651. *Thiadiazoles. Part X.* The Synthesis and Isomerisation of 2-Aryl-5-arylamino-3-arylimino-Δ^4-1,2,4-thiadiazolines.*

By Frederick Kurzer and Phyllis M. Sanderson.

Oxidising agents cyclise 1-aryl-3-(*NN'*-diarylamidino)thioureas to 2-aryl-5-arylamino-3-arylimino-Δ^4-1,2,4-thiadiazolines, which isomerise readily to 2-(*NN'*-diarylguanidino)benzothiazoles. The structure of the latter compounds is confirmed by degradation and independent synthesis.

Previous parts of this series [1] have shown the general applicability of the synthesis of 1,2,4-thiadiazoles by oxidative ring closure of compounds incorporating the grouping $-C(:NH)\cdot NH\cdot C(S)-$. To establish whether secondary amino-groups could take part in cyclisations of this type, suitably substituted compounds have now been examined. Although trisubstituted amidinothioureas (I) are not the simplest models complying with the structural requirements, they were chosen for two reasons: First, such experiments formed an extension to work on simpler amidinothioureas and 3,5-diamino-1,2,4-thiadiazoles,[1] providing data for comparison with such prototypes. Secondly, further information could reasonably be expected concerning the relative ease of formation of the (benzo)-thiazole and 1,2,4-thiadiazole nucleus.

1-(*NN'*-Diphenylamidino)-3-phenylthiourea (I; R = H, Ar = Ph) was rapidly oxidised by bromine or acidified hydrogen peroxide in the familiar manner [1] to yield, respectively, the hydrobromide or hydrochloride of a base, which, from its mode of formation, composition, and properties, is formulated as 5-anilino-2-phenyl-3-phenylimino-Δ^4-1,2,4-thiadiazoline (II; R = H, Ar = Ph). The 5-*p*-tolylamino-homologue (II; R = Me, Ar = Ph) was similarly prepared, but the structure of its isomer derived from 1-phenyl-3-(*N*-phenyl-*N'*-*p*-tolylamidino)thiourea (I; R = H, Ar = *p*-C_6H_4Me) remains undecided in one detail; depending whether the *p*-tolylamino- or anilino-group is concerned in the ring closure, this compound is to be formulated as 5-anilino-3-phenylimino-2-*p*-tolyl- or -2-phenyl-3-*p*-tolylimino-1,2,4-thiadiazoline. The ultraviolet absorption spectra of the three thiadiazolines (II) were almost identical (cf. Figure and Table). The influence of the replacement of a phenyl by a *p*-tolyl group in this complex molecule was evidently too feeble to produce more than the slightest bathochromic displacement of the high-intensity absorption maxima; [2] the relative position of the *p*-tolyl moiety was without influence on the outline of the absorption curve.

Treatment of arylthioureas with bromine, under essentially the conditions of the present synthesis, yields 2-aminobenzothiazoles.[3a] With compounds capable of cyclising to either 1,2,4-thiadiazoles or benzothiazoles [*e.g.*, amidinoarylthioureas,[4] $Ar\cdot NH\cdot CS\cdot NH\cdot C(:NH)\cdot NH_2$], the former is invariably the preferred reaction. The participation of partially blocked amino-groups in the formation of 1,2,4-thiadiazolines in the present reaction, in which the alternative ring closure to benzothiazoles (III) might be expected to predominate, shows more clearly than before the great ease with which the 1,2,4-thiadiazole system is built up. The fact that thiadiazolines (II) were formed preferentially appears particularly remarkable, because, once isolated from their salts, they isomerise readily to the 2-guanidinobenzothiazoles (III) (see below).

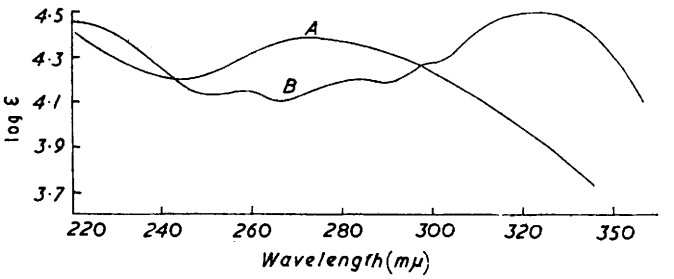
In common with comparable 1,2,4-thiadiazoles,[4] the thiadiazolines (II) were monoacid bases, forming well-characterised if somewhat labile salts, including hydrohalides, toluene-*p*-sulphonates, picrates, and picrolonates. Although anilino-substituents greatly increase

* Part IX, preceding paper.

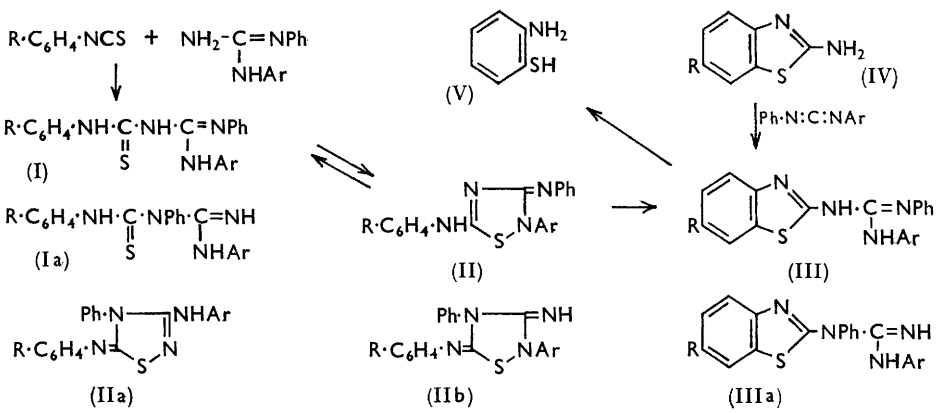
[1] Kurzer, *J.*, 1955, 1, and subsequent papers.
[2] Jones, *Chem. Rev.*, 1943, **32**, 11.
[3] Sprague and Land, in Elderfield (ed.), "Heterocyclic Compounds," Wiley, New York, 1957, Vol. V, pp. (*a*) 511, 581, (*b*) 689, 695.
[4] Kurzer, *J.*, 1956, 2345.

the stability of 1,2,4-thiadiazoles, the highly substituted thiadiazolines (II) were much less stable than comparable thiadiazoles (*e.g.*, 3,5-dianilino-,[4] 3-amino-5-anilino-,[4] 3-amino-5-phenyl[5] derivatives). Unlike the latter, they were readily cleaved at the N–S link by hydrogen sulphide under the mildest conditions, the parent amidinothioureas (I) being regenerated almost quantitatively. Alkaline hydrolysis ruptured the nucleus completely, yielding (from II; R = H, Ar = Ph) diphenylurea and phenylcyanamide which arose, respectively, from the $N_{(2)}$–$C_{(3)}$ and the $N_{(4)}$–$C_{(5)}$ fragment of the nucleus. Alkaline sodium plumbite caused rapid desulphurisation. The lower stability of the thiadiazolines (II) than of 1,2,4-thiadiazoles is likely to be bound up with the disappearance of the aromatic character of the structure. Well-known parallel cases in related heterocyclic fields include the contrasting stability of the heteroaromatic[6] thiazoles and the heteroethylenic[6] thiazolines, ring-opening occurring relatively readily in the latter group.[3b]

The outstanding property of the thiadiazolines (II), once liberated from their salts, was their tendency to isomerise irreversibly to 2-(*NN'*-diarylguanidino)benzothiazoles (III). The bases (II) were sufficiently stable to be stored indefinitely in the solid state, and



Ultraviolet absorption spectrum of 5-anilino-2-phenyl-3-phenylimino-Δ⁴-1,2,4-thiadiazoline (A) and 2-(NN'-diphenylguanidino)benzothiazole (B).



The occurrence of tautomerism wherever possible is understood.

to be quickly recrystallised, with care, from hot solvents. In boiling ethanol, however, the isomerisation (II ⟶ III) occurred nearly quantitatively and in a short time. In very dilute solution at room temperature, the interconversion proceeded sufficiently slowly for its progress to be followed by ultraviolet-absorption measurements, the characteristic spectrum of the starting material giving way gradually to that of the product (cf. Figure). Such measurements showed that even in M/20,000-ethanolic solution, the conversion (II ⟶ III) was complete within 4—5 days. The isomerisation necessarily involves the

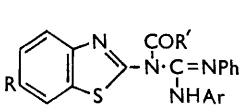
[5] Kurzer, *J.*, 1956, 4524.
[6] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959.

opening of the thiadiazoline ring at the N–S bond, as usually the weakest link in the nucleus; one possible mechanism is its hydrolytic fission, with simultaneous addition, at $N_{(2)}$ and $S_{(1)}$ of the ring, of hydrogen and hydroxyl, respectively; elimination of the latter together with *ortho*-hydrogen from the 5-anilino-residue, in the form of water, would give rise to the new ring system directly.

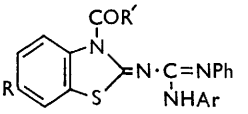
At first, difficulties were experienced in identifying the 2-guanidinobenzothiazoles (III) because of their exceptional stability; they were unaffected by hydrolytic, reducing, and oxidising agents under fairly severe conditions (cf. Experimental section). In common with that of 2-aminobenzothiazoles,[7] however, the ring system of the molecule (III; R = H, Ar = Ph or *p*-C_6H_4Me) was cleaved at high temperatures by fused alkalis, yielding *o*-aminothiophenol (V) which was recovered almost quantitatively as the di- or tri-benzoyl derivative, while the side chain was degraded to aniline and ammonia.

Trisubstituted guanidines have been obtained by the addition of primary amines to carbodi-imides.[8,9,10] Accordingly, the identity of the guanidinobenzothiazoles (III) was finally established by their unequivocal synthesis from 2-aminobenzothiazole (and its 6-methyl homologue) (IV; R = H or Me) and diarylcarbodi-imides. In anhydrous benzene, the products (III) were formed smoothly and almost quantitatively, and were identical with those formed by isomerisation of the 1,2,4-thiadiazolines (II).

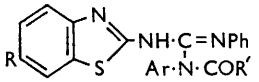
2-(*NN'*-Diarylguanidino)benzothiazoles were monoacid bases, forming stable salts and monoacyl derivatives. Since acylation of 2-aminothiazoles [11] and 2-aminobenzothiazoles [12] generally yield 2-acylamino-compounds, and 2-guanidinobenzothiazole [13] yields only a diacetyl derivative, formula (VIa) (rather than VIb or c) appears the likely structure of the derivatives. The highly characteristic ultraviolet absorption spectra of all three diaryl-guanidinobenzothiazoles (III; R = H, Ar = Ph or *p*-C_6H_4Me; R = Me, Ar = Ph) were practically identical, but differed sharply from that of 2-guanidinobenzthiazole (cf. Table).



(VIa)



(VIb)



(VIc)

Triarylamidinothioureas (I) required as precursors of 1,2,4-thiadiazolines (II) were obtained by the condensation of *s*-diphenylguanidine and aryl isothiocyanates. The interaction of *s*-diphenylguanidine and phenyl isothiocyanate in benzene was first investigated by Rathke who represented the product as *NN'*-diphenyl-*N'*-(phenyl-amidino)thiourea [14] (Ia; R = H, Ar = Ph). The more probable structure (I; R = H, Ar = Ph) was subsequently suggested,[15] based on the observation that *s*-triphenylguanidine failed to react with phenyl isothiocyanate. The present work confirms the view that triphenylamidinothiourea, now obtained by Rathke's reaction, in both benzene and pyridine, and by reduction of 5-anilino-2-phenyl-3-phenylimino-Δ^4-1,2,4-thiadiazoline, has structure (I; R = H, Ar = Ph): its isomer (Ia; R = H, Ar = Ph) would yield, on successive oxidation and isomerisation, the thiadiazoline (IIa) (or possibly IIb) (R = H, Ar = Ph) and thence the 2-diphenylguanidinobenzothiazole (IIIa; R = H, Ar = Ph)

[7] Hofmann, *Ber.*, 1880, **13**, 20.
[8] Huhn, *Ber.*, 1886, **19**, 2404.
[9] Weith, *Ber.*, 1873, **6**, 1395; 1874, **7**, 10, 1306.
[10] Khorana, *Chem. Rev.*, 1953, **53**, 145.
[11] Traumann, *Annalen*, 1888, **249**, 31; Wagner-Jauregg and Helmert, *Ber.*, 1942, **75**, 935; Jensen and Thorsteinsson, *Dansk Tiddskr. Farm.*, 1941, **15**, 41.
[12] Hugershoff, *Ber.*, 1903, **36**, 3121; 1901, **34**, 3130.
[13] Smith, Mason, and Carroll, *J. Amer. Chem. Soc.*, 1931, **53**, 4103.
[14] Rathke, *Ber.*, 1879, **12**, 774; see also Wingfoot Corp., French P. 835,261/1938.
[15] Rathke, *Ber.*, 1887, **20**, 1065; Rathke and Oppenheim, *Ber.*, 1890, **23**, 1668; Flemming and Klein, G.F. 464,319/1928.

isomeric with, but different from, the product actually obtained (III; R = H, Ar = Ph), the structure of which is established by independent synthesis from diphenylcarbodi-imide.

Interaction of *s*-diphenylguanidine and *p*-tolyl isothiocyanate gave two distinct products according to the solvent employed in the condensation. In benzene at moderate temperatures the reaction took the normal course, yielding the expected 1-(*NN'*-diphenylamidino)-3-*p*-tolylthiourea (I; R = Me, Ar = Ph). From hot pyridine, however, an isomeric amidinothiourea was isolated which, based on its eventual conversion into 2-(*N*-phenyl-*N'*-*p*-tolylguanidino)benzothiazole (I ⟶ II ⟶ III), is formulated as 1-phenyl-3-(*N*-phenyl-*N'*-*p*-tolylamidino)thiourea. The observations suggest that, in pyridine, the primarily formed amidinothiourea (I; R = Me, Ar = Ph) isomerises to (I; R = H, Ar = *p*-C_6H_4Me), but no information is as yet available concerning the mechanism of this intramolecular rearrangement. The remarkable ease with which trisubstituted amidinothioureas undergo changes in pyridine is further illustrated by the unexpected observation that 1-(*NN'*-diphenylamidino)-3-phenylthiourea, isolated in low yield, was the product of the interaction of *s*-diphenylguanidine and methyl isothiocyanate in this medium.

Experimental

The solvent used for preparing M-bromine was chloroform. Pyridine was the commercially available anhydrous grade.

Ultraviolet absorption measurements were made with a " Unicam S.P. 500 " spectrophotometer, for 0·00005M-ethanolic solutions (cf. Table).

Triarylamidinothioureas.

1-(NN'-*Diphenylamidino*)-3-*phenylthiourea.*—(*a*) A solution of *s*-diphenylguanidine (29·5 g., 0·14 mole) (previously dried at 60—70°) in anhydrous pyridine (140 ml.) at 35—45° was treated with phenyl isothiocyanate (16·2 g., 0·12 mole), and the brown clear liquid kept at 100° during 45 min. The crude granular product obtained on stirring the liquid into ice (1 kg.) and concentrated hydrochloric acid (150 ml.) was collected, washed with water, air-dried (35—40 g.), and twice crystallised from acetone–ethanol (10 and 4 ml. per g., respectively), yielding prisms of 1-(*NN'*-diphenylamidino)-3-phenylthiourea, m. p. 164—166° (decomp.) (total yield, 28·2—34·0 g., 68—82%) [Found: C, 69·5; H, 5·4; N, 16·4; S, 9·1%; *M* (cryoscopic, in thymol), 357. Calc. for $C_{20}H_{18}N_4S$: C, 69·4; H, 5·2; N, 16·2; S, 9·25%; *M*, 346]. Alkaline sodium plumbite gave lead sulphide rapidly on warming.

(*b*) A solution of *s*-diphenylguanidine (4·22 g., 0·02 mole) in anhydrous benzene (50 ml.), treated with phenyl isothiocyanate (2·7 g., 0·02 mole), was set aside at room temperature during 1 week, the separating crystalline mass being crushed from time to time. The collected solid (m. p. 162—165°; 5·7 g., 82%), on crystallisation as above, gave the thiourea, m. p. and mixed m. p. (with product obtained by procedure *a*) 164—166° (decomp.). The m. p. in the literature is variously given [14,15] between 150° and 172°.

(*c*) 5-Anilino-2-phenyl-3-phenylimino-Δ^4-1,2,4-thiadiazoline (see below) (1·03 g., 0·003 mole) was dissolved in ethanol (20 ml.) with warming, and a slow stream of hydrogen sulphide passed through the solution at room temperature during 0·5 hr. The white crystalline precipitate, which began to separate immediately, was collected at 0°, rinsed with a little ethanol (1·05 g.), and twice crystallised from acetone–ethanol as above [a little sulphur (0·05 g.) being removed by filtration], giving 1-(*NN'*-diphenylamidino)-3-phenylthiourea, m. p. and mixed m. p. 164—166° (total, 0·85 g., 82%) (Found: C, 69·9; H, 5·0%).

(*d*) Interaction of *s*-diphenylguanidine (2·53 g., 0·012 mole) and methyl isothiocyanate (0·73 g., 0·01 mole) in pyridine (10 ml.) at 100° during 1 hr. gave, on addition to ice–hydrochloric acid, a soft crude product which yielded, after crystallisation as above, 1-(*NN'*-diphenylamidino)-3-phenylthiourea, m. p. and mixed m. p. 164—166° (0·35—0·5 g.) (Found: C, 69·6; H, 5·4%). The filtrates contained intractable oil.

1-(NN'-*Diphenylamidino*)-3-p-*tolylthiourea.*—A solution of *s*-diphenylguanidine (6·35 g., 0·03 mole) and *p*-tolyl isothiocyanate (3·75 g., 0·025 mole) in anhydrous benzene (50 ml.) was treated with triethylamine (0·5 ml.). The liquid was kept at 40—45° during 2 hr., then set aside at room temperature overnight, crystallisation then occurring. The mixture was warmed

to redissolve the solid and gradually diluted with light petroleum (b. p. 60—80°; 25 ml.), and the separated product collected at 0° and rinsed with 1 : 1 benzene–light petroleum (m. p. 139—141°; 7·6 g., 85%). Crystallisation from cold chloroform–light petroleum (b. p. 40—60°) gave prisms of the *amidinothiourea*, m. p. 142—143° (Found: C, 70·1; H, 5·45. $C_{21}H_{20}N_4S$ requires C, 70·0; H, 5·55%).

1-*Phenyl*-3-(N-*phenyl*-N′-p-*tolylamidino*)*thiourea*.—(i) *s*-Diphenylguanidine (12·7 g., 0·06 mole) in pyridine (60 ml.), treated with *p*-tolyl isothiocyanate (7·45 g., 0·05 mole), was heated on the steam-bath during 1 hr., and the clear liquid stirred into ice and hydrochloric acid. The precipitated soft sticky material solidified at 0°, and was then collected (18 g.), air-dried, and crystallised three times from chloroform or acetone (30 ml.) and ethanol (20 ml.), yielding the substituted *amidinothiourea*, m. p. 156—158° (Found: C, 69·9; H, 5·4; N, 15·3; S, 9·0. $C_{21}H_{20}N_4S$ requires C, 70·0; H, 5·55; N, 15·55; S, 8·9%) (4·5—5·4 g., 25—30%).

Evaporation of the combined filtrates to small volume, and repeated crystallisation (as above) of the separated product (approx. 6 g.), gave more of the amidinothiourea (m. p. 148—152°; 1·5—2·5 g., 8—14%). The final fractions (3—5 g.) were lower-melting (m. p. 125—130°) and non-homogeneous; their ultraviolet absorption spectra were identical with those of the pure product, and they probably consisted of mixtures of 1-(*NN*′-diphenylamidino)-3-*p*-tolyl- and 1-phenyl-3-(*N*-phenyl-*N*′-*p*-tolylamidino)-thiourea.

(ii) Reduction of 5-anilino-3-phenylimino-2-*p*-Δ^4-tolyl-1,2,4-thiadiazoline (see below) by hydrogen sulphide according to procedure (*c*) gave the same amidinothiourea, m. p. and mixed m. p. 154—156° (yield, 70%).

Ultraviolet absorption spectra.

	λ (mμ) ($\log_{10}\varepsilon$ in parentheses)
1-(*NN*′-Diphenylamidino)-3-phenylthiourea	min. 255 (4·02); max. 300 (4·44)
1-(*NN*′-Diphenylamidino)-3-*p*-tolylthiourea	min. 255 (4·04); max. 300 (4·43)
1-Phenyl-3-(*N*-phenyl-*N*′-*p*-tolylamidino)thiourea	min. 255 (4·02); max. 300 (4·45)
5-Anilino-2-phenyl-3-phenylimino-Δ^4-1,2,4-thiadiazoline	shallow min. 243 (4·21); shallow max. 273 (4·39)
2-Phenyl-3-phenylimino-5-*p*-tolylamino-Δ^4-1,2,4-thiadiazoline	shallow min. 245 (4·20); shallow max. 275 (4·36)
5-Anilino-2-phenyl-3-*p*-tolylimino(or 3-phenylimino-2-*p*-tolyl)-Δ^4-1,2,4-thiadiazoline	shallow min. 244 (4·22); shallow max. 274 (4·40)
2-Aminobenzothiazole	max. 223 (4·50); min. 242 (3·71); max. 262 (4·09);
2-Guanidinobenzothiazole [13]	s 222 (4·22); max. 234 (4·32); min. 246 (4·00); max. 248 (4·02); min. 255 (3·65); s 280 (4·20); max. 288 (4·30); min. 293 (4·27); s 300—304 (4·34); max. 308 (4·35)
2-(*NN*′-Diphenylguanidino)benzothiazole	min. 252 (4·15); max. 258 (4·17); min. 265 (4·10); shallow max. 285 (4·22); min. 290 (4·19); s 297—300 (4·26); shallow max. 323 (4·51)
2-(*N*-Phenyl-*N*′-*p*-tolylguanidino)benzothiazole	min. 251 (4·16); max. 258 (4·17); min. 266 (4·12); max. 285 (4·23); min. 290 (4·21); s 299 (4·28); shallow max. 321 (4·51)
2-(*NN*′-Diphenylguanidino)-6-methylbenzothiazole	min. 250 (4·15); max. 260 (4·18); min. 269 (4·15); max. 286 (4·22); min. 293 (4·19); s 302 (4·28) shallow max. 325 (4·50)

s = shoulder.

1,2,4-*Thiadiazolines*.

5-*Anilino*-2-*phenyl*-3-*phenylimino*-Δ^4-1,2,4-*thiadiazoline*.—*Hydrobromide*. Finely powdered 1-(*NN*′-diphenylamidino)-3-phenylthiourea (3·46 g., 0·01 mole) was dissolved in chloroform (40 ml.) with warming, and then treated, at room temperature, with M-bromine (10 ml., 0·01 mole) which was rapidly decolorised. The resulting clear liquid was distilled to dryness in a vacuum at little above room temperature, and the remaining white solid stirred with water (10 ml.), collected, and washed with a little cold acetone to remove unchanged reactant [m. p. 220—222° (decomp.), 3·6—3·9 g., 85—92%]. Crystallisation from boiling nitrobenzene (10 ml. per g.), followed by dilution of the cold solution with an equal volume of ethanol, gave (approx. 50% recovery) white opaque prisms of *5-anilino-2-phenyl-3-phenylimino-*Δ^4*-1,2,4-thiadiazoline hydrobromide*, m. p. 226—228° (decomp.) (Found: C, 56·5; H, 4·35; Br, 19·1. $C_{20}H_{16}N_4S$,HBr requires C, 56·5; H, 4·0; Br, 18·8%). The salt did not give lead sulphide on being heated with alkaline lead plumbite.

Hydrochloride. A boiling solution of 1-(*NN'*-diphenylamidino)-3-phenylthiourea (13·85 g., 0·04 mole) in acetone–ethanol (1 : 1; 280 ml.) containing concentrated hydrochloric acid (20 ml., 0·2 mole) was removed from the source of heat and treated dropwise with 30% hydrogen peroxide (13·5 ml., 0·12 mole) during 3—5 min. The exothermic nature of the reaction kept the mixture at the b. p. throughout the addition; crystals began to separate when about half the oxidising agent had been added. The product, collected at 0°, and washed with acetone, consisted of opaque white minute prisms of the *hydrochloride*, m. p. 229—232° (decomp.) (11·4—12·2 g., 75—80%) (Found: C, 62·6; H, 4·6; N, 14·0; S, 8·3; Cl, 9·3. $C_{20}H_{16}N_4S$,HCl requires C, 63·1; H, 4·5; N, 14·7; S, 8·4; Cl, 9·3%). The product decomposed on attempted crystallisation from boiling ethanol–water (2 : 1). The use of less hydrogen peroxide (0·05 mole) or of 6% solutions resulted in reduced yields.

Base. (*a*) A stirred suspension of the hydrochloride (19·03 g., 0·05 mole) in ethanol (180 ml.) was treated, at room temperature, with 3N-aqueous ammonia (33·3 ml., 0·1 mole) during 3 min. The suspended microcrystalline material changed to a very pale yellow solid, which was collected after storage at 0° during 0·5 hr. and rinsed with small portions of ethanol. The air-dried product, a pale-yellow microcrystalline powder [m. p. 137—139° (decomp.); 14·6—15·5 g., 85—90%] was suitable for further experiments. Small portions (1 g.) were crystallisable by being quickly dissolved in boiling ethanol (8 ml. per g., recovery approx. 60%); massive lemon-yellow prisms of the 1,2,4-*thiadiazoline*, m. p. 138—140° (decomp.); were obtained (Found: C, 70·5, 70·2; H, 4·7, 4·6; N, 15·7; S, 9·15. $C_{20}H_{16}N_4S$ requires C, 69·8; H, 4·65; N, 16·3; S, 9·3%). The uncrystallised product was stored unchanged during several months. It gave lead sulphide with boiling alkaline sodium plumbite (in the presence of a little ethanol to dissolve the compound).

(*b*) A cold suspension of the hydrobromide (2·12 g., 0·005 mole) in ethanol (30 ml.) and water (10 ml.), on treatment with 3N-ammonia (4 ml., 0·012 mole) or 3N-sodium hydroxide (2·5 ml., 0·0075 mole), gave, by the same procedure, the identical base (75 and 60% respectively), m. p. and mixed m. p. 136—138° (decomp.).

5-*Anilino*-2-*phenyl*-3-*phenylimino*-Δ^4-1,2,4-*thiadiazoline.*—*Salts.* The following salts were prepared preferably from the freshly precipitated uncrystallised reactant; they decomposed on attempted crystallisation, but were analytically pure when first prepared and washed with ethanol.

A filtered solution of the base (0·69 g., 0·002 mole) in hot ethanol, treated with 3N-hydrochloric acid (1 ml., 0·003 mole), gave the hydrochloride, m. p. and mixed m. p. 231—233° (decomp.) (0·7 g., 92%). A solution of the reactant (0·001 mole) in warm ethanol (15 ml.), treated with toluene-*p*-sulphonic acid monohydrate (0·19 g., 0·001 mole) in ethanol (2 ml.), slowly deposited prismatic needles of the *toluene*-p-*sulphonate*, m. p. 182—184° (decomp.) (0·32 g., 62%) (Found: C, 62·8; H, 4·4; N, 10·7. $C_{20}H_{16}N_4S,C_7H_8O_3S$ requires C, 62·8; H, 4·65; N, 10·85%). Solutions of the reactant (0·001 mole) and picric acid (0·23 g., 0·001 mole) in hot ethanol (6 and 3 ml.) similarly deposited deep yellow prisms (95%) of the *picrate*, m. p. 183—185° (decomp.) (Found: C, 54·4; H, 3·3. $C_{20}H_{16}N_4S,C_6H_3O_7N_3$ requires C, 54·45; H, 3·3%). Solutions of the reactant (0·001 mole) and picrolonic acid (0·27 g., 0·001 mole) in hot ethanol (6 and 8 ml. respectively) similarly deposited golden-yellow prisms (93%) of the *picrolonate*, m. p. 182—183° (decomp.) (Found: C, 59·5; H, 3·75. $C_{20}H_{16}N_4S,C_{10}H_8O_5N_4$ requires C, 59·2; H, 3·95%).

5-*Anilino*-2-*phenyl*-3-*phenylimino*-Δ^4-1,2,4-*thiadiazoline.*—*Alkaline hydrolysis.* A solution of freshly prepared (uncrystallised) reactant (1·72 g., 0·005 mole) in ethanol (20 ml.) was treated with 3N-sodium hydroxide (20 ml., 0·06 mole) and refluxed during 0·5 hr. The liquid became green temporarily, and a crystalline precipitate began to separate after 5 minutes' boiling. The solid, collected at 0° (m. p. 232—235°; 0·75 g., 71%), recrystallised from ethanol and gave *s*-diphenylurea, m. p. 240—242° (decomp.) (Found: C, 73·7; H, 5·8; N, 13·1. Calc. for $C_{13}H_{12}N_2O$: C, 73·6; H, 5·7; N, 13·2%). The alkaline filtrate (which evolved hydrogen sulphide on acidification) was partly neutralised with 3N-hydrochloric acid (10 ml., 0·03 mole), partially evaporated at atmospheric pressure (to approx. 10 ml.), diluted with 5N-sodium hydroxide (10 ml.), and shaken with benzoyl chloride (2·8 g., 0·02 mole). The resulting precipitate was *N*-benzoylphenylcyanamide, m. p. and mixed m. p. 124—125° (from ethanol) (0·75 g., 68%).

2-*Phenyl*-3-*phenylimino*-5-p-*tolylamino*-Δ^4-1,2,4-*thiadiazoline.*—Oxidation of 1-(*NN'*-diphenylamidino)-3-*p*-tolylthiourea (3·60 g., 0·01 mole) with bromine (as described for the 1-phenyl

homologue) gave an immediate precipitate [m. p. 220—222° (decomp.); 3·9 g., 89%], which was crystallised from boiling methanol (30 ml. per g., recovery 75%), yielding large prisms of the *hydrobromide*, m. p. 220—222° (decomp.) (Found: C, 55·6; H, 4·6; N, 12·9; Br, 17·9. $C_{21}H_{18}N_4S$,HBr,H_2O requires C, 55·2; H, 4·6; N, 12·25; Br, 17·5%).

A stirred suspension of the powdered hydrobromide (2·2 g., 0·005 mole) in methanol (30 ml.) was treated dropwise with 3N-ammonia (5 ml., 0·015 mole). The yellow crystalline powder, which was collected after 1 hr. and rinsed with methanol containing a few drops of water, was the *base*, m. p. 130—132° (Found: C, 70·1; H, 5·3. $C_{21}H_{18}N_4S$ requires C, 70·4; H, 5·0%) (1·48 g., 82%).

5-*Anilino*-3-*phenylimino*-2-p-*tolyl*(or -2-*phenyl*-3-p-*tolylimino*)-Δ^4-1,2,4-*thiadiazoline*.—A solution of 1-phenyl-3-(*N*-phenyl-*N'*-*p*-tolylamidino)thiourea (3·60 g., 0·01 mole) in chloroform (25 ml.) was treated, at room temperature, with M-bromine (10 ml., 0·01 mole). The white powder obtained on evaporating the resulting clear colourless liquid in a vacuum at room temperature was stirred with chloroform (5—8 ml.), and the suspension diluted with ether (10 ml.). The product, collected at 0° and rinsed successively with chloroform–ether (1 : 1) and ether [m. p. 224—228° (decomp.), 3·70 g., 84%], was quickly crystallised from methanol (25 ml. per g., recovery approx. 60%), giving short prismatic needles of the *hydrobromide*, m. p. 227—229° (decomp.) (Found: C, 57·2; H, 4·55; N, 12·2; S, 8·0. $C_{21}H_{18}N_4S$,HBr requires C, 57·4; H, 4·3; N, 12·8; S, 7·3%).

A stirred suspension of finely powdered (uncrystallised) hydrobromide (4·40 g., 0·01 mole) in cold methanol (50 ml.) was treated dropwise with 3N-ammonia (10 ml., 0·03 mole). The resulting clear yellow liquid gradually deposited, on storage and scratching, at first a soft, later microcrystalline very pale-yellow solid, which was collected at 0° and washed with 50% aqueous methanol [m. p. 137—139° (decomp.); 2·6 g., 72%]. Rapid crystallisation from methanol (12 ml. per g., with subsequent addition of drops of water) gave the *thiadiazoline* as pale yellow prisms, m. p. 135—137° (decomp.) (Found: C, 69·9; H, 5·0; N, 16·0; S, 9·3. $C_{21}H_{18}N_4S$ requires C, 70·4; H, 5·0; N, 15·6; S, 8·9%).

Interaction of the (crude) thiadiazoline and picric acid (0·001 mole each) in methanol (5 ml.) gave, on storage at 0°, the *picrate*, forming deep yellow prisms, m. p. 179—180° (decomp.), from methanol–acetone (70%) (Found: C, 54·9; H, 3·2. $C_{21}H_{18}N_4S$,$C_6H_3O_7N_3$ requires C, 55·2; H, 3·6%).

2-*Guanidinobenzothiazoles*.

2-(NN'-*Diphenylguanidino*)*benzothiazole*.—(a) *By isomerisation of* 5-*anilino*-2-*phenyl*-3-*phenylimino*-Δ^4-1,2,4-*thiadiazoline*. Freshly prepared (uncrystallised) 5-anilino-2-phenyl-3-phenylimino-Δ^4-1,2,4-thiadiazoline (17·2 g., 0·05 mole), dissolved in ethanol (120 ml.), was boiled during 1 hr. and the hot liquid was treated with water (5 ml.). The separated, very pale yellow, crystalline solid [m. p. 131—133° (decomp., after sintering at 128°); approx. 15 g.] was powdered, then refluxed in ethanol (150 ml.)–3N-aqueous sodium hydroxide (100 ml.) during 0·5 hr. and next diluted with hot water (20 ml.). The colourless product which crystallised on cooling was collected at 0° [m. p. 131—133° (decomp., after sintering at 130°); 13·8—14·6 g., 80—85%]. Crystallisation from ethanol–acetone (10 and 3 ml. per g.) or chloroform–ethanol (2 and 4 ml. per g.) gave large prisms of 2-(NN'-*diphenylguanidino*)*benzothiazole*, m. p. 131—133° (decomp.) [Found: C, 70·1; H, 4·3; N, 16·4; S, 9·25%; *M* (cryoscopically in thymol), 360. $C_{20}H_{16}N_4S$ requires C, 69·8; H, 4·65; N, 16·3; S, 9·3%; *M*, 344]. The product did not give lead sulphide with alkaline sodium plumbite.

The sodium hydroxide treatment may be omitted, but an additional preliminary crystallisation from ethanol (15—20 ml. per g., recovery 84—92%) is then desirable, and the product remains pale yellow [m. p. and mixed m. p. 131—133° (decomp.)] [Found: C, 69·2; H, 4·7%; *M* (cryoscopic in thymol), 340].

(b) *From* 2-*aminobenzothiazole*. A solution of 2-aminobenzothiazole (0·825 g., 0·0055 mole) in anhydrous benzene (8 ml.), treated with diphenylcarbodi-imide [16] (1·0 g., 0·005 mole) was refluxed during 2 hr. The pale yellow liquid was rapidly evaporated in a vacuum, and the residual viscous oil dissolved in ethanol (6 ml.). The solution deposited crystals (m. p. 128—130°, after sintering at 126°; 1·46 g., 85%) which consisted, after crystallisation as above, of 2-(*NN'*-diphenylguanidino)benzothiazole, m. p. and mixed m. p. (with material prepared by method a) 131—133° (decomp.). Ultraviolet absorption spectra of specimens prepared by methods (a) and (b) were identical (cf. Table).

(c) This benzothiazole was recovered almost quantitatively in each of the following experiments. (i) Attempted hydrolysis: The base (0·01 mole) was refluxed during 1 hr. in 1·5N-sodium hydroxide in 50% ethanol (100 ml.), or 2 hr. in N-ethanolic potassium hydroxide. (ii) Attempted oxidation: A boiling ethanolic solution of the base was treated with 6% hydrogen peroxide (3 mols.), in the presence of either acid or alkali. (iii) Attempted reduction: Its ethanolic solution was treated with hydrogen sulphide under the usual conditions (see above). A boiling solution of the base (0·005 mole) in ethanol (50 ml.) containing suspended zinc wool (4 g.) was treated dropwise with concentrated hydrochloric acid (8 ml.) during 1 hr. The decanted partly evaporated (vacuum) liquid gave, on addition to N-hydrochloric acid (50 ml.), the crude hydrochloride, from which the starting material was recovered (70%) by dissolution in acetone–3N-sodium hydroxide, addition to water, and crystallisation of the resulting precipitate. A trace of acetone-insoluble product was *s*-diphenylurea, m. p. and mixed m. p. 228—234° (decomp.).

2-(NN′-*Diphenylguanidino*)*benzothiazole.*—*Salts.* A solution of the reactant (0·34 g., 0·001 mole) in hot ethanol (10 ml.), treated with 3N-hydrochloric acid (0·5 ml., 0·0015 mole), slowly deposited small needles of the *hydrochloride*, m. p. 233—235° (decomp.) (0·35 g., 90%) (Found: C, 63·6; H, 4·5; N, 14·2; Cl, 9·2. $C_{20}H_{16}N_4S$,HCl requires C, 63·1; H, 4·5; N, 14·7; Cl, 9·3%). Solutions of the reactant and toluene-*p*-sulphonic acid monohydrate (0·001 mole each) in boiling ethanol (total, 15 ml.) were mixed and deposited in 24 hr. at 0° a solid that consisted, after crystallisation from ethanol (30 ml. per g.), of very pale yellow prisms of the *toluene*-p-*sulphonate*, m. p. 209—211° (decomp.) (0·4 g., 77%) (Found: C, 62·65; H, 4·3; N, 10·65; S, 12·5. $C_{20}H_{16}N_4S,C_7H_8O_3S$ requires C, 62·8; H, 4·65; N, 10·85; S, 12·4%). Addition of picric acid (scale as above, in total of 8 ml. ethanol) slowly gave, on storage, the *picrate*, m. p. 142—145° (decomp.), forming yellow prisms (0·37 g., 64%) from very little acetone–ethanol, with addition of a few drops of water (Found: C, 53·3, 53·0; H, 3·4, 3·35. $C_{20}H_{16}N_4S,C_6H_3N_3O_7,H_2O$ requires C, 52·8; H, 3·55%). Addition of picrolonic acid (scale as above, in total of 25 ml. of ethanol) gave a mustard-yellow precipitate, which, crystallised from a large volume of ethanol, gave golden-yellow prisms of the *picrolonate*, m. p. 232—233° (decomp.) (0·55 g., 90%) (Found: C, 59·4; H, 3·7. $C_{20}H_{16}N_4S,C_{10}H_8N_4O_5$ requires C, 59·2; H, 3·95%).

Derivatives. A solution of the reactant (0·86 g., 0·0025 mole) in acetic anhydride (6 ml.) was refluxed during 0·5 hr., and the crude product obtained on addition of the liquid to water crystallised from acetone–ethanol (1 : 1, 40 ml.), affording white needles of the *monoacetyl derivative*, m. p. 245—248° (0·24 g., 25%) (Found: C, 68·9; H, 3·95; N, 15·0. $C_{22}H_{18}N_4OS$ requires C, 68·4; H, 4·7; N, 14·5%). A solution of the reactant (0·0025 mole) in pyridine (8 ml.), treated with benzoyl chloride (0·7 g., 0·005 mole), was heated on the steam-bath during 0·5 hr. Addition of the mixture to ice and hydrochloric acid gave an oil which solidified after being boiled briefly with water (20 ml.). Crystallisation from benzene–methanol (1 : 1; 15 ml.) gave pale-yellow opaque prisms of the *monobenzoyl derivative*, m. p. 169—171° (total, 0·65 g., 58%) (Found: C, 72·7; H, 4·2; N, 12·2. $C_{27}H_{20}N_4OS$ requires C, 72·3; H, 4·5; N, 12·5%).

NS-*Dibenzoyl-* and NNS-*Tribenzoyl-*o-*aminothiophenol.*—The conditions for the following benzoylations were chosen to be comparable with those required in identifying *o*-aminothiophenol obtained in the alkaline fusion of 2-(*NN*′-diphenylguanidino)benzothiazole (see below).

(i) *Use of excess of benzoyl chloride.* *o*-Aminothiophenol (0·94 g., 0·0075 mole) was dissolved in a solution of sodium hydroxide and 85% potassium hydroxide (10 g. each) in water (60 ml.). The yellow liquid was shaken and treated, during 15 min., with benzoyl chloride (8·4 g., 0·06 mole), the temperature rising to approx. 50°. The collected washed granular product consisted, after two crystallisations from ethanol (20 ml. per g.), of massive prisms of NNS-*tribenzoyl*-o-*aminothiophenol*, m. p. 136—138° (decomp.) (2·45 g., 75%) [Found: C, 73·85; H, 4·2; N, 3·3; S, 6·9%; equiv. (by hydrolysis), 145. $C_{27}H_{19}NO_3S$ requires C, 74·1; H, 4·35; N, 3·2; S, 7·3%; equiv., 146). The final mother-liquors contained small quantities of the dibenzoyl derivative, m. p. 152°.

(ii) *Use of two equivalents of benzoyl chloride.* In an identical experiment using less benzoyl chloride (2·25 g., 0·016 mole), there were obtained elongated platelets (total, 1·35 g., 54%) of the *NS*-dibenzoyl derivative, m. p. 153—154° (from ethanol) [Found: C, 71·8; H, 4·2%; equiv. (by hydrolysis), 170. Calc. for $C_{20}H_{15}NO_2S$: C, 72·1; H, 4·5%; equiv., 166·5]. The filtrates contained further small quantities of the dibenzoyl (admixed with a little tribenzoyl) derivative.

2-(NN′-*Diphenylguanidino*)*benzothiazole.*—*Alkaline fusion.* To a fused mixture of sodium hydroxide (8 g.) and 85% potassium hydroxide (10 g.), contained in a thick-walled 50 ml.

distilling flask, 2-(*NN'*-diphenylguanidino)benzothiazole (2·05 g., 0·006 mole) was added at 200°, and the temperature was raised to 240° during 5 min., and kept thereat during 10 min., and finally at 260—280° during another 5 min. The reactant decomposed with effervescence, ammonia was evolved, and a colourless distillate was collected in a flask containing water (10 ml.). The distillate was treated with 40% aqueous sodium hydroxide (20 ml.) and shaken with benzoyl chloride (4·2 g., 0·03 mole). The resulting precipitate was benzanilide, m. p. and mixed m. p. 161—163° (from ethanol) (1·89 g., 80%). The cooled alkaline melt was dissolved in successive portions of water (total, 50 ml.). The solution was extracted once with ether (30 ml.) to remove the last traces of aniline, and shaken with benzoyl chloride (5·6 g., 0·04 mole), the temperature being allowed to rise to 50°. The separated soft granules, crystallised from ethanol, were *NNS*-tribenzoyl-*o*-aminothiophenol, m. p. and mixed m. p. 135—137° (1·84 g., 70%) [Found: C, 74·0; H, 4·2; N, 2·8%; equiv. (by hydrolysis), 148. Calc. for $C_{27}H_{19}NO_3S$: C, 74·1; H, 4·35; N, 3·2%; equiv., 146].

Alternatively, treatment of the alkaline extracts with a smaller proportion of benzoyl chloride (2·1 g., 0·015 mole) gave 1·0 g. (50%) of *NS*-dibenzoyl-*o*-aminothiophenol, m. p. and mixed m. p. 153—154° (from ethanol) (Found: C, 71·9; H, 4·8; N, 4·2; S, 9·5. Calc. for $C_{20}H_{15}NO_2S$: C, 72·1; H, 4·5; N, 4·2; S, 9·6%). The mother-liquors contained a mixture of the di- and tri-benzoyl derivative. Bearing in mind the yields of benzoyl derivatives obtained in the above model experiments, this represents an almost quantitative recovery of *o*-aminothiophenol.

2-(NN'-*Diphenylguanidino*)-6-*methylbenzothiazole*.—(*a*) 2-Phenyl-3-phenylimino-5-*p*-tolylamino-Δ^4-1,2,4-thiadiazoline (1·79 g. 0·005 mole) was added to boiling ethanol (20 ml.), and the resulting yellow liquid refluxed during 1 hr. The solution gradually became colourless and began to deposit crystals. These were collected at 0° and recrystallised from acetone–ethanol, yielding prisms of the *benzothiazole*, m. p. 168—170° (1·11 g., 62%) (Found: C, 70·4; H, 4·8; S, 8·3. $C_{21}H_{18}N_4S$ requires C, 70·4; H, 5·0; S, 8·9%).

(*b*) Interaction, during 2 hr., of 2-amino-6-methylbenzothiazole [17] (0·90 g., 0·0055 mole) and diphenylcarbodi-imide [16] (1·0 g., 0·005 mole) in boiling anhydrous benzene (8 ml.), vacuum-evaporation of the solution, and dissolution of the residual oil in boiling ethanol (5 ml.), gave an immediate crystalline deposit which consisted, after recrystallisation, of prisms of the benzothiazole, m. p. and mixed m. p. 170—171° (total 1·52 g., 85%) (Found: C, 70·1; H, 4·9%). The ultraviolet absorption spectra of specimens prepared by procedures (*a*) and (*b*) were identical (cf. Table).

2-(N-*Phenyl*-N'-p-*tolylguanidino*)*benzothiazole*.—(*a*) A solution of 5-anilino-3-phenylimino-2-*p*-tolyl-Δ^4-1,2,4-thiadiazoline (1·8 g., 0·005 mole) in ethanol (15—20 ml.) was refluxed during 1 hr., 3N-sodium hydroxide (5 ml.) added, and refluxing continued for another 1 hr. The cooled liquid was slowly diluted with water until no further precipitation occurred, and the granular precipitate (1·7 g.) was collected at 0°. Crystallisation from ethanol and finally ethanol–acetone (4 : 1) afforded a small quantity of prisms, m. p. 118—123° (cf. Note). The combined filtrates gave, on evaporation and crystallisation from ethanol, prisms of 2-(N-*phenyl*-N'-p-*tolylguanidino*)-*benzothiazole*, m. p. 110—112° (total, 1·1 g., 61%) (Found: C, 70·25; H, 4·8; N, 15·9; S, 9·0. $C_{21}H_{18}N_4S$ requires C, 70·4; H, 5·0; N, 15·6; S, 8·9%).

Note: The higher-melting fraction had an ultraviolet spectrum identical with that of the product; it was probably a mixture of 2-(*N*-phenyl-*N'*-*p*-tolylguanidino)- and 2-(*NN'*-diphenylguanidino)-6-methyl-benzothiazole.

Alkaline fusion of the product, as described for the 2-(*NN'*-diphenylguanidino)-homologue, gave *NNS*-tribenzoyl-*o*-aminothiophenol, m. p. and mixed m. p. 136—137°, in 82% yield (Found: C, 74·2; H, 4·35%).

(*b*) To a stirred boiling solution of *N*-phenyl-*N'*-*p*-tolylthiourea [18] (3·63 g., 0·015 mole) in dry benzene (100 ml.) containing a little anhydrous sodium sulphate, yellow mercuric oxide (6·5 g., 0·03 mole) was added, and the mixture refluxed during 10 min. The resulting mercuric sulphide was removed at the pump (double filter paper), the filtrate treated with 2-aminobenzothiazole (1·50 g., 0·01 mole), and the solution distilled to quarter volume and refluxed during 2 hr. (protected against atmospheric moisture). After removal of the solvent in a vacuum, the residual oil was redissolved in hot ethanol (12 ml.) and treated with 3N-ethanolic hydrochloric

[16] Schmidt, Hitzler, and Lahde, *Ber.*, 1938, **71**, 1933 and subsequent papers.
[17] Hunter, *J.*, 1926, 1385.
[18] Gebhardt, *Ber.*, 1884, **17**, 3033.

acid (10 ml., 0·03 mole), followed by ether (12 ml.). The separated hydrochloride, collected at 0° [m. p. 226—228° (decomp.); total, 3·50 g.] was dissolved in hot ethanol (40 ml.) and the solution basified with 3N-sodium hydroxide (12 ml., 0·036 mole), boiled, and stirred into ice-water (400 ml.). The curdy white precipitate was collected, washed with water, cautiously dried (tendency to " glass "-formation), and crystallised from boiling ethanol (25 ml.); lustrous prisms of the benzothiazole, m. p. 111—113°, separated (total, 2·9 g., 81%) (Found: C, 70·3; H, 4·9%). The ultraviolet absorption spectra of the compound prepared by methods (*a*) and (*b*) were identical (cf. Table).

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE (UNIVERSITY OF LONDON),
8 HUNTER STREET, LONDON, W.C.1.
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