488. *Hydrophilic Derivatives of 4-Aminodiphenyl.*

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In order to obtain derivatives of 4-aminodiphenyl containing water-solubilising groups, 2-*p*-diphenylylaminoethanol and 3-*p*-diphenylylaminopropane-1 : 2-diol have been prepared; the former alcohol could be obtained in 70% overall yield from 4-aminodiphenyl by hydroxyethylation of *N*-*p*-diphenylyltoluene-*p*-sulphonamide. *N*-*p*-Diphenylylethylamine has been obtained by two methods from 4-acetamidodiphenyl. The basic strengths and oil–water partition coefficients at pH 7·2 of these bases, as well as of the related 4-(*NN*-bis-2-hydroxyethylamino)diphenyl and 4-dimethylaminodiphenyl, have been determined, and the results are discussed.

For investigation of the effect on antituberculous activity when water-solubility is increased and the lipoid–water partition coefficient decreased, some derivatives of 4-aminodiphenyl containing water-solubilising groups such as hydroxy- or dihydroxy-alkyl were required.

2-*p*-Diphenylylaminoethanol was prepared (Baxter and Cymerman-Craig, *J.*, 1953, 1940) in 36% yield by reaction of 2-bromoethanol with *N*-4-benzylideneaminodiphenyl, followed by acid hydrolysis. Reaction of 4-aminodiphenyl with 2-bromoethanol in 2-ethoxyethanol gave only (64%) 4-(*NN*-bis-2-hydroxyethylamino)diphenyl, previously obtained by Ross (*J.*, 1949, 184). The same reaction, carried out in acetone solution, gave a 39% yield of this compound, as well as 4% of the desired monoalcohol. If 2-chloroethanol was used, only 6% of bishydroxyethyl compound was formed in 2-ethoxyethanol solution; no reaction occurred in acetone.

Treatment of the sodium salt of *N*-*p*-diphenylyltoluene-*p*-sulphonamide with 2-bromoethanol gave 84% of a 1 : 1 molecular compound, m. p. 131° of the starting sulphonamide and the desired *N*-*p*-diphenylyl-*N*-2′-hydroxyethyltoluene-*p*-sulphonamide. Attempts to resolve this complex by treatment with sodium hydroxide failed. However, prolonged hydrolysis with 24% hydrochloric acid readily gave 84% of 2-*p*-diphenylylaminoethanol (overall yield 70·5%), and 63% of unchanged sulphonamide. Molecular-weight determin-

ations of the complex gave 350 (Rast) and 341 (cryoscopic in benzene) respectively, almost exactly the mean of the molecular weights of the two components (345), indicating complete dissociation in solution, from which however it crystallises unchanged.

Two substances of similar structure but without the hydrophilic group were also prepared. Alkylation of 4-acetamidodiphenyl with ethyl iodide gave 24% of *N*-*p*-diphenylylethylamine, also obtained in 87% yield by lithium aluminium hydride reduction of the amide.

Several analogues of glycerol, including 3-aminopropane-1 : 2-diol, have been found by Bloch, Matter, and Suter (*Amer. Rev. Tuberc.*, 1947, **55**, 540) to increase the oxygen uptake of the tubercle bacillus, and Baker, Querry, and Kadish (*J. Org. Chem.*, 1950, **15**, 402) have prepared 4-amino-4'-(2 : 3-dihydroxypropylamino)diphenyl sulphone. Reaction of 4-aminodiphenyl with glycidol (Rider and Hill, *J. Amer. Chem. Soc.*, 1930, **52**, 1525) readily afforded the water-soluble 3-*p*-diphenylylaminopropane-1 : 2-diol in 88·5% yield. The presence of a catalytic amount of pyridine reduced the yield to 70%.

The basic strengths of the amines were determined in 50% aqueous-alcoholic solution by potentiometric titration (Carswell, Cymerman, and Lyons, *J.*, 1952, 430). Calculations were carried out by means of equation (1) which takes into account the effect of hydrogen ion; in the low concentrations used, this correction becomes appreciable at pH values below 4. The results are shown in Table 1.

$$pK_a = pH - \log \frac{[B] + [H^+]}{[BH^+] - [H^+]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It is seen that increase in basic strength resulting on substitution of the amino-group in 4-aminodiphenyl by two methyl groups or one ethyl group is paralleled by that occurring in the corresponding anilines (Hall and Spinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472). The lowering of pK_a due to the introduction of a 2-hydroxyethyl group, known to possess $+I$ character (Dewar, "The Electronic Theory of Organic Chemistry," Oxford, 1949), is clearly shown in the diphenyl series, and also by ethylamine, aminoethanol, and bishydroxyethylamine. Whereas introduction of a hydroxyl group directly on the nitrogen atom of a base depresses the pK_a by 3·25 units (ammonia 9·25; hydroxylamine 6·0), the same group on the β-carbon atom of an *N*-ethyl group depresses pK_a by only 0·77 unit, and in the γ-position, as in 3-*p*-diphenylylaminopropane-1 : 2-diol, further by only 0·41 unit.

TABLE 1. *Ionisation of substituted 4-aminodiphenyls in 50% alcohol at 20° ± 1°.*

Compound	pK_a	Compound	pK_a
$C_6H_4Ph\cdot NH_2$	4·05 [1]	NH_2Ph	4·58 [2]
$C_6H_4Ph\cdot NMe_2$	4·47	$NPhMe_2$	5·06 [2]
$C_6H_4Ph\cdot NHEt$	4·52	NHPhEt	5·11 [2]
$C_6H_4Ph\cdot NH\cdot CH_2\cdot CH_2\cdot OH$	3·75	NH_2Et	10·62 [2]
$C_6H_4Ph\cdot N(CH_2\cdot CH_2\cdot OH)_2$	3·20	$NH_2\cdot CH_2\cdot CH_2\cdot OH$	9·09 [2]
$C_6H_4Ph\cdot NH\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot OH$	3·34	$NH(CH_2\cdot CH_2\cdot OH)_2$	8·88 [2]

[1] Carswell, Cymerman, and Lyons, *J.*, 1952, 430. [2] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472. Measurement in water at 25°.

TABLE 2. *Oil–water partition coefficients of substituted 4-aminodiphenyls between liquid paraffin and phosphate buffer* (pH 7·2) *at 20° ± 2°.*

Compound	k'	$\lambda_{max.}$ (mμ)	log ε	Compound	k'	$\lambda_{max.}$ (mμ)	log ε
$C_6H_4Ph\cdot NHEt$	1550	282	4·33	$C_6H_4Ph\cdot NH\cdot CH_2\cdot CH_2\cdot OH$	2·65	282·5	4·29
$C_6H_4Ph\cdot NH_2$	92	270	4·21	$C_6H_4Ph\cdot N(CH_2\cdot CH_2\cdot OH)_2$	0·26	300	4·32
				$C_6H_4Ph\cdot NH\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot OH$	0·085	283·5	4·28

The partition coefficients between liquid paraffin (B.P., 1932) and water at pH 7·2 (the physiological pH) were determined by the spectrophotometric method of Cymerman-Craig and Diamantis (*J.*, 1953, 1619), and the value of the apparent partition coefficient (k') is given in Table 2, together with the wave-length of the absorption maximum and the intensity of absorption. Table 2 shows the stepwise increase in hydrophilic properties caused by the introduction of one or two 2-hydroxyethyl groups or the 2 : 3-dihydroxypropyl group, as well as the corresponding increase in lipophilic nature resulting on

substitution of the amino-group in 4-aminodiphenyl by two methyl groups or one ethyl group. Since the pK_a of the bases in Table 2 does not exceed 4·5, it follows that, as shown by equation (2) (Cymerman-Craig and Diamantis, *loc. cit.*), the apparent partition coefficient (k') measured in this determination is equal to the true partition coefficient (k) for these compounds.

$$k/k' = 1 + \text{antilog}\ (\text{p}K_a - \text{pH}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The activities *in vitro* of the bases in Table 2, kindly determined by Professor S. D. Rubbo, were uniformly low, complete inhibition of bacterial growth of *Mycobact. tuberculosis* (H37Rv), in the presence of 10% of serum, requiring dilutions of M/2000 to M/4000; an account of the bacteriological aspects will be given elsewhere. Variation in partition coefficient thus appears to have no effect on activity in this series.

Experimental

2-p-*Diphenylylaminoethanol* [with W. S. Gilbert].—(*a*) A mixture of 4-aminodiphenyl (17 g., 0·1 mol.), 2-bromoethanol (18·7 g., 0·15 mol.), and powdered calcium carbonate (5 g.) was refluxed with 2-ethoxyethanol (150 c.c.) and water (10 c.c.) for 31·5 hr. The solution was cooled, made alkaline to brilliant-yellow with sodium hydroxide (2N), and filtered. The filtrate was evaporated to low bulk *in vacuo* and the crystalline precipitate triturated with water (100 c.c.) and filtered off. Crystallisation from 95% alcohol afforded nacreous plates, m. p. 154°, of 4-(*NN*-bis-2-hydroxyethylamino)diphenyl (12·4 g., 64% calc. on 2-bromoethanol) (Found: C, 74·2, 74·45; H, 7·85, 7·3; N, 5·35; O, 12·5. Calc. for $C_{16}H_{19}O_2N$: C, 74·65; H, 7·45; N, 5·45; O, 12·45%), insoluble in boiling ether. Ross (*J.*, 1949, 184) gives m. p. 149—151°. From ethyl acetate the *hydrochloride* crystallised in needles, m. p. 191·5—192° (Found: C, 65·6; H, 6·95; N, 4·65. $C_{16}H_{19}O_2N$,HCl requires C, 65·4; H, 6·85; N, 4·75%), and the *picrate* as needles, m. p. 153° (Found: C, 54·35, 54·4; H, 4·55, 4·6; N, 11·4, 11·6. $C_{16}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 54·35; H, 4·55; N, 11·5%).

(*b*) A similar preparation from 4-aminodiphenyl (17 g.), 2-bromoethanol (18·7 g.), and anhydrous potassium carbonate (6·9 g.), refluxed in dry acetone (100 c.c.) for 28·5 hr., gave 7·9 g. (39%), m. p. 154°, identical with the material obtained as in (*a*). The mother-liquors were treated with excess of sodium hydroxide solution and extracted with ether. The dried ethereal extracts gave (apart from unchanged 4-aminodiphenyl) 0·8 g. (4%) of 2-*p*-diphenylylaminoethanol, crystallising from light petroleum (b. p. 60—90°) as needles, m. p. 111·5—113° (Found: C, 78·35; H, 6·95; N, 7·0. Calc. for $C_{14}H_{15}ON$: C, 78·85; H, 7·1; N, 6·6%). Baxter and Cymerman-Craig (*J.*, 1953, 1940) give m. p. 112°.

Reaction of N-(4-*Diphenylyl*)*toluene*-p-*sulphonamide with* 2-*Bromoethanol*.—To a solution of sodium ethoxide [from sodium (1·8 g.) in absolute alcohol (300 c.c.)] was added *N*-*p*-diphenylyltoluene-*p*-sulphonamide (25·85 g.), the sodium salt crystallising. After addition of 2-bromoethanol (10 g.) in absolute alcohol (100 c.c.) the mixture was refluxed for 5 hr. The clear solution was evaporated and gave, after removal of sodium bromide, 23·2 g. (84%) of a product, m. p. 129—130°, crystallising from *iso*propanol as needles, m. p. 130·5—131°, of a molecular *compound* (1 : 1) of *N*-(4-diphenylyl)toluene-*p*-sulphonamide and *N*-(2-hydroxyethyl)-*N*-(4-diphenylyl)toluene-*p*-sulphonamide [Found: C, 69·55, 69·65; H, 5·75, 5·55; N, 4·85; S, 9·4, 9·3, 9·45; O, 11·5%; *M*, (Rast) 350, (cryoscopic, C_6H_6) 341. $C_{19}H_{17}O_2NS,C_{21}H_{21}O_3NS$ requires C, 69·55; H, 5·55; N, 4·1; S, 9·3; O, 11·6%; *M*, 690. Calc. for $C_{21}H_{21}O_3NS$: C, 68·65; H, 5·75; N, 3·8; S, 8·7; O, 13·05%; *M*, 367. Calc. for $C_{19}H_{17}O_2NS$: C, 70·55; H, 5·3; N, 4·35; S, 9·9; O, 9·9%; *M*, 323].

2-p-*Diphenylylaminoethanol*.—The molecular compound (m. p. 130·5—131°; 13·1 g.) was refluxed for 18 hr. with hydrochloric acid (180 c.c.; 24% w/v) and filtered hot. The residue (R) was extracted with boiling water (200 c.c.) and the combined filtrates were cooled, basified, and extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extracts gave 3·35 g. (83%) of 2-*p*-diphenylylaminoethanol, m. p. 111·5—112°. The residue (R) (3·85 g., 63%) was *N*-(4-diphenylyl)toluene-*p*-sulphonamide, m. p. 153—154°, undepressed on admixture with an authentic sample (m. p. 158°).

N-p-*Diphenylylethylamine*.—(*a*) A mixture of 4-acetamidodiphenyl (6·33 g.), dry xylene (50 c.c.) and sodium (0·7 g.) was refluxed for 2·5 hr., cooled, and, after the addition of ethyl iodide (3·5 c.c., 50% excess), refluxed for a further 0·5 hr. After removal of the xylene by distillation, the residue was poured into water and extracted with ether. The residue left on evaporation of the washed and dried (Na_2SO_4) ethereal extracts was refluxed with alcoholic

potassium hydroxide (50 c.c.; 1% w/v) for 7 hr. The mixture was poured into water and extracted with ether. Dry hydrogen chloride was passed into the dried ethereal solution, giving 1·65 g. (24%) of N-p-*diphenylylethylammonium chloride*, crystallising from 95% alcohol as prisms, m. p. 208—209° (Found: C, 71·9; H, 6·85; N, 6·4. $C_{14}H_{16}NCl$ requires C, 71·95; H, 6·9; N, 6·0%). Treatment of this with aqueous alkali gave N-p-*diphenylylethylamine*, crystallising from light petroleum (b. p. 40—70°) as plates, m. p. 67—69° (Found: N, 7·25. $C_{14}H_{15}N$ requires N, 7·1%).

(*b*) A solution of 4-acetamidodiphenyl (2·5 g.) in dry ether (500 c.c.) was refluxed with lithium aluminium hydride (0·3 g.) for 13·5 hr. The complex was decomposed by successive addition of water, sodium hydroxide solution, and ammonium chloride, and the mixture extracted with ether. The residue left on evaporation of the dried (Na_2SO_4) extracts was refluxed with light petroleum (b. p. 40—70°; 50 c.c.) and filtered, leaving unchanged 4-acetamidodiphenyl (1·15 g., 46%), m. p. 167·5—168°, undepressed on admixture with an authentic sample (m. p. 169·5—170°). The filtrate gave *N-p*-diphenylylethylamine (1·1 g., 87% calc. on acetamidodiphenyl which reacted), m. p. 66—68°, undepressed on admixture with the material obtained by method *a*.

N-4-*Diphenylyl*-NN-*dimethylammonium chloride* had m. p. 129° (decomp.) (Found: N, 5·9. $C_{14}H_{15}N$,HCl requires N, 6·0%).

3-p-*Diphenylylaminopropane*-1 : 2-*diol*.—4-Aminodiphenyl (6·76 g., 0·04 mol.) and glycidol (2·96 g., 0·04 mol.) were heated at 100° for 4 hr. Trituration with ether or light petroleum (b. p. 40—70°) gave a white solid (8·6 g., 88·5%), m. p. 103—108°, almost insoluble in boiling ether but soluble in hot benzene and hot water. Crystallisation from aqueous alcohol gave plates, m. p. 128°, of 3-p-*diphenylylaminopropane*-1 : 2-*diol* (Found: N, 5·95. $C_{15}H_{17}O_2N$ requires N, 5·75%). The *hydrochloride* crystallised from ethanol in plates, m. p. 186° (Found: N, 5·3%; equiv., 273. $C_{15}H_{17}O_2N$,HCl requires N, 5·0%; equiv., 280).

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