870. *Thiadiazoles. Part IV.*[1] *The Oxidation of* N-(*Aroylamidino*)*thioureas.*

By Frederick Kurzer.

Oxidative cyclisation of *N*-(aroylamidino)thioureas (I) by hydrogen peroxide in acid yields the expected 5-amino-3-aroylamino-1 : 2 : 4-thiadiazoles (II), but affords 3-amino-5-aryl-1 : 2 : 4-thiadiazoles (III), with simultaneous evolution of carbon dioxide, in the absence of acid. Mixtures of the two products (II, III) result when bromine, or hydrogen peroxide in media of intermediate acidity, is employed.

Some properties, particularly degradations, of 3-amino-5-aryl-1 : 2 : 4-thiadiazoles and their acyl derivatives are described.

Previous parts of this series [1] have dealt with the synthesis of 1 : 2 : 4-thiadiazoles by oxidative cyclisation of amidinothiourea and its *N*-mono- and *NN'*-di-substituted homologues. This paper describes the normal, as well as the anomalous, behaviour of *N*-(aroylamidino)thioureas (I) in this general reaction.

N-(Aroylamidino)thioureas (I) were prepared, according to the method of Kaiser,

[1] Parts I—III, Kurzer, (*a*) *J.*, 1955, 1; (*b*) *J.*, 1955, 2288; (*c*) *J.*, 1956, 2345.

Thurston, and their co-workers,[2] by the addition of the elements of hydrogen sulphide to *N*-aroyl-*N'*-cyanoguanidines, R·CO·NH·C(:NH)·NH·CN. The sensitivity of these cyanamido-derivatives, particularly to hydrolysis, precluded their isolation in the pure state. When treated without delay with hydrogen sulphide in ethanol, however, the crude intermediates afforded moderate to fair yields of the required thioureas (I). *N*-(Aroylamidino)thioureas were desulphurised by sodium plumbite almost instantly on slight warming.

In the presence of an equivalent of hydrochloric acid, hydrogen peroxide oxidised *N*-(aroylamidino)thioureas (I) to 5-amino-3-aroylamino-1 : 2 : 4-thiadiazoles (II). This formulation is based on the known ease with which compounds incorporating the –C(:NH)·NH·CS– system in their structure, including amidinothioureas,[1] thioaroylguanidines,[3] and *N*-arylimidoarylthioamides,[4] are cyclised to 1 : 2 : 4-thiadiazoles. The structure (II) assigned is in agreement with the ultimate composition, molecular weights, and chemical behaviour of the oxidation products: thus, 5-amino-3-benzamido-1 : 2 : 4-thiadiazole was desulphurised only very slowly by sodium plumbite; it gave benzoic acid on alkaline hydrolysis, and benzaldehyde together with hydrogen sulphide on reduction with zinc and alcoholic hydrochloric acid. The above cyclisation thus provides a route to monoacyl derivatives (II) not otherwise available, since acylation of the parent compound, 3 : 5-diamino-1 : 2 : 4-thiadiazole, yields di- and tri-substituted products directly.[1b]

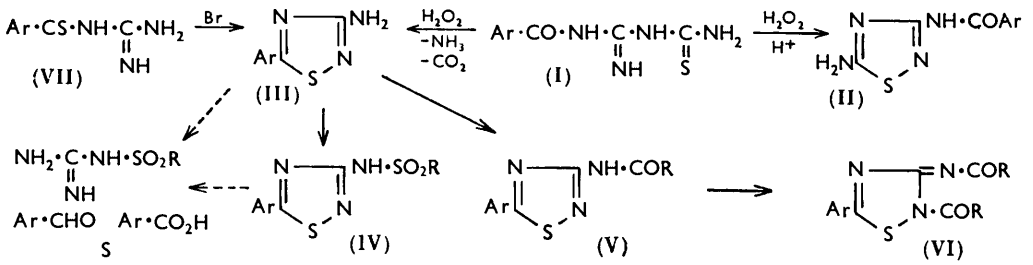
In the absence of mineral acid, however, the oxidation of *N*-(aroylamidino)thioureas took a different and unexpected course, proceeding with simultaneous fission and ring closure to afford excellent yields of 3-amino-5-aryl-1 : 2 : 4-thiadiazoles (III). The parent compound (III; Ar = Ph) of this series, for example, was rapidly formed in 80% yield on treatment of *N*-(benzoylamidino)thiourea in boiling ethanol with an excess of peroxide, carbon dioxide being vigorously evolved, particularly after the addition of the first equivalent of the oxidising agent. The decisive influence of the acidity of the medium in controlling the direction of the cyclisation was clearly shown by the results of a series of oxidations [of (I; Ar = Ph)] employing intermediate concentrations of mineral acid: mixtures of the two possible oxidation products, 5-amino-3-benzamido- (II; Ar = Ph) and 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (III; Ar = Ph), were obtained, the proportion of the former increasing, and that of the latter decreasing, as the quantity of mineral acid present was raised (cf. Table, p. 4530).

It was therefore not unexpected that bromine, another excellent reagent for cyclising amidinothioureas to 1 : 2 : 4-thiadiazoles,[1c] also oxidised *N*-(benzoylamidino)thiourea to the same mixture [of (II and III; Ar = Ph)]. In the initially neutral medium, cyclisation (I) ⟶ (III) should predominate in the opening stages; the simultaneous liberation of hydrogen bromide raises the acidity of the medium, so that the alternative cyclisation (I) ⟶ (II) presently becomes the main reaction: the two products (II, III; Ar = Ph) are in fact obtained in approximately equal yields.

The structure of 3-amino-5-aryl-1 : 2 : 4-thiadiazoles was assigned on the basis of the properties and degradation of the phenyl homologue and its derivatives (IV, V, VI). The parent compound (III; Ar = Ph) was a base, capable of forming mono- and di-acyl derivatives. Its resistance to alkylation by methyl iodide (absence of thiol [5]), and to desulphurisation by lead plumbite was in accord with a structure incorporating sulphur in a ring system. The product was remarkably stable towards hydrolysis: it was cleaved only very slowly by boiling concentrated sodium hydroxide or hydrochloric acid, sulphur (or hydrogen sulphide) and benzoic acid being the main products isolated. Reduction by zinc and hydrochloric acid gave benzaldehyde and hydrogen sulphide. These observations established the linking of the aryl radical to a carbon atom. The presence of the guanidino-grouping, suggested by the occasional isolation of minute quantities of guanidine in hydrolysis experiments, was clearly shown by the reduction of the toluene-*p*-sulphonyl derivative (IV; R = *p*-C_6H_4Me) to toluene-*p*-sulphonylguanidine in good yield. All this evidence, together with the ultimate composition and molecular weight of the product,

[2] Adams, Kaiser, Nagy, Peter, Sperry, and Thurston, *J. Org. Chem.*, 1952, **17**, 1162.
[3] Goerdeler and Fincke, *Chem. Ber.*, 1956, **89**, 1033.
[4] Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1928, **7**, 237.
[5] Fromm, *Annalen*, 1893, **275**, 20; Fairfull and Peak, *J.*, 1955, 803.

and its non-identity with the known 5-amino-3-phenyl-1 : 2 : 4-thiadiazole,[6] indicated the high probability of its having the isomeric 3-amino-5-aryl structure (III; Ar = Ph). Meanwhile, decisive proof for this view became available by Goerdeler and Fincke's [3] very recent unequivocal synthesis, from thiobenzoylguanidine (VII), of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole, with which the phenyl homologue of the present series of compounds (III) proved to be identical.



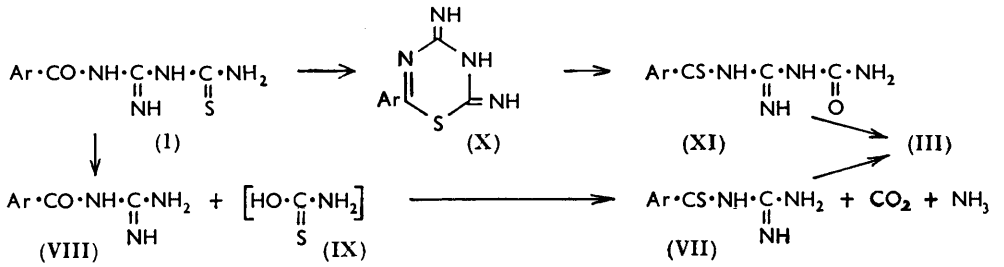
In view of the considerable reactivity [1b,3] of the 3-amino-group in the 1 : 2 : 4-thiadiazole system, monoacyl compounds are formulated as 3-acylamino-derivatives (IV, V). A tautomeric displacement of hydrogen into the 4-position being inadmissible, the easily accessible dibenzoyl derivative is represented as 3-benzimido-2-benzoyl-2 : 3-dihydro-5-phenyl-1 : 2 : 4-thiadiazole (VI; R = Ph). Attention is drawn to the result of the reduction of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (III) and its 3-toluene-*p*-sulphonyl derivative (IV), neither of which is cleaved solely at the $S_{(1)}$–$N_{(2)}$ bond, as are 3 : 5-diamino-derivatives; [1] in this respect, the *C*-arylated 1 : 2 : 4-thiadiazoles approach the behaviour of " Hector's bases." [7]

The smooth cyclisation (I) ⟶ (III) is remarkable for its rapidity and for the absence of side reactions, in spite of its being necessarily a multistage process. Whatever the mechanism of this reaction, the immediate precursor of the final product (III) is almost certain to incorporate the thioaroylguanidino-grouping, from which the 1 : 2 : 4-thiadiazole ring system may arise by dehydrogenation in the usual way. Of the possible routes that would account for the initial stages, attention may be drawn to a preliminary hydrolytic removal from the starting material (I) of the elements of (hypothetical) thiocarbamic acid (IX) which may (either directly, or in the form of nascent carbon oxysulphide) change the remaining benzoylguanidine (VIII) into the required precursor (VII). The well-known conversion of benzoyl into thiobenzoyl derivatives by means of phosphorus pentasulphide [8] or aluminium sulphide,[9] and the established mobility of the sulphur atoms in thion- [10] and dithio-carboxylic [11] acids and their derivatives would appear to lend support to this view. A mechanism involving the initial removal, from the reactant (I), of the terminal thioamide group by its complete oxidation to sulphur is ruled out, since benzoylguanidine (VIII) failed to yield 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (III) on treatment, under the usual experimental conditions, with hydrogen peroxide in the presence of sulphur (the latter being provided in the form of either hydrogen sulphide or an ethanolic solution of the element).

An interesting alternative possibility involves the cyclic dehydration of the starting material to the substituted 1 : 3 : 5-thiadiazine (X), which, followed by hydration across the $S_{(1)}$–$C_{(2)}$ bond, would furnish the thiobenzoylguanidino-compound (XI) directly. It is well established that the nucleus of related 1 : 3 : 5-thiadiazines is cleaved relatively easily.[12]

[6] Goerdeler, *Chem. Ber.*, 1954, **87**, 57, 66.
[7] Hector, *Ber.*, 1892, **25**, ref. 799.
[8] Kindler, *Annalen*, 1923, **431**, 209; Gatewood and Johnson, *J. Amer. Chem. Soc.*, 1926, **48**, 2904; Miyamichi, *J. pharm. Soc. Japan*, 1928, **48**, 114.
[9] Kindler and Finndorf, *Ber.*, 1921, **54**, 1079.
[10] Jepson, Lawson, and Lawton, *J.*, 1955, 1791.
[11] Todd, Bergel, and Karimullah, *J.*, 1936, 1557; Kjaer, *Acta Chem. Scand.*, 1950, **4**, 1347; 1952, **6**, 27, 1374.
[12] Wagner-Jauregg, *Annalen*, 1948, **561**, 87.

However, the absence, amongst the reaction products, of at least small proportions of 5-phenyl-3-ureido-1 : 2 : 4-thiadiazole [presumably the primary oxidation product of (XI)] casts doubt on this interpretation, because the necessary further degradation of the substituted urea to the amine (III) is unlikely to be rapid and complete. Experiments on the mechanism of this cyclisation (I) ⟶ (III) are being continued.



The benzoylguanidine required in this work was readily prepared in consistent, if moderate, yields by the interaction of guanidine hydrochloride and benzoyl chloride at 190—220°. This adaptation of Korndörfer's method [13] avoids the use of pressure equipment which had previously been regarded [13] as essential.

Experimental

Picrates were prepared from equimolar proportions of the appropriate amidinothioureas or 1 : 2 : 4-thiadiazoles and picric acid in hot or boiling ethanol. Light petroleum was of boiling range 60—80°.

N-(*Aroylamidino*)*thioureas.*

N-(Benzoylamidino)thiourea was prepared from dicyandiamide by the method of Adams *et al.*[2] in 46—54% (overall) yield and formed, after two crystallisations from ethanol, deep yellow lustrous cubes, m. p. 170—171° (decomp.) (Found : C, 48·6; H, 4·8; N, 25·2. Calc. for $C_9H_{10}ON_4S$: C, 48·65; H, 4·5; N, 25·2%). Its *picrate* formed deep-yellow prisms, m. p. 206—207° (decomp.) (from ethanol) (Found : C, 40·1; H, 2·9. $C_{15}H_{13}O_8N_7S$ requires C, 39·9; H, 2·9%).

N-(p-*Nitrobenzoylamidino*)*thiourea.*—Dicyandiamide (12·6 g., 0·15 mole) was dissolved in a solution of potassium hydroxide (85%; 20 g., 0·3 mole) in water (50 ml.) and diluted with acetone (50 ml.). The stirred liquid was treated, during 20 min., with a solution of *p*-nitrobenzoyl chloride (25 g., 0·135 mole) in acetone (60 ml.) kept at <10°. The resulting suspension was diluted with water (to a total volume of 2 l.) and acidified with concentrated hydrochloric acid (25 ml.). The finely divided precipitate was collected on a large Buchner funnel and successively washed with water and a little ethanol (filtration slow). The thoroughly drained crude intermediate *N*-*p*-nitrobenzoyl-*N'*-cyanoguanidine was suspended in absolute ethanol (250 ml.), and treated with hydrogen sulphide during 5 hr. at 50—60°. The finely divided white reactant gradually changed to an orange-yellow crystalline light material and a deep scarlet heavy crystalline deposit. The latter (m. p. 201—202°; 4·35—5·45 g., 12—15%) was readily isolated by decantation of the supernatant suspension; two crystallisations from acetone–ethanol gave scarlet prisms of N-(p-*nitrobenzoylamidino*)*thiourea*, m. p. 203—204° (decomp.) (Found: C, 39·9; H, 3·8; N, 26·5; S, 11·5. $C_9H_9O_3N_5S$ requires C, 40·45; H, 3·4; N, 26·2; S, 12·0%). The orange-yellow by-product, and the material remaining in the ethanol solution, were non-homogeneous. The *picrate* formed dark orange needles, m. p. 197—198° (decomp.) (from aqueous ethanol) (Found : C, 36·35; H, 2·6. $C_{15}H_{12}O_{10}N_8S$ requires C, 36·3; H, 2·4%).

N-(p-*Chlorobenzoylamidino*)*thiourea.*—Dicyandiamide (0·075 mole) and *p*-chlorobenzoyl chloride (11·8 g., 0·0675 mole) were condensed under the conditions detailed immediately above, and the intermediate crude *N*-*p*-chlorobenzoyl-*N'*-cyanoguanidine was suspended in ethanol (150 ml.), treated with hydrogen sulphide [1 hr. each at 25°, 40°, 50°, and 65°]. The resulting orange suspension was filtered at the pump while hot (solid : A), the filtrate evaporated nearly to dryness in a vacuum, and the residue dissolved in boiling acetone (40—60 ml.). The colourless plates which separated on addition of an equal volume of light petroleum, and cooling, were removed and rinsed with a little light petroleum (solid : B). By repeating this process, further

[13] Korndörfer, *Archiv Pharm.*, 1903, **241**, 476.

fractions of colourless platelets were removed, if necessary. The more soluble product, crystallising slowly from the concentrated acetone solution on addition of light petroleum and partial evaporation, consisted of successive fractions (total 6—7·8 g., 35—45%) of orange granular material, which gave, after crystallisation from ethanol–light petroleum, orange-yellow prisms of N-(p-*chlorobenzoylamidino*)*thiourea*, m. p. 152—154° (decomp.) (Found: C, 42·1; H, 3·55; N, 21·6; S, 11·9; Cl, 13·6. $C_9H_9ON_4SCl$ requires C, 42·1; H, 3·5; N, 21·8; S, 12·5; Cl, 13·8%). The fractions less soluble in acetone (A, B; total 2·5—3·5 g., 24—33%) consisted, after crystallisation from ethanol–water (2 : 1), of platelets of *p*-chlorobenzoic acid, m. p. 236—238° (Found: C, 53·6; H, 3·1; Cl, 22·7. Calc. for $C_7H_5O_2Cl$: C, 53·7; H, 3·2; Cl, 22·7%).

Solutions of the above *N*-(aroylamidino)thioureas in N-sodium hydroxide, treated with aqueous lead acetate, rapidly gave a copious precipitate of lead sulphide on gentle warming.

5-*Amino*-3-*aroylamino*-1 : 2 : 4-*thiadiazoles*.

5-*Amino*-3-*benzamido*-1 : 2 : 4-*thiadiazole*.—A boiling solution of *N*-(benzoylamidino)thiourea (2·22 g., 0·01 mole) in ethanol (20 ml.) containing concentrated hydrochloric acid (1 ml., 0·01 mole) was treated with 6% hydrogen peroxide (17 ml., 0·03 mole) during 5 min. (colour change from deep to pale yellow). Most of the ethanol was removed by distillation under reduced pressure during 5 min. and separation of the crystalline product completed by storage at 0°. Two crystallisations from acetone–ethanol afforded scales of 5-*amino*-3-*benzamido*-1 : 2 : 4-*thiadiazole*, m. p. 215—217° (sintering at 208°) (yield, including material from the mother-liquors, 1·32 g., 60%) [Found: C, 49·3; H, 3·4; N, 25·5; S, 14·7%; *M* (cryoscopically, in thymol), 210. $C_9H_8ON_4S$ requires C, 49·1; H, 3·6; N, 25·45; S, 14·5%; *M*, 220].

A solution of the product in N-sodium hydroxide, treated with aqueous lead acetate, remained clear after 3 minutes' boiling. In boiling 3N-alkali, finely divided lead sulphide was slowly deposited. Reduction of 5-amino-3-benzamido-1 : 2 : 4-thiadiazole (conditions as for III, R = Ph; see below) gave benzaldehyde (isolated as the 2 : 4-dinitrophenylhydrazone) in 56% yield.

5-*Amino*-3-p-*nitrobenzamido*-1 : 2 : 4-*thiadiazole*.—Addition of hydrogen peroxide (3 × 0·005 moles) to *N*-(*p*-nitrobenzoylamidino)thiourea (1·34 g., 0·005 mole) in boiling ethanol (60 ml.)–hydrochloric acid (0·5 ml., 0·005 mole), followed by addition of the mixture to water (250 ml.), gave a flocculent yellow precipitate. This was coagulated by warming, collected (dry wt., 1·05 g.), and crystallised from ethanol–benzene–acetone (2 : 2 : 1; 500 ml.). The separated yellow microcrystalline powder (0·64 g., 48%) was 5-*amino*-3-p-*nitrobenzamido*-1 : 2 : 4-*thiadiazole*, m. p. 258—260° (decomp.) (Found: C, 40·45; H, 2·75; N, 26·2; S, 11·8. $C_9H_7O_3N_5S$ requires C, 40·75; H, 2·6; N, 26·4; S, 12·1%). Partial evaporation of the filtrates gave a little more of the above product, and finally deposited (0·17 g., 15%) the more soluble 3-amino-5-*p*-nitrophenyl-1 : 2 : 4-thiadiazole, m. p. 233—235° (see below), formed as by-product.

5-*Amino*-3-p-*chlorobenzamido*-1 : 2 : 4-*thiadiazole*.—" Acidic " oxidation of *N*-(*p*-chlorobenzoylamidino)thiourea (1·28 g., 0·005 mole) (as described for the *p*-nitro-derivative) gave a white granular powder. After being extracted with boiling ethanol (25 ml.), the undissolved material was twice crystallised from boiling nitrobenzene–ethanol and gave white platelets of 5-*amino*-3-p-*chlorobenzamido*-1 : 2 : 4-*thiadiazole*, m. p. 260—262° (decomp.) (Found: C, 42·35; H, 2·6; N, 21·7; S, 12·7; Cl, 13·6. $C_9H_7ON_4SCl$ requires C, 42·4; H, 2·75; N, 22·0; S, 12·6; Cl, 13·9%).

3-*Amino*-5-*aryl*-1 : 2 : 4-*thiadiazoles*.

3-*Amino*-5-*phenyl*-1 : 2 : 4-*thiadiazole*.—A boiling solution of *N*-(benzoylamidino)thiourea (6·65 g., 0·03 mole) in ethanol (50 ml.) was treated with 6% hydrogen peroxide (51 ml., 0·09 mole) in three portions at 3 min. intervals. After the addition of the second equivalent, the original deep yellow colour of the solution was completely discharged; carbon dioxide was evolved throughout the oxidation. The colourless liquid was evaporated to half its bulk in a vacuum, and the white crystals were collected after storage at 0° during 12 hr. Two crystallisations from ethanol (8 ml. per g.) or water (250 ml. per g.) gave lustrous elongated prisms (or needles, respectively) of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole, m. p. and mixed m. p. (with material prepared by the method of Goerdeler and Fincke [3]) 132—134° (yield, including material from the mother-liquors, 4·0—4·35 g., 75—82%) [Found: C, 53·8, 53·7; H, 3·8, 4·0; N, 23·5, 24·0, 23·9; S, 17·7%; *M* (cryoscopically in naphthalene) 195, (in thymol) 180. Calc. for $C_8H_7N_3S$: C, 54·2; H, 4·0; N 23·7; S, 18·1%; *M*, 177). In a blank experiment no carbon dioxide was evolved in the absence of *N*-(benzoylamidino)thiourea by the otherwise identical reaction mixture.

The *picrate*, prepared in either boiling ethanol or warm 3N-hydrochloric acid, by the use of either one or two equivs. of picric acid, crystallised from ethanol as yellow blades, m. p. 148—150° (Found: C, 41·4; H, 3·2; N, 20·8; S, 7·0. $C_{14}H_{10}O_7N_6S$ requires C, 41·4; H, 2·5; N, 20·7; S, 7·9%).

3-Acetamido-5-phenyl-1 : 2 : 4-thiadiazole, prepared from the amino-compound, formed platelets, m. p. 147—149° (Found: C, 54·8; H, 4·2. Calc. for $C_{10}H_9ON_3S$: C, 54·8; H, 4·1%). Goerdeler and Fincke [3] give m. p. 143°. 3-*p*-Aminobenzenesulphonamido-5-phenyl-1 : 2 : 4-thiadiazole consisted of needles, m. p. 193—194° (after sintering at 187°); Goerdeler and Fincke [3] give m. p. 187°.

3-*Amino*-5-*phenyl*-1 : 2 : 4-*thiadiazole*.—*Alkaline hydrolysis*. A suspension of the finely powdered reactant (1·77 g., 0·01 mole) in 20% w/w aqueous potassium hydroxide (45 g.) was refluxed until all the material had dissolved (2·5 hr.), and boiling was continued for 1 hr. more; ammonia was evolved continuously. The yellow liquid was acidified with concentrated hydrochloric acid (15 ml.) (evolution of hydrogen sulphide), and the resulting precipitate, collected at 0° (filtrate A), separated by means of boiling water (25 ml.) into sulphur (0·18 g., 56%) and benzoic acid (0·80 g., 65%), m. p. and mixed m. p. 119—121°. More benzoic acid (0·11 g., 9%) was recovered from filtrate A by extraction with ether.

In ethanolic 15% potassium hydroxide, almost half the reactant was recovered after 3 hours' refluxing.

Acid hydrolysis. A solution of the reactant (0·01 mole) in hydrochloric acid (constant-boiling mixture; 40 ml.) was refluxed during 5 hr. Hydrogen sulphide was slowly evolved, while the resulting turbidity gradually gave place to yellow globules. The boiling clear aqueous phase was readily decanted from the sulphur (0·24 g., 75%); the solid separating from the solution (0°) was benzoic acid, m. p. and mixed m. p. 119—121° (from water) (0·85 g., 70%). The filtrate therefrom was treated with toluene-*p*-sulphonic acid monohydrate (1 g.); the non-homogeneous solid (0·45 g.) which appeared on partial spontaneous evaporation was fractionated from ethanol and gave (in some but not all experiments) guanidine toluene-*p*-sulphonate, m. p. and mixed m. p. 225—226° (0·18 g., 8%). The final aqueous filtrate contained much ammonium salt.

More than half of the reactant was recovered unchanged when its solution in 3N-hydrochloric acid was refluxed during 1 hr.

Reduction. A solution of the reactant (0·01 mole) in boiling ethanol (40 ml.) containing zinc foil (4 g.) was treated during 5 min. with concentrated hydrochloric acid (4 ml.), and refluxed for another 10 min. (evolution of hydrogen sulphide). The decanted ethanolic solution was concentrated in a vacuum (smell of benzaldehyde) and treated with 2 : 4-dinitrophenylhydrazine (2 g., 0·01 mole), dissolved in ethanol (30 ml.) containing concentrated hydrochloric acid (5 ml.). The orange granular precipitate (m. p. 231—234; 1·86 g., 65%) was benzaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235—236° (from acetone–ethanol).

3-Amino-5-phenyl-1 : 2 : 4-thiadiazole (0·005 mole) was recovered unchanged after being refluxed with methyl iodide (0·15 mole) in methanol during 2 hr. The product very gradually deposited traces of lead sulphide on prolonged boiling in 3N-sodium hydroxide containing lead acetate.

3-*Benzamido*-5-*phenyl*-1 : 2 : 4-*thiadiazole*.—Addition of benzoyl chloride (0·7 g., 0·005 mole) to a solution of 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (0·88 g., 0·005 mole) in pyridine (15 ml.), and storage of the liquid at 100° during 30 min., followed by its addition to N-hydrochloric acid (150 ml.) at 0°, gave a white granular solid. Crystallisation from ethanol gave lustrous needles of 3-*benzamido*-5-*phenyl*-1 : 2 : 4-*thiadiazole*, m. p. 154—155° (0·85 g., 61%) (Found: C, 64·1; H, 3·7; N, 14·6; S, 11·0. $C_{15}H_{11}ON_3S$ requires C, 64·1; H, 3·9; N, 14·95; S, 11·4%).

With an excess of benzoyl chloride (4·22 g., 0·03 mole) the reactant (0·005 mole) gave, under identical conditions and treatment, a viscous oil. The supernatant aqueous phase was discarded, the oil heated with ethanol (15 ml.), and the white granular solid, which separated instantly, collected at 0° (m. p. 205—210°; 1·75 g., 90%). Two crystallisations from benzene–ethanol (50 : 15 ml.) gave prisms of 3-*benzimido*-2-*benzoyl*-2 : 3-*dihydro*-5-*phenyl*-1 : 2 : 4-*thiadiazole*, m. p. 215—217° (Found: C, 68·9; H, 4·2; N, 10·4; S, 7·6. $C_{22}H_{15}O_2N_3S$ requires C, 68·6; H, 3·9; N, 10·9; S, 8·3%).

3-p-*Nitrobenzamido*-5-*phenyl*-1 : 2 : 4-*thiadiazole*, similarly prepared from equivalent quantities of the reactants in pyridine, crystallised from acetone–ethanol as pale yellow platelets, m. p. 210—212° (75%) (Found: C, 55·0; H, 3·4; N, 17·1; S, 9·7. $C_{15}H_{10}O_3N_4S$ requires C, 55·2; H, 3·1; N, 17·2; S, 9·8%).

5-*Phenyl*-3-*toluene*-p-*sulphonamido*-1 : 2 : 4-*thiadiazole*.—A solution of the amino-compound

(3·54 g., 0·02 mole) in pyridine (50 ml.), treated with toluene-*p*-sulphonyl chloride (11·4 g., 0·06 mole), was kept at 100° during 0·5 hr. The solid obtained when the mixture was poured into 2N-hydrochloric acid (300 ml.) at 0° was twice crystallised from acetone–benzene–ethanol (1 : 1 : 1; carbon) and yielded platelets of 5-*phenyl*-3-*toluene*-p-*sulphonamido*-1 : 2 : 4-*thiadiazole*, m. p. 206—208° (4·3—4·75 g., 65—72%) (Found: C, 54·0, 54·3; H, 4·2, 3·9; N, 12·7; S, 19·0. $C_{15}H_{13}O_2N_3S_2$ requires C, 54·4; H, 3·9; N, 12·7; S, 19·3%). The use of a larger excess of sulphonyl chloride (6 mols.) gave again only the monosulphonyl derivative, in somewhat improved (75—80%) yields.

Reduction. A boiling suspension of the derivative (1·66 g., 0·005 mole) in ethanol (40 ml.) containing zinc turnings (4 g.) was treated with concentrated hydrochloric acid (6 × 1 ml., at 3 min. intervals) and refluxing continued for a total of 45 min. The reactant rapidly dissolved, and hydrogen sulphide was evolved. The decanted, filtered liquid was concentrated (to 10 ml.) in a vacuum and diluted with 3N-hydrochloric acid (10 ml.), and the clear (absence of starting material) liquid made alkaline with 3N-sodium hydroxide. The collected thick precipitate was washed with a little water, then dried, and the product separated from the zinc oxide by exhaustive extraction with boiling ethanol (6 × 10 ml.). The combined filtered extracts gave, on concentration, crystals (m. p. 202—204°; 0·69 g., 60%) which afforded, by one crystallisation from ethanol, needles of toluene-*p*-sulphonylguanidine hydrate, m. p. and mixed m. p. 204—205° (Found: C, 41·6; H, 5·4. Calc. for $C_8H_{11}O_2N_3S,H_2O$: C, 41·6; H, 5·6%).

Oxidation of N-(*Benzoylamidino*)*thiourea by Bromine.*—A solution of the reactant (2·22 g., 0·01 mole) in ethanol (30 ml.) at 40—45° was treated with bromine (1·6 g., 0·01 mole) in chloroform (5 ml.). The decolorised liquid was distilled to half its bulk in a vacuum, the residual solution stirred into water (120 ml.), and the collected dried product (1·95 g.) dissolved in 1 : 1 ethanol–acetone (120 ml.). The separated crystals were 5-amino-3-benzamido-1 : 2 : 4-thiadiazole (0·9 g., 41%), forming platelets, m. p. and mixed m. p. (with material prepared by " acidic " hydrogen peroxide oxidation) 215—217°, on further crystallisation (Found: C, 49·2; H, 3·5%). The filtrates therefrom, distilled to small bulk (10 ml.), deposited 3-amino-5-phenyl-1 : 2 : 4-thiadiazole (0·62 g., 35%), m. p. and mixed m. p. (with material prepared by " neutral " hydrogen peroxide oxidation) 132—133° (from ethanol).

Oxidation of N-(*Benzoylamidino*)*thiourea by Hydrogen Peroxide in Media of Differing Acidities.*—Oxidation of the reactant (0·01 mole) in ethanol containing different amounts of hydrochloric acid, followed by separation of the products as described immediately above, gave the following results:

Equivs. of acid	0·05	0·10	0·50	0·66	0·80
Yield (%) of (II; Ar = Ph)	3	5	35	45	50
Yield (%) of (III; Ar = Ph)	80	70	27	9	—

3-*Amino*-5-p-*nitrophenyl*-1 : 2 : 4-*thiadiazole.*—To *N*-(*p*-nitrobenzoylamidino)thiourea (1·33 g., 0·005 mole) in boiling ethanol (40 ml.) containing 1 drop of 3N-hydrochloric acid, 6% hydrogen peroxide (8·5 ml., 0·015 mole) was added during 6 min. The deep scarlet liquid became light orange, while carbon dioxide was evolved. The yellow solid which separated towards the end of the reaction was collected at 0° (m. p. 224—228°; 1·0 g., 90%) and gave, on two crystallisations from acetone–ethanol (60 and 20 ml. respectively), followed by evaporation on the steam bath until crystallisation just set in), yellow needles of 3-*amino*-5-p-*nitrophenyl*-1 : 2 : 4-*thiadiazole*, m. p. 234—236° [Found: C, 42·9, 43·4; H, 2·8, 2·8; N, 25·0; S, 14·6%; *M* (cryoscopically in thymol), 210. $C_8H_6O_2N_4S$ requires C, 43·2; H, 2·7; N, 25·2; S, 14·4%; *M*, 222]. Attempts to obtain the picrate were unsuccessful, the unchanged thiadiazole being recovered when its ethanolic or acetone solution was treated with picric acid (1 equiv.) in ethanol.

3-*Amino*-5-p-*chlorophenyl*-1 : 2 : 4-*thiadiazole.*—" Neutral " oxidation of *N*-(*p*-chlorobenzoylamidino)thiourea (1·28 g., 0·005 mole) (as described for the *p*-nitro-derivative) gave a white granular solid. This was refluxed with acetone (30 ml.), the suspension quickly filtered at the pump while hot (residue A), and the filtrate evaporated to 10 ml. and diluted with ethanol (10 ml.). Further crystallisation of the separated product from the same solvents gave massive needles (0·60 g., 56%) of 3-*amino*-5-p-*chlorophenyl*-1 : 2 : 4-*thiadiazole*, m. p. 196—197° (Found: C, 45·6; H, 2·9; N, 20·0; S, 14·7; Cl, 16·4. $C_8H_6N_3SCl$ requires C, 45·4; H, 2·8; N, 19·9; S, 15·1; Cl, 16·8%). Residue A (0·25 g., 20%) consisted of 5-amino-3-*p*-chlorobenzamido-1 : 2 : 4-thiadiazole, m. p. and mixed m. p. (with material prepared by " acidic " oxidation) 260—262° (decomp.) (after crystallisation from nitrobenzene–ethanol).

Benzoylguanidine.—A mixture of guanidine hydrochloride (28·65 g., 0·3 mole) and benzoyl

chloride (42·0 g., 0·3 mole) was kept, during successive 25-min. periods, at 180—185°, 190—195°, and 210—220°. At 190—195° the solid gradually dissolved, reaction being complete when distinct evolution of hydrogen chloride ceased. The yellow viscid liquid was carefully, yet rapidly diluted with ethanol (120 ml.); the resulting yellow solution was quickly filled with crystalline solid which was collected after 6 hr. at room temperature. Crystallisation from ethanol gave white prisms of benzoylguanidine hydrochloride, m. p. 210—212° (after sintering at 206°) (yield, including good material from mother-liquors, 18—21 g., 30—35%). Further crystallisation from water (10 ml. per g., with addition of 2 drops of 3N-hydrochloric acid) gave prisms of the solvated product, m. p. 208—212° (after sintering at 206°) (Found: C, 44·4; H, 5·3. Calc. for $C_8H_9ON_3,HCl,H_2O$: C, 44·15; H, 5·5%).

A solution of the hydrochloride (10·0 g., 0·05 mole) in water (75 ml.), acidified with concentrated hydrochloric acid (0·5 ml.) at 70°, was allowed to cool until crystallisation was about to set in (60°), treated with aqueous 3N-sodium hydroxide (25 ml., 0·075 mole), and quickly cooled. The product, collected at 0°, and pressed between filter-paper, was dissolved in warm acetone (20 ml.), and the filtered solution diluted with light petroleum (30 ml.). The separated benzoylguanidine formed prisms, m. p. 162—164° (yield, including satisfactory material from mother-liquors, 6·1—7·0 g., 75—85%) (Found: C, 59·0; H, 5·9; N, 26·2. Calc. for $C_8H_9ON_3$: C, 58·9; H, 5·5; N, 25·8%).

Interaction of guanidine thiocyanate and benzoyl chloride (1 : 1·1 mol.) in pyridine at 60° or 100° during 30 min. gave mainly intractable oils. Traube's synthesis [14] gave, in our hands, mainly guanidine benzoate, m. p. and mixed m. p. with authentic material [15] 226—228° (after sintering at 220°) (Found: C, 52·6; H, 5·7; N, 22·8. Calc. for $CH_5N_3,C_7H_6O_2$: C, 53·0; H, 6·1; N, 23·2%).

Benzoylguanidine failed to yield 3-amino-5-phenyl-1 : 2 : 4-thiadiazole when the base or its hydrochloride (0·01 mole) in boiling ethanol [either containing dissolved sulphur (0·01 mole) or being simultaneously treated with a slow stream of hydrogen sulphide] was oxidised with hydrogen peroxide (0·03 mole) in the usual manner.

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[15] Walker, *J.*, 1949, 1996.