369. *The Chemotherapy of Tuberculosis. Part I. Some Substituted N-4-Diphenylylamidines.*

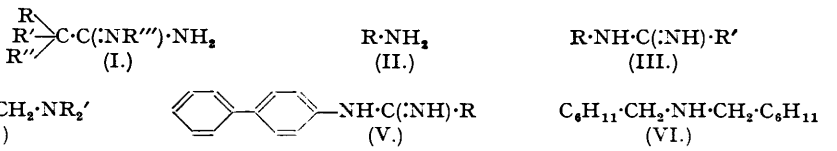
By L. Bauer and J. Cymerman.

In order to increase the basic strength and lipoid solubility of 4-aminodiphenyl, a substance of known anti-tuberculous activity, twelve substituted N-4-*diphenylylamidines* (V) have been prepared by reaction between a 4-diphenylylammonium salt and a series of aliphatic, aromatic, alicyclic, and hydroaromatic cyanides, and these amidines have been characterised by their *salts*.

Since it is felt that a combined bacteriological and physico-chemical approach is necessary for a more exact understanding of the relation between antituberculous activity and chemical

structure, an investigation into the influence of three physico-chemical factors has been undertaken in this connection: first, the effect of variation in lipoid solubility; secondly, the use of basic substances of different basic strengths; and, thirdly, the effect of alteration in molecular size, particularly in surface area, since adsorption is an important factor in many biological systems.

Newbery and Webster (*J.*, 1947, 738) have prepared a series of aliphatic monoamidines of general formula (I) containing seven to eighteen carbon atoms, some of which showed marked activities *in vitro* against *Mycobacterium tuberculosis*. In a series of publications (*Helv. Chim. Acta*, 1945, **28**, 1406; 1947, **30**, 2058; 1948, **31**, 75; 1949, **32**, 605) Erlenmeyer, Bloch, and their co-workers have compared the activities *in vitro* for a number of aromatic amines.



4-Aminodiphenyl, a lipophilic base possessing a flat surface, was taken as the starting point for this investigation. Its tuberculostatic activity was first reported by Erlenmeyer, Becker, Sorkin, Bloch, and Suter (1947, *loc. cit.*) who quote it as bacteriostatic *in vitro* in a dilution of 8×10^{-6} moles/l. Application of the above criteria to this compound led us to increase its lipoid solubility and basic strength. These properties in the case of an amine (II) may be conveniently improved by conversion into the corresponding amidine (III) (in which basic strength is greatly enhanced because of resonance possibilities; cf. Schwarzenbach and Lutz, *ibid.*, 1940, **23**, 1162), or the derived ω-dialkylaminoalkylamine, *e.g.*, (IV). A series of the latter have been synthesised and will be reported in a forthcoming communication. In this paper we report the preparation of a number of *N*-4-diphenylylamidines (V) possessing high basic strengths and containing a wide range of lipoid-solubilising substituents R.

These amidines were prepared by the elegant method of Oxley and Short (*J.*, 1946, 147), from a 4-diphenylylammonium salt and a series of aliphatic, aromatic, alicyclic, and hydroaromatic cyanides. For the preparation of aliphatic cyanides, the procedure recently given by La Forge, Green, and Gersdorff (*J. Amer. Chem. Soc.*, 1948, **70**, 3709), using ethylene glycol as solvent, proved convenient. Reaction temperatures between 100° and 185° were used, depending on the reactivity of the bromo-compound and its boiling point; and a catalytic amount of potassium iodide, added to the reaction mixture, was found to improve the yield in some cases. By this method *n*-heptyl cyanide was obtained in 86% yield from the corresponding bromide. The hydroaromatic compound, *cyclo*pent-1-enyl cyanide was obtained in 80·5% yield from the cyanohydrin.

The method of La Forge *et al.* (*loc. cit.*) failed to give *cyclo*hexyl cyanide from *cyclo*hexyl bromide. In the preparation of this cyanide by catalytic hydrogenation of *cyclo*hex-1-enyl cyanide there was also obtained a small yield of *biscyclo*hexylmethylamine (VI) (identified as the hydrochloride), previously obtained by Winans and Adkins (*ibid.*, 1933, **55**, 2051) from *cyclo*hexyl cyanide.

Twelve amidines (V) were obtained by fusion of a mixture of 4-diphenylylammonium benzenesulphonate or the corresponding toluene-*p*-sulphonate with cyanides of the types mentioned above. Temperatures between 180° and 250° for from 0·75 to 6 hours afforded yields ranging from 12 to 83%, and the bases obtained were characterised as their hydrochlorides, benzenesulphonates, toluene-*p*-sulphonates, or picrates. A by-product in the preparation of (V; R = *n*-$C_{16}H_{33}$) was the corresponding amide, *N*-4′-diphenylylhexadecane-1-carboxyamide. Results of bacteriological and other examinations of these compounds will be reported elsewhere in due course.

Experimental.

4-*Diphenylylammonium Benzenesulphonate* (A), *etc.*—Prepared by mixing equivalent amounts of 4-aminodiphenyl (in ether) and benzenesulphonic acid (in methanol), this *salt* [referred to as (*A*) below] crystallised from water in plates, m. p. 284° (Found: N, 4·3. $C_{18}H_{17}O_3NS$ requires N, 4·3%). 4-Diphenylylammonium chloride separated from water in plates, m. p. 285° (decomp.) (Found: N, 6·9. Calc. for $C_{12}H_{12}NCl$: N, 6·8%) (Hubner, *Annalen*, 1882, **209**, 342, does not give a m. p.). 4-Diphenylylammonium toluene-*p*-sulphonate formed needles (from alcohol), m. p. 249° (Found N, 4·2. Calc. for $C_{19}H_{19}O_3NS$: N, 4·1%) (Noller and Liang, *J. Amer. Chem. Soc.*, 1932, **54**, 670, give m. p. 246·6—247·6°).

N-4-*Diphenylylacetamidine.*—A mixture of 4-diphenylylammonium benzenesulphonate (10 g.) and methyl cyanide (15 c.c.) was heated in an autoclave for 5 hours at 180° (bath-temp.). The reaction

product was triturated with methanol–ether (1 : 10), and the residue extracted with boiling water (2 l.). Basification of the filtrate at 0° (ice) liberated the amidine which was filtered off, washed with ice-water, and dissolved in alcoholic hydrochloric acid. Evaporation of this solution and recrystallisation of the residue from acetone gave the *hydrochloride* as white plates, m. p. 180—181° (0·8 g., 12%) (Found : N, 11·5. $C_{14}H_{15}N_2Cl$ requires N, 11·4%). The *amidine* crystallised from light petroleum (b. p. 90—120°) in plates, m. p. 146—147° (Found : N, 13·4. $C_{14}H_{14}N_2$ requires N, 13·3%). The *picrate* separated from aqueous methanol or acetone–light petroleum in orange needles, m. p. 214—215°, which did not lose water of crystallisation even when dried at 115° (Found : N, 15·2, 15·0. $C_{20}H_{17}O_7N_5,H_2O$ requires N, 15·3%).

1-4′-*Diphenylylamidino*-n-*pentane*.—A solution of the salt (*A*) (5 g.) in *n*-amyl cyanide (5 g.) was refluxed for 6 hours at 220° (bath). Trituration of the cooled reaction product with ether gave the *benzenesulphonate* (3·5 g., 54%) crystallising from water in plates, m. p. 179° (Found : N, 6·7. $C_{24}H_{28}O_3N_2S$ requires N, 6·6%). The *amidine* formed flat needles [from light petroleum (b. p. 60—90°)], m. p. 128·5° (Found : N, 10·2. $C_{18}H_{22}N_2$ requires N, 10·5%). The *hydrochloride* separated from dilute hydrochloric acid (5N.) as needles, m. p. 231—232° (Found : N, 9·25. $C_{18}H_{23}N_2Cl$ requires N, 9·25%).

n-*Heptyl Cyanide*.—A mixture of *n*-heptyl bromide (36 g.), potassium cyanide (20 g., 1·5 mols.), and potassium iodide (1 g.) was stirred in ethylene glycol (80 c.c.) at 140° (bath) for 4 hours. The solution was diluted with water and extracted with ether. Distillation of the dried (Na_2SO_4) extracts gave *n*-heptyl cyanide (21·5 g., 86%), b. p. 102—105°/27 mm. (Newbery and Webster, *J.*, 1947, 738, give 59%, b. p. 111°/37 mm.)

1-4′-*Diphenylylamidino*-n-*heptane*.—A mixture of *n*-heptyl cyanide (11 g.) and (*A*) (10 g.) was heated at 220° (bath) for 6 hours. Dilution with ether afforded the *benzenesulphonate* (8·1 g., 59%), crystallising from acetone in needles, m. p. 158—159° (Found : N, 6·0. $C_{26}H_{32}O_3N_2S$ requires N, 6·2%). The *amidine* formed plates [from light petroleum (b. p. 60—90°)], m. p. 124° (Found : N, 9·4. $C_{20}H_{26}N_2$ requires N, 9·5%).

The *hydrochloride* separated from water in plates, m. p., 159—160° (Found : N, 8·0, 8·2. $C_{20}H_{27}N_2Cl,H_2O$ requires N, 8·0%).

1-4′-*Diphenylylamidino*-n-*hexadecane*.—A mixture of (*A*) (9 g.) and *n*-hexadecyl cyanide (13 g.) was heated at 250° for 4·5 hours. Treatment of the cold reaction mixture with methanol precipitated N-4′-*diphenylylhexadecane*-1-*carboxyamide* (2·5 g., 22%), crystallising from methanol in plates, m. p. 141—142° (Found : N, 3·7. $C_{29}H_{43}ON$ requires N, 3·3%). The filtrates on dilution with water and ether gave separation of 1-4′-*diphenylylamidino*-n-*hexadecane benzenesulphonate* at the interface (5 g., 31%), m. p. 135—139°, crystallising from aqueous methanol in needles or plates, m. p. 141—143° (Found : N, 4·8. $C_{35}H_{50}O_3N_2S$ requires N, 4·8%). A solution of this salt in methanol was treated with cold methanolic potassium hydroxide solution, and then diluted with water, affording the *amidine*, crystallising from light petroleum (b. p. 40—70°) in plates, m. p. 118—119° (Found : N, 6·4. $C_{29}H_{44}N_2$ requires N, 6·7%). The *picrate* separated as yellow plates from dilute alcohol, m. p. 113—114° (Found : N, 10·7. $C_{35}H_{47}O_7N_5$ requires N, 10·8%).

cyclo*Pent*-1-*enyl Cyanide*.—A solution of *cyclo*pentanone cyanohydrin (20 g.) in chloroform (40 c.c.) was treated with thionyl chloride (30 c.c.) at such a rate that gentle ebullition took place. The solution was then refluxed until evolution of gases had ceased (3 hours). Distillation gave *cyclo*pent-1-enyl cyanide (13·5 g., 80·5%), b. p. 62°/15 mm., n_D^{20} 1·4710 (Linstead and Meade, *J.*, 1934, 956, give 67%, b. p. 69°/15 mm.).

1-4′-*Diphenylylamidino*cyclo*pent*-1-*ene*.—A solution of 4-diphenylylammonium toluene-*p*-sulphonate (13 g.) in *cyclo*pent-1-enyl cyanide (13·5 g.) was heated for 1 hour at 200° and a further hour at 180°. The dark reaction product was triturated with ether to remove unchanged cyanide, and the residue extracted with boiling water. The aqueous extract, on cooling, gave colourless plates of the *amidine toluene*-p-*sulphonate*, m. p. 216—218° (decomp.) (Found : N, 6·7. $C_{25}H_{26}O_3N_2S$ requires N, 6·5%). The free *amidine* crystallised from ligroin (b. p. 90—120°) in needles, m. p. 166—166·5° (Found : N, 10·7. $C_{18}H_{18}N_2$ requires N, 10·7%). The *hydrochloride* formed rhombic plates (from water), m. p. 203—205° (Found : N, 9·5. $C_{18}H_{19}N_2Cl$ requires N, 9·4%). The *picrate* separated from acetone–light petroleum in yellow prisms, m. p. 147—148° (decomp.) (Found : N, 13·7. $C_{24}H_{21}O_7N_5$ requires N, 14·25%).

1-4′-*Diphenylylamidino*cyclo*hex*-1-*ene*.—A mixture of 4-diphenylylammonium toluene-*p*-sulphonate (34 g.) and *cyclo*hex-1-enyl cyanide (22 g., 2 mols.) was heated at 200—210° for 2 hours. The cooled melt was triturated with acetone and ether, and the residue (37 g., 83%) crystallised from methanol–ether as white needles, m. p. 248° (22 g., 50%) of the *amidine toluene*-p-*sulphonate* (Found : N, 6·3. $C_{26}H_{28}O_3N_2S$ requires N, 6·3%). The free *amidine* separated from light petroleum (b. p. 60—90°) in clusters of white needles, m. p. 141—142° (Found : N, 10·0. $C_{19}H_{20}N_2$ requires N, 10·1%). The *hydrochloride* formed flat needles (from 5N-hydrochloric acid), m. p. 231—232° (decomp.) (Found : N, 9·0. $C_{19}H_{21}N_2Cl$ requires N, 9·0%), and the *benzenesulphonate* was obtained in feathery needles, m. p. 232—233° (decomp.) (Found : N, 6·8. $C_{25}H_{26}O_3N_2S$ requires N, 6·5%). The *picrate* separated from acetone–light petroleum in yellow needles, m. p. 184—185° (Found : N, 13·7. $C_{25}H_{23}O_7N_5$ requires N, 13·9%).

cyclo*Hexyl Cyanide*.—Distillation of the product obtained by hydrogenation of *cyclo*hex-1-enyl cyanide (13·5 g.) in methanol (200 c.c.) using a platinic oxide catalyst gave *cyclo*hexyl cyanide (5 g., 31%), b. p. 72—73°/16 mm., n_D^{19} 1·4543 (Grignard, Bellet, and Courtot, *Ann. Chim.*, 1919, **12**, 368, give 50%, b. p. 75—77°/16 mm., n_D^{25} 1·453), followed by bis*cyclo*hexylmethylamine, b. p. 160°/16 mm., which gives a hydrochloride, m. p. 293° (decomp.), as rhombic plates from dilute hydrochloric acid (Found : C, 68·7; H, 11·3; N, 6·1. Calc. for $C_{14}H_{28}NCl$: C, 68·4; H, 11·5; N, 5·7%) (Winans and Adkins, *J. Amer. Chem. Soc.*, 1933, **55**, 2051, give b. p. 150—155°/14 mm. for the base and m. p. 298—299° for the salt).

1-4′-*Diphenylylamidino*cyclo*hexane*.—*cyclo*Hexyl cyanide (5 g.) and 4-diphenylammonium toluene-*p*-sulphonate (12 g.) were heated together for 3 hours at 200°. The product was taken up in methanol and treated with ether, giving the *amidine toluene*-p-*sulphonate* (12·3 g., 78%), m. p. 200—205°, crystallising from *iso*propanol–ether in colourless prisms, m. p. 206° (Found : N, 5·9. $C_{26}H_{30}O_3N_2S$

requires N, 6·2%). The free *amidine* separated from light petroleum (b. p. 96—100°) in tufts of needles, m. p. 161° (Found : N, 10·0. $C_{19}H_{22}N_2$ requires N, 10·1%). The *hydrochloride* crystallised from alcohol–ether in rhombs, m. p. 223—225° (decomp.) (Found : N, 7·95, 8·05. $C_{19}H_{23}N_2Cl,2H_2O$ requires N, 8·0%).

N-4-*Diphenylylbenzamidine*.—A solution of (*A*) (6·6 g.) in phenyl cyanide (5 c.c.) was refluxed at 220° for 4½ hours. Treatment of the cooled mixture with acetone gave the *benzenesulphonate* (4 g., 46%) crystallising from water as lustrous plates, m. p. 218—219° (Found : N, 6·5. $C_{25}H_{22}O_3N_2S$ requires N, 6·5%). The *amidine* crystallised from chloroform–light petroleum (b. p. 30—60°) in flat needles, m. p. 185° (Found : N, 10·4. $C_{19}H_{16}N_2$ requires N, 10·3%). The *hydrochloride* separated from alcohol–ether in colourless crystals, m. p. 233—234° (Found : N, 9·1. $C_{19}H_{17}N_2Cl$ requires N, 9·1%).

p-*Chloro*-N-4′-*diphenylylbenzamidine*.—Fusion of *p*-chlorophenyl cyanide (2·5 g.) and 4-diphenylylammonium toluene *p*-sulphonate (5·5 g.) at 200° for 0·75 hour and treatment of the cooled reaction mixture with methanol and ether gave the *amidine toluene*-p-*sulphonate* (5·9 g., 76%), crystallising from *iso*propanol or water in plates, m. p. 266—267° (Found : N, 5·9. $C_{26}H_{23}O_3N_2SCl$ requires N, 5·9%). The free *amidine* separated from chloroform in colourless rhombs, m. p. 216—217° (Found : N, 9·0. $C_{19}H_{15}N_2Cl$ requires N, 9·1%). The *hydrochloride* formed rhombs (from alcohol–ether), m. p. 279° (decomp.) (Found : N, 8·2. $C_{19}H_{16}N_2Cl_2$ requires N, 8·2%).

p-*Ethoxy*-N-4′-*diphenylylbenzamidine*.—A mixture of (*A*) (3·3 g.) and *p*-ethoxyphenyl cyanide (2 g.) was heated at 220° for 4 hours. Cooling and trituration with acetone gave the *benzenesulphonate* (2·5 g., 52%) crystallising from water in plates, m. p. 232—234° (Found : N, 6·0. $C_{27}H_{26}O_4N_2S$ requires N, 5·9%). The *amidine* separated from ethyl acetate in lustrous plates, m. p. 217—218° (Found : N, 9·0. $C_{21}H_{20}ON_2$ requires N, 8·9%), and the *hydrochloride* formed hexagonal plates (from water), m. p. 266—267° (decomp.) (Found : N, 7·7. $C_{21}H_{21}ON_2Cl$ requires N, 7·9%).

3 : 4-*Dimethoxy*-N-4′-*diphenylylbenzamidine*.—3 : 4-Dimethoxyphenyl cyanide (2·8 g.) and 4-diphenylylammonium toluene-*p*-sulphonate (5·1 g.) were fused at 200° for 2 hours. Working up of the cooled melt afforded the *amidine toluene*-p-*sulphonate* (5·8 g., 77%), crystallising from *iso*propanol in colourless rhombs, m. p. 217—218° (Found : N, 5·6. $C_{28}H_{28}O_5N_2S$ requires N, 5·6%). The *amidine* crystallised from chloroform–light petroleum (b. p. 40—70°) in needles, m. p. 206—207° (Found : N, 8·5. $C_{21}H_{20}O_2N_2$ requires N, 8·4%), and the *hydrochloride* formed needles, m. p. 230—232° (Found : N, 7·0. $C_{21}H_{21}O_2N_2Cl,2H_2O$ requires N, 6·9%).

p-*Carbethoxy*-N-4′-*Diphenylylbenzamidine*.—A mixture of *p*-carbethoxyphenyl cyanide (2·5 g.) and (*A*) (3·5 g.) was heated at 220° for 0·75 hour. The cooled melt was extracted with hot methanol (150 c.c.), and the insoluble *benzenesulphonate* (1·8 g., 34%) filtered off and crystallised from *iso*propanol, forming colourless rhombs, m. p. 250—251° (Found : N, 5·8, 5·9. $C_{28}H_{26}O_5N_2S$ requires N, 5·6%). The methanolic filtrates on treatment with methanolic potassium hydroxide gave the *amidine* (0·8 g., 22%), separating from alcohol in rhombs, m. p. 187—188° (Found : N, 8·3, 8·3. $C_{22}H_{20}O_2N_2$ requires N, 8·1%). Treatment of the base with alcoholic hydrogen chloride and ether yielded the *hydrochloride*, m. p. 216—217° (Found : N, 6·8, 6·75. $C_{22}H_{21}O_2N_2Cl,2H_2O$ requires N, 6·75%).

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ORGANIC CHEMISTRY DEPARTMENT,
UNIVERSITY OF SYDNEY.

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