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A QUEBRACHAMINE MODEL

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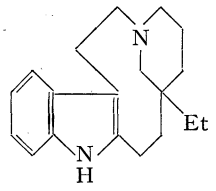
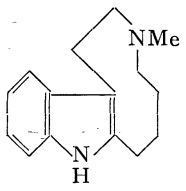
Chemical studies, biogenetic considerations (1) and mass-spectrometric analysis (2) have led to the proposal of I as the structure of quebrachamine. While probably biogenetically related to the natural pentacyclic *Aspidosperma* bases (3), tetracyclic quebrachamine possesses an unusual nine-membered ring. This rare structural feature has now been incorporated in a synthetic model (II) by a method which, in principle, is applicable to the total synthesis of the indole alkaloid itself.

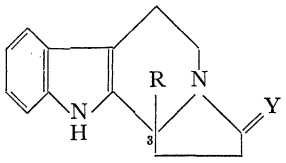


I

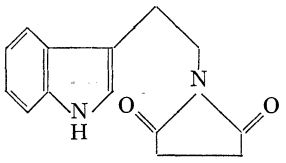


II

The first synthetic goal was the indolopyrrocoline system III. It was obtained in form of the lactam ester III*a* by the condensation of ethyl α-ketoglutarate with tryptamine. Alternatively, it was produced as the amine III*c* by the acid-catalyzed condensation of tryptamine and α-ketoglutaric acid, pyrolytic decarboxylation–dehydration, and lithium aluminum hydride reduction of the resultant lactam III*b*—a procedure published by Corsano and Algieri (4). The proton magnetic resonance spectrum of the base III*c* [a one-proton multiplet at 4.0–4.2 p.p.m. characteristic of C(3)—H] showed it to possess a cis-pyrrocoline configuration (5). An alternative synthesis of III*c*, via the intermediacy of IV and modelled after recorded reactions with tryptimides (6), failed in the crucial cyclization step.



III*a*, R = CO_2Et, Y = O
b, R = H, Y = O
c, R = H, Y = H_2



IV

Conversion of III*c* to its methiodide and treatment of the latter with lithium in liquid ammonia yielded the medium-sized ring, compound II (cf. 7).

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EXPERIMENTAL

All melting points were observed on a Kofler microscope hot stage. Ultraviolet spectra were run on 95% ethanol solutions on a Cary model 12 spectrophotometer, while infrared spectra were obtained on a Perkin–Elmer infrared spectrophotometer. Proton magnetic resonance spectra were measured on deuterochloroform solutions with tetramethylsilane as internal standard on a Varian A-60 spectrometer (courtesy of the Department of Chemistry, Indiana University, Bloomington, Indiana, U.S.A.).

Lactam IIIa

A solution of 1.20 g of tryptamine hydrochloride and 1.00 g of ethyl α-ketoglutarate in 10 ml of ethanol was refluxed for 60 hours under nitrogen. Evaporation of the solvent left 0.88 g of crystalline residue whose recrystallization from methanol yielded colorless prisms of lactam ester III*a*, m.p. 225–226°; μ (Nujol) NH 3.00 (s), C=O 5.75 (s), 5.92 (s), C=C 6.30 (w); λ_{max} 223 mμ (log ϵ 4.60), 282 mμ (log ϵ 3.95), and 292 mμ (log ϵ 3.85); δ broad NH singlet 8.58 p.p.m., ester CH_2 quartet 4.25 p.p.m. (J = 7 c.p.s.), ester CH_3 triplet 1.29 p.p.m. (J = 7 c.p.s.). Anal. Calc. for $C_{17}H_{18}O_3N_2$: C, 68.45; H, 6.08. Found: C, 68.15; H, 6.02.

N-[β-(3-Indolyl)ethyl]succinimide (IV)

A suspension of an intimate mixture of 1.14 g of tryptamine and 0.70 g of succinic anhydride in 120 ml of benzene was refluxed for 5 hours. The cooled suspension was decanted and the solution extracted with 5% sodium hydroxide solution and with water. The solid residue from the decantation was dissolved in 5% sodium hydroxide solution and thereafter combined with the previous basic extract. The joint alkaline extracts were acidified with 5% hydrochloric acid and the resultant solid taken up in ethyl acetate. The organic solution was dried over anhydrous magnesium sulphate and evaporated under reduced pressure. Crystallization of the solid residue, 1.36 g, from ethyl acetate yielded N_b-succinoyl tryptamine, m.p. 138–139°. Anal. Calc. for $C_{14}H_{16}O_3N_2$: C, 64.58; H, 6.20; N, 10.77. Found: C, 64.77; H, 6.27; N, 10.62. An ether solution of an excess diazomethane was added to a solution of 82 mg of the amide acid in 10 ml of methanol and the mixture left standing for 30 minutes. Evaporation of the solvent and crystallization of the resultant solid, 85 mg, from methanol yielded colorless plates of the amide ester, m.p. 110–111°; μ (Nujol) NH 2.95 (s), 3.0–3.1 (m), C=O 5.80 (s), 6.03 (s); δ ester CH_3 singlet 3.62 p.p.m.

N_b-Succinoyl tryptamine, 1.44 g, was heated for 10 minutes at 200° under slightly reduced pressure. Crystallization of the dark brown reaction residue from methanol yielded the imide IV, m.p. 166–167°; μ (Nujol) NH 2.95 (s), C=O 5.60 (w), 5.85 (s); δ two succinoyl CH_2 singlet 2.58 p.p.m. Anal. Calc. for $C_{14}H_{14}O_2N_2$: C, 69.37; H, 5.82; N, 11.56. Found: C, 69.34; H, 5.92; N, 11.47.

Amine II

A solution of 188 mg of the amine III*c* and an excess of methyl iodide in 10 ml of ether was left standing for 8 hours. The resultant precipitate was filtered and dried. (Since this methiodide was exceedingly hygroscopic, its isolation had to be carried out rapidly.) The dried salt, 275 mg, was dissolved in 5 ml of absolute ethanol and 75 ml of liquid ammonia and enough lithium added to the stirring solution until the resultant blue color persisted for 1 hour. Then solid ammonium chloride was added, the ammonia allowed to evaporate, and the residue dissolved in water. Sodium hydroxide, 5%, was added and the aqueous solution extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulphate, and evaporated under reduced pressure. Chromatography of the residue, 136 mg, on alumina and elution with 1:1 chloroform–benzene yielded 44 mg of crystals whose crystallizations from aqueous ethanol led to amine II, m.p. 128–130°; δ N—CH_3 singlet 2.38 p.p.m., no C—CH_3 present. Anal. Calc. for $C_{15}H_{20}N_2$: C, 78.89; H, 8.83; N, 12.27; C-alkyl, 0.00. Found: C, 78.70; H, 8.89; N, 12.28; C-alkyl, negative.

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