HODGKINSINE, THE ALKALOID OF *HODGKINSONIA FRUTESCENS* F. MUELL.*

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Following the observation by Webb (1949) that positive results were obtained in spot tests for alkaloids from the leaves of *Hodgkinsonia frutescens* F. Muell. (Order Rubiaceae), a shrub growing in the coastal and tableland regions of tropical Queensland, an extraction of the leaves has been undertaken. A crude amorphous alkaloid fraction was readily obtained but initially all attempts to isolate pure crystalline constituents were fruitless. However, subsequently, during one attempted purification by chromatography on alumina with benzene, an operation which had been performed many times previously, a few crystals were observed to form in the eluate. By using these as seeds, no difficulty was then experienced in crystallizing the major portion of the alkaloid fraction from benzene. The substance so obtained, after drying at room temperature and pressure, analysed for $C_{28}H_{32}N_4$. On drying at 80 °C/1 mm, it slowly lost benzene of crystallization, but the parent amorphous substance, hodgkinsine, $C_{22}H_{26}N_4$ (analyses and molecular weight), was more readily obtained by dissolving the crystals in dilute acid, shaking with ether, to remove the liberated benzene, and regenerating the base with alkali. All attempts to crystallize the alkaloid from any solvent other than benzene failed, but the crystalline benzene-solvated form was readily obtained.

Hodgkinsine, which was optically active and had pK_a values of 8·45 and 6·45 (in 50% ethanol), contained two *N*-methyl groups. At least one of the other two nitrogen atoms was present as an imino group since the i.r. spectrum had a band at 3320 cm^{-1} (Nujol). The spectrum also revealed the presence of an *o*-disubstituted benzene nucleus (bands at 740, 750 cm^{-1}).

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Experimentally, the alkaloid was a peculiarly unsatisfactory substance. Numerous attempts to prepare crystalline salts, or derivatives, or degradation products by oxidation, reduction, or Hofman degradation were unsuccessful. By heating the alkaloid with zinc dust, there was obtained a small amount of oil which was presumably a mixture of indole derivatives, since a positive test was obtained with Erlich's reagent in the cold.

Hodgkinsine is isomeric with calycanthine, the structure of which has recently been elucidated (Hamor *et al.* 1960; Woodward *et al.* 1960) and is probably closely related to it, at least biogenetically. They have similar u.v. spectra (hodgkinsine: $\lambda_{max.}$ 232, 252, 310, 326 mμ, log ε 4·59, 4·48, 4·02, 3·93, respectively, in ethanol, scarcely different in 4% ethanolic hydrochloric acid; calycanthine: $\lambda_{max.}$ 252, 310 mμ, log ε 4·26, 3·80, respectively, in acetonitrile, $\lambda_{max.}$ 252, 311 mμ, log ε 4·5, 3·8, respectively, in dioxan), but calycanine, the very characteristic degradation product of calycanthine, could not be obtained from hodgkinsine. However, it is suggested that the formation of hodgkinsine, like that of calycanthine, involves the ββ′-oxidative coupling of *N*-methyltryptamine.

Experimental

Melting points are uncorrected. Analyses were performed by Dr. J. E. Fildes of this Department.

(*a*) *Extraction of Hodgkinsine.*—A dried mixture of the milled leaves (10 kg) and lime was exhausted with ether at room temperature and the combined extracts evaporated to about 3000 ml. The concentrate was shaken with 2N HCl (200 ml portions) until alkaloid was no longer extracted. The acid-extract was filtered and basified with ammonia. The precipitated alkaloid was collected, washed thoroughly with water, and dried. The crude alkaloid (60 g) was finely powdered and shaken with ether. After filtering from a small amount of insoluble material, the ether was evaporated and the residue crystallized from benzene with the aid of seeds obtained as described above. After three recrystallizations, colourless needles, m.p. 128 °C, were obtained (Found: C, 79·0; H, 7·5; N, 13·1%. Calc. for $C_{28}H_{32}N_4$: C, 79·2; H, 7·6; N, 13·2%). Amorphous solvent-free hodgkinsine was obtained by drying at 80 °C/1 mm or by dissolving the crystalline material in dil. HCl, removing the liberated benzene with ether, basifying the aqueous solution, extracting the base with ether, and evaporating the ether, finally, at 1 mm. The substance had $[\alpha]_D^{23}$ +60° (c, 1·0 in 0·3N HCl) (Found: C, 75·9; H, 7·5; N, 16·0; (*N*)CH_3, 13·7%; mol. wt., 360 (ebullioscopic in ethanol). Calc. for $C_{22}H_{26}N_4$: C, 76·2; H, 7·6; N, 16·2; 2×(*N*)CH_3, 16·7%; mol. wt., 346).

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