282. 5-*Alkylacridines. Part II.*[1] *Dialkylaminoalkylacridines.*

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A series of 5-dialkylaminoalkylacridines has been prepared, *viz.* R·$[CH_2]_n$·NR'_2 where R = 5-acridinyl, n = 1—4, R' = Me or Et, together with certain corresponding mono- and di-quaternary compounds. Hofmann degradation of 5-acridinylmethyltrimethylammonium iodide gave 5-vinylacridine.

The availability [1] of the reactive 5-methylacridine prompted further work on 5-ω-dialkylaminoalkylacridines as potential chemotherapeutic agents.

5-Bromomethylacridine with dimethyl- and diethyl-amine gave the corresponding 5-dialkylaminomethylacridines. The dimethylamino-compound so formed with dimethyl sulphate at room temperature furnished 5-acridinylmethyltrimethylammonium monomethosulphate, and this on further treatment with dimethyl sulphate, at 90°, gave the dimethosulphate. The monoquaternary bromides of 5-dimethylaminomethyl- and 5-diethylaminomethyl-acridine were obtained directly on treatment of 5-bromomethylacridine with trimethyl- and triethyl-amine respectively.

5-Methylacridine, formaldehyde, and dimethylamine under normal Mannich conditions gave the known 5-(2-dimethylaminoethyl)acridine.[2] In a comparable manner, the 5-(2-dimethylaminoethyl) analogues of 3-chloro- and 2-chloro-7-methoxy-acridine were prepared. Stepwise quaternisation of the first of these three products was achieved, as above, by treatment with dimethyl sulphate.

Hofmann degradation of the monomethiodide or monomethosulphate of the 5-(2-dimethylaminoethyl)acridine gave 5-vinylacridine. A boiling dilute solution of the latter in 2N-hydrochloric acid was transformed into a clear yellow polymer on cooling. Catalytic reduction of 5-vinylacridine gave the known 5-ethylacridine.[3]

Methyl β-5-acridinylpropionate was reduced by lithium aluminium hydride to 3-5′-acridanylpropan-1-ol, which on oxidation by ferric chloride furnished 3-5′-acridinylpropan-1-ol. The latter alcohol with hydrobromic acid gave 3-5′-acridinylpropyl bromide and thence by treatment with dimethylamine 5-(3-dimethylaminopropyl)acridine. The 3-chloroacridine analogues were also prepared. Mono- and di-methosulphates of 5-(3-dimethylaminopropyl)acridine were obtained as in the previous cases.

5-(2-Hydroxyethyl)acridine was converted by thionyl chloride into the chloroethyl compound, converted by the malonic ester synthesis into γ-5-acridinylbutyric acid. In a manner comparable with that described above, the derived methyl ester was converted into 5-(4-dimethylaminobutyl)acridine, whose mono- and di-methosulphate were also prepared.

Experimental

5-Dimethylaminomethylacridine Dihydrochloride.—5-Bromomethylacridine (3·5 g.) in benzene (150 c.c.) was refluxed while dry dimethylamine was slowly bubbled through it (2 hr.), then washed with water and evaporated. The crystalline residue was redissolved in dry ether, and hydrogen chloride bubbled in to precipitate the crude *dihydrochloride.* Recrystallisation of this from hydrochloric acid–acetone gave yellow aggregates (3 g.), m. p. above 180° (decomp.), fusing ~250° (Found: C, 62·2; H, 6·0; N, 9·3. $C_{16}H_{18}N_2Cl_2$ requires C, 62·2; H, 5·9; N, 9·1%).

Similarly, 5-bromomethylacridine (5·7 g.) with diethylamine (15 c.c.) in boiling benzene (150 c.c.) (2 hr.) gave *5-diethylaminomethylacridine dihydrochloride,* needles (from ethanol–ether), m. p. >180° (decomp.), fuses ~245° (Found: C, 63·7; H, 6·7; N, 8·0. $C_{18}H_{22}N_2Cl_2$ requires C, 64·1; H, 6·6; N, 8·3%).

5-Acridinylmethyltrimethylammonium Bromide.—5-Bromomethylacridine (4 g.) in boiling

[1] Part I, Campbell, Franklin, Morgan, and Tivey, *J.*, 1958, 1145; Morgan and Tivey, B.P. 789,696.
[2] Monti and Procopio, *Gazzetta*, 1933, **63**, 724.
[3] Koenigs, *Ber.*, 1899, **32**, 3599.

benzene (150 c.c.), when treated with dry trimethylamine (3 hr.), gave yellow needles of 5-*acridinylmethyltrimethylammonium bromide* (3·4 g.), m. p. ~200° (decomp.), fuses 240—245° (Found: C, 61·4; H, 5·9; N, 8·6. $C_{17}H_{19}N_2Br$ requires C, 61·6; H, 5·8; N, 8·5%).

Similarly, 5-bromomethylacridine (2·5 g.) in benzene (50 c.c.), refluxed for 2 hr. with triethylamine (10 c.c.), deposited pale yellow leaflets of 5-*acridinylmethyltriethylammonium bromide* (2 g.), m. p. ~190° (decomp.), fuses ~235° (Found: C, 62·7; H, 7·0; N, 7·6. $C_{20}H_{25}N_2Br,0{\cdot}5H_2O$ requires C, 62·8; H, 6·9; N, 7·3%).

5-*Acridinylmethyltrimethylammonium Methyl Sulphate.*—5-Dimethylaminomethylacridine (10 g.) in benzene (100 c.c.) was treated with dimethyl sulphate (15 c.c.) in benzene (30 c.c.) at room temperature. The crystalline precipitate which separated was recrystallised from ethanol–ether to give 5-*acridinylmethyltrimethylammonium methyl sulphate* (10·7 g.), m. p. 184—186° (decomp.) (Found: C, 58·7; H, 6·4. $C_{18}H_{22}O_4N_2S,0{\cdot}5H_2O$ requires C, 58·2; H, 6·0%). The latter (1 g.) was heated with dimethyl sulphate (6 c.c.) at 90° for 5 min. After cooling, the separated lower layer recrystallised from absolute ethanol–acetone, to give the *dimethosulphate*, m. p. 206—208° (decomp.) (Found: C, 47·5; H, 5·4. $C_{20}H_{28}O_8N_2S_2,H_2O$ requires C, 47·4; H, 5·6%).

3-*Chloro*-5-(2-*dimethylaminoethyl*)*acridine Dihydrochloride.*—3-Chloro-5-methylacridine (6·8 g.), hydrochloric acid (2·5 c.c.), water (40 c.c.), dimethylamine hydrochloride (3·5 g.) and 40% aqueous formaldehyde (3·5 c.c.) were refluxed together for 2 hr., cooled, and filtered and the filtrate was basified with aqueous ammonia and extracted with benzene. The benzene residue was dissolved in hydrochloric acid, and acetone added. The resultant precipitate of 3-*chloro*-5-(2-*dimethylaminoethyl*)*acridine dihydrochloride* (3 g.) recrystallised from hydrochloric acid–acetone as needles, m. p. 205° (decomp.) (Found: C, 54·9; H, 5·7; N, 7·9. $C_{17}H_{19}N_2Cl_3,H_2O$ requires C, 54·5; H, 5·7; N, 7·5%).

Similarly prepared, 2-*chloro*-5-(2-*dimethylaminoethyl*)-7-*methoxyacridine dihydrochloride*, m. p. ~215° (decomp.), recrystallised in yellow-orange needles from hydrochloric acid–acetone (Found: C, 53·7; H, 5·5; N, 6·8; Cl, 26·3. $C_{18}H_{21}ON_2Cl_3,H_2O$ requires C, 53·3; H, 5·7; N, 6·9; Cl, 26·2%).

2-5′-*Acridinylethyltrimethylammonium Methyl Sulphate.*—5-2′-Dimethylaminoethylacridine (5 g.) in dry benzene (80 c.c.) when shaken with dimethyl sulphate (7 c.c.), reacted exothermically and a pale yellow solid was precipitated which, when recrystallised from ethanol, gave pale yellow prisms of 2-5′-*acridinylethyltrimethylammonium methyl sulphate* (7 g.), m. p. >190° (decomp.), fuses ~220° (Found: C, 60·6; H, 6·5; N, 7·4; S, 8·4. $C_{19}H_{24}O_4N_2S$ requires C, 60·6; H, 6·4; N, 7·4; S, 8·5%). Similarly, the *monomethiodide*, m. p. >220° (decomp.), fuses 228°, crystallised in pale yellow prismatic needles from ethanol (Found: C, 54·8; H, 5·4; N, 8·1; I, 31·4. $C_{18}H_{21}N_2I$ requires C, 55·1; H, 5·4; N, 7·1; I, 32·3%). The *dimethosulphate* was prepared by heating the monomethosulphate (2·6 g.) in dimethyl sulphate (15 c.c.) for a few minutes at 90°. The solidified reaction mixture crystallised from methanol in yellow needles, m. p. 161° (Found: C, 48·6; H, 5·8; N, 5·7; S, 12·5. $C_{21}H_{30}O_8N_2S_2,H_2O$ requires C, 48·5; H, 6·2; N, 5·4; S, 12·3%).

5-*Vinylacridine.*—2-5′-Acridinylethyltrimethylammonium methiodide (2·3 g.) in water (100 c.c.) was heated with 5N-sodium hydroxide (5 c.c.) on a water-bath for 0·5 hr. The mixture, when cold, was filtered to give a pale green solid (1·3 g.), m. p. 74—84°, which was dissolved in light petroleum containing 5% of benzene and purified chromatographically on alumina. Recrystallisation from light petroleum (b. p. 60—80°) then gave lemon needles of 5-*vinylacridine*, m. p. 86°, resetting, and remelting at 89° [Found: C, 87·7; H, 5·5; N, 6·9%; *M* (Rast), 198. $C_{15}H_{11}N$ requires C, 87·8; H, 5·4; N, 6·8%; *M*, 205]. The *hydrochloride* crystallised from ethanol–ether in yellow needles, m. p. 232° (decomp.) (Found: Cl, 14·7. $C_{15}H_{11}N,HCl$ requires Cl, 14·7%).

5-*Ethylacridine.*—5-Vinylacridine (208 mg.) in ethanol (15 c.c.) was hydrogenated at room temperature and pressure over platinum oxide (0·1 g.). After filtration and evaporation to dryness, the ethanolic residue (200 mg.; m. p. 106—110°) was oxidised with aqueous ferric chloride in the usual manner to give, on recrystallisation from light petroleum (b. p. 60—80°), yellow needles of 5-ethylacridine (100 mg.), m. p. and mixed m. p. 110—111°. The *picrate* recrystallised from ethanol in needles, m. p. 203° (Found: N, 12·7. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires N, 12·8%).

3-5′-*Acridinylpropan*-1-*ol.*—Methyl β-5′-acridinylpropionate [1] (30 g.) in dry ether (750 c.c.) was added to a suspension of lithium aluminium hydride (6·5 g.) in ether (400 c.c.), and the

mixture refluxed for 5 hr. After decomposition of the excess of hydride by Micovic and Mihailovic's method [4] the ether layer was evaporated to dryness. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave colourless needles of 3-5′-*acridanylpropan*-1-*ol*, m. p. 116—117° (Found: C, 79·9; H, 7·2; N, 5·9. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%). The latter (24·5 g.) was treated in boiling dilute hydrochloric acid (1200 c.c.) with powdered ferric chloride until the reaction was complete. On cooling, the mixture was basified with aqueous ammonia and the precipitate, when dried, extracted with ethyl acetate. The residue crystallised from ethyl acetate, to give yellow needles of 3-5′-*acridinylpropan*-1-*ol*, m. p. 159—161° (Found: C, 81·1; H, 6·4; N, 5·8. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4; N, 5·9%).

3-5′-*Acridinylpropyl Bromide*.—3-5′-Acridinylpropan-1-ol (24 g.), when refluxed in 48% aqueous hydrobromic acid (200 c.c.), gave, on cooling, the *bromide hydrobromide* (31·7 g.), which recrystallised in yellow needles, m. p. 238—240°, from ethanol (Found: C, 50·6; H, 4·0; N, 3·7. $C_{16}H_{15}NBr_2$ requires C, 50·4; H, 3·9; N, 4·0%). Treatment of the salt in aqueous solution with ammonia furnished 3-5′-*acridinylpropyl bromide* which recrystallised in yellow needles, m. p. 103—104°, from ethanol (Found: C, 63·3; H, 4·8; N, 4·9. $C_{16}H_{14}NBr,0{\cdot}25H_2O$ requires C, 63·1; H, 4·8; N, 4·6%).

5-(3-*Dimethylaminopropyl*)*acridine Dihydrochloride*.—Dry dimethylamine was passed for 2 hr. through a stirred solution of 3-5′-acridinylpropyl bromide (30·7 g.) in ethanol (350 c.c.) at 70°. The ethanol was removed and the residue treated with 2N-sodium hydroxide and extracted with ethyl acetate. Evaporation of the ethyl acetate layer left an oil which was taken up in the minimum of hydrochloric acid and treated with acetone. The crude precipitate, when further treated with hydrochloric acid–acetone, gave yellow needles of 5-(3-*dimethylaminopropyl*)*acridine dihydrochloride* (34 g.), m. p. 276—278° (Found: C, 58·1; H, 7·1; N, 7·3. $C_{18}H_{22}N_2Cl_2,2H_2O$ requires C, 57·9; H, 7·0; N, 7·5%).

3-5′-*Acridinylpropyltrimethylammonium Methyl Sulphate*.—Crude 5-(3-dimethylaminopropyl)-acridine (prepared from the foregoing hydrochloride) (21 g.) in benzene (60 c.c.) was treated with dimethyl sulphate (15 c.c.) at room temperature. The separated oil, when solid (30·7 g.), was filtered off and recrystallised from acetone–propan-2-ol, to give 3-5′-*acridinylpropyltrimethylammonium methyl sulphate*, m. p. 190—192° (decomp.) (Found: C, 58·0; H, 6·7. $C_{20}H_{26}O_4N_2S,H_2O$ requires C, 58·2; H, 6·9%).

This sulphate (10 g.) was treated for 15 min. with dimethyl sulphate (4 c.c.) in boiling nitromethane (50 c.c.). On cooling, benzene was added to the mixture to give a crude product which, when recrystallised from absolute ethanol, gave pale yellow needles of the *dimethosulphate* (6·5 g.), m. p. 230—232° (decomp.) (Found: C, 46·2; H, 6·6; N, 5·0. $C_{22}H_{32}O_8N_2S_2,3H_2O$ requires C, 46·3; H, 6·7; N, 4·9%).

3-*Chloro*-5-(3-*hydroxypropyl*)*acridine*.—Ethyl β-(3-chloro-5-acridinyl)propionate [1] (8 g.) in tetrahydrofuran (50 c.c.) was refluxed with lithium borohydride (0·06 mol.) in tetrahydrofuran [5] (60 c.c.) for 6 hr., then decomposed,[4] and extracted with ethyl acetate. Evaporation of the extract left an oil which was oxidised by ferric chloride in the usual manner. On cooling, the yellow crystalline hydrochloride (7·4 g.), m. p. 220° (decomp.), which separated was filtered off l washed with acetone. Basification, extraction with chloroform, and recrystallisation gave e yellow needles of the *alcohol*, m. p 189—190° (Found: C, 70·0; H, 5·3. $C_{16}H_{14}ONCl$ uires C, 70·7; H, 5·2%).

3-*Chloro*-5-(3-*dimethylaminopropyl*)*acridine dihydrochloride*, m. p. 270°, needles from aqueous .tone (Found: C, 58·1; H, 5·8; N, 7·5. $C_{18}H_{21}N_2Cl_3$ requires C, 58·1; H, 5·7; N, 7·5%), s prepared, as the unsubstituted analogue, by conversion of the foregoing propanol into 3-*chloro*-5-*acridinyl*)*propyl bromide*, m. p. 83—85°, needles from light petroleum (b. p. 60—80°))und: C, 57·3; H, 4·0. $C_{16}H_{13}NBrCl$ requires C, 57·4; H, 3·9%), and treatment of this th dimethylamine in ethanol at 70°.

Methyl γ-5-*Acridinylbutyrate*.—5-2′-Hydroxyethylacridine (114 g.) in chloroform (950 c.c.) ıs refluxed with thionyl chloride (175 c.c.) for 2 hr. On cooling, the crystalline hydrochloride ıs filtered off and dried (yield, 168 g.), powdered, and added to a stirred solution of sodium (09·4 g.) and diethyl malonate (420 c.c.) in ethanol (800 c.c.), and the mixture was refluxed for 5 hr. On cooling, hydrochloric acid–water (1 : 1; 1 l.) was added, the ethanol was distilled off, and the aqueous residue refluxed for 2 hr. This solution deposited a crystalline hydrochloride

[4] Micovic and Mihailovic, *J. Org. Chem.*, 1953, **18**, 1192.
[5] Paul and Joseph, *Bull. Soc. chim.*, 1953, 758.

(125 g.), m. p. 267—270°, on cooling, a solution of which (65 g.) in aqueous sodium hydroxide (250 c.c.) was diluted with water (250 c.c.) and acidified with glacial acetic acid (290 g.). The resultant precipitate, when dried and recrystallised from acetic acid, gave γ-5′-acridinylbutyric acid, m. p. >220° (decomp.). Esterification in the usual manner furnished the *methyl ester*, m. p. 92—93°, in rectangular plates [from light petroleum (b. p. 60—80°)] (Found: C, 77·8; H, 6·3; N, 5·1. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

5-(4-*Dimethylaminobutyl*)*acridine Dihydrochloride*.—Reduction of this ester with lithium aluminium hydride gave 4-5′-*acridinylbutan*-1-*ol*, m. p. 117—119°, leaflets from benzene (Found: C, 80·4; H, 7·7; N, 5·5. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·6; N, 5·5%), and this on oxidation furnished 4-5′-*acridinylbutan*-1-*ol*, m. p. 146—147°, yellow needles from ethyl acetate (Found: C, 81·2; H, 6·7; N, 5·7. $C_{17}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%). The last compound was converted into 4-5′-*acridinylbutyl bromide hydrobromide*, m. p. 213—215° (decomp.), yellow needles from ethanol (Found: C, 51·8; H, 4·3; N, 3·5. $C_{17}H_{17}NBr_2$ requires C, 51·9; H, 4·4; N, 3·6%), and this with dimethylamine, as above, gave 5-(4-*dimethylaminobutyl*)*acridine dihydrochloride*, m. p. 226—228°, yellow needles from ethanol–ether (Found: C, 64·7; H, 7·0; N, 7·9. $C_{19}H_{24}N_2Cl_2$ requires C, 65·0; H, 6·9; N, 8·0%).

4-5′-*Acridinylbutyltrimethylammonium methyl sulphate*, m. p. 198—200°, pale yellow needles (from ethanol) (Found: C, 62·4; H, 6·9; N, 6·8. $C_{21}H_{28}O_4N_2S$ requires C, 62·4; H, 7·0; N, 6·9%), and the corresponding *dimethosulphate*, m. p. 152—155°, yellow prisms (from ethanol) (Found: C, 51·5; H, 6·9; N, 4·8. $C_{23}H_{34}O_8N_2S_2,0{\cdot}5H_2O$ requires C, 51·2; H, 6·5; N, 5·2%), were obtained as above.

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