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A SYNTHESIS OF EVOXANTHINE

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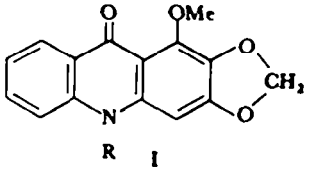
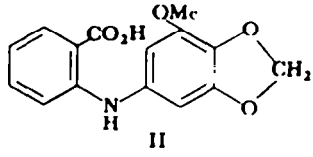
Abstract—A synthesis of the acridone alkaloid evoxanthine is reported.

THE alkaloid evoxanthine first isolated[1] from the bark of *Evodia xanthoxyloides* F. Muell was later reported[2,3] in several other species of Rutacea. It was assigned structure I (R = CH_3) on the basis of degradative evidence. Evoxanthidine,[4] isolated from the leaves of *E. xanthoxyloides*, was shown to be I[5] (R = H) since it lacked a methylimino group and was converted to evoxanthine by boiling with potassium carbonate and methyl iodide in acetone. A synthesis of these two alkaloids is now reported.



I



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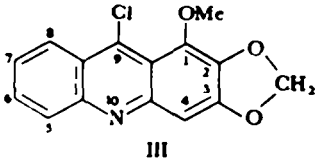

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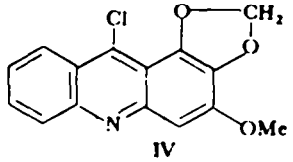

IV

The diphenylamine-2-carboxylic acid II was prepared in moderate yield by Ullmann condensation of 3-methoxy-4,5-methylenedioxyaniline[6] with 2-bromobenzoic acid. Ring closure of II with phosphorus oxychloride can take place in two ways giving the 1-methoxy III and/or the 3-methoxy-9-chloroacridine (IV). As was revealed by TLC, a mixture of these 9-chloroacridines was obtained and chromatography over alumina afforded A (m.p. 172–174°) and B (m.p. 218–220°) in the proportion 4:1. The orientation of these two isomers was in agreement with the previous findings[7–9]

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[2] H. G. Boit, *Ergebnisse der Alkaloid-Chemie bis* 1960. Akademi-Verlag, Berlin (1961).
[3] F. D. Popp and D. P. Chakraborty, *J. Pharm. Sci.* **53**, 968 (1964).
[4] G. K. Hughes, K. G. Neill and E. Ritchie, *Austral. J. Sci. Res.* **A5**, 401 (1952).
[5] J. R. Cannon, G. K. Hughes, K. G. Neill and E. Ritchie, *Austral. J. Sci. Res.* **A5**, 406 (1952).
[6] A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin, F. W. Holly, N. G. Brink and K. Folkers, *J. Am. Chem. Soc.* **81**, 4983 (1959).
[7] A. Albert and W. H. Linnell, *J. Chem. Soc.* **88**, (1936).
[8] K. Lehmstedt and K. Schrader, *Ber. Dtsch. Chim. ges.* **70**, 838 (1937).
[9] F. R. Bradbury and W. H. Linnell, *J. Chem. Soc.* 377 (1942).

that in such cyclizations, the 1-isomer has the lower m.p. and is formed in greater amount than the 3-isomer. By analogy,[10] compound A with the lower m.p. was proved to be 1-methoxy-9-chloroacridine (III) since on hydrolysis the corresponding acridone had properties typical of a 1-methoxyacridone[11] and its physical constants were in agreement with those reported for evoxanthidine[5] and further the N-methyl derivative proved to be identical with natural evoxanthine.

EXPERIMENTAL[12]

3'-Methoxy-4',5'-methylenedioxydiphenylamine-2-carboxylic acid. A mixture of 3-methoxy-4,5-methylenedioxyaniline[6] (1 g), 2-bromobenzoic acid (0·8 g), anhyd K_2CO_3 (1·2 g), freshly pptd Cu powder (30 mg) and amyl alcohol (12 ml) was heated under gentle reflux for 1 hr in an oil bath at 150°. After being steam distilled to remove amyl alcohol, the reaction mixture was clarified with charcoal, filtered hot and acidified with dil HCl under strong cooling. The resulting ppt was filtered, dried (1 g) and recrystallized from benzene–pet. ether (b.p. 40–60°) giving pale yellow stout needles (0·8 g), m.p. 179–181°. (Found: C, 62·92; H, 4·61. $C_{15}H_{13}O_5N$ requires: C, 62·72; H, 4·53%.)

1-Methoxy-2,3-methylenedioxy and *3-methoxy-1,2-methylenedioxy-9-chloroacridine.* The foregoing diphenylamine-2-carboxylic acid (0·4 g) and $POCl_3$ (6 ml) were heated under gentle reflux in an oil bath (130–135°) for 2 hr. After removal of the excess of $POCl_3$ *in vacuo*, crushed ice and conc NH_4OH were added, the resulting yellow ppt was collected, washed thoroughly with ice-water and dried (0·4 g). This crude material (m.p. 146–152°, TLC two spots) was dissolved in the minimum amount of chf (intense green fluorescence), adsorbed over a column of alumina (May & Baker) and eluted with chf–ligroin (b.p. 60–80°) (1:2). Fractions were collected and analysed by TLC. The initial fractions which consisted of 3-methoxy-1,2-methylenedioxy-9-chloroacridine were combined and recrystallized from MeOH giving deep yellow short needles (68 mg), exhibiting an intense green fluorescence in chf, m.p. 218–220°, λ_{max} 240, 280, 365–370 (sh), 380, 420 mμ (log ε, 4·43, 4·82, 3·60, 3·88, 3·52). (Found: C, 62·76; H, 3·74. $C_{15}H_{10}O_3NCl$ requires: C, 62·61; H, 3·48%.) The intermediate fractions were mixtures and submitted for rechromatography. The later fractions were combined and crystallized from EtOH to give 1-methoxy-2,3-methylenedioxy-9-chloroacridine as yellow fibrous needles (0·26 g), m.p. 172–174°, λ_{max} 240, 265, 375 mμ (log ε 4·41, 4·78, 4·05). It showed a bluish-violet fluorescence in chf. (Found: C, 59·17; H, 4·08. $C_{15}H_{10}O_3NCl·H_2O$ requires: C, 58·92; H, 3·93%.)

1-Methoxy-2,3-methylenedioxyacridone (Evoxanthidine). A soln of 1-methoxy-2,3-methylenedioxy-9-chloroacridine (0·2 g) in HClaq (1%; 15 ml) was refluxed gently (oil bath, 150–155°) for 1 hr. The reaction mixture was cooled and basified with dil NH_4OH. The resulting yellow ppt was collected, washed thoroughly with water and dried. Recrystallization from alcohol afforded yellow needles (146 mg), m.p. 310–312° (dec). Hughes *et al.*[4] have reported m.p. 312–313° for evoxanthidine. It showed a blue fluorescence in alcohol. λ_{max} 275, 305 (sh), 320 (sh), 385, 395 mμ (log ε 4·68, 3·36, 3·11, 3·80, 3·80). (Found: C, 66·81; H, 4·04. $C_{14}H_{11}O_4N$ requires: C, 66·91; H, 4·09%.)

1-Hydroxy-2,3-methylenedioxyacridone (Norevoxanthidine). The dry hydrochloride of 1-methoxy-2,3-methylenedioxyacridone, prepared by warming it with con. HClaq was held at 170–180° (oil bath) for ½ hr and the product crystallized from alcohol giving deep yellow needles, m.p. 325–327° (dec). Cannon *et al.*[5] have reported m.p. 327° for norevoxanthidine. It gave an intense green colour with alcoholic $FeCl_3$ and showed no fluorescence. λ_{max} 240, 275, 315, 330 (sh), 405 mμ (log ε 4·36, 4·65, 3·59, 3·46, 3·74). (Found: C, 65·62; H, 3·91. $C_{14}H_9O_4N$ requires: C, 65·89; H, 3·5%.)

1-Methoxy-2,3-methylenedioxy-10-methylacridone (Evoxanthine). A mixture of 1-methoxy-2,3-methylenedioxyacridone (0·1 g), ignited K_2CO_3 (4 g), MeI (6 ml) and acetone (40 ml) was refluxed

[10] Cairns and Kermack, *J. Chem. Soc.* 1322 (1950), have reported instances where this generalization does not hold. However, in the present case the orientation of the isomers can be further verified by conversion to the respective acridones since a 1-methoxyl group in an acridone has unique properties (Ref. 11).

[11] R. M. Acheson, *Acridines* p. 188. Interscience, New York (1956).

[12] M.ps are uncorrected and the UV spectra were measured in 95% EtOH using a Beckman model DU spectrophotometer.

for 32 hr. After work up, the product was crystallized from alcohol giving 1-methoxy-2,3-methylenedioxy-10-methylacridone as yellow needles, m.p. 217–218°, λ_{max} 240 (sh), 275, 320 (sh), 400 mμ (log ε 4·26, 4·70, 3·54, 3·96). It was identical in all respects (m.m.p., IR, TLC) with a natural sample of evoxanthine. (Found: C, 67·54; H, 4·56. $C_{15}H_{13}O_4N$ requires: C, 67·84; H, 4·59%.)

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