639. *Carcinogenic Nitrogen Compounds. Part VIII.* Further Syntheses of Hydroxybenzacridines and Hydroxydibenzacridines.*

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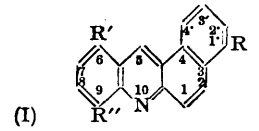
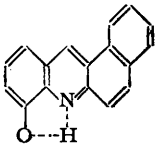
In continuation of earlier work, several new 3 : 4-benzacridines, and 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridines bearing one or two hydroxy- or alkoxy-groups, have been synthesised by known methods for biological examination. Incidentally, the chemistry of some dihydroxynaphthalenes was more closely investigated, and several new derivatives were prepared. Monomethylation of 1 : 6-dihydroxynaphthalene was shown to yield 5-methoxy-2-naphthol, in accordance with the theory relating reactivity to π-electron densities.

Recently, the synthesis was described of several angular hydroxybenzacridines required for preliminary experiments with compounds similar to expected metabolites of the carcinogenic 1 : 2- and 3 : 4-benzacridines (Buu-Hoï, *J.*, 1950, 2096). The present work extends this research to two further new substitution products of 3 : 4-benzacridine, *viz.*, the 1'- (I; R = OH, R' = R'' = H) and the 9-hydroxy-derivative (I; R = R' = H, R'' = OH). The first isomer was obtained by demethylation of the corresponding methyl ether, the product from an Ullmann–Fetvadjian reaction (*Ber.*, 1903, **36**, 1029) between β-naphthol, *o*-anisidine, and paraformaldehyde. 9-Hydroxy-3 : 4-benzacridine is far lower-melting and more soluble than the isomerides hitherto known, properties apparently caused by intramolecular hydrogen bonding as shown in (II). Like 8-hydroxyquinoline and 1-hydroxyacridine, it readily gave chelation products


(I)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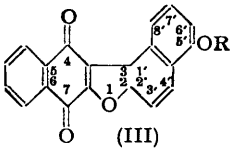
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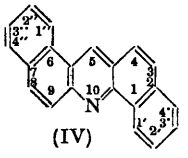
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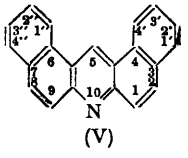
(V)

with the cations of a wide series of metals, and is also more strongly antibacterial against *Staphylococcus aureus* than its non-chelating isomerides, two properties which might well be linked (cf. Albert, " The Acridines," London, 1951, p. 259). The similar synthesis of 1'-hydroxy-3 : 4-benzacridine, starting from aniline, paraformaldehyde, and 5-methoxy-2-naphthol, was of interest because it involved an investigation of the constitution of monoalkylation products of 1 : 6-dihydroxynaphthalene. For instance, monomethylation with one molecule of methyl sulphate in the presence of one molecule of potassium hydroxide would yield 5-methoxy-2-naphthol, 6-methoxy-1-naphthol, or a mixture of the two. In fact, the first substance was formed, as the reaction product gave a sharp-melting picrate and reacted readily with one molecule of 2 : 3-dichloro-1 : 4-naphthaquinone to give the compound (III; R = Me). Such a reaction, observed by Eistert for β-naphthol itself (*Ber.*, 1947, **80**, 52), and more recently extended to its 6-substituted derivatives (Buu-Hoï, Le Bihan, and Binon, *J. Org. Chem.*, 1951, **16**, 185), is now found to be highly characteristic of 2-naphthols having their 1-position free, and not to occur with 1-naphthols. The constitution of our brasan derivative was proved by the identity of its demethylation product with the 1'-hydroxy-compound (III; R = H) prepared directly from 1 : 6-dihydroxynaphthalene.

2 : 6-Dimethoxyaniline underwent readily an Ullmann–Fetvadjian reaction with β-naphthol and paraformaldehyde, to give 6 : 9-dimethoxy-3 : 4-benzacridine (I; R = H, R' = R'' = OMe); demethylation afforded, apparently, 6 : 9-dihydroxy-3 : 4-benzacridine (I; R = H, R' = R'' = OH), but its instability prevented complete purification.

Whereas some 5-hydroxyaryldibenzacridines are already known (Buu-Hoï, *J.*, 1950, 2096), no dibenzacridines bearing *Bz*-hydroxy- or -ether groups have yet been described. Of the thir-

* Part VII, preceding paper.

teen possible monohydroxy-derivatives of 1 : 2-6 : 7-dibenzacridine (IV), five have now been prepared by a method analogous to that employed earlier, *viz.*, 2'-, 4'-, 2''-, 3''-, and 4''-hydroxy-1 : 2-6 : 7-dibenzacridine. In the 3 : 4-6 : 7-dibenzacridine series (V), the 1'-, 2'-, and 3'-hydroxy-derivatives were prepared.

All these hydroxydibenzacridines were very similar to each other and to the hydroxy-3 : 4-benzacridines already described. No such compounds have yet been detected in the urine and fæces of animals fed with the carcinogenic 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridines.

Experimental.

9-Hydroxy-3 : 4-benzacridine.—To a boiling mixture of β-naphthol (20 g.) and *o*-anisidine (15 g.), paraformaldehyde (3 g.) was cautiously added in small portions. The reaction product was boiled for 5 minutes in the air to complete the dehydrogenation of the intermediary acridan formed. A mixture of the crude 9-methoxy-3 : 4-benzacridine (15 g.), obtained on vacuum-distillation (b. p. 280—285°/15 mm.), and pyridine hydrochloride (50 g.) was boiled for 10 minutes. After the product had cooled, water (250 c.c.) was added, and the orange-yellow precipitate of 9-hydroxy-3 : 4-benzacridine hydrochloride obtained on scratching with a glass rod was collected and decomposed with dilute aqueous ammonia. *9-Hydroxy-3 : 4-benzacridine* (8 g.) formed, from benzene, greenish-yellow silky needles, m. p. 159—160°, which dissolved readily in aqueous sodium hydroxide with a yellow colour (Found: C, 83·1; H, 4·1. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%). An attempt to prepare the isomeric 9-hydroxy-1 : 2-benzacridine in the same way from α-naphthol, *o*-anisidine, and paraformaldehyde failed.

Methylation of 1 : 6-*Dihydroxynaphthalene.*—A suspension of 1 : 6-dihydroxynaphthalene (32 g.) and methyl sulphate (30 g.) in water was treated with concentrated aqueous potassium hydroxide (12 g.), in small portions, with vigorous shaking. The shaking was continued for a few minutes, some more alkali was added, and the reaction product was extracted with ether. The dark oil obtained on acidification with hydrochloric acid of the aqueous layer was taken up in ether and dried (Na_2SO_4), the solvent removed, and the residue distilled in a vacuum. *5-Methoxy-2-naphthol* (23 g.) formed a pale yellow viscous oil, b. p. 208—210°/20 mm., which did not solidify on prolonged storage in the refrigerator and darkened rapidly on exposure to air (Found: C, 75·7; H, 5·8. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·7%). The picrate formed, from ethanol, silky orange-red needles, m. p. 172°. 6-Methoxy-1-naphthol had been summarily recorded in a patent (*Chem. Centr.*, 1921, II, 504) as a solid, b. p. 185°/12 mm.

5'-Methoxy-5 : 6-benzonaphtho(2' : 1'-2 : 3)coumarone-4 : 7-quinone (III; R = Me).—A mixture of 2 : 3-dichloro-1 : 4-naphthaquinone (Ullmann and Ettisch, *Ber.*, 1921, **54**, 259) (2 g.), 5-methoxy-2-naphthol (2 g.), and anhydrous pyridine (12 c.c.) was brought to the boil, and, after the violent initial reaction had subsided, refluxed for 30 minutes. After the mixture had cooled, methanol was added, and the *quinone* which crystallised was collected, washed with water, and recrystallised from toluene. The fine orange-red sublimable needles (2·5 g.) obtained had m. p. 261—262° and gave an intense greenish-blue colour with sulphuric acid (Found: C, 76·5; H, 3·6. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

5'-Hydroxy-5 : 6-benzonaphtho(2' : 1'-2 : 3)coumarone-4 : 7-quinone (III; R = H).—A mixture of the foregoing compound (1 g.) with pyridine hydrochloride (8 g.) was boiled for 5 minutes, and water added to the cooled product. The precipitate obtained was collected, washed with water, dried, and recrystallised from chlorobenzene, giving fine brown-red needles, m. p. 303—304°, of the *hydroxy*-compound, soluble in sulphuric acid with a deep blue colour and in aqueous sodium hydroxide to give deep violet-blue solutions (Found: C, 76·0; H, 3·1. $C_{20}H_{10}O_4$ requires C, 76·4; H, 3·1%). The same product was obtained directly by refluxing for 2 hours a mixture of 1 : 6-dihydroxynaphthalene (2 g.), 2 : 3-dichloro-1 : 4-naphthaquinone (1·9 g.), and pyridine (12 c.c.).

6 : 9-Dimethoxy-3 : 4-benzacridine.—A mixture of β-naphthol (20 c.), and 2 : 6-dimethoxyaniline (15 g.) was treated with paraformaldehyde (2·5 g.) in the usual way. *6 : 9-Dimethoxy-3 : 4-benzacridine*, the fraction boiling at 302—306°/15 mm. (12 g.), crystallised from methanol in long yellow silky needles, m. p. 168°, giving with sulphuric acid a brown-red colour (Found: C, 78·8; H, 5·1. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2%). The picrate formed from nitrobenzene shiny orange-red needles, m. p. *ca.* 267—269° (decomp.). Five minutes' refluxing of a mixture of 6 : 9-dimethoxy-3 : 4-benzacridine (2 g.) and pyridine hydrochloride (15 g.) yielded after cooling a brown water-insoluble hydrochloride; on treatment with dilute aqueous ammonia, this gave a greenish product, which dissolved readily in aqueous caustic alkalis with a deep yellow colour, and was probably 6 : 9-dihydroxy-3 : 4-benzacridine but could not be purified sufficiently for analysis.

1'-Hydroxy-3 : 4-benzacridine (I; R = OH, R' = R'' = H).—This *compound* formed from nitrobenzene fine pale yellow, sublimable needles, m. p. 275° (Found: C, 83·0; H, 4·6. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%). The corresponding *methyl ether* formed, from ethanol, long silky pale yellow needles, m. p. 172° (Found: N, 5·4. $C_{18}H_{13}ON$ requires N, 5·4%), giving an orange picrate (silky needles from nitrobenzene), m. p. 289—290°.

4''-Methoxy-1 : 2-6 : 7-dibenzacridine.—To a boiling mixture of 5-methoxy-2-naphthol (5 g.) and α-naphthylamine (4·5 g.), paraformaldehyde (1 g.) was added in small portions. The thick orange *ether* boiling above 300°/12 mm. (4 g.) crystallised readily from benzene in pale yellow silky needles, m. p. 214°, giving with sulphuric acid a deep yellow colour (Found: C, 85·1; H, 4·8. $C_{22}H_{15}ON$ requires C, 85·4; H, 4·8%).

4''-Hydroxy-1 : 2-6 : 7-dibenzacridine.—The usual demethylation of the foregoing compound yielded a water-insoluble red hydrochloride; the free *4''-hydroxy-1 : 2-6 : 7-dibenzacridine* obtained on basification with dilute aqueous ammonia formed, from nitrobenzene, yellowish silky, sublimable needles, m. p. 304—305°, whose alkaline solutions were deep yellow (Found: C, 85·2; H, 4·5. $C_{21}H_{13}ON$ requires C, 85·4; H, 4·4%).

3''-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—The 6-methoxy-2-naphthol used for this synthesis was prepared by monomethylation of 2 : 6-dihydroxynaphthalene according to Fischer and Hammerschmidt (*J. pr. Chem.*, 1916, **94**, 24). 3''-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine* formed from nitrobenzene fine greenish-yellow needles, melting above 330° (Found : C, 85·1; H, 4·2%), giving an orange-red water-insoluble hydrochloride. The corresponding *methyl ether* crystallised from benzene in shiny pale yellow needles, m. p. 181—182° (Found : N, 4·5. $C_{22}H_{15}ON$ requires N, 4·5%).

2''-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—The 7-methoxy-2-naphthol used was prepared by monomethylation of 2 : 7-dihydroxynaphthalene; 2''-*hydroxy*-1 : 2-6 : 7-*dibenzacridine* formed, from nitrobenzene, yellow needles, m. p. 271—272° (Found : C, 85·2; H, 4·6%), giving with aqueous sodium hydroxide yellow solutions, and brown-red ones with alcoholic sodium hydroxide; the hydrochloride formed orange-yellow needles, insoluble in water. The *methyl ether* crystallised from benzene in pale yellow fluffy needles, m. p. 209—210° (Found : C, 85·4; H, 5·0%).

4'-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—5-Methoxy-1-naphthylamine (12 g.) was prepared from 5-amino-1-naphthol (16 g.), methyl sulphate (15 g.), and sodium hydroxide (5 g.); 4'-*hydroxy*-1 : 2-6 : 7-*dibenzacridine* formed from nitrobenzene fine greenish-yellow needles, m. p. 295—296° (Found : C, 85·1; H, 4·8%), giving a red hydrochloride and dissolving in aqueous sodium hydroxide with an intense yellow colour. 4'-*Methoxy*-1 : 2-6 : 7-*dibenzacridine* formed from benzene silky pale yellow needles, m. p. 210° (Found : C, 85·2; H, 4·9%), and gave a picrate crystallising from nitrobenzene in shiny orange prisms, m. p. 268—269°.

4'-*Allyloxy*-1 : 2-6 : 7-*dibenzacridine* (cf. Buu-Hoï, *J.*, 1950, 2096) formed, from benzene, pale yellow silky needles, m. p. 195—196° (Found : N, 4·1. $C_{24}H_{17}ON$ requires N, 4·2%).

2'-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—The 7-methoxy-1-naphthylamine (b. p. 192—193°/14 mm.) was prepared from methyl sulphate, sodium hydroxide, and 1-amino-2-naphthol; 2'-*hydroxy*-1 : 2-6 : 7-*dibenzacridine* formed, from nitrobenzene, fine pale yellow needles, m. p. 258° (Found : C, 85·2; H, 4·6%). The corresponding methyl ether crystallised from ethanol in pale yellow fluffy needles, m. p. 181—182°.

1'-*Methoxy*-3 : 4-6 : 7-*dibenzacridine*.—Obtained in 40% yield from 5-methoxy-2-naphthol (5 g.), β-naphthylamine (5 g.), and paraformaldehyde (1 g.), this *ether* crystallised from ethanol–benzene as shiny silky yellowish needles, m. p. 239—240° (Found : N, 4·2%). 1'-*Hydroxy*-3 : 4-6 : 7-*dibenzacridine* formed from nitrobenzene fine yellow needles, m. p. 285° (Found : C, 85·2; H, 4·5%).

2'-*Hydroxy*-3 : 4-6 : 7-*dibenzacridine* formed, from nitrobenzene, greenish-yellow prisms, m. p. >340° (Found : C, 85·1; H, 4·6%), giving a hydrochloride which was readily hydrolysed. The isomeric 3'-*hydroxy*-3 : 4-6 : 7-*dibenzacridine* crystallised from nitrobenzene in velvety yellow needles, m. p. 332—333° (decomp.) (Found : C, 85·2; H, 4·4%).

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