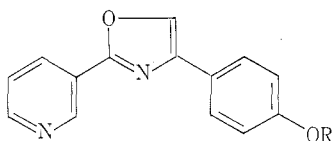


ALKALOIDS OF THE AUSTRALIAN RUTACEAE:
HALFORDIA SCLEROXYLA AND *HALFORDIA KENDACK**

IV.† CO-OCCURRENCE OF OXAZOLE AND QUINOLINE ALKALOIDS

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From the biosynthetic point of view, the isolation¹ of 5-phenyl-2-pyridyl-oxazole alkaloids (I) from *Halfordia scleroxyla* represented a departure from the more usual quinoline pattern observed in the Rutaceae. It was a matter of some interest to establish whether the quinoline pathways were completely suppressed in this genus, or whether their end products had merely been lost in the rather complex isolation process. The presence of large amounts of coumarins² and quaternary base could well have led to this result. *Halfordia kendack* was known to contain less of these components from earlier tests, and so seemed a suitable subject for investigation.



- (Ia) R = H
 (Ib) R = CH₂CH(OH)CH(OH)Me₂
 (Ic) R = CH₂COCHMe₂

The quaternary base fraction was of little interest, containing only *N*-methyl-halfordinium chloride (methochloride of (Ib)), as in the case of *H. scleroxyla*. Chromatography of the small tertiary base fraction afforded halfordine (Ib), halfordinone (Ic), and dictamnine (IV); no halfordinol (Ia) could be detected. The tertiary bases thus consisted of some 60% furoquinolines, in contrast to the previously reported 100% oxazole content in *H. scleroxyla*. The residues from a large extraction of the bark of this

species were still available, and were re-examined. Repeated chromatography resulted in the isolation of two alkaloids, halfordamine (m.p. 240–241°) and halfordine (m.p. 150–151°); the yields were insignificant, and no chemical degradation was possible. The results of physical measurements, leading to tentative structures, are presented below.

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† Part III, *Aust. J. Chem.*, 1965, **18**, 1433.

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¹ Crow, W. D., and Hodgkin, J. H., *Aust. J. Chem.*, 1964, **17**, 119.

² Hegarty, M. P., and Lahey, F. N., *Aust. J. Chem.*, 1956, **9**, 120.

Halfordamine

The molecular ion (m/e 235.08435) established the formula $C_{12}H_{13}NO_4$ (mol. wt 235.08445), and the major transitions in the spectrum (Fig. 1) indicated the presence of two methoxys (235 \rightarrow 220 \rightarrow 192 \rightarrow 177 \rightarrow 149, and 235 \rightarrow 205 \rightarrow

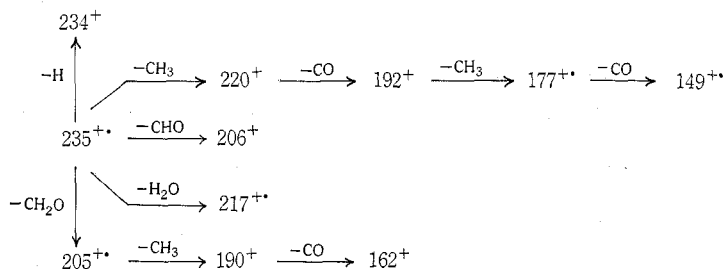
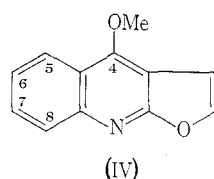
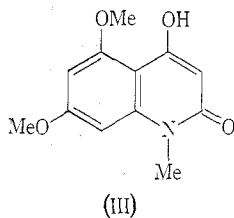
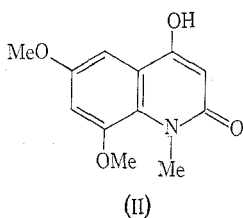


Fig. 1.—70-eV mass spectral transitions in halfordamine ($m^* \pm 0.2$ of calc.).

190 \rightarrow 162) and possibly a phenolic hydroxyl (M—206 and M—18). The n.m.r. spectrum showed signals at τ 0.32 (H, exchanged D_2O), 3.15 and 3.37 (H,H, doublets J 3), 4.05 (H, singlet), and 6.05, 6.08, 6.16 (3H each, singlets). This last group of signals, coupled with the mass spectral results and the signals at 3.15 and 3.37, lead to the assumption of a 1,3-dimethoxybenzene nucleus; the presence of i.r. bands at 1640 cm^{-1} and 3180 cm^{-1} is consistent with the fusion of this to a 2,4-dihydroxypyridine nucleus, as in (II) or (III). The u.v. spectrum (Experimental) is consistent with such structures, as is the mass spectrum. The difference in chemical shift of the aromatic protons suggests that (II) is perhaps to be preferred.

*Halfordinine*

The molecular formula $C_{15}H_{15}NO_5$ (mol. wt. 289.09501) was assigned on the basis of accurate mass determination (molecular ion 289.09491). The mass spectrum down to mass 130 differed from that of acronycidine (5,7,8-trimethoxy derivative of dictamnine) only in relative intensity of the peaks. The n.m.r. spectrum, unaltered on deuterium exchange, showed typical AB doublets at τ 2.43, 2.00 (J 3), characteristic of the furoquinolines.³ A singlet at 2.72 (H) and four singlets at 5.60, 5.83, 5.94, and 6.02 (3H each) completed the spectrum, which was consistent with the structure of a trimethoxydictamnine. The clear lack of identity with acronycidine (m.p. 136–137°) would place the single aromatic proton (τ 2.72) at the 5-, 7-, or 8-position in (IV), but the available data do not permit further speculation.

³ Robertson, A. V., *Aust. J. Chem.*, 1963, **16**, 451.

Experimental

Isolation of Alkaloids (H. kendack)

The procedure was broadly similar to that described previously.¹ Yields stated refer to 18 kg of milled bark. The total crude extract was adjusted to pH 7 and exhausted with ether to remove coumarins and essential oils, together with the tertiary bases. These were recovered by extraction with 10% HCl. Quaternary bases were isolated in the manner described previously, and afforded *N*-methylhalfordinium chloride (18.2 g, identified as the perchlorate, m.p. 206°). The total tertiary base fraction (2.90 g) was chromatographed over alumina (activity I) in benzene → ether → chloroform → methanol. Benzene eluted a gum (1.7 g), while ether eluted traces of halfordinone (0.02 g), m.p. 132°. Chloroform eluted halfordine (0.34 g), m.p. 163–164°. Identification in both cases was by comparison with authentic samples. The benzene eluates were fractionally extracted from ether with 0.01N HCl. The stronger base fraction was converted into the picrates; fractional crystallization afforded a small amount of a picrate, m.p. 212–215° (recovered base, m.p. 169–171°), possibly kokusaginine picrate. The weaker base fractions crystallized readily from methanol to give dictamnine (0.53 g, m.p. 131–132°, undepressed on admixture with an authentic specimen).

Examination of *H. scleroxyla* Residues

The residues (0.25 g) were distributed between ether and 2N HCl, and the basic fraction separated into weaker and stronger base fractions as described above. Chromatography of the weaker bases over alumina in ether resulted in the isolation of *halfordamine* (0.06 g, m.p. 240–241°), which was eluted just prior to halfordine, and crystallized from benzene–light petroleum. The infrared spectrum (Nujol mull) showed bands at 3180, 1640, 1622, 1578, 1480, 1465, 1400, 1365, 1272, 1219, 1202, 1142, 1078, 1040, and 811 cm⁻¹, and the u.v. spectrum in 95% EtOH showed λ_{\max} 251 (log ϵ 4.41), 290sh (3.35), 300sh (3.59), 312 (3.72), 327sh (3.55), and 342 (3.41) m μ .

The stronger bases were chromatographed over alumina in benzene → ether. Earlier fractions gave intractable basic gums, but later fractions slowly crystallized, and the crystals were collected by careful trituration with methanol in the cold. After several recrystallizations from benzene–light petroleum *halfordinine* was obtained as colourless needles, m.p. 150–151°. The infrared spectrum (Nujol mull) showed bands at 1600, 1572, 1540, 1498, 1307, 1297, 1259, 1230, 1180, 1145, 1130, 1080, 1031, 992, 980, 952, 918, 821, 788, 753, 740, 727, and 695 cm⁻¹.

Acknowledgments

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