145. *A Study of the Properties of Fluorine-substituted 5-Aminoacridines and Related Compounds. Part I. The Monofluoro-5-aminoacridines.*

By J. H. Wilkinson and I. L. Finar.

The four isomeric monofluoro-derivatives of 5-aminoacridine have been prepared. Owing to the comparative inaccessibility of *o*-fluoroaniline an alternative route to the 1-fluoro-derivative *via* *o*-bromofluorobenzene has been investigated. As anticipated, the new derivatives possessed properties closely resembling those of the chlorine analogues, though the 1-fluoro-compound exhibited a number of anomalies.

The study of fluorine-substituted chemotherapeutic agents seems to have been somewhat neglected, only a comparatively small number having been described. The antibacterial properties of a series of aromatic acids have been investigated by Hager and Starkey (*J. Amer. Pharm. Assoc.*, 1942, **32**, 44), who have shown that fluorine substitution generally produced a slight increase in activity with but little effect on the toxicity. Magidson and Trawin (*J. Gen. Chem. Russia*, 1941, **11**, 243) have reported that 2-fluoro-5-(4-diethylamino-1-methylbutyl)-amino-7-methoxyacridine (the fluorine analogue of mepacrine) was inactive against Plasmodia, but no details of the antibacterial activity are given. The Russian workers do, however, state that it was highly toxic because of hydrolysis. In view of the comparative paucity of information concerning this aspect of the organic chemistry of fluorine, we considered it of interest to prepare a number of fluorine-substituted 5-aminoacridines since the parent compound has powerful antiseptic properties (Rubbo, Albert, and Maxwell, *Brit. J. Exp. Path.*, 1942, **23**, 69).

The monofluoro-compounds described in this paper were prepared by ring closure of the corresponding fluorodiphenylamine-2-carboxylic acids followed by conversion of the resulting 5-chloroacridines into aminoacridines by the method of Albert and Ritchie (*Org. Synth.*, 1942, **22**, 5).

Preparation of Fluorodiphenylamine-2-carboxylic Acids.—(a) via *Fluoroanilines*. Thermal decomposition of the corresponding nitrobenzenediazonium borofluorides prepared by the method of Balz and Schiemann (*Ber.*, 1927, **60**, 1186) gave yields of 55% and 40% respectively of the *m*- and *p*-fluoronitrobenzenes which were reduced catalytically to the fluoroanilines in *ca.* 90% yield. These underwent the Ullmann condensation with *o*-iodobenzoic acid to give 3′- and 4′-*fluorodiphenylamine-2-carboxylic acids* in 64% and 81% yields respectively.

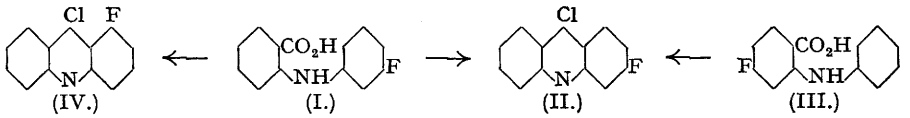
o-Nitrobenzenediazonium borofluoride, however, decomposed vigorously giving a large quantity of a black porous substance from which only about 4% of the required *o*-fluoronitrobenzene could be isolated (cf. Bennett, Brooks, and Glasstone, *J.*, 1935, 1821). Owing to the hazardous nature of this decomposition, no further investigation of the reaction was undertaken. The method of Swarts (*Bull. Acad. roy. Belg.*, 1914, 178) whereby a 6% yield of the ortho-isomer was obtained on nitration of fluorobenzene, was rejected owing to the laborious nature of the separation involved. The alternative route to *o*-fluoroaniline *via* a modified Hofmann degradation of *o*-fluorobenzamide (Rinkes, *Chem. Weekblad*, 1919, **16**, 212; Schiemann and Baumgarten, *Ber.*, 1937, **70**, 1416) was not pursued, as we found it possible to prepare 2′-*fluorodiphenylamine-2-carboxylic acid* in satisfactory yield by method (b).

(b) via o-*Bromofluorobenzene*. *o*-Bromofluorobenzene, prepared from *o*-bromoaniline *via* the diazonium borofluoride, condensed with anthranilic acid in the presence of cuprous chloride according to the method of Goldberg (G.P. 173,523) to give 2′-fluorodiphenylamine-2-carboxylic acid. When this condensation was performed in amyl alcohol a yield of 38% was obtained, but replacement of this reaction medium by *cyclo*hexanol resulted in an increase to 52%.

Preparation of 5-Chlorofluoroacridines.—These compounds were prepared by ring closure of the fluorodiphenylamine-2-carboxylic acids by means of phosphoryl chloride. Whereas the 2′- and 4′-substituted acids gave 5-*chloro*-1- and -3-*fluoroacridines* respectively in practically quantitative yields, the 3′-fluoro-acid (I) gave a mixture of the 2- and 4-substituted 5-chloroacridines since both ortho- and para-closure (Goldberg and Kelly, *J.*, 1946, 102) occur simultaneously. Lehmstedt and Schrader (*Ber.*, 1937, **70**, 838) have reported that negative substituents (*e.g.*, NO_2, Cl) in the 3′-position gave a ratio of ortho- to para-closure of 75 : 25, whereas a positive substituent (*e.g.*, methyl) gave about 20 : 80. Subsequently, however, Gleu and Nitzsche (*J. pr. Chem.*, 1939, **153**, 200) pointed out an error in the orientation of the methylacridones obtained by these workers, the true ratio in the case of the methyl substituted compounds being 80 : 20. Our experience with fluorine in the 3′-position differs from these results since the ratio of ortho- to para-closure was about 40 : 60.

5-*Chloro*-2-*fluoroacridine* (II) was separated from its isomer (IV) by fractional crystallisation

from alcohol. It proved to be identical with the product obtained by ring closure of *5-fluorodiphenylamine-2-carboxylic acid* (III) (see Experimental).



Owing to its very high solubility in practically all organic solvents, 5-chloro-4-fluoroacridine (IV) could not be obtained in a pure state. As it proved possible, however, to separate the 2- and 4-fluoro-5-aminoacridine hydrochlorides by virtue of their differing solubilities in water, we did not pursue the problem of separating the chlorofluoroacridines.

Properties of the Fluoro-5-aminoacridines.—These bases closely resembled 5-aminoacridine and the corresponding chloro-derivatives in physical properties, although *1-fluoro-5-aminoacridine* exhibited a number of anomalies. The accompanying table summarises the properties in which it differs from its isomers and from the chloro- and methyl analogues.

Physical Properties of Substituted 5-Aminoacridines.

Position of Substituent.	M. p. Substituent.			pK_a value. Substituent.			Solubility in alcohol (g. per 100 c.c.) (20°). Substituent.
	F.	Cl.[1]	Me.	F.	Cl.[4]	Me.[4]	F.
1	307°	235°	197° [2]	8·5	8·3	10·2	0·3
2	276	277	230—231 [3]	9·3	9·0	10·2	2·8
3	280	288—289	252 [1]	9·3	8·8	10·0	3·5
4	266	270	248—249 [1]	9·2	8·4	10·0	3·0

[1] Wilkinson and Finar, *J.*, 1946, 115.
[2] Albert and Gledhill, *Pharm. J.*, 1945, **154**, 127.
[3] Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169.
[4] Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exp. Path.*, 1945, **26**, 160.

The pK_a values were determined by a method similar to that of Albert and Goldacre (*J.*, 1943, 454). As Albert and his colleagues made an allowance of +0·5 unit for the effect of the 50% alcohol used as solvent (see also Mizutani, *Z. physikal. Chem.*, 1925, **118**, 327), a similar correction was added to our figures so as to obtain a fair basis for comparison.

The high melting point, the relatively low pK_a value in comparison with those of its isomers, and its low solubility in alcohol suggest that the 1-fluoro-compound exists in a fairly high degree of association.

The examination of the fluoro-compounds for bacteriostatic activity is not yet complete and a summary of the results will appear in a further communication. Results so far obtained indicate that the compounds of this group are powerful bacteriostatic agents, thus supporting the hypothesis of Albert, Rubbo, *et al.* (*loc. cit.*) that, in the acridine series, a pK_a value greater than 7·0 is an essential requirement for powerful antibacterial activity.

Acetyl Derivatives.—The fluoro-5-aminoacridines formed mono- and di-acetyl derivatives under similar conditions to those employed for the chloro-compounds (Wilkinson and Finar, *loc. cit.*). All exhibited fluorescence in ultra-violet light both in the solid state and in alcoholic solution. In general, the properties of both mono- and di-acetyl derivatives resembled those of their chlorine analogues.

Quaternary Salts.—A number of quaternary salts were prepared by the methods of Albert and Ritchie (*J.*, 1943, 458) and, of these, the antibacterial activity of *2-fluoro-5-amino-10-methylacridinium bromide* is being compared with that of the corresponding *2-chloro*-compound.

Experimental.

(M. p.'s are corrected unless over 300°).

m- *and* p-*Fluoroaniline.*—*m*- or *p*-Nitrobenzenediazonium borofluoride (Balz and Schiemann, *loc. cit.*) was decomposed in 10 g. portions by cautious direct heating, and the fluoronitrobenzene isolated from the residue and distillate by steam distillation. *m*-Fluoronitrobenzene had b. p. 198—200°/760 mm. (Swarts, *Rec. Trav. chim.*, 1913, **32**, 60, gives b. p. 200°/756 mm.). *p*-Fluoronitrobenzene had b. p. 203—205°/745 mm. (Swarts, *ibid.*, 1914, **33**, 265, gives b. p. 205°/735 mm.).

Each fluoronitrobenzene was reduced catalytically by hydrogenation in methanol (5 vols.) under 5 atms. pressure at 20° in the presence of 3% Adams's platinum oxide. The theoretical amount of hydrogen was absorbed. Solvent was removed, and the residue dissolved in warm 2N-hydrochloric acid and extracted with benzene to remove any non-basic impurities. Excess of 50% sodium hydroxide was added to regenerate the base, which was extracted with ether. The extract was dried (KOH), the

solvent removed, and the product distilled. *m*-Fluoroaniline was obtained in 90% yield, b. p. 185—187°/770 mm. (Swarts, *Bull. Acad. roy. Belg.*, 1912, 481, gives b. p. 186°/754 mm.). *p*-Fluoroaniline (yield 91%) had b. p. 187—188°/762 mm. (Swarts, *loc. cit.*, gives b. p. 187°/753 mm.).

o-Bromofluorobenzene was prepared according to the method of Bergmann, Engel, and Sándor (*Z. physikal. Chem.*, 1930, **10**, 106). Our product had b. p. 44°/11 mm. (lit., 57°/22 mm.).

Preparation of Fluorodiphenylamine-2-carboxylic Acids.—(a) *From* m- *and* p-*fluoroanilines.* The appropriate fluoroaniline (7·9 g.) and copper-bronze catalyst (0·5 g.) were refluxed with a solution of *o*-iodobenzoic acid (12·45 g.) and potassium carbonate (7 g.) in water (50 c.c.) for 3 hours. The excess of fluoroaniline was removed by steam distillation and the liquid filtered. Ammonium chloride solution (30% *w*/*v*, 50 c.c.) was added to precipitate the product as ammonium salt. This was dissolved in N-sodium hydroxide (50 c.c.) and the free acid liberated by treatment with hydrochloric acid. 3′-*Fluorodiphenylamine-2-carboxylic acid* (7·5 g., 64%) crystallised from 90% alcohol in light fawn rhombic plates, m. p. 164° (Found: C, 67·6; H, 4·5; N, 6·2. $C_{13}H_{10}O_2NF$ requires C, 67·6; H, 4·3; N, 6·05%). 4′-*Fluorodiphenylamine-2-carboxylic acid* (9·3 g., 81%) crystallised from benzene in colourless hexagonal plates, m. p. 200° (Found: C, 67·6; H, 4·3; N, 6·1%).

(b) *From* o-*bromofluorobenzene.* Anthranilic acid (2·74 g., 0·02 mol.) was dissolved in *cyclo*hexanol (14 c.c.) and treated with anhydrous potassium carbonate (2·8 g., 0·04 equiv.). The solution was heated to boiling and allowed to cool to obtain the potassium salt in a voluminous form, a procedure since recommended by Goldberg and Kelly (*loc. cit.*). *o*-Bromofluorobenzene (3·5 g., 2·25 c.c., 0·02 mol.) and cuprous chloride (1 g.) were added and the mixture was refluxed for 8 hours. *cyclo*Hexanol was removed by steam distillation and the liquid filtered. The filtrate was concentrated to about 15 c.c. and treated with ammonium chloride solution (30% *w*/*v*, 20 c.c.). The precipitated ammonium salt was converted into the free acid as in (a) above. 2′-*Fluorodiphenylamine-2-carboxylic acid* (yield, 2·47 g., 52%) crystallised from benzene in colourless plates, m. p. 186° (Found: C, 67·8; H, 4·7; N, 5·9%).

(c) 5-*Fluorodiphenylamine-2-carboxylic acid.* 2-Chloro-4-fluorobenzoic acid (Magidson and Trawin, *loc. cit.*) (0·5 g.) was dissolved in hot amyl alcohol (5 c.c.) and the solution treated with anhydrous potassium carbonate (0·4 g.). When evolution of carbon dioxide ceased, aniline (0·4 g., 40% excess) and copper-bronze catalyst (0·1 g.) were added and the mixture was refluxed for 3½ hours. Aniline and amyl alcohol were removed by steam distillation and the liquid was filtered. The filtrate was acidified with 2N-hydrochloric acid to precipitate the product. The ammonium salt could not be isolated by addition of ammonium chloride. The *acid* crystallised from benzene in colourless needles, m. p. 183°. Admixture with 2-chloro-4-fluorobenzoic acid caused a depression of 25° (Found: C, 67·9; H, 4·8; N, 6·3%).

Preparation of 5-Chloroacridines.—(a) 5-*Chloro*-1- and -3-*fluoroacridines.* The corresponding fluorodiphenylamine-2-carboxylic acid (1 g.) was refluxed for 45 minutes with phosphoryl chloride (4 c.c.) after which most of the excess of the latter was removed under reduced pressure. The residue was dissolved in chloroform (15 c.c.) and the solution treated with excess of ammonia cooled with ice. The chloroform layer was separated and the solvent removed; the yield was practically quantitative. 5-*Chloro*-1-*fluoroacridine* crystallised from anhydrous benzene–light petroleum (b. p. 80—100°) in pale yellow needles, m. p. 142°. Partial hydrolysis to the corresponding acridone occurred when the solvents were not specially dried (Found: N, 6·1. $C_{13}H_7NClF$ requires N, 6·05%). 5-*Chloro*-3-*fluoroacridine* crystallised from a mixture of 90 parts of alcohol and 10 parts of 2N-ammonia in colourless plates, which slowly turned brown on prolonged exposure to the air, m. p. 137° (Found: N, 6·1%).

(b) 5-*Chloro*-2- *and* -4-*fluoroacridines.* 3′-Fluorodiphenylamine-2-carboxylic acid (15 g.) underwent ring closure as in (a). The crude mixture of 5-chloroacridines (15 g.) was dissolved in a hot mixture (250 c.c.) of 90 parts of alcohol and 10 parts of ammonia (*d* 0·88). The solution was cooled to 15° and the solid which crystallised (9·1 g., 60%) collected and recrystallised from 90% alcoholic ammonia, then from 80% alcoholic ammonia. The *acridine* was obtained in pale yellow needles, m. p. 151°, identical with the product obtained by ring closure of 5-fluorodiphenylamine-2-carboxylic acid (Found: N, 6·2%). Excess of water was added to the mother liquors to precipitate 5-chloro-4-fluoroacridine. Repetition of this treatment followed by repeated crystallisation from 40% alcoholic ammonia gave a substance, m. p. 106°. This was highly soluble in all the common organic solvents, but as a mixed m. p. with 5-chloro-2-fluoroacridine invariably showed a rise whatever proportions were admixed, it was concluded that it was a eutectic mixture of the two isomers (Found: N, 6·2%).

Preparation of 5-Aminoacridines.—The 5-chlorofluoroacridine (6·95 g., 0·03 mol.) was dissolved in phenol (20 g.) at 70—75°; finely powdered ammonium carbonate (2 g.) was added as rapidly as practicable and the temperature raised to 120° for 1 hour, with constant stirring throughout. Acetone (100 c.c.) was added to the cooled reaction mixture to precipitate the hydrochloride of the product, from which the base was obtained by treatment with sodium hydroxide.

1-*Fluoro*-5-*aminoacridine* (yield, 3·50 g., 55%) crystallised from chlorobenzene in bright yellow prisms, sparingly soluble in alcohol and benzene but readily soluble in acetic acid, m. p. 307° (corr.) (Found: C, 72·9; H, 4·1; N, 13·3. $C_{13}H_9N_2F$ requires C, 73·4; H, 4·25; N, 13·2%). The *hydrochloride monohydrate* crystallised in lemon-yellow prisms, m. p. > 360°, soluble in about 180 parts of water (Found: N, 10·7; loss at 130°/15 mm., 6·9. $C_{13}H_9N_2F,HCl,H_2O$ requires N, 10·5; H_2O, 6·75%).

2-*Fluoro*-5-*aminoacridine* (yield, 4·05 g., 64%) crystallised from 50% alcohol in bright yellow elongated prisms, m. p. 276° (Found: C, 73·0; H, 4·4; N, 13·2%). The *hydrochloride hemihydrate*, which was soluble in 500 parts of water, crystallised from 90% alcohol in lemon-yellow prisms, m. p. *ca.* 345° (decomp., with charring at about 320°) (Found: C, 60·6; H, 4·5; N, 10·9; loss at 130°/18 mm., 3·6. $C_{13}H_9N_2F,HCl,\frac{1}{2}H_2O$ requires C, 60·6; H, 4·3; N, 10·9; H_2O, 3·6%).

3-*Fluoro*-5-*aminoacridine* (yield, 4·35 g., 68%), crystallised from chlorobenzene in bright yellow elongated prisms, soluble in alcohol, m. p. 280° (Found: C, 73·5; H, 4·2; N, 13·2%). The *hydrochloride monohydrate* crystallised from 90% alcohol in lemon-yellow rectangular prisms, soluble in 1000 parts of water, m. p. 358° (decomp., with charring at about 340°) (Found: N, 10·5; loss at 130°/15 mm., 6·5%).

Separation of 2- *and* 4-*Fluoro*-5-*aminoacridines.*—The mixture of 5-chloro-2- and -4-fluoroacridines resulting from the ring closure of 3′-fluorodiphenylamine-2-carboxylic acid was converted into a mixture

of the corresponding 5-aminoacridines. The mixed hydrochlorides (3·0 g.) were extracted with water (45 c.c.); the mixture was cooled to *ca.* 10° and filtered. The residue (1·55 g.) consisted almost entirely of the hydrochloride of the 2-fluoro-isomer. The filtrate was made alkaline with 2N-sodium hydroxide to precipitate 4-*fluoro*-5-*aminoacridine* (1·12 g.) which was purified by conversion into its hydrochloride and extraction with water (30 c.c.). The filtered aqueous extract on treatment with alkali gave the base (0·93 g.), m. p. 263—265°. Admixture with pure 2-fluoro-5-aminoacridine produced a depression of 2°. 4-Fluoro-5-aminoacridine crystallised from absolute alcohol in deep yellow prisms (Found: C, 73·4; H, 4·3; N, 13·2%), readily soluble in alcohol, m. p. 266°, depressed to 264° by admixture with its isomer. The *hydrochloride* crystallised from 90% alcohol in lemon-yellow prisms, soluble in about 35 parts of water and highly soluble in alcohol, m. p. 346° (decomp. with charring at *ca.* 320°) (Found: N, 11·1. $C_{13}H_9N_2F,HCl$ requires N, 11·25%).

With the exception of the 2-fluoro-isomer, all the bases exhibited a faint green fluorescence in ultra-violet light in the solid state, whilst under similar conditions alcoholic solutions of all four showed a vivid light blue fluorescence unaffected by the presence of acid or alkali. Dilute solutions of bases and hydrochlorides exhibited an intense blue fluorescence by daylight.

Acetyl Derivatives.—The mono- and di-acetyl derivatives were prepared by methods similar to those used for the chlorine analogues (*J.*, 1946, 115). The base (1 g.) was heated at 105° for 30 minutes with acetic anhydride (3 c.c.) and the cooled mixture treated with water. After neutralisation with ammonia, the monoacetyl derivatives were collected (yield about 90%).

1-*Fluoro*-5-*acetamidoacridine* crystallised from 70% alcohol in cream-white needles, m. p. 272° (Found: N, 10·9. $C_{15}H_{11}ON_2F$ requires N, 11·0%). 2-*Fluoro*-5-*acetamidoacridine* crystallised from 50% alcohol in fine colourless needles, m. p. 273° (with some preliminary charring) (Found: N, 10·85%). 3-*Fluoro*-5-*acetamidoacridine* crystallised from 60% alcohol in cream-white silky needles, m. p. 292° (Found: N, 10·8%). 4-*Fluoro*-5-*acetamidoacridine* crystallised from 70% alcohol in pale yellow needles, m. p. 264° (with some preliminary charring) (Found: N, 10·9%).

The diacetyl derivatives were prepared by refluxing the base (1 g.) with acetic anhydride (4 c.c.) for 30 minutes, the products being isolated in the same manner as the monoacetyl derivatives.

1-*Fluoro*-5-*diacetylaminoacridine* was obtained in cream white hexagonal plates, m. p. 193°, from absolute alcohol (Found: N, 9·3. $C_{17}H_{13}O_2N_2F$ requires N, 9·45%). 2-*Fluoro*-5-*diacetylaminoacridine* crystallised from 60% alcohol in colourless rhombic plates, m. p. 178—179° (Found: N, 9·6%). 3-*Fluoro*-5-*diacetylaminoacridine* crystallised from 60% alcohol in highly refractive colourless needles, m. p. 173° (Found: N, 9·6%). 4-*Fluoro*-5-*diacetylaminoacridine* crystallised from 60% alcohol in coloulress refractive rhombs, m. p. 171—172° (Found: N, 9·6%).

In the solid state, both series of acetyl derivatives resembled the chlorine compounds in exhibiting a blue fluorescence under ultra-violet light, but that of the fluorine compounds was less vivid. In alcoholic solution under the same conditions, both series fluoresced blue or violet, the fluorescence being discharged or considerably diminished by acid, but turned to a vivid green by alkali. None exhibited fluorescence by daylight.

Like the chlorine and methyl analogues, the fluorinated acetyl derivatives showed evidence of their basic nature by the deep yellow colour of their solutions in mineral acids.

Quaternary Salts.—2-Fluoro-5-acetamidoacridine (0·4 g.) was heated with methyl toluene-*p*-sulphonate (0·4 g.) in nitrobenzene (4 c.c.)at 180° for 30 minutes, according to the method of Albert and Ritchie (*loc. cit.*). Benzene (10 c.c.) was added to the cooled mixture, and, after 24 hours, the solid was separated by decantation, dissolved in water (5 c.c.), and hydrolysed by heating on a steam-bath for 15 minutes with hydrobromic acid (50%, 2 c.c.). 2-*Fluoro*-5-*amino*-10-*methylacridinium bromide*, which separated on cooling (0·4 g.), crystallised from water, in which it was readily soluble, in deep yellow irregular prisms, m. p. 300° (decomp.) (Found: N, 9·1. $C_{14}H_{12}N_2BrF$ requires N, 9·1%). An attempt to prepare the 3-fluoro-isomer by the same method led to the production of a considerable amount of tar, but the corresponding iodide was prepared by the alternative procedure also described by Albert and Ritchie (*loc. cit.*). 3-Fluoro-5-aminoacridine (1 g.) was refluxed for 4 hours with methanol (4 c.c.) and methyl iodide (2·5 g.). The solid (1·25 g.) was filtered off and refluxed for 20 minutes with acetone (20 c.c.) to remove the red impurity, presumably methylated in the 5-position. The product gave no precipitate when an aqueous solution was treated with N-sodium hydrogen carbonate. 3-*Fluoro*-5-*amino*-10-*methylacridinium iodide* crystallised from water in bright yellow prisms, m. p. 288° (decomp.) (Found: N, 7·9. $C_{14}H_{12}N_2IF$ requires N, 7·9%).

The following new chlorine derivatives were prepared for comparison by the first method. 2-*Chloro*-5-*amino*-10-*methylacridinium bromide* crystallised from water in bright yellow prisms, m. p. 319° (decomp.) (Found: N, 8·7. $C_{14}H_{12}N_2ClBr$ requires N, 8·65%). 3-*Chloro*-5-*amino*-10-*methylacridinium bromide* crystallised from water in small bright yellow irregular prisms, m. p. 312—314° (decomp.) (Found: N, 8·5%).

Determination of Dissociation Constants.—The fluoroaminoacridine (0·00025 g.-mol.) was dissolved in neutral 50% alcohol (*ca.* 40—50 c.c.) at 20° in a beaker provided with a compressed air stirrer. Glass and calomel electrodes were connected by means of screened leads to a Cambridge pH meter, standardised against buffer solutions of pH 3·97, 6·20, 8·00, and 9·00. The solution was titrated with 0·5N-hydrochloric acid from a microburette, the readings being plotted against the pH, and the pK_a value read off from the resulting curve.

The authors wish to thank Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, and Dr. H. J. Barber and the Directors of May and Baker Ltd. for facilities kindly placed at the disposal of one of them (J. H. W.).

S.W. Essex Technical College, Forest Road, E.17.
Research Laboratories, May & Baker Ltd.,
Dagenham, Essex.

[*Received, September 17th*, 1946.]