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431. *The Chemistry of Carcinogenic Nitrogen Compounds. Part V. Angular Hydroxybenzacridines and Hydroxydibenzacridines.*

By Ng.Ph. Buu-Hoï.

A number of new 1 : 2- and 3 : 4-benzacridines containing hydroxy- or alkoxy-groups have been prepared for biological examination; similar compounds in the three biangular dibenzacridine series were also synthesised. Several allyloxy-benzacridines were rearranged by the Claisen method. The thermal condensation of naphthols with aromatic aldehydes and amines to give benzacridines was more closely investigated.

A number of carcinogenic polycyclic hydrocarbons are known to undergo metabolic conversion into the corresponding hydroxy-compounds. Polycyclic nitrogen-containing carcinogens have not yet been studied in this respect, but their close structural analogy with isocyclic hydrocarbons suggests that their metabolism might follow a similar pattern. To obtain some experience with compounds similar to the expected metabolites, and in view of the increased interest attached to hydroxy-acridines, a series of hydroxy-derivatives of 1 : 2- and 3 : 4-benzacridine has now been synthesised.

Many such compounds, mostly in the 3 : 4-benzacridine series, have already been reported; some in very scanty detail. Baezner (*Ber.*, 1904, **37**, 3080) prepared 3′-hydroxy-3 : 4-benzacridine by reduction of a mixture of *o*-nitrobenzyl chloride and 2 : 7-dihydroxynaphthalene, and by condensing *N*-*o*-aminobenzylaniline with the latter. Similar reduction of 2-nitrobenzyl chloride and 2 : 6-dihydroxynaphthalene yielded the isomeric 2′-hydroxy-3 : 4-benzacridine (Baezner and Gueorguieff, *Ber.*, 1906, **39**, 2445) and the same authors (*ibid.*, p. 2439) prepared 8-hydroxy-3 : 4-benzacridine by acid hydrolysis of the corresponding 8-amino-compound. More recently, the preparation of the 2-hydroxy-compound from 3-amino-1-naphthol was briefly mentioned in a patent, without any description of the procedure or the product (D.R.P. 384,790/1922). Saftien (*Ber.*, 1925, **58**, 1958) obtained 7-methoxy-3 : 4-benzacridine by decarboxylation of the 5-carboxylic acid from the Fries condensation of 4 : 5-benzcoumaran-2 : 3-dione with *p*-anisidine, no demethylation however being attempted.

We found that 7-methoxy-3 : 4-benzacridine was very easily prepared by the Ullmann–Fettvadjian reaction (*Ber.*, 1903, **36**, 1029) from 2-naphthol, *p*-anisidine, and paraformaldehyde; subsequent demethylation to 7-hydroxy-3 : 4-benzacridine was conveniently achieved by means

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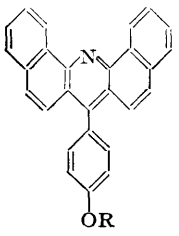
of pyridine hydrochloride; 7-hydroxy-2′-*tert.*-butyl- and -2′-*tert.*-amyl-3 : 4-benzacridine were similarly obtained from 6-*tert.*-butyl- and 6-*tert.*-amyl-2-naphthol. Homologues of 7-hydroxy-3 : 4-benzacridine having substituents in the *meso*-position were prepared from *N*-*p*-methoxyphenyl-2-naphthylamine by a modified Bernthsen reaction (Buu-Hoï, *J.*, 1946, 792; 1949, 670), and demethylation of the intermediary methyl ethers: 7-hydroxy-5-methyl-, -5-ethyl-, and -5-*iso*propyl-3 : 4-benzacridine were thus obtained.

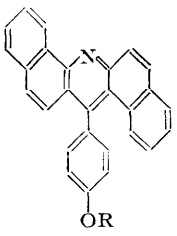
In the 1 : 2-benzacridine series, the Ullmann–Fettvadjian reaction with 1-naphthol was much less satisfactory than with 2-naphthol, but the 7-hydroxy-compound was nevertheless obtained *via* 7-methoxy-1 : 2-benzacridine.

The allyl ether of 7-hydroxy-3 : 4-benzacridine readily underwent the Claisen rearrangement, 7-hydroxy-6-allyl-3 : 4-benzacridine being formed quantitatively after some minutes in boiling dimethylaniline. This high reactivity of the 6-position makes it analogous to the α-position in 2-naphthol and 2-anthrol.

It was found, as previously reported by others, that benzacridines obtained from 2-naphthol by means of the Ullmann (*Ber.*, 1900, **33**, 907) and similar reactions (Senier and Austin, *J.*, 1907, **91**, 1237) have the 3 : 4-benzacridine structure and not the alternative 2 : 3-benzacridine, as derivatives of the latter nucleus give a violet colour with sulphuric acid and deep-red to violet salts (Schöpff, *Ber.*, 1894, **27**, 2843) instead of the corresponding yellow-orange colour observed with 3 : 4-benzacridines.

Senier and Austin (*loc. cit.*) prepared 5-*p*-methoxyphenyl-1 : 2-8 : 9-dibenzacridine (I; R = Me) by adding anisaldehyde to a boiling mixture of 1-naphthylamine and 1-naphthol. Contrary to Senier and Austin's claims, an extension of this reaction to mixtures of 2-naphthol with 1- and 2-naphthylamine was possible, and allowed of the preparation of 5-*p*-methoxyphenyl-1 : 2-6 : 7- (II; R = Me) and -3 : 4-6 : 7-dibenzacridine (III; R = Me). Pyridine hydrochloride demethylation of Senier and Austin's compound and its two isomers gave the


(I.)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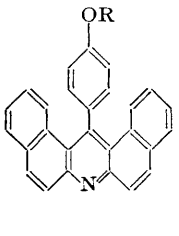
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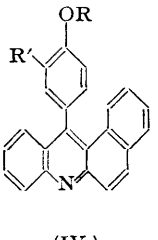
(IV.)

corresponding phenols, high-melting substances similar to 5-*p*-hydroxyphenylacridine prepared by Landauer (*Bull. Soc. chim.*, 1904, **31**, 1091) from *p*-hydroxybenzoic acid by the Bernthsen reaction. Furthermore, we have found that anisaldehyde reacted with mixtures of 2-naphthol and aniline or its homologues, the intermediary 5 : 10-dihydroacridines being oxidised by prolonged heating in air. 5-*p*-Methoxyphenyl-3 : 4-benzacridine (IV; R = Me, R′ = H) and its 7-methyl, 7 : 9-dimethyl, 8 : 9-dimethyl, and 7-phenyl homologues were thus prepared; demethylation gave 5-*p*-hydroxyphenyl-3 : 4-benzacridine (IV; R = R′ = H) and homologues. The allyl ethers of these phenols readily underwent the Claisen rearrangement, although much less rapidly than in the case of 7-hydroxy-3 : 4-benzacridine. 5-(4-Hydroxy-3-allylphenyl)-3 : 4-benzacridine (IV; R = H, R′ = CH_2·CH:CH_2) and its 7-methyl and 8 : 9-dimethyl homologues were thus obtained.

Experimental.

7-Methoxy-3 : 4-benzacridine.—Paraformaldehyde (1·5 g.) was added in small portions to a boiling mixture of *p*-anisidine (15 g.) and 2-naphthol (15 g.). After the violent reaction had subsided, the product obtained was boiled in the air for some minutes, and then vacuum-distilled. The fraction, b. p. 290—300°/18 mm. (16 g.), solidified on being left in ethanol. After two recrystallisations from this solvent, long silky, pale-yellow needles, m. p. 158°, were obtained (Saftien, *loc. cit.*, gave m. p. 157°). The corresponding picrate formed, from nitrobenzene, shiny, silky, orange-yellow prisms, m. p. 295—296° (decomp.).

7-Hydroxy-3 : 4-benzacridine.—A mixture of the methoxy-compound (10 g.) and pyridine hydrochloride (50 g.) was refluxed for 10 minutes, the supernatant layer completely disappearing. After cooling, hot water (100 c.c.) was added, and the orange precipitate of 7-hydroxy-3 : 4-benzacridine hydrochloride collected and washed with water. Basification with dilute aqueous ammonia gave the base, which was dried and recrystallised from nitrobenzene. *7-Hydroxy-3 : 4-benzacridine* (8 g.) formed shiny, greenish-yellow needles, m. p. 310°, which gave a deep-yellow solution in aqueous sodium hydroxide (Found: C, 82·9; H, 4·4. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%).

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7-*Hydroxy*-6-*allyl*-3 : 4-*benzacridine*.—The 7-hydroxy-benzacridine (2·5 g.) was treated with potassium hydroxide (1 g.) in ethanol, and the resulting solution refluxed for five minutes with allyl bromide (1·5 g.). The solvent was removed in vacuum, water added to the residue, and the cloudy suspension left overnight. 7-*Allyloxy*-3 : 4-*benzacridine* thus obtained (2·5 g.) crystallised from light petroleum in long silky, pale-yellow needles, m. p. 92°, extremely soluble in ethanol (Found: N, 4·6. $C_{20}H_{15}ON$ requires N, 4·9%). The corresponding *picrate* formed, from xylene, orange-yellow needles, m. p. 260—262° (decomp. >240°) (Found: N, 10·6. $C_{26}H_{18}O_8N_4$ requires N, 10·9%). A solution of this allyl ether (2 g.) in anhydrous dimethylaniline (10 c.c.) was refluxed for one hour, and the solvent removed in vacuum; the solid obtained was washed with methanol, and recrystallised from pyridine, giving readily sublimable, silky yellowish needles (1·6 g.), m. p. 288—289° (decomp.), of 7-*hydroxy*-6-*allyl*-3 : 4-*benzacridine* which gave an orange solution in ethanolic potassium hydroxide (Found: C, 84·2; H, 5·8. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·2%).

7-*Hydroxy*-2′-tert.-*butyl*-3 : 4-*benzacridine*.—This was obtained by demethylation of the crude orange-red viscous distillate (b. p. >300°/18 mm.) from the Ullmann–Fettvadjian reaction of 6-*tert*.-butyl-2-naphthol (2 g.), *p*-anisidine (2 g.), and paraformaldehyde (0·5 g.). The hydrochloride was orange-yellow, and the *base* (0·6 g.) formed, from xylene, pale-yellow needles, m. p. 288° (Found: C, 83·6; H, 6·5. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·3%).

7-*Hydroxy*-2′-tert.-*amyl*-3 : 4-*benzacridine*.—This, prepared in the same way as the *tert*.-butyl compound, formed, from xylene, shiny yellowish needles, m. p. 280—281° (Found: C, 83·5; H, 6·8. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·6%). These two hydroxy-benzacridines with a free 6-position, shared with 7-hydroxy-3 : 4-benzacridine the property of reacting with 2 : 3-dichloro-1 : 4-naphthaquinone in pyridine solution to give high-melting, sublimable, orange-red products (cf. Eistert, *Ber.*, 1947, **80**, 52).

7-*Methoxy*-1 : 2-*benzacridine*.—A boiling mixture of 1-naphthol (15 g.) and *p*-anisidine (15 g.) was treated with paraformaldehyde (1·5 g.). Vacuum-distillation of the product gave a resinous portion (3 g.), b. p. 280—310°/16 mm., which solidified when left with ethanol; it gave after recrystallisation from this solvent, fluffy, shiny, pale-yellow needles, m. p. 155° (Found: C, 83·3; H, 5·2. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). Its *picrate* formed, from nitrobenzene, silky orange-yellow, sublimable prisms, m. p. 246—248° (decomp.) (Found: N, 11·2. $C_{18}H_{13}ON,C_6H_3O_7N_3$ requires N, 11·5%).

7-*Hydroxy*-1 : 2-*benzacridine*.—This *acridine* was obtained in almost quantitative yield from the demethylation of the 7-methoxy-base, and formed, from nitrobenzene, fine pale-yellow needles, m. p. 217—218° (Found: C, 83·1; H, 4·4. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%), giving yellow alkaline solutions and an orange hydrochloride.

7-*Methoxy*-5-*methyl*-3 : 4-*benzacridine*.—*N*-*p*-Methoxyphenyl-2-naphthylamine used in this work was best prepared in the following way: a mixture of 2-naphthol (45 g.), *p*-anisidine (40 g.), and iodine (0·2 g.) was gently refluxed for 20 hours; the product was taken up in benzene, washed with dilute aqueous sodium hydroxide, dried (Na_2SO_4) and vacuum-distilled after removal of the solvent, giving the amine (60 g.), b. p. 263—265°/16 mm. This (10 g.) was heated under reflux for 18 hours with acetic anhydride (7 g.) and fused zinc chloride (10 g.); and the hot product was treated with toluene and concentrated aqueous sodium hydroxide (Buu-Hoï, *loc. cit.*), leaving a large residue of insoluble charred material. The toluene solution was dried (Na_2SO_4), the solvent removed, and the residue vacuum-distilled (b. p. *ca.* 285—300°/16 mm.). After repeated recrystallisations from methanol, 7-*methoxy*-5-*methyl*-3 : 4-*benzacridine* (0·5 g.) formed silky, pale-yellow needles, m. p. 144° (Found: C, 83·3; H, 5·6. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5%), and gave a picrate crystallising from nitrobenzene in silky, orange-yellow prisms, m. p. 254—256° (decomp.).

7-*Hydroxy*-5-*methyl*-3 : 4-*benzacridine*.—Prepared by demethylation of the 7-methoxy-compound, this *acridine* formed, from nitrobenzene, readily sublimable, pale yellow needles, m. p. 290—291° (decomp.), which gave yellow solutions in alkali (Found: C, 83·5; H, 5·2. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). 7-*Hydroxy*-5-*ethyl*-3 : 4-*benzacridine*, similarly prepared by demethylation of the crude, distilled product from *N*-*p*-methoxyphenyl-2-naphthylamine (5 g.), propionic anhydride (5 g.), and zinc chloride (5 g.), formed yellow needles from xylene, sublimating above 275—280° and charring at 286—290° (Found: C, 83·2; H, 5·4. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5%). 7-*Hydroxy*-5-iso*propyl*-3 : 4-*benzacridine*, obtained by replacement of propionic anhydride in the previous synthesis by *iso*butyric acid, formed fine yellow needles, from nitrobenzene, which darkened and sublimed above 275°, and decomposed above 285—286° (Found: C, 83·5; H, 5·8. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9%).

5-p-*Methoxyphenyl*-1 : 2-6 : 7-*dibenzacridine*.—To a boiling mixture of 2-naphthol (5 g.) and 1-naphthylamine (5 g.), anisaldehyde (4 g.) was cautiously added, and the product boiled for a further five minutes and then vacuum-distilled; the portion, b. p. >350°/18 mm., solidified on trituration with ethanol, and formed fine, almost colourless needles (1·5 g.), m. p. 202°, of the *acridine* from benzene (Found: N, 3·4. $C_{28}H_{19}ON$ requires N, 3·6%). The corresponding picrate crystallised from xylene in orange-yellow needles, m. p. 272—273°. 5-p-*Hydroxyphenyl*-1 : 2-6 : 7-*dibenzacridine* formed readily sublimable, greenish-yellow needles, m. p. 301°, from nitrobenzene (Found: C, 87·1; H, 4·6. $C_{27}H_{17}ON$ requires C, 87·3; H, 4·5%); this compound gave a deep yellow colour in alcoholic sodium hydroxide solution; its orange-yellow hydrochloride was only sparingly soluble in molten pyridine hydrochloride.

5-p-*Methoxyphenyl*-3 : 4-6 : 7-*dibenzacridine*.—Obtained in similar yield from β-naphthol (5 g.), β-naphthylamine (5 g.), and anisaldehyde (4 g.), this *dibenzacridine* formed long silky, pale yellow, sublimable needles, m. p. 274—275°, from benzene (Found: N, 3·4. $C_{28}H_{19}ON$ requires N, 3·6%). 5-p-*Hydroxyphenyl*-3 : 4-6 : 7-*dibenzacridine* was sparingly soluble in nitrobenzene, and from this solvent formed fine deep-yellow, sublimable needles, m. p. 370—372° (Found: C, 87·0; H, 4·7. $C_{27}H_{17}ON$ requires C, 87·3; H, 4·5%).

5-p-*Hydroxyphenyl*-1 : 2-8 : 9-*dibenzacridine*.—This *acridine* formed large, transparent, yellowish crystals, m. p. 248°, from aqueous acetone (Found: C, 87·2; H, 4·8. $C_{27}H_{17}ON$ requires C, 87·3; H, 4·5%). Its methyl ether was prepared in 30% yield by Senier and Austin's method (*loc. cit.*).

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5-p-*Methoxyphenyl*-3 : 4-*benzacridine*.—Anisaldehyde (15 g.) was cautiously dropped into a boiling mixture of β-naphthol (20 g.) and aniline (15 g.); after a further 5 minutes' boiling in the air, the product was vacuum-fractionated. The fraction, b. p. *ca.* 300—320°/14 mm. (8 g.), gave, after two crystallisations from ethanol, pale-yellow, silky needles, m. p. 181° (Found : N, 4·0. $C_{24}H_{17}ON$ requires N, 4·1%). The corresponding *picrate* formed silky orange needles, m. p. 253—254°, from toluene (Found : N, 9·6. $C_{30}H_{20}O_8N_4$ requires N, 9·9%).

5-p-*Hydroxyphenyl*-3 : 4-*benzacridine*.—This *compound* formed readily sublimable, shiny, pale yellow leaflets, m. p. 306°, from nitrobenzene (Found : C, 85·7; H, 4·8. $C_{23}H_{15}ON$ requires C, 85·9; H, 4·7%).

5-p-*Allyloxyphenyl*-3 : 4-*benzacridine*.—The 5-p-*allyloxyphenyl* derivative, prepared from the potassium salt of the hydroxyphenyl compound and allyl bromide in alcoholic solution, crystallised from acetone in large pale-yellow tablets, m. p. 176—177° (Found : N, 3·8. $C_{26}H_{19}ON$ requires N, 3·9%); its picrate formed silky orange-yellow needles, m. p. 223—224°, from toluene.

5-(4-*Hydroxy*-3-*allylphenyl*)-3 : 4-*benzacridine*.—This was obtained by refluxing a dimethylaniline solution of the foregoing allyl ether for 12 hours; it formed fine pale-yellow prisms, m. p. 255°, from acetone, and gave yellow solutions in alcoholic sodium hydroxide (Found : C, 86·2; H, 5·3. $C_{26}H_{19}ON$ requires C, 86·4; H, 5·2%).

5-p-*Methoxyphenyl*-7-*methyl*-3 : 4-*benzacridine*.—This compound (10 g.), obtained as above from 2-naphthol (20 g.), *p*-toluidine (18 g.), and anisaldehyde (15 g.), had b. p. 325—330°/14 mm., and formed pale yellow, silky, sublimable needles, m. p. 231—232°, from much ethanol (Found : N, 4·0. $C_{25}H_{19}ON$ requires N, 4·0%); its *picrate* formed orange prisms, m. p. 249—250°, from toluene (Found : N, 9·6. $C_{31}H_{22}O_8N_4$ requires N, 9·5%).

5-p-*Hydroxyphenyl*-7-*methyl*-3 : 4-*benzacridine*.—The p-*hydroxyphenyl* compound, obtained in theoretical yield, crystallised from nitrobenzene in long silky, pale-yellow, readily sublimable needles, m. p. 326—327°, which gave greenish-yellow solutions with alcoholic sodium hydroxide (Found : C, 86·0; H, 5·2. $C_{24}H_{17}ON$ requires C, 85·9; H, 5·0%).

5-p-*Allyloxyphenyl*-7-*methyl*-3 : 4-*benzacridine*.—The *allyloxy*-compound formed long, silky, pale-yellow needles, m. p. 171°, from ethanol (Found : N, 3·5. $C_{27}H_{21}ON$ requires N, 3·7%); its rearrangement product, 5-(4-*hydroxy*-3-*allylphenyl*)-7-*methyl*-3 : 4-*benzacridine*, crystallised from nitrobenzene in shiny yellowish needles, m. p. 243—244° (Found : C, 86·2; H, 5·7. $C_{27}H_{21}ON$ requires C, 86·4; H, 5·6%); the 4-*allyloxyphenyl*-3-*allyl* compound formed fine colourless needles, m. p. 131—132°, from methanol (Found : N, 3·2. $C_{30}H_{25}ON$ requires N, 3·3%), the picrate of which separated from ethanol in deep-orange needles, m. p. 209°.

5-*p*-*Methoxyphenyl*-7 : 9-*dimethyl*-3 : 4-*benzacridine*.—This could not be obtained in a pure state directly by the condensation of anisaldehyde with 2-naphthol and 2 : 4-dimethylaniline, which yielded at the same time a great quantity of a high-melting impurity believed to be the corresponding 5 : 10-dihydroacridine. It was therefore prepared by methylation of the hydroxy-compound described below, and formed pale-yellow needles, m. p. 177—178°, from ethanol (Found : C, 85·6; H, 5·9. $C_{26}H_{21}ON$ requires C, 85·9; H, 5·7%).

5-p-*Hydroxyphenyl*-7 : 9-*dimethyl*-3 : 4-*benzacridine*.—The 5-p-*hydroxyphenylbenzacridine* was prepared by heating with pyridine hydrochloride the crude acridine–dihydroacridine mixture described above; it formed sublimable, glinting, pale-yellow needles, m. p. 313—315°, from nitrobenzene (Found : C, 85·8; H, 5·6. $C_{25}H_{19}ON$ requires C, 85·9; H, 5·4%).

5-p-*Methoxyphenyl*-8 : 9-*dimethyl*-3 : 4-*benzacridine*.—This *compound* (8 g.), readily obtained from 2-naphthol (20 g.), 3 : 4-dimethylaniline (15 g.), and anisaldehyde (15 g.), formed long silky, pale-yellow needles, m. p. 208°, from benzene–ethanol (Found : C, 85·6; H, 5·7. $C_{26}H_{21}ON$ requires C, 85·9; H, 5·7%), and gave a picrate which crystallised from benzene in long silky orange needles, m. p. 250°; no higher-melting impurity was obtained in this experiment.

5-p-*Hydroxyphenyl*-8 : 9-*dimethyl*-3 : 4-*benzacridine*.—This *compound* crystallised from nitrobenzene in sublimable, short, yellow prisms, m. p. 306—307° (Found : C, 85·8; H, 5·6. $C_{25}H_{19}ON$ requires C, 85·9; H, 5·4%); its *allyl ether* formed almost colourless needles, m. p. 215°, from ethanol (Found : N, 3·5. $C_{28}H_{23}ON$ requires N, 3·6%), which gave a picrate as silky orange needles, m. p. 238—240° (decomp. above 205°), from ethanol. 5-(4-*Hydroxy*-3-*allylphenyl*)-8 : 9-*dimethyl*-3 : 4-*benzacridine* crystallised from xylene in shiny, fine, yellowish prisms, m. p. 216°, giving a yellow solution with aqueous-alcoholic alkalis (Found : C, 86·1; H, 6·2. $C_{28}H_{23}ON$ requires C, 86·3; H, 5·9%).

7-*Phenyl*-5-p-*methoxyphenyl*-3 : 4-*benzacridine*.—Obtained from 2-naphthol (15 g.), 4-aminodiphenyl (19 g.), and anisaldehyde (10 g.), this *acridine* had b. p. >330°/15 mm. and formed iridescent, bright-yellow leaflets, m. p. 164—165°, from ethanol–benzene (Found : C, 87·2; H, 5·0. $C_{30}H_{21}ON$ requires C, 87·5; H, 5·1%); it gave with picric acid an addition compound crystallising from ethanol in orange needles, m. p. 203—204°.

This work is part of a cancer research scheme, carried out under Professor A. Lacassagne, with the financial support of the United States Public Health Service (Federal Security Agency). The author expresses his thanks to the authorities concerned. The phenolic acridines described above are under investigation for possible fungicidal and virucidal activities (especially against hereditary mammary adenocarcinoma in mice).

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