315. *Thiadiazoles. Part XI.* Synthesis and Cyclisation of N-(Thiobenzamido)guanidines and Related Compounds.*

By Frederick Kurzer.

N-Thiobenzamido-guanidine, -urea, and -thiourea and their *N'*-phenyl-analogues are synthesised by thiobenzoylation of the appropriate hydrazino-compounds. They are readily cyclised in acid media to a variety of substituted 1,3,4-thiadiazoles in excellent yield.

Aminoguanidine reacts with isocyanate and isothiocyanate esters, at either its hydrazino-[1] or its amidino-group,[2] to yield substituted ureas or thioureas which are versatile starting materials in heterocyclic syntheses (for summary see ref. 2). Condensation products of the general structure R·NH·CS·NH·C(:NH)·NH·NH_2, for example, have recently been converted, by hydrolytic or oxidative cyclisation, into substituted 1,2,4-triazoles[2] or 1,2,4-thiadiazoles,[3] respectively. In this connexion, the examination of analogous

* Part X, *J.*, 1960, 3240.

[1] Fantl and Silbermann, *Annalen*, 1928, **467**, 281; Fry and Lambie, B.P. 741,228, 741,280/1955.
[2] Godfrey and Kurzer, *J.*, 1960, 3437.
[3] Godfrey and Kurzer, *J.*, unpublished work.

reactions of simpler related structures that would result from the thioacylation of aminoguanidine appeared of interest.

Amongst thioacylating agents,[4] (thiobenzoylthio)acetic acid, first prepared by Holmberg [5,6] in 1944, has proved particularly useful in thiobenzoylating amino-acids [6-9] and hydrazine derivatives.[5,8-10] In studies concerning nickel-complexing agents related to thiosemicarbazide,[11] Jensen and Miquel [8] described products obtained by thiobenzoylating aminoguanidine, semicarbazide, and thiosemicarbazide with this reagent.

$Ph{\cdot}CS{\cdot}NH{\cdot}NH{\cdot}C(:NH){\cdot}NH_2$ (II) $NH_2{\cdot}N(Ph{\cdot}CS){\cdot}C(:NH){\cdot}NH_2$ (IIa) $NH_2{\cdot}NH{\cdot}C(:NH){\cdot}NH{\cdot}CS{\cdot}Ph$ (IIb)

Aminoguanidine (I) and sodium (thiobenzoylthio)acetate reacted in aqueous solution at room temperature, under the conditions of Holmberg's general procedure,[5,6] to afford good yields of *N*-(thiobenzamido)guanidine (II), together with small quantities of 2,5-diphenyl-1,3,4-thiadiazole (IX). The guanidine derivative (II) differed materially from Jensen and Miquel's product [8] (m. p. 146—147°, from water), in forming a hemihydrate (m. p. 164—166°) when crystallised from water, or the anhydrous base (m. p. 180—182°) from organic solvents. Three isomeric thiobenzoyl derivatives (II, IIa, IIb) of aminoguanidine are theoretically possible; the formulation of the product as (II) is based on the marked difference in the reactivity of hydrazino- and guanidino-groups towards (thiobenzoylthio)acetic acid. Thus, structure (IIb) may be rejected because aminoguanidine having its hydrazino-group blocked (*e.g.*, X) failed to yield a thiobenzoyl derivative. Guanidine itself is known to react only very incompletely with other thiobenzoylating agents [12] and hardly at all with (thiobenzoylthio)acetic acid.[9] Although methylhydrazine is attacked at the methylamino-group [10] (to yield $Ph{\cdot}CS{\cdot}MeN{\cdot}NH_2$), a comparable structure (IIa) for the present compound is excluded by the results of cyclisation experiments, which are readily interpreted in terms of structure (II) but are not compatible with (IIa).

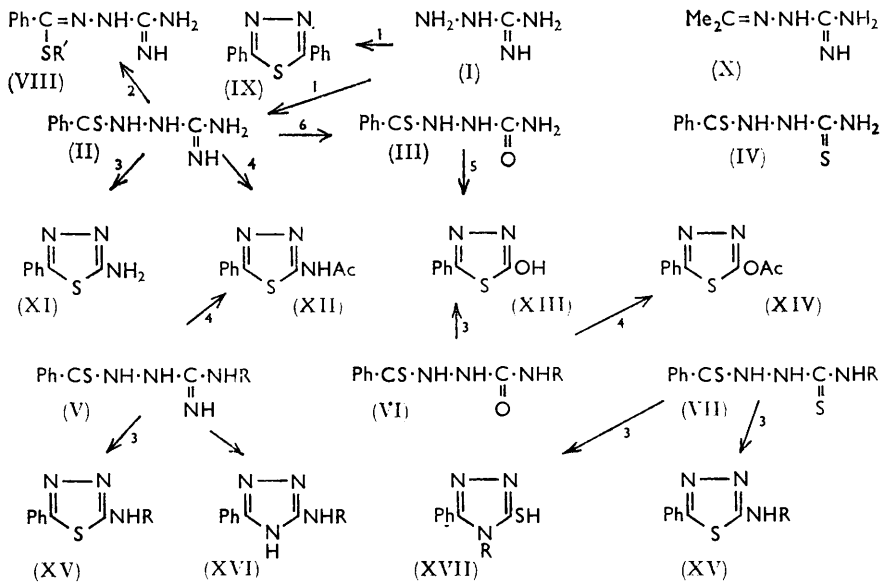
In agreement with its constitution, *N*-(thiobenzamido)guanidine (II) displays both acidic and basic properties, dissolving in alkalis or acids, and forming a picrate. Alkylation gave products, which evolved alkanethiol on hydrolysis and are therefore formulated as *S*-alkylthio-derivatives (VIII; R′ = Et or $Ph{\cdot}CH_2$). Boiling hydrochloric acid or acetic anhydride rapidly cyclised the compound (II), with loss of ammonia. to 2-amino-5-phenyl-1,3,4-thiadiazole (XI) or the corresponding acetyl derivative (XII). These results are complementary to the analogous ring-closure of *N*-(thiobenzamido)urea (III) and thiourea (IV) to 2-hydroxy(or mercapto)-5-phenyl-1,3,4-thiadiazole described by Lawson and Searle.[9] Treatment of *N*-(thiobenzamido)guanidine (II) with alkalis, however, did not eliminate the elements of hydrogen sulphide to yield 1,2,4-triazoles, which are readily obtained from the structurally related *N*-(thioureido)guanidines,[1] but resulted merely in hydrolysis to *N*-(thiobenzamido)urea (III). In this respect, the compound (II) behaved as the parent aminoguanidine (I), which is converted chiefly into semicarbazide [13] on alkaline hydrolysis.

The wider applicability of the synthesis, and the consistent behaviour of compounds of types (V—VII) was apparent from an examination of the aryl derivatives. Thiobenzoylation of 1-amino-3-phenylguanidine, and its 3-*p*-tolyl homologue, gave the expected 1-aryl-3-(thiobenzamido)guanidines (V; R = Ph or p-C_6H_4Me) in moderate yields. A

[4] McOmie, *Ann. Reports*, 1948, **45**, 207.
[5] Holmberg, *Arkiv Kemi, Min., Geol.*, 1944, **17**, *A*, No. 23.
[6] Holmberg, " Svedberg Memorial Volume," Uppsala, 1944, p. 299.
[7] Elliott, *Nature*, 1948, **162**, 658; Kjaer, *Acta Chem. Scand.*, 1950, **4**, 1347; Crawhall and Elliott, *J.*, 1951, 2071; Kjaer, *Acta Chem. Scand.*, 1952, **6**, 1374; Jepson, Lawson, and Lawton, *J.*, 1955, 1791.
[8] Jensen and Miquel, *Acta Chem. Scand.*, 1952, **6**, 189.
[9] Lawson and Searle, *J.*, 1957, 1556.
[10] Holmberg, *Arkiv Kemi*, 1956, **9**, 47.
[11] Jensen, *Z. anorg. Chem.*, 1934, **219**, 243; 1934, **221**, 6, 11.
[12] Goerdeler and Fincke, *Chem. Ber.*, 1956, **89**, 1033.
[13] Thiele, *Annalen*, 1892, **270**, 1; Lieber and Smith, *J. Amer. Chem. Soc.*, 1937, **59**, 2283; *Chem. Rev.*, 1939, **25**, 213, 226.

by-product of this reaction is formulated, on the basis of its origin, composition, and molecular weight, as 3-anilino-5-phenyl-1,2,4-triazole (XVI), being formed (from V) by loss of hydrogen sulphide and cyclisation. This representation of the product, rather than the alternative 3-amino-4,5-diphenyl-1,2,4-triazole structure, is preferred on the assumption that an amino- rather than anilino-group is involved in the cyclisation. Like its prototype (II), 1-phenyl-3-(thiobenzamido)guanidine (V; R = Ph) was not cyclised to the 1,2,4-triazole by strong alkalis, from which it was recovered even after prolonged boiling. In acid media, on the other hand, cyclisation occurred rapidly and completely; in mineral acid it gave the expected 2-anilino-5-phenyl-1,3,4-thiadiazole (XV; R = Ph), whilst with acetic anhydride, eliminating aniline instead of ammonia, it yielded 2-acetamido-5-phenyl-1,3,4-thiadiazole (XII).

4-Phenyl-1-(thiobenzoyl)semicarbazide (VI), the oxygen analogue of the series, was readily produced in good yield, together with small quantities of 2,5-diphenyl-1,3,4-



Reagents: 1, Ph·CS·S·CH_2·CO_2H. 2, R′X. 3, HCl. 4, Ac_2O. 5, H_2O. 6, NaOH.

thiadiazole (IX) as by product, by the general reaction. The compound was unaffected by alkalis, in which it was soluble. In contrast with the reaction of (V), elimination of a basic component by acidic reagents from (VI) can occur in one way only; accordingly, both hydrochloric acid and acetic anhydride cyclised the semicarbazide (VI), with loss of aniline, to 2-hydroxy(or acetoxy)-5-phenyl-1,3,4-thiadiazole (XIII, XIV).

Thiobenzoylation of 4-phenyl(thiosemicarbazide) occurred in the normal way in good yield; the expected product (VII; R = Ph) could not be characterised, however, because it cyclised spontaneously (to XVII) when attempts were made to isolate it. Under the influence of mineral acid, ring-closure occurred nearly quantitatively, with elimination of hydrogen sulphide, and proceeded along two routes simultaneously to yield mixtures of 3-mercapto-4,5-diphenyl-1,2,4-triazole (XVII; R = Ph) and 2-anilino-5-phenyl-1,3,4-thiadiazole (XV; R = Ph), the former predominating. It is noteworthy that in this case the usual elimination of the basic component by action of the acidic cyclising agent, resulting in the formation of 2-mercapto-5-phenyl-1,3,4-thiadiazole (as from IV [9]) does not occur. The reaction thus resembles closely the ready cyclodehydration of 1-benzoyl-4-phenyl(thiosemicarbazide), which affords varying proportions of the same products (XV

and XVII), either on pyrolysis,[14] or on treatment with phosphoric acid,[15] acyl chlorides,[14-16] or alkalis.[17]

In common with their parent compounds [8] (II—IV), the aryl-substituted analogues (V—VII) gave deep-brown nickel complexes; the *S*-alkyl derivatives (VIII), however, failed to do so. This observation is accounted for adequately by Jensen and Miquel's general formulation [8] of thiobenzhydrazide-nickel complexes of this type.

(A) Ph·CS·NH·NH·CX·NHR Ph·NH·CS·NH·NH·CX·NHR (B)

2,5-Diphenyl-1,3,4-thiadiazole (IX), formed as a by-product in the thiobenzoylation of aminoguanidine (I) and 4-phenylsemicarbazide, arises directly by a side-reaction. Thus, in the former case, it cannot originate from intermediate *N*-(thiobenzamido)guanidine (II), either in the alkaline environment, or during its recrystallisation, since reaction (of II) with alkali proceeds differently (yielding III), while even prolonged action of boiling water is without effect. It is probable that small quantities of hydrazine, formed hydrolytically from aminoguanidine [13] or 4-phenylsemicarbazide [18] yield *NN'*-di(thiobenzoyl)hydrazine, and thence, with loss of hydrogen sulphide, the thiadiazole (IX). The production of significant proportions of 2,5-diphenyl-1,3,4-thiadiazole (IX) in the thiobenzoylation of hydrazine has been observed by Holmberg.[5]

A comparison of the behaviour of the two series of compounds (A) and (B) demonstrates the increased stability of the former structures (A; X = :NH, :O, :S) towards alkalis; they are, in general, unaffected under conditions which cyclise *N*-(thioureido)-guanidines (B; X = :NH),[1] -ureas (B; X = :O),[19] and thioureas (B; X = :S), [19,20] with elimination of hydrogen sulphide, to substituted 1,2,4-triazoles. The higher resistance in alkaline media to elimination of the thiobenzoyl-sulphur over that of a thioureido-group may be due to the greater acidity of the thiobenzoyl moiety, which is thus more effectively stabilised by alkali-salt formation. On the other hand, there emerges a general parallel behaviour of structures (A) and (B) in their ring-closure to substituted 1,3,4-thiadiazoles [20,21] in neutral and acid media.

Experimental

Light petroleum had b. p. 60—80°.

N-(*Thiobenzamido*)*guanidine*.—A solution of aminoguanidine sulphate monohydrate (13·2 g., 0·1 mole) in water (50 ml.) was treated, at room temperature, with 3N-sodium hydroxide (33·3 ml., 0·1 mole), followed immediately by a solution of (thiobenzoylthio)acetic acid (15·9 g., 0·075 mole) in N-sodium hydroxide (75 ml., 0·075 mole). The clear deep red liquid became orange, later pale yellow, and yellow crystals separated rapidly. After 24 hours' storage at room temperature, and 6 hours' at 0°, the product was collected (12 g.) and crystallised from boiling water (15 ml. per g., insoluble residue: R), yielding needles of N-(*thiobenzamido*)*guanidine hemihydrate*, m. p. 164—166° (decomp.) (10·9 g., 72%) (Found: C, 48·0, 47·8; H, 5·1, 5·2; N, 28·0; S, 15·2. $C_8H_{10}N_4S,\frac{1}{2}H_2O$ requires C, 47·3; H, 5·4; N, 27·6; S, 15·8%). The use of an excess of (thiobenzoylthio)acetic acid (1·1 or 1·25 mol.) gave 56 and 64% yields (based on aminoguanidine) respectively, while an excess of aminoguanidine (2 mol.) raised yields to 80% [based on (thiobenzoylthio)acetic acid].

A specimen of the material (2 g.), suspended in boiling ether (10 ml.), was dissolved by the addition of hot methanol (6 ml.). The solution, diluted with more ether (20 ml.), slowly deposited prisms, which on drying gave a white powder of the anhydrous substituted *guanidine*,

[14] Marckwald and Bott, *Ber.*, 1896, **29**, 2914; Dymek, *Ann. Univ. Mariae Curie-Sklodowska*, 1954, **9**, *AA*, 61.
[15] Hoggarth, *J.*, 1949, 1166.
[16] Pulvermacher, *Ber.*, 1894, **27**, 622.
[17] Fromm and Trnka, *Annalen*, 1925, **442**, 156; Sugii, *Yakugaku Zasshi*, 1958, **78**, 283.
[18] Curtius and Heidenreich, *Ber.*, 1894, **27**, 56; *J. prakt. Chem.*, 1895, **52**, 465.
[19] Arndt, Milde, and Tschenscher, *Ber.*, 1922, **55**, 341.
[20] Arndt and Milde, *Ber.*, 1921, **54**, 2089, 2101.
[21] Freund, *Ber.*, 1894, **27**, 1774; 1895, **28**, 946; Busch and Schmidt, *Ber.*, 1913, **46**, 2240; Busch and Lotz, *J. prakt. Chem.*, 1914, **90**, 257.

m. p. 180—182° (decomp.) (Found: C, 49·2; H, 5·0; N, 29·4; S, 16·8. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·15; N, 28·9; S, 16·5%). Jensen and Miquel [8] give m. p. 146—147°.

The compound was highly soluble in cold methanol, ethanol, and acetone, but sparingly soluble in boiling benzene, light petroleum, and ether. It dissolved in 2N-hydrochloric or acetic acid and in 2N-sodium hydroxide or ammonia. With alkaline sodium plumbite, it gave a white precipitate which remained unchanged on boiling.

The water-insoluble residue R (0·45—0·6 g.) consisted, after crystallisation from ethanol, of platelets of 2,5-diphenyl-1,3,4-thiadiazole, m. p. 138—140° (0·35 g., 4%) (Found: C, 70·6; H, 4·0; N, 11·7; S, 13·6. Calc. for $C_{14}H_{10}N_2S$: C, 70·6; H, 4·2; N, 11·8; S, 13·4%). Stolle [22] gives m. p. 141—142°.

N-(Thiobenzamido)guanidine hemihydrate was recovered almost quantitatively (on cooling) from its 5% aqueous solution which had been refluxed during 3 hr.

A solution of the hemihydrate (0·001 mole) in water (40 ml.) at 30° was treated with 0·05M-aqueous picric acid (0·001 mole). The yellow precipitate was dissolved in ethanol (10 ml.); the filtered solution deposited needles (0·05 g.) of 2-amino-5-phenyl-1,3,4-thiadiazole picrate, m. p. and mixed m. p. (see below) 256—258° (decomp.). The filtrate, on spontaneous evaporation to one-third bulk gave N-(*thiobenzamido*)*guanidine picrate*, m. p. 212—214° (decomp.), as an opaque orange powder (50%) (Found: C, 39·8; H, 2·9. $C_8H_{10}N_4S,C_6H_3N_3O_7$ requires C, 39·7; H, 3·1%).

N-(*Thiobenzamido*)*guanidine*.—S-*Ethyl derivative*. A solution of *N*-(thiobenzamido)guanidine hemihydrate (5·1 g., 0·025 mole) in ethanol (25 ml.)–ethyl bromide (13·6 g., 0·125 mole) was refluxed during 3 hr., another portion of ethyl bromide (0·125 mole) being added after 1·5 hr. The yellow liquid was concentrated *in vacuo* to small volume, and the remaining viscous liquid (approx. 15 ml.) diluted with water. The resulting clear liquid, on treatment with 3N-ammonia (10 ml.), gave an immediate precipitate of oil which solidified when stirred and kept. It was collected at 0°, dried, and crystallised from benzene containing 5% of methanol (50 ml.), and gave prisms (4·45 g., 80%) of the S-*ethyl derivative*, m. p. 142—144° [Found: C, 54·1; H, 6·3; N, 25·4; S, 14·8%; *M* (cryoscopically, in thymol), 220. $C_{10}H_{14}N_4S$ requires C, 54·05; H, 6·3; N, 25·2; S, 14·4%; *M*, 222].

The compound was highly soluble in methanol, ethanol, and acetone, soluble in boiling benzene and water, and sparingly soluble in light petroleum, cold benzene, and water. It evolved ethanethiol when boiled with 3N-hydrochloric acid. A 0·1M-aqueous solution of the *S*-derivative, refluxed during 2 hr., evolved only traces of ethanethiol, the compound being recovered almost quantitatively on cooling.

S-*Benzyl derivative*. A solution of *N*-(thiobenzamido)guanidine hemihydrate (2·03 g., 0·01 mole) in ethanol (10 ml.) was successively treated with benzyl chloride (1·9 g., 0·015 mole) and 3N-sodium hydroxide (3·3 ml., 0·01 mole). The clear liquid was kept at 60° during 30 min., concentrated to one-third bulk, and stirred into water (75 ml.). After 48 hours' storage, the precipitated oil had solidified and was collected. Crystallisation from chloroform–light petroleum (5 and 6 ml. per g.) gave platelets (2·0 g., 70%) of the S-*benzyl derivative*, m. p. 112—114° (Found: C, 63·7; H, 5·4; N, 19·7; S, 11·1. $C_{15}H_{16}N_4S$ requires C, 63·4; H, 5·6; N, 19·7; S, 11·3%). Alternatively, crystallisation from ethanol–light petroleum (b. p. 40—60°) (3 ml. each per g.) gave the white granular (2·65 g., 80%) *solvated derivative*, m. p. 132—134° (Found: C, 61·9; H, 5·9. $C_{15}H_{16}N_4S,C_2H_5{\cdot}OH$ requires C, 61·8; H, 6·7%). It evolved toluene-ω-thiol when boiled with 3N-hydrochloric acid or 3N-sodium hydroxide, followed by acidification.

N-(*Thiobenzamido*)*guanidine*.—(a) *Action of hydrochloric acid*. The reactant (hemihydrate; 1·02 g., 0·005 mole) was refluxed in 3N-hydrochloric acid (20 ml., 0·06 mole) during 15 min., the originally bright yellow solution becoming colourless within 1—2 min. The liquid was basified at room temperature, and the crystalline precipitate was collected at 0°, rinsed with a little water, and crystallised from acetone-ethanol (1 : 2), rectangular prisms of 2-amino-5-phenyl-1,3,4-thiadiazole, m. p. 222—224°, being obtained (total, 0·83 g., 93%) (Found: C, 54·7; H, 4·2; N, 24·2; S, 18·2. Calc. for $C_8H_7N_3S$: C, 54·2; H, 3·95; N, 23·7; S, 18·1%). Young and Eyre [23] give m. p. 222—223°. The picrate formed needles, m. p. 256—258° (decomp.) (from a large volume of ethanol) (Found: C, 41·3; H, 2·7. Calc. for $C_8H_7N_3S,C_6H_3N_3O_7$: C, 41·4; H, 2·5%). Lawson and Searle [9] give m. p. 268—271° (decomp.).

[22] Stolle, *Ber.*, 1899, **32**, 797; *J. prakt. Chem.*, 1904, **69**, 366.
[23] Young and Eyre, *J.*, 1901, **79**, 54.

(b) *Action of acetic anhydride.* A suspension of the reactant (0·005 mole) in acetic anhydride (10 ml.) was heated to boiling and gave a clear yellow liquid which became colourless and deposited a copious white crystalline precipitate almost immediately. Heating at 100° was continued during 1 hr., the suspension stirred into water, and the crystalline product collected at 0°. Crystallisation from boiling ethanol (200 ml.) gave silky needles (1·0 g., 91%) of 2-acetamido-5-phenyl-1,3,4-thiadiazole, m. p. 276—278° (Found: C, 54·8; H, 4·0. Calc. for $C_{10}H_9N_3OS$: C, 54·8; H, 4·1%). Young and Eyre [23] give m. p. 276°.

N-(*Thiobenzamido*)*urea.*—(*a*) This compound, prepared in 90% yield according to the method of Jensen and Miquel,[8] formed pale-yellow needles (from water) or plates, m. p. 160—162° (decomp.) (from ethanol–light petroleum) (Found: C, 49·6; H, 4·8. Calc. for $C_8H_9N_3OS$: C, 49·2; H, 4·6%). Jensen and Miquel [8] give m. p. 155°.

(*b*) *N*-(Thiobenzamido)guanidine hemihydrate (3·05 g., 0·015 mole) in 3N-sodium hydroxide (30 ml., 0·09 mole) was refluxed during 30 min., ammonia being slowly evolved. The filtered nearly colourless liquid was acidified (to Congo Red) with concentrated hydrochloric acid (10 ml.). A little hydrogen sulphide was evolved, the liquid became bright yellow, and yellow plates began to separate, and were collected after 12 hr. at 0°. Crystallisation from ethanol (12 ml. per g.) gave pale yellow leaflets (1·61 g., 55%) of *N*-(thiobenzamido)urea, m. p. and mixed m. p. (with product *a*) 161—162° (decomp.) [Found: C, 49·6; H, 4·7; N, 21·6; S, 16·3%; *M* (cryoscopically, in thymol), 190. Calc. for $C_8H_9N_3OS$: C, 49·2; H, 4·6; N, 21·5; S, 16·4%; *M*, 195].

(*c*) A solution of the urea (0·98 g., 0·005 mole) in water (25 ml.) was refluxed during 30 min., and then concentrated to one-third volume during 15 min. The crystals which had begun to separate during refluxing were collected at 0° (0·58 g., 65%) and consisted of 2-hydroxy-5-phenyl-1,3,4-thiadiazole, m. p. 146—148° (from chloroform–light petroleum) (Found: C, 53·8; H, 3·4. Calc. for $C_8H_6N_2OS$: C, 53·9; H, 3·4%). Lit.,[24] m. p. 146—148°.

N-(*Isopropylideneamino*)*guanidine.*—To the suspension obtained on introducing sodium (1·15 g., 0·05 g.-atom) into anhydrous acetone (50 ml.), finely powdered aminoguanidine sulphate monohydrate (6·6 g., 0·05 mole) was added, and the stirred suspension refluxed during 30 min. The acetone was distilled off in a vacuum, and the residue successively treated with water (25 ml.) [which dissolved all except a few oily droplets] and toluene-*p*-sulphonic acid monohydrate (9·5 g., 0·05 mole) in water (8 ml.). Crystallisation was facilitated by the addition of ethanol (5—10 ml.), and the product collected after 12 hr. at 0° (m. p. 168—170°, after sintering at 164°; 9·3 g., 65%). Crystallisation from ethanol (6 ml. per g., removal of traces of inorganic material under suction; recovery 85%) gave plates of N-(*isopropylideneamino*)*guanidine toluene*-p-*sulphonate*, m. p. 172—174° (decomp.) (Found: C, 46·3; H, 6·2; N, 16·2; S, 10·9. $C_4H_{10}N_4,C_7H_8O_3S$ requires C, 46·15; H, 6·3; N, 16·8; S, 11·2%). Addition of an equimolar quantity of 0·05M-aqueous picric acid to an aliquot portion of the original solution gave an orange-yellow precipitate (85%) of the picrate, m. p. 203—206° (decomp.) [from ethanol–water (10 : 1)] (Found: C, 34·8; H, 3·6. Calc. for $C_4H_{10}N_4,C_6H_3N_3O_7$: C, 35·0; H, 3·8%). Finnegan, Henry, and Smith [25] give m. p. 205·5—206·5°.

Attempted thiobenzoylation of the toluene-*p*-sulphonate under the usual conditions gave a deep red solution, from which (thiobenzoylthio)acetic acid was recovered (90%) after 24 hr. at room temperature.

Aromatic Analogues

1-Amino-3-phenylguanidine was prepared by the following modification of the method of Finnegan, Henry, and Lieber.[26] To a solution of *S*-methyl-*N*-phenylthiouronium iodide (29·4 g., 0·1 mole) in water (50 ml.), aqueous 10% hydrazine hydrate (50 ml., 0·1 mole) was added at room temperature, and the resulting two-phase system was stirred during 6 hr. A clear solution was gradually formed, while methanethiol was evolved. The liquid was treated, at 50°, with a solution of silver nitrate (17·0 g., 0·1 mole) in water (30 ml.), any slight excess of silver ions then being removed by dropwise addition of 3N-hydrochloric acid. The silver

[24] Fujii, Yoshikawa, and Yuasa, *J. Pharm. Soc. Japan*, 1954, **74**, 1056; Sato and Ohta, *J. Pharm. Soc. Japan*, 1955, **75**, 1535.
[25] Finnegan, Henry, and Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 2981.
[26] Finnegan, Henry, and Lieber, *J. Org. Chem.*, 1953, **18**, 779; Kirsten and Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 800.

iodide was filtered off and twice extracted with boiling water (2 × 20 ml.). The combined filtrates were evaporated in a vacuum to approx. 25 ml.; they deposited massive prisms, which were collected at 0° and rinsed with a little ice-water and finally ether [m. p. 119—122° (decomp.), 14·9—16 g., 70—75%]. Crystallisation from ethanol (2 ml. per g.) gave nearly colourless prisms of 1-amino-3-phenylguanidine nitrate, m. p. 120—122° (decomp.) (recovery 90—96%). Finnegan *et al.*[26] give m. p. 121—122°. Interaction of the reactants at 100° resulted in considerable resinification, darkening, and diminished yields.

1-*Amino*-3-p-*tolylguanidine*.—A solution of *S*-methyl-*N*-*p*-tolylthiouronium iodide (15·4 g., 0·05 mole) in water (25 ml.), treated with aqueous 10% hydrazine hydrate (25 ml., 0·05 mole), was stirred at room temperature, until all the methanethiol had volatilised (15 hr.). Treatment with silver nitrate (0·05 mole) as above gave eventually a yellow syrup (approx. 15 ml.) which deposited massive crystals (m. p. 90—94°; 2·3 g., 20%) on prolonged storage at 0° (filtrate: P). Crystallisation from ethanol–ether (10 and 50 ml. per g.) gave prisms of 1-*amino* 3-p-*tolylguanidine nitrate*, m. p. 91—93° (decomp.) (Found: C, 42·35, H, 5·8; N, 31·3. $C_8H_{12}N_4,HNO_3$ requires C, 42·3; H, 5·7; N, 30·8%). Filtrate P (together with the ethanol–ether washing liquids) failed to deposit more product on evaporation and storage. The remaining syrup was dissolved in warm ethanol (10 ml.) and treated with a hot solution of picric acid (9·2 g., 0·04 mole) in ethanol (35 ml.). The product, collected at 0° (10·2 g., 52%), crystallised from ethanol (50 ml. per g.) to yield needles of the *picrate*, m. p. 162—164° (decomp.) (Found: C, 43·1; H, 3·8. $C_8H_{12}N_4,C_6H_3N_3O_7$ requires C, 42·75; H, 3·8%).

1-*Phenyl*-3-(*thiobenzamido*)*guanidine and* 3-*Anilino*-5-*phenyl*-1,2,4-*triazole*.—Solutions of 1-amino-3-phenylguanidine nitrate (6·4 g., 0·03 mole) in water (360 ml.) and 3N-sodium hydroxide (15 ml., 0·045 mole), and of (thiobenzoylthio)acetic acid (6·35 g., 0·03 mole) in water (360 ml.) and 3N-sodium hydroxide (15 ml., 0·045 mole) were mixed and set aside at room temperature during 24 hr. The clear orange-red liquid became turbid suddenly after a few minutes, and a bright yellow granular solid separated gradually. This was collected at 0°, rinsed with water (filtrate G), and carefully air-dried at room temperature (to avoid its conversion into a soft resin) (7—8 g.). The product was dissolved in boiling ethanol (25 ml.), and the filtered liquid gradually diluted with light petroleum (total, 20 ml.). It slowly deposited a crust of yellow crystals (m. p. 171—173°; 2·8—3·6 g., 35—45%) (filtrate F), which gave, after further crystallisation from ethanol–light petroleum (10 and 8 ml. respectively, per g.), pale-yellow granular 1-*phenyl*-3-(*thiobenzamido*)*guanidine*, m. p. 170—172° (decomp.) (Found: C, 62·3; H, 4·6; N, 21·2, 20·3; S, 12·0, 11·5. $C_{14}H_{14}N_4S$ requires C, 62·2; H, 5·2; N, 20·7; S, 11·85%). The product was soluble in sodium hydroxide and reprecipitated by acetic acid.

Filtrate F, on spontaneous evaporation, in two stages (the second with addition of acetone), gave large prisms (0·85—1·05 g., 12—15%). They crystallised from acetone (60 ml. per g., followed by partial evaporation) and afforded prisms of 3-*anilino*-5-*phenyl*-1,2,4-*triazole*, m. p. 220—222° [Found: C, 71·1; H, 5·2; N, 23·9%; *M* (cryoscopically in thymol), 225. $C_{14}H_{12}N_4$ requires C, 71·2; H, 5·1; N, 23·7%; *M*, 236], highly soluble in ethanol–acetone.

The aqueous alkaline filtrate G, on slow spontaneous evaporation to small volume, deposited white solid. Crystallisation from acetone as above gave 3-anilino-5-phenyl-1,2,4-triazole, m. p. 220—222° (0·6 g., 8%).

The *triazole picrate*, obtained quantitatively in ethanol, formed prisms, m. p. 268—270° (decomp.) (from a large volume of ethanol) (Found: C, 52·2; H, 2·8. $C_{14}H_{12}N_4,C_6H_3N_3O_7$ requires C, 51·6; H, 3·2%). The *diacetyl derivative*, obtained nearly quantitatively on refluxing a solution of the triazole (0·002 mole) in acetic anhydride (8 ml.) during 30 min. and stirring the liquid into water, formed prisms, m. p. 200—202° (from acetone–ethanol) (Found: C, 68·1; H, 5·05; N, 17·45. $C_{18}H_{16}N_4O_2$ requires C, 67·5; H, 5·0; N, 17·5%).

When the thiobenzoylation was performed in more concentrated solution, or at higher temperatures, the crude product separated as a yellow sticky resin that crystallised with greater difficulty and was obtained in diminished yield.

1-*Thiobenzamido*-3-p-*tolylguanidine*.—1-Amino-3-*p*-tolylguanidine nitrate (1·135 g., 0·005 mole) was thiobenzoylated as described in the foregoing example. The crude resinous product was ground with water, filtered, dried at room temperature (1·2 g.), and dissolved in ethanol (6 ml.), and the filtered orange solution was diluted with light petroleum (6 ml.). On prolonged storage and partial evaporation the liquid set to a crystalline mass: the collected solid gave, on crystallisation from ethanol–light petroleum (1 : 1 mixture of materials of b. p. 60—80° and 40—60°), white needles (0·54 g., 38%), of 1-*thiobenzamido*-3-p-*tolylguanidine*, m. p. 174—176°

(decomp.) (Found: C, 62·9; H, 5·8; N, 19·8; S, 11·6. $C_{15}H_{16}N_4S$ requires C, 63·4; H, 5·6; N, 19·7; S, 11·3%).

1-*Phenyl*-3-(*thiobenzamido*)*guanidine*.—(a) *Action of hydrochloric acid.* A solution of the reactant (0·54 g., 0·002 mole) in 3N hydrochloric acid (25 ml.) was refluxed during 10 min. and the resulting liquid, containing a trace of semisolid globules, basified with 3N-sodium hydroxide. The resulting crystalline precipitate (0·48 g.) was collected at 0° and formed prismatic needles (total, 0·4 g., 79%) of 2-anilino-5-phenyl-1,3,4-thiadiazole, m. p. 198—200° (from acetone–ethanol) (Found: C, 66·2; H, 4·2. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·35%). Young and Eyre [23] give m. p. 199—200°. The *picrate*, precipitated (90%) when hot saturated ethanolic solutions of the components were mixed, formed prisms, m. p. 202—204° (decomp.) (from a large volume of ethanol) (Found: C, 50·15; H, 3·1. $C_{14}H_{11}N_3S,C_6H_3N_3O_7$ requires C, 49·8; H, 2·9%).

(b) *Action of acetic anhydride.* A solution of the reactant (0·002 mole) in acetic anhydride (8 ml.) was refluxed during 30 min. and then stirred into warm water (50 ml.). The resulting solidified white product (0·42 g.), recrystallised from a large volume of ethanol, yielded needles (0·33 g., 75%) of 2-acetamido-5-phenyl-1,3,4-thiadiazole, m. p. and mixed m. p. (see above) 276—278°.

(c) *Alkali.* The reactant was recovered almost quantitatively after 20 minutes' refluxing in 3N-sodium hydroxide (10% solution).

4-*Phenyl*-1-(*thiobenzoyl*)*semicarbazide*.—(a) *Preparation.* To a stirred solution of (thiobenzoylthio)acetic acid (7·0 g., 0·033 mole) in 0·75N-sodium hydroxide (110 ml., 0·083 mole) at 40°, freshly crystallised, finely powdered 4-phenylsemicarbazide (7·55 g., 0·05 mole) was added; it dissolved rapidly. At room temperature the liquid gradually deposited a granular precipitate, which was collected after 4 hr. (solid S). The filtrate was acidified with 3N-hydrochloric acid (to Congo Red), and gave a copious precipitate, which was collected at 0°, rinsed with water, dried (7 g.), and crystallised from ethanol (40 ml. per g.), platelets of 4-*phenyl*-1-(*thiobenzoyl*)*semicarbazide*, m. p. 188—190° (decomp.), being obtained (5·8—6·7 g., 65—75%) (Found: C, 62·1; H, 5·1; N, 15·6; S, 11·4. $C_{14}H_{13}N_3OS$ requires C, 62·0; H, 4·8; N, 15·5; S, 11·8%).

Solid S (0·6—0·8 g., 15—20%) consisted, after crystallisation from ethanol, of 2,5-diphenyl-1,3,4-thiadiazole, m. p. and mixed m. p. 138—140° (Found: C, 70·3; H, 4·1. Calc. for $C_{14}H_{10}N_2S$: C, 70·6; H, 4·2%).

(b) *Action of hydrochloric acid.* A refluxing solution of the reactant (1·36 g., 0·005 mole) in ethanol (40 ml.) and concentrated hydrochloric acid (8 ml.), which was initially yellow, was decolorised during 3—5 min. Boiling was continued during 15 min., and the liquid then evaporated in a vacuum to small volume (10 ml.) and diluted with water (15 ml.). The crystalline precipitate (0·85 g., 95%) was collected at 0° (filtrate F) and consisted, after crystallisation, of 2-hydroxy 5-phenyl-1,3,4-thiadiazole, m. p. and mixed m. p. (see above) 146—148° (from chloroform–light petroleum).

Filtrate F, treated with 40% aqueous sodium hydroxide (40 ml.) and shaken with benzoyl chloride (5 ml.), gave benzanilide contaminated with ethyl benzoate. The products, isolated by extraction with ether, were separated by removing the solvent and treating the residual mixture with light petroleum (15 ml.). The crystalline solid (0·84 g., 85%) was benzanilide, m. p. and mixed m. p. 162—163° (from ethanol).

(c) *Action of acetic anhydride.* A solution of the reactant (0·005 mole) in acetic anhydride (10 ml.) was refluxed during 20 min. (rapid colour change from deep orange to pale yellow). The solid (m. p. 110—118°; 0·93 g., 85%) obtained on stirring the liquid into warm water (40 ml.), crystallised from ethanol–water (5 : 1), giving 2-acetoxy-5-phenyl-1,3,4-thiadiazole, plates, m. p. 117—119° (Found: C, 54·5; H, 3·5. Calc. for $C_{10}H_8N_2O_2S$: C, 54·5; H, 3·6%). Lawson and Searle [9] give m. p. 117—119°.

(d) *Alkali.* The reactant was recovered almost quantitatively after 20 min. in refluxing 3N-sodium hydroxide (10% solution).

Thiobenzoylation of 4-*Phenyl*-3-*thiosemicarbazide*.—(*a*) The reactant (3·35 g., 0·02 mole), dissolved in water (60 ml.) and 3N-sodium hydroxide (13·3 ml., 0·04 mole) at 40°, was treated with (thiobenzoylthio)acetic acid (4·24 g., 0·02 mole), dissolved in 0·5N-sodium hydroxide (40 ml., 0·02 mole), at the same temperature. The orange liquid was kept at 35° during 0·5 hr., at room temperature during 1 hr., and at 0° during 3 hr.; the whole was then filled with opaque white needles. They were collected at the pump and successively washed with very little ice-water, ethanol–ether, and ether (filtrates: S). The solid (4—5 g.) gave, on crystallisation

from ethanol–ether (10 and 5 ml. per g.), white needles of *sodium 3-mercapto-4,5-diphenyl-1,2,4-triazole trihydrate*, m. p. 151—154° (decomp.) (3·85—4·2 g., 58—64%) (Found: C, 50·8; H, 4·8; N, 12·35; S, 9·5. $C_{14}H_{10}N_3SNa,3H_2O$ requires C, 51·1; H, 4·9; N, 12·8; S, 9·7%). Spontaneous evaporation of the alkaline filtrates S and washing liquids at room temperature (to approx. 50 ml.) resulted once again in a crystalline mass, from which more sodium salt was isolated (up to 1·05 g., 16%). The salt dissolved in water with a strongly alkaline reaction.

(*b*) The solution obtained in the thiobenzoylation [as described in (*a*)] was slowly treated with concentrated hydrochloric acid (30 ml., 0·30 mole). The suspension, which evolved hydrogen sulphide copiously, was boiled during 10 min. and the resulting granular white product collected at 0°. The dried product (5 g.) was dissolved in acetone–ethanol (1 : 1; 300 ml.), and successive crops of solid were obtained by evaporating the liquid in stages. The combined first crops (m. p. 275—282°; 2·5—3·3 g., 50—65%) gave, on crystallisation from acetone–ethanol, needles of 3-mercapto-4,5-diphenyl-1,2,4-triazole, m. p. 280—282° (Found: C, 66·9; H, 4·45; N, 16·65; S, 12·6. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·4; N, 16·6; S, 12·65%); Hoggarth [15] gives m. p. 282°. Dissolution of the thiophenol in an equivalent of 0·5N-sodium hydroxide gave the sodium salt trihydrate, m. p. and mixed m. p. 150—152° (decomp.), almost quantitatively.

The final crops (m. p. 190—195°; 1·0—1·8 g., 20—35%) gave, on further crystallisation from acetone–ethanol, pale yellow needles of 2-anilino-5-phenyl-1,3,4-thiadiazole, m. p. and mixed m. p. (see above) 196—198° (Found: C, 66·1; H, 4·6; N, 16·3; S, 12·35. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·4; N, 16·6; S, 12·65%).

Nickel Complexes.—An approximately 5% solution of the compound in ethanol was treated dropwise with 5% nickel chloride in 0·3N-hydrochloric acid. The following gave deep-brown solutions: V (R = Ph; *p*-MeC_6H_4); VI (R = Ph). The following did not react: VIII (R′ = Et, $Ph{\cdot}CH_2$).

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