213. *Nitration Products of 5-Aminoacridine, and the Synthesis of 1 : 5- and 4 : 5-Diaminoacridine.*

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The nitration of 5-aminoacridine gave 3 : 7-*dinitro-5-aminoacridine*, 1 : 3 : 7-*trinitro-5-aminoacridine*, and 1 : 3 : 7-*trinitroacridone*. The last compound, which arises by hydrolysis of the trinitro-amine was identified by synthesis from 2 : 4 : 4′-*trinitrodiphenylamine-2′-carboxylic acid*. It was also isolated after the nitration of 3-nitroacridone. 3 : 5 : 7-*Triaminoacridine* and 1 : 5- and 4 : 5-*diaminoacridine* were also prepared.

An unorientated dinitro-derivative was obtained from 5-aminoacridine by Meister, Lucius, and Brüning (G.P. 364,033). It has now been found that nitration of 5-aminoacridine below 5° in concentrated sulphuric acid with nitric acid (2·1 mols.) affords 3 : 7-*dinitro-* and 1 : 3 : 7-*trinitro-5-aminoacridine*. These compounds are hydrolysed to the corresponding nitroacridones, the ease of hydrolysis being expressed by the sequence 5-amino- (cf. Albert and Ritchie, *J.*, 1943, 458) < 3 : 7-dinitro-5-amino- < 1 : 3 : 7-trinitro-5-amino-acridine. The structure of the dinitro-compound was established by preparing it from 3 : 7-dinitroacridone (Lehmstedt, *Ber.*, 1931, **64**, 2381) by successive treatment with phosphoryl chloride in nitrobenzene solution (cf. Walls, *J.*, 1945, 294) and with ammonium carbonate in presence of phenol (cf. Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169T). Since the dinitroaminoacridine had no m. p., the identity of the specimens prepared by the alternative methods was established by reducing them to 3 : 5 : 7-*triaminoacridine*. Similarly, the acridone obtained by hydrolysis of the dinitro-5-aminoacridine was reduced to 3 : 7-diaminoacridone, identical with a specimen prepared by reducing 3 : 7-dinitroacridone.

The constitution of the trinitro-5-aminoacridine was determined by an independent synthesis of the 1 : 3 : 7-*trinitroacridone* which it gave on hydrolysis. This acridone was obtained by the action of phosphoryl chloride on 2 : 4 : 4′-*trinitrodiphenylamine-2′-carboxylic acid*, prepared either by nitrating 2 : 4-dinitrodiphenylamine-2′-carboxylic acid (Schroeter and Eisleb, *Annalen*, 1909, **367**, 101), or, in poor yield, by synthesis from 1-chloro-2 : 4-dinitrobenzene and 5-nitro-anthranilic acid. 1 : 3 : 7-Trinitroacridone was also obtained as a by-product in the nitration of 3-nitroacridone.

The yield of 5-chloro-1-nitroacridine was considerably improved by using nitrobenzene at 180° in place of xylene as solvent in the reaction of 1-nitroacridone with phosphoryl chloride (Albert and Gledhill, *loc. cit.*). There was considerable decomposition when ammonia was passed into a solution of 5-chloro-1-nitroacridine at 110°, but 1-nitro-5-aminoacridine was obtained in 76% yield at 60°, a lower temperature than hitherto employed in the amination of 5-chloroacridines. The nitro-amine was converted into 1 : 5-*diaminoacridine* by reduction with stannous chloride. The mixture of 5-chloro-2- and -4-nitroacridines prepared from 3-nitrodiphenylamine-2′-carboxylic acid and phosphoryl chloride (Lehmstedt and Schrader, *Ber.*, 1937, **70**, 838) was aminated by the same method, and 4-nitro-5-aminoacridine, extracted from the resulting mixture of nitro-amines with chloroform, was reduced to 4 : 5-*diaminoacridine* with nascent ferrous carbonate (Albert and Gledhill, *J. Soc. Chem. Ind.*, 1942, **61**, 159T). Some physical and antibacterial

properties of 1 : 5- and 4 : 5-diaminoacridine are reported by Albert and Goldacre (*Nature*, 1948, **161**, 95); their preparation completes the series of diaminoacridines having an amino-group in position 5 (Albert and Gledhill, *loc. cit.*, 1942; Albert and Ritchie, *loc. cit.*).

Experimental.

The chloronitroacridines described here have a very labile chlorine atom and are strongly irritant to delicate portions of the skin.

Nitration of 5-Aminoacridine.—5-Aminoacridine (5 g.) was dissolved in concentrated sulphuric acid (20 ml.), and concentrated nitric acid (3·54 ml., *d* 1·41, 5% excess) dropped in during 1 hour, the temperature being kept between 0° and 5°. After standing overnight, the mixture was poured into a stirred mixture of ice (250 g.) and water (500 ml.). The orange product was immediately filtered off and, after being washed with cold water, suspended in hot water (150 ml.). This mixture was made slightly alkaline with ammonia, boiled for 5 minutes, cooled, and filtered. The solid, after removal of a little red impurity (probably 3-nitro-5-aminoacridine) by boiling with alcohol (50 ml.), weighed 4·50 g. and on recrystallisation from pyridine gave red needles which at 120° lost solvent and became orange; yield, 3·40 g. (47%) (Found: N, 19·9. Calc. for dinitroaminoacridine, $C_{13}H_8O_4N_4$: N, 19·7%).

The dilute sulphuric acid filtrate was boiled for 10 minutes, and the yellow precipitate (2·03 g., m. p. 260—270°) collected. After one recrystallisation from glacial acetic acid (200 ml., concentrated to *ca.* 100 ml.) and five from acetone (250 ml./g., concentrated to crystallisation), use being made of a mixture of kieselguhr and charcoal to remove an orange-coloured impurity, the 1 : 3 : 7-*trinitroacridone* was obtained as bright yellow needles, m. p. 277° (Found: C, 47·2; H, 1·9; N, 16·8. $C_{13}H_6O_7N_4$ requires C, 47·3; H, 1·8; N, 17·0%).

If the filtrate was run into a slight excess of 8N-ammonia solution (120 ml.), and the red gelatinous precipitate flocculated by warming, an orange solid (2·2 g.) was obtained. This was dissolved in boiling alcohol (225 ml.), the solution filtered, and the filtrate concentrated to half volume. The crystalline product, after two recrystallisations from alcohol, formed red needles (0·93 g.), m. p. 284° (decomp.), of 1 : 3 : 7-*trinitro-5-aminoacridine* (Found: C, 47·5; H, 2·2; N, 21·0. $C_{13}H_7O_6N_5$ requires C, 47·4; H, 2·1; N, 21·3%). The compound dissolved easily in cold dilute sulphuric acid and the solution when heated or kept deposited the insoluble 1 : 3 : 7-trinitroacridone. The trinitroaminoacridine was almost insoluble in water and benzene, moderately soluble in alcohol, easily soluble in acetone and pyridine. Solutions in dilute hydrochloric acid fluoresced a yellow-green.

5-*Chloro*-3 : 7-*dinitroacridine.*—A mixture of 3 : 7-dinitroacridone (Lehmstedt, *loc. cit.*, 1931) (5 g.), phosphorus oxychloride (25 g.), nitrobenzene (38 ml.), and one drop of concentrated hydrochloric acid was heated under reflux in an oil-bath at 180° for 8 hours, complete dissolution occurring in 1 hour. After vacuum evaporation the residue was ground and added with stirring to a mixture of ice and excess of ammonia. The solid was collected and dried in a vacuum (5·96 g.). This was used without further purification for the preparation of 3 : 7-dinitro-5-aminoacridine.

Heating of 3 : 7-dinitroacridone with phosphorus pentachloride in chlorobenzene or nitrobenzene solution did not give appreciable amounts of the 5-chloro-compound, and heating with phosphorus oxychloride alone gave low yields.

3 : 7-*Dinitro-5-aminoacridine.*—An intimate mixture of 5-chloro-3 : 7-dinitroacridine (2·38 g.) and ammonium carbonate (1 g.) was added in portions to phenol (10 g.) at 110°, and the mixture kept at 120° for 1 hour; the phenol was removed by steam distillation, the residual solution made ammoniacal, and the mixture boiled for 5 minutes, cooled, and filtered. The solid was boiled with dilute sulphuric acid (5% v./v., 1600 ml.) for a few minutes, and the filtrate cooled immediately to prevent hydrolysis. The orange needles of the sulphate were filtered off and suspended in hot water (100 ml.), and a slight excess of ammonia added. The orange *base* weighed 1·02 g. (51%, from the acridone). For analysis it was recrystallised from pyridine (25 ml.) (Found: C, 55·0; H, 2·86; N, 19·8. $C_{13}H_8O_4N_4$ requires C, 54·9; H, 2·84; N, 19·7%). Prolonged boiling of the amine with dilute acids, mineral or organic, resulted in hydrolysis to the acridone, the rate of hydrolysis being greater in the case of the organic acids used, *i.e.*, oxalic, acetic, and citric.

3 : 7-Dinitro-5-aminoacridine was insoluble in water and benzene, very slightly soluble in alcohol, slightly in hot acetone, easily in hot pyridine. Solutions in dilute hydrochloric acid and alcohol showed a greenish-yellow fluorescence.

3 : 5 : 7-*Triaminoacridine.*—3 : 7-Dinitro-5-aminoacridine (5 g.) was added cautiously to a boiling solution of stannous chloride dihydrate (31 g.) in concentrated hydrochloric acid (40 ml.). The mixture was heated on a steam-bath for 30 minutes and then cooled, and the yellow double salt filtered off and washed with cold concentrated hydrochloric acid. After dissolution in cold water (300 ml.), the base was obtained as an old-gold, crystalline precipitate by addition of excess of aqueous 30% sodium hydroxide. It was dissolved in 5% acetic acid (70 ml.), the solution clarified, and the base reprecipitated. The yield after vacuum drying was 3·87 g. (98%); m. p. 245° (decomp.). It crystallised from alcohol–light petroleum as yellow plates. The m. p. varied with rate of the heating, but with a period of heating of 10—15 minutes a constant value of 264—265° (decomp., sealed) was obtained. For analysis it was dried at 15 mm. over potassium hydroxide (Found: C, 64·4; H, 5·9. $C_{13}H_{12}N_4,H_2O$ requires C, 64·4; H, 5·8%). Similar analytical figures were obtained for the *triaminoacridine* synthesised *via* the nitration of 5-aminoacridine. A mixed m. p. of the two preparations showed no depression, and both were insoluble in benzene, light petroleum, ether, or chloroform, slightly soluble in acetone, and moderately so in alcohol. The solubility in cold water was approximately 1 in 3000, and in hot water 1 in 900. Solutions in alcohol and water fluoresced green and darkened rapidly when exposed to the air. In ultra-violet light, solutions in concentrated hydrochloric acid showed a green-yellow fluorescence which changed first to brick-red and then to yellow, on addition of water.

3 : 5 : 7-Triaminoacridine formed a yellow *hydrochloride* which crystallised from dilute hydrochloric acid (Found: C, 42·4; H, 5·3; N, 14·8; Cl, 28·4. $C_{13}H_{12}N_4,3HCl,2H_2O$ requires C, 42·2; H, 5·2; N.

15·2; Cl, 28·8%). A similar analysis was obtained for the hydrochloride of the triaminoacridine synthesised *via* the nitration of 5-aminoacridine.

Hydrolysis of the Dinitro-5-aminoacridine from Nitration of 5-Aminoacridine.—The dinitro-5-aminoacridine (2 g.) was ground to a thin paste with water and added with stirring to boiling dilute sulphuric acid (1% v./v., 1 l.). After being heated under reflux for 3 hours, the mixture was cooled to 60° and the crystalline solid (1·94 g.) filtered off. This was obtained as yellow plates by the addition of hot water (980 ml.) to the hot solution in pyridine (420 ml.). Analysis showed the compound to be a *dinitroacridone* (Found : N, 14·6. $C_{13}H_7O_5N_3$ requires N, 14·7%).

3 : 7-*Diaminoacridone.*—3 : 7-Dinitroacridone (1 g.), obtained by nitration of acridone (Lehmstedt, *loc. cit.*, 1931), was heated under reflux for 3 hours with a solution of hydrated stannous chloride (6·2 g.) in concentrated hydrochloric acid (10 ml.). The mixture was cooled, and the hydrochloride filtered off and washed with cold concentrated hydrochloric acid. A solution of the salt in hot water was boiled with charcoal, and the base precipitated by addition of excess of ammonia. The product was extracted with boiling alcohol (150 ml.), and the filtrate after treatment with charcoal was concentrated to *ca.* 5 ml. Recrystallisation of the resulting crystals from alcohol gave orange prisms (0·42 g., 54%), m. p. 300—310° (decomp.; sealed). Bogert, Hirschfelder, and Lauffer (*Coll. Czech. Chem. Comm.*, 1930, **2**, 383) reported m p. 325° (corr.) for this compound. A mixed m. p. with the diaminoacridone obtained by a similar reduction of the dinitroacridone from the hydrolysis described above showed no depression (Found : C, 68·4; H, 5·2; N, 18·2. Calc. for $C_{13}H_{11}ON_3$: C, 69·3; H, 5·2; N, 18·7%). Similar analytical figures were obtained for the diamine synthesised *via* the hydrolysis of the dinitro-5-aminoacridine. Solutions of the compound in alcohol fluoresced strongly yellow-green in daylight, and in ultra-violet light solutions in dilute hydrochloric acid fluoresced a delicate rose-pink.

2 : 4 : 4′-*Trinitrodiphenylamine-2′-carboxylic Acid.*—(a) *By Ullmann condensation.* An intimate mixture of 5-nitroanthranilic acid (2 g.), 2 : 4-dinitrochlorobenzene (5·76 g.), anhydrous sodium carbonate (1·165 g.), and freshly precipitated copper (0·08 g.) was heated in an oil-bath at 200° for 30 minutes and then at 220—225° for 4 hours with occasional stirring. Ether (30 ml.) was added to the cooled mixture, the solid filtered off and extracted twice with boiling 1% sodium carbonate solution (250, 200 ml., respectively), and the combined extracts acidified at 70° with hydrochloric acid. The hot mixture was filtered, and the solid, after being washed with hot water, was dissolved in a boiling solution of sodium carbonate (0·28 g.) in water (200 ml.). The solution was treated with charcoal (0·2 g.), and 3N-sodium hydroxide (30 ml.) added to the hot filtrate. On cooling, the sodium salt separated as a red-brown gelatinous mass. After two recrystallisations from dilute sodium hydroxide, the salt was dissolved in water and the *carboxylic acid* precipitated with hydrochloric acid; yield, 0·38 g. (10%); m. p. 253°. It crystallised from glacial acetic acid as a yellow powder, m. p. 254—255° (Found : C, 44·4; H, 2·4; N, 16·0. $C_{13}H_8O_8N_4$ requires C, 44·8; H, 2·3; N, 16·1%).

(b) *By nitration of* 2 : 4-*dinitrodiphenylamine-2′-carboxylic acid.* This acid (Schroeter and Eisleb, *Annalen*, 1909, **367**, 101) (10 g.) was suspended in glacial acetic acid (200 ml.), concentrated nitric acid (2·5 ml., *d* 1·41) added, and the mixture brought to the boil. After gentle boiling for 15 minutes the solution was concentrated to *ca.* 20 ml. The bright yellow solid obtained on cooling was recrystallised from glacial acetic acid (charcoal); yield, 7·55 g. (66%); m. p. 254—255°. This substance did not depress the melting point of 2 : 4 : 4′-trinitrodiphenylamine-2′-carboxylic acid.

1 : 3 : 7-*Trinitroacridone.*—The foregoing acid (1 g.) was refluxed with phosphorus oxychloride (6 ml.) for 1·5 hours, and the solution cooled and poured with stirring on a mixture of ice and excess of ammonia. A slight excess of acetic acid was added, the mixture boiled for a few minutes and cooled, and the solid filtered off. This was ground under 4N-ammonia (250 ml.) at 40°, and the mixture cooled to room temperature and filtered from the insoluble ammonium salt of unchanged starting material. Neutralisation of the filtrate with concentrated hydrochloric acid yielded a pale-yellow crystalline solid which on recrystallisation from acetone (by concentration), using a mixture of kieselguhr and charcoal, gave yellow needles (0·25 g., 26%), m. p. 277° (Found : C, 46·9; H, 1·8; N, 16·8%). The m. p. was not depressed by the trinitroacridone from the nitration of 5-aminoacridine. Both these compounds were insoluble in water and benzene, slightly soluble in alcohol, moderately soluble in acetone, soluble in dilute ammonia.

A yellow by-product formed in the preparation of 3 : 7-dinitroacridone by nitration of 3-nitroacridone (19 g.) (Lehmstedt, *loc. cit.*, 1931) was found to be 1 : 3 : 7-trinitroacridone. The aqueous pyridine mother-liquors from the recrystallisation of 3 : 7-dinitroacridone were evaporated in a vacuum. The residue (4·37 g.) was heated under reflux with glacial acetic acid (440 ml.) for 20 minutes, and the filtered extract, after being boiled with charcoal, deposited a yellow-brown solid (1·62 g.) on cooling. It was dissolved in glacial acetic acid, and the filtrate concentrated until solid separated. Recrystallisation from acetone as described above yielded bright yellow needles (0·9 g.), m. p. 277° (Found : C, 47·1; H, 1·8; N, 17·0%). A mixed m. p. with 1 : 3 : 7-trinitroacridone showed no depression.

5-*Chloro*-1-*nitroacridine.*—A mixture of 1-nitroacridone (Clemo, Perkin, and Robinson, *J.*, 1924, **125**, 1751) (10 g.), nitrobenzene (40 ml.), phosphorus oxychloride (35 ml.), and one drop of concentrated hydrochloric acid was heated in an oil-bath at 180° for 10 hours. After vacuum evaporation, the powdered residue was triturated with ice and excess of ammonia. The chloro-compound was filtered off, washed with ice-water and then alcohol, and dried in a vacuum; yield 10·3 g. (96%); m. p. 195—196°. Albert and Gledhill (*loc. cit.*, 1945) gave m. p. 195°. The product could be distilled at 12 mm. with slight decomposition; b. p. 265°.

1-*Nitro*-5-*aminoacridine.*—A stream of dry ammonia was passed for 4 hours through a solution of 5-chloro-1-nitroacridine (1 g.) in phenol (3·5 g.) kept in an oil-bath at 65°. Sodium hydroxide (3 g. in 40 ml. of water) was added to the cooled mixture, the precipitate collected and triturated with cold 2% acetic acid (30 ml.), and insoluble material filtered off and washed with more solvent. The combined filtrates on basification with sodium hydroxide yielded a bright red solid (0·71 g., 76%), m. p. 191—193°. Albert and Gledhill (*loc. cit.*, p. 1945) give m. p. 193°.

1 : 5-*Diaminoacridine.*—Finely powdered 1-nitro-5-aminoacridine (2 g.) was added gradually with mechanical stirring to a boiling solution of hydrated stannous chloride (7·3 g.) in concentrated hydro-

chloric acid (16 ml.), and the mixture heated on the water-bath for 1 hour. After cooling, sodium hydroxide (60 ml., 30%) was added, the precipitate filtered off and dissolved in 2% acetic acid (40 ml.), the solution clarified, and the base reprecipitated. Fractional precipitation with dilute sodium hydroxide from a solution of the crude base in 10% acetic acid (30 ml.) eventually yielded a yellow solid (0·83 g., 48%), m. p. 178°. The 1 : 5-*diaminoacridine* was obtained from aqueous acetone as yellow-brown crystals, m. p. 178—179° (Found : C, 74·0; H, 5·3; N, 20·0. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%); it was insoluble in water and benzene, easily soluble in acetone and alcohol. Solutions in alcohol and dilute hydrochloric acid fluoresced green.

4-*Nitro*-5-*aminoacridine*.—A mixture of 5-chloro-2- and -4-nitroacridines (9·74 g., Lehmstedt and Schrader, *loc. cit.*) was aminated in the manner described for 5-chloro-1-nitroacridine; crude yield, 5·98 g. The finely ground material was extracted twice with cold chloroform (900, 300 ml.), and the combined extracts were evaporated to dryness. The residue was dissolved in boiling benzene (550 ml.), and the solution filtered and concentrated to *ca.* 50 ml. The solid (3·1 g.), on recrystallisation from benzene (450 ml.) by concentration, gave red crystals of 4-nitro-5-aminoacridine (2·5 g.) (88% based on mixed chloro-compounds), m. p. 233—235°. Albert and Gledhill (*loc. cit.*, p. 1945) gave m. p. 234°.

4 : 5-*Diaminoacridine*.—Powdered 4-nitro-5-aminoacridine (1·25 g.) was stirred into a solution of ferrous sulphate crystals (9·7 g.) in water (35 ml.) at 75—80°. Precipitated chalk (3·2 g.) was added during 30 minutes at the same temperature, and the stirring continued at this temperature for a further hour, the mixture was brought to the boil and filtered, and the cake washed with boiling water (6 ml.). Red crystals of the sulphate which separated from the filtrate on cooling were dissolved in hot water (130 ml.), the solution clarified, cooled to 10°, and the base precipitated with N-sodium hydroxide. The product (0·8 g.) was extracted with boiling benzene (80 ml.), and the extract after treatment with charcoal and kieselguhr evaporated to dryness. The crystalline residue was dissolved in hot 0·1N-hydrochloric acid (10 ml.), the solution treated with charcoal, and concentrated hydrochloric acid (0·5 ml.) added; large orange-red crystals of the hydrochloride (0·61 g., 43%), m. p. 345° (decomp.), were obtained. Recrystallisation from dilute hydrochloric acid (charcoal) gave fine, silky, orange needles of the *monohydrochloride*, m. p. 346—347° (decomp.). For analysis it was dried at 25 mm. over calcium chloride (Found : C, 57·3; H, 5·6; N, 15·2; Cl, 13·3. $C_{13}H_{11}N_3,HCl,1{\cdot}5H_2O$ requires C, 57·2; H, 5·6; N, 15·4; Cl, 13·0%).

The *base* crystallised from benzene (by concentration) or benzene–light petroleum as orange needles, m. p. 147—148° (Found : C, 73·9; H, 5·4; N, 19·7. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). It was insoluble in water, moderately soluble in hot benzene, easily in acetone. Solutions in alcohol and dilute hydrochloric acid showed a weak green fluorescence.

All melting points given are uncorrected.

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