424. *The Chemotherapy of Tuberculosis. Part II. Some* N-*Substituted* p-*Phenylbenzamidines.*

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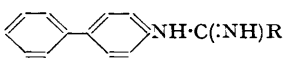
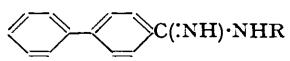
In order to obtain isomers of the substituted *N*-4-diphenylylamidines (I) (Part I, *J.*, 1950, 1826) which, whilst possessing similar lipoid solubilities and basic strengths, are devoid of the *p*-aminobenzoic acid skeleton present in (I), a series of *N*-substituted *p*-phenylbenzamidines (II) has been prepared by interaction of 4-cyanodiphenyl and the arylsulphonates of a number of aliphatic, aromatic, and alicyclic amines. Two closely-related cyclic amidines, 2-4′-diphenylyl-4 : 5-dihydroglyoxaline and 2-4′-diphenylylbenziminazole have also been prepared.

In order to increase the lipoid solubility and basic strength of 4-aminodiphenyl, a substance of known antituberculous activity (Erlenmeyer, Becker, Sorkin, Bloch, and Suter, *Helv. Chim. Acta*, 1947, **30**, 2058), a series of substituted *N*-4-diphenylylamidines (I) was prepared (Part I, *J.*, 1950, 1826) so that the correlation between physico-chemical properties and bacteriological activity might be examined. Activity was found to vary with structure, and will be discussed in full elsewhere.

It will be seen that the *N*-4-diphenylylamidines (I) possess the *p*-aminobenzoic acid skeleton, the presence of which has been claimed by a number of workers (cf. Erlenmeyer *et al.*, *loc. cit.*) to enhance antituberculous activity.

(I.) 

 (II.)

Thus Erlenmeyer *et al.* (*loc. cit.*) examined *p*-aminobenzoic acid and its *n*-alkyl esters (methyl—*n*-heptyl) whilst *p*-aminobenzamidine and 2-*p*-aminophenylpropene were prepared and tested

by Erlenmeyer, Noll, and Sorkin (*Helv. Chim. Acta*, 1949, **32**, 1676). Other compounds possessing the *p*-aminobenzoic acid structure, and found active *in vitro*, include 4-aminodiphenyl and its isostere 2-*p*-aminophenylpyridine (Erlenmeyer *et al.*, *loc. cit.*), 4-aminosalicylic acid (Lehmann, *Lancet*, 1946, 15), and 2-naphthylamine (Bloch, Lehr, and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1406).

In order to test whether the presence of this structure has any beneficial effect on antituberculous activity, the synthesis of a series of *N*-substituted *p*-phenylbenzamidines (II) was undertaken, and forms the subject of this communication. In these compounds, which do not possess the *p*-aminobenzoic acid skeleton, physical properties such as lipoid solubility and basic strength must approach closely to those of the isomeric *N*-4-diphenylylamidines (I), and a comparison of their bacteriological activities should therefore afford some evidence regarding the effect of the presence or absence of the *p*-aminobenzoic acid residue.

p-Phenylbenzamidine and the following *N*-substituted phenylbenzamidines were prepared by Oxley and Short's method (*J.*, 1947, 147) from 4-cyanodiphenyl and the arylsulphonates of a series of aliphatic, aromatic, and alicyclic amines: *N*-*n*-butyl-, *N*-*cyclo*hexyl-, *N*-phenyl-, *N*-*p*'-chlorophenyl-, *N*-*p*'-ethoxyphenyl-, *N*-*p*'-butoxyphenyl-, *N*-4-diphenylyl-, and *N*-*p*'-piperidinophenyl-. 4-Cyanodiphenyl was obtained in good yield by thermal decomposition *in vacuo* of the copper complex obtained by the action of potassium cuprocyanide on diazotised 4-aminodiphenyl, the cyanide distilling as formed. Reaction between the amine arylsulphonates and the cyanide took place at temperatures between 180° and 270° and required from 0·75 to 7 hours' heating. The yields ranged from 18 to 95%. The bases obtained were characterised as their benzenesulphonates, hydrochlorides, picrates, or toluene-*p*-sulphonates.

To examine the effect of additional cyclisation of the *p*-phenylbenzamidine molecule (II), the corresponding dihydroglyoxaline, 2-4'-diphenylyl-4 : 5-dihydroglyoxaline was prepared in excellent yield from 4-cyanodiphenyl and ethylenediamine by the method outlined by Oxley and Short (*J.*, 1947, 500). Reaction of the cyanide with *o*-phenylenediamine by Holljes and Wagner's method (*J. Org. Chem.*, 1944, **9**, 31) gave 2-4'-diphenylylbenziminazole, an analogue of (II; R = Ph) from which it differs by only two hydrogen atoms. Results of bacteriological and other examinations of these compounds will be reported elsewhere.

Experimental.

4-Cyanodiphenyl.—A hot solution of 4-aminodiphenyl (18·6 g.) in water (400 c.c.) containing hydrochloric acid (10 c.c.; 10N.) was poured on ice (200 g.). The stirred suspension of the hydrochloride was cooled to 5° and treated successively with hydrochloric acid (24 c.c.; 10N.) and sodium nitrite (8·6 g.) in water (20 c.c.). Sodium carbonate was added until the diazo-solution was almost neutral, whereupon it was slowly added to a solution of potassium cuprocyanide [from potassium cyanide (30 g.) in water (50 c.c.) and copper sulphate (26·6 g.) in warm water (100 c.c.)] at 60—70°. Nitrogen was evolved and a brown complex precipitated which was filtered off, washed, dried, and distilled under reduced pressure; 4-cyanodiphenyl (9·8 g., 50%) distilled at 120—140°/0·05 mm., solidifying to a solid, m. p. 80—82°. Recrystallisation from light petroleum (b. p. 60—80°) gave crystals, m. p. 85—86° (Dobner, *Annalen*, 1874, **172**, 111, gives m. p. 84—85°).

p-*Phenylbenzamidine.*—A mixture of 4-cyanodiphenyl (2·5 g.) and ammonium benzenesulphonate (5 g., 2 mol.) was fused at 270° (bath temp.) for 3 hours. Trituration of the cooled melt with acetone, and crystallisation from aqueous alcohol gave the *benzenesulphonate* (2·9 g., 59%) crystallising from water in plates, m. p. 285° (Found: N, 7·6, 7·6. $C_{13}H_{12}N_2,C_6H_6O_3S$ requires N, 7·9%). A similar fusion at 250° for 4 hours gave only 35% of the salt. The *amidine* separated from chloroform–light petroleum (b. p. 40—70°) in plates, m. p. 171—172° (Found: N, 14·3. $C_{13}H_{12}N_2$ requires N, 14·3%). The *picrate* formed yellow needles, m. p. 211—212°, from aqueous alcohol. It retained water of crystallisation even after being dried at 115° (Found: N, 15·15, 15·3, 15·25. $C_{13}H_{12}N_2,C_6H_3O_7N_3,2H_2O$ requires N, 15·2%). The *hydrochloride* crystallised from dilute hydrochloric acid (1 : 1) in plates, m. p. 238—239°, which also retained water of crystallisation even after being dried at 135° (Found: C, 61·9; H, 5·9; N, 11·2, 11·0, 11·2. $C_{13}H_{12}N_2,HCl,H_2O$ requires C, 62·2; H, 6·0; N, 11·2%).

n-*Butylammonium Benzenesulphonate.*—Prepared by mixing equivalent quantities of the amine in ether with the acid in methanol, this *salt* separated from methanol–ether in plates, m. p. 108·5° (Found: N, 6·0. $C_4H_{11}N,C_6H_6O_3S$ requires N, 6·1%).

p-*Phenyl*-N-n-*butylbenzamidine.*—Fusion of *n*-butylammonium benzenesulphonate (2 g.) and 4-cyanodiphenyl (0·9 g.) at 225° for 7 hours gave, on treatment with cold ether, unreacted cyanide (0·6 g.). The residue on crystallisation from water afforded plates of the *benzenesulphonate* (0·2 g., 29% calculated on recovered cyanide), m. p. 164—165° (Found: N, 6·7. $C_{17}H_{20}N_2,C_6H_6O_3S$ requires N, 6·8%). A similar fusion at 255° for 2 hours gave 12% of the benzenesulphonate. The *hydrochloride* separated from hydrochloric acid (1 : 1) in plates, m. p. 220—221° (Found: N, 9·8. $C_{17}H_{20}N_2,HCl$ requires N, 9·7%).

cyclo*Hexylammonium Benzenesulphonate.*—This *salt* crystallised in needles, m. p. 213°, from alcohol–ether (Found: N, 5·6. $C_6H_{13}N,C_6H_6O_3S$ requires N, 5·5%).

N-cyclo*Hexyl*-p-*phenylbenzamidine*.—A mixture of 4-cyanodiphenyl (1·8 g.) and *cyclo*hexylammonium benzenesulphonate (5 g.) was heated at 220° for 6 hours. The crude benzenesulphonate (0·8 g., 18%) was converted into the *hydrochloride*, which crystallised from hydrochloric acid (1 : 1) in prisms, m. p. 267—269° (decomp.) (Found : N, 9·2. $C_{19}H_{22}N_2$,HCl requires N, 8·9%). The *amidine* crystallised in prisms, m. p. 131·5°, from light petroleum (b. p. 60—90°) (Found : N, 9·9. $C_{19}H_{22}N_2$ requires N, 10·1%).

N : p-*Diphenylbenzamidine*.—Anilinium benzenesulphonate (1·9 g.) and 4-cyanodiphenyl (1 g.) were heated at 210° for 5 hours. Extraction with boiling water gave the *benzenesulphonate* (2 g., 83%) in plates, m. p. 191—192° (Found : N, 6·7. $C_{19}H_{16}N_2$,$C_6H_6O_3S$ requires N, 6·5%). The *amidine* crystallised in rhombs, m. p. 175·5°, from chloroform–light petroleum (b. p. 40—70°) (Found : N, 10·2. $C_{19}H_{16}N_2$ requires N, 10·3%).

p-*Phenyl*-N-p′-*chlorophenylbenzamidine*.—Fusion of 4-cyanodiphenyl (2·2 g.) and *p*′-chloroanilinium toluene-*p*-sulphonate (4·5 g.) at 200° for 1 hour gave the *toluene*-p-*sulphonate* (5·6 g., 95%) crystallising as plates, m. p. 270° (decomp.), from water (Found : N, 5·85. $C_{19}H_{15}N_2Cl$,$C_7H_8O_3S$ requires N, 5·85%). The *amidine* formed plates, m. p. 202°, from chloroform–light petroleum (Found : N, 9·25. $C_{19}H_{15}N_2Cl$ requires N, 9·15%).

p-*Phenyl*-N-p′-*ethoxyphenylbenzamidine*.—*p*-Ethoxyanilinium benzenesulphonate (3 g.) and 4-cyanodiphenyl (1·8 g.) reacted at 180° for 2·75 hours by which time the reaction mixture had solidified. Trituration with acetone gave the pure *benzenesulphonate* (3·8 g., 80%), m. p. 222—224°, unchanged on recrystallisation from water (Found : N, 6·2. $C_{21}H_{20}ON_2$,$C_6H_6O_3S$ requires N, 5·9%). The *amidine* crystallised from chloroform–light petroleum in plates, m. p. 206—207° (Found : N, 9·2. $C_{21}H_{20}ON_2$ requires N, 8·9%). The *hydrochloride* consisted of flat needles, m. p. 256—257° (Found : N, 7·9. $C_{21}H_{20}ON_2$,HCl requires N, 7·9%).

p-n-*Butoxyphenylammonium Benzenesulphonate*.—This *salt* separated from methanol–ether in stout needles, m. p. 186—187° (Found : N, 4·5. $C_{10}H_{15}ON$,$C_6H_6O_3S$ requires N, 4·3%).

p-*Phenyl*-N-p′-n-*butoxyphenylbenzamidine*.—Reaction of 4-cyanodiphenyl (1·8 g.) with *p*-*n*-butoxyphenylammonium benzenesulphonate (1·6 g.) at 180° for 4 hours gave the *benzenesulphonate* (49%) crystallising from water in colourless needles, m. p. 188° (Found : N, 5·8. $C_{23}H_{24}ON_2$,$C_6H_6O_3S$ requires N, 5·6%). The *amidine* crystallised from chloroform–light petroleum in rhombs, m. p. 212—213° (Found : N, 8·3. $C_{23}H_{24}ON_2$ requires N, 8·1%).

p-*Phenyl*-N-4-*diphenylylbenzamidine*.—A mixture of 4-cyanodiphenyl (1 g.) and 4-diphenylylammonium benzenesulphonate (2 g.) (Bauer and Cymerman, *J.*, 1950, 1826) was heated at 250—255° for 3 hours. After trituration with acetone, the *benzenesulphonate* (1·6 g., 57%) recrystallised from aqueous methanol in cream needles, m. p. 246—247° (Found : N, 5·3. $C_{25}H_{20}N_2$,$C_6H_6O_3S$ requires N, 5·5%). The *amidine* formed colourless plates, m. p. 283—284°, from 2-ethoxyethanol (Found : N, 8·3. $C_{25}H_{20}N_2$ requires N, 8·0%).

p-*Piperidinophenylammonium Ditoluene*-p-*sulphonate*.—Prepared from *p*-piperidinoaniline, b. p. 125—130°/0·05 mm., n_D^{25} 1·5980, the *ditoluene*-p-*sulphonate* separated in rhombs, m. p. 192—193°, from methanol–ether (Found : N, 5·5. $C_{11}H_{16}N_2$,$2C_7H_8O_3S$ requires N, 5·4%). The dihydrochloride separated from alcohol–ether in flat needles, m. p. 227—228° (decomp.) (sealed tube) (Found : N, 11·2. Calc. for $C_{11}H_{16}N_2$,2HCl : N, 11·2%). Leppla (*Ber.*, 1888, **21**, 2285) reports a hydrochloride monohydrate ; no m. p. is given.

p-*Phenyl*-N-p′-*piperidinophenylbenzamidine*.—The melt obtained by fusion of cyanodiphenyl (1·8 g.) and *p*-piperidinophenylammonium ditoluene-*p*-sulphonate (7·5 g.) at 200° for 0·75 hours was cooled and dissolved in methanol, and the solution was basified with cold methanolic potassium hydroxide. The crude amidine was dissolved in dilute hydrochloric acid (200 c.c. ; 2·5N.), the solution filtered and extracted with ether, and the base liberated at 0° ; the *amidine* crystallised from ligroin (b. p. 96—100°) or alcohol as clusters of needles, m. p. 207° (decomp.) (Found : N, 11·9. $C_{24}H_{25}N_3$ requires N, 11·8%). The *dihydrochloride* separated from alcohol–ether in buff rhombs, m. p. 260° (decomp.) (Found : N, 9·8. $C_{24}H_{25}N_3$,2HCl requires N, 9·8%).

2-4′-*Diphenylyl*-4 : 5-*dihydroglyoxaline*.—Reaction of 4-cyanodiphenyl (1·8 g.) with ethylenediamine ditoluene-*p*-sulphonate (8·1 g., 2 mols.) and ethylenediamine (1·2 g.) at 200° for 5·5 hours gave the *toluene*-p-*sulphonate* (3·75 g., 95%), crystallising from water in colourless plates, m. p. 261—262° (Found : N, 7·0. $C_{15}H_{14}N_2$,$C_7H_8O_3S$ requires N, 7·1%). The *base* formed needles, m. p. 198°, from chloroform–light petroleum (Found : N, 12·6. $C_{15}H_{14}N_2$ requires N, 12·6%).

2-4′-*Diphenylylbenziminazole*.—A mixture of 4-cyanodiphenyl (2 g.) and *o*-phenylenediamine dihydrochloride (1·8 g.) was heated at 200° (bath temp.) for 2 hours. The cooled melt was triturated with ether, and the residue extracted with boiling water (500 c.c.) and filtered. The residue (0·9 g., 30%) crystallised from *iso*propanol–ether in white rhombic plates, m. p. 316—317°, of 2-4′-*diphenylylbenziminazole hydrochloride* (Found : N, 9·2. $C_{19}H_{14}N_2$,HCl requires N, 9·15%). The aqueous filtrate was basified at 0° with concentrated ammonia solution giving the *base* (0·6 g., 22%) which crystallised from aqueous acetone in prisms, m. p. 291·5—292° (Found : N, 10·5. $C_{19}H_{14}N_2$ requires N, 10·4%).

This work was carried out under the auspices of the National Health and Medical Research Council, to whom thanks are due for financial assistance.

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