867. *Thiadiazoles. Part XV.* 5-Substituted 3-Hydrazino-1,2,4-thiadiazoles.*

By Leonard E. A. Godfrey and Frederick Kurzer.

Oxidation of 1-alkyl(or aryl)-3-(aminoamidino)thioureas, as their hydrazones, yields 5-alkyl(or aryl)amino-3-alkylidene(or arylidene)hydrazino-1,2,4-thiadiazoles, which are hydrolysed to the free hydrazines under carefully controlled conditions.

The convertibility of the 3-hydrazino-1,2,4-thiadiazoles, on treatment with acetylacetone, into the corresponding 3-(3,5-dimethylpyrazol-1-yl) derivatives, which are in their turn accessible from 1-amidino-3,5-dimethylpyrazole, supports the structure of the former. Some of the properties of 3-hydrazino-1,2,4-thiadiazoles, particularly their rearrangement into triazoles, are described and discussed.

During recent years, a number of thiadiazolylhydrazines have been obtained, generally by classical syntheses. These included the replacement, by hydrazinolysis of halogen [1-4] or alkanesulphonyl [2,5] substituents, and the reduction of nitrosamino- [1,2,4-6] or nitroamino-thiadiazoles.[1] The majority of examples studied concern 2-hydrazino-1,3,4-thiadiazoles [1,2,5,6] but the methods are also applicable to 5-hydrazino-1,2,4-thiadiazoles.[3,4] Most recently, Sandström [7] described a group of syntheses of 2-hydrazino-1,3,4-thiadiazoles, comprising cyclisations of thiocarbohydrazide (in the form of its hydrazones) by oxidation,[7a] and by the agency of orthoesters,[7b] dialkyl trithiocarbonates,[7c] or carbon

* Part XIV, Kurzer and Sanderson, *J.*, 1963, 3336.

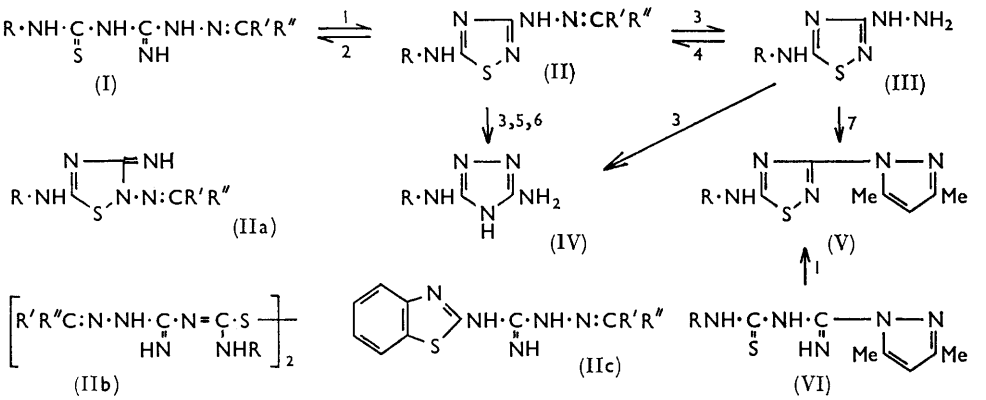
[1] Kanaoka, *J. Pharm. Soc. Japan*, 1955, **75**, 1149.
[2] Kanaoka, *Pharm. Bull.*, 1957, **5**, 385.
[3] Goerdeler and Sperling, *Chem. Ber.*, 1957, **90**, 892.
[4] Goerdeler and Deselaers, *Chem. Ber.*, 1958, **91**, 1025.
[5] Fujii, Yoshikawa, and Yuasu, *J. Pharm. Soc. Japan*, 1954, **74**, 1056.
[6] Stollé and Fehrenbach, *J. prakt. Chem.*, 1929, **122**, 289.
[7] Sandström, (*a*) *Arkiv Kemi*, 1956, **9**, 255; (*b*—*d*) *Acta Chem. Scand.*, 1960, **14**, (*b*) 1037, (*c*) 1939; (*d*) 1961, **15**, 1295.

disulphide.[7d] Analogous cyclisations involving phenylthiocarbohydrazide had been reported by Guha and Roy-Choudhury.[8]

3-Hydrazino-1,2,4-thiadiazoles have apparently not been obtained previously: because of the inertness of the corresponding 3-halogen-derivatives,[9] the established replacement methods are inapplicable, while reduction of nitroamino- and similar derivatives is precluded by the ease with which the heterocyclic ring is cleaved under reducing conditions.[10,11] The ready accessibility of 1-substituted 3-(aminoamidino)thioureas, in the form of their hydrazones (I), has recently [12] provided intermediates containing both the amidinothiono- [·C(SH):N·C(:NH)·] and the hydrazino-grouping. Oxidative cyclisation of the former system [10] was expected to yield the desired heterocyclic hydrazines (II, III) in the usual way.

The reagents commonly used for cyclising amidinothioureas [10] are acidified hydrogen peroxide or bromine. 1-Substituted 3-(aminoamidino)thioureas (I) are, however, exceptionally sensitive towards mineral acids, being rapidly cyclised to 3-amino-5-mercapto-1,2,4-triazole under the mildest conditions.[12] Accordingly, hydrogen peroxide proved unsuitable in the present ring-closure: extensive decomposition, with elimination of sulphur, occurred when only traces of acid were employed, even when acetone, designed to suppress the possible hydrolysis of the hydrazone (II), was the solvent. Aqueous ferric chloride, successfully used in the preparation of 2-hydrazino-1,3,4-thiadiazoles,[7a] resulted similarly in total decomposition of the reactants (I).

Equimolar proportions of bromine in chloroform, on the other hand, effected the cyclisation (I ⟶ II) rapidly in high yield. The thiadiazol-3-ylhydrazones (II), isolated from the resulting hydrobromides by use of cold ammonia, are monoacid bases, which are readily reconverted into the parent thioureas (I) on mild reduction by sulphur dioxide. They were decomposed by mineral acids, with extrusion of sulphur, and rearrangement to 3-amino-5-arylamino-1,2,4-triazoles (IV; R = Ph or *p*-C_6H_4Me). This reaction undoubtedly contributed further to the difficulty of effecting the ring-closure (I ⟶ II) by

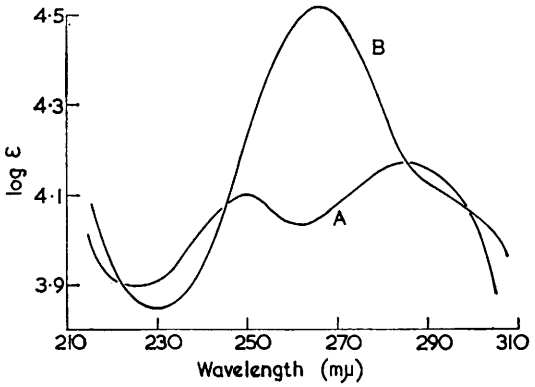


acidified peroxide (see above). The same change (II ⟶ IV) was brought about by ethanolic hydrazine, or by alkalis, though more slowly in the last case, presumably because of the expected [13] relative resistance of hydrazones to hydrolysis in alkaline media;

[8] Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, 1928, **3**, 149, 163.
[9] Kurzer and Taylor, *J.*, 1960, 3234.
[10] Kurzer, *J.*, 1955, 1 and later papers.
[11] Godfrey and Kurzer, following paper.
[12] Godfrey and Kurzer, *J.*, 1960, 3437.
[13] Houben-Weil, " Methoden der Organischen Chemie," Thieme, Stuttgart 1954, Vol., VII, Part I, pp. 461, 474.

thus, up to 40% of the reactant (II; R = Ph, R′ = R″ = Me) was recovered after 1·5 hours' boiling in ethanolic sodium hydroxide.

The production of the free 3-hydrazines (III) from their hydrazones (II) required special care because of the sensitivity of both types of compound towards acids. Under sufficiently restrained conditions, however, the reaction failed to go to completion and



Ultraviolet absorption spectra of (A) 5-anilino-3-hydrazino-1,2,4-thiadiazole and (B) 5-anilino-3-(ethylidenehydrazino)-1,2,4-thiadiazole.

yields were erratic and poor. Addition of a reagent to remove the liberated carbonyl compound (R′R″CO) was found to displace the equilibrium position of the reversible reaction in the desired direction and thus made the use of very mild hydrolytic conditions effective: brief treatment of the hydrazone (II; R = Ph, R′ = R″ = Me) with 1·5N-hydrochloric acid at 50° in the presence of a large excess of aminoguanidine afforded 5-anilino-3-hydrazino-1,2,4-thiadiazole (III; R = Ph) without difficulty in consistently high yields.

5-Anilino-3-hydrazino-1,2,4-thiadiazole is a monoacid base which formed a picrate and yielded mono-, tri-, and tetra-acyl derivatives, depending on the experimental conditions: its monotoluene-*p*-sulphonyl, triacetyl, and tetrabenzoyl derivatives are described. With aldehydes and ketones, hydrazones (II) were formed as expected. So readily was acetaldehyde taken up by the hydrazino-residue that the ultraviolet spectrum of 5-anilino-3-hydrazino-1,2,4-thiadiazole (III; R = Ph) in pure ethanol (0·0005M-solution) changed completely to that of the 3-ethylidenehydrazino-compound (II; R = Ph, R′ = H, R″ = Me) after a few days' storage at room temperature (see Figure), the acetaldehyde arising in traces by air-oxidation of the alcohol, a view supported by the observed marked acceleration of this change by aeration of the solution.

On treatment with boiling hydrochloric acid, 5-anilino-3-hydrazino-1,2,4-thiadiazole (III; R = Ph) gave sulphur and 3-amino-5-anilino-4*H*-1,2,4-triazole (IV; R = Ph) rapidly in high yield. The previously observed [14] formation of 3-amino-1,2,4-triazole by the action of hydrazine on 3-methylthio-1,2,4-thiadiazole is a comparable reaction. The tendency of 1,2,4-thiadiazol-3-ylhydrazines (and their hydrazones, see above) to undergo this rearrangement is in marked contrast to the stability of the 5-hydrazines,[3,4] and may indeed be accounted for in terms of the position of the 3-hydrazino-group in relation to the rest of the structure. Whatever its detailed mechanism, an approach of the terminal hydrazino-nitrogen to the 5-carbon atom (in III) would create spatially favourable conditions for the formation of the new five-membered ring (IV), by simple extrusion of sulphur requiring no further rearrangement. In the 5-hydrazino-series this potential configuration is absent.

5-Anilino-3-hydrazino-1,2,4-thiadiazole (III; R = Ph) and acetylacetone gave, by the standard pyrazole synthesis,[15] 90% yields of 5-anilino-3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazole (V; R = Ph). This compound had previously been obtained by Scott

[14] Goerdeler and Budnowski, *Chem. Ber.*, 1961, **94**, 1682.
[15] Jacobs, in Elderfield's " Heterocyclic Compounds," Vol. V, Wiley, New York, 1957, pp. 45 *et seq.*

and Reilly [16] in the attempted halogenation of 3,5-dimethyl-1-phenyl(thiocarbamoyl)-amidinopyrazole (VI; R = Ph), and, though first formulated as a disulphide,[16] was later [17] recognised as the 1,2,4-thiadiazole (V; R = Ph). Our compound was identical with the product prepared from (VI; R = Ph) by Scott and Reilly's method, starting with phenyl isothiocyanate and 1-amidino-3,5-dimethylpyrazole.[16,18] Attempts to employ the nitrate of the pyrazole,[18] and dimethylformamide as solvent, in this initial condensation resulted in the production of small yields of the thiadiazole (V; R = Ph) directly, the oxidising action of the nitric acid cyclising the intermediate (VI) as soon as it was formed. Incorporating the 3-hydrazino-side-chain (of III) into the pyrazole ring (in V) had a striking stabilising effect on the 1,2,4-thiadiazole ring. In contrast to (III), the bicyclic compound (V) was remarkably stable, being unaffected, for example, by prolonged treatment with boiling hydrochloric acid or aniline.

In the present synthesis of 5-substituted 3-hydrazino-1,2,4-thiadiazoles (II, III) from 1-alkyl(or aryl)-3-(aminoamidino)thioureas (I), the absence of gross changes in the molecular skeleton is proved by the regeneration of the starting materials (I) on reduction. At least three structures (IIa—c) other than 1,2,4-thiadiazoles might theoretically still be formed in the absence of such rearrangements; these alternatives are eliminated as follows: Disulphide formation (IIb) is excluded on the basis of the equimolar bromine uptake (by I), the observed molecular weight of the products (III), and the well-known instability of dithioformamidines [19] (IIb) that would arise. Cyclisation involving the thiol group, and the penultimate hydrazino-nitrogen (in I) would yield a 1,2,4-thiadiazoline of type (IIa), which, though still capable of forming Schiff's bases with carbonyl compounds, cannot yield the observed pyrazolyl derivative (V) with acetylacetone. Finally, oxidation of arylthioureas with halogens in inert solvents is a standard benzothiazole synthesis.[20] 2-(Aminoguanidino)benzothiazoles (IIc) that would arise in the present case, should exhibit the usual stability of this ring-system: [20] this formulation (IIc) cannot therefore be reconciled with the observed rearrangement of the products to 1,2,4-triazoles (IV). Moreover, the aliphatic thiourea (I; R = Me, R′ = H, R″ = Ph), which cannot yield a benzothiazole, undergoes oxidation in the usual way. The present oxidative cyclisation (I ⟶ II) thus provides yet another example of the preferential formation of 1,2,4-thiadiazoles over that of benzothiazoles.[11,21]

Experimental

M-Bromine was a chloroform solution unless otherwise specified. The light petroleum had b. p. 60—80°.

Ultraviolet absorption measurements were made with a Unicam S.P. 500 spectrophotometer, and 0·00005—0·0001M-ethanolic solutions.

5-Anilino-3-(isopropylidenehydrazino)-1,2,4-thiadiazole.—A stirred solution of 1-(isopropylideneamino)amidino-3-phenylthiourea [12] (9·95 g., 0·04 mole) in boiling chloroform (350 ml.) was cooled to ~35° and treated dropwise, with external cooling, with M-bromine (40 ml., 0·04 mole) during 30 min. The white powder, which began to separate half way through the addition, was collected after 2 hours' storage at 0°, rinsed with chloroform, and dried [m. p. 153—155° (decomp.); 9·2—11·0 g., 70—84%, calc. as anhydrous hydrobromide]. Crystallisation from ethanol–ether (5 ml. each, per g., recovery 50%) or ethanol (5 ml. per g., recovery 30%) gave needles of the *hydrobromide monohydrate*, m. p. 174—176° (decomp.) (Found: C, 38·2; H, 4·3; S, 9·2. $C_{11}H_{13}N_5S,HBr,H_2O$ requires C, 38·2; H, 4·6; S, 9·25%). Recovery of hydrobromide from the mother-liquors was not practicable. Alternatively, rapid crystallisation from ethanol–light petroleum (10 and 33 ml. per g., recovery 75%) gave colourless prisms, m. p. 165—170°

[16] Scott and Reilly, *J. Amer. Chem. Soc.*, 1952, **74**, 4562.
[17] Scott, *Chem. and Ind.*, 1958, 463.
[18] Thiele and Dralle, *Annalen*, 1898, **302**, 275, 294.
[19] Kurzer and Sanderson, *J.*, 1957, 4461; 1959, 1058; 1963, 3336.
[20] Sprague and Land, in Elderfield's "Heterocyclic Compounds," Vol. V, Wiley, New York, 1957, pp. 484, 510, 580.
[21] Kurzer and Sanderson, *J.*, 1960, 3240.

Ultraviolet absorption spectra of 3,5-disubstituted 1,2,4-thiadiazoles.

		λ (mμ) ($\log_{10}\varepsilon$ in parentheses)			
3-Subst.	5-Subst.	min.	max.	min.	max.
NH_2·NH	Ph·NH	225 (3·90)	249 (4·10)	262 (4·04)	285 (4·17)
,,	*p*-C_6H_4Me·NH	225 (3·88)	250 (4·05)	262 (3·99)	285 (4·17)
Me·CH:N·NH	Ph·NH	229 (3·84)	266 (4·52)	[sh. 285—295	(4·17—4·10)]
Me_2C:N·NH	,,	227 (3·88)	265 (4·53)	[sh. 290—300	(4·13—4·05)]
,,	*p*-C_6H_4Me·NH	228 (3·90)	266 (4·51)	[sh. 290—300	(4·16—4·08)]
Ph·CH:N·NH	Ph·NH	221 (4·10)	232 (4·15)	249 (3·92)	.292 (4·55)
		max.	min.	max.	min.
,,	Me·NH	228 (4·20)	239 (4·15)	259 (4·30)	284 (3·90)

Sh = slight shoulder.

(decomp., after sintering at 162°). The salt did not give a precipitate of lead sulphide when boiled with sodium plumbite in 3N-sodium hydroxide.

When the precipitated crude hydrobromide was in contact with the reaction mixture for longer periods, yields were lower, probably owing to hydrolysis under the influence of hydrogen bromide.

The crude hydrobromide (3·28 g., 0·01 mole) was quickly dissolved in ethanol (20 ml.) at 55° and the somewhat cooled liquid stirred into 3N-ammonia (10 ml., 0·03 mole) and ice (40 g.). The yellow precipitate changed to a white granular solid presently and was collected at 0° (2 g.). It was dissolved in boiling acetone (100—120 ml.), the filtered solution reduced successively to half and then to small volume in a vacuum, and the nearly white microcrystalline powder collected at 0° in each case [m. p. 174—176° (decomp.); 1·45—1·73 g., 60—70%]. Further crystallisation from acetone (80 ml. per g., followed by partial evaporation) gave felted needles of 5-*anilino*-3-(*isopropylidenehydrazino*)-1,2,4-*thiadiazole*, m. p. 177—179° (decomp. vigorously to a black pitch) [Found: C, 53·4; 52·9; H, 5·2; 5·1; N, 28·9; S, 13·0%; *M* (cryoscopically, in thymol), 237. $C_{11}H_{13}N_5S$ requires C, 53·4; H, 5·3; N, 28·3; S, 13·0%; *M*, 247].

This compound, m. p. and mixed m. p. 177—179° (decomp., as above), was obtained almost quantitatively when 5-anilino-3-hydrazino-1,2,4-thiadiazole (see below) was dissolved in the minimum volume of boiling acetone, and the solution was diluted with light petroleum.

It did not give a picrate. Equimolar proportions of the compound and picric acid (0·0005 mole each) in ethanol (6 ml.), diluted with light petroleum (b. p. 40—60°), slowly deposited yellow solid in storage. This gave impure 5-anilino-3-hydrazino-1,2,4-thiadiazole picrate (from ethanol–light petroleum), m. p. and mixed m. p. (see below) 220—224° (decomp.), presumably formed after initial hydrolytic removal of the isopropylidene group.

Attempts to effect the above oxidation by the use of 6% hydrogen peroxide under the conditions of comparable cyclisations [10] were unsuccessful or inconclusive, yielding mostly intractable resins, together with traces of powdery solid, m. p. 115—120°. These attempts included treatment of the reactant (0·005 mole) in ethanol or acetone with 6% hydrogen peroxide (0·0125 mole), in the presence or absence of hydrochloric acid (0·005 mole), or in acetic acid. These oxidations were attended by the evolution of a nauseating sulphurous odour, absent in successful oxidative cyclisations in this field.[10]

The action of 2 mol. of ferric chloride (2M-aqueous or -ethanolic solution) on the reactant in acetone at room temperature gave only some sulphur and intractable dark resins or powders.

Reactions of 5-Anilino-3-(isopropylidenehydrazino)-1,2,4-thiadiazole.—(*a*) *With ethanolic hydrochloric acid.* A solution of the reactant (0·74 g., 0·003 mole) in ethanol (12 ml.) and 3N-hydrochloric acid (12 ml.) was kept on the steam-bath during 30 min., then decanted from the separated coagulated sulphur (0·08 g., 83%) into N-ammonia (60 ml.). The liquid was evaporated by distillation (to ~40 ml.), and the solid collected at 0° (0·4 g., 75%). Successive crystallisation from a little water, and light petroleum containing a few drops of ethanol, gave prisms of 3-amino-5-anilino-1,2,4-triazole, m. p. and mixed m. p. with authentic material [22] 159—162° (Found: C, 55·1; H, 5·25. Calc. for $C_8H_9N_5$: C, 54·9; H, 5·1%).

(*b*) *With hydrazine.* A solution of the reactant (0·74 g., 0·003 mole) in ethanol (20 ml.) containing 80% hydrazine hydrate (2 ml., 0·032 mole) was stirred at room temperature during 8 hr., and the clear brown solution set aside overnight. The liquid was decanted from the

[22] Fromm and Kapeller-Adler, *Annalen*, 1928, **467**, 240, 266.

small deposit of resin (R), acidified with 3N-hydrochloric acid (10—12 ml., to pH 4), and treated with toluene-*p*-sulphonic acid monohydrate (1·9 g., 0·01 mole). On partial spontaneous evaporation (to ~10 ml.) at room temperature, the colourless liquid deposited prisms which were collected, rinsed with a little cold water (m. p. 188—192°; 0·67 g., 64%), and crystallised from water, affording prisms of 3-amino-5-anilino-1,2,4-triazole toluene-*p*-sulphonate, m. p. and mixed m. p. (with authentic material, see below) 189—191° (decomp.). The resin R, on being stirred with dilute hydrochloric acid, evolved hydrogen sulphide and deposited sulphur.

A solution of 3-amino-5-anilino-1,2,4-triazole (0·35 g., 0·002 mole) in boiling water (10 ml.), when treated with toluene-*p*-sulphonic acid monohydrate (0·42 g., 0·0022 mole), rapidly deposited crystals, which were collected at 0° (95%) and afforded needles of the *toluene*-p-*sulphonate*, m. p. 188—190° (decomp.) (from water; 60 ml. per g., recovery over 90%) (Found: C, 51·4; H, 5·3; N, 20·5. $C_8H_9N_5,C_7H_8O_3S$ requires C, 51·9; H, 4·9; N, 20·2%).

(*c*) *With sodium hydroxide.* The reactant (0·5 g., 0·002 mole) slowly dissolved in boiling ethanol (10 ml.)–3N-sodium hydroxide (10 ml.); the liquid was refluxed during 1·5 hr., then about half the ethanol was distilled off. The solid which separated on cooling (collected at 0°) was the starting material, m. p. and mixed m. p. 177—179° (decomp.) (from acetone) (0·2 g., 40%). The aqueous filtrate therefrom was acidified with 3N-hydrochloric acid (evolution of hydrogen sulphide) and treated with 0·05N-picric acid, yielding 3-amino-5-anilino-1,2,4-triazole picrate, m. p. and mixed m. p. [12] 230—232° (from 80% ethanol) (0·34 g., 42%).

(*d*) *Reduction by sulphur dioxide.* A slow stream of sulphur dioxide was bubbled, during 4 hr., through a refluxing solution of the reactant (0·50 g., 0·002 mole) in acetone (40 ml.); the yellow liquid became colourless within 30 min. The solvent was almost completely removed at ~35° in a vacuum, and the residual liquid (5—6 ml.) treated with 3N-ammonia (3—4 ml.). The crystals which separated from the resulting two-phase mixture were collected after 24 hours' storage at 0° and rinsed with a little water [m. p. 168—170° (decomp.); 0·34 g., 68%]. They consisted, after crystallisation from acetone, of prisms of 1-(isopropylideneaminoamidino)-3-phenylthiourea, m. p. and mixed m. p.[12] 168—169° (decomp.). The product rapidly gave lead sulphide on being heated with alkaline sodium plumbite. Its ultraviolet absorption curve [$\lambda_{min.}$ 253 mμ (log ε 3·84); $\lambda_{max.}$ 295 mμ (log ε 4·45)] was coincident with that of an authentic sample.[12]

5-*Anilino*-3-*hydrazino*-1,2,4-*thiadiazole*.—(*a*) A suspension of 5-anilino-3-(isopropylidenehydrazino)-1,2,4-thiadiazole (4·95 g., 0·02 mole) and finely powdered aminoguanidine sulphate monohydrate (7·9 g., 0·06 mole) in ethanol (40 ml.)–3N-hydrochloric acid (40 ml.) was warmed to 50°; dissolution occurred. The yellow liquid was kept at this temperature during 15 min. (a slight opalescence appearing towards the end in some experiments), stirred into ice–water (200 ml.), and basified (to pH 9) with 3N-ammonia (60 ml.). The white flocculent precipitate was collected after 2 hours' storage at 0° (use of a fairly large Buchner funnel essential), and the dried powdery solid (4 g.) was dissolved in refluxing ethanol (80—100 ml. per g.). The filtered solution deposited felted needles of 5-*anilino*-3-*hydrazino*-1,2,4-*thiadiazole*, m. p. 164—165° (decomp., depending somewhat on the rate of heating) (yield, including material from the mother-liquors, 3·0—3·4 g., 72—82%) [Found: C, 45·9; 46·8; H, 4·0, 5·1; N, 33·0; S, 15·0%; *M* (cryoscopically in thymol), 215. $C_8H_9N_5S$ requires C, 46·4; H, 4·35; N, 33·8; S, 15·5%; *M*, 207]. The compound was insoluble in aqueous 3N-hydrochloric acid. It did not give lead sulphide with sodium plumbite in boiling 3N-sodium hydroxide.

(*b*) The 3-(isopropylidenehydrazino)-compound (0·99 g., 0·004 mole), suspended in ethanol (10 ml.), dissolved on addition of 3N-hydrochloric acid (10 ml., 0·03 mole). The yellow solution was set aside at room temperature during 8—12 hr., or at 50° during 45 min., stirred into 3N-ammonia (15 ml., 0·045 mole) and ice, and the white flocculent precipitate was collected at 0° (0·9 g.). Crystallisation from ethanol (50 ml. per g.) gave felted needles (0·37—0·46 g., 45—55%) of 5-anilino-3-hydrazino-1,2,4-thiadiazole, m. p. 164—165° (decomp., rate-dependent). The ethanolic filtrates therefrom gave, on partial evaporation under reduced pressure, prisms of the starting material, m. p. and mixed m. p. 176—178° (decomp.) (0·3—0·4 g., 30—40%). The use of 0·2N-ethanolic hydrochloric acid at the b. p. during 20 min. gave mainly unchanged starting material (45%).

The reactant (0·002 mole) was mostly recovered (60%) after its solution in ethanol (15 ml.)–3N-acetic acid (10 ml.) had been heated on the steam-bath during 30 min.

5-Anilino-3-hydrazino-1,2,4-thiadiazole (0·1 g., 0·0005 mole) dissolved when heated with water (10 ml.) containing 3N-hydrochloric acid (0·33 ml., 0·001 mole). Addition of 0·05M-picric

acid (10 ml., 0·0005 mole) and storage at 0° during 48 hr. gave needles (0·2 g.) which afforded, on crystallisation from ethanol–light petroleum (5 ml. each), yellow prisms (0·1 g.) of the *picrate*, m. p. indefinite, decomp. 221—224°, sinters at 135—140° (Found: C, 38·9; H, 3·0; S, 7·75. $C_8H_9N_5S,C_6H_3N_3O_7$ requires C, 38·5; H, 2·75; S, 7·3%).

5-Anilino-3-hydrazino-1,2,4-thiadiazole (0·003 mole), on treatment with ethanolic hydrochloric acid as described for the 3-(isopropylidenehydrazino)-derivative, similarly gave 3-amino-5-anilino-1,2,4-triazole (80%) and sulphur (85%).

(*c*) *Derivatives.* The reactant (0·21 g., 0·001 mole) dissolved when heated in acetic anhydride (4 ml.) at 100° during 20 min. The buff precipitate (0·32 g.) obtained on addition of the liquid to water gave, on crystallisation from ethanol (carbon), leaflets of the *triacetyl derivative*, m. p. 212—214° (decomp.) (0·20 g., 60%) (Found: C, 50·2; H, 4·3; N, 21·15; S, 9·6. $C_{14}H_{15}N_5O_3S$ requires C, 50·45; H, 4·5; N, 21·0; S, 9·6%).

The reactant (0·001 mole) was heated with benzoyl chloride (1·4 g., 0·01 mole) in pyridine (5 ml.) at 100° during 30 min., then stirred into ice and concentrated hydrochloric acid (5 ml.). The precipitated oil (from which the aqueous phase was decanted) was covered with methanol; the crystals which separated slowly at 0° (m. p. 154—157°; 0·5 g., 80%) gave, on crystallisation from methanol, granules of the *tetrabenzoyl derivative*, m. p. 163—165° (Found: C, 69·5; H, 3·9; N, 12·0; S, 4·9. $C_{36}H_{25}N_5O_4S$ requires C, 69·3; H, 4·0; N, 11·2; S, 5·1%).

The use of toluene-*p*-sulphonyl chloride (0·23 g., 0·0012 mole) similarly gave, after addition to hydrochloric acid, a buff powder (0·35 g.) which afforded, after two crystallisations from ethanol (carbon; 60 ml. per g.), prisms (0·15 g., 42%) of the *monotoluene-p-sulphonyl derivative*, m. p. 193—195° (Found: C, 50·2; H, 4·1; N, 19·3. $C_{15}H_{15}N_5O_2S_2$ requires C, 49·9; H, 4·15; N, 19·4%).

(*d*) *Other attempted syntheses.* 5-Anilino-3-methylthio-1,2,4-thiadiazole [23] (0·22 g., 0·001 mole), when (i) refluxed in ethanol (10 ml.)–20% aqueous hydrazine hydrate (20 ml.) during 3 hr. (odour of methanethiol) or (ii) heated with 0·2M-ethanolic hydrazine (10 ml., 0·002 mole) during 8 hr. at 110—120° in a sealed tube, was recovered nearly quantitatively after acidification of the cooled reaction mixture. 5-Anilino-3-benzylthio-1,2,4-thiadiazole [23] failed to yield, by procedure (i), even traces of toluene-ω-thiol.

5-Anilino-3-chloro-1,2,4-thiadiazole [9] (0·0005 mole), when refluxed in ethanol (2 ml.) and 10% aqueous hydrazine hydrate (1 ml.), failed to yield the desired product. Attempts to reduce the diazonium salt (obtained in solution from 5-anilino-3-amino-1,2,4-thiadiazole as previously described [9]) by alkaline sodium sulphite were also unsuccessful.

5-*Anilino*-3-(3,5-*dimethylpyrazol*-1-*yl*)-1,2,4-*thiadiazole*.—(*a*) 5-Anilino-3-hydrazino-1,2,4-thiadiazole (0·62 g., 0·003 mole) dissolved rapidly when heated in ethanol (15 ml.), acetylacetone (0·30 g., 0·003 mole), and glacial acetic acid (1 ml.) on the steam-bath, but solid began to separate again presently. After 15 minutes' heating, the mixture was set aside at 0° overnight, and the product collected (m. p. 230—234°; 0·73 g., 90%). Crystallisation from ethanol (35 ml. per g., recovery 80%) gave needles of 5-anilino-3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazole, m. p. and mixed m. p. (with *c*, below) 232—235° [Found: C, 57·5; H, 5·1%; *M* (cryoscopically in thymol), 250. Calc. for $C_{13}H_{13}N_5S$: C, 57·6; H, 4·8%; *M*, 271], $\lambda_{min.}$ 228 (log ε 3·91), $\lambda_{max.}$ 256 (4·50); $\lambda_{min.}$ 274 (4·12); $\lambda_{max.}$ 288 (4·19), in agreement with the figures given by Scott.[17]

5-Anilino-3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazole (0·54 g., 0·002 mole) was recovered (85%) after being refluxed with aniline (5 ml.) during 2—24 hr.

(*b*) A solution of 1-amidino-3,5-dimethylpyrazole nitrate [18] (2·40 g., 0·012 mole) and phenyl isothiocyanate (1·35 g., 0·01 mole) in anhydrous dimethylformamide (6 ml.) was kept at 100° during 12 hr. (effervescence). The mixture was stirred into water (50 ml.), and a dark brown oil, which solidified on storage at 0°, was collected and rinsed with ether. Crystallisation of the resulting powder (1 g.) from ethanol (carbon) gave needles (0·81 g., 30%) of 5-anilino-3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazole, m. p. and mixed m. p. (with *c*, below) 231—233°. Heating the above liquid at 152° (*i.e.*, b. p.) during 0·5 hr., or at 120° during 1 hr., or at 100° during 48 hr. gave somewhat diminished yields (20%).

(*c*) A solution of 3,5-dimethyl-1-[*N*-(anilinothioformyl)amidino]pyrazole [16] (0·82 g., 0·003 mole) in chloroform (5 ml.) decolorised M-bromine (3 ml., 0·003 mole) as rapidly as it was added. Removal of the solvent, dissolution of the residue in ethanol (15 ml.), basification with ammonia,

[23] Kurzer and Taylor, *J.*, 1959, 1064.

and crystallisation from ethanol gave needles of 5-anilino-3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazole, m. p. 232—234° (total, 0·73 g., 90%). This is essentially the method of Scott and Reilly [16] who used an excess of bromine,[16] iodine–sodium acetate,[17] or acidified hydrogen peroxide [17] as oxidising agent.

5-Anilino-3-(ethylidenehydrazino)-1,2,4-thiadiazole.—5-Anilino-3-hydrazino-1,2,4-thiadiazole (0·41 g., 0·002 mole), suspended in ethanol (2 ml.), dissolved rapidly with slight warming when a large excess of acetaldehyde (2 ml.) was added. After short storage at room temperature, the solution was diluted with light petroleum (1 : 1, b. p. 40—60° and 60—80°; 15 ml.), crystallisation occurring rapidly. The product, collected at 0° (m. p. 130—131°, after sintering at 125°; 0·38 g., 75%) gave, on crystallisation from ethanol–light petroleum (b. p. 40—80°, as above), prisms of *5-anilino-3-(ethylidenehydrazino)-1,2,4-thiadiazole monohydrate*, m. p. 131—132° (decomp., after shrinking at 127°) (Found: C, 47·8; 47·9; H, 5·1, 5·2; N, 27·6; S, 12·6. $C_{10}H_{11}N_5S,H_2O$ requires C, 47·8; H, 5·2; N, 27·9; S, 12·75%).

The ultraviolet absorption spectrum of 5-anilino-3-hydrazino-1,2,4-thiadiazole in 0·0005—0·001M-ethanolic solution changed to that of the 3-(ethylidenehydrazino)-compound (see Figure) (except for the somewhat lower absorption intensity of the maximum at 266 mμ) (log ε 4·3; 4·4 after 3 and 5 days' storage, respectively). This change was greatly accelerated and nearly completed on shaking the solution at room temperature (log ε 4·35, 4·4, 4·45 after 6, 16, 24 hr., respectively).

5-Anilino-3-(benzylidenehydrazino)-1,2,4-thiadiazole.—(*a*) *From 1-Benzylideneaminoamidino-3-phenylthiourea.* The reactant [12] (2·97 g., 0·01 mole) was dissolved in boiling chloroform (150 ml.), allowed to cool to ~25°, and treated with M-bromine (10 ml., 0·01 mole). The crystalline precipitate, which began to separate towards the end of the addition, was collected after 24 hr. at 0°, washed with chloroform and ether (3·7 g.), and quickly boiled with ethanol (20 ml.); the undissolved powdery *hydrobromide* was filtered off while hot [m. p. 200—204° (decomp.); 3·20 g., 85%]. Crystallisation from ethanol (40 ml. per g., recovery 50%) gave needles, m. p. 200—202° (decomp.) (Found: C, 48·05; H, 4·2; Br, 21·15; N, 18·2. $C_{15}H_{13}N_5S,HBr$ requires C, 47·9; H, 3·7; Br, 21·3; N, 18·6%).

The salt (1·13 g., 0·003 mole) was dissolved in boiling ethanol (45 ml.), added to 3N-ammonia (10 ml., 0·03 mole) and ice–water (50 ml.), and the collected precipitate (0·75 g.) crystallised from ethanol (120 ml.) to yield felted needles of *5-anilino-3-(benzylidenehydrazino)-1,2,4-thiadiazole*, m. p. 233—235° (decomp.) (0·62 g., 70%) (Found: C, 60·8; H, 4·2; N, 22·9. $C_{15}H_{13}N_5S$ requires C, 61·0; H, 4·4; N, 23·7%).

(*b*) *From 5-anilino-3-hydrazino-1,2,4-thiadiazole.* A solution of the reactant (0·21 g., 0·001 mole) in ethanol (20 ml.), treated with benzaldehyde (1·05 g., 0·01 mole), was refluxed during 1 hr. The crystals (0·25 g.), collected at 0°, recrystallised from ethanol as felted needles (0·21 g., 70%), m. p. 226—228° (decomp.) [mixed m. p. with (*a*) 232—235° (decomp.)] (Found: N, 23·8; S, 10·6%). The ultraviolet absorption curves of specimens (*a*) and (*b*) were coincident (cf. Table).

3-(Isopropylidenehydrazino)-5-p-toluidino-1,2,4-thiadiazole.—(*a*) *Preparation.* A stirred solution of 1-isopropylideneaminoamidino-3-*p*-tolylthiourea [12] (5·26 g., 0·02 mole) in hot chloroform (60 ml.), subsequently externally cooled, was treated with M-bromine (20 ml., 0·02 mole) dropwise during 20 min. The resulting powder was collected after 3 hr. at 0°, rinsed with chloroform, and dried [m. p. 155—158° (decomp.); 4·8—5·1 g., 70—75%, calc. as non-solvated hydrobromide]. Crystallisation from ethanol (8 ml. per g., recovery 60%) gave ivory prisms of the solvated *hydrobromide*, m. p. 180—181° (decomp.) (Found: C, 43·0; H, 5·6; S, 8·55. $C_{12}H_{15}N_5S,HBr,C_2H_5{\cdot}OH$ requires C, 43·3; H, 5·7; S, 8·25%). When the precipitated crude hydrobromide was in contact with the reaction mixture for longer periods, yields were substantially decreased, probably by hydrolysis under the influence of hydrogen bromide.

The crude (non-solvated) hydrobromide (3·42 g., 0·01 mole), dissolved in boiling ethanol (30 ml.), was added to 3N-ammonia (10 ml., 0·03 mole) and ice (40 g.); the resulting very finely divided precipitate was collected, washed with water, dried (2 g.), and dissolved in boiling acetone (80 ml. per g.). The filtered pale yellow liquid was successively reduced to approximately half and quarter volume in a vacuum. The pale yellow microcrystalline product, collected at 0°, was *3-(iso-propylidenehydrazino)-5-p-toluidino-1,2,4-thiadiazole*, m. p. 175—177° (decomp.) (total, 1·45—1·7 g., 55—65%). Further crystallisation from acetone gave felted ivory needles, m. p. 178—179° (decomp. violently, to a black pitch) (Found: C, 55·7; H, 5·5; N, 26·4; S, 12·05. $C_{12}H_{15}N_5S$ requires C, 55·2; H, 5·75; N, 26·8; S, 12·3%).

(*b*) *Action of hydrochloric acid.* A solution of the reactant (0·52 g., 0·002 mole) in ethanol (10 ml.)–3N-hydrochloric acid (10 ml.) was heated on the steam-bath during 30 min. The clear supernatant liquid was decanted from the greenish-yellow deposit, into N-ammonia (50 ml.). The precipitated 3-amino-5-*p*-toluidino-1,2,4-triazole was collected after 12 hr. at 0° (0·34 g.) and formed needles, m. p. and mixed m. p.[12,24] 178—180° (from water) (0·29 g., 77%) The deposit was sulphur (0·045 g., 70%).

3-*Hydrazino*-5-p-*toluidino*-1,2,4-*thiadiazole*.—The 3-(isopropylidenehydrazino)-compound (0·78 g., 0·003 mole), suspended in cold ethanol (10 ml.), dissolved as soon as 3N-hydrochloric acid (10 ml.) was added. The solution was kept at 45—50° during 30 min.; when an incipient turbidity was observed, the liquid was stirred into 3N-ammonia (15 ml.)–ice (50 g.). The white gelatinous precipitate was collected, washed with water, dried, and dissolved in boiling ethanol (15—20 ml.). The filtered liquid deposited a solid (filtrate F), which gave, on further crystallisation from ethanol (50 ml. per g.), felted needles (0·24 g., 36%) of the 1,2,4-*thiadiazole*, m. p. 163—165° (decomp.) (Found: C, 48·5; H, 5·3; N, 32·0; S, 14·5. $C_9H_{11}N_5S$ requires C, 48·9; H, 5·0; N, 31·7; S, 14·5%). Filtrate F, on spontaneous evaporation, deposited platelets of starting material (0·23 g., 30%), m. p. 175—177° (decomp.) (from acetone).

The *picrate*, prepared in very little ethanol, formed yellow prisms (50%), m. p. 228—232° (decomp., after shrinking seriously from 140°) (from ethanol–light petroleum) (Found: C, 40·4; H, 2·9. $C_9H_{11}N_5S,C_6H_3N_3O_7$ requires C, 40·0; H, 3·1%).

3-(*Benzylidenehydrazino*)-5-*methylamino*-1,2,4-*thiadiazole*.—1-(Benzylideneaminoamidino)-3-methylthiourea hydrochloride [12] (1·09 g., 0·004 mole) was dissolved in hot chloroform (50 ml.), the solution cooled, and treated with M-bromine (4 ml., 0·004 mole). The separated hydrobromide (1·05 g.) was collected after storage at 0°, rinsed with chloroform, and dried. It was suspended in boiling ethanol (40 ml.) and treated with 3N-ammonia (10 ml.), and the resulting clear solution immediately poured on ice (50 g.). The crystalline powder, which separated gradually, was collected at 0° [m. p. 215—217° (decomp.); 0·7 g., 75%] and crystallised from ethanol (100 ml. per g.), affording platelets of 3-(*benzylidenehydrazino*)-5-*methylamino*-1,2,4-*thiadiazole*, m. p. 218—220° (decomp.) (Found: C, 51·7; H, 4·8; N, 30·1. $C_{10}H_{11}N_5S$ requires C, 51·5; H, 4·7; N, 30·0%).

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[24] Fromm, Brück, Runkel, and Meyer, *Annalen*, 1924, **437**, 106, 112.