520. *The Chemotherapy of Tuberculosis. Part III.* Some N-Substituted 4-Aminodiphenyls.*

By L. Bauer, J. Cymerman, and W. J. Sheldon.

To investigate the effect of basic strength on antituberculous activity, two *N*-alkyl derivatives of 4-aminodiphenyl, *viz.*, *N'*-4'-diphenylyl-*NN*-diethylethylenediamine, and *N*-4'-diphenylyl-2-morpholinoethylamine, have been prepared, as well as the oxygen analogue of the former, 4-2'-diethylaminoethoxydiphenyl.

The highly basic 4-diphenylyl-guanidine and -diguanide were obtained, and the latter was found to condense readily with acetone to give a dihydrotriazine.

Condensation of 4-aminodiphenyl with a number of substituted benzaldehydes gave the expected Schiff's bases which were reduced catalytically to the 4-benzylaminodiphenyls.

The importance of primary aromatic amines in the chemotherapy of tuberculosis was early appreciated (Kuroya, *Jap. J. Exp. Med.*, 1929, **7**, 255). Systematic investigation of a series of these bases by Erlenmeyer *et al.* (*Helv. Chim. Acta*, 1945, **28**, 1406; 1947, **30**, 539, 2058; 1948, **31**, 75, 991; 1949, **32**, 605, 1209, 1275, 1674) and by Doub and Youmans (*Amer. Rev. Tuberc.*, 1950, **61**, 407) showed the most active compounds to be 4-aminodiphenyl, its isosteres, and β-naphthylamine.

Antibacterial activity in basic compounds has been found to depend on a high degree of ionisation (greater than 50%) at the physiological pH (7·2) (Albert, Rubbo, *et al.*, *Brit. J. Exp.*

* Part II, *J.*, 1950, 2078.

Path., 1945, **26**, 160; 1949, **30**, 159). In the cases of both 4-aminodiphenyl (pK_a 4·27 at 25°; Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3474) and β-naphthylamine (pK_a 4·3 at 25°; Farmer and Warth, *J.*, 1904, 1726) the percentage of base ionised at pH 7·2 does not exceed 1%; the antibacterial properties of these compounds might therefore conceivably be improved by an increase in their ionisation, provided of course that their antituberculous activity resides in the cations and not in the undissociated molecules.

The aim of the present work was then to discover the correlation between basicity and antibacterial activity in a series of *N*-substituted derivatives of 4-aminodiphenyl and β-naphthylamine, and concurrently to examine two other effects: (*a*) variation in lipoid solubility, and (*b*) possession of optimal flat surface area, in view of the results of Albert *et al.* (*loc. cit.*) showing that, even in highly ionised compounds, possession of a minimal flat area was essential for antibacterial activity to appear. It should be noted that both diphenyl and naphthalene exist as planar molecules (Dhar, *Indian J. Physics*, 1932, **7**, 43; Robertson, *Proc. Roy. Soc.*, 1933, *A*, 142, 674).

In the *N*-4-diphenylylamidines previously reported (Part I, *J.*, 1950, 1826), basicity has been increased to the required extent (pK_a 8—9 at 20°; forthcoming publication) and at the same time an isomeric series of *p*-phenylbenzamidines was prepared (*J.*, 1950, 2078) which was devoid of the *p*-aminobenzoic acid skeleton claimed to be essential for activity. After this work had been completed, the papers by Partridge *et al.* (*J.*, 1949, 3043; 1950, 459) came to hand, in which a series of *p*-alkoxy- and *p*-ω-alkoxyalkoxy-*N*-arylbenzamidines are described and examined for antituberculous activity, and we now learn that *N*-4-diphenylylbenzamidine, described in Part I of our series, was prepared independently in Dr. Short's laboratory in 1948 (Drs. D. A. Peak and W. F. Short, private communication). We wish to express our apology to Drs. Peak and Short and their collaborators for the lack of consultation in this matter. An extensive series of publications, concerned with direct correlation between chemical structure and antituberculous activity, is now emanating from Dr. Short's laboratory (*J.*, 1949, 2680, 2683, 3043; 1950, 445; and subsequent papers).

The present paper describes the preparation of some *N*-alkyl derivatives of 4-aminodiphenyl, prepared in order to obtain compounds of basic strength intermediate between those of the primary amine and of the amidines described earlier. Condensation of 4-aminodiphenyl and 2-diethylaminoethyl chloride afforded *N'*-4'-diphenylyl-*NN*-diethylethylenediamine (I) which on treatment with methyl iodide gave the dimethiodide of *N'*-4'-diphenylyl-*NN*-diethyl-*N'*-methylethylenediamine. Reaction of 4-aminodiphenyl with 2-morpholinoethyl chloride gave the analogous *N*-4'-diphenylyl-2-morpholinoethylamine (II), which with methyl iodide similarly afforded the dimethiodide of *N*-4'-diphenylyl-*N*-methyl-2-morpholinoethylamine. Treatment of 4-hydroxydiphenyl with 2-diethylaminoethyl chloride gave the oxygen analogue, 4-2'-diethylaminoethoxydiphenyl (III).

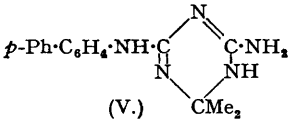
It is well known that the introduction of a guanidine or diguanide grouping leads to an even greater enhancement of basic strength; thus phenylguanidine and *N'*-phenyldiguanide have pK_a 10·9 (Davies and Elderfield, *J. Amer. Chem. Soc.*, 1932, **54**, 1499) and 10·7 (Albert *et al.*, *loc. cit.*) respectively at 20°; moreover the guanidinium and diguanide ions are themselves flat (cf. Tutida, *Rev. Phys. Chem. Jap.*, 1939, **13**, 31; Albert *et al.*, *loc. cit.*). Reaction of 4-aminodiphenyl with *S*-methylthiuronium sulphate at 200° afforded 60% of 4-diphenylylguanidine, and condensation of 4-diphenylylammonium benzenesulphonate and dicyandiamide at 155—180° gave *N'*-4-diphenylyldiguanide (IV). The free diguanide on prolonged boiling with acetone afforded a compound which is believed to be 6-amino-4-4'-diphenylylamino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (V) for which it gave correct analytical figures.

p-Ph·C$_6$H$_4$·NH·CH$_2$·CH$_2$·NEt$_2$ (I.)

p-Ph·C$_6$H$_4$·NH·CH$_2$·CH$_2$·N<[(CH$_2$)]$_4$>O (II.)

p-Ph·C$_6$H$_4$·O·CH$_2$·CH$_2$·NEt$_2$ (III.)

p-Ph·C$_6$H$_4$·NH·C(:NH)·NH·C(:NH)·NH$_2$ (IV.)



(V.)

A similar easy formation of a dihydrotriazine by condensation of a diguanide with acetone has been reported by Birtwell, Curd, Hendry, and Rose (*J.*, 1948, 1650). Treatment of this base with benzenesulphonic acid afforded two salts; one analysed correctly for the expected triazine dibenzenesulphonate, and the other for *N*-4-diphenylylguanidinium benzenesulphonate, with

which it was identical (mixed m. p.). No previous instance has, to the authors' knowledge, been recorded of such a ready degradation of a dihydrotriazine to a guanidine.

The preparation of Schiff's bases from tuberculostatically active aromatic amines was reported by Erlenmeyer (*Helv. Chim. Acta*, 1945, **28**, 1413). Condensation of 4-aminodiphenyl with *p*-hydroxy-, *p*-dimethylamino-, *p*-nitro-, and *p*-methoxy-benzaldehyde gave the expected benzylidene derivatives in quantitative yield. Reduction of the methine linkage by means of sodium and alcohol (Fischer, *Annalen*, 1887, **241**, 330) having proved unsuccessful for these compounds, uptake of hydrogen (1 mol.) in the presence of Adams's catalyst proceeded smoothly at atmospheric pressure to give the required benzylamino-compounds; 4-benzylaminodiphenyl was prepared similarly.

These bases and the corresponding hydrochlorides showed the expected properties, with the exception of the *N*-*p*-hydroxybenzyl compound which possessed in abnormally high m. p. (288°) and resisted all attempts to form a hydrochloride. It is therefore concluded that this compound exists predominantly in the zwitterionic form owing to internal salt formation. Catalytic reduction of 4-*p*-nitrobenzylideneaminodiphenyl did not proceed normally, but gave a mixture of products (cf. Phillips and Maggiolo, *J. Org. Chem.*, 1950, **15**, 659) which were not further investigated.

Experimental.

*N'-4'-Diphenylyl-*NN*-diethylethylenediamine.*—4-Aminodiphenyl (8·5 g.) was refluxed for 6 hours with a solution of 2-diethylaminoethyl chloride hydrochloride (10 g.) in aqueous alcohol (100 c.c.; 70%) containing potassium carbonate (10 g.). Water was added to the cooled mixture and the oil which separated was taken up in ether and dried (KOH). Distillation gave the base (9·7 g., 71%) as a light yellow viscous oil, b. p. 232—244°/11 mm., n_D^{16} 1·6050. The *dibenzenesulphonate* crystallised from methanol–ether in white needles, m. p. 124·5° (Found: C, 61·7; H, 6·3; N, 4·2, 5·3, 5·3. $C_{30}H_{36}O_6N_2S_2$ requires C, 61·6; H, 6·2; N, 4·8%). This salt was very soluble in water. The very hygroscopic *dihydrochloride* formed clusters of needles, m. p. 138° (sealed tube), from methanol–ether (Found: C, 8·0. $C_{18}H_{26}N_2Cl_2$ requires N, 8·2%). The *picrate* crystallised in yellow needles, m. p. 138—139° (Found: C, 57·5; H, 5·3; N, 14·3, 14·3. $C_{24}H_{27}O_7N_5$ requires C, 57·9; H, 5·5; N, 14·1%).

Treatment of a solution of the base in ether with an excess of methyl iodide at room temperature gave an oil which after several months solidified and then afforded colourless rhombic plates (from ethanol), m. p. 148° (Found: C, 43·9; H, 5·7; N, 4·6. $C_{21}H_{32}N_2I_2$ requires C, 44·5; H, 5·7; N, 4·9), and was *N'-4'-diphenylyl-*NN*-diethyl-*NN*'N'-trimethylethylenediammonium di-iodide.*

N-4'-Diphenylyl-2-morpholinoethylamine.—4-Aminodiphenyl (8·5 g.) and 2-morpholinoethyl chloride hydrochloride (19 g.; Mason and Black, *J. Amer. Chem. Soc.*, 1940, **62**, 1443) similarly (5 hours) afforded an oil which, dried (K_2CO_3) in ether, gave the *base* (9 g., 64%) as a viscous yellow oil, b. p. 210—230°/0·02 mm., which slowly solidified and crystallised from light petroleum (b. p. 40—70°) in needles, m. p. 80—81° (Found: N, 9·95. $C_{18}H_{22}ON_2$ requires N, 9·95%). Treatment with dry alcoholic hydrogen chloride and then ether gave the *dihydrochloride*, m. p. 240° (decomp.) with previous softening at 180° (Found: N, 7·4. $C_{18}H_{24}ON_2Cl_2$ requires N, 7·9%). Treatment of the base with a solution of methyl iodide in ether gave, on storage, a gum which solidified when boiled with ethyl acetate to yield the *dimethiodide* as white micro-crystals, m. p. 240° (decomp.) (Found: C, 43·5; H, 5·75. $C_{21}H_{30}ON_2I_2$ requires C, 43·45; H, 5·2%).

Table I.

p'-*Substituted* 4-*Benzylideneaminodiphenyls*, R·C_6H_4·CH:N·C_6H_4Ph.

R.	M. p.	Formula.	N, %. Found.	N, %. Reqd.
NH_2 *	152—153°	$C_{19}H_{15}N$	5·75	5·45
OH	249—250	$C_{19}H_{15}ON$	5·1	5·1
NMe_2	210—211	$C_{21}H_{20}N_2$	9·8	9·3
OMe	163—164	$C_{20}H_{17}NO$	5·35	4·9
NO_2	179—180	$C_{19}H_{14}N_2O_2$	9·35	9·25

* Previously prepared by Bell and Kenyon, *J.*, 1926, 2705, who give m. p. 148°.

Table II.

p'-*Substituted* 4-*Benzylaminodiphenyls*, R·C_6H_4·CH_2·NH·C_6H_4Ph.

	Base.								Hydrochloride.		
			Found, %.			Reqd., %.				Found,	Reqd.,
R.	M. p.	Formula.	C.	H.	N.	C.	H.	N.	M. p.	N, %.	N, %.
H	100—101°	$C_{19}H_{17}N$	87·9	6·55	5·5	88·0	6·6	5·4	200—201°	4·7	4·75
OH	288	$C_{19}H_{17}NO$	—	—	5·45	—	—	5·1	—	—	—
NMe_2	113·5—114	$C_{21}H_{22}N_2$	—	—	9·3	—	—	9·25	265	7·8	7·5
OMe	118—120	$C_{20}H_{19}NO$	87·5	7·05	—	87·85	7·05	—	272—273	4·6	4·3

4-2′-*Diethylaminoethoxydiphenyl*.—4-Hydroxydiphenyl (5·4 g.) was added to a solution of sodium methoxide [from sodium (1·5 g.)] in methanol (100 c.c.), followed by 2-diethylaminoethyl chloride hydrochloride (6 g.), and the mixture was refluxed for 4 hours. Excess of methanol was removed *in vacuo* and the residue distilled to give a mixture of the phenol and the required basic ether (b. p. 135—145°/0·06 mm.). Trituration with light petroleum (b. p. 40—70°) left the unchanged phenol which was filtered off, and evaporation of the solvent afforded the base as an oil, n_D^{17} 1·5746, which readily gave a *hydrochloride* crystallising from ethanol–ether in silky needles, m. p. 179—179·5° (Found : N, 4·7. $C_{18}H_{24}ONCl$ requires N, 4·6%). The *methiodide* (prepared in ether), m. p. 194—194·5°, separated from methanol–ether in rhombs (Found : N, 3·3. $C_{19}H_{26}ONI$ requires N, 3·4%). Both the hydrochloride and the methiodide were very soluble in water. The *picrate* formed golden-yellow plates (from alcohol), m. p. 91—92° (Found : N, 11·1. $C_{24}H_{27}O_8N_4$ requires N, 11·3%). The preparation of this base is claimed in B.P. 521,575 (*Chem. Abs.*, 1942, **36**, 783) where b. p. 154—157°/1·1 mm. is given.

4-*Diphenylylguanidine*.—4-Aminodiphenyl (8 g.) and *S*-methylthiuronium sulphate (5·5 g.) was heated at 200° for 2·5 hours, whereafter evolution of methanethiol had ceased. The cooled mass was triturated with ether and then cold water, and then boiled with water (300 c.c.) and filtered. The undissolved residue (6 g., 60%) was insoluble in ether or acetone, and crystallised from methanol–ether as white needles, m. p. 245°, of 4-*diphenylylguanidine sulphate* (Found : N, 16·15, 16·2. $C_{26}H_{28}O_4N_6S$ requires N, 16·15%). A solution of this salt in N-hydrochloric acid was treated with hot aqueous barium hydroxide until neutral (Congo-red), the precipitated barium sulphate filtered off, and the filtrate basified at 0° with barium hydroxide solution. The precipitate (85% yield) crystallised from chloroform–light petroleum in rhombic plates of 4-*diphenylylguanidine*, m. p. 189—190° (Found : C, 73·5; H, 6·4. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·15%). The *picrate* separated from dilute methanol as yellow prisms, m. p. 253° (decomp.) (Found : N, 19·15. $C_{19}H_{16}O_7N_6$ requires N, 19·1%) and the *benzenesulphonate* from *iso*propyl alcohol as nacreous plates, m. p. 170—171° (Found : N, 11·2. $C_{19}H_{19}O_3N_3S$ requires N, 11·4%).

N′-4-*Diphenylyldiguanide*.—A mixture of 4-diphenylylammonium benzenesulphonate (8·35 g.) and dicyandiamide (2·2 g., 1·04 mols.) was heated at 155° (bath-temp.) for 1·5 hours and then at 180° for a further 1·5 hours. The cooled solid was boiled with water (500 c.c.) and filtered, the filtrate on cooling affording white needles (3·1 g., 30%) of N′-4-*diphenylyldiguanide benzenesulphonate*, m. p. 214° (Found : N, 17·45. $C_{20}H_{21}O_3N_5S$ requires N, 17·05%). The aqueous filtrate from this salt was basified and the precipitated base crystallised, after prolonged boiling, from dilute acetone to give white crystals (1·5 g., 21%), m. p. 181—182° (decomp.), separating from light petroleum–chloroform as prisms of unchanged m. p., of 6-*amino*-4-4′-*diphenylylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (Found : C, 69·6; H, 6·35; N, 23·6, 23·3. $C_{17}H_{19}N_5$ requires C, 69·7; H, 6·5; N, 23·8%). This base on treatment with a solution of benzenesulphonic acid in methanol afforded prisms, m. p. 232·5°, from *iso*propyl alcohol, of the *dibenzenesulphonate* (Found : N, 11·45, 11·3; S, 10·3. $C_{29}H_{31}O_6N_5S_2$ requires N, 11·5; S, 10·5%) and from the mother-liquors a more soluble salt, crystallising from *iso*propyl alcohol as white plates identified as *N*-4-diphenylylguanidine benzenesulphonate, m. p. 170° (Found : C, 61·3; H, 5·0; S, 8·95. Calc. for $C_{19}H_{19}O_3N_3S$: C, 61·75; H, 5·15; S, 8·7%), undepressed on admixture with an authentic specimen (m. p. 170—171°). The triazine also gave a *dipicrate*, crystallising from aqueous ethanol as needles, m. p. 244—245° (Found : N, 20·1. $C_{29}H_{25}O_{14}N_{11}$ requires N, 20·5%).

A solution of the diguanide benzenesulphonate (m. p. 214°) in methanol was treated with methanolic potassium hydroxide till alkaline to brilliant-yellow, the solution evaporated to dryness, and the residue extracted with boiling chloroform, affording quantitative conversion into N′-4-*diphenylyldiguanide*, crystallising from chloroform–light petroleum or aqueous alcohol as white plates, m. p. 189° (decomp.) (Found : N, 27·1. $C_{14}H_{15}N_5$ requires N, 27·65%). The *picrate* separated from aqueous alcohol in yellow needles, m. p. 203·5—204° (Found : N, 23·7. $C_{20}H_{18}O_7N_8$ requires N, 23·25%).

p′-*Substituted* 4-*Benzylideneaminodiphenyls*.—Formed in quantitative yield by refluxing an alcoholic solution containing equivalent quantities of 4-aminodiphenyl and the substituted benzaldehyde for 0·25 hour, the Schiff's *bases* were recrystallised from alcohol or acetone. Their properties are given in Table I.

p′-*Substituted* 4-*Benzylaminodiphenyls*.—The Schiff's bases (*ca.* 2 g.) described above were reduced by shaking them in ethyl acetate (*ca.* 100 c.c.) with hydrogen in presence of Adams's catalyst (*ca.* 0·02 g.) until 1·1 mols. of hydrogen had been absorbed. Filtration and evaporation of the filtrate afforded a theoretical yield of the *bases*, which were recrystallised from alcohol or ethyl acetate (see Table II). Their *hydrochlorides* (Table II) were prepared by the action of dry hydrogen chloride in ether.

We acknowledge our indebtedness to Dr. W. F. Short for his fundamental work on the chemistry of amidines (*J.*, 1946, 147, and subsequent papers), which made possible the preparation of the substances described in Parts I and II of this series. The present work was carried out under the auspices of the National Health and Medical Research Council, to whom thanks are offered for financial assistance. The authors also thank Mrs. E. Bielski for microanalyses.

UNIVERSITY OF SYDNEY. [*Received, March 20th*, 1951.]