109. *Synthesis of Diaminoacridines. Part II.*

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1 : 6- and 1 : 9-Diaminoacridines have been synthesised for examination as bacterial inhibitors. Attempts to prepare 4 : 6-diaminoacridine have not been successful.

Of the ten theoretically possible (1—4) : (6—9)-diamino-acridines seven have previously been described, *viz.*, 1 : 7-, 1 : 8-, 2 : 6-, 2 : 7-, 2 : 8-, 3 : 6-, and 3 : 7-diaminoacridines (Benda, *Ber.*, 1912, **45**, 1787; Bogert, Hirschfelder, and Lauffer, *Coll. Trav. Chim., Czeckoslov.*, **1930**, **5**—6, 382; Lehmstedt and Hundertmark, *Ber.*, 1931, **64**, 2386; Scherlin *et alii*, *Annalen*, 1935, **516**, 218; Albert and Linnell, *J.*, 1936, 89 and 1614; Lehmstedt, *Ber.*, 1937, **70**, 846; Albert, Dyer, and Linnell, *Quart. J. Pharm. Pharmacol.*, 1937, **10**, 649; Albert and Linnell, *J.*, 1938, 22; Goldberg and Kelly, *J.*, 1946, 102). The present communication records the synthesis of 1 : 6- and 1 : 9-diaminoacridines together with attempts to obtain the remaining unknown 4 : 6-isomeride. The compounds were prepared for examination as bacterial inhibitors.

2-Chloro-3-nitrobenzoic acid condensed with *m*-nitroaniline to give 6 : 3′-*dinitrodiphenylamine*-2-*carboxylic acid*, which on treatment with sulphuric acid cyclised to 1 : 6-*dinitroacridone*; reduction of the latter with stannous chloride yielded 1 : 6-*diaminoacridone*, m. p. 320—322°, and this on further reduction with sodium amalgam followed by oxidation was converted into 1 : 6-*diaminoacridine*, m. p. 194—196°. Similarly 2-chloro-3-nitrobenzoic acid condensed with *m*-phenylenediamine to give 6-*nitro*-3′-*aminodiphenylamine*-2-*carboxylic acid*, which with sulphuric acid cyclised to 1-nitro-8-aminoacridone; this by standard methods yielded 1 : 8-diaminoacridone, m. p. 360—362°, and 1 : 8-diaminoacridine, m. p. 248—250° (cf. Albert and Linnell,

J., 1936, 1614, who made this compound from 2-chloro-4-nitrobenzoic acid and *o*-nitroaniline following by cyclisation and reduction). This constitutes an additional example (cf. Part I, *J.*, 1946, 103) of the directional cyclisation of 3'-substituted diphenylamine-2-carboxylic acids, *viz.*, with the 3'-nitro-series *ortho*-closure of the acridone ring prevails, while with the 3'-amino-series *para*-closure predominates.

2-Chloro-3-nitrobenzoic acid condensed with *o*-nitroaniline to give 6 : 2'-*dinitrodiphenylamine-2-carboxylic acid*, which by similar methods was converted into 1 : 9-*dinitroacridone*, 1 : 9-*diaminoacridone*, and 1 : 9-*diaminoacridine*.

2-Chloro-6-nitrobenzoic acid failed to condense with *m*-nitroaniline, both reactants being recovered under all the experimental conditions employed; this accords with the failure of 2-chloro-6-nitrobenzoic acid to condense with aniline (Tuttle, *J. Amer. Chem. Soc.*, 1923, **45**, 1916) and the failure of 6-nitro-2-aminobenzoic acid to condense with *o*-chloronitrobenzene (Bogert *et al.*, *loc. cit.*). On the other hand 2-chloro-6-acetamidobenzoic acid readily condensed with *m*-nitroaniline to yield 3'-*nitro*-3-*acetamidodiphenylamine*-2-*carboxylic acid*, but this compound could not be induced to cyclise into the desired acridone on treatment with sulphuric acid, phosphoryl chloride, phosphoric acid, fused boric acid, thionyl chloride, or stannic chloride (cf. the inability of 3-nitrodiphenylamine-2-carboxylic acid to cyclise to 4-nitroacridone, Lehmstedt and Schrader, *Ber.*, 1937, **70**, 1528).

The antibacterial properties of 1 : 6- and 1 : 9-diaminoacridines will be reported shortly.

Experimental.

The Ullmann condensations were normally carried out by the same method as that described previously.

6 : 3'-*Dinitrodiphenylamine*-2-*carboxylic Acid*.—2-Chloro-3-nitrobenzoic acid (10 g.), *m*-nitroaniline (8 g.), potassium carbonate (8 g.), and copper powder (0·2 g.) were melted together and kept at 180° for 5 hours. The resulting product was boiled with water (200 c.c.), the insoluble material removed, and the hot solution acidified with 5N-hydrochloric acid. The precipitate was collected and recrystallised from aqueous alcohol, the *acid* being obtained in yellow prisms (7·5 g.), m. p. 196—198° (Found : N, 13·9; *M* (titration), 298. $C_{13}H_9O_6N_3$ requires N, 13·9%; *M*, 303).

1 : 6-*Dinitroacridone*.—A solution of the foregoing acid (13 g.) in sulphuric acid (91 c.c.) was heated at 90° for ½ hour, cooled, and poured on excess of crushed ice. The precipitate was filtered off, and stirred with dilute ammonia, and the insoluble 1 : 6-dinitroacridone collected, washed with water, and dried (12 g.; m. p. 324—328°). Recrystallisation of a sample from aqueous pyridine gave the pure *compound* in yellow needles, m. p. 332—334° with softening at 320° (Found : N, 14·9. $C_{13}H_7O_5N_3$ requires N, 14·7%).

1 : 6-*Diaminoacridone*.—Crude 1 : 6-dinitroacridone (12 g.) was stirred with a solution of stannous chloride crystals (120 g.) in 10N-hydrochloric acid (120 c.c.) at 100° for 1 hour. The resulting liquid was cooled, the precipitate of the stannichloride complex collected and stirred with N-sodium hydroxide (300 c.c.) for ½ hour, and the insoluble diaminoacridone (9 g.; m. p. 312°) collected and washed. Recrystallisation from aqueous pyridine gave 1 : 6-*diaminoacridone* in felted yellow needles, m. p. 320—322° depressed by admixture with 1 : 8-diaminoacridone obtained by cyclisation of 6-nitro-3'-aminodiphenylamine-2-carboxylic acid followed by reduction (Found : C, 69·2; H, 5·0; N, 18·7. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%).

1 : 6-*Diaminoacridine*.—A suspension of crude 1 : 6-diaminoacridone (5·0 g.) in 60% ethyl alcohol (400 c.c.) was saturated with carbon dioxide and stirred with sodium amalgam (4%; 200 g.) for 1 hour at 20° and then for a further 1 hour at 60°, the stream of carbon dioxide being maintained throughout. Ferric chloride solution (10%; 5 c.c.) was added and a current of air passed into the rapidly stirred suspension at 60° for 1½ hours. The filtered solution was evaporated to small volume and allowed to stand. 1 : 6-Diaminoacridine separated in dark brown prisms (3·0 g.; m. p. 188—190°). Recrystallisation from aqueous alcohol gave the pure *compound* in orange brown needles, m. p. 194—196° (Found : C, 74·2; H, 5·4; N, 20·4. $C_{13}H_{11}O_3$ requires C, 74·6; H, 5·3; N, 20·1%). The hydrochloride is easily soluble in cold water.

6-*Nitro*-3'-*aminodiphenylamine*-2-*carboxylic Acid*.—2-Chloro-3-nitrobenzoic acid (6·7 g.), *m*-phenylenediamine (5·4 g.), potassium carbonate (5·0 g.), copper powder (0·2 g.), and amyl alcohol (30 c.c.) were heated at 120—125° (bath temp.) for 2 hours and the product isolated in the manner formerly described. The crude amino-acid (5·3 g.) had m. p. 240—280° (slow decomposition) and could not be purified by crystallisation. Acetylation by the method previously used (Goldberg and Kelly, *J.*, 1946, 107) yielded 6-*nitro*-3'-*acetamidodiphenylamine*-2-*carboxylic acid* which separated from aqueous alcohol in vermilion needles, m. p. 226—228° (Found : C, 56·8; H, 4·2; N, 13·2. $C_{15}H_{13}O_5N_3$ requires C, 57·1; H, 4·1; N, 13·3%).

1-*Nitro*-8-*aminoacridone*.—Crude 6-nitro-3'-amino-diphenylamine-2-carboxylic acid (3·1 g.) was dissolved in sulphuric acid (22 c.c.), and the solution heated to 90—95° for ½ hour and poured on powdered ice. The mixture was basified with ammonia and the crude 1-nitro-8-aminoacridone (2·5 g.; m. p. 304—306°) collected; recrystallisation from aqueous pyridine gave the pure *compound* in purple brown needles, m. p. 314—316° (Found : N, 16·4. $C_{13}H_9O_3N_3$ requires N, 16·5%).

1 : 8-*Diaminoacridone*.—Crude 1-nitro-8-aminoacridone (2·0 g.) was heated with a solution of stannous chloride crystals (20 g.) in concentrated hydrochloric acid (20 c.c.) for 1 hour at 100°, the solution cooled, and the precipitate of the stannichloride complex collected. This was dissolved in water, excess of cold 5N-sodium hydroxide solution added, and the precipitate (1·1 g.; m. p. 356—358°) collected and washed

with water; recrystallisation from aqueous pyridine gave 1 : 8-diaminoacridone in golden brown needles, m. p. 360—362° (Albert and Linnell, *J.*, 1936, 1614 record m. p. >360° for 1 : 8-diaminoacridone prepared by a different synthetic method) (Found : C, 69·0; H, 5·1; N, 18·6. Calc. for $C_{13}H_{11}ON_3$: C, 69·3; H, 4·9; N, 18·7%).

1 : 8-*Diaminoacridine*.—Reduction of the foregoing diaminoacridone by the same method as described for the 1 : 6-isomeride yielded 1 : 8-diaminoacridine in 65% yield; it crystallised from alcohol in felted orange needles, m. p. 248—250° (Found : N, 20·3. Calc. for $C_{13}H_{11}N_3$: N, 20·1%).

6 : 2′-*Dinitrodiphenylamine-2-carboxylic Acid*.—2-Chloro-3-nitrobenzoic acid (10 g.), *o*-nitroaniline (8 g.), potassium carbonate (8 g.), copper powder (0·2 g.), and amyl alcohol (20 c.c.) were heated to 180° (internal) for 5 hours, the solvent being allowed to distil slowly. The *acid* isolated in the usual manner crystallised from aqueous alcohol in golden yellow needles (3·6 g.), m. p. 252—254° (Found : C, 51·6; H, 3·0; N, 13·9. $C_{13}H_8O_6N_3$ requires C, 51·5; H, 3·0; N, 13·9%).

1 : 9-*Dinitroacridone*.—The foregoing acid (11 g.) cyclised in the same manner as described for the 1 : 6-isomeride yielded crude 1 : 9-dinitroacridone, m. p. 264—266°, as a yellow powder (9·6 g.). Recrystallisation of a sample from aqueous pyridine gave the pure *compound* in slender yellow needles, m. p. 266—268° (Found : C, 54·9; H, 2·3; N, 14·9. $C_{13}H_7O_5N_3$ requires C, 54·7; H, 2·5; N, 14·7%).

1 : 9-*Diaminoacridone*.—1 : 9-Dinitroacridone (13 g.) was heated with a solution of stannous chloride crystals (130 g.) in concentrated hydrochloric acid (130 c.c.) at 100° for 3 hours. The product was treated in the usual manner and yielded crude 1 : 9-diaminoacridone (10 g.; m. p. 330°) as a yellow powder which crystallised from dilute pyridine in olive green needles, m. p. 340—342° (Found : C, 69·2; H, 5·0; N, 18·7. $C_{13}H_{11}ON_3$ requires C, 69·2; H, 4·9; N, 18·7%). The hydrochloride is almost insoluble in water while the free diamine is easily soluble in dilute sodium hydroxide.

1 : 9-*Diaminoacridine*.—A suspension of 1 : 9-diaminoacridone (5·0 g.) in 60% alcohol was stirred with 4% sodium amalgam (220 g.) for 2 hours at 20° and then for a further 1 hour at 60°; during the whole time the suspension was kept saturated with carbon dioxide. Ferric chloride (10%; 5 c.c.) was added and a current of air beaten into the rapidly stirred suspension at 60° for 2 hours. Boiling alcohol (200 c.c.) was added, the liquid filtered hot, and the filtrate evaporated to small volume and allowed to cool; 1 : 9-diaminoacridine separated in brown needles (3·9 g.), m. p. 180—182°. Recrystallisation from dilute alcohol gave the pure *compound* in orange brown needles, m. p. 182° (Found : C, 73·8; H, 5·1; N, 20·1. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). The hydrochloride dissolves easily in cold water.

3′-*Nitro*-3-*acetamidodiphenylamine-2-carboxylic Acid*.—2-Chloro-6-acetamidobenzoic acid (30 g.), *m*-nitroaniline (24 g.), potassium carbonate (21 g.), and copper powder (0·5 g.) were heated with *cyclo*hexanol (80 c.c.) at 190° (bath temp.) for 4 hours. The crude acid was isolated in the normal manner, extracted with boiling water (3 × 500 c.c.), the residual insoluble acid dissolved in N-sodium hydroxide solution (200 c.c.), and the sodium salt precipitated by the addition of saturated sodium chloride solution (200 c.c.). The salt was collected, washed with cold brine, and dissolved in water, and the filtered solution acidified with hydrochloric acid; the crude precipitated acid (19 g.) was collected and recrystallised from aqueous alcohol, 3′-*nitro*-3-*acetamidodiphenylamine-2-carboxylic acid* separating in yellow needles, m. p. 182—184° (Found : N, 13·6; *M* (titration), 320. $C_{15}H_{13}O_5N_3$ requires N, 13·4%; *M*, 315).

Attempted Cyclodehydration of 3′-*Nitro*-3-*acetamidodiphenylamine-2-carboxylic Acid*.—The foregoing acid (6·1 g.) was heated with sulphuric acid (43 c.c.) at 100° for 1½ hours, the solution cooled, water (25 c.c.) added, and the heating at 100° continued for ½ hour. Basification with ammonia yielded a brown gum which was purified by dissolution in dilute hydrochloric acid (charcoal) and reprecipitation with ammonia. Recrystallisation of this from aqueous methyl alcohol yielded 3-*nitro*-3′-*aminodiphenylamine* (1·7 g.) in scarlet needles, m. p. 120—122° (Found : C, 62·6; H, 5·0; N, 18·5. $C_{13}H_{11}O_2N_3$ requires C, 62·8; H, 4·8; N, 18·2%). The same diphenylamine was obtained when attempts were made to effect cyclisation with phosphoric acid. With phosphorus pentachloride–aluminium chloride, thionyl chloride–aluminium chloride, fused boric acid, or stannic chloride no nitro-amino-acridone could be isolated; either the original compound was recovered or else the nitro-amino-diphenylamine was obtained by loss of carbon dioxide.

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