164. *The Bromination of Some 4-Quinolones.*

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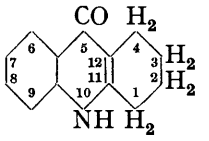
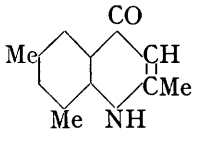
The bromination of 1 : 2 : 3 : 4-tetrahydroacridone has given the 7-bromo- and the 7 : 9-*dibromo*-derivative, which are best characterised by conversion into the corresponding 7-*bromo*- and 7 : 9-*dibromo*-5-*chloro*-1 : 2 : 3 : 4-*tetrahydroacridines*, and also by-products containing an atom of bromine which is much more reactive than that in the simple substitution products and is presumably attached to the partly reduced ring. The bromination of 7 : 9-dimethyl-1 : 2 : 3 : 4-tetrahydroacridone gives a similar reactive *monobromo*-derivative as the main product.

A study of the bromination of certain 2 : 3-disubstituted 4-quinolones has shown that the reaction is not entirely restricted to the introduction of bromine at the expected positions in the benzene ring. Treatment of 1 : 2 : 3 : 4-tetrahydroacridone (I; hereafter called "tetrahydroacridone") with one molecular proportion of bromine in glacial acetic acid gave 7-bromotetrahydroacridone as the main product, the structure of which followed from its synthesis, by an application of Tiedtke's method (*Ber.*, 1909, **42**, 621), from 5-bromoanthranilic acid and *cyclo*hexanone. Since these 4-quinolones are in general high-melting substances not particularly suitable for direct comparison, the identity of the two specimens was confirmed by converting each into the more characteristic 5-*chloro*-7-*bromotetrahydroacridine* by heating with a mixture of phosphorus oxychloride and phosphorus pentachloride. Extraction of the crude bromination product with alcohol removed, however, a fraction which differed fundamentally from the 7-bromo-derivative, for it contained reactive bromine and gave a pyridinium salt, soluble in water, when its solution in pyridine was heated. Attempts to obtain a pure compound from this fraction have been unsuccessful and it seemed probable that at least two substances were present, one more basic than the other. Possible explanations of the formation of these by-products, which were found on analysis to contain one atom of bromine in the molecule, involve substitution in the partly reduced ring or primary addition of bromine at the 11 : 12-position with subsequent elimination of hydrogen bromide or replacement of one bromine by hydroxyl. It must, however, be borne in mind that a bromine atom in the 6-position of the tetrahydroacridone skeleton would exhibit some degree of activity (compare Nisbet, J., 1933, 1372).

(I.) 



(II.)

The further bromination of tetrahydroacridone with two molecular proportions of bromine gave 7 : 9-*dibromotetrahydroacridone*, but the yield was only moderate and it was clear that by-products were again formed in considerable quantity. The 7 : 9-dibromo-compound was also prepared from 3 : 5-dibromoanthranilic acid and *cyclo*hexanone, and characterised by conversion into 5-*chloro*-7 : 9-*dibromotetrahydroacridine*. The formation of the 7-bromo- and the 7 : 9-dibromo-derivative is in accordance with the observation of Perkin and Sedgwick (J., 1924, **125**, 2437) that the nitration of tetrahydroacridone leads to a mixture of 7- and 9-nitrotetrahydroacridone.

A *monobromo*-derivative similar to the by-products described above was obtained in an apparently pure condition as the main product during the bromination under analogous conditions of 7 : 9-dimethyltetrahydroacridone, in which substitution in the more reactive positions is prevented by the presence of the methyl groups. It is impossible to say where the bromine is located in this product, but it is presumably attached to the reduced ring, since the substance readily combines with pyridine. The bromination of 2 : 6 : 8-trimethyl-4-quinolone (II), on the other hand, has given a *monobromo*-derivative from which the halogen is not removed by pyridine, and, since the 3-position is unsubstituted in the starting material, it is likely that the bromine has entered at this point. It proved to be impossible to determine the structure of the product by converting it into 2 : 3 : 6 : 8-

tetramethyl-4-quinolone, which was prepared by condensing *m*-4-xylidine with ethyl acetoacetate, introducing a methyl group through the sodium derivative, and heating the product to 260°.

The method used by Tiedtke (*loc. cit.*) for the preparation of tetrahydroacridone from anthranilic acid and *cyclo*hexanone, and extended in this work to the preparation of some derivatives, is an application of that used by Niementowski (*Ber.*, 1894, **27**, 1394) to obtain 2-phenyl-4-quinolone. We have also prepared 2 : 3-dimethyl-4-quinolone, 2-phenyl-3-methyl-4-quinolone, 3-phenyl-2-benzyl-4-quinolone, and 5-*keto*-5 : 6 : 7 : 10-*tetrahydroacrindoline* by an analogous procedure from anthranilic acid and methyl ethyl ketone, propiophenone, dibenzyl ketone, and 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole respectively, but the yields were not so good as that of tetrahydroacridone. Anthranilic acid has been condensed with *cyclo*hexane-1 : 2- and -1 : 4-dione with the formation of a *monoanil* from the former and a *dianil* from the latter, but neither could be transformed into the corresponding 4-quinolone. Attempts to apply Niementowski's reaction to acetone and *n*-valerophenone were unsuccessful.

Experimental.

Preparation of 7-Bromotetrahydroacridone.—Bromine (20 g.), dissolved in glacial acetic acid (170 c.c.), was added gradually to a solution of tetrahydroacridone (25 g., prepared by the method of Tiedtke, *loc. cit.*) in acetic acid (500 c.c.), the whole being kept at room temperature and constantly shaken. The mixture was made alkaline with ice–aqueous ammonia, and the resulting solid collected, dried on the steam-bath, and extracted with boiling alcohol (200 c.c.). The residue was crystallised from *cyclo*hexanone, and 7-bromotetrahydroacridone obtained in small colourless prisms, m. p. 367° (Found : C, 56·4; H, 4·3. Calc. : C, 56·1; H, 4·3%). The same substance (mixed m. p.) was obtained by heating a mixture of 5-bromoanthranilic acid (10 g.) and *cyclo*hexanone (8 c.c.), first at 150° for ½ hour and then at 220° for ½ hour, extracting the impurities from the product with boiling benzene, and crystallising the residue from *cyclo*hexanone. 7-Bromotetrahydroacridone differs from tetrahydroacridone in being insoluble in dilute hydrochloric acid. It is evidently identical with the substance (m. p. > 300°) obtained by Hughes and Lions (*J. Proc. Roy. Soc. N.S.W.*, 1938, **71**, 458) by condensing *p*-bromoaniline with ethyl *cyclo*hexanone-2-carboxylate.

Both the direct bromination product and the synthetical specimen (2·8 g.) in phosphorus oxychloride (10 c.c.) were treated with phosphorus pentachloride (2·2 g.) and refluxed for an hour in an oil-bath at 130°. The cooled solutions were poured into ice-water, filtered after a few hours to remove a small quantity of amorphous material, and made alkaline with ammonia. When the precipitate was crystallised from alcohol, *5-chloro-7-bromotetrahydroacridine* was obtained in each case (mixed m. p.) in colourless needles, m. p. 99° (Found : C, 52·6; H, 3·9. $C_{13}H_{11}NClBr$ requires C, 52·6; H, 3·7%). It was readily soluble in dilute hydrochloric acid to give a yellow solution.

When the alcoholic extract from the direct bromination product was cooled, a solid (usually about 3 g.) separated. Although this dissolved completely in concentrated hydrochloric acid, when its solution in hot alcohol was poured into dilute hydrochloric acid (3%) it was resolved into an insoluble and a soluble fraction, the latter being recovered from the acid solution, after filtration, by the addition of ammonia. Both melted with decomposition at about 195°, but they have not been obtained sufficiently pure for concordant analytical results, although it is certain that both contain one atom of bromine in the molecule. The bromine is in both cases reactive, since pyridinium salts, readily soluble in water and insoluble in the common organic solvents, separated when solutions of the products in pyridine were boiled. In the case of the substance more soluble in hydrochloric acid a pure *compound*, colourless plates, m. p. 152°, from alcohol, giving the analytical figures corresponding to a chlorobromotetrahydroacridine, was obtained by refluxing with phosphorus oxychloride and phosphorus pentachloride in the manner described above (Found : C, 52·6; H, 3·5%).

Preparation of 7 : 9-Dibromotetrahydroacridone.—(a) When synthesised from 3 : 5-dibromoanthranilic acid by a process similar to that used for the 7-bromo-compound, the yield of *7 : 9-dibromotetrahydroacridone*, small colourless prisms, m. p. 287°, from pyridine, amounted to 35% of the theoretical (Found : C, 43·9; H, 3·3. $C_{13}H_{11}ONBr_2$ requires C, 43·7; H, 3·1%). It did not give a compound with pyridine, since its solution in this solvent remained clear after being refluxed for an hour and the substance separated unchanged on cooling. It was also found to be insoluble in dilute acids and alkalis.

After a mixture of the dibromo-compound (3·5 g.), phosphorus oxychloride (10 c.c.), and phosphorus pentachloride (2·2 g.) had been refluxed for an hour in an oil-bath at 130°, cooled, and stirred with an excess of ice-water, the solid which separated was ground with concentrated hydrochloric acid. When the filtered solution was diluted with water, *5-chloro-7 : 9-dibromotetrahydroacridine*, colourless prisms, m. p. 170—173°, from *cyclo*hexanone, was precipitated (Found : C, 41·5; H, 2·8. $C_{13}H_{10}NClBr_2$ requires C, 41·5; H, 2·7%).

(b) When tetrahydroacridone (10 g.) in glacial acetic acid (200 c.c.) at room temperature was treated gradually with bromine (18 g.), dissolved in acetic acid (165 c.c.), the whole made alkaline with ammonia, and the solid product crystallised from pyridine, 7 : 9-dibromotetrahydroacridone (about 8 g.) was obtained, although on a few occasions the yield was considerably less. Its identity was established by mixed m. p. and by conversion into 5-chloro-7 : 9-dibromotetrahydroacridine. A similar result was obtained when 7-bromotetrahydroacridone was treated under analogous conditions with 1 molecular proportion of bromine.

7 : 9-*Dimethyltetrahydroacridone and its Bromination.*—7 : 9-Dimethyltetrahydroacridone has been prepared by Sen and Basu (*J. Indian Chem. Soc.*, 1930, **7**, 435) by condensing *m*-4-xylidine with ethyl *cyclo*hexanone-2-carboxylate and heating the resulting unsaturated ester, which they were unable to obtain solid. We have now found that the condensation takes place much more rapidly on the addition of a trace of hydrochloric acid, as reported in analogous cases by Coffey, Thomson, and Wilson (J., 1936, 856), and that the ester can be obtained in colourless needles, m. p. 69°, from alcohol (Found : N, 5·2. Calc. : N, 5·1%). The 7 : 9-dimethyltetrahydroacridone obtained by heating the ester to 265° crystallised from *cyclo*hexanone in small colourless needles, m. p. 318°. It dissolved readily in very dilute hydrochloric acid, but the hydrochloride was sparingly soluble in more concentrated acid. It was converted into *5-chloro-7 : 9-dimethyltetrahydroacridine*, colourless needles, m. p. 94°, from alcohol, by a process similar to that described for 7-bromotetrahydroacridone (Found : C, 73·2; H, 6·6. $C_{15}H_{16}NCl$ requires C, 73·3; H, 6·5%).

After 7 : 9-dimethyltetrahydroacridone (6·9 g.) in glacial acetic acid (150 c.c.) had been treated gradually at room temperature with bromine (4·8 g.) dissolved in acetic acid (45 c.c.), the solution was filtered to remove a small amount of precipitated solid, and the filtrate diluted with water (1 l.). The whole was left for an hour, the solid then collected and dissolved in boiling alcohol, and the solution poured into 2% hydrochloric acid (1 l.). The *monobromo*-derivative which slowly separated was collected after 24 hours, some unchanged 7 : 9-dimethyltetrahydroacridone remaining in solution. It crystallised from alcohol in pale yellow plates, m. p. 196° (decomp.) (Found : C, 58·5; H, 5·2; Br, 27·0. $C_{15}H_{16}ONBr$ requires C, 58·8; H, 5·2; Br, 26·1%). It gave a pyridinium salt, which separated as a white solid, soluble in water, when a solution of the monobromo-compound in pyridine was heated on the steam-bath.

Bromination of 2 : 6 : 8-*Trimethyl-4-quinolone.*—When this substance (4·7 g., prepared by the method of Conrad and Limpach, *Ber.*, 1888, **21**, 523) in glacial acetic acid (100 c.c.) was treated with bromine (4 g. in a small amount of acetic acid) at room temperature, an orange precipitate soon separated, but this dissolved on shaking to give a clear solution, from which the hydrobromide (7 g.) of *?-bromo-2 : 6 : 8-trimethyl-4-quinolone* was deposited on standing. The salt was ground with aqueous ammonia, and the base obtained in small colourless needles, m. p. 272—274°, on crystallisation from *cyclo*hexanone (Found : C, 54·3; H, 4·5. $C_{12}H_{12}ONBr$ requires C, 54·1; H, 4·5%). It crystallised unchanged after its solution in pyridine had been boiled for an hour, and was converted into *4-chloro-?-bromo-2 : 6 : 8-trimethylquinoline*, colourless needles, m. p. 107°, from alcohol, by a process similar to that described in the case of 7-bromotetrahydroacridone (Found : C, 50·4; H, 3·7. $C_{12}H_{11}NClBr$ requires C, 50·6; H, 3·9%).

2 : 3 : 6 : 8-*Tetramethyl-4-quinolone.*—After a mixture of *m*-4-xylidine (50 g.) and ethyl acetoacetate (54 g.) to which a drop of concentrated hydrochloric acid had been added had been left for 12 hours under reduced pressure in a desiccator, it was dissolved in benzene, and the solution dried with sodium sulphate and treated with sodium wire (9 g.). When the sodium had completely reacted, methyl iodide (25 c.c.) was added, and the whole warmed for a short time on the steam-bath, cooled, and poured into water. After the benzene layer had been dried and evaporated, the residual oil was heated at 265° for 15 minutes. The 2 : 3 : 6 : 8-*tetramethyl-4-quinolone* which remained was washed with boiling benzene and further purified by boiling its solution in an excess of alcohol with charcoal. It crystallised from the filtered solution after most of the solvent had been removed, and was then obtained from *cyclo*hexanone in colourless needles, m. p. 300° (rapid heating on account of considerable previous darkening) (Found : N, 7·2. $C_{13}H_{15}ON$ requires N, 7·0%). By a process similar to that applied to 7-bromotetra-

hydroacridone it was converted into 4-*chloro*-2 : 3 : 6 : 8-*tetramethylquinoline*, colourless needles, m. p. 89°, from alcohol (Found : C, 71·5; H, 6·1. $C_{13}H_{14}NCl$ requires C, 71·0; H, 6·4%).

Applications of Niementowski's Reaction.—(a) When a mixture of anthranilic acid (5 g.) and methyl ethyl ketone (5 c.c.) was heated at 280° for an hour under a reflux air condenser, and the remaining solid washed with boiling benzene, 2 : 3-dimethyl-4-quinolone, colourless needles, m. p. 325°, from alcohol, was obtained in a yield of 11% (of the theoretical) (Found : C, 76·5; H, 6·3. Calc. : C, 76·3; H, 6·3%). It was obviously identical with the compound obtained by Conrad and Limpach (*Ber.*, 1891, **24**, 2991) from ethyl β-anilino-α-methylcrotonate, and by Wohnlich (*Arch. Pharm.*, 1913, **251**, 526) from *o*-acetamidopropiophenone.

(b) 2-Phenyl-3-methyl-4-quinolone, colourless needles, m. p. 280°, from alcohol, was similarly prepared in 23% yield from propiophenone (Found : C, 81·8; H, 5·5. Calc. : C, 81·7; H, 5·5%). Wohnlich (*loc. cit.*) and Dziewoński and Mayer (*Chem. Zentr.*, 1933, ii, 3569) prepared this substance from *o*-benzamidopropiophenone, and 4-anilino-2-phenyl-3-methylquinoline, respectively.

(c) 3-Phenyl-2-benzyl-4-quinolone, colourless needles, m. p. 312°, from alcohol, was obtained in 35% yield by a similar process from dibenzyl ketone, and was apparently identical with the compound obtained by von Braun and Heymons (*Ber.*, 1930, **63**, 3191) from 4-anilino-3-phenyl-2-benzylquinoline (Found : C, 84·7; H, 5·6. Calc. : C, 84·9; H, 5·5%).

(d) 5-*Keto*-5 : 6 : 7 : 10-*tetrahydroacrindoline* (yield 23%), a yellow micro-crystalline solid, m. p. above 360°, from *cyclo*hexanone, was prepared by heating anthranilic acid (1·5 g.) with 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (2 g.) at 280° for ½ hour and washing the product with boiling benzene (Found : C, 79·5; H, 5·0. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%).

Condensation of Anthranilic Acid with cyclo*Hexane*-1 : 2- *and* -1 : 4-*dione.*—(a) After *cyclo*hexane-1 : 2-dione (3 g.) and anthranilic acid (3 g.) in alcohol (25 c.c.) had been refluxed for 12 hours, N-2′-*keto*cyclo*hexylideneanthranilic acid* separated on cooling in pale greenish-yellow plates, m. p. 172° (Found : C, 67·7; H, 5·7. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%).

(b) The *di*-o-*carboxyanil* of *cyclo*hexane-1 : 4-dione separated when a solution of the diketone (2 g.) and anthranilic acid (2·5 g.) in alcohol (40 c.c.) was boiled under reflux. After 12 hours the product (3 g.) was collected and obtained from acetophenone in small colourless prisms, m. p. 261° (decomp.) (Found : C, 69·2; H, 5·1. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1%).

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