Tetrahedron Vol. 29, pp. 1215 to 1216 Pergamon Press 1973 Printed in Great Britain

SYNTHESIS OF HALFORDAMINE, AN ALKALOID FROM *HALFORDIA KENDACK*

R. STORER and D. W. YOUNG
School of Molecular Sciences, University of Sussex, Brighton BN1 9QJ, U.K.

(*Received in UK* 13 *December* 1972; *Accepted for publication* 16 *January* 1973)

Abstract—Synthesis has shown that the structure of the alkaloid halfordamine from *Halfordia kendack* is **1** (R_1 = Me, R_2 = H) and not **1**, (R_1 = H, R_2 = Me) as was previously thought to be the case.

The alkaloid halfordamine was isolated from *Halfordia kendack* by Crow and Hodgkin[1] who assigned the structure **1** (R_1 = H, R_2 = Me) or **2** (R_1 = H, R_2 = Me) to it. These authors favoured structure **1** (R_1 = H, R_2 = Me) on the basis of the chemical shift difference in the aromatic protons.

The structures **1** and **2** (R_1 = H, R_2 = Me) were supported by the NMR spectrum with its two *meta* coupled aromatic protons, its olefinic singlet and the three 3-proton singlets in the N—Me—O—Me region, and by the IR spectrum. An UV study,[2] however, led us to suspect that if the compound were a 4-hydroxy-2-quinolone, it should show a shift to the blue in base. A sample of natural halfordamine[3] had no such shift and so we favoured **1** (R_1 = Me, R_2 = H) as a more appropriate formulation for the structure of the alkaloid. We now report in full the synthetic studies which confirm this speculation.

2,4-Dimethoxyaniline and diethylmalonate reacted together to yield the ester **3** (R = Et), $C_{13}H_{17}NO_5$ as needles, m.p. 106–108°, and this could be hydrolysed with IN NaOH to the corresponding acid **3** (R = H), $C_{11}H_{13}NO_5$, m.p. 144–145°. The acid was cyclised by treatment with polyphosphoric acid to yield 4-hydroxy-6,8-dimethoxy-2-quinolone, $C_{11}H_{11}NO_4$, which afforded 4,6,8-trimethoxy-2-quinolone on treatment with diazomethane. This material was identical in all respects with a sample of halfordamine[3] and a mixed m.p. was undepressed.

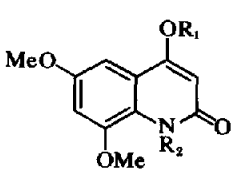
The original formulation for halfordamine, 4-hydroxy-6,8-dimethoxy-1-methyl-2-quinolone (**1**, R_1 = H, R_2 = Me) could readily be obtained from 4-hydroxy-6,8-dimethoxy-2-quinolone by first methylating to 1-methyl-4,6,8-trimethoxy-2-quinolone by the method used for N—O-dimethylations by Harnisch and Brack[4] and then by hydrolysing the 4-OMe group in acid.

EXPERIMENTAL

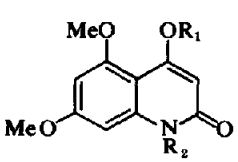
M.ps were determined using a Kofler block and are uncorrected. IR spectra were recorded on a Perkin Elmer 237 spectrophotomerer, UV spectra on a Unicam SP800 spectrophotometer, NMR spectra on Varian T60 or HA100 spectrometers using TMS as internal and external standard, and mass spectra on a Hitachi RMU-6 spectrometer. We thank Mr. A. G. Olney and his staff, for microanalyses and Messrs. P. Dew and A. Greenway for NMR and mass spectra, respectively.

The ester (**3**, R = Et). 2,4-Dimethoxyaniline (10 g) was dissolved in redistilled diethylmalonate (100 g) and the mixture heated to 190° (oil bath temp) in an open flask for 1 hr. The soln was cooled and the volume was reduced to one third and two parts of ether were added. On cooling in an ice bath a solid product was obtained. This crystallised from diisopropyl ether as needles (15 g, 90%), m.p. 106–108°, (Found: C, 58·72; H, 6·58; N, 5·25; $C_{13}H_{17}NO_5$ requires: C, 58·45; H, 6·37; N, 5·25%); $\nu_{max}^{CHCl_3}$ = 3320 (NH), 1722 (ester) and 1673 cm^{-1} (amide), λ_{max}^{MeOH} = 252, 287, 298 (sh) nm. The compound has a parent ion at 267 in the mass spectrum and the NMR spectrum ($CDCl_3$) showed absorption at τ 0·83 (1H, broad s, exchangeable with H_2O, NH), 1·85 (1H, d, J = 9 Hz, aromatic), 2·55 (1H, d, J = 2 Hz, aromatic), 2·56 (1H, d × d, J_1 = 9, J_2 = 2 Hz, aromatic), 5·72 (2H, q, J = 7 Hz, OCH_2CH_3) 6·10 (3H, s, OCH_3), 6·18 (3H, s, OCH_3), 6·52 (2H, s, $COCH_2CO$), 8·67 (3H, t, J = 7 Hz − CH_2CH_3).

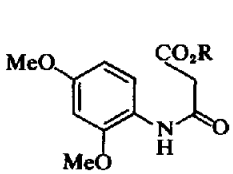
Hydrolysis of ester (**3**, R = Et). The ester **3** (R = Et, 12·5 g), was shaken for 3 hr with IN NaOH (350 ml). The alkaline soln was filtered, washed with chloroform, and acidified with 2N HCl. The white ppt was filtered off,



1



2



3

washed well with water and dried *in vacuo*. Recrystallisation from chloroform afforded white needles (9·9 g, 88%), m.p. 144–145°, (Found: C, 55·35; H, 5·68; N, 5·73; $C_{11}H_{13}NO_5$ requires: C, 55·23; H, 5·48; N, 5·86%); ν_{max}^{NUJOL} = 3250 (NH), 2900 (CO_2H), 1715 (CO_2H) and 1635 cm^{-1} (amide); λ_{max}^{MeOH} = 252, 288, 299 nm. The compound had a parent ion at 239 in the mass spectrum, and the NMR spectrum (TFA) showed absorption at τ 2·71 (1H, d, J = 9 Hz, aromatic) 3·74 (1H, d, J = 2 Hz, aromatic), 3·82 (1H, d × d, J_1 = 9, J_2 = 2 Hz) 6·48 (3H, s, O$\underline{CH_3}$), 6·53 (3H, s, O$\underline{CH_3}$), 6·56 (2H, s, CO$\underline{CH_2}$CO).

4-*Hydroxy*-6,8-*dimethoxy*-2-*quinolone* (1, $R_1 = R_2$ = H). The acid 3 (R = H; 5 g) was suspended in polyphosphoric acid (sp.gr. = 2·2; 25 g) and the mixture heated at 90–95° for 25 min. The mixture was cooled, diluted with water and the resultant gum solidified on prolonged standing. The solid was filtered and dried *in vacuo*. Recrystallisation from pyridine afforded almost colourless diamonds (1·03 g, 22%), m.p. 288–291°, (Found: C, 60·61; H, 5·08; N, 6·47; $C_{11}H_{11}NO_4$ requires: C, 59·72; H, 5·01; N, 6·33%); ν_{max}^{NUJOL} = 3380 (OH, NH) and 1640 cm^{-1} (amide); λ_{max}^{MeOH} = 248 (4·54), 276 (3·94) 287 (3·92), 339 (3·54), 350 nm (sh, 3·44) shifting on addition of base to 245 (4·53), 290 (4·02), 325 (sh, 3·55), 340 (sh, log ϵ 3·40) nm. The compound had a parent ion at 221 in the mass spectrum and the NMR spectrum (TFA) showed absorption at τ 3·25 (1H, d, aromatic), 3·42 (1H, d, aromatic) 3·73 (1H, s, olefinic), 6·38 (3H, s, O$\underline{CH_3}$) and 6·48 (3H, s, O$\underline{CH_3}$).

4,6,8-*Trimethoxy*-2-*quinolone* (1, R_1 = Me, R_2 = H). 4-Hydroxy-6,8-dimethoxy-2-quinolone (1, $R_1 = R_2$ = H; 100 mg) was dissolved in MeOH (75 ml) and an excess of ethereal soln of diazomethane was added. The solvent was removed *in vacuo* and the residue was recrystallised from benzene to afford colourless prisms (56 mg, 53%), m.p. 240–242° (Found: C, 61·61; H, 5·69; N, 5·88; $C_{12}H_{13}NO_4$ requires: C, 61·27; H, 5·57; N, 5·96%); ν_{max}^{NUJOL} = 3140 (NH), 1638 (amide) and 1618 cm^{-1} (aromatic); λ_{max}^{MeOH} = 249 (4·43), 262 (sh, 3·98) 272 (3·76), 281 (3·67), 321 (sh, 3·31), 338 (3·49) 350 nm (sh, log ϵ 3·40). The compound had a parent ion at 235 in the mass spectrum, and the NMR spectrum (TFA) showed absorption at τ 3·89 (1H, d, J = 2 Hz, aromatic) 4·06 (1H, d, J = 2 Hz, aromatic) 4·46 (1H, s, olefinic) 6·87 (3H, s, OCH_3), 7·02 (3H, s, OCH_3), 7·12 (3H, s, OCH_3).

The compound had identical spectra to a sample of naturally occurring halfordamine[3] and a m.m.p. was undepressed.

1-*Methyl*-4,6,8-*trimethoxy*-2-*quinolone* (1, $R_1 = R_2$ = Me). 1, ($R_1 = R_2$ = H; 625 mg) was suspended in DMF (40 ml), powdered anhyd KOH (2·1 gm) was added and the mixture was shaken until all the quinolone had dissolved. Me_2SO_4 (3·125 g) was added with stirring at such a rate that the temp did not exceed 45°. The mixture was heated with stirring at 50–55° for 8 hr and cooled to room temp and diluted with water (1 l.). The product separated as white needles which were filtered, washed well with water and dried *in vacuo*. Recrystallisation from light petroleum (80–100°) afforded white needles (475 mg 69%) m.p. 161–162°, (Found: C, 62·56; H, 6·24; N, 5·51; $C_{13}H_{15}NO_4$ required: C, 62·64; H, 6·07; N, 5·62%), ν_{max}^{NUJOL} = 1645 cm^{-1} (amide), λ_{max}^{MeOH} = 231, 250, 272 (sh), 284, 326 (sh) 342, 353 nm (sh). The compound had a parent ion at 249 in the mass spectrum and the NMR spectrum ($CDCl_3$) showed absorption at τ 3·08 (1H, d, J = 2 Hz, aromatic), 3·36 (1H, d, J = 2 Hz, aromatic) 4·00 (1H, s, olefinic), 6·10 (3H, s, O$\underline{CH_3}$), 6·15 (9H, s, —O$\underline{CH_3}$, —N$\underline{CH_3}$).

4-*Hydroxy*-6,8-*dimethoxy*-1-*methyl*-2-*quinolone* (1, R_1 = H, R_2 = Me). Compound 1 ($R_1 = R_2$ = Me; 400 mg) was suspended in 6N HCl (20 ml) and the mixture heated under reflux for 3 hr. The soln was cooled and the resultant ppt filtered, dissolved in 2N NaOH and filtered. The filtrate was made acid with glacial AcOH and the ppt filtered off, washed with water and dried *in vacuo*. Recrystallisation from glacian AcOH afforded needles (270 mg, 72%), m.p. 294–296° (Found: C, 61·17; H, 5·89; N, 6·05; $C_{12}H_{13}NO_4$ requires: C, 61·27; H, 5·57; N, 5·96%); ν_{max}^{NUJOL} = 1640 cm^{-1} (amide); λ_{max}^{MeOH} = 230 (4·39), 249 (4·38), 267 (sh, 3·68), 278 (3·71), 289 (3·74) 329 (sh, 3·28), 343 (3·41) and 358 nm (log ϵ 3·24) shifting on addition of base to 228 (4·42), 241 (sh, 4·39), 249 (sh, 4·35), 297 (3·83), 330 (sh, 3·49) and 345 nm. (sh, log ϵ, 3·38). The compound had a parent ion at 235 in the mass spectrum, and the NMR spectrum (TFA) showed absorption at τ 3·70 (1H, d, J = 2 Hz, aromatic), 3·94 (1H, d, J = 2 Hz, aromatic), 4·28 (1H, s, olefinic) 6·77, 7·03 and 7·07 (all 3H, s, O$\underline{CH_3}$ or N$\underline{CH_3}$).

Acknowledgements—One of us (R.S.) wishes to thank the S.R.C. for a studentship.

REFERENCES

[1]W. D. Crow and J. H. Hodgkin, *Austral. J. Chem.* 21, 3075 (1968)

[2]R. Storer and D. W. Young, *Tetrahedron Letters* 1555 (1972)

[3]We thank Dr. W. D. Crow, The Australian National University, Canberra, for supplying us with a sample of natural halfordamine for comparison.

[4]H. Harnisch and A. Brack, *Liebigs Ann*, 740, 164 (1970)