455. *Thiadiazoles. Part III.** 3-*Amino*-5-*arylamino*- *and* 3 : 5-*Di*(*aralkylamino*)-1 : 2 : 4-*thiadiazoles.*

By Frederick Kurzer.

Oxidative cyclisation of amidinothioureas is extended to the synthesis of 3-amino-5-arylamino- and 3 : 5-di(aralkylamino)-1 : 2 : 4-thiadiazoles. Bromine is an additional suitable oxidising agent in this general reaction. Hydrolysis, reduction, and acylation reactions of the new 1 : 2 : 4-thiadiazoles are described. 3 : 5-Dianilino-1 : 2 : 4-thiadiazole is isomeric, but not identical with "Hector's base."

Although comparatively little is known about 1 : 2 : 4-thiadiazoles, there exist considerable confusion and conjecture on structural questions in this field.[1] However, two general and unequivocal synthetic routes to this ring system have recently been provided, namely, Goerdeler's [2] versatile condensation of thiocyanate with *N*-halogenated amidines, *iso*ureas, and guanidines, and the oxidative cyclisation of amidinothioureas, described in the present series of papers.[3] The latter method has now been extended to the production of the two series of 1 : 2 : 4-thiadiazoles named in the title of this paper. The results suggest that unlike thiourea and its alkyl and aryl homologues which form a variety of oxidation products under comparable conditions (for references, see below), amidinothioureas yield 1 : 2 : 4-thiadiazoles whenever this is possible.

N-Mono- and *NN'*-di-substituted amidinothioureas, used as starting materials in this synthesis, were obtained by the method of Slotta, Tschesche, and Dressler,[4] who had

* Part II, *J.*, 1955, 2288.

[1] Bambas, "The Chemistry of Heterocyclic Compounds," Interscience Publ. Inc., New York, 1952, Vol. IV, pp. 35—80.
[2] Goerdeler and co-workers, *Chem. Ber.*, 1954, **87**, 57, 68; 1955, **88**, 843, 1071.
[3] Kurzer, *J.*, 1955, 1, 2288.
[4] Slotta, Tschesche, and Dressler, *Ber.*, 1930, **63**, 208.

reported, however, that appropriate products were not obtainable from *N*-aralkylguanidines. In contrast, *NN'*-di(aralkyl)amidinothioureas have now been prepared without difficulty by condensing *iso*thiocyanates with monosubstituted guanidines in acetone in the presence of sodium alkoxides, provided that care was taken to bring the guanidines into solution. *N*-Phenyl-*N'*-phenylamidinothiourea, m. p. 130—132°, readily synthesised by this method in 85% yield, differed from two products that have previously been thus formulated. They are a compound $C_{14}H_{14}N_4S$, m. p. 197°, obtained by Fromm *et al.*[5] by the interaction of "phenylthiuret" (probably 3-imino-5-phenylimino-1 : 2 : 4-dithiazolidine) or its methyl or ethyl homologue with aniline; and a compound $C_{14}H_{14}N_4S$, m. p. 188°, claimed by Slotta *et al.*[4] to result in 4% yield during the prolonged interaction of *N*-cyano-*N'*-phenylthiourea and aniline. In the present experiments, Fromm's compound (m. p. 197°) was found to resist desulphurisation and oxidation by the usual reagents; the assigned structure may therefore be rejected. Attempts to obtain Slotta's compound (m. p. 188°) were entirely unsuccessful.

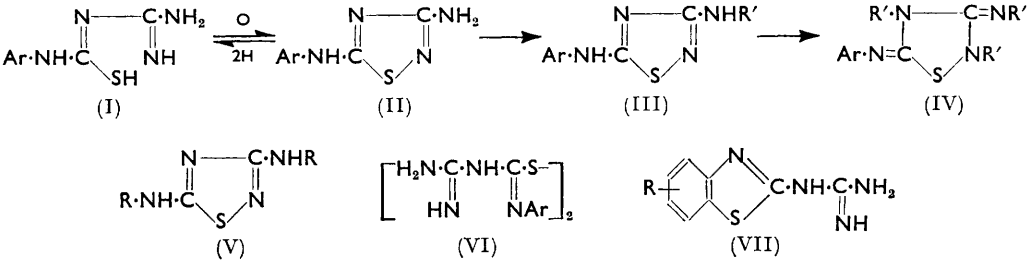
Excess of hydrogen peroxide in aqueous-ethanolic media containing mineral acid smoothly cyclised the two series of substituted amidinothioureas to the appropriate 1 : 2 : 4-thiadiazoles (II and V, respectively) in 60—85% yields. Bromine was found to be an excellent alternative cyclising agent, being consumed almost instantaneously, in equimolecular proportions, in both ethanolic and chloroform solution. The reagent afforded comparable or better yields than hydrogen peroxide, and, moreover, proved suitable in cases where hydrogen peroxide failed, *e.g.*, for (II; Ar = *p*-Br·C_6H_4). In contrast, the interaction of aryl-substituted amidinothioureas and iodine, like that of the parent compound,[3] was reversible: alcoholic solutions of the *N*-phenyl derivative (I; Ar = Ph), for example, absorbed less than half the theoretically required amount of this oxidising agent. Although disulphide formation (VI) suggested by the iodine uptake was not observed, and the desired cyclisation did in fact occur, iodine was clearly a less satisfactory reagent in this synthesis. The non-reversibility of the corresponding reaction involving bromine is no doubt due to the less powerful reducing properties of the hydrobromic acid liberated during the cyclisation.

3-Amino-5-arylamino- and 3 : 5-di(aralkylamino)-1 : 2 : 4-thiadiazoles (II and V) were predominantly basic: they dissolved in dilute mineral acids with salt formation, and were reprecipitated by alkalis. They formed very sparingly soluble monopicrates, which were suitable for their characterisation. The weakly acidic properties of members of the former series of homologues (II) were indicated by their remarkable solubility in hot caustic alkalis, from which they were deposited unchanged, however, on cooling. The heterocyclic nucleus of the 1 : 2 : 4-thiadiazoles (II and V) was smoothly reopened, with regeneration of the original amidinothioureas, upon reduction. In contrast, it proved remarkably resistant to alkaline hydrolysis: 3-amino-5-anilino-1 : 2 : 4-thiadiazole was substantially recovered after several hours' refluxing in 3N-sodium hydroxide, only a small proportion being cleaved to aniline, ammonia, and carbon dioxide. The easy alkaline fission of the parent compound [3] (II; R = H) to amidinourea being recalled, the variation in the stability of the 1 : 2 : 4-thiadiazole system with change of substituents [3] is again exemplified.

The oxidation of thiourea [6,7] and its *N*-alkyl [8] and *N*-aryl derivatives [7,9–12] may afford, under similar conditions, compounds having totally unrelated structures. The assignment of 1 : 2 : 4-thiadiazole structures (II) to the present aromatic products is therefore not admissible solely by analogy with the parent compound and its alkyl derivatives,[3] and was confirmed as follows. A possible disulphide formula (VI), almost indistinguishable from

[5] Fromm and co-workers, *Annalen*, 1907, **356**, 178, 180; 1908, **361**, 321.
[6] Böeseken, *Proc. k. ned. Akad. Wetenschap.*, 1936, **39**, 717; 1938, **41**, 70; *Rec. Trav. chim.*, 1936, **55**, 1040; 1948, **67**, 603; Claus, *Annalen*, 1875, **179**, 139; E. A. Werner, *J.*, 1912, **101**, 2177.
[7] Fromm and Heyder, *Ber.*, 1909, **42**, 3804.
[8] A. E. A. Werner, *Sci. Proc. Roy. Dublin Soc.*, 1941, **22**, 387; Preisler, *J. Amer. Chem. Soc.*, 1949, **71**, 2849.
[9] Hugershoff, *Ber.*, 1901, **34**, 3131; 1903, **36**, 3121.
[10] Besthorn, *Ber.*, 1910, **43**, 1519; Passing, *J. prakt. Chem.*, 1939, **153**, 10.
[11] Hector, *Ber.*, 1889, **22**, 1177; 1890, **23**, 357; 1892, **25**, Ref., 799; Dost, *Ber.*, 1906, **39**, 863; Lal and Krall, *J. Indian Chem. Soc.*, 1939, **16**, 31.
[12] Hofmann and Gabriel, *Ber.*, 1892, **25**, 1578.

(II) analytically, is eliminated by the results of molecular-weight determinations, and by the observed bromine uptake of the arylamidinothioureas (I). The oxidation of arylthioureas by bromine proceeds differently in chloroform or ethanol, yielding 2-aminobenzothiazoles [9, 10, 13] or compounds formulated as 1 : 2 : 4-thiadiazolidines [9, 11, 12] respectively.



In the above representations (I—VII) the occurrence of tautomerism wherever possible is understood.

The possible representation of the present series of products, obtained by bromine oxidation in *either* medium, as substituted 2-guanidinobenzothiazoles (VII), is readily dismissed because of the non-identity of the phenyl homologue (II; Ar = Ph) with the known 2-guanidinobenzothiazole (VII; R = H).[14] Finally, the smooth reconversion of the products into the original *N*-amidino-*N*′-arylthioureas by reduction, previously observed [3] with the parent compound, supports the thiadiazole structure. Separate experiments showed that the benzothiazole nucleus (in 2-aminobenzothiazole) was not cleaved by reduction under identical conditions.

The oxidation of aromatic thioureas in ionising media [7, 9, 11, 12] proceeds by a mechanism not fully elucidated, to yield so-called " Hector's bases," to which a 2 : 4-diaryl-3 : 5-diimino-1 : 2 : 4-thiadiazolidine structure is generally ascribed. This view has yet to be confirmed,[1] and possible isomeric 1 : 2 : 4-thiadiazole structures have been considered.[11] The alternative 3 : 5-diarylamino-1 : 2 : 4-thiadiazole (V) structure for these bases, however, discussed by Hofmann and Gabriel,[12] has now been definitely excluded, in view of the non-identity of " Hector's base " [11] derived from phenylthiourea, and 3 : 5-dianilino-1 : 2 : 4-thiadiazole (V; R = Ph) obtained in the present synthesis.

In its reactions with acylating agents, a representative of the 3-amino-5-arylamino-1 : 2 : 4-thiadiazole series (II; Ar = Ph) resembled the corresponding aliphatic compounds, being converted, according to the conditions, into mono-, di-, and tri-acyl derivatives (or mixtures thereof) on treatment with acetic anhydride, benzoyl chloride, or toluene-*p*-sulphonyl chloride (cf. Experimental section). The only anomalous observation was the ability of the aryl-substituted thiadiazole (II; Ar = Ph) to form di- and tri-acetyl derivatives; under identical conditions 3-amino-5-alkylamino- and 3 : 5-diamino-1 : 2 : 4-thiadiazoles are capable of incorporating only one or two acetyl groups, respectively.[3] In accordance with previous arguments,[3] the new monoacyl derivatives are formulated as 3-acylamino-5-arylamino-1 : 2 : 4-thiadiazoles (III; R′ = acyl), while the triacyl compounds are regarded as 3-acylimido-5-arylimino-2 : 4-diacyl-1 : 2 : 4-thiadiazolidines (IV; R′ = acyl).

Like " Hector's base," 3 : 5-dianilino-1 : 2 : 4-thiadiazole (V; R = Ph) gave only monoacetyl and -benzoyl derivatives, irrespective of the excess of acylating agent employed. The structure of these derivatives is not certain; in view of the demonstrated [2] superior reactivity of the 4- over the 2-position in the thiadiazole system, their formulation as 4-acyl-3-anilino-4 : 5-dihydro-5-phenylimino-1 : 2 : 4-thiadiazoles appears likely. Toluene-*p*-sulphonyl chloride, on the other hand, readily afforded a disulphonyl derivative, represented as the 2 : 4-disubstituted thiadiazolidine.

[13] Fischer and Besthorn, *Annalen*, 1882, **212**, 331.
[14] Smith, Mason, and Carroll, *J. Amer. Chem. Soc.*, 1931, **53**, 4103; Torizo, Takahashi, and Niino, *J. Pharm. Soc. Japan*, 1943, **63**, 249.

Experimental

Light petroleum was of boiling range 60—80°. The commercial pure redistilled grade of acetone did not require special drying before being used in the preparation of substituted amidinothioureas (cf. Slotta *et al.*[4]). *p*-Tolyl *iso*thiocyanate was prepared in 45% yield by applying the general method of Dains, Brewster, and Olander.[15] Picrates were prepared from equimolar proportions of the appropriate amidinothioureas or 1 : 2 : 4-thiadiazoles and picric acid in saturated hot or boiling ethanolic solution.

3-*Amino*-5-*arylamino*-1 : 2 : 4-*thiadiazoles*.—*N*-Amidino-*N'*-phenylthiourea, m. p. 176—178°, was prepared by the method of Slotta, Tschesche, and Dressler[4] in 75—80% yield. Its picrate, crystallised from acetone–ethanol, formed felted needles (90%), m. p. 222—224° (decomp.) (Found: C, 39·4; H, 3·3. Calc. for $C_{14}H_{13}O_7N_7S$: C, 39·7; H, 3·1%). Slotta *et al.*[4] give m. p. 250° (decomp., blackening from 232°).

N-*Amidino*-N'-p-*tolylthiourea*. Sliced sodium (1·50 g., 0·065 g.-atom) was introduced into acetone (80 ml.) during 5 min., and the hot pale-orange paste-like suspension thus formed was treated with guanidine thiocyanate (8·85 g., 0·075 mole). To the resulting solution, *p*-tolyl *iso*thiocyanate (7·45 g., 0·05 mole) was added during 1 min. The boiling liquid was kept on the steam-bath during 5 min. (resulting in the removal of part of the acetone), set aside at room temperature during 0·5 hr., and finally stirred into ice-water (500 ml.). The collected air-dried greenish-yellow product was dissolved in acetone, the boiling solution filtered at the pump, and the clear filtrate distilled to incipient crystallisation and diluted with half its volume of boiling ethanol. N-*Amidino*-N'-p-*tolylthiourea* thus obtained formed lustrous prisms, m. p. 198—200° (decomp.) [subject to the rate of heating] (yield, including material from the mother-liquors, 7·3—8·3 g., 70—80%) (Found: C, 51·7; H, 5·6; N, 27·2. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9%). The product decomposed above its m. p., with evolution of *p*-tolyl *iso*thiocyanate. Its *picrate* formed yellow prisms (from aqueous ethanol), m. p. 268—270° (decomp., after sintering severely at 250°) (Found: C, 41·0; H, 3·7. $C_{15}H_{15}O_7N_7S$ requires C, 41·2; H, 3·4%).

N-*Amidino*-N'-p-*bromophenylthiourea* was prepared similarly from *p*-bromophenyl *iso*thiocyanate.[15] The crude granular yellow product was twice crystallised from acetone–ethanol (8 ml. each, per g.) and consisted of lustrous prisms, m. p. 186—188° (decomp.) (yield, 10·6 g., 78%) (Found: C, 35·8; H, 3·4; N, 20·4; S, 11·35; Br, 29·2. $C_8H_9N_4SBr$ requires C, 35·2; H, 3·3; N, 20·5; S, 11·7; Br, 29·3%). Its *picrate*, crystallised from ethanol–acetone–water, formed yellow felted needles, m. p. 250° (decomp., after sintering severely at 230°) (Found: C, 33·5; H, 2·6. $C_{14}H_{12}O_7N_7SBr$ requires C, 33·5; H, 2·4%).

3-*Amino*-5-*anilino*-1 : 2 : 4-*thiadiazole*.—(*a*) A boiling solution of *N*-amidino-*N'*-phenylthiourea (9·70 g., 0·05 mole) in ethanol (100 ml.) containing concentrated hydrochloric acid (5 ml., 0·05 mole) was treated with aqueous hydrogen peroxide (6%, 85 ml., 0·15 mole) during 6 min. The solution was evaporated in a vacuum to half volume during 6—12 min., and the residual hot purple liquid quickly filtered (carbon) at the pump; the filtrate deposited the crude product as pale purple needles. Crystallisation from ethanol–benzene (4 and 15 ml. per g.) gave prismatic needles of a solvated product, m. p. 76—78°. Alternatively, crystallisation from ethanol (8—10 ml. per g.) gave lustrous prisms of a solvated product, m. p. 188—192° (after sintering at 180—185°) (total yield, 7·7—8·9 g., 65—75%, calc. as $C_8H_8N_4S,C_2H_5{\cdot}OH$). [The composition of the solvates was not ascertained: both gave widely fluctuating results on analysis; the latter (m. p. 188—192°) showed no significant loss in weight after being kept at 150—180° for 15 min. and then at 200—210° for 15 min.]

Two crystallisations of either solvate from boiling water (150 ml. per g.; carbon) gave needles of 3-*amino*-5-*anilino*-1 : 2 : 4-*thiadiazole*, m. p. 210—212° [Found: C, 49·9, 50·0; H, 4·3, 4·1; N, 29·0; S, 17·0, 17·1%; *M* (cryoscopically, in thymol), 180, 185. $C_8H_8N_4S$ requires C, 50·0; H, 4·2; N, 29·2; S, 16·7%; *M*, 192]. The product was highly soluble in warm dilute hydrochloric, hydriodic, and sulphuric acids, hot 2N-sodium hydroxide, less so in dilute acetic acid, and very sparingly soluble in cold caustic alkalis, hot sodium carbonate, and ammonia solution. Its *picrate* crystallised from aqueous ethanol as orange-yellow needles (75%), m. p. 205—206° (decomp.) (Found: C, 39·5; H, 2·7. $C_{14}H_{11}O_7N_7S$ requires C, 39·9; H, 2·6%).

(*b*) Finely powdered *N*-amidino-*N'*-phenylthiourea (1·94 g., 0·01 mole) was boiled with chloroform (400 ml.), and the suspension allowed to cool somewhat and treated with a solution of bromine (1·6 g., 0·01 mole) in chloroform (5 ml.), which was instantly decolorised. The resulting clear liquid was quickly evaporated to dryness in a vacuum, the semisolid residue

[15] Dains, Brewster, and Olander, *Org. Synth.*, Coll. Vol. I., 1941, p. 448.

dissolved in warm ethanol (15 ml.) and filtered with carbon, and the filtrate made just alkaline (to litmus) with aqueous 3N-sodium hydroxide (3·3 ml., 0·01 mole). The platelets, collected at 0° (m. p. 206—212°; 1·31 g., 68%), were crystallised from water and formed 3-amino-5-anilino-1 : 2 : 4-thiadiazole, m. p. and mixed m. p. with material prepared by method (*a*), 210—211° (Found: C, 50·3; H, 4·4; N, 28·5; S, 16·5%). The identity of the products obtained by methods (*a*) and (*b*) was confirmed by a comparison of their monotoluene-*p*-sulphonyl derivatives, m. p. 256—258° (see below).

(*c*) The same product resulted (75% yield) when the reactant (0·01 mole), dissolved in warm ethanol (50 ml.), was oxidised by bromine (0·01 mole), as described above.

(*d*) A warm solution of *N*-amidino-*N'*-phenylthiourea (0·01 mole) in ethanol (35 ml.) was treated with N-ethanolic iodine until the liquid remained deep yellow (uptake: 8 ml., *i.e.*, 40% of the theory). Evaporation to small volume (6—8 ml.) in a vacuum, followed by dilution with water (10 ml.), gave a dark-brown liquid, which was decolorised and made alkaline (to litmus) by dropwise addition of aqueous 3N-sodium hydroxide. Dilution with ice-water (to 100 ml.) gave crystals which were collected at 0° (1·75 g.), dissolved in acetone (15 ml.), filtered hot, and diluted with ethanol (10 ml.). Slow partial evaporation caused deposition of two kinds of crystal, which were collected and readily separated mechanically: (A) light platelets (m. p. approx. 200°) gave, after recrystallisation from water, needles of 3-amino-5-anilino-1 : 2 : 4-thiadiazole (0·48 g., 25%), m. p. and mixed m. p. (with specimens prepared by methods *a*—*c*) 209—211°; (B) massive prisms consisting of unchanged *N*-amidino-*N'*-phenylthiourea, m. p. and mixed m. p. 175—177°, from acetone–ethanol (yield, 0·54 g., 28%).

3-*Amino*-5-*anilino*-1 : 2 : 4-*thiadiazole*.—*Reduction*. A boiling solution of the reactant (1·92 g., 0·01 mole) in ethanol (40 ml.) containing zinc turnings (4 g.) was treated with concentrated hydrochloric acid (4 ml.) during 1 min., and refluxed during 10 min. Evaporation of the decanted solution to small volume (6—8 ml.), dilution of the filtered residual liquid with warm water (30 ml.), and storage at 0° gave crystals (1·84 g., 80%) which recrystallised from ethanol–light petroleum (6 ml. each, per g.) and consisted of *N*-amidino-*N'*-phenylthiourea hydrochloride, m. p. 174—178° (decomp.) (lit.,[4] m. p. 178°) (Found: Cl, 13·9. Calc. for $C_8H_{11}N_4SCl,H_2O$: Cl, 14·3%). Its identity was confirmed by almost quantitative conversion into the free base, m. p. 176—178°, by the addition of the calculated quantity of aqueous 3N-sodium hydroxide to a warm 20% solution of the hydrochloride in ethanol.

2-Aminobenzthiazole, when subjected to the action of zinc and hydrochloric acid under the above conditions, was recovered unchanged.

Alkaline Hydrolysis.—A solution of the reactant (1·44 g., 0·0075 mole) in aqueous sodium hydroxide (12%, 25 ml.) (protected against atmospheric carbon dioxide) was refluxed during 8 hr. Only during the second half of the period of heating was ammonia slowly evolved, and aniline appeared in the refluxing liquid. The solid which separated on cooling was collected at 0°: it was unchanged starting material (1·02 g., 71%; m. p. and mixed m. p. 208—212°, from water). The combined alkaline filtrate (which evolved carbon dioxide strongly on acidification), and washing water (20 ml.) were distilled, and the basified distillate (20 ml.) was shaken with benzoyl chloride (1·4 g., 0·01 mole). The precipitated material consisted, after crystallisation from ethanol, of benzanilide, m. p. and mixed m. p. 161—163° (0·28 g., 64%, based on the weight of reactant consumed).

3-*Acetimino*-2 : 4-*diacetyl*-5-*phenylimino*-1 : 2 : 4-*thiadiazolidine*.—3-Amino-5-anilino-1 : 2 : 4-thiadiazole (1·92 g., 0·01 mole) in pyridine (15 ml.) was treated with acetic anhydride (7·65 g., 0·075 mole), kept on the steam-bath during 0·5 hr., and stirred into ice-water (120 ml.) containing concentrated hydrochloric acid (15 ml.). The collected dried crystalline precipitate was boiled with ethanol (25 ml.), and the undissolved material [m. p. 265—269° (decomp.); 1·45 g., 53%] collected at the pump (filtrate A); it afforded, after crystallisation from benzene–ethanol (3 : 2; 100 ml. per g.), platelets of the *diacetyl derivative*, m. p. 272—274° (decomp.) (Found: C, 52·0, 52·1; H, 4·6, 4·45; N, 20·4; S, 11·55. $C_{12}H_{12}O_2N_4S$ requires C, 52·2; H, 4·35; N, 20·3; S, 11·6%). Partial evaporation of filtrate A gave prisms, which were twice crystallised from ethanol (a minute amount of the undissolved diacetyl derivative being each time filtered off), yielding prisms of 3-*acetimino*-2 : 4-*diacetyl*-5-*phenylimino*-1 : 2 : 4-*thiadiazolidine*, m. p. 165—167° (total, 0·85 g. 27%) (Found: C, 53·0; H, 4·3; N, 17·2; S, 9·95. $C_{14}H_{14}O_3N_4S$ requires C, 52·8; H, 4·4; N, 17·6; S, 10·1%).

5-*Anilino*-3-*benzamido*-1 : 2 : 4-*thiadiazole*.—3-Amino-5-anilino-1 : 2 : 4-thiadiazole (0·01 mole) in pyridine (24 ml.), treated with benzoyl chloride (1·4 g., 0·01 mole), was kept at 100° during 0·5 hr. The crude granular product, isolated in the usual manner, was dissolved in boiling ethanol (150 ml.). The product which separated on cooling (ethanolic filtrate A) gave,

on further crystallisation from ethanol, needles (1·65 g., 56%) of 5-*anilino*-3-*benzamido*-1 : 2 : 4-*thiadiazole*, m. p. 212—213° (decomp.) (Found : C, 60·7; H, 4·2; N, 18·1; S, 10·5. $C_{15}H_{12}ON_4S$ requires C, 60·8; H, 4·05; N, 18·9; S, 10·8%). Filtrate A contained small quantities of the tribenzoyl derivative (see following paragraph).

2 : 4-*Dibenzoyl*-3-*benzoylimino*-5-*phenylimino*-1 : 2 : 4-*thiadiazolidine*.—(*a*) Interaction of the thiadiazole (0·01 mole) and excess of benzoyl chloride (0·06 mole) as above gave an oil as crude product. After being stirred with water (2 × 100 ml.) at 95° (removal of benzoic acid), the residual semisolid mass was boiled with ethanol (25 ml.). The deposited white solid was collected at 0° (m. p. 172—176°; 3·7 g., 73%) and gave, on crystallisation from acetone–ethanol (6 and 8 ml. per g.), prisms of 2 : 4-*dibenzoyl*-3-*benzoylimino*-5-*phenylimino*-1 : 2 : 4 *thiadiazolidine*, m. p. 179—180° (Found : C, 68·8; H, 3·95; N, 11·4; S, 6·5. $C_{29}H_{20}O_3N_4S$ requires C, 69·05; H, 4·0; N, 11·1; S, 6·35%).

(*b*) Treatment of 5-anilino-3-benzamido-1 : 2 : 4-thiadiazole (0·01 mole) with an excess of benzoyl chloride (0·05 mole) as above gave the same tribenzoyl derivative (75%), m. p. and mixed m. p. 179—180°.

5-*Anilino*-3-*toluene*-p-*sulphonamido*-1 : 2 : 4-*thiadiazole*.—Interaction of the thiadiazole (0·01 mole) and toluene-*p*-sulphonyl chloride (0·012 or 0·02 mole) in pyridine (15 ml.) at 100° during 0·5 hr. gave a product which was isolated in the usual manner, and twice crystallised from ethanol–acetone–benzene (3 : 3 : 1; 100 ml. per g.). The resulting 5-*anilino*-3-*toluene*-p-*sulphonamido*-1 : 2 : 4-*thiadiazole* formed prisms, m. p. 256—258° (63 or 72%, respectively) (Found : C, 52·0; H, 4·1; N, 16·0; S, 18·2. $C_{15}H_{14}O_2N_4S_2$ requires C, 52·0; H, 4·05; N, 16·2; S, 18·5%).

Di- and Tri-sulphonyl Derivatives.—The use of an excess of toluene-*p*-sulphonyl chloride (0·04 mole) under the above conditions gave a crude granular product (4·7 g.) which was boiled with ethanol–benzene (1 : 1; 100 ml.). The undissolved material (0·65 g., 19%) consisted of the monotoluene-*p*-sulphonyl derivative, m. p. and mixed m. p. 256—258° (after crystallisation, see above). The filtrate was evaporated to half its bulk : it deposited, on prolonged storage, two kinds of crystals which were collected and readily separated mechanically : (i) light microcrystalline material (0·85 g., 13%) which was crystallised by dissolution in ethanol–acetone–benzene (3 : 3 : 1), followed by partial evaporation, and afforded needles of 5-*phenylimino*-3-*toluene*-p-*sulphonimido*-2 : 4-*ditoluene*-p-*sulphonyl*-1 : 2 : 4-*thiadiazolidine*, m. p. 236—238° (Found : C, 53·6; H, 3·8; N, 8·4; S, 19·2. $C_{29}H_{26}O_6N_4S_4$ requires C, 53·2; H, 4·0; N, 8·6; S, 19·6%); (ii) massive prisms (2·1 g., 42%) which, recrystallised from boiling ethanol (25 ml. per g.), gave platelets of the *ditoluene*-p-*sulphonyl derivative*, m. p. 204—205° (Found : C, 53·5; H, 4·0; N, 11·1; S, 19·1. $C_{22}H_{20}O_4N_4S_3$ requires C, 52·8; H, 4·0; N, 11·2; S, 19·2%).

3-*Amino*-5-p-*tolylamino*-1 : 2 : 4-*thiadiazole*.—(*a*) *N*-Amidino-*N'*-*p*-tolylthiourea (0·01 mole) in ethanol (20 ml.) was oxidised with aqueous hydrogen peroxide as described for the phenyl homologue. The product was twice crystallised from boiling water (750 ml. per g.) or ethanol (20 ml. per g.), giving platelets of 3-*amino*-5-p-*tolylamino*-1 : 2 : 4-*thiadiazole*, m. p. 200—202° (1·35 g., 65%) (Found : C, 52·1; H, 5·0; N, 27·1; S, 16·0. $C_9H_{10}N_4S$ requires C, 52·4; H, 4·85; N, 27·2; S, 15·5%). Its *picrate* crystallised from aqueous ethanol as deep-yellow felted needles, m. p. 233—234° (decomp.) (Found : C, 41·6; H, 3·2. $C_{15}H_{13}O_7N_7S$ requires C, 41·4; H, 3·0%). (*b*) The same product [70%; m. p. and mixed m. p. with material prepared by method (*a*) 201—203°] resulted when the reactant (0·01 mole), suspended in hot chloroform, was oxidised by bromine (cf. phenyl homologue).

3-*Amino*-5-p-*bromoanilino*-1 : 2 : 4-*thiadiazole*.—A suspension of finely powdered *N*-amidino-*N'*-*p*-bromophenylthiourea (2·73 g., 0·01 mole) in warm chloroform (250 ml.) was oxidised with bromine (cf. phenyl homologue, *b*). The crude product (2·05 g., 75%) gave, after two crystallisations from acetone–ethanol–water (10, 15, and 5 ml. per g.), spherical aggregates of needles of 3-*amino*-5-p-*bromoanilino*-1 : 2 : 4-*thiadiazole*, m. p. 212—214° (Found : C, 34·8; H, 2·6; N, 20·8; S, 11·5; Br, 28·9. $C_8H_7N_4SBr$ requires C, 35·4; H, 2·6; N, 20·7; S, 11·8; Br, 29·5%). Its *picrate*, crystallised from aqueous ethanol, formed yellow felted needles, m. p. 231—232° (Found : C, 33·5; H, 2·1. $C_{14}H_{10}O_7N_7SBr$ requires C, 33·6; H, 2·0%).

3 : 5-*Di*(*aralkylamino*)-1 : 2 : 4-*thiadiazoles*.

N-*Phenyl*-N'-*phenylamidinothiourea*.—The hot orange suspension obtained by introducing sodium (3·0 g., 0·13 g.-atom) into acetone (200 ml.) was treated successively with a hot solution of phenylguanidine nitrate[16] (29·7 g., 0·15 mole) in acetone (30 ml.) and, during 2 min., with

[16] Kämpf, *Ber.*, 1904, **37**, 1681.

phenyl *iso*thiocyanate (13·5 g., 0·1 mole). After being refluxed during 20 min., the suspension was rapidly evaporated under reduced pressure to one-third of its bulk, and stirred into ice-water (1 l.). The precipitated pale-yellow granular solid gave, on crystallisation from ethanol–light petroleum (5 ml. each, per g.) and then from ethanol alone, prisms of N-*phenyl*-N′-*phenylamidinothiourea*, m. p. 130—132° (23·0 g., 85%) (Found: C, 61·95; H, 5·1; N, 21·2; S, 12·25. $C_{14}H_{14}N_4S$ requires C, 62·2; H, 5·2; N, 20·7; S, 11·85%).

N-*Methylamidino*-N′-*phenylthiourea*.—Powdered methylguanidine sulphate (6·1 g., 0·05 mole) was refluxed with stirring during 1 hr. in the suspension obtained by adding sodium (0·92 g., 0·04 g.-atom) to acetone (150 ml.), the heavy prisms of the starting material gradually giving way to a fine suspension of sodium sulphate. Treatment with phenyl *iso*thiocyanate (4·05 g., 0·03 mole), and refluxing for 0·5 hr., followed by isolation (as detailed immediately above), afforded an oil which solidified slowly at 0°. Crystallisation from ethanol (10 ml. per g.) gave prisms (3·4 g., 55%) of N-*methylamidino*-N′-*phenylthiourea*, m. p. 136—137° (Found: C, 51·9; H, 5·6; N, 27·2; S, 15·7. $C_9H_{12}N_4S$ requires C, 51·9; N, 5·8; N, 26·9; S, 15·4%). The *hydrochloride*, obtained almost quantitatively by dissolving the base in the minimum of warm concentrated hydrochloric acid, followed by crystallisation from water (3 ml. per g.), formed hydrated platelets, m. p. 85—87° (decomp.) (Found: C, 41·1; H, 5·8; Cl, 12·8. $C_9H_{12}N_4S,HCl,H_2O$ requires C, 41·15; H, 5·7; Cl, 13·5%).

N-*Methyl*-N′-*phenylamidinothiourea*.—A warm solution of phenylguanidine in acetone (quantities and details as for the *NN*′-diphenyl homologue) was treated with methyl *iso*thiocyanate (7·3 g., 0·1 mole), and the resulting suspension distilled to 80—100 ml. and refluxed during 1 hr. The mixture was then evaporated to 40 ml. and stirred into ice-water (400 ml.), and the precipitated oil exhaustively extracted with ether. Vacuum-evaporation of the combined washed (warm water) extracts, with addition of benzene (removal of moisture), gave a dark oily residue, which was dissolved, with ice-cooling, in 4N-ethanolic hydrochloric acid (30 ml., 0·12 mole). Slow dilution of this liquid with ether (total, 500 ml.) gave successive crops of crystalline solid. Recrystallisation of the combined material (14·2 g., 54%) from water (3 ml. per g.), with addition of a few drops of 3N-hydrochloric acid, afforded prisms of hydrated N-*methyl*-N′-*phenylamidinothiourea hydrochloride*, m. p. 114—117° (Found: C, 41·5; H, 5·3; N, 20·9; S, 11·7; Cl, 13·1. $C_9H_{12}N_4S,HCl,H_2O$ requires C, 41·15; H, 5·7; N, 21·3; S, 12·2; Cl, 13·5%).

3 : 5-*Dianilino*-1 : 2 : 4-*thiadiazole*.—(*a*) *N*-Phenyl-*N*′-phenylamidinothiourea (5·40 g., 0·02 mole) was oxidised with 6% hydrogen peroxide (0·06 mole) in the usual way. Crystallisation of the bronze-coloured product (m. p. 198—200°, after sintering at 195°; 4·3 g., 80%) from ethanol–acetone (15 and 3 ml. per g.; carbon) gave platelets (65—70%) of 3 : 5-*dianilino*-1 : 2 : 4-*thiadiazole*, m. p. 200—202° [Found: C, 62·85; H, 4·4; N, 21·0; S, 12·0%; *M* (cryoscopically, in thymol), 255. $C_{14}H_{12}N_4S$ requires C, 62·7; H, 4·5; N, 20·9; S, 11·9%; *M*, 268]. The product was not appreciably soluble in mineral acids and alkalis.

(*b*) A warm (35—40°) solution of *N*-phenyl-*N*′-phenylamidinothiourea (0·01 mole) in ethanol (20 ml.) was oxidised with bromine (0·01 mole), and the product isolated by removal of most of the solvent, followed by basification with aqueous sodium hydroxide (6%; 8 ml.). The product, collected at 0° and crystallised as before, was 3 : 5-dianilino-1 : 2 : 4-thiadiazole (1·5 g., 56%), m. p. and mixed m. p. 199—202° (Found: C, 62·5; H, 4·4; N, 19·7; S, 12·1%).

Reduction. Zinc–hydrochloric acid treatment (as detailed for the 5-anilino-homologue above) followed by basification, reconverted the thiadiazole into *N*-phenyl-*N*′-phenylamidinothiourea, m. p. and mixed m. p. 130—132°, in 48% yield.

Monoacyl Derivatives.—Interaction of 3 : 5-dianilino-1 : 2 : 4-thiadiazole with 8 equivs. of acetic anhydride in pyridine (conditions, isolation as above) gave, after crystallisation from benzene–ethanol (4 : 1), a crystalline powder (88%) of the *acetyl derivative*, m. p. 238—240° (Found: C, 62·2; H, 4·3; N, 17·9; S, 10·2. $C_{16}H_{14}ON_4S$ requires C, 61·9; H, 4·5; N, 18·1; S, 10·3%). Analogously, there was obtained (85%) a *benzoyl derivative*, forming truncated columns, m. p. 190—192° (from acetone–ethanol) (Found: C, 67·4; H, 4·15; N, 15·0; S, 8·5. $C_{21}H_{16}ON_4S$ requires C, 67·7; H, 4·3; N, 15·05; S, 8·6%).

Diacyl Derivative.—Treatment of the thiadiazole with 6 equivs. of toluene-*p*-sulphonyl chloride (usual conditions) gave (52%) prisms of 3 : 5-*di*(*phenylimino*)-2 : 4-*ditoluene*-p-*sulphonyl*-1 : 2 : 4-*thiadiazolidine*, m. p. 240—242° (from acetone–ethanol) (Found: C, 57·95; H, 3·9; N, 10·0; S, 16·3. $C_{28}H_{24}O_4N_4S_3$ requires C, 58·3; H, 4·2; N, 9·7; S, 16·7%).

5-*Anilino*-3-*methylamino*-1 : 2 : 4-*thiadiazole*.—A boiling solution of *N*-methylamidino-*N*′-phenylthiourea hydrochloride (2·63 g., 0·01 mole) in ethanol (25 ml.) and concentrated hydrochloric acid (0·5 ml.) was treated with hydrogen peroxide (0·03 mole) during 5 min., and distilled

to half-volume under reduced pressure. Addition of the clear residual liquid to ice-water (100 ml.), followed by basification (to litmus) with sodium hydroxide, precipitated the crude material (1·65 g.), which gave, after crystallisation from benzene (20 ml. per g.), white granules of **5-*anilino*-3-*methylamino*-1 : 2 : 4-*thiadiazole***, m. p. 137—138° (1·35 g., 65%) (Found : C, 52·45; H, 4·9; N, 27·3; S, 15·5. $C_9H_{10}N_4S$ requires C, 52·4; H, 4·85; N, 27·2; S, 15·5%).

3-*Anilino*-5-*methylamino*-1 : 2 : 4-*thiadiazole*.—Oxidation of *N*-methyl-*N'*-phenylamidinothiourea hydrochloride (as immediately above) afforded a crude product (1·45 g.) which consisted, after crystallisation from benzene (15 ml. per g.), of prisms (slow cooling) or felted needles (rapid cooling) of **3-*anilino*-5-*methylamino*-1 : 2 : 4-*thiadiazole***, m. p. 147—149° (1·24 g., 60%) [Found : C, 52·6; H, 4·95; N, 27·0; S, 15·5%; *M* (cryoscopically, in thymol), 200, 205. $C_9H_{10}N_4S$ requires C, 52·4; H, 4·85; N, 27·2; S, 15·5%; *M*, 206].

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