224. 5-*Alkylacridines. Part I. Synthesis of* 5-*Methylacridine and Certain Substituted Analogues.*

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A new synthesis of 5-methylacridine is described. Reaction of 5-chloroacridine with ethyl malonate and degradative hydrolysis of the product afforded 5-methylacridine in high yield. This and certain of its homologues with *N*-bromosuccinimide gave the reactive 5-bromomethyl compounds. Syntheses of 5-(*N*-dichloroacetyl-*N*-2-hydroxyethylaminomethyl)acridine (V) and 2-chloro-7-methoxy-5-(4-diethylamino-1-methylbutylaminomethyl)-acridine (IX) are also described.

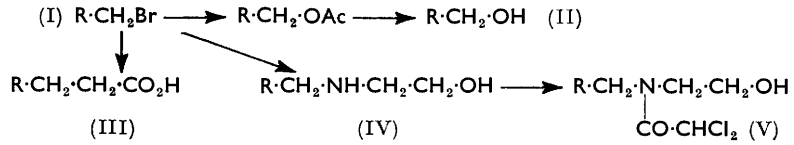
In a chemotherapeutic investigation certain substituted 5-methylacridines have been prepared. Existing syntheses [1] of the versatile intermediate 5-methylacridine and certain of its homologues are unsuitable for large-scale preparation and give poor yields. Condensing 5-chloroacridine with diethyl malonate in presence of sodium ethoxide and

[1] Albert, " The Acridines," Edward Arnold & Co., London, 1951, p. 128.

hydrolysing intermediate ethyl acridinylmalonate *in situ* by acid gave 5-methylacridine in almost quantitative yield:

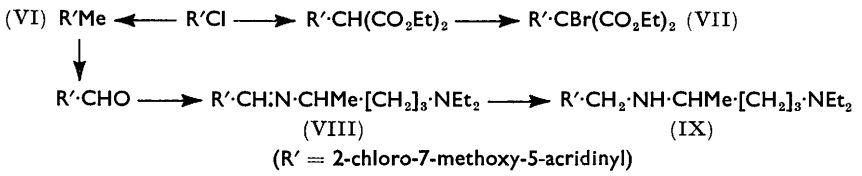
$$RCl \longrightarrow R{\cdot}CH(CO_2Et)_2 \longrightarrow RMe \ (R = 5\text{-acridinyl})$$

5-Methylacridine with *N*-bromosuccinimide furnished the reactive bromomethyl compound (I). With potassium acetate this gave 5-acetoxymethylacridine, which was hydrolysed to 5-hydroxymethylacridine (II), and with sodio-malonic ester gave, after hydrolysis, 2-5′-acridinylpropionic acid (III).



Recent publications [2,3] describing the amœbicidal activity of certain *N*-benzyl-*N*-hydroxyalkyldichloroacetamides prompted the synthesis of an acridine isostere. 5-Bromomethylacridine and ethanolamine in chloroform yielded 5-(2′-hydroxyethylaminomethyl)-acridine (IV). This, on treatment with dichloroacetyl chloride, gave the amide (V), an analogue which proved to be less active than other known substituted heterocyclic halogenoacetamides.[4]

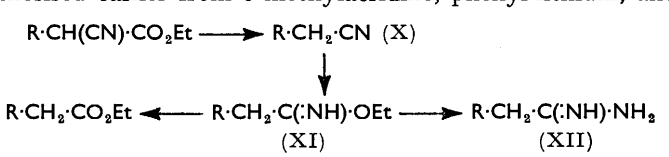
Synthesis of a mepacrine analogue, carrying an intervening $-CH_2-$ link between the nucleus and the side-chain, could not be achieved *via* a corresponding 5-bromomethyl intermediate. 2-Chloro-7-methoxy-5-methylacridine (VI) was not brominated by *N*-bromosuccinimide in the manner expected. Further, although the intermediate diethyl



(R′ = 2-chloro-7-methoxy-5-acridinyl)

2-chloro-7-methoxy-5-acridinylmalonate was brominated to give the ester (VII), this did not react with 4-amino-*NN*-diethylpentylamine in a controllable manner. The successful synthesis, established in the quinoline series,[5] involved catalytic reduction of the anil (VIII), derived from 2-chloro-5-formyl-7-methoxyacridine [6] and the diamine, and gave the 2-chloro-7-methoxy-5-(4-diethylamino-1-methylbutylaminomethyl)acridine (IX), isolated as a trihydrochloride. The much lower antimalarial activity of the latter compound reflected experience with this type of compound in the quinoline field.[5]

Mild alkaline hydrolysis of ethyl 5-acridinylcyanoacetate [7] furnished 5-cyanomethylacridine (X), synthesised earlier from 5-methylacridine, phenyl-lithium, and *N*-cyano-*N*-



methylaniline.[8] Alcoholic hydrogen chloride converted 5-cyanomethylacridine into the imidoate (XI) which with alcoholic ammonia gave 5-amidinomethylacridine (XII) and, on hydrolysis, ethyl 5-acridinylacetate.

[2] Surrey, *J. Amer. Chem. Soc.*, 1954, **76**, 2214.
[3] Surrey and Rukwid, *ibid.*, 1955, **77**, 3798.
[4] Elslager, Benton, Short, and Tendick, *ibid.*, 1956, **78**, 3453.
[5] Work, *J.*, 1942, 426.
[6] Perrine and Sargent, *J. Org. Chem.*, 1949, **14**, 583.
[7] Goldberg and Kelly, B.P. 600,354/1948.
[8] Lettré, Jungmann, and Salfeld, *Chem. Ber.*, 1952, **85**, 397.

Experimental

Diethyl 5-Acridinylmalonate.—A solution of the sodio-derivative from ethyl malonate (100 g., 0·62 mol.) and sodium (13·8 g., 0·6 g.-atom) in absolute ethanol (255 c.c.) was treated with 5-chloroacridine (86 g., 0·4 mol.) (irritant) and refluxed with stirring for 16 hr. Pouring the mixture into water–hydrochloric acid (1 : 1; 800 c.c.) gave a solid hydrochloride and this, when treated in aqueous solution with 2N-sodium hydroxide, afforded a crude base. Recrystallisation of the latter from light petroleum (b. p. 80—100°) gave pale yellow flattened needles of *diethyl 5-acridinylmalonate* (101·9 g., 75%), m. p. 101—102° (Found: C, 71·3; H, 5·6; N, 4·2. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·7; N, 4·2%).

Similarly prepared, *diethyl 2-chloro-7-methoxy-5-acridinylmalonate* (65%), m. p. 115°, recrystallised from ethanol in stout needles (Found: C, 62·7; H, 5·1; N, 3·6. $C_{21}H_{20}O_5NCl$ requires C, 62·8; H, 5·0; N, 3·5%).

5-Methylacridine.—(i) In the foregoing preparation of diethyl acridinylmalonate, the 5-chloroacridine (86 g.) in hot toluene (255 c.c.) was added to the ethyl sodiomalonate in ethanol, and the mixture refluxed for 16 hr. After the addition of water–hydrochloric acid (1 : 1; 800 c.c.) the ethanol and toluene were distilled off, and the resultant aqueous solution refluxed for 4 hr. More water (800 c.c.) was then added and the solution filtered (charcoal) hot. The filtrate slowly deposited crystalline 5-methylacridine hydrochloride. The latter in water (2 l.) was treated with sufficient 2N-sodium hydroxide to precipitate the crude base. Recrystallisation from ethyl acetate gave pure 5-methylacridine (72 g., 92·7%), m. p. 115—116°.

(ii) Ethyl 5-acridinylmalonate (1 g.) was refluxed in aqueous hydrochloric acid (1 : 1; 6 c.c.) for 4 hr. and kept overnight. The hydrochloride which crystallised (0·94 g.), when dissolved in water and basified with ammonia, furnished the crude base (0·55 g., 96%). Recrystallisation from light petroleum (b. p. 40—60°) gave 5-methylacridine, m. p. 115—116°.

The following *acridines* were prepared as in method (i):

3-Chloro-5-methyl- (72%), m. p. 124—125°, pale yellow elongated plates from ethanol (Found: C, 73·3; H, 4·6; N, 6·2. $C_{14}H_{10}NCl$ requires C, 73·8; H, 4·4; N, 6·2%). The *hydrochloride* separated from water in needles, m. p. ~250° (decomp.) (Found: C, 63·4; H, 4·2; N, 5·4. $C_{14}H_{11}NCl_2$ requires C, 63·6; H, 4·2; N, 5·3%).

2 : 8-Dichloro-5-methyl- (70%), m. p. 214°, yellow needles from ethanol (Found: C, 63·8; H, 3·6; N, 5·5. $C_{14}H_9NCl_2$ requires C, 64·1; H, 3·5; N, 5·3%).

2-Chloro-7-methoxy-5-methyl- (VI) (77%), m. p. 169°, pale yellow needles from ethanol. Perrine and Sargent [6] record m. p. 169—170°.

5-Bromomethylacridine (I).—5-Methylacridine (39·5 g.) and *N*-bromosuccinimide (34 g.) were refluxed in carbon tetrachloride (770 c.c.) in presence of benzoyl peroxide (2 g.) for 4·5 hr. Filtration and storage at room temperature led to a crystalline precipitate (36 g.), m. p. 145—160° (decomp.). Recrystallisation of this from carbon tetrachloride gave pale yellow plates (slowly) of *5-bromomethylacridine*, m. p. 169—170° (decomp.), resolidifying immediately (Found: C, 61·5; H, 3·7; N, 5·3; Br, 29·1. $C_{14}H_{10}NBr$ requires C, 61·8; H, 3·7; N, 5·2; Br, 29·4%).

Similarly prepared, *5-bromomethyl-3-chloroacridine* (Found: C, 54·5; H, 3·3. $C_{14}H_9NClBr$ requires C, 54·8; H, 3·2%) recrystallised from carbon tetrachloride in pale yellow needles, decomp. >200°.

Diethyl α-Bromo-2-chloro-7-methoxy-5-acridinylmalonate (VII).—Diethyl 2-chloro-7-methoxy-5-acridinylmalonate (1 g.) was heated under reflux with *N*-bromosuccinimide (0·42 g.) in carbon tetrachloride (100 c.c.) for 2 hr. Next morning the mixture was filtered and evaporated. The residue recrystallised from light petroleum (b. p. 80—100°), to give needles of *bromo-ester*, m. p. 137° (Found: C, 52·6; H, 4·1; N, 3·0. $C_{21}H_{19}O_5NBrCl$ requires C, 52·5; H, 4·0; N, 2·8%).

5-Hydroxymethylacridine (II).—5-Bromomethylacridine (2 g.) and potassium acetate (2 g.) were refluxed in absolute ethanol (20 c.c.) for 2 hr. The cooled mixture was then poured into water (100 c.c.), and the suspension shaken with ether. Crystallisation of the ether-residue from aqueous alcohol gave pale yellow needles of *5-acetoxymethylacridine* (1·4 g.), m. p. 124° (Found: C, 76·3; H, 5·2; N, 5·5. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). Hydrolysis of the acetoxy-compound (1·4 g.) in ethanol (100 c.c.) containing N-sodium hydroxide (18 c.c.), at room temperature for 17 hr., gave *5-hydroxymethylacridine* (0·8 g.), m. p. 164—165° (decomp.) (preheated to 158°) (Found: C, 80·0; H, 5·4; N, 6·7. $C_{14}H_{11}ON$ requires C, 80·3; H, 5·3; N, 6·7%).

β-*5-Acridinylpropionic Acid.*—5-Bromomethylacridine (1·36 g., 0·005 mole) was stirred into

a solution of ethyl sodiomalonate (0·01 mole) in absolute ethanol (15 c.c.), and the mixture refluxed for 1 hr. Water–hydrochloric acid (1 : 1; 20 c.c.) was then added and the ethanol removed by distillation. The resulting aqueous solution was refluxed for 4 hr., then cooled in ice and filtered to give a yellow crystalline product (1·4 g.). The latter was dissolved in water containing a little hydrochloric acid, and aqueous potassium carbonate [3 g., in water (15 c.c.)] added to the solution. After a few minutes' cooling, the suspension was filtered and the solid recrystallised from acetic acid, to give yellow needles of β-5-acridinylpropionic acid, m. p. 305° (decomp.). Jensen and Howland [9] record m. p. 310° (decomp.). The *methyl ester* recrystallised from aqueous ethanol in pale yellow plates, m. p. 92—93° (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%).

Similarly prepared β-3-*chloro*-5-*acridinylpropionic acid*, m. p. 263° (decomp.) (Found: C, 66·7; H, 4·3. $C_{16}H_{12}O_2NCl$ requires C, 67·2; H, 4·4%), recrystallised from acetic acid in yellow needles. The *ethyl ester*, b. p. 197—198°/0·4 mm., recrystallised from light petroleum (b. p. 40—60°) in yellow needles, m. p. 59° (Found: C, 68·4; H, 5·1. $C_{18}H_{16}O_2NCl$ requires C, 68·9; H, 5·1%).

5-(2-*Hydroxyethylaminomethyl*)*acridine* (IV).—5-Bromomethylacridine (35 g.) in chloroform (500 c.c.) was treated with ethanolamine (100 c.c.) and kept at room temperature overnight, then washed with water and the chloroform layer evaporated. Recrystallisation of the residue from chloroform–light petroleum (b. p. 60—80°) gave straw-coloured needles of 5-(2-*hydroxyethylaminomethyl*)*acridine* (24 g.), m. p. 133—134° (decomp.) (Found: C, 70·6; H, 6·8; N, 10·7. $C_{16}H_{16}ON_2,H_2O$ requires C, 71·1; H, 6·7; N, 10·4%).

5-(N-*Dichloroacetyl*-N-2-*hydroxyethylaminomethyl*)*acridine* (V).—Dichloroacetyl chloride (5 g.) was added, with cooling, to a solution of 5-(2-hydroxyethylaminomethyl)acridine (10 g.) in chloroform (250 c.c.) and kept overnight at room temperature. The resultant precipitate was collected, dissolved in water, and treated with aqueous sodium hydrogen carbonate, to give 5-(N-*dichloroacetyl*-N-2-*hydroxyethylaminomethyl*)*acridine* (6·5 g.), m. p. 174° (decomp.), which recrystallised in pale yellow needles from dimethylformamide (Found: C, 59·3; H, 4·3; N, 7·5. $C_{18}H_{16}O_2N_2Cl_2$ requires C, 59·5; H, 4·4; N, 7·7%).

2-*Chloro*-7-*methoxy*-5-(4-*diethylamino*-1-*methylbutylaminomethyl*)*acridine Trihydrochloride* (IX).—2-Chloro-5-formyl-7-methoxyacridine [6] (7 g.), suspended in benzene (130 c.c.), and 4-amino-*NN*-diethylpentylamine (8 c.c.) were refluxed together for 2 hr., then kept overnight. The residue obtained on complete removal of the benzene recrystallised from light petroleum (b. p. 60—80°), to give yellow needles of the *anil* (VIII) (9·2 g.), m. p. 86—87° (Found: C, 67·5; H, 7·4; N, 9·5. $C_{24}H_{30}ON_3Cl$ requires C, 67·1; H, 7·3; N, 9·8%). The latter (9 g.), suspended in dry ethanol (150 c.c.), was reduced catalytically in presence of platinum [prepared *in situ*, from platinum oxide (0·6 g.) in ethanol (20 c.c.), before addition of the anil suspension]. After removal of the catalyst, the filtrate was evaporated to dryness and the residual gum dissolved in 2N-hydrochloric acid (150 c.c.). On addition of a slight excess of aqueous ferric chloride the solution was boiled for 15 min. and set aside. The cold mixture was filtered, to give an unidentified red solid (1·8 g.), and the filtrate basified with excess of solid potassium carbonate. The resultant precipitate was extracted several times with acetone, and the acetone layer added to water. Extraction of this precipitate with ethyl acetate gave, on evaporation of the solvent, an oil. This, when treated with concentrated hydrochloric acid and water (1 : 1; 100 c.c.) and subsequently boiled and cooled, gave an orange microcrystalline precipitate of 2-*chloro*-7-*methoxy*-5-(4-*diethylamino*-1-*methylbutylaminomethyl*)*acridine trihydrochloride* (3 g.), decomp. >160°, fusing at 245° (Found: C, 55·0; H, 6·6; N, 8·0. $C_{24}H_{32}ON_3Cl,3HCl$ requires C, 55·1; H, 6·7; N, 8·0%). A further crop (2·8 g.) was obtained on treatment of the filtrate with acetone; the infrared spectrum of this material was identical with that of the main crop. Attempts to recrystallise the trihydrochloride were unsuccessful.

5-*Cyanomethylacridine* (X).—Ethyl 5-acridinyl-α-cyanoacetate (37 g.) was refluxed, with stirring, in 10% aqueous sodium carbonate (1500 c.c.) for 1·5 hr. The mixture deposited, at the b. p., a yellow solid (11 g.) which, when filtered off, dried, and recrystallised gave 5-cyanomethylacridine, m. p. 227—228°, in deep red plates from benzene, or fine yellow needles from methanol. Lettré, Jungmann, and Salfeld [8] record m. p. 227°.

5-*Amidinomethylacridine* (XII).—5-Cyanomethylacridine (20 g.) in dry ethanol (250 c.c.) at 0° was treated with dry hydrogen chloride until the original precipitate dissolved. The solution, at 0° (2 days), deposited the corresponding *ethyl* 5-*acridinylacetimidoate dihydrochloride* (XI) (20 g.),

[9] Jensen and Howland, *J. Amer. Chem. Soc.*, 1926, **48**, 1988.

m. p. 237—238° (decomp.) (Found: C, 57·0; H, 5·7; N, 8·2. $C_{17}H_{16}ON_2,2HCl,H_2O$ requires C, 57·4; H, 5·7; N, 7·9%). This (20 g.) was shaken with 8% alcoholic ammonia (60 c.c.); after *ca.* 10 min., the mixture solidified. The precipitate was filtered off and extracted with dry ethanol to give, on cooling, *5-amidinomethylacridine hydrochloride* (11·8 g.), m. p. 268—269° (Found: C, 60·2; H, 5·7; N, 14·3. $C_{15}H_{14}N_3Cl,1·5H_2O$ requires C, 60·5; H, 5·7; N, 14·1%). The foregoing imidoate dihydrochloride (0·5 g.) was boiled in water (10 c.c.) for 3 hr. When the resultant solution was made alkaline with ammonia, a buff-coloured precipitate was obtained which, when dried and recrystallised from light petroleum (b. p. 40—60°), gave pale yellow prismatic needles of *ethyl 5-acridinylacetate* (0·3 g.), m. p. 127—128° (Found: C, 76·8; H, 5·8; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 76·9; H, 5·7; N, 5·4%).

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