Heterocyclic Compounds from Urea Derivatives. Part XVIII.[1] Adducts from Aminoguanidines and Aroyl Isothiocyanates and Their Cyclisation

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Equimolar quantities of aroyl isothiocyanates and aminoguanidine hydrochloride react additively in aqueous methanol affording excellent yields of 1-amidino-4-aroyl(thiosemicarbazides), isolable as hydrochlorides, picrates, or free bases. 1-Amidino-4-benzoyl(thiosemicarbazide) hydrochloride is cyclised by hydrochloric or *ortho*phosphoric acid to 2-amino-5-benzamido-1,3,4-thiadiazole, by acetic anhydride to the corresponding acetyl derivative, and by alkali to 3-mercapto-5-phenyl-1,2,4-triazole. 1-Amino-2-phenylguanidine salts undergo an analogous series of reactions. The mechanism of these addition–cyclisations is discussed and correlated with those of comparable reactions.

AMINOGUANIDINE reacts with heterocumulenes such as isocyanate [2] and isothiocyanate esters [2] or carbodiimides [3,4] to yield addition compounds, the cyclisation of which is a versatile general route to triazoles and thiadiazoles.[5] With isothiocyanates, aminoguanidine reacts preferentially at its hydrazino-group, yielding 4-substituted 1-amidinothiosemicarbazides, but addition occurs at its amidino-group when the hydrazino-group is suitably blocked.[4,6]

Although benzoyl isothiocyanate has been known for many years,[7] aroyl isothiocyanates have been used only recently to any extent in addition reactions. Examples include a synthesis of arylthioureas by the aminolysis of benzoyl isothiocyanate, followed by debenzoylation of the intermediate *N*-benzoyl-*N'*-arylthioureas,[8] and Elmore's studies [9] of the addition of benzoyl isothiocyanate to amino-acids, aiming at the stepwise degradation of peptides from the *N*-terminus.

With hydrazine and its derivatives, aroyl isothiocyanates yield adducts which are generally cyclisable to give heterocyclic products. Compounds that have been studied from this point of view include hydrazine,[10] phenylhydrazine,[11] alkylhydrazines [12] and their hydrazones,[13] ethoxycarbonylhydrazine,[14] and thiosemicarbazide [15] and its oxygen analogue.[16] We have now examined the synthesis and ring closure of adducts derived from aroyl isothiocyanates and aminoguanidines or diaminoguanidines.

Equimolar quantities of aroyl isothiocyanates (I) and aminoguanidine (II) hydrochloride reacted additively in aqueous methanol at room temperature affording excellent yields of 1-amidino-4-aroyl(thiosemicarbazides) (III; R = Ph, *p*-C_6H_4Cl, or *p*-C_6H_4·OMe). Their failure to give ketonic derivatives, and the results of their cyclisation (see later) exclude the alternative formulation [as (IIIa)]. As in comparable reactions of aminoguanidine,[4,6] the present addition occurs at the more reactive hydrazino-group, and proceeds so readily that several possible side reactions do not occur to any significant extent. Varying small proportions of the aroyl isothiocyanates (I) were lost as thiocarbamate esters (V), being added to the methanol present as solvent.[7] The evolution of a little hydrogen sulphide from the reaction mixture, even at room temperature, suggests that the adducts (III), once formed, tend to cyclise, presumably to the triazoles (IV), but the amounts so formed were too small to be isolated.

The adducts (III) were prepared advantageously as salts, such as hydrochlorides (72—90%); the bases (III) were sufficiently stable to be isolated, but were obtained in yields lower than those of their highly crystalline salts. 1-Amidino-4-benzoyl(thiosemicarbazide) (III; R = Ph), for example, was directly accessible in 55% yield when the addition reaction was performed in dimethylformamide; alternatively it was liberated, though not without appreciable loss, from the purified hydrochloride.

1-Amino-2-phenylguanidine (XIII; R' = Ph) and aroyl isothiocyanates reacted analogously in methanol, producing excellent yields of 4-aroyl-1-phenylamidino-(thiosemicarbazides) (XIV; R = Ph, *p*-C_6H_4Cl, or *p*-C_6H_4·OMe, R' = Ph), which were also isolable as salts.

Like most substituted thiosemicarbazides,[17–19] the adducts (III) and (XIV) thus obtained were cyclisable

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to 1,2,4-triazoles in alkaline, and to 1,3,4-thiadiazoles in acid media.

Caustic alkali converted 1-amidino-4-benzoyl(thiosemicarbazide) (III; R = Ph) into 3-mercapto-5-phenyl-1,2,4-triazole (VII; R = Ph). The reaction is visualised to involve the formation, by loss of water, of the intermediate 1-amidinotriazole (VI), and hydrolytic removal of its 1-substituent in the strongly alkaline medium. Analogues of the postulated intermediates, such as (XXI)[3] and, more particularly, (XXII)[14] have been isolated in related reactions. Furthermore, 4-aroyl-1-phenylamidino(thiosemicarbazides) (XIV; R = Ph or *p*-C_6H_4Cl, R′ = Ph) were also converted into 5-aryl-3-mercapto-1,2,4-triazoles (VII; R = Ph, *p*-C_6H_4Cl; 80—90%) by alkali; here, the removal of the 1-phenylamidino-substituent from the intermediates (XV; R = Ph or *p*-C_6H_4Cl, R′ = Ph) must result in the same products (VII).

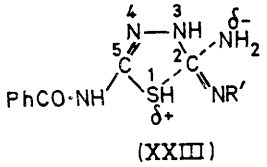
The cyclisation of the adducts (III) in acidic media proceeded with loss of ammonia, giving principally 2-amino-5-benzamido-1,3,4-thiadiazole (IX; R = Ph). Thus, the action of boiling 3N-hydrochloric acid on 1-amidino-4-benzoyl(thiosemicarbazide) hydrochloride (III; R = Ph) gave the heterocyclic hydrochloride (IX; R = Ph); owing to incompleteness of the reaction, and the probable occurrence of side-reactions (indicated, for example, by the evolution of hydrogen sulphide), yields were only moderate (40—45%). Orthophosphoric acid effected the cyclisation in improved yields (55%), as did boiling acetic anhydride, which gave the corresponding acetyl derivative (65%), formulated as 2-acetamido-5-benzamido-1,3,4-thiadiazole (X; R = Ph, R″ = Me).

The analogous cyclisation of 4-benzoyl-1-phenylamidino(thiosemicarbazide) (XIV; R = R′ = Ph) can proceed with loss of either ammonia or aniline from the phenylamidino-group, giving 2-anilino- or 2-amino-5-benzamido-1,3,4-thiadiazole (XVIII or IX; R = R′ = Ph), respectively. Boiling 3N-hydrochloric acid chiefly gave the former (XVIII). The cyclisation proceeded relatively slowly, affording 35—45% of the heterocyclic product after 1 hr. together with 20% of starting material. The same reaction took place in orthophosphoric acid at 120—140°. In acetic anhydride at 100° cyclisation occurred by both reaction paths, giving the monoacetyl derivatives of 5-amino- and 5-anilino-2-benzamido-1,3,4-thiadiazole (X and XIX; R = R′ = Ph, R″ = Me) (25 and 55% respectively). The cyclisation of the adduct by orthophosphoric acid or acetic anhydride required the use of its toluene-*p*-sulphonate rather than the nitrate, since these reagents

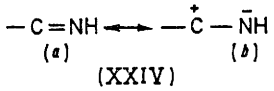
liberated nitrous fumes from the latter salt, resulting in its extensive resinification and destruction.

The interaction of 1-amino-2-phenylguanidine (nitrate) (XIII; R′ = Ph) and aroyl isothiocyanates (I) in dimethylformamide at 100° resulted in addition and cyclisation simultaneously, affording 2-anilino-5-aroylamido-1,3,4-thiadiazoles (XVIII; R = Ph, *p*-C_6H_4OMe, or *p*-C_6H_4Cl, R′ = Ph) directly in good yields; the same cyclisation occurred on heating the isolated adduct [*e.g.* (XIV; R = R′ = Ph; nitrate)] in dimethylformamide. In contrast, the condensation employing aminoguanidine (hydrochloride) (II) under the same conditions terminated with the formation of the open-chain adducts (III). The reason for this difference in the behaviour of the adducts (III) *vs.* (XIV) is therefore attributed to their only structural difference, *i.e.* to the effect of the phenyl group (R′) in (XIV).

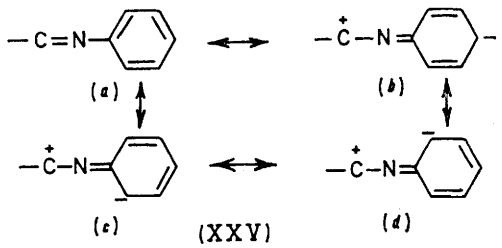
If the ring-closure is visualised to proceed by the intramolecular nucleophilic attack by the mercapto-sulphur atom on the amidino-carbon atom [of (III) or (XIV)] involving a transition complex of type (XXIII), this process will be favoured by an increase in the electrophilic character of the carbon atom C-2 in (XXIII).



(XXIII)

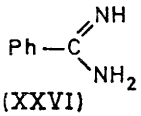


(XXIV)

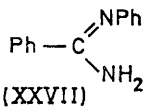


(XXV)

That this increase, leading to cyclisation, is brought about by the presence of the phenyl group in the amidino-group of the molecule (XIV) may be argued as follows. The imino- (XXIV) and substituted imino-groups (XXV) may be regarded, like keto-groups, as resonance hybrids, with contributions from the neutral (*a*) and dipolar canonical structures (*b*—*d*). The electrophilic character of the imino-carbon atom will be enhanced in proportion to the magnitude of the dipolar contribution. The dipolar nature of the overall resonance structure is likely to be more pronounced in the phenylimino- than in the imino-group, dipolar contributions to the former being stabilised by the delocalisation of the negative charge over the aromatic nucleus. The resulting increased electrophilicity of the imino-carbon atom [in (XIV)], and hence its greater susceptibility towards nucleophilic attack favouring cyclisation thus accounts for the observed results.



(XXVI)



(XXVII)

This interpretation, being based on the electron-withdrawing effect of the phenyl group in the particular environment, receives support from the fact that benzamidine (XXVI) (pK_a 11·2) [20] is a stronger base than *N*-phenylbenzamidine (XXVII) (pK_a 8·2).[21] Since protonation of these amidines occurs at their imino-nitrogen atoms,[22] their basicity depends on the electron availability at this site; this will be lower in the phenylimino- [of (XXVII)] than the imino-group [of (XXVI)], for the reasons already given, *i.e.* electron delocalisation over the aromatic nucleus.

Benzamido-1,3,4-thiadiazoles have previously been prepared by the ring closure of acylbithioureas [15,23,24] or by acylation of the appropriate aminothiadiazoles [25,26] in aqueous alkali. In the present work, authentic benzamidothiadiazoles, (IX), (XII), XVIII), and (XIX), required for comparison with the cyclisation products were synthesised from the pre-formed heterocyclic system. The action of benzoyl chloride (1 or 2 mol.) in pyridine readily converted 2,5-diamino-1,3,4-thiadiazole (XI) [25,27,28] into 2-amino-5-benzamido- (IX; R = Ph) or 2,5-dibenzamido-1,3,4-thiadiazole (XII; R = Ph), respectively. Mono- or di-benzoylation of the 5-anilino-analogue (XVII; R′ = Ph) [2b] similarly gave 2-anilino-5-benzamido-1,3,4-thiadiazole (XVIII; R = R′ = Ph), or a dibenzoyl derivative formulated as 2-benzamido-5-(*N*-phenylbenzamido)-1,3,4-thiadiazole (XIX; R = R′ = R″ = Ph). Under the usual conditions, acylation of (XI) or (XVII) appears to terminate at the diacyl stage: thus, treatment of 2,5-diamino-1,3,4-thiadiazole (XI) with a large excess of benzoyl chloride gave again the 2,5-dibenzamido-compound (XII; R = Ph), while further acetylation of the monobenzoyl derivatives (IX) and (XVIII) introduced only one acetyl residue.

The mono acetylated 2-amino- and 2-anilino-5-benzamido-1,3,4-thiadiazoles were identical with the products obtained by cyclising 4-benzoyl-1-(phenyl)-amidino(thiosemicarbazides) (III and XIV; R = R′ = Ph) with acetic anhydride and are formulated as (X; R = Ph, R″ = Me) and (XIX; R = R′ = Ph, R″ = Me), respectively. These structures, rather than isomeric ring *N*-acetyl structures, are supported by the spectroscopic evidence: their observed i.r. peaks in the 1660—1680 $cm.^{-1}$ range are assigned to the carbonyl

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stretching frequency of exocyclic amido-carbonyl rather than ring *N*-acetyl groups, the latter being known to give rise to bands at higher frequencies (1745 ± 35 cm.$^{-1}$) in comparable heterocyclic systems.[29] The compounds were rapidly deacetylated, but not debenzoylated by alkali, the original benzamido-compounds being recovered in excellent yields. Indeed, the benzamidothiadiazoles were markedly resistant to alkaline hydrolysis: 2-amino-5-benzamido-1,3,4-thiadiazole (IX) was recovered (80%) after prolonged refluxing in 2N-sodium hydroxide, 2,5-dibenzamido-1,3,4-thiadiazole (XII) slowly lost one of its benzoyl groups (*ca.* 10% after 1 hr.), and 2-anilino-5-benzamido-1,3,4-thiadiazole (XVIII) was substantially unaffected (75%). The cause of the stability to alkali of benzamido-groups in this structural environment is not clear, but attention may be drawn to the anomalous resistance to alkaline hydrolysis of certain adducts of benzoyl isothiocyanate with secondary amines (*i.e.* PhCONH·CS·NR_2; *e.g.* R = Me or Et), which renders them unsuitable as intermediates in an otherwise general synthesis of substituted thioureas.[8]

Before the products of the acid cyclisation had been identified as benzamidothiadiazoles (IX), (XII), and (XVIII), their true nature had been obscured by their solubility in alkali, and by their resistance to debenzoylation, which prompted the consideration of alternative formulations. The possible isomeric 1,3,4,6-oxatriazepine structure (XX), examples of which have recently been described[13] as products of the interaction of benzoyl isothiocyanate and 1-alkyl-2-isopropylidenehydrazines, was disposed of by the synthetic evidence.

The i.r. spectra of the compounds now described showed absorption peaks that were in general readily correlated[30,31] with their structural features (*cf.* Experimental section). The stretching frequency of the thiocarbonyl group, though uncertain, has been assigned[32,33] to the 1150 ± 70 cm.$^{-1}$ range, but the band may disappear when 'mixing' between the thiocarbonyl stretching motion and other vibrations of very similar frequencies occurs, *e.g.* in spectra of primary thioamides and thioureides.[34,35] Both these observations were made in the present series of compounds. Thus, each of the 4-aroyl-1-(aryl)amidino(thiosemicarbazides) (III and XIV; R = Ph, *p*-C_6H_4·OMe, or *p*-C_6H_4Cl, R′ = Ph) gave rise to a strong band at 1175 ± 10 cm.$^{-1}$, which is regarded as a thiocarbonyl stretching frequency. The high-intensity peak at 1210 cm.$^{-1}$ in the spectrum of methyl N-(*p*-chlorobenzoyl)thiocarbamate (V; R = *p*-C_6H_4Cl) is attributed to the same origin. Hydrazodi(thioformamide) (H_2N·CS·NH·NH·CS·NH_2), on the other hand, lacked the absorption band in this region.

EXPERIMENTAL

Light petroleum had b.p. 60—80°. Dimethylformamide was redistilled, and the water-containing fore-run was rejected. Pyridine was the pure anhydrous grade.

U.v. absorption measurements were made with a Unicam SP 800A spectrophotometer for ethanolic 0·00005M-solutions. I.r. spectra were determined with a Unicam SP 200 instrument, by use of discs containing the compound (1 mg.) in potassium bromide (400 mg.).

Aminoguanidine

1-*Amidino-4-benzoyl(thiosemicarbazide)*.—(a) *Hydrochloride*. A stirred solution of aminoguanidine hydrochloride (2·43 g., 0·022 mole) in methanol–water (6 : 1; 14 ml.) at room temperature was treated with benzoyl isothiocyanate (3·26 g., 0·02 mole) during 5 min., set aside at room temperature for 2—4 hr. (odour of hydrogen sulphide), then diluted with ether (25 ml.) and stored at 0° (crude: m.p. 185—189°; 4·65 g., 85%). Crystallisation from (cold) methanol–ether (10 ml. each per g.) or acetone–methanol–ether gave 1-*amidino-4-benzoyl(thiosemicarbazide) hydrochloride*, m.p. 189—192° (decomp.), as a white opaque powder (Found: C, 39·4; H, 4·6; Cl, 12·9; N, 26·2; S, 11·8. $C_9H_{11}N_5OS$,HCl requires C, 39·5; H, 4·4; Cl, 13·0; N, 25·6; S, 11·7%), $\lambda_{min.}$ 218 mμ (log ε 3·94), $\lambda_{max.}$ 242 (4·26), $\lambda_{min.}$ 261 (4·02), $\lambda_{max.}$ (shallow) 280 (4·12), $\nu_{max.}$ 3360s, 3130s, and 1560m (NH), 2960s and 2860s (shoulders, NH^+), 1670s (amide CO), 1630ms (C=N?), 1600m and 715s (Ph), 1170s (C=S), 1520s, 1490s, 1255ms, 1070ms, and 800s cm.$^{-1}$.

(b) *Base*. Aminoguanidine hydrochloride (2·43 g., 0·022 mole) was dissolved in dimethylformamide (18 ml.) with heating; the solution was allowed to cool to 60°, treated with benzoyl isothiocyanate (3·26 g., 0·02 mole), and kept at 100° during 2 hr. Most of the dimethylformamide was removed in a vacuum, and the residual viscous liquid was stirred and ground with 3N-ammonia (25 ml.). The product was collected at 0° (2·60 g., 55%). Its solution in a little ethanol slowly deposited prisms of 1-*amidino-4-benzoyl(thiosemicarbazide)*, m.p. 183—186° (decomp., rate-dependent, due to pyrolytic cyclisation) (Found: C, 45·4; H, 4·6; N, 30·1; S, 13·4. $C_9H_{11}N_5OS$ requires C, 45·6; H, 4·6; N, 29·5; S, 13·5%), $\lambda_{min.}$ 218 mμ (log ε 4·10), $\lambda_{max.}$ 252 (4·31), plateau 290—305 (3·90), $\nu_{max.}$ 3440s, 3170s, and 1550s (NH), 1660s (amide CO), 1650s (NH_2?), 1605ms, 1500ms, and 700ms (Ph), 1190s (C=S), 1485ms, 1360ms, 805ms, and 780ms cm.$^{-1}$.

Alternatively, a suspension of the hydrochloride (2·75 g., 0·01 mole) in water (15 ml.) was treated with 3N-ammonia (10 ml.) in one portion. The resulting soft resinous mass resolidified rapidly, was collected, and was dropped into boiling ethanol (10 ml.). It dissolved instantly, giving prisms (1·2 g., 51%) of the base, m.p. 183—186°, on cooling.

(c) *Picrate*. The *picrate*, obtained (80%) in ethanol, formed needles, m.p. 208—210° (decomp.) [from ethanol–acetone–water (4 : 2 : 1; 25 ml. per g.); recovery 85%]

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(Found: C, 38·8; H, 3·0; N, 25·2; S, 7·25. $C_9H_{11}N_5OS$,-$C_6H_3N_3O_7$ requires C, 38·6; H, 3·0; N, 24·0; S, 6·9%).

1-*Amidino-4-benzoyl(thiosemicarbazide) Hydrochloride*.—(a) *Action of alkali*. A solution of the reactant (2·75 g., 0·01 mole) in 3N-sodium hydroxide (40 ml.) was refluxed during 20 min. The resulting solution was cooled and acidified (to pH 2—3) with concentrated hydrochloric acid, and the precipitate was collected at 0° (m.p. 259—261°; 1·40—1·66 g., 72—85%; calc. as hydrate). Crystallisation from acetone–ethanol gave prisms of 3-mercapto-5-phenyl-1,2,4-triazole, m.p. 257—259° (lit.,[10] 256°) (Found: C, 54·3; H, 4·0; N, 23·85; S, 17·65. Calc. for $C_8H_7N_3S$: C, 54·2; H, 3·95; N, 23·7; S, 18·1%), $\nu_{max.}$ 3060s (CH arom.), 2890s, 2820s, and 1565s (NH), 1610w (C=N), 1505s, 695, and 680ms (doublet) (Ph), 1220s (C=S), 1590w, 1485s, 965s, and 780m,br cm.$^{-1}$.

3-Benzylthio-5-phenyl-1,2,4-triazole, prepared [14] from the foregoing 3-mercapto-compound, had $\nu_{max.}$ 3140s, 3000s, and 2780s (NH), 3080s (CH arom.), 2920s, 2860s, and 1465s (CH_2), 1560ms (C=N?), 1490ms, 725s, and 695s (Ph), 1430ms, 1340s, 1285ms, 1265s, 1235s, 1140s, 985s, and 780s cm.$^{-1}$

(b) *Action of hydrochloric acid*. (i) A solution of the reactant (2·75 g., 0·01 mole) in 3N-hydrochloric acid (35 ml.) was refluxed for 1·5 hr. Slight evolution of hydrogen sulphide occurred, and solid began to separate after 5—15 min. This was collected at 0°, boiled with ethanol (12 ml.), and again collected at 0° [m.p. 268—274° (decomp.); 1·03 g., 40%]. Crystallisation from acetone–ethanol–water (100, 50, and 15 ml. per g.; filtration and partial evaporation necessary) gave microprisms of 2-*amino*-5-*benzamido*-1,3,4-*thiadiazole hydrochloride*, m.p. 282—284° (decomp.) (Found: C, 41·6; H, 3·5; Cl, 13·3; N, 21·2; S, 13·1. $C_9H_8N_4OS$,HCl requires C, 42·1; H, 3·5; Cl, 13·8; N, 21·8; S, 12·5%), $\nu_{max.}$ 3320ms, 3150s to *ca.* 2900s,br, and 1560s (NH), 1660ms (CO), 1630s (NH_2), 1580s (C=N or NH_2?), 1500ms (Ph), 1300s (C·NH_2 arom.), 1470ms, 1260ms, 895s, 800ms, 710s, and 670ms cm.$^{-1}$, $\lambda_{max.}$ 235 mμ (log ε, 4·13), $\lambda_{min.}$ 253 (3·87), $\lambda_{max.}$ (shallow) 279 (4·10).

A solution of this hydrochloride (1·28 g., 0·005 mole) in boiling 0·25M-hydrochloric acid (12 ml.) was basified with concentrated ammonia. The pale yellow precipitate (0·9 g., 82%) was 2-amino-5-benzamido-1,3,4-thiadiazole, m.p. 280—282° (decomp.) [platelets from ethanol–acetone–water (2 : 2 : 1; 75 ml. per g.)] (lit.,[27] 277—278·5°; lit.,[15] 280°) (Found: C, 49·35; H, 3·6; N, 25·4; S, 14·5. Calc. for $C_9H_8N_4OS$: C, 49·1; H, 3·6; N, 25·45; S, 14·5%), $\nu_{max.}$ 3380ms, 3160s, 3000ms, and 1520s (NH), 1670s (CO), 1640s (NH_2), 1605ms, 1500s, and 710s (Ph), 1565s (C=N), 1310s,br (C·NH_2), 1460ms, 900s, and 800ms cm.$^{-1}$, $\lambda_{max.}$ 231 mμ (log ε 4·10), $\lambda_{min.}$ 255 (3·68), $\lambda_{max.}$ (shallow) 299 (4·02).

The *picrate*, obtained in 80% yield from the hydrochloride, formed needles, m.p. 261—263° (decomp.; darkening from 230°) (from acetone–ethanol–water) (Found: C, 40·2; H, 2·6; N, 22·6. $C_9H_8N_4OS$,$C_6H_3N_3O_7$ requires C, 40·1; H, 2·45; N, 21·8%), $\nu_{max.}$ 3400ms, 3100s, 1640s,br, 1575s, 1540s, 1500ms, 1480ms, 1435ms, 1365s, 1340—1265s (multiplet), 1155ms, 1080ms, 915m, 895m, 795s, and 710s cm.$^{-1}$.

(ii) Aminoguanidine hydrochloride (0·066 mole) and benzoyl isothiocyanate (0·06 mole) were heated in dimethylformamide (45 ml.) at 100° for 2 hr.; the liquid was added to water (200 ml.), and a finely divided precipitate was filtered off. The aqueous filtrate was treated with concentrated hydrochloric acid (33 ml.) and refluxed for 1 hr.; slight evolution of hydrogen sulphide occurred and the pale yellow colour of the liquid was completely discharged. The precipitate separating on cooling (and a further crop obtained after concentration of the filtrate in a vacuum), collected at 0°, was 2-amino-5-benzamido-1,3,4-thiadiazole hydrochloride (32—45%).

Treatment with acid for only 20 min. reduced the yields of the hydrochloride to 20—25%; the filtrates therefrom gave, on addition of 0·05M-picric acid until precipitation was complete, 1-amidino-4-benzoyl(thiosemicarbazide) picrate (up to 40%), m.p. and mixed m.p. (see before) 208—210° (decomp.) (Found: C, 38·7; H, 3·4%).

(c) *Action of orthophosphoric acid*. To melted orthophosphoric acid (25 g.), the finely powdered reactant (2·75 g., 0·01 mole) was added, and the liquid was kept at 120° for 30 min., then at 140° for 30 min. The cooled (60°) liquid was stirred into ice (100 g.) and concentrated ammonia (50 ml.), and the precipitate was collected at once and washed with water. Crystallisation from acetone–ethanol gave platelets of 2-amino-5-benzamido-1,3,4-thiadiazole, m.p. and mixed m.p. 280—282° (1·22 g., 55%), also identified by its i.r. spectrum (see later).

(d) *Action of acetic anhydride*. The reactant (2·75 g., 0·01 mole) dissolved almost completely when boiled in acetic anhydride (25 ml.), but the liquid soon deposited a mass of needles. Refluxing was continued for 30 min., the cooled suspension was stirred into water (200 ml.), and the precipitate was collected (m.p. 320—325°; 1·7 g., 65%). Crystallisation from a large volume of acetone–ethanol (partial evaporation necessary) gave microcrystalline 3-*acetamido*-5-*benzamido*-1,3,4-*thiadiazole*, m.p. 334—336° (Found: C, 50·0; H, 4·1; N, 21·0; S, 11·7. $C_{11}H_{10}N_4O_2S$ requires C, 50·4; H, 3·8; N, 21·4; S, 12·2%), $\nu_{max.}$ 3450ms, 3200s, 2810ms, and 1535ms (NH), 2950s,br (NH and/or CH_3), 1675s (amide CO), 1580s (C=N), 1500ms, and 700s (Ph), 1460m and 1370ms (CH_3), 1320ms to 1300s,br (C·N, arom. amine), 1250ms, and 900ms cm.$^{-1}$.

The preparation of this compound by the action of acetic anhydride on benzoylhydrazodithioamide is on record,[15] but no m.p. was given in the abstract.

1-*Amidino*-4-p-*methoxybenzoyl(thiosemicarbazide) Hydrochloride*.—A solution of aminoguanidine hydrochloride (2·43 g., 0·022 mole) in methanol–water (10 : 1; 22 ml.) was treated at *ca.* 35—40° with *p*-methoxybenzoyl isothiocyanate (3·85 g., 0·02 mole). The resulting liquid deposited the product directly (m.p. 200—202°; 5·45 g., 90%); it was crystallised from 90% ethanol (12 ml. per g., recovery 75%), giving needles of the solvated *hydrochloride*, m.p. 202—204° (decomp.) (Found: C, 40·8; H, 5·7; Cl, 10·3; N, 20·1; S, 9·4. $C_{10}H_{13}N_5O_2S$,HCl,C_2H_5OH requires C, 41·2; H, 5·7; Cl, 10·15; N, 20·0; S, 9·2%), $\nu_{max.}$ 3400s, 3120s, and 1525ms (NH), 2940ms and 2820ms (NH^+), 1665s (amide CO), 1605s (Ph and NH_2), 1495s (Ph and CH_3), 1165s (C=S), 760ms and 700ms (Ph), 1255s,br, 1120m, 1020m, and 840m cm.$^{-1}$.

The *picrate*, obtained in 90% ethanol from the hydrochloride, formed platelets (50%), m.p. 210—213° (from 80% ethanol) (Found: C, 38·9; H, 3·1; N, 22·7. $C_{10}H_{13}N_5O_2S$,$C_6H_3N_3O_7$ requires C, 38·7; H, 3·2; N, 22·6%).

1-*Amidino*-4-p-*chlorobenzoyl(thiosemicarbazide) hydrochloride* was similarly prepared, from *p*-chlorobenzoyl isothiocyanate (3·95 g., 0·02 mole). The separated salt

(m.p. 190—195°; 4·4 g., 72%) (filtrate F) gave, on crystallisation from 90% ethanol (15 ml. per g., recovery 80%), prisms of the *hydrochloride*, m.p. 203—205° (Found: C, 35·3; H, 4·0; N, 22·1; S, 9·8. $C_9H_{10}ClN_5OS,HCl$ requires C, 35·1; H, 3·6; N, 22·7; S, 10·4%), $\nu_{max.}$ 3370s,br, 3125s,br, and 1520s,br (NH), 2950s and 2860s (NH^+), 1670s,br (amide CO), 1630ms (NH_2), 1595s, 1490s, and 750s (Ph), 1170s,br (C=S), 1260ms,br, 1095s, 1015s, 850ms, and 800ms cm.$^{-1}$.

The *picrate* (60%) formed prismatic needles, m.p. 206—209° (from 80% ethanol) (Found: C, 35·9; H, 2·4; N, 22·9. $C_9H_{10}ClN_5OS,C_6H_3N_3O_7$ requires C, 36·0; H, 2·6; N, 22·4%).

Filtrate F slowly deposited needles (m.p. 124—128°; up to 0·7 g., 15%) of *methyl* (N-p-*chlorobenzoyl*)*thiocarbamate*, m.p. 130—132° [from ethanol (5 ml. per g.)] (Found: C, 47·2; H, 3·5; Cl, 14·95; N, 6·3; S, 13·4. $C_9H_8ClNO_2S$ requires C, 47·1; H, 3·5; Cl, 15·45; N, 6·1; S, 13·9%), $\nu_{max.}$ 3300s and 1520s (NH), 1720s (*CO*·NH·CS), 1595ms (NH_2), 1490ms, 745s, and 680ms (Ph), 1455s (CH_3), 1210vs (*CS*·NH·CO), 1310s,br, 1260ms, 1140ms, 1095s, 1035ms, 1015s, 875s, 850s, and 780ms cm.$^{-1}$.

Methyl (N-p-*Chlorobenzoyl*)*thiocarbamate*.—To a solution of *p*-chlorobenzoyl isothiocyanate (1·0 g., 0·005 mole) in warm methanol (10 ml.), 3N-hydrochloric acid (2 drops) was added. Crystallisation was completed by storage at room temperature and finally at 0°. The product (m.p. 122—126°; 0·98 g., 85%) gave needles of methyl (N-*p*-chlorobenzoyl)thiocarbamate, m.p. 128—130° (Found: C, 46·7; H, 3·3%). Its i.r. spectrum was identical with that of the foregoing specimen.

3-*Mercapto*-5-p-*chlorophenyl*-1,2,4-*triazole*.—A solution of 1-amidino-4-*p*-chlorobenzoyl(thiosemicarbazide) hydrochloride (1·55 g., 0·005 mole) in 2N-sodium hydroxide (30 ml.) was refluxed for 30 min., allowed to cool, and acidified (to pH 2) with 3N-hydrochloric acid. The precipitate (m.p. 290—292°; 0·95 g., 90%) gave [from 60% ethanol (25 ml. per g., recovery 60%)] microcrystalline 3-mercapto-5-*p*-chlorophenyl-1,2,4-triazole, m.p. 295—297° (decomp.) (Found: C, 45·7; H, 2·8; N, 19·8; S, 15·2. Calc. for $C_8H_6ClN_3S$: C, 45·4; H, 2·8; N, 19·9; S, 15·1%) (lit.,[10] m.p. 296—297°), $\nu_{max.}$ 3100s,br, 3000s, 2900s,br, and 1560s (NH), 1605s, 1505s, 1445ms, and 690ms (Ph), 1225ms,br (C=S), 1485ms, 1095s, 1015s, 970s, 840s, and 725ms cm.$^{-1}$.

1-*Amino*-2-*phenylguanidine*

4-*Benzoyl*-1-*phenylamidino*(*thiosemicarbazide*).— (i) *Nitrate*. 1-Amino-2-phenylguanidine nitrate (8·5 g., 0·04 mole), dissolved in methanol (40 ml.), was slowly treated, at room temperature during 1—2 min., with benzoyl isothiocyanate (6·5 g., 0·04 mole). The resulting warm liquid (odour of hydrogen sulphide) was set aside at room temperature for 3 hr. Traces of black flocculent material were removed and the filtrate, diluted with ether to incipient turbidity, was set aside, finally at 0°. The crystals were collected and rinsed with ether containing a little methanol. They consisted of one of the following forms of the *nitrate* which, except for solvation, were identical, as shown by their i.r. spectra (yield 11·3—12·3 g., 75—82%, calc. as non-solvated nitrate): (*a*) m.p. 126—130° (Found: C, 46·6; H, 4·5; N, 21·2; S, 8·0. $C_{15}H_{15}N_5OS,HNO_3,CH_3OH$ requires C, 47·1; H, 4·9; N, 20·6; S, 7·8%); (*b*) m.p. 146—150° or (*c*) m.p. 162—166° (Found: C, 47·4; H, 4·4; N, 22·1; S, 8·8. $C_{15}H_{15}N_5OS,HNO_3$ requires C, 47·9; H, 4·25; N, 22·3; S, 8·5%). Rapid crystallisation from ethanol–ether (5 ml. each per g., recovery 50%) gave the crystalline form (*b*) of m.p. 146—149°, $\nu_{max.}$ 3150s,vbr, 1530, and 1518ms (doublet) (NH), 1660s (amide CO), 1630s (NH_2), 1590 and 1580ms (doublet), 1500 and 1495s (doublet), 790ms, and 705s,br (Ph), 1180s,br (C=S), 1450m, 1385s, 1070ms, and 760ms cm.$^{-1}$.

The compound slowly gave a black precipitate when boiled in 3N-alkali containing a few drops of 10% lead acetate.

(ii) *Toluene*-p-*sulphonate*. The experiment was performed as in (i), but the filtered liquid was treated with toluene-*p*-sulphonic acid monohydrate (8·40 g., 0·044 mole) in water (8 ml.). The crystalline solid which separated gradually was collected at 0° (m.p. 169—172°; 7·75—9·7 g., 40—50%). When distilled to 25—30 ml. at the lowest possible temperature, and diluted with ether, the filtrate gave more of the same material (i.r. spectrum) (2·9—1·9 g., 15—10%). Crystallisation from 95% ethanol (20 ml. per g., recovery 50%) gave prisms of the *toluene*-p-*sulphonate*, m.p. 180—182° (Found: C, 54·0; H, 5·2; N, 14·0; S, 12·7. $C_{15}H_{15}N_5OS,C_7H_7SO_3H$ requires C, 54·4; H, 4·7; N, 14·4; S, 13·2%), $\nu_{max.}$ 3400s,br, 3150s,br, and 1530s (NH), 1675s (amide CO), 1630ms (NH_2), 1595s, 1505s, 755ms, and 690s (Ph), 1175s,vbr (C=S), 1310ms, 1125s, 1035s, 1015s, and 820ms cm.$^{-1}$.

(iii) The *picrate*, prepared from the foregoing nitrate or toluene-*p*-sulphonate, formed platelets, m.p. 184—186° (from 80% ethanol) (Found: C, 46·6; H, 3·4; N, 21·2; S, 6·2. $C_{15}H_{15}N_5OS,C_6H_3N_3O_7$ requires C, 46·5; H, 3·3; N, 20·7; S, 5·9%), $\nu_{max.}$ 3400s, 3220s, 3150s, 2960ms, 1675s, 1630s,br, 1560s, 1520s, 1490s, 1430ms, 1365ms, 1335s, 1315s, 1260s, 1170ms, 1080ms, 795ms, 745ms, and 710s (doublet) cm.$^{-1}$.

4-*Benzoyl*-1-*phenylamidino*(*thiosemicarbazide*) *Nitrate*.—(a) *Action of alkali*. A solution of the reactant (1·88 g., 0·005 mole) in 2N-sodium hydroxide (30 ml.), boiled under reflux for 30 min. and acidified with 3N-hydrochloric acid, gave 3-mercapto-5-phenyl-1,2,4-triazole (0·71 g., 80%), m.p. and mixed m.p.[10] 256—258° (from acetone–ethanol).

(b) *Action of hydrochloric acid*. The reactant (3·76 g., 0·01 mole) dissolved when boiled in ethanol–hydrochloric acid (3N) (5 : 6; 44 ml.) (odour of hydrogen sulphide), but the liquid soon began to deposit a solid. Refluxing was continued for 40 min., and the solid was collected at 0° (m.p. 235—240°; 1·8—2·2 g.) (filtrate F), and extracted with boiling ethanol (20 ml.). The remaining solid (m.p. 275—278°; 1·04—1·33 g., 35—45%) was 2-anilino-5-benzamido-1,3,4-thiadiazole, forming microprisms, m.p. 276—278° (from 90% ethanol, or from 2-ethoxyethanol, 30 ml. per g., recovery 60%) (Found: C, 60·75; H, 4·1; N, 19·1; S, 10·6. Calc. for $C_{15}H_{12}N_4OS$: C, 60·8; H, 4·05; N, 18·9; S, 10·8%). Its i.r. spectrum was identical with that of authentic material (see later).

Filtrate F slowly deposited crystalline solid (m.p. 198—200°; 0·42—0·63 g., 12—18%) which gave, on crystallisation from ethanol (15 ml. per g., recovery 50%), platelets of 4-*benzoyl*-1-*phenylamidino*(*thiosemicarbazide*) *hydrochloride*, m.p. 200—202° (Found: C, 50·9; H, 4·2; Cl, 10·5; N, 19·75. $C_{15}H_{15}N_5OS,HCl$ requires C, 51·5; H, 4·6; Cl, 10·1; N, 20·0%), $\nu_{max.}$ 3250s, 3125s, and 1530s (NH), 2900s (NH^+), 1665s (amide CO), 1630s (NH_2), 1600ms, 1500s, 760s, and 705s (Ph), 1180 and 1165s (C=S), 1445ms, and 1265ms cm.$^{-1}$. The identity of the hydrochloride was

confirmed by its almost quantitative conversion into the picrate, m.p. 184—186° (Found: C, 46·8; H, 3·7; N, 20·1%).

(c) *Cyclisation in dimethylformamide.* A solution of the nitrate (1·88 g., 0·005 mole) in dimethylformamide (10 ml.) was kept at 100° for 2 hr., then stirred into ice–water (80 ml.). The resulting precipitate was extracted with boiling ethanol (10 ml.): the residue (0·86 g., 58%) was 2-anilino-5-benzamido-1,3,4-thiadiazole, m.p. 278—280°, identified by its i.r. spectrum.

4-*Benzoyl*-1-*phenylamidino*(*thiosemicarbazide*) *Toluene*-p-*sulphonate.*—(a) *Action of orthophosphoric acid.* A mixture of the finely powdered reactant (4·85 g., 0·01 mole) and orthophosphoric acid (25 g.) was kept at 120° for 1 hr. and at 140° for 30 min. The cooled (60°) liquid was stirred into concentrated ammonia (50 ml.) and ice (250 g.) (odour of aniline); the yellow precipitate was collected at once and warmed with water (removal of ammonium phosphate). The remaining solid was collected, air-dried, extracted by being refluxed with ethanol (20 ml.), and set aside. The collected white solid (m.p. 265—270°; 0·98—1·32 g., 33—45%) was crystallised from acetone–ethanol, giving microprisms of 2-anilino-5-benzamido-1,3,4-thiadiazole, m.p. 276—278° (Found: C, 60·5; H, 4·0; N, 19·5; S, 10·7. Calc. for $C_{15}H_{12}N_4OS$: C, 60·8; H, 4·05; N, 18·9; S, 10·8%), identified by its i.r. spectrum (see later).

(b) *Action of acetic anhydride.* The reactant (1·45 g., 0·003 mole) in acetic anhydride (10 ml.) was kept at 100° for 1 hr. The suspended material dissolved, but solid soon reappeared. The suspension was stirred into water (100 ml.); the solidified product was collected and washed with water. Crystallisation from a large volume of acetone–ethanol (residue R) gave needles of 2-*N*-acetylanilino-5-benzamido-1,3,4-thiadiazole (total 0·56 g., 55%), identical with synthetic material (see later) [mixed m.p. (236—238°) and i.r. spectrum].

Residue R gave, after dissolution in a very large volume of acetone–ethanol (2 : 1) and partial evaporation, microcrystalline 3-acetamido-5-benzamido-1,3,4-thiadiazole, m.p. and mixed m.p. 334—336° (0·2 g., 25%), also identified by its i.r. spectrum (see before) (Found: C, 50·3; H, 3·9; N, 21·4. Calc. for $C_{11}H_{10}N_4O_2S$: C, 50·4; H, 3·8; N, 21·4%).

The use of the adduct nitrate in reactions (a) and (b) resulted in copious brown nitrous fumes being evolved, giving dark mixtures that yielded only intractable gums.

Interaction of Benzoyl Isothiocyanate and 1-*Amino*-2-*phenylguanidine Nitrate in Dimethylformamide.*—1-Amino-2-phenylguanidine nitrate (4·26 g., 0·02 mole) in dimethylformamide (18 ml.) at room temperature was treated dropwise with benzoyl isothiocyanate (3·25 g., 0·02 mole). The deep yellow liquid was kept on a steam-bath for 2 hr. (odour of hydrogen sulphide), then stirred into ice–water (150 ml.). The precipitate (m.p. 268—272°; 3·91—4·62 g., 66—78%) gave, on crystallisation as before, needles of 2-anilino-5-benzamido-1,3,4-thiadiazole, m.p. 276—278° (Found: C, 61·2; H, 4·1; N, 19·5; S, 11·2. Calc. for $C_{15}H_{12}N_4OS$: C, 60·8; H, 4·05; N, 18·9; S, 10·8%). Its i.r. spectrum was identical with that of synthetic material (see later).

4-p-*Methoxybenzoyl*-1-*phenylamidino*(*thiosemicarbazide*) *nitrate*, prepared as the 4-benzoyl analogue, formed a crystalline solid (m.p. 150—155°; 60%) which gave, on rapid crystallisation from methanol–ether (8 ml. each per g., recovery 60%), *microplatelets*, m.p. 156—158° (decomp.) (Found: C, 46·9; H, 4·7; N, 20·95; S, 8·3. $C_{16}H_{17}N_5O_2S,HNO_3$ requires C, 47·3; H, 4·4; N, 20·7; S, 7·9%), $\nu_{max.}$ 3480ms, 3280s, 3150s, and 1525s (NH), 1670s (amide CO), 1635s (NH_2), 1605s, 1505s, 765s, and 695s (Ph), 1175s (C=S), 1385s, 1260ms, 1225ms, 1030ms, and 850ms cm.$^{-1}$.

4-p-*Chlorobenzoyl*-1-*phenylamidino*(*thiosemicarbazide*) *nitrate* was similarly obtained, the crude salt (m.p. 133—136°; 3·7 g., 45%) giving minute platelets, m.p. 132—135° (decomp.), from ethanol–ether (8 and 15 ml. per g., recovery 60%) (Found: C, 43·35; H, 3·9; Cl, 8·45; N, 19·6; S, 7·3. $C_{15}H_{14}ClN_5OS,HNO_3$ requires C, 43·85; H, 3·65; Cl, 8·6; N, 20·5; S, 7·8%), $\nu_{max.}$ 3500ms,sh, 3290ms, 3180s, and 1535s (NH), 1665s (CO), 1638s (NH_2), 1595s, 1495s, 760ms, and 690m (Ph), 1185s (C=S), 1390s, 1095s, 1020ms, 855ms, and 800ms cm.$^{-1}$.

2-*Anilino*-5-p-*methoxybenzamido*-1,3,4-*thiadiazole.*—1-Amino-2-phenylguanidine nitrate (6·4 g., 0·03 mole) in dimethylformamide (30 ml.) was treated at room temperature with *p*-methoxybenzoyl isothiocyanate (5·8 g., 0·03 mole) and the resulting liquid was kept at 100° for 2 hr.; white solid separated temporarily after 20 min. The mixture was added to ice–water (300 ml.) and the precipitate (m.p. 265—270°; 6·65 g., 68%) was collected and crystallised from 2-ethoxyethanol–ethanol (recovery poor), giving faintly yellow microcrystalline 2-*anilino*-5-p-*methoxybenzamido*-1,3,4-*thiadiazole*, m.p. 290—292° (Found: C, 58·3; H, 4·5; N, 16·5; S, 9·2. $C_{16}H_{14}N_4O_2S$ requires C, 58·9; H, 4·3; N, 17·2; S, 9·8%), $\nu_{max.}$ 3350ms (free NH), 3200ms,br, 2940ms, and 1550ms,br (NH), 1640s (amide CO), 1605s, 1505s, 750s, and 690s (Ph), 1315s, 1300s (doublet) (C–N), 1445ms, 1255s,br, 1175s, 1105ms, 1025ms, 900ms, and 845ms cm.$^{-1}$.

The same compound (m.p. and mixed m.p. 290—292°, and identical i.r. spectrum) was obtained (90%) from 2-amino-5-anilino-1,3,4-thiadiazole and *p*-methoxybenzoyl chloride (0·005 mole each) in anhydrous pyridine (15 ml.) at 100° during 30 min.

2-*Anilino*-5-p-*chlorobenzamido*-1,3,4-*thiadiazole* was obtained from *p*-chlorobenzoyl isothiocyanate (6·0 g., 0·03 mole) by the foregoing procedure. The crude product (m.p. 300—305°; 6·4 g., 65%) was crystallised from dimethylformamide (5 ml. per g., recovery 65%) giving granules of the *substituted thiadiazole*, m.p. 322—325° (Found: C, 53·7; H, 3·3; Cl, 10·9. $C_{15}H_{11}ClN_4OS$ requires C, 54·5; H, 3·3; Cl, 10·7%), $\nu_{max.}$ 3350s (free NH), 3150ms, 3100ms, and 1545s (NH), 1645s (CO), 1600ms (doublet), 1510 and 1500s (doublet), 750s, 695, and 700ms (Ph), 1315s (C–N), 1450ms, 1300ms, 1245w,br, 1095ms, 1020ms, 900ms, and 850ms cm.$^{-1}$

Authentic Acylamido-1,3,4-*thiadiazoles*

Hydrazodithioformamide was prepared in 48—52% (crude) yields from hydrazine sulphate and ammonium thiocyanate,[27,28] and formed prisms from water (10 ml. per g., recovery 70%), m.p. 216—218° (decomp., rate-dependent) (Found: C, 15·6; H, 4·0; N, 37·4; S, 42·2. Calc. for $C_2H_6N_4S_2$: C, 16·0; H, 4·0; N, 37·3; S, 42·7%), $\lambda_{max.}$ 206 mμ (log ε 4·04), $\lambda_{min.}$ 223 (3·58), $\lambda_{max.}$ 253 (4·42) (*cf.* ref. 36), $\nu_{max.}$ 3390s, 3300s, 3180s,br, and 2950s (NH), 1640ms (C=N), 1615s (NH_2), 1520s, 1470s, 1290ms, 1045s,br, 830ms, and 690m cm.$^{-1}$. The compound did not give a picrate in aqueous ethanol.

[36] S. L. Janniah and P. C. Guha, *J. Amer. Chem. Soc.*, 1930, **52**, 4860.

2,5-*Diamino*-1,3,4-*thiadiazole* was prepared in 72—82% yield by the oxidation of hydrazodithioformamide with hydrogen peroxide[25] as prismatic needles, m.p. 208—210° (rate-dependent) (from water) (Found: C, 20·7; H, 3·3; N, 48·6; S, 27·7. Calc. for $C_2H_4N_4S$: C, 20·7; H, 3·45; N, 48·3; S, 27·6%), $\lambda_{max.}$ 265br mμ (log ε 3·78) (*cf.* ref. 37), $\nu_{max.}$ 3450s, 3390s, 3300s, and 3140s,br (NH), 1615s,br (NH_2), 1565s (C=N), 1520s,br, 1310s, 1010ms, 820m,br, 770m,br, and 675ms cm.$^{-1}$.

The *picrate* (90%) formed needles, m.p. 274—277° (from a large volume of 80% ethanol) (Found: C, 27·6; H, 1·9; N, 28·8; S, 9·6. $C_2H_4N_4S,C_6H_3N_3O_7$ requires C, 27·8; H, 2·0; N, 28·4; S, 9·3%). The use of 2 mol. of picric acid gave the same monopicrate nearly quantitatively.

2-*Amino*-5-*benzamido*-1,3,4-*thiadiazole*.—(a) *Preparation*. 2,5-Diamino-1,3,4-thiadiazole (0·58 g., 0·005 mole) was dissolved in boiling pyridine (20 ml.), then treated at room temperature dropwise with benzoyl chloride (0·63 g., 0·0045 mole). The liquid was kept at 100° for 30 min., then stirred into ice–water (120 ml.). Crystallisation of the precipitate (0·75 g., 75%) as before gave 2-amino-5-benzamido-1,3,4-thiadiazole, m.p. and mixed m.p. 280—282° (decomp.) (lit.,[15] 280°; lit.,[24] 277—278·5°). Its u.v. and i.r. spectra were identical with those of a specimen prepared by the cyclisation of 1-amidino-4-benzoyl(thiosemicarbazide) (see before). The picrates and hydrochlorides obtained from both souces were also identical.

(b) *Debenzoylation attempts*. (i) The compound (0·005 mole) was recovered (80%), when its solution in 3N-sodium hydroxide–ethanol (2 : 1; 18 ml.) was refluxed for 4 hr., the liquid was distilled to half-bulk, acidified with 3N-acetic acid and nearly neutralised with ammonia (m.p. and mixed m.p. 280—282°, decomp.). Refluxing (1 hr.) in aqueous 2N-sodium hydroxide gave almost the same result.

(ii) A solution of the compound (0·005 mole) in 3N-hydrochloric acid–ethanol (5 : 2; 35 ml.) was refluxed for 6 hr. The hydrochloride of the starting material separated on cooling (m.p. and mixed m.p. 282—284°) (60%). The liquid smelled of ethyl benzoate, showing that some debenzoylation had occurred.

3-*Acetamido*-5-*benzamido*-1,3,4-*thiadiazole*.— 3-Amino-5-benzamido-1,3,4-thiadiazole (0·22 g., 0·001 mole) was boiled in acetic anhydride (8 ml.) for 30 min. Complete dissolution did not occur, but the suspended material changed in appearance. The suspension was stirred into water: the precipitate was 3-acetamido-5-benzamido-1,3,4-thiadiazole, m.p. 334—336° (from acetone–ethanol) (0·18 g., 70%), identical (i.r. spectrum) with the cyclisation product of 1-amidino-4-benzoyl(thiosemicarbazide) (by acetic anhydride; see before).

2,5-*Dibenzamido*-1,3,4-*thiadiazole*.— (a) *Preparation*. Interaction of 2,5-diamino-1,3,4-thiadiazole (1·16 g., 0·01 mole) and benzoyl chloride (3·1 g., 0·022 mole) in pyridine (35 ml.) at 100° for 1 hr., and usual work-up gave a solid (3 g.), which was extracted with boiling ethanol (25 ml.). The residual solid (m.p. 344—346°; 2·05 g., 64%) gave, on crystallisation from acetone–ethanol (200 and 100 ml. per g., and partial evaporation), white microprisms of 2,5-dibenzamido-1,3,4-thiadiazole, m.p. 348—350° (lit.,[23,25] 'above 280°') (Found: C, 58·9; H, 3·65; N, 17·45; S, 9·8. Calc. for $C_{16}H_{12}N_4O_2S$: C, 59·3; H, 3·7; N, 17·3; S, 9·9%), $\nu_{max.}$ 3150s, 2920s, 1565s, and 1550s (NH), 3050s (CH, arom.); 1670s,br (amide CO), 1600m, 1500s, and 705s,br (Ph), 1310s,br (C–N), 1455s, 1255s, 1185ms, 1100ms, 1070m, 1025m, 895s, 805m, 690s, and 660s cm.$^{-1}$.

The use of a large excess of benzoyl chloride (0·05 mole) gave the same dibenzoyl derivative in 70% yield.

(b) *Attempted debenzoylation*. A solution of the dibenzamido-compound (0·97 g., 0·003 mole) in 2N-sodium hydroxide (12 ml.) was refluxed for 1 hr., then acidified. The precipitate of starting material (72%) was filtered off. Treatment of the filtrate with aqueous 0·05M-picric acid gave 2-amino-5-benzamido-1,3,4-thiadiazole picrate (0·15 g., 11%), identified by mixed m.p. 261—263° (from 80% ethanol), and i.r. spectrum.

2-*Anilino*-5-*benzamido*-1,3,4-*thiadiazole*.—(a) *Preparation*. A solution of 2-amino-5-anilino-1,3,4-thiadiazole[26] (1·92 g., 0·01 mole) in pyridine (30 ml.) was treated with benzoyl chloride (1·40 g., 0·01 mole), kept at 100° for 30 min., then stirred into ice (150 g.) and concentrated hydrochloric acid (30 ml.). The precipitate was extracted with boiling ethanol (50 ml.) and the resulting solid (m.p. 276—279°; 2·2—2·4 g., 75—82%) crystallised from acetone–ethanol (*ca.* 200 and 100 ml. each per g., followed by vacuum evaporation to one-third bulk, recovery 60—70%) or from 90% ethanol (150 ml. per g., recovery 60%), giving microprisms of 2-anilino-5-benzamido-1,3,4-thiadiazole, m.p. 276—278° (Found: C, 60·4; H, 3·9; N, 19·1; S, 10·9. Calc. for $C_{15}H_{12}N_4OS$: C, 60·8; H, 4·05; N, 18·9; S, 10·8%) (lit.,[26] m.p. 278°), $\nu_{max.}$ 3370s (free NH), 3160ms, 3050ms, and 1545s (NH), 1645s, (CO), 1605s, 1505s, 750s, and 690s (Ph), 1310s (C–N), 1450ms, 1240m,br, 900ms, 710s, and 670ms cm.$^{-1}$.

To a solution of the foregoing thiadiazole (0·1 g., 0·00033 mole) in boiling acetone–ethanol (2 : 1; 45 ml.), picric acid (0·08 g., 0·00035 mole) was added, and the solution was distilled to *ca.* one-third volume. The separated *picrate* formed needles, m.p. 216—220° (decomp.) (80%) (Found: C, 48·35; H, 3·3; N, 18·2; S, 6·1. $C_{15}H_{12}N_4OS,C_6H_3N_3O_7$ requires C, 48·0; H, 2·9; N, 18·7; S, 6·1%), $\nu_{max.}$ 3480ms,br, 3160s, 3070s, 1665ms, 1620s,br, 1560s, 1545s, 1500s, 1360s, 1320s,br, 1270s,br, 1160m, 1080m, 790ms, and 705s cm.$^{-1}$. The salt decomposed into its components on attempted crystallisation from 85% ethanol.

(b) *Attempted debenzoylation*. (i) 2-Anilino-5-benzamido-1,3,4-thiadiazole (1·5 g., 0·005 mole) was recovered (75%) (and identified by mixed m.p. and i.r. spectrum), when its solution in aqueous 2N-sodium hydroxide was refluxed for 1 hr. and the product was reprecipitated by 3N-hydrochloric acid.

(ii) The use of boiling 1 : 1 aqueous ethanolic 2N-sodium hydroxide for 3 hr. similarly resulted in 80% recovery of starting material.

(c) *Acetylation*. (i) A suspension of the foregoing compound (0·59 g., 0·002 mole) in acetic anhydride (10 ml.) was kept at 100° for 1·5 hr., then stirred into water (100 ml.); the solidified product was crystallised from acetone–ethanol (75 and 25 ml. per g.), giving needles (0·5—0·54 g., 75—80%) of 2-N-*acetylanilino*-5-*benzamido*-1,3,4-*thiadiazole*, m.p. 236—238° (Found: C, 60·1; H, 4·2; N, 16·7; S, 9·75. $C_{17}H_{14}N_4O_2S$ requires C, 60·35; H, 4·1; N, 16·6; S, 9·5%), $\nu_{max.}$ 3170s, 2940s, and 1545br (NH), 3060s (C–H, arom.), 1680s and 1660s (CO), 1600m, 1495m, 755m, and 695s (Ph), 1310s,br (C–N), 1470s, 1370s, 1260ms, 1030m, and 895ms cm.$^{-1}$.

(ii) *Hydrolysis*. A solution of the foregoing acetyl derivative (0·67 g., 0·002 mole) in ethanol–40% aqueous sodium hydroxide (9 : 2; 22 ml.) was refluxed for 1·5 hr., acidified

[37] M. Ohta and A. Mifune, *J. Pharm. Soc. Japan*, 1952, **72**, 373.

with 3N-hydrochloric acid, and diluted with water (15 ml.); the precipitate, collected at 0° (m.p. 282—285°; 0·44 g., 75%), was 2-anilino-5-benzamido-1,3,4-thiadiazole, m.p. 276—278° (from 2-ethoxyethanol) (Found: C, 60·4; H, 3·6; N, 18·1; S, 11·1%), identified by its i.r. spectrum.

(d) *Benzoylation.* (i) A solution of the reactant (0·98 g., 0·0033 mole) in pyridine (15 ml.) was treated dropwise with benzoyl chloride (2·8 g., 0·02 mole), kept on a steam-bath for 20 min., and stirred into ice–concentrated hydrochloric acid (15 ml.). The precipitated resin was treated with boiling ethanol (20 ml.). The solid which separated was collected at 0°; crystallisation from acetone (500 ml. per g.) gave needles (total, 0·92 g., 70%) of 2-*benzamido*-5-N-*benzoylanilino*-1,3,4-*thiadiazole*, m.p. 278—280° (Found: C, 65·2; H, 3·8; N, 13·5; S, 8·1. $C_{22}H_{16}N_4O_2S$ requires C, 66·0; H, 4·0; N, 14·0; S, 8·0%), $\nu_{max.}$ 3200s, 2960ms, and 1550s,br (NH), 3080s (C–H, arom.) 1670s,br and 1650s (CO), 1595m, 1495ms, 750ms, and 700s,br (Ph), 1325s to 1310s,br (C–N), 1470s, 1260ms, 1180m, 1030m, 945m, 900ms, 845m, and 675ms $cm.^{-1}$.

(ii) Treatment of 2-amino-5-anilino-1,3,4-thiadiazole (0·96 g., 0·005 mole) in pyridine (15 ml.) with benzoyl chloride (2·8 g., 0·02 mole) at 100° for 20 min., followed by isolation and purification as in (i), gave the same dibenzoyl derivative, m.p. 278—280° (1·8 g., 90%), identified by its i.r. spectrum.

[9/2109 *Received, December 9th*, 1969]