755. *Bisquaternary Ammonium Salts. Part IV.*[1] *3-Alkylbenzene-1,ω-bistrimethylammonium Salts.*

By J. N. Ashley and S. S. Berg.

A series of 3-alkylbenzene-1,ω-bistrimethylammonium di-iodides (I) has been prepared. These compounds are much less active as ganglion-blocking agents than are the corresponding isomers in the 4-alkylbenzene series.

Some 4-alkylbenzene-1,ω-bistrialkylammonium di-iodides were described by Ashley and Leeds [1] in Part III of this series. Certain of these compounds were of interest as ganglion- or neuromuscular blocking agents, and in view of this it was decided to prepare some of the *m*-isomers, and of these the products where $n = 1$, 2, 3, and 4 were prepared and tested. The pharmacological results have been reported by Wien and Mason.[2] No compound of this *m*-series was as active as its *p*-isomer; when $n = 2$, the *m*-compound had only 50% of the ganglion-blocking activity of the corresponding *p*-isomer.[1,2]

(I) $m\text{-}Me_3N^+\cdot C_6H_4\cdot[CH_2]_n\cdot NMe_3^+ \ 2I^-$

The four compounds were prepared without difficulty; for the case where $n = 1$, 3-aminobenzyldimethylamine (prepared in excellent yield by modification of the methods used by Bennett and Willis [3] and Stedman [4]) was readily converted into the di-iodide (I;

[1] Part III, Ashley and Leeds, *J.*, 1957, 2706.
[2] Wien and Mason, *Brit. J. Pharmacol.*, 1953, **8**, 306.
[3] Bennett and Willis, *J.*, 1929, 264.
[4] Stedman, *J.*, 1927, 1906.

$n = 1$) by methylation and quaternisation with methyl iodide and sodium carbonate in methanol.

In the other cases (I; $n = 2$, 3, and 4), the synthesis followed the lines used earlier by Ashley and Leeds:

$$m\text{-}NMe_2\cdot C_6H_4\cdot CO\cdot[CH_2]_{n-1}\cdot H \xrightarrow[S]{NHMe_2} m\text{-}NMe_2\cdot C_6H_4\cdot[CH_2]_{n-1}\cdot CS\cdot NMe_2$$
(II) (III)

$$\xrightarrow{LiAlH_4} m\text{-}NMe_2\cdot C_6H_4\cdot[CH_2]_n\cdot NMe_2 \quad (IV)$$

The ketones (II; $n = 2$—4) were prepared from the appropriate alkyl phenyl ketone by successive nitration, reduction, methylation, quaternisation, and distillation of the quaternary salt *in vacuo*.

The Kindler–Willgerodt reaction was used to convert the ketones (II; $n = 2$—4) into the thioamides (III) which were smoothly reduced to the diamines (IV) by lithium aluminium hydride. The bisquaternary salts (I; $n = 2$—4) were prepared by treating the diamines with methyl iodide. They were white, crystalline, water-soluble compounds. The use of charcoal at any stage during the purification of these salts gave pale yellow products. The synthesis of the corresponding pentane (IV; $n = 5$) was not completed and only 3-nitro-[5] and 3-amino-valerophenone[5] were prepared in this synthesis.

A few preliminary experiments were also carried out on a possible alternative route to the di-iodide (I; $n = 5$), but this was not pursued further than 4-dimethylaminobutyl chloride hydrochloride.

Experimental

NN-*Dimethyl*-3-*nitrobenzylamine*, b. p. 131—132°/11 mm., was prepared (96%) as described by Bennett and Willis.[3] The picrate (from ethanol) had m. p. 215—217°.

3-*Amino*-NN-*dimethylbenzylamine*.—The foregoing nitro-compound (8 g.) in methanol (40 ml.) was reduced catalytically by using Adams catalyst (0·4 g.). Reduction was complete in 2 hr. and gave the diamine (6·3 g., 96%), pale yellow needles, m. p. 44—46° [from light petroleum (b. p. 60—80°)] (Stedman,[4] who reduced the nitro-compound with tin and hydrochloric acid, gives m. p. 46°).

3-*Dimethylamino*-NN-*dimethylbenzylamine Bismethiodide*.—The above diamine (5·0 g.), methyl iodide (30 ml.), anhydrous sodium carbonate (3·6 g.), and methanol (30 ml.) were refluxed together for 6 hr. The solution, after being mixed with methanol (30 ml.), was cooled to 5°; the *product* was filtered off and recrystallised twice from ethanol, forming prisms (8 g., 52%), m. p. 194—195° (decomp.) (Found: N, 6·5; I, 54·6. $C_{13}H_{24}N_2I_2$ requires N, 6·7; I, 54·9%).

3-Nitrovalerophenone (66%), b. p. 135—136°/0·3 mm. (lit.,[5] 145—150°/3 mm.), d_{25} 1·155, 3-nitropropiophenone (58%), m. p. 96—98° (lit.,[6] 98°), 3-nitrobutyrophenone (36%), m. p. 61° (lit.,[7] 61—62°), 3-aminoacetophenone (90%), m. p. 95—97° (lit.,[8] 90·5°), 3-aminopropiophenone (89%), m. p. 41—43° (lit.,[7] 42°), b. p. 125—127°/9·5 mm., 3-aminobutyrophenone (77%), m. p. 26—28° (lit.,[7] 27—28°), b. p. 168—169°/9 mm., 3-aminovalerophenone (88%), b. p. 180—183° (bath-temp.)/10 mm. (lit.,[5] 160—163°/3 mm.), and 3-dimethylaminoacetophenone (71%), m. p. 40—43°, b. p. 145—147°/11 mm. (lit.,[9] m. p. 42—43°, b. p. 148°/13 mm.), were prepared by the recorded methods.

3-*Dimethylaminopropiophenone*.—3-Aminopropiophenone (35 g.), methyl iodide (105 ml.), anhydrous sodium carbonate (26 g.), and methanol (105 ml.) were refluxed overnight. The mixture was evaporated under reduced pressure and the residue was distilled at 15 mm. The distillate afforded 3-*dimethylaminopropiophenone* (35 g., 84%), m. p. 31—33°, b. p. 150°/10 mm. (Found: C, 74·2; H, 8·4; N, 7·6. $C_{11}H_{15}ON$ requires C, 74·6; H, 8·4; N, 7·9%). 3-*Dimethylaminobutyrophenone* (30 g., 85%), b. p. 163—164°/12 mm. (Found: C, 75·1; H, 8·9; N, 7·2. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%), was prepared similarly.

[5] Hartung and Munch, *J. Amer. Chem. Soc.*, 1929, **51**, 2570.
[6] Comanducci and Pescitelli, *Gazzetta*, 1906, **36**, 787.
[7] Elson, Gibson, and Johnson, *J.*, 1930, 1128.
[8] Camps, *Arch. Pharm.*, 1902, **240**, 1.
[9] Braun, Rupe, and Zembruski, *Ber.*, 1901, **34**, 3524.

3-*Dimethylamino*-NN-*dimethylphenylthioacetamide*.—3-Dimethylaminoacetophenone (8·2 g.), redistilled dimethylamine (4·8 ml.), and sulphur (2·4 g.) were heated in a sealed tube at 160—165° for 4 hr. The resulting dark oil was extracted with benzene (5 × 50 ml.); the red solution, after being separated from tar, afforded an oil. Distillation of this at 0·2 mm. afforded two fractions: (*a*) (3·4 g.), b. p. 90—150° (bath-temp.) and (*b*) (5·2 g.), b. p. 150—160° (bath-temp.). Redistillation of the latter gave an oil (4·2 g.), b. p. 142—146°/0·1 mm., which slowly solidified and recrystallised from ether, giving the *thio-compound* (3·4 g., 26%), pale yellow needles, m. p. 63—64° (Found: C, 64·95; H, 8·05; N, 12·3. $C_{12}H_{18}N_2S$ requires C, 64·9; H, 8·1; N, 12·6%).

3-*Dimethylamino*-NN-*dimethylphenyl-thiopropionamide* (14·8%), b. p. 175—180° (bath-temp.)/0·2 mm. (Found: C, 65·7; H, 8·4; N, 12·1. $C_{13}H_{20}N_2S$ requires C, 66·1; H, 8·5; N, 11·9%) and -*thiobutyramide* (9·6%), b. p. 176—178°/0·1 mm. (Found: C, 67·5; H, 8·5; N, 11·0. $C_{14}H_{22}N_2S$ requires C, 67·2; H, 8·8; N, 11·2%), were prepared similarly, the sealed-tube reactions being carried out at 180°.

3-*Dimethylamino*-NN-*dimethylphenethylamine*.—3-Dimethylamino-*NN*-dimethylphenylthioacetamide (8·4 g.) in anhydrous ether (400 ml.) was added during 0·75 hr. to a stirred suspension of lithium aluminium hydride (2 g.) in anhydrous ether (100 ml.) at room temperature. The mixture was then stirred for 1 hr., water (30 ml.) was added, and the base extracted with 2N-hydrochloric acid. The diamine (6·4 g., 88·9%) was an oil, b. p. 85—90° (bath temp)/0·2 mm. (Found: C, 74·1, 74·4; H, 10·6, 10·5; N, 13·9. $C_{12}H_{20}N_2$ requires C, 75·0; H, 10·4; N, 14·0%). 3-*Dimethylamino*-NN-*dimethylphenyl-propylamine* (83%), b. p. 100—102°/0·8 mm. (Found: C, 75·3; H, 10·7; N, 11·3. $C_{13}H_{22}N_2$ requires C, 75·7; H, 10·7; N, 13·6%), and -*butylamine* (85%), b. p. 118—120°/0·7 mm. (Found: C, 76·6; H, 10·8; N, 12·9. $C_{14}H_{24}N_2$ requires C, 76·4; H, 10·9; N, 12·7%), were prepared similarly.

3-*Ethylbenzene*-1,2′-*bis*(*trimethylammonium Iodide*).—3-Dimethylamino-*NN*-dimethylphenethylamine (6·0 g.) and methyl iodide (20 ml.) were refluxed in methanol (100 ml.) for 5 hr., to give the bisquaternary *salt* which crystallised from methanol in rhombs (8 g., 54%), m. p. 231—233° (decomp.) (Found: N, 5·9; I, 53·0. $C_{14}H_{26}N_2I_2$ requires N, 5·9; I, 53·35%). 3-n-*Propylbenzene*-1,3′-*bis*(*trimethylammonium iodide*) [46·5% from methanol–acetone (1 : 3)], m. p. 197—198° (decomp.) (Found: N, 5·4; I, 51·6. $C_{15}H_{28}N_2I_2$ requires N, 5·7; I, 51·8%), and 3-n-*butylbenzene*-1,4′-*bis*(*trimethylammonium iodide*) [42%, from methanol–acetone (1 : 4)], m. p. 212—214° (decomp.) (Found: N, 5·5; I, 50·7. $C_{16}H_{30}N_2I_2$ requires N, 5·7; I, 50·4%), were prepared similarly.

4-*Dimethylaminobutyl Acetate*.—4-Bromobutyl acetate [10] (33·1 g., 24 ml.) and dimethylamine (16·8 g., 25 ml.) in toluene (50 ml.) were heated in a sealed tube at 100—110° for 4 hr. The contents were extracted with 10% hydrochloric acid; basification of the aqueous layer yielded 4-*dimethylaminobutyl acetate* (14·2 g., 54%), b. p. 89—90°/12 mm. (Found: C, 60·2; H, 10·8; N, 8·8. $C_8H_{17}O_2N$ requires C, 60·4; H, 10·7; N, 8·8%). The *picrate* formed yellow plates (from acetic acid), m. p. 199—200° (Found: N, 14·6. $C_8H_{17}O_2N,C_6H_3O_7N_3$ requires N, 14·4%).

4-*Dimethylaminobutanol*.—The above acetate (25 g.) was refluxed with potassium hydroxide (25 g.) in water (50 ml.) and ethanol (170 ml.) for 8 hr. and afforded the alcohol (17·8 g., 97%), b. p. 90°/12 mm. (Lukeš and Přeučil,[11] who prepared it by distilling 1,1-dimethylpyrrolidinium hydroxide, give b. p. 187—189°) (Found: C, 61·2; H, 12·8; N, 12·2. Calc. for $C_6H_{15}ON$: C, 61·5; N, 12·8; N, 12·0%). The *picrate* crystallised in yellow prisms (from ethanol), m. p. 77—78° (Found: N, 16·4. $C_6H_{15}ON,C_6H_3O_7N_3$ requires N, 16·6%).

4-*Dimethylaminobutyl Chloride Hydrochloride*.—Thionyl chloride (12·5 ml.) in anhydrous chloroform (50 ml.) was added during 0·5 hr. to the above alcohol (9·8 g.) in chloroform (17 ml.) at −10° to −5°. The solution was stirred for 2 hr. and the temperature allowed to rise to 25°. Removal of the solvent *in vacuo* at 20—25° left pale yellow, hydroscopic crystals (10·5 g., 74%). The *picrate* crystallised in yellow rhombs (from ethanol), m. p. 97—98° (Found: N, 15·4; Cl, 9·6. $C_6H_{14}NCl,C_6H_3O_7N_3$ requires N, 15·35; Cl, 9·7%).

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DAGENHAM, ESSEX. [*Received, June 2nd,* 1959.]

[10] Gold'Farb and Smoranski, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 113.
[11] Lukeš and Přeučil, *Coll. Czech. Chem. Comm.*, 1938, **10**, 384.