected almost quantitatively by the action of an excess of diazomethane.[8] Absence of simultaneous *N*-methylation is noteworthy in view of its ready occurrence in hydrazines[9] and nitrogenous heterocyclic systems.[10]

The action of an excess of dimethyl sulphate in alkali on either 1-thiobenzoylsemicarbazide (**9a**) or its *S*-methyl derivative (**13**) gave good yields of the *S*,2-dimethyl homologue (**15**). It also arose as the minor product [together with (**13**)] on treatment of 1-thiobenzoylsemicarbazide (**9a**) with iodomethane and 2 or more mol equiv. of sodium methoxide. Neither 1-benzoylthiosemicarbazide [the isomer of (**9a**)] nor the 4-methyl homologue (**9b**) underwent a comparable dimethylation under these conditions: the former was merely cyclised by the alkaline medium in the familiar manner[11] to 2-amino-5-phenyl-1,3,4-oxadiazole (45%), and the latter resinified completely.

Formulation of the *S*,2-dimethyl homologue (**15**) is in accord with the following observations: one of its methyl groups is part of an *S*-methylthio moiety, as shown (a) by the origin of the compound from the *S*-methyl derivative (**13**), and (b) evolution of methanethiol upon its decomposition. The presence of an unsubstituted amino group, indicated by the ^{1}H n.m.r. spectrum, excludes the ultimate N-4-nitrogen as the site of the second methyl group, as is also shown by the non-identity of the authentic *S*,4-dimethyl-isomer (**14**) with the product in question. The remaining choice between structure (**15**) and the isomeric *O*-methylisosemicarbazide structure [PhC(SMe):NN:C(OMe)NH$_2$] is decided in favour of the former by reference to the ^{13}C n.m.r. chemical shift of the relevant methyl carbon (35 p.p.m.), which falls outside the range of methoxy but within that of *N*-methyl groups.[12] The conclusion conforms to the generally preferred *N*- over *O*-alkylation in urea-derivatives,[13] notwithstanding an isolated report of the conversion of urea into *O*-methylisourea by dimethyl sulphate under severe conditions.[14]



Scheme 1.

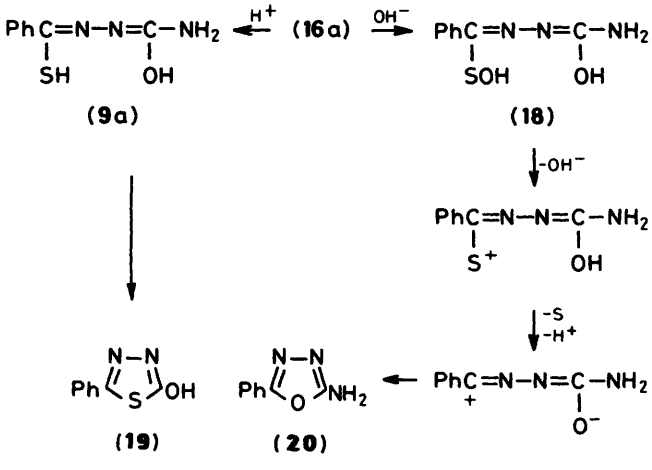
Oxidation.—Molecular bromine in neutral solvents,[1] or hydrogen peroxide in acid media[1] converted 1-thioacylsemicarbazides (**9**) and (**10**) into products formulated, on the basis of their origin and properties, as bisformimidoyl disulphides (**16**) and (**17**).

The parent compound, 1-thiobenzoylsemicarbazide (**9a**) reacted with bromine (0.5 mol) in chloroform almost instantly, but an 'end-point' of the reaction was not apparent because of continued, though less rapid, halogen uptake beyond this stage. In the alternative procedure employing hydrogen peroxide, 2,5-diphenyl-1,3,4-thiadiazole appeared as a by-product (4—12%), and increasing amounts of 2-amino-5-phenyl-1,3,4-oxadiazole (up to 35%) and elemental sulphur were formed on more prolonged treatment, with corresponding reduction in the yields of disulphide (**16a**). The use of equimolar quantities of oxidants sufficient for intramolecular cyclisation did not afford 1,2,4,5-thiatriazines, but resulted in inferior yields of the bisformimidoyl disulphides.

Because of their almost identical elementary composition, the disulphide (**16**) and thiatriazine structures (**4**) are not distinguishable by analysis. Further, the products are soluble only with difficulty and are thermolabile so that their molecular masses were unobtainable by cryoscopic or spectrometric methods. Their linear disulphide structure (**16**) and (**17**) was first surmised from the significantly faster uptake of the initial equivalent of bromine in their synthesis from (**9**), and from the fact that their catalytic reduction terminated on addition of only half a mol of hydrogen [per hydrazino moiety present in (**16a**—**c**)], with regeneration of the original 1-thiobenzoylsemicarbazide (**9a**—**c**) in 65—75% yields. The ^{1}H n.m.r. spectrum of the disulphide (**16a**) included an aromatic multiplet at 7.25—7.8 p.p.m. and signals at 6.65 and 9.25 p.p.m., the last two disappearing on deuterium exchange. The observed proton integration (in the ratio 5:1:2) indicates, in (**16a**), the presence of three NH-protons per aryl group: it thus excludes the thiatriazine structure (**4**) and supports the symmetrical disulphide formulation. The ^{1}H n.m.r. spectra of other members of the series (**16b**) and (**17a**) were consistent with this interpretation (see Table 3).

In their chemical reactions, the bisformimidoyl disulphides (**16**) and (**17**) are invariably cleaved at their disulphide link, the products arising from the primary fragments

Acid hydrolysis. On being subjected to acid hydrolysis the disulphide (**16a**) gave 2-hydroxy-5-phenyl-1,3,4-thiadiazole (**19**) and 2-amino-5-phenyl-1,3,4-oxadiazole (**20**) in 50 and 25% yield, respectively, together with elemental sulphur. The initial hydrolytic step is thought to produce equimolar quantities of the original 1-thiobenzoylsemicarbazide (**9a**) and the corresponding sulphenic acid (**18**).[15] Rapid cyclisation of the former to the thiadiazole (**19**) in acid media is well established.[4,5] Conversion of the sulphenic acid (**18**) into the oxadiazole (**20**), involving a net dehydration and extrusion of sulphur may proceed as suggested in Scheme 2. This accounts also for the



Scheme 2.

Table 1a. ^{13}C N.m.r. spectra of 1-thiobenzoylsemicarbazides and related compounds

Compd.	Solvent[a]	C=S or C–S–	C-3	NCH_3	SCH_3	C-1′	C-2′[b]	C-3′[b]	C-4′
(9a)	P	189.7s[c]	159.1s	—	—	140.3s	*128.4d	*128.3d	130.7d
(9b)	P	189.4s[c]	158.5s	26.9q	—	140.2s	*128.4d	*128.3d	130.8d
(9c)	P	188.6s[c]	155.0s	—	—	140.3s[d]	*128.5d	•128.3d	130.7d
						140.2s	119.5d	129.3d	123.0d
(10b)	P	184.9s	158.5s	26.9q	—	139.2s	*129.9d	•128.3d	136.0s
(13)	C	144.0s	156.9s	—	15.7q	135.1s	*128.7d	*128.2d	129.7d
(14)	C	143.0s	155.9s	26.5q	15.6q	135.2s	•128.6d	*128.1d	129.6d
(BTS)[e]	P	167.6s[f]	185.1s[c,g]	—	—	133.5s	*128.8d	•128.2d	132.2d
(15)	C	166.8s	160.2s	34.9q	16.2q	135.3s	•128.5d	*128.3d	130.1d
	D	167.6s	159.2s	35.0q	15.7q	134.7s	•128.5d	*128.3d	129.7d
$PhCSNH_2$	C	202.8s[c]	—	—	—	139.1s	•128.5d	*126.9d	130.0d

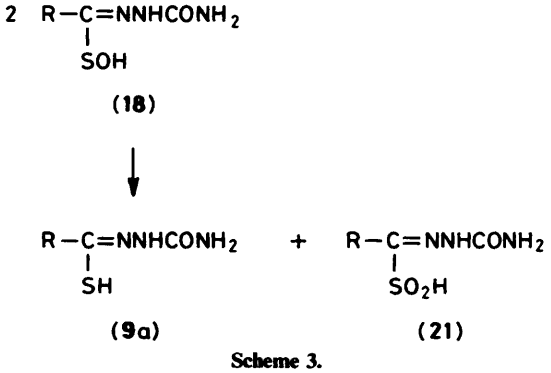
Table 1b. ^{13}C N.m.r. spectra of bisformimidoyl disulphides

(16a)	P	138.1s[h]	157.5s	—	—	136.6s	*128.9d	•128.8d	129.9d
	D	136.8s[h]	155.2s	—	—	135.3s	•128.1d	•127.7d	129.1d
(16b)	P	137.9s[h]	155.4s	26.5q	—	135.4s	*128.4d	*128.1d	129.5d
(16c)	P	135.5s[h]	153.0s	—	—	136.1s[d]	*128.8d	*128.7d	129.9d
						139.6s	120.5d	129.1d	123.5d
(17b)	P	136.4s[h]	156.0s	26.8q	—	+135.4s	•129.9d	*128.8d	+135.3s

* Figures may be interchanged horizontally. [a] Solvents: P = [$^2H_5$]pyridine; C = deuteriochloroform; D = [$^2H_6$]dimethyl sulphoxide. [b] The doublets of C-2′ and C-3′ are displayed in conformity with assignments for thiobenzophenone[21c]. [c] Broad signal of very low intensity. [d] Upper line: thiobenzoylphenyl; lower line: 4-phenyl. The latter is assigned in conformity with the spectrum of acetanilide.[22d] [e] BTS = 1-benzoylthiosemicarbazide. [f] Signal of benzoyl-carbonyl. [g] Signal of C-3-thiocarbonyl. [h] Sharp signal of reduced intensity.

appearance of 2-amino-5-phenyl-1,3,4-oxadiazole and sulphur as by-products in the synthesis of the disulphide in acid media, [*e.g.*, compounds (**9c**) and (**16c**)].

Alkaline hydrolysis. On being subjected to alkaline hydrolysis the disulphide (**16a**) regenerated the precursor (**9a**) in yields up to 75%. The intermediate sulphenic acid fraction (**18**) produced, by disproportionation,[16] a further 0.5 mol of 1-thiobenzoylsemicarbazide (**9a**), together with the corresponding sulphinic acid (**21**) (see Scheme 3). In the acidic work-up, the labile



Scheme 3.

sulphinic acid (**21**) should yield sulphonic acid and disulphoxide as stable end products,[16] but such compounds were not isolable.

Methylation. On being subjected to methylation the bisformimidoyl disulphide (**16a**) was cleaved to give the derivatives (**13**) or (**15**) identical with those obtained from its thiobenzoyl precursor (**9a**), but in diminished yields commensurate with the hydrolytically available thiobenzoyl fraction. Similarly, both 1-thiobenzoylsemicarbazide (**9a**) and the disulphide (**16a**) gave the same toluene-*p*-sulphonyl derivative, formulated as PhCS-NHN(SO_2Tol-*p*)$CONH_2$, in conformity with the likely substitution at the 'activated' N-2-position of the semicarbazide moiety (see above[5–7]), and the persistence of a primary amide band (3 470 cm^{-1}) in its i.r. spectrum.[17]

Table 2. Observed and calculated chemical shifts (p.p.m.) of thiocarbonyl carbon signals

	δ_{CO} or δ_{CS} of (thio)carbonyl		δ_{C-3}	
Compound	Found	Calc.	Found	Calc.
$PhCONH_2$[21a]	170.4	171.9	—	—
$PhCSNH_2$	202.8	200.6	—	—
$PhCONHNHCSNH_2$	167.6	162.9	185.1	184.2
$PhCSNHNHCONH_2$	189.7	196.5	159.1	159.7

^{13}C N.m.r. spectra and their assignment. The assigned ^{13}C n.m.r. specta of the 1-thioaroylsemicarbazides (**9**) and (**10**) and bisformimidoyl disulphides (**16**) and (**17**) are displayed in Table 1. The spectra of two model structures (1-benzoylthiosemicarbazide and thiobenzamide) which were determined for comparison are also included.

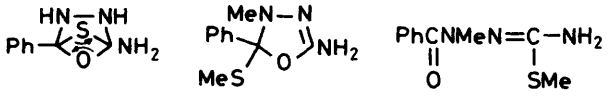
Singlets. The members of both series give rise to a singlet (155—159 p.p.m.), attributable to the 3-carbonyl carbon of their semicarbazide moiety, matching known chemical shifts (150—165 p.p.m.) of amide carbon in ureas[12,18,19] and semicarbazones.[20] The broad singlet of low intensity produced near 190 p.p.m. by the 1-thioaroylsemicarbazides (**9a—c**) and (**10b**) is assigned to their thioamide-carbon; like that of thioureas,[18] it appears below the normal range (199—212 p.p.m.)[12c] of signals of the >N–CS– system, implying an enhanced shielding of the thioxo carbon due to electron release by the adjacent hydrazino-group [in compound (**9**)]. The thioxo carbon of 1-benzoylthiosemicarbazide, located between a hydrazino and amino group, significantly produces this singlet at even higher field (185.1 p.p.m.); that of thiobenzamide appears at 202.8 p.p.m. The assignments are further corroborated by the agreement of the observed chemical shifts and those calculated according to Kalinowski and Kessler's[18] correlation of carbonyl and thiocarbonyl resonances in comparable structures ($\delta_{C=S} = 1.45 \cdot \delta_{C=O} - 46.5$; see Table 2).

In passing from the 1-thioaroylsemicarbazides (**9**) and (**10**) to their *S*-methyl derivatives (**13**) and (**14**) and bisformimidoyl

disulphides (**16**) and (**17**), the weak low-field singlet gives way to a more intense one at 136—144 p.p.m., matching the recognised range of the >C–S– moiety (δ_C = 132—142 p.p.m.).[12c] The remaining singlet of the 1-thiobenzoylsemicarbazides (**9a**—**c**) and (**10b**) (*ca.* 140 p.p.m.) is allotted by exclusion to C-1′ of their aromatic ring, and is, moreover, identified unequivocally in thiobenzamide (δ_C = 139.1 p.p.m.). Shielding of C-1′ in response to *S*-methylation (in **13**—**15**) and disulphide formation [in (**16**) and (**17**)] results in its upfield displacement (to *ca.* 136 p.p.m.).

Doublets and quartets. The doublets of the aromatic ring are assigned in conformity with precedent.[12,21c] The methylamino and *S*-methylthio carbon produce *quartets* consistently at *ca.* 27 and 16 p.p.m., respectively, within or close to the established ranges for these structural entities,[12a,22] and matching the chemical shifts of methyl signals of comparable structures (*e.g.* MeNH·CO_2Et, 27.4 p.p.m.,[23a] PhSMe, 15.6 p.p.m.[23b]).

The ^{13}C n.m.r. spectrum of the dimethylated 1-thiobenzoylsemicarbazide (**15**) includes a singlet which, compared with those of the related structures [especially (**13**) and (**14**)], appears at unexpectedly lowfield (δ, 167 p.p.m.). The observation is explicable in terms of a steric interaction between the *S*-methyl- and *N*(2)-methyl groups resulting in distortion of the >C=N– system from planarity. The consequent reduction in the double-bond character and concomitant increased polarisation of the >C=N– moiety would lead to the observed deshielding of the isothiocarbonyl-carbon of structure (**15**). Comparable bond order changes in the $>C\overset{+}{=}N<$ system in 6-aminofulvenes due to steric effects have been established by Ollis *et al.*[24] The less pronounced deshielding of the 3-carbonyl-carbon [in (**15**)] resembles effects that are also found in amides (e.g. $PhCONH_2$,[21a] $PhCONMe_2$,[21b] δ_{CO}, 170.4, 174.7 p.p.m., respectively). Singlets of the ^{13}C n.m.r. spectrum of structure

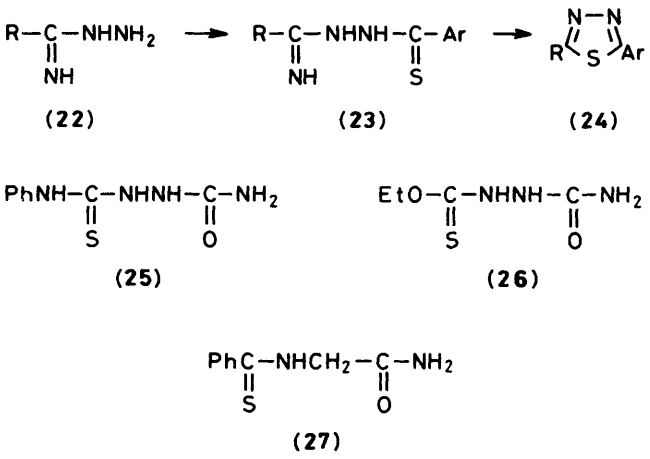


(**15a**) (**15b**) (**15c**)

(**15**) are in fact more readily assignable to the isomeric 1,*S*-dimethyl-1-benzoylthiosemicarbazide (**15c**), which might possibly arise by a mechanism involving transient cyclic intermediates of type (**15a**) or (**15b**). This formulation is rejected, however, because: 1-thiobenzoylsemicarbazide (**9a**) proved highly stable towards alkali, even under severe conditions, and authentic 1-benzoylthiosemicarbazide did not undergo a comparable dimethylation.

1-Thioacylamidrazones and other Amidrazonothioxo Compounds.—1-Thiobenzoylamidrazones (**23**), obtained from amidrazones (**22**) by thiobenzoylation,[25] were rapidly converted by hydrogen peroxide or bromine, even under the mildest conditions, into 2,5-disubstituted 1,3,4-thiadiazoles (**24**). Under the prevailing acidic conditions, the usual cyclisation[25] with loss of ammonia occurs so readily as to preclude possible alternative reactions. Neither disulphides comparable with structure (**16**), nor six-membered heterocyclic compounds were obtainable by the standard oxidation procedure from 1-phenyl-2-thiobiurea (**25**),[26] 1-ethoxythiocarbonylsemicarbazide (**26**),[27] or 1-thiobenzoylglycinamide (**27**).[28]

Conclusion.—The substituted bisformimidoyl disulphides described are a new variant of the relatively little known diimidoyl disulphides, the parent compounds [RC(:NH)S·SC(:NH)R] of which arise in the controlled oxidation of primary thioamides.[29,30] Other representatives have occasionally been



(**22**) (**23**) (**24**)

(**25**) (**26**)

(**27**)

obtained from thiohydrazides,[31] thiohydrazones,[32] and dithiocarbohydrazones (*e.g.*, MeS·CSNHN:CHMe),[33] but more frequently from thioureas.[34] Di-imidoyl disulphides are labile compounds which tend to decompose to monosulphides,[35] heterocyclics, especially thiadiazoles, and sulphur-free products;[29–34] they therefore function more often as intermediates rather than final products. The ready formation and relative stability of the present bisformimidoyl disulphides (**16**) and (**17**) is therefore noteworthy, particularly since several closely related structures were not similarly accessible [from (**23**) and (**25**)—(**27**)].

The failure of 1-thiobenzoylsemicarbazides (**9**) and (**10**) and other structures incorporating the CS·NHNH·C(:NH) group (**23**), (**25**)—(**27**) to undergo an intramolecular oxidative cyclisation to 1,2,4,5-thiatriazines (**4**) contrasts strikingly with the facile conversion of CS·NHC(:NH) compounds into 1,2,4-thiadiazoles (**1**) ⟶ (**2**). The fully heteroaromatic nature and consequent enhanced resonance stabilisation of the latter is a factor likely to contribute to this difference. It is further recalled that six-membered S,N-heterocyclics (including the formally comparable 1,2,5-[36] and 1,3,4-thiadiazines[37] tend to ring-contract, with extrusion of sulphur, or by other changes, to more stable five-membered heteroaromatic structures. Compounds of the 1,2,4,5-thiatriazine system remain at present unknown.

Experimental

U.v. and i.r. spectra were determined on Unicam SP 500 and SP 200 instruments, respectively. Those for the 1-thioaroylsemicarbazides (**9a**—**c**), (**10a**—**c**), (**13**), and (**14**), and their reactions with alkaline sodium plumbite are recorded in Supplementary Publication No. 56634 (2 pp.).* Mass spectra were obtained on an AEI MS-902 instrument operating at 70 eV. ^{1}H N.m.r spectra were measured in [$^2H_6$]dimethyl sulphoxide at 60 MHz. The ^{13}C n.m.r. spectra were determined on a Bruker WM 250 Fourier Transform instrument operating at 62.89 MHz, and the broad band proton noise decoupled and DEPT spectra recorded. In both measurements, the internal standard was Me_4Si.

Light petroleum (b.p. 60—80 °C) unless otherwise specified.

1-Thioaroylsemicarbazides

1-Thiobenzoylsemicarbazide (**9a**).—*Stability to alkali.* When compound (**9a**) (10 mmol) was boiled under reflux in 3M-

* For details of Supplementary Publications, see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1.

sodium hydroxide (30 ml) for 30 min (faint odour of benzonitrile and ammonia), it was recovered (72%) upon acidification. The filtrate, on partial evaporation gave 2,5-diphenyl-1,3,4-thiadiazole (12%), identified by mixed m.p. 138—140 °C[38] and i.r. spectra.[25]

Toluene-p-*sulphonyl Derivative*.—A solution of (**9a**) (0.98 g, 5 mmol) in anhydrous pyridine (20 ml) was treated at room temperature with toluene-*p*-sulphonyl chloride (1.05 g, 5.5 mmol), set aside for 6 h, and then stirred into concentrated hydrochloric acid (20 ml)–ice. The precipitate gave platelets (0.88 g, 50%) of the *toluene*-p-*sulphonyl derivative*, m.p. 169—170 °C (from ethanol) (Found: C, 51.9; H, 4.2; N, 12.1; S, 17.9. $C_{15}H_{15}N_3O_3S_2$ requires C, 51.6; H, 4.3; N, 12.0; S, 18.3%).

S-*Methyl*-1-*thiobenzoylsemicarbazide* (**13**).—(*a*) A suspension of 1-thiobenzoylsemicarbazide (**9a**) (3.90 g, 20 mmol) in methanol (50 ml) and iodomethane (57 g, 0.4 mol) was treated with sodium (0.46 g, 20 mmol) dissolved in methanol (15 ml). The solution was refluxed for 30 min, distilled to half volume, and stirred into ice–water. The precipitate gave, on crystallisation from ethanol or chloroform, prisms (3.55 g, 85%) of (**13**), m.p. 155—156 °C (decomp., with evolution of methanethiol) (Found: C, 51.7; H, 5.1; N, 20.0; S, 15.35. $C_9H_{11}N_3OS$ requires C, 51.7; H, 5.3; N, 20.1; S, 15.3%).

In experiments using an excess of sodium methoxide (80 mmol) and a reflux time of 1.5 h, addition of the evaporated reaction mixture to water precipitated a rapidly solidifying resin which gave (**13**) (40%) as above. The filtrate then deposited, on spontaneous partial evaporation at room temperature, pale yellow crystals, m.p. 112—114 °C (45%, from ethanol–light petroleum) identical with (**15**) (see below). Under intermediate conditions [*e.g.*, sodium methoxide (40 mmol), 30 mins refluxing], (**13**) and (**15**) were formed in 65 and 15% yield, respectively.

(*b*) Finely powdered (**9a**) (1.95 g, 10 mmol), suspended in ether (120 ml), was treated during 2—3 min with ethereal diazomethane (from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide,[40] 'Diazald,' 40 mmol), when effervescence and temporary dissolution of the reactant occurred. Spontaneous evaporation of the suspension left white crystals, which gave (**13**) (80—90%, from chloroform–ethanol), identical with material obtained in (a).

S,2-*Dimethyl*-1-*thiobenzoylsemicarbazide* (**15**).—(*a*) A solution of (**9a**) (2.95 g, 15 mmol) in 3M-sodium hydroxide (60 ml, 180 mmol) at 35—40 °C was treated with dimethyl sulphate (10.0 g, 80 mmol) in two portions at 1 min interval, shaken during 10 min, and the solidified oil collected at 0 °C. Crystallisation from ethanol–light petroleum (10 ml each) gave platelets (2.6 g, 78%) of (**15**), m.p. 112—113 °C (Found: C, 54.1; H, 5.5; N, 18.7; S, 13.7. $C_{10}H_{13}N_3OS$ requires C, 53.8; H, 5.8; N, 18.8; S, 14.3%). Its u.v. absorption decreases with increasing wavelength, with plateaus at 220—230 nm (log ε 4.05) and 275—300 (3.50); $\nu_{max.}$ 3 470s (NH_2), 3 280ms, 3 180s (NH), 2 900w (CH_3), 1 670s (C=N), 1 580ms br (C–N–H), 760s, 695s (Ph), 1 440—1 420m br, and 1 380ms br cm^{-1}; δ_H 2.13 (3 H, s, SMe), 3.29 (3 H, s, NMe), 5.71 (2 H, s, NH_2), and 7.4—7.6 (5 H, m, Ph); *m/z* 223w ($M^{+\cdot}$), 207vw [M − 16 (NH_2)], 176vs [M − 47 (SMe)], 132m [M − 47 − 44 ($CONH_2$)], 119s [M − 47 − 44 − 14 (N) + 1], 104s [M − 47 − 44 − 14 − 15 (*i.e.* PhCN + 1)], 177w, 164vw, 133m, 121s, 91ms, and 77s.

(*b*) A solution of (**13**) (1.05 g, 5 mmol) in 3M-sodium hydroxide (30 ml, 90 mmol) at 60 °C was treated with dimethyl sulphate (3.8 g, 30 mmol), and the product isolated as above. The resulting product (**15**) formed platelets (0.56 g, 50%) identical with the product obtained in (*a*). When 1-benzoylthiosemicarbazide[40] was subjected to the foregoing methylation procedure, the product, crystallised from acetone, was 2-amino-5-phenyl-1,3,4-oxadiazole (45%), identical (mixed m.p. 238—240 °C, i.r. spectrum) with authentic material (see below) (Found: C, 59.4; H, 4.3; N, 25.5. Calc. for $C_8H_7N_3O$: C, 59.6; H, 4.35; N, 26.1%). The mother liquors gave only intractable oils.

4-*Methyl*-1-*thiobenzoylsemicarbazide* (**9b**).—A stirred solution of 4-methylsemicarbazide[41] (5.3 g, 60 mmol) in 0.5M-sodium hydroxide (120 ml, 60 mmol) was treated at room temperature during 20 min with thiobenzoylthioacetic acid[42] (8.48 g, 40 mmol) dissolved in M-sodium hydroxide (50 mmol). Stirring at toom temperature was continued for 1.5 h, after which the liquid (containing a small amount of precipitate) was adjusted to pH 8 with 2M-acetic acid, and the now more substantial precipitate (R) filtered off after 12 h. The filtrate was acidified with 2M-acetic acid; the yellow precipitate (m.p. 155—158 °C (decomp.); 5.36—6.0 g, 64—72%) gave, on crystallisation from ethanol (15 ml per g, recovery 80%) platelets of (**9b**), m.p. 161—162 °C (Found: C, 51.9; H, 5.5; N, 20.1; S, 15.4. $C_9H_{11}N_3OS$ requires C, 51.7; H, 5.3; N, 20.1; S, 15.3%). Solid R (0.48—0.57 g, 10—12%) was 2,5-diphenyl-1,3,4-thiadiazole, identical (mixed m.p.[38] 138—140 °C and i.r.[25]) with authentic material.

S,4-*Dimethyl*-1-*thiobenzoylsemicarbazide* (**14**).—Sodium (0.12 g, 5 mmol) and (**9b**) (1.05 g, 5 mmol) in methanol (20 ml) was treated with iodomethane (8 ml), the solution boiled under reflux for 15 min, distilled to half bulk and stirred into ice–water (100 ml). The solidified precipitate gave white *microneedles* (0.67 g, 60%) of (**14**), m.p. 99—101 °C (from ethanol) (Found: C, 53.8; H, 5.4; N, 18.65; S, 14.4. $C_{10}H_{13}N_3OS$ requires C, 53.8; H, 5.8; N, 18.8; S, 14.3%).

1-p-*Chlorothiobenzoylsemicarbazide* (**10a**).—A solution of semicarbazide hydrochloride (11.15 g, 100 mmol) in M-sodium hydroxide (100 ml, 100 mmol) was treated at room temperature with *p*-chlorothiobenzoylthioacetic acid[25] (12.33 g, 50 mmol) dissolved in M-sodium hydroxide (100 ml, 100 mmol) and set aside for 2 h. Acidification (to pH 3—4) with 3M-acetic acid precipitated a yellow solid, which gave, on crystallisation from ethanol (40 ml per g, recovery 70%; 8.6—9.2 g, 75—80%), yellow felted *needles* of (**10a**), m.p. 181—182 °C (decomp.) (Found: C, 41.8; H, 3.4; N, 19.0; S, 13.5; Cl, 14.9. $C_8H_8ClN_3OS$ requires C, 41.8; H, 3.4; N, 18.3; S, 13.9; Cl, 15.45%).

1-p-*Chlorothiobenzoyl*-4-*methylsemicarbazide* (**10b**).—This compound was obtained (56%) by the method given for the 1-thiobenzoyl analogue (**9b**) but using *p*-chlorothiobenzoylthioacetic acid[25] (40 mmol), and formed pale-yellow *platelets*, m.p. 149—150 °C (from ethanol) (Found: C, 44.1; H, 4.5; N, 17.2. $C_9H_{10}ClN_3OS$ requires C, 44.4; H, 4.1; N, 17.25%). $\nu_{max.}$ 3 320s, 3 160—3 200s (NH), 2 950w (CH_3), 1 650s (CO) and 850ms cm^{-1} (1,4-disub. aryl).

1-p-*Chlorothiobenzoyl*-4-*phenylsemicarbazide* (**10c**).—This compound was similarly obtained by the addition of finely powdered 4-phenylsemicarbazide (15 mmol) to a stirred solution of *p*-chlorothiobenzoylthioacetic acid[25] (10 mmol) in M-sodium hydroxide (30 mmol) at 35 °C, followed by stirring for 45 min and isolation by acidification. It formed pale-yellow *needles* (2.25 g, 74%), m.p. 186—188 °C (decomp.) (from ethanol) (Found: C, 54.85; H, 4.1; Cl, 11.4; N, 13.65; S, 10.25. $C_{14}H_{12}ClN_3OS$ requires C, 55.0; H, 3.9; Cl, 11.6; N, 13.75; S, 10.5%).

In this and the preceding experiment, a precipitate separating prior to the isolation of the main product by acidification was

filtered off. It was 2,5-bis(*p*-chlorophenyl)-1,3,4-thiadiazole (up to 15%), forming platelets, m.p. 225—228 °C (from ethoxyethanol); lit.,[43] m.p. 225 °C (Found: C, 54.2; H, 3.0. Calc. for $C_{14}H_8Cl_2N_2S$: C, 54.7; H, 2.6%). $\nu_{max.}$ 3 050w (CH arom.), 835, 825s d (1,4-disub. aryl), and 785m cm^{-1} (aryl).

Bisformimidoyl Disulphides

Bis(C-*phenyl*-N-*ureido*)*formimidoyl Disulphide* (**16a**).—(*a*) *Oxidation by bromine in methanol.* A stirred solution of 1-thiobenzoylsemicarbazide (**9a**) (1.95 g, 10 mmol) in methanol (30 ml) was rapidly treated at room temperature with freshly prepared M-bromine in chloroform (5.0 ml, 5 mmol), which was instantly decolourised. The liquid was distilled (vacuum) at 35—40 °C to *ca.* half volume, and then stirred into ice–water (200 ml). The pale yellow precipitate was collected, washed neutral with water, and carefully air-dried at room temperature (to prevent its turning into a sticky resin). The yellow powder was added in one portion to boiling ethanol (15 ml): it dissolved, and quickly reappeared as a sparingly soluble yellow crystalline precipitate (m.p. 167—169 °C; 1.25—1.40 g, 65—72%). Crystallisation by dissolution in a large volume of acetone (4 × 50 ml per g) and vacuum evaporation of the filtered liquid (to half-volume or less) gave opaque deep-yellow microcrystalline (**16a**), m.p. 166—168 °C (decomp.) (Found: C, 49.4; H, 4.1; N, 21.8; S, 16.65. $C_{16}H_{16}N_6O_2S_2$ requires C, 49.5; H, 4.1; N, 21.65; S, 16.5%); $\nu_{max.}$ 3 460s (NH_2), 3 250—3 100s mult (NH), 1 730s (C=N), 1 700—1 660s mult (CO), 1 580s br (C–N–H), 760, 685s (Ph), 1 440s, 1 310m, 1 235m, 1 140—1 090s mult and 910ms cm^{-1} (all bands broad); δ_H 6.65 (2 H, s, NH_2), 7.25—7.8 (5 H, mult, Ph), and 9.25 (1 H, s, NH) p.p.m.

The disulphide was also recrystallisable from ethyleneglycol–ethanol (10 and 4 ml per g, recovery 50%; from 2-methoxyethanol–ethanol–water (4, 4, and 3 ml per g, recovery 70%); or from dioxane–light petroleum (12 and 50 ml, b.p. 40—60 °C, per g, recovery 50%). It dissolved in cold glacial acetic acid and in thymol, but reproducible values of its molecular mass were not obtainable cryoscopically in the latter solvent.

(*b*) *Oxidation by hydrogen peroxide.* A boiling solution of (**9a**) (3.9 g, 20 mmol) in ethanol (60 ml) was treated during 1 min with 6% hydrogen peroxide (6.3 ml, 11 mmol; acidified with 2 drops of concentrated hydrochloric acid); the yellow liquid was boiled for 3 min, and then stirred into ice–water (250 ml). The precipitate gave, on treatment as described for (*a*), microcrystalline (**16a**), m.p. 162—164 °C (2.5—2.95 g, 65—76%) (Found: C, 49.5; H, 4.0; N, 20.3; S, 16.6%).

Evaporation of the ethanolic filtrate from the isolation procedure gave a discoloured residue, which afforded platelets (0.2—0.3 g, 8—12%) of 2,5-diphenyl-1,3,4-thiadiazole, m.p. 138—140 °C,[38] identified by i.r.[25] spectroscopy.

When the reaction mixture was stirred into less ice–water (100 ml), the aqueous ethanolic filtrate from the main product slowly deposited small amounts of well-developed yellow prisms of the *disulphide dihydrate*, m.p. 161—162 °C (decomp.) (Found: C, 45.75; H, 4.0; N, 19.8; S, 15.35. $C_{16}H_{16}N_6O_2S_2 \cdot 2H_2O$ requires C, 45.3; H, 4.7; N, 19.8; S, 15.1%). Its i.r. spectrum was identical with that of non-solvated disulphide, except for the characteristic broadening of the peak at 3 480 cm^{-1}.

(*c*) *Prolonged action of hydrogen peroxide.* A solution of (**9a**) (20 mmol) in boiling ethanol (100 ml) was treated with 6% hydrogen peroxide (30 mmol)–concentrated hydrochloric acid (0.5 ml) during 5 min, and then boiled for 30 min. The solution deposited a little sulphur; the decanted liquid gave, on addition to water (800 ml), a precipitate (2.5—3.0 g) (filtrate: F) which was crystallised from ethanol (35 ml). The first crop of needles (0.58 g, 18%), collected after 30 min, was 2-amino-5-phenyl-1,3,4-oxadiazole, identical (mixed m.p., i.r.) with authentic material (see below). Prolonged storage of the filtrate therefrom gave the disulphide (**16a**), m.p. 163—165 °C (decomp.), (1.1—1.25 g, 28—32%). Filtrate F was treated with 0.05M aqueous picric acid (200 ml, 10 mmol) and gave 2-amino-5-phenyl-1,3,4-oxadiazole picrate, m.p. 201—203 °C (decomp.) identical with authentic material (see below) (1.40 g, 18%).

Bis(C-*phenyl*-N-*ureido*)*formimidoyl Disulphide* (**16a**).—(*a*) *Catalytic reduction.* The disulphide (**16a**) (1.95 g, 5 mmol) was dissolved with heating in propanol (300 ml), and the yellow liquid so obtained allowed to cool to room temperature; it was then shaken in hydrogen in the presence of Adams' catalyst[44] (0.40 g). Hydrogen uptake ceased after 60—80 min (observed: 200 ml; calc., for catalyst, 75 ml; for reactant 112 ml; at S.T.P.). The filtered solution was evaporated to small volume giving yellow platelets (1.40 g, 72%) of 1-thiobenzoylsemicarbazide (**9a**), identified by mixed m.p. and i.r. spectroscopy.

(*b*) *Action of toluene*-p-*sulphonyl chloride.* Treatment of a solution of (**16a**) (0.97 g, 2.5 mmol) in pyridine (25 ml) with toluene-*p*-sulphonyl chloride (1.05 g, 5.5 mmol) (6 h at room temperature), followed by work-up as described for (**9a**), gave an orange resin, which formed, after two crystallisations from ethanol, platelets (20—30%) of the toluene-*p*-sulphonyl derivative of (**9a**), m.p. 169—170 °C.

(*c*) *Action of iodomethane.* The disulphide (**16a**) (1.94 g, 5 mmol) was dissolved in a solution of sodium (0.23 g, 0.01 mmol) in methanol (30 ml) and iodomethane (20 ml), the liquid refluxed for 1 h, distilled to small bulk (15 ml) and added to water. The resulting solidified oil gave, after three crystallisations from ethanol–light petroleum, prisms (32%) of (**13**), identified by i.r. spectroscopy (Found: C, 51.9; H, 5.4; N, 20.0; S, 15.0%).

(*d*) *Action of dimethyl sulphate.* The disulphide (**16a**) (2.9 g, 7.5 mmol) and dimethyl sulphate (7 g) were added to 3M-sodium hydroxide (60 ml) at 40—45 °C and the suspension was shaken vigorously; the temperature rose (to *ca.* 70 °C) when dissolution occurred. More dimethyl sulphate (3 g, total 80 mmol) was added and shaking continued for 20 min. The resulting yellow precipitate, collected at 0 °C (m.p. 96—100 °C; 2.1—2.4 g, 62—72%) and crystallised from ethanol–light petroleum (1:5), gave (**15**) as platelets, m.p. 110—112 °C, identified by i.r. spectroscopy (Found: C, 53.4; H, 5.5; N, 19.2; S, 13.8%). Slower addition of less dimethyl sulphate (3.15 g, 25 mmol) at room temperature gave a crude product (1.5—2.2 g), which afforded on fractionation from ethanol, smaller yields of the *S*-monomethyl-(**13**), m.p. 155—156 °C, (28—40%) and the more soluble *S*,2-dimethyl-compound (**15**), m.p. 111—112 °C, (5—8%).

(*e*) *Action of hydrochloric acid.* A solution of (**16a**) (0.97 g, 2.5 mmol) in methanol (15 ml)–concentrated hydrochloric acid (2 ml) was refluxed for 20 min (odour of methyl benzoate). The clear liquid was decanted from coagulated sulphur and diluted with water. The white solid, collected at 0 °C (filtrate: F) gave, on crystallisation from chloroform–light petroleum, needles (72—82%) of 2-hydroxy-5-phenyl-1,3,4-thiadiazole, identified by mixed m.p. 146—148 °C and i.r. spectroscopy.[4,5] Addition of 0.05M aqueous picric acid (50 ml, 2.5 mmol) to filtrate F precipitated 2-amino-5-phenyl-1,3,4-oxadiazole picrate (up to 0.34 g, 35%), m.p. 201—203 °C (decomp.), (from ethanol), identical with authentic material (see below).

(f) *Action of sodium hydroxide.* Finely powdered (**16a**) (1.94 g, 5 mmol) was refluxed in 3M sodium hydroxide (20 ml) for 20 min. The colourless turbid liquid was slowly acidified with 3M hydrochloric acid (ice–cooling; successive evolution of hydrogen sulphide and sulphur dioxide). The resulting pale-yellow precipitate of (**9a**) [60—70%; calc. on the basis of the formation of 1.5 moles of (**9a**) from one of (**16a**)] afforded yellow platelets, m.p. 158—160 °C (from ethanol).

Table 3. Substituted bisformimidoyl disulphides

Compd.	Ar	R	Method of Prep.[a]	M.p. °C (decomp.) Yield	Molecular formula	Found %	Reqd. %	Spectra
(16b)[b]	Ph	Me	(*b*)	136—140[c] 68—80%	$C_{18}H_{20}N_6O_2S_2$[d]	C, 52.0 H, 4.6 N, 20.1 S, 15.5	51.9 4.8 20.2 15.4	δ_H 2.7 (3 H, d, CH_3), 7.0 (1 H, q, NHMe), 7.2—7.8 (5 H, m, Ph), 9.4 (1 H, s, NH) p.p.m. $\nu_{max.}$ 3 400s centre of mult (NH), 2 950w (CH_3), 1 680s br (CO), 1 535s br (C–N–H), 765ms, 690ms (Ph), 1 285—1 295m tr cm^{-1}
(16c)[e,f]	Ph	Ph	(*a*)	198—200[g] 65—80%	$C_{28}H_{24}N_6O_2S_2$[h]	C, 61.6 H, 4.5 N, 15.0 S, 12.4	62.2 4.4 15.55 11.85	$\nu_{max.}$ 3 400ms, 3 160m, 3 090m (NH), 1 690s br (CO/C=N), 1 535s br (C–N–H), 765, 755 ms d, 695ms (Ph) cm^{-1}
			(*b*)	188—196 56—68%				
(17a)[i]	*p*-ClC_6H_4	H	(*a*)	196—198[k] 56%	$C_{16}H_{14}Cl_2N_6O_2S_2$	C, 41.5 H, 3.5 Cl, 15.3 N, 17.8 S, 14.8	42.0 3.1 15.5 18.4 14.0	δ_H 6.7 (2 H, s, NH_2), 7.2—7.8 (4 H, q, C_6H_4), 9.4 (1 H, s, NH) p.p.m. $\nu_{max.}$ 3 470s (NH_2), 3 220, 3 130s d (NH), 1 685s br (CO/C=N), 1 580s br (C–N–H), 830s (1,4-disub. Ar), 760m (Ar) cm^{-1}
			(*b*)	195—198 72%				
(17b)[i]	*p*-ClC_6H_4	Me	(*b*)	184—188[l] 85%	$C_{18}H_{18}Cl_2N_6O_2S_2$	C, 44.4 H, 3.8 Cl, 14.3 N, 17.2 S, 13.4	44.5 3.7 14.6 17.3 13.2	$\nu_{max.}$ 3 420s, 3 330s (NH), 2 950w (CH_3), 1 685s br (CO/C=N), 1 520s br (C–N–H), 840ms (1,4-disub. Ar) cm^{-1}
(17c)[i]	*p*-ClC_6H_4	Ph	(*a*)	184—186 64%	$C_{28}H_{22}Cl_2N_6O_2S_2$	C, 55.7 H, 4.1 Cl, 11.5 N, 13.4 S, 10.1	55.2 3.6 11.65 13.8 10.5	$\nu_{max.}$ 3 400—3 050ms mult (NH), 1 670s br (CO/C=N), 1 535s br (C–N–H), 835ms (1,4-disub. Ar), 750s, 690ms (Ph) cm^{-1}
			(*b*)	186—188[m] 82%				

[a] Oxidation by (*a*) bromine in methanol; (*b*) hydrogen peroxide. [b] The compound, in propan-1-ol, absorbed hydrogen (0.55 mol) during 20 min, yielding 65% of (**9b**). [c] Readily from ethanol. Resolidifies after fusion and remelts at 218—222 °C (decomp.). [d] After drying for 5 h at 110 °C/2mmHg. Separates initially as a dihydrate. [e] The compound, in propan-1-ol, absorbed hydrogen (0.65 mol) during 15 min, yielding 70% of (**9c**). [f] Alkaline hydrolysis gave (**9c**) (72%). [g] From dimethylformamide–ethanol. Sinters from 185 °C. [h] Analysis sample extracted with carbon disulphide prior to crystallisation. [i] Oxidation performed in 2-ethoxyethanol at 90 °C. [k] Material separating directly from boiling ethanol. Attempted recrystallisation caused decomposition. [l] From a large volume of ethanol. [m] From 1,4-dioxane.

Bis(C-*aryl*-N-*ureido*)*formimidoyl Disulphides* (**16b,c**); (**17a—c**).—These compounds were prepared by procedures (*a*) or (*b*) [as described for (**16a**)], with the results given in Table 3.

N-*Acetimidoyl*-N′-*thiobenzoylhydrazine*.[25]—*Action of hydrogen peroxide*. A solution of the reactant (0.97 g, 5 mmol) in ethanol (25 ml) was treated at room temperature with 6% hydrogen peroxide (1.42 ml, 2.5 mmol), after which the resulting yellow liquid was set aside for 5 min, and then stirred into water (120 ml). The precipitate (0.36 g), and more material which separated slowly on storage (0.3 g, total 75%) was 2-methyl-5-phenyl-1,3,4-thiadiazole, identified by mixed m.p.[32] 103—105 °C, and i.r. spectroscopy.[25] The same procedure, carried out at the b.p. of ethanol (3 min, giving an orange liquid), produced a mixture of 2,5-diphenyl- and 2-methyl-5-phenyl-1,3,4-thiadiazole, each in *ca.* 15% yield.

N-*Benzimidoyl*-N′-*thiobenzoylhydrazine*[25] gave, on identical treatment at room temperature, 2,5-diphenyl-1,3,4-thiadiazole in 75—80% yield.

2-*Amino*-5-*phenyl*-1,3,4-*oxadiazole*.—Authentic material was prepared (40%) by the method of Stollé and Fehrenbach[45] by the prolonged action (6 h) of mercuric oxide on 1-benzoylthiosemicarbazide[40] in boiling ethanol. It formed needles, m.p. 239—241 °C (decomp.) (from ethanol); $\nu_{max.}$ 3 300s, 3 120s (NH), 1 650s br (C=N), 1 590s (C–N–H), 770s, 690s (Ph), 1 025s, and 740s cm^{-1}. Its *picrate*, obtained (80%) from the components (1 mmol each) in ethanol (18 ml), formed pale yellow microcrystals, m.p. 201—203 °C (from ethanol) (Found: C, 43.3; H, 2.5; N, 21.2. $C_8H_7N_3O{\cdot}C_6H_3N_3O_7$ requires C, 43.1; H, 2.6; N, 21.5%).

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