6. *A Study of the Properties of Fluorine-substituted 5-Aminoacridines and Related Compounds. Part II. 5-Amino-2- and -4-trifluoromethyl acridines.*

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

5-Amino-2- and -4-trifluoromethylacridines have been prepared and their properties studied. The new derivatives did not exhibit any outstanding antibacterial activity.

The study of the monofluoro-5-aminoacridines (Part I, *J.*, 1947, 759) has now been extended to include 5-*amino*-2- and -4-*trifluoromethylacridines*. Although the trifluoromethyl group has found useful applications in the preparation of dyes, numerous examples appearing in the patent literature, few trifluoromethyl compounds have been examined from the chemotherapeutic standpoint. Recently, however, Gilman and his collaborators (*J. Amer. Chem. Soc.*, 1946, **68**, 426) have reported the preparation of a number of such substances for examination for antimalarial activity, but we have been unable to find any report of antibacterial tests with compounds of this type. No trifluoromethyl derivatives of acridine have been described in the literature, though Bachman and Picha (*J. Amer. Chem. Soc.*, 1946, **68**, 2112) attempted the preparation of 2 : 5-dichloro-6- and -8-trifluoromethylacridines from 5-chloro-3′-trifluoromethyldiphenylamine-2-carboxylic acid, but were unable to separate the products in a pure state.

The compounds described in this paper were prepared from *m*-aminobenzotrifluoride which condensed with *o*-iodobenzoic acid, under the conditions described in Part I, to give 3′-*trifluoromethyldiphenylamine*-2-*carboxylic acid* in 61% yield. This underwent cyclisation with phosphoryl chloride to a mixture of 5-chloro-2- and -4-trifluoromethylacridines from which only the 2-*trifluoromethyl* isomer could be isolated in a pure state. However, when the mixed 5-chloroacridines were converted into the corresponding 5-amino-compounds by treatment with ammonium carbonate in phenol at 120° (Magidson and Grigorowski, *Ber.*, 1933, **66**, 866; Albert and Ritchie, *Org. Synth.*, 1942, **22**, 5), only 5-*amino*-2-*trifluoromethylacridine hydrochloride* was precipitated by the addition of acetone to the phenol melt. The 4-*trifluoromethyl* compound was obtained from the phenolic liquors by treatment with sodium hydroxide.

The relative proportions of the 2- and 4-substituted compounds resembled those obtained by cyclisation of 3′-methyldiphenylamine-2-carboxylic acid rather than those of the halogen-substituted derivatives :

Substituent	CF_3	Me	F	Cl
2-Derivative, %	35	20	60	60
4- ,, ...	65	80	40	40

The above figures were obtained as a result of experiments carried out in these laboratories. W were unable to confirm the ratio of 25 : 75 in favour of the 4-chloro-derivative reported by Lehmsted and Schräder (*Ber.*, 1937, **70**, 838).

The orientation of the trifluoromethyl derivatives has not been confirmed by unambiguous synthesis, but all the evidence we have leads to the conclusion that the more soluble compound is substituted in the 4 position. 4-Substituted 5-aminoacridines generally have lower melting points than their 2-isomers, thus : 2-chloro-, 277°; 4-chloro-, 270°; 2-fluoro-, 276°; 4-fluoro-, 266°; 2-nitro-, 290—295°; and 4-nitro-, 230°. In the case of the methyl derivatives, however, the difference is negligible : 2-methyl, 248°; 4-methyl, 248—249°. Albert and Ritchie (*J. Soc. Chem. Ind.*, 1941, **60**, 120) have shown that the hydrochlorides of 2- and 4-aminoacridine can be separated by virtue of the relatively high solubility of the latter, and we have demonstrated that this enhancement is general for a number of different substituents in the 4 position of 5-aminoacridine (see table).

The trifluoromethyl derivatives had m. ps. 246° and 229—230° whilst their hydrochlorides had solubilities of 0·2 and 3·3 g. per 100 c.c. respectively. There seems little doubt therefore that the former is substituted in the 2 position.

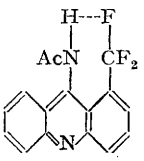
Solubility (g. per 100 c.c.) of Substituted 5-Aminoacridine Hydrochlorides in Water at 20°.

Substituent.	Position of substituent. 1.	2.	3.	4.
Fluorine [1]	0·55	0·2	0·1	2·8
Chlorine [2]	0·2	0·05	0·1	0·7
Nitro	—	0·2	—	0·4
Methyl	0·5[3]	1·0	0·1[2]	3·5[2]

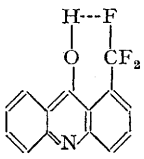
[1] Part I.
[2] Wilkinson and Finar, *J.*, 1946, 115.
[3] Albert and Gledhill, *Pharm. J.*, 1945, **154**, 127.

5-Amino-2-trifluoromethylacridine displayed no unexpected physical or chemical properties : it closely resembled the corresponding methyl derivative in solubility, salt formation, and reaction with acetic anhydride to give both *mono-* and *di-acetyl* derivatives. Like 5-aminoacridine it was hydrolysed to the corresponding *acridone* on prolonged refluxing with alcoholic potash (cf. Albert and Ritchie, *J.*, 1943, 458).

The 4-trifluoromethyl derivative proved to be highly soluble in most organic solvents but relatively sparingly so in acetone from which it crystallised readily. The *hydrochloride*, however, had an unexpectedly high solubility in this solvent. With acetic anhydride, the base readily gave the *monoacetyl* derivative under the conditions normally used for monoacetylation (Albert and Goldacre, *J.*, 1943, 454), but no diacetyl derivative could be isolated after refluxing the base or monoacetyl derivative with a large excess of acetic anhydride for several hours. The difficulty experienced in preparing the diacetyl derivative may be due to hydrogen bonding between the trifluoromethyl group and the neighbouring amino-group (I). It was considered



(I.)



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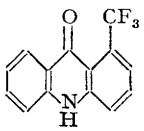

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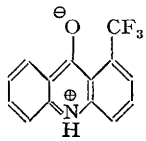

(IV.)

possible that a similar structure (II) might be found in 5-hydroxy-4-trifluoromethylacridine. However, the properties of this substance, prepared by alkaline hydrolysis of the corresponding 5-aminoacridine, so closely resembled those of acridone that it must be formulated as 4-*trifluoromethylacridone*, *i.e.*, a resonance hybrid of (III) and (IV) (cf. Albert and Goldacre, *loc. cit.*; Hunter, *J.*, 1945, 809).

The monofluoro-5-aminoacridines and other substances described in Part I together with the compounds described in this paper have been examined for antibacterial activity against *Staph. aureus*, *B. coli*, and *Ps. pyocyanea*. The only compounds which compared favourably with 5-aminoacridine (cf. Rubbo, Albert, and Maxwell, *Brit. J. Exp. Path.*, 1942, **23**, 69) were 2-fluoro-5-amino-10-methylacridinium bromide which exhibited higher activity against *B. coli*, and 2-chloro-5-amino-10-methylacridinium bromide which gave higher activity against *Staph. aureus*. However, both compounds showed diminished activity against the latter organism in the presence of blood.

Experimental.

(M. ps. are corrected unless above 300°.)

3′-Trifluoromethyldiphenylamine-2-carboxylic Acid.—*o*-Iodobenzoic acid (49·6 g.) was dissolved in a solution of potassium carbonate (30 g.) in water (110 c.c.); *m*-aminobenzotrifluoride (35 g., 10% excess) and copper-bronze catalyst (3 g.) were added and the mixture was refluxed for 3 hours. Water (100 c.c.) was added and an equal volume distilled out to remove unreacted amine. The hot solution was filtered (charcoal) and the filtrate vigorously shaken with 30% ammonium chloride solution (200 c.c.) and cooled in ice. The precipitated ammonium salt was collected, washed with 30% ammonium chloride solution, and dissolved in 2N-sodium hydroxide (100 c.c.). The resulting solution was poured with stirring into N/2-hydrochloric acid (1 l.). The product separated as a gum which hardened on standing to a pale yellow powder (34·3 g., 61%). *3′-Trifluoromethyldiphenylamine-2-carboxylic acid* crystallised from 50% alcohol in pale yellow needles, m. p. 125° (Found : C, 59·8; H, 3·7; N, 4·95. $C_{14}H_{10}O_2NF_3$ requires C, 59·7; H, 3·56; N, 4·98%). The *p-nitrobenzyl* ester crystallised from 50% alcohol in pale yellow plates, m. p. 94° (Found : N, 6·55. $C_{21}H_{15}O_4N_2F_3$ requires N, 6·75%).

5-Chloro-2-trifluoromethylacridine.—3′-Trifluoromethyldiphenylamine-2-carboxylic acid (14 g.) was refluxed for 2 hours with phosphoryl chloride (25 c.c.) after which the excess of the latter was removed by distillation. The residue was dissolved in chloroform (60 c.c.) and the solution cooled with ice and

stirred with ammonia solution (100 c.c., *d* 0·880) for 30 minutes. The chloroform layer was separated, dried (K_2CO_3), and the solvent removed. The crude 5-chloroacridines (14 g.) were dissolved in a boiling mixture of alcohol (80 c.c.) and 2N-ammonia (10 c.c.), and the solid (6·95 g.) which separated was recrystallised from a similar mixture of ammonia and alcohol (40 c.c.). It was then dissolved in dry benzene (100 c.c.); the solution was passed through a column of alumina and the eluent evaporated. 5-*Chloro-2-trifluoromethylacridine* crystallised from 90% alcohol in very pale yellow needles, m. p. 120° (Found: C, 59·6; H, 2·6; N, 5·1. $C_{14}H_7NClF_3$ requires C, 59·6; H, 2·5; N, 5·0%).

2-*Trifluoromethylacridone*.—5-Chloro-2-trifluoromethylacridine (2 g.) was heated on a steam-bath with N-hydrochloric acid (20 c.c.) for 2 hours. The precipitate was collected, washed with water, and dried at 100°. 2-*Trifluoromethylacridone* crystallised from nitrobenzene in pale yellow elongated rectangular plates, m. p. > 360° (Found: C, 64·4; H, 3·1; N, 5·5. $C_{14}H_8ONF_3$ requires C, 63·9; H, 3·04; N, 5·3%). Yield, 1·56 g. (84%).

5-*Amino-2-trifluoromethylacridine*.—5-Chloro-2-trifluoromethylacridine (4 g.) was dissolved in phenol (6 g.) at 70°. Ammonium carbonate (1·5 g.) was added and the temperature raised to 120° for 1 hour. Acetone (50 c.c.) was added to the cooled solution to precipitate the hydrochloride of the product, which was dissolved in boiling water (400 c.c.) and the solution made alkaline with sodium hydroxide. 5-*Amino-2-trifluoromethylacridine* crystallised from 70% alcohol in bright yellow prisms, readily soluble in acetone, m. p. 246° (Found: C, 64·4; H, 3·8; N, 10·6. $C_{14}H_9N_2F_3$ requires C, 64·1; H, 3·4; N, 10·7%). Yield, 2·86 g. (77%). The *hydrochloride monohydrate* crystallised in lemon-yellow prisms, m. p. 344—346° (decomp.), soluble in about 450 parts of water (Found: N, 8·8; Cl, 11·5; loss in weight at 130°/10 mm., 5·75. $C_{14}H_9N_2F_3,HCl,H_2O$ requires N, 8·85; Cl, 11·25; H_2O, 5·7%). The *monoacetyl* derivative crystallised in colourless needles from alcohol, m. p. 288° (Found: N, 9·4. $C_{16}H_{11}ON_2F_3$ requires N, 9·2%). The *diacetyl* derivative was obtained in colourless rhombs from alcohol, m. p. 151° (Found: C, 62·6; H, 4·3; N, 8·0. $C_{18}H_{13}O_2N_2F_3$ requires C, 62·5; H, 3·8; N, 8·1%). Both acetyl derivatives were readily soluble in alcohol giving solutions which exhibited a blue fluorescence in ultra-violet light. The addition of mineral acid produced a deep yellow colour (cf. Wilkinson and Finar, *J.*, 1946, 115).

5-*Amino-4-trifluoromethylacridine*.—The mixed 5-chloro-2- and -4-trifluoromethylacridines (2 g.) were dissolved in phenol (4 g.) at 70°. Ammonium carbonate (0·5 g.) was added and the temperature maintained at 120° for 1 hour. Acetone (30 c.c.) was added to the cooled mixture to precipitate the hydrochloride of 5-amino-2-trifluoromethylacridine which was dissolved in hot water and treated with sodium hydroxide to liberate the base (0·65 g., 35%). Acetone was removed from the liquors by distillation; the residue was treated with 2N-sodium hydroxide (50 c.c.) and set aside overnight. The solid was collected and ground with 2N-sodium hydroxide to remove the last traces of phenol. Yield, 1·14 g. (61%). It was purified by solution in benzene–alcohol (80 : 20) (100 c.c.) and passage through an alumina column. On concentration to about 10 c.c., 5-*amino-4-trifluoromethylacridine* separated in small bright yellow prisms, m. p. 229—230°. Recrystallisation had no effect on the m. p. The product was readily soluble in alcohol and benzene but less soluble in acetone (Found: C, 64·3; H, 3·7; N, 10·8%). The *hydrochloride* was obtained in small lemon-yellow elongated rectangular prisms readily soluble in water and alcohol, m. p. 300—302° (decomp.) (Found: N, 9·7. $C_{14}H_9N_2F_3,HCl$ requires N, 9·7%). The *monoacetyl* derivative crystallised from benzene in colourless needles, m. p. 236° (Found: N, 9·4%). This derivative was also obtained when the base was refluxed for 3 hours with a large excess of acetic anhydride.

Hydrolysis with Alcoholic Potassium Hydroxide.—The 5-aminotrifluoromethylacridines (1 g.) were refluxed for 24 hours with 5N 80% alcoholic potassium hydroxide (100 c.c.). The cooled solutions were then acidified with 2N-acetic acid (300 c.c.) to precipitate the products. 2-Trifluoromethylacridone, identical with that obtained by hydrolysis of 5-chloro-2-trifluoromethylacridine, was obtained in 97% yield (Found: N, 5·45%). 4-*Trifluoromethylacridone* (yield, 92%) crystallised from 80% aqueous pyridine in pale yellow rectangular prisms, m. p. above 360° (Found: N, 5·5%). Both trifluoromethylacridones were sparingly soluble in most organic solvents. Alcoholic solutions exhibited a blue fluorescence, which became vivid green on the addition of alkali.

Attempted Verification of Orientation.—2-Trifluoromethylacridone (0·5 g.) was refluxed with 70% sulphuric acid (10 c.c.) until the evolution of hydrogen fluoride ceased (cf. Rouche, *Bull. Acad. roy. Belg.*, 1927, **13**, 346). The cooled solution was poured into a mixture of crushed ice (50 g.) and alcohol (50 c.c.) and the solid collected (0·45 g.). Purification was effected by solution in N/2-sodium bicarbonate (10 c.c.) followed by precipitation with N/2-hydrochloric acid in the presence of alcohol (10 c.c.). Instead of the expected acridone-2-carboxylic acid, the product appeared to be partly sulphonated [Found: N, 4·3; S, 9·1. Calc. for $C_{14}H_9O_6NS$ (2-carboxyacridone-*x*-sulphonic acid): N, 4·4; S, 10·0%]. It was an orange-yellow powder, m. p. > 360°, sparingly soluble in organic solvents, but readily soluble in aqueous alkali giving a yellow solution which exhibited a vivid blue fluorescence on dilution. The same product was obtained when hydrolysis was effected with 50% sulphuric acid. We were unable to remove the sulphonic acid group by heating with hydrochloric acid in a sealed tube at 140°.

Attempted Preparation of Acridone-2-carboxylic Acid.—Bromoterephthalic acid (1·22 g., 0·005 g.-mol.) was dissolved in amyl alcohol (6 c.c.) and the solution treated with anhydrous potassium carbonate (1·05 g., 0·0075 g.-mol.). Aniline (0·6 g., 0·0065 g.-mol.) and copper-bronze catalyst (0·1 g.) were added and the mixture refluxed for 4 hours. Amyl alcohol and unreacted aniline were removed by steam distillation; the aqueous residue was clarified by filtration and the product (0·55 g.) precipitated by acidification with 2N-acetic acid. *Diphenylamine-2 : 5-dicarboxylic acid* crystallised from 90% alcohol in small bright yellow prisms, m. p. 318—319° (decomp.) (Found: N, 5·25. $C_{14}H_{11}O_4N$ requires N, 5·45%). An attempt to cyclise this substance to acridone-2-carboxylic acid by heating on a steam-bath with sulphuric acid gave an orange-coloured solid, containing sulphur, which resisted purification.

Determination of Dissociation Constants.—The pK_a values of both 5-aminoacridines were determined by the method described in Part I. The results were: 2-trifluoromethyl derivative, 8·3; 4-trifluoromethyl derivative, 7·9; a correction of 0·5 unit having been added to allow for the effect of the 50% alcohol used as solvent.

The authors wish to thank Mr. S. Bance, B.Sc., A.R.I.C. for the semi-micro-analyses, the Biological Division, May and Baker Ltd., for the biological results, 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, Walthamstow, E.17.
Research Laboratories, May and Baker Ltd., Dagenham, Essex.

[*Received, February 22nd,* 1947.]