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TOTAL SYNTHESIS OF *dl*-ELAEOCARPINE AND *dl*-ISOELAEOCARPINE

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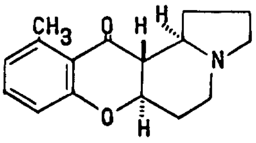
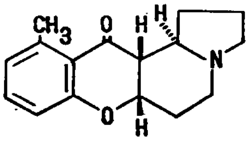
(±)-Elaeocarpine and (±)-isoelaeocarpine, major alkaloids isolated from *Elaeocarpus polydactylus*, Schl., and related species growing in New Guinea were reported recently by Johns et al. to have the structures Ia and Ib respectively (1). We now wish to report the total synthesis of the alkaloids having the novel indolizidine skeleton.

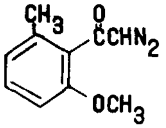


Ia

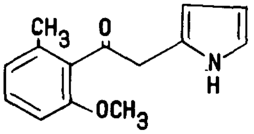


Ib

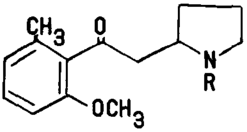
The aromatic component (II) was synthesized by reaction of diazomethane with the acid chloride of 6-methoxy-2-methyl benzoic acid (2) which was derived from ethyl 6-methyl-2-oxocyclohex-3-ene carboxylate (3) by dehydrogenation according to the Bohlmann's procedure (4), followed by hydrolysis and methylation. The diazoketone (II) was condensed with excess pyrrole in the presence of copper powder at 50-60° (5) to give, after chromatographic purification on silica gel using *n*-hexane-diethyl ether, the 2-pyrrolylmethyl ketone (III), m.p. 92-93°, IR ν ($CHCl_3$): 3420, 1685cm^{-1}; NMR ($CDCl_3$) τ: 7.91 (3H, s., $-CH_3$), 6.15 (3H, s., $-OCH_3$), 5.88 (2H, s., $-CH_2\overset{|}{C}=O$), in 33% yield. Catalytic hydrogenation of III over platinum oxide in acetic acid at room temperature gave the 2-pyrrolidylmethyl ketone (IV) as an unstable oil, IR ν(liquid): 3280, 1680cm^{-1}; MS m/e: 233 (M^+); the hydrochloride m.p. 172-174°, in 78% yield. The carbonyl function of III was not reduced under these conditions because of steric hindrance by the bulky *ortho* substituents. Addition of ethyl acrylate to IV in refluxing acetonitrile gave the aminoester (V) as a colorless oil, IR ν(liquid): 1720, 1680cm^{-1}; NMR (CDCl$_3$) τ: 7.77 (3H, s., $-CH_3$), 6.18 (3H, s., $-OCH_3$), 8.75 (3H, t., J=7cps, $-CH_2\underset{\sim\sim}{CH_3}$), 5.86 (2H, q., J=7cps, $-\underset{\sim\sim}{CH_2}CH_3$); MS m/e: 333 (M$^+$), in 81% yield. The Dieckmann condensation of V using sodium hydride in refluxing toluene (6) followed by chromatographic separation on silica gel using chloroform-methanol afforded the diketoindolizidine (VI) as an yellow oil, IR ν(liquid): 2780 (Bohlmann's bands), 1700-1600cm^{-1} (conjugatedchelation of β-diketone); the picrate m.p. 181-182°, in 63% yield. In conformity with its structure, VI had an acidic character and gave a positive ferric reaction.



II

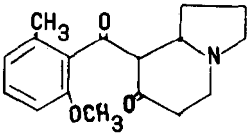


III

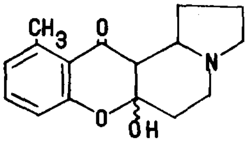


IV R= -H

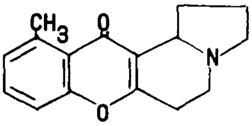
V R= $-CH_2CH_2COOC_2H_5$



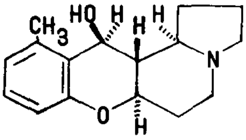
VI



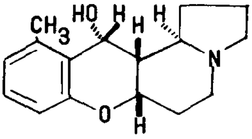
VII



VIII



IXa



IXb

Fission of the methyl ether function in VI took place by treatment with boron tribromide in dichloromethane at room temperature (7), accompanied with spontaneous cyclization to furnish the chromanone (VII) (8), as colorless needles, m.p. 139-140°, IR ν(nujol): 3410, 1660cm^{-1}; UV $\lambda_{max}^{ethanol}$mμ(ε): 256 (6600), 316 (2200); NMR ($CDCl_3$) τ: 7.38 (3H, s., $-CH_3$); MS m/e: 273 (M^+), in 52% yield. Configuration of the hydroxyl group in VII was not clarified. By refluxing VII with methanolic hydrogen chloride, the chromone (VIII) was obtained as colorless leaflets, m.p. 102-103°, IR ν(nujol): 1630cm^{-1}; UV $\lambda_{max}^{ethanol}$mμ(ε): 230 (49000), 308 (12000); NMR ($CDCl_3$) τ: 7.14 (3H, s., $-CH_3$), in 78% yield.

Since attempts to obtain Ia or Ib directly from VIII by catalytic hydrogenation were fruitless, efforts were now made to obtain the saturated alcohol (IX) as a prepiminary step. Sodium borohydride reductiin of VIII in refluxing ethanol gave, after chromatographic separation on alumina using n-hexane-diethyl ether, two isomeric alcohols in a ratio of about 7:1 (9). The structure of the former, m.p. 168-169°, IR ν(nujol): 3130, 2740cm^{-1} (Bohlmann's bands); NMR ($CDCl_3$) τ: 7.55 (3H, s., $-CH_3$), 4.78 (1H, d., J=6.4cps, $HO-\overset{|}{\underset{\sim}{CH}}-\overset{|}{CH}$), MS m/e: 259 ($M^+$), was attributable to one of the alcohols, (IXb) m.p. 202-202.5°[*1], derived by Johns et al. from (±)-isoelaeocarpine, by comparison of their NMR spectra. The latter, m.p. 192-193°, IR ν(nujol): 3130, 2740cm^{-1} (Bohlmann's bands); MS m/e: 259 (M^+), was also ascribable to the Johns' alcohol (IXa), m.p. 197-198°[*1].

Finally, the alcohol (IXb) was oxidized with chromium trioxide in acetic acid at room temperature to give Ib, m.p. 75-76°[*1], and oxidation of IXa by the same procedure afforded Ia, m.p. 81-82°[*1][*2]. The IR spectra (in chloroform) of the synthetic products were identical with those of the natural products as was

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[*1] The melting points for Ia and Ib reported by Johns et al. were 81-82° and 51-52° respectively. The discrepancy in the melting points of each pair between the products of synthetic and of natural origin, especially in isoelaeocarpine series, may be due to the facts that the natural products were not completely racemic since the same workers observed a slight remainders of optical activity in them.

[*2] All melting points are uncorrected.

also their behavior on thin layer silica chromato-plates in the system diethyl ether-methanol (9:1) using iodine vapor as the developing agent.

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