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THE STRUCTURE OF HALFORDAMINE

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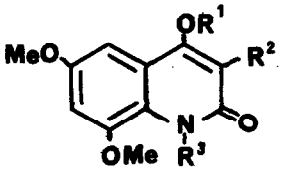
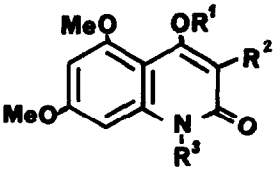
The alkaloid halfordamine from Halfordia kendack was assumed to have structure Ic or IIc by Crow and Hodgkin[1] on the basis of an n.m.r. spectrum with two meta coupled aromatic protons, an olefinic singlet and three three-proton singlets in the N-methyl-O-methyl region. The 4-hydroxy-2-quinolone structure was in keeping with the infra-red and ultra-violet data, and the presence of a phenolic group was deduced by mass spectral speculation.



I

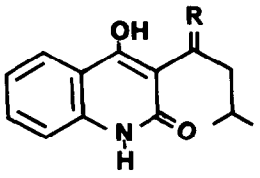


II

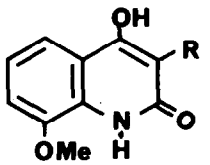
a	R^1=H	R^2=H	R^3=H
b	R^1=CH_3	R^2=H	R^3=H
c	R^1=H	R^2=H	R^3=CH_3
d	R^1=CH_3	R^2=H	R^3=CH_3
e	R^1=H	R^2=CH_2CH_3	R^3=H

In connection with our interest[2] in the metabolites of Dictamnus albus L., we had recourse to synthesise a variety of variously substituted 4-hydroxy-2-quinolones including the 3-ethyl-4-hydroxyquinolones Ie[3] and IIe with the two possible methoxyl substitution patterns for halfordamine. In all of the cases which we have examined, 2-quinolones with a free 4-hydroxyl group have showed a characteristic blue shift of the high wavelength absorptions in the ultra-violet spectrum on addition of base unless there is an acyl group at position 3 (see table). Crow and Hodgkin noted no base shift for halfordamine, although the ultra-violet spectrum of 4-hydroxy-2-quinolones in base is, surprisingly, rarely

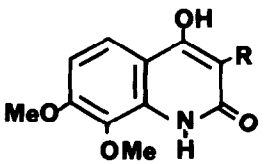
noted in the literature. We were interested to see if our apparently general observation would be of help in the elucidation of the structure of halfordamine and we obtained a sample of the natural product from Dr. W.D. Crow. In our laboratories the ultra-violet spectrum was different from that reported,[1] but there was certainly no shift on addition of alkali. Structures (Ib) and (IIb) are therefore more reasonable for halfordamine than the structure first suggested. Further, the substitution pattern of Ib was the more likely of the two on the basis of the chemical shift difference in the aromatic protons.[1]



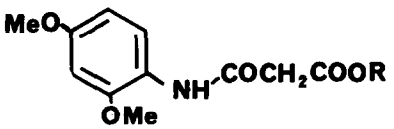
III a R = H_2
b R = O



IV a R = $CH_2CH{=}C(CH_3)_2$
b R = $COCH(CH_3)_2$



V a R = H
b R = $CH_2CH{=}C(CH_3)_2$



VI a R = CH_2CH_3
b R = H

We have verified that Ib is the structure of halfordamine by synthesis. 2,4-Dimethoxyaniline was reacted with excess diethyl malonate to yield the ester, (VIa)[e], $C_{13}H_{17}NO_5$, m.p. 106-8°C, and this was hydrolysed with sodium hydroxide to give the acid (VIb)[e] $C_{11}H_{13}NO_5$, m.p. 144-145°C. The acid was cyclised using polyphosphoric acid to yield the quinolone (Ia)[e], $C_{11}H_{11}NO_4$, m.p. 288-291°C which had a characteristic ultra-violet spectrum and exhibited our expected blue shift (see table). Treatment of the quinolone with diazomethane yielded the quinolone (Ib)[e], $C_{12}H_{13}NO_4$, m.p. 240-242°C undepressed on admixture with halfordamine. The infra-red and ultra-violet spectra of the synthetic and natural specimens were identical.

The 4-hydroxy-1-methylquinolone structure (Ic) for halfordamine was

Ultra Violet Spectra of Some Substituted 2-Quinolones

Compound	Solvent	Spectrum λ(nm) (log ε)
Ie	CH_3OH	237(4.67) 247(4.63) 279(4.04) 289(4.02) 337(3.76) 348(3.63)
	CH_3OH/OH^-	227(4.58) 250(4.63) 305(4.19) 337(3.68)
IIe	CH_3OH	228(4.40) 243(4.20) 253(4.13) 295(3.97) 309(3.98) 322(3.98)
	CH_3OH /OH^-	230(4.38) 247(4.34) 307(4.03)
IIIa (ref.4)	Alcohol	227(4.44) 276(3.72) 312(3.67) 325(3.60)
	Alcohol/OH^-	225(4.40) 252(3.86) 305(3.90)
IVa	CH_3OH	243(4.49) 250(4.47) 278(3.97) 288(3.97) 320(3.58) 334(3.41)
	CH_3OH/OH^-	237(4.55) 248(4.39) 257(4.18) 301(4.03)
Va	CH_3OH	242(4.31) 250(4.11) 280(3.87) 288(3.94) 309(3.94) 320(3.79)
	CH_3OH/OH	239(4.45) 297(4.08) 311(4.02)
Vb	CH_3OH	243(4.29) 252(4.22) 290(3.93) 315(4.02) 327(3.97)
	CH_3OH/OH^-	246(4.46) 311(4.07)
IVb (ref.5)	Alcohol	248(4.30) 308(4.12) 316(4.13)
	Alcohol/Base	242(4.49) 267(4.03) 310(3.96)
IIIb (ref.4)	Alcohol	234(4.19) 300(3.81)
	Alcohol/Base	230(4.21) 265(3.73) 310(3.73)
Halfordamine (ref.1)		251(4.41) 290(3.35) 300(3.59) 312(3.72) 327(3.55) 342(3.41)
Halfordamine and Ib	CH_3OH	249(4.43) 262(3.98) 272(3.76) 281(3.67) 321(3.31) 338(3.49) 350(3.40)
Ia	CH_3OH	248(4.54) 276(3.94) 287(3.92) 339(3.54) 350(3.44)
	CH_3OH/OH^-	245(4.53) 290(4.02) 325(3.55) 340(3.40)
Ic	CH_3OH	230(4.39) 249(4.38) 267(3.68) 278(3.71) 289(3.74) 329(3.28) 343(3.41) 358(3.24)
	CH_3OH/OH^-	228(4.42) 241(4.39) 249(4.35) 297(3.83) 330(3.49) 345(3.38)

readily synthesised from the quinolone (Ia). Methylation with dimethyl sulphate /potassium hydroxide using the method of Harnisch and Brack[7] yielded the

dimethylated product (Id)[6] $C_{13}H_{15}NO_4$ m.p. = 161-162°C which was hydrolysed with 6N hydrochloric acid to yield quinoline Ic, $C_{12}H_{13}NO_4$, m.p. 294-296°. This compound exhibited the expected blue shift (see table).

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