New Imidazole Alkaloids from *Cypholophus friesianus*

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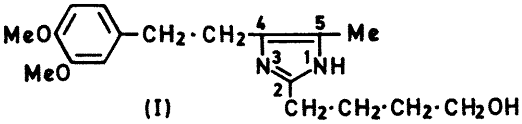
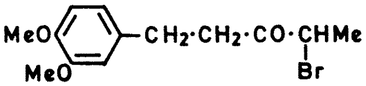
Summary The structures of the new imidazole alkaloids cypholophine (I) and *O*-acetylcypholophine have been established by synthesis.

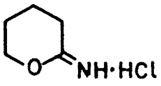
CYPHOLOPHINE, $C_{18}H_{26}N_2O_3$, m.p. 126—127°, $[\alpha]_D \pm 0°$ ($CHCl_3$), M^+ 318, the major alkaloid of the New Guinea species *Cypholophus friesianus* (K.Schum.)H.Winkl. (family Urticaceae), is shown to be (I). Cypholophine is oxidized by aqueous $KMnO_4$ to give 3,4-dimethoxybenzoic acid in high yield, and acetylation of (I) with acetic anhydride–pyridine at room temperature affords *O*-acetylcypholophine, a colourless gum, ν_{max} 1725 cm^{-1} ($CHCl_3$), δ 2·00 (CH_3·CO·O),† identical with the minor alkaloid from *C. friesianus*. The presence of an NH group which is not readily acetylated is indicated in the i.r. (ν_{max} 3500 cm^{-1} in $CHCl_3$) and n.m.r. (broad singlet at δ 7·40 from a proton exchangeable with D_2O) spectra of *O*-acetylcypholophine. The ω-hydroxybutyl chain in (I) is indicated by the n.m.r. spectrum δ 3·57 (t, 2H, *J* 6 Hz, CH_2OH), 2·60 (t, 2H, *J* 6 Hz, $ArCH_2$), 1·4—1·9 (br m, 4H, mid-chain CH_2 groups); a relatively sharp signal at 2·72 (4H) can be assigned to the two adjacent methylene groups of closely similar chemical shift situated between the two aromatic systems, and a signal at 1·94 (s, 3H) can be assigned to the $ArCH_3$ group. The spectroscopic properties of cypholophine can be explained by the presence of a 2,4,5-trisubstituted imidazole ring, and the ω-hydroxybutyl chain can be placed at C-2 because cypholophine, when heated with toluene-*p*-sulphonyl chloride in pyridine, is converted into a mixture of two compounds which have no NH or OH groups and are formed by cyclization to N-1 and N-3 respectively.



(I)



(II)



(III)

Proof of the presence of the imidazole ring and of the overall structure of the alkaloid has been obtained by synthesis of (I). γ-(3,4-Dimethoxyphenyl)propionyl chloride[1] with diazoethane at $-20°$ affords an α-diazo-ketone which reacts with 48% HBr in ethereal solution to give crude 4-bromo-1-(3′,4′-dimethoxyphenyl)pentan-3-one (II) as an oil (purity 66% estimated from n.m.r. spectrum). The bromo-ketone (II) and 2-iminotetrahydropyran hydrochloride[2] (III) heated with methanolic ammonia (20% NH_3 w/v) in a steel bomb at 143° for 2·5 hr. gives a mixture of products from which (I), identical with the natural alkaloid, has been isolated in 6% overall yield.

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† All n.m.r. spectra were measured at 100 MHz in $CDCl_3$ solution and chemical shifts are relative to $SiMe_4$.

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[2] H. Nohira, Y. Nishikawa, Y. Furuya, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1965, **38**, 897.