Tetrahedron, 1967, Vol. 23, pp. 2061 to 2065. Pergamon Press Ltd. Printed in Northern Ireland

THE STRUCTURES OF EDULITINE AND EDULININE—XXIV[1]

SPECTRA AND STEREOCHEMISTRY

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(*Received in USA* 2 *September* 1966; *accepted for publication* 10 *October* 1966)

Abstract—The structures of two quinoline alkaloids, edulitine and edulinine, constituents of *Casimiroa edulis*, have been established by NMR and mass spectrometry.

The isolation of several new alkaloids from *Casimiroa edulis* Llave et Lex. (Rutaceae) has been described,[2] and the structures of two of these, edulein[3] (I), and casimiroin[4] (II) elucidated.[2] We have examined two further quinoline alkaloids from this plant, edulitine (III) and edulinine (IV),[5] and have established their structures on the basis of their NMR and mass spectra.

Edulitine is 4,8-dimethoxycarbostyril. Sondheimer[2b] established the molecular formula $C_{11}H_{11}O_3N$. Analyses further demonstrated the presence of two MeO groups and one active hydrogen. The IR and UV spectra[2b] indicate that the compound is a substituted quinoline.

In the NMR spectrum, there are two sharp three-proton singlets at δ 3·93 and 3·94 ascribed to the two MeO groups. The proton on the nitrogen atom gives rise to a broad signal at δ 8·9. A sharp one-proton singlet at δ 5·94 arises from the proton at C_3. The protons on the homocyclic ring produce a first order ABC pattern with signals at δ 6·94, 7·09 and 7·45 split by *ortho*-coupling of 8 c/s. The δ 7·09 signal shows two such couplings, while the other two protons are mutually *meta*-coupled (J_{meta} = 1·5 c/s). These couplings have been substantiated by double-irradiation experiments.

The presence of a MeO group at position 8 follows from the mass spectrum. It has been shown[6] that among the monomethoxyquinolines, only the 2- and 8-isomers have strong M-1 ions, while an M-3 fragment is produced by 8-methoxyquinoline alone. The molecular ion (*m/e* 205) of edulitine is the base peak of the spectrum. The M-1 peak has an abundance of 90% relative to it, while the intensity of the M-3 peak is 6%; these are of the same order as in 8-methoxyquinoline.[6] Metastable peaks substantiate these losses of one followed by two mass units $\left(203 = \frac{204^2}{205};\ 200 = \frac{202^2}{204}\right)$. Other fragmentations confirmed by the relevant metastable peaks are the loss of a Me radical $\left(m/e\ 190;\ 176 = \frac{190^2}{205}\right)$ followed by carbon monoxide (*m/e* 162) (this fragment

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[1] Part XXIII, A. D. Cross, *Biochem. J.* **100**, 238 (1966).

[2] [a] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956); [b] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *Ibid.* 4170 (1956).

[3] F. Sondheimer and A. Meisels, *J. Org. Chem.* **23**, 762 (1958).

[4] A. Meisels and F. Sondheimer, *J. Am. Chem. Soc.* **79**, 6328 (1957).

[5] Samples from the Syntex collection, isolated in the original investigation.[2]

[6] D. M. Clugston and D. B. MacLean, *Canad. J. Chem.* **44**, 781 (1966).

is also formed by a concerted decomposition, as shown by a metastable peak at m/e $128{\cdot}5 = \left(\frac{162^2}{205}\right)$. A CHO radical is expelled $\left(m/e\ 176;\ \text{metastable}\ m/e\ 151{\cdot}5 = \frac{176^2}{205}\right)$, and the M-30 peak reported[6] in the spectra of methoxyquinolines (m/e 175; 61%) is also present.

Table 1. NMR spectra of some substituted quinolines

Compound	Methyl resonances*	C_8—H*	Ref
Casimiroin (II)	3·83, 3·92	7·57	7[a]
Flindersamine (V)	4·28, 4·40	7·28	7[b]
VI	3·87, 3·92	7·52	7[c]
VII	3·92, 4·00	~7·5	7[d]
VIII	3·87, 3·92	8·05	7[e]
IX	3·77, 3·87	8·00	7[f]
Edulein (I)	3·90	8·34	5
2-Methoxyquinoline	4·03	—	8
N-methyl-2-quinolone	3·67	—	8
Edulitine (III)	3·93, 3·94	7·45	2
Edulinine (IV)	3·69, 3·94	7·80	2

* All resonances are reported for solns in $CDCl_3$. They are given in ppm from TMS on the δ scale.

The ABC aromatic pattern in the NMR is thus due to the protons at positions 5, 6, and 7. The chemical shift of the C_8 proton (δ 7·45) shows that the second MeO group is at C_4. Some features of the NMR spectra of substituted quinolines are shown in Table 1.

A CO group at C_4 deshields the C_5-proton strongly e.g., to δ 8·34 in edulein. With an additional ether function at position 8 (VIII and IX) this resonance shifts to about δ 8·0. In the compounds with an ether group at C_4 (II, VI and VII) this proton resonates at about δ 7·5 (the 6-Me group in (V) appears to shield the C_5-proton to the extent of about 0·25 ppm). The resonance at δ 7·45 in edulitine indicates a MeO at C_4. The structure III for edulitine is thus established.

Edulinine has the structure IV. The molecular formula was shown[2b] to be $C_{16}H_{21}O_4N$. It was further found to contain one MeO group. The UV spectrum is very similar to that of edulitine, except that the max at 248 mμ in the latter is reduced in intensity and appears as an inflection at 244 mμ.

A signal at δ 3·94 in the NMR spectrum is assigned to the MeO group. The homocyclic ring is unsubstituted and its protons produce a first order ABCD system. The assignment of these signals can be made on the basis of the fact that in N-methyl-2-quinolone no resonance other than that of the C_4 proton lies downfield of δ 7·6, while edulinine exhibits a pair of doublets at δ 7·80. This signal can be ascribed most reasonably to the proton at C_5, deshielded by a peri electronegative function at C_4. The proton at C_8 resonates at δ 7·25 and shows the following spin couplings: $J_{7,8} = 8{\cdot}4$ c/s., $J_{6,8} = 1{\cdot}5$ c/s, $J_{5,8} = 0{\cdot}6$ c/s. This signal is further broadened, presumably by

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[7] [a] Varian Associates *High Resolution NMR Spectra* Catalog Spectrum 291 (1962); [b] *Ibid.* Spectrum 304; [c] *Ibid.* Spectrum 312; [d] *Ibid.* Spectrum 313; [e] *Ibid.* Spectrum 300; [f] *Ibid.* Spectrum 311.

[8] Our sincere thanks to Dr. I. Harrison of this Institute for syntheses of these two compounds.

the nitrogen quadrupole. The C_7 and C_6 protons are at δ 7·35 and δ 7·54 respectively and are mutually *ortho*-coupled ($J_{6,7}$ = 6·8 c/s); the proton at C_7 is *meta*-coupled with the C_5-proton ($J_{5,7}$ = 1·6 c/s). Finally, this latter proton (δ 7·80) shows mutual *ortho*-coupling with C_6 ($J_{5,6}$ = 7·6 c/s). All these couplings have been substantiated by double irradiation experiments. The position of the C_5-proton resonance is indicative of a 4-MeO group (Table 1), the signal being shifted to lower field by about 0·3 ppm in the absence of an oxygen function at position 8 (edulinine (IV) is related to VI as I is to VIII and IX). The N–Me group at δ 3·69 resonates at the same frequency as the corresponding group in N-methyl-2-quinolone. The downfield shift of other N–Me resonances in Table 1 may be attributed to deshielding by the neighboring 8-oxygen functions.

The nature of the side chain at C_3 may be deduced from the NMR and the mass spectra. The geminal dimethyl group gives rise to a six-proton singlet at δ 1·31, a position characteristic of the dimethylcarbinol function. The proton on the carbon bearing the other OH group (δ 3·60) was shown by double irradiation to be vicinally coupled to the benzylic protons at δ 2·70 and 3·09 only, with coupling constants of 10 and 2 c/s respectively; the benzylic protons exhibit a mutual geminal coupling of 13 c/s.

The mass spectrum contains only a trace of the molecular ion (*m/e* 291). Small peaks indicate the loss of water (*m/e* 273), and of a Me radical (*m/e* 276) followed by water $\left(m/e\ 258;\ \text{metastable}\ 241 = \frac{258^2}{276}\right)$. By far the most intense peak in the spectrum is *m/e* 232, which corresponds to the loss of the terminal dimethylcarbinol radical (59 mass units) of the side chain, substantiated by an appreciable metastable peak $\left(187 = \frac{232^2}{291}\right)$. The side chain also fragments at the benzylic position (*m/e* 203) and at C_3 $\left(m/e\ 188;\ \text{metastable}\ 121 = \frac{188^2}{291}\right)$. These fragmentations all follow established pathways,[9] as do the subsequent fragmentations based on the aromatic MeO group $\left(m/e\ 203\text{–}CH_3\cdot \rightarrow m/e\ 188;\ \text{metastable}\ 174 = \frac{188^2}{203};\ m/e\ 188\text{–}CO \rightarrow m/e\ 160\right)$.

The structure IV for edulinine is interesting in that it lies between those of the quinoline alkaloids and that of the furoquinoline alkaloid lunacrine (X).[10] Edulinine would appear to be closely related to lunacridine (XI).[11] Both of these compounds have been isolated from Rutaceae species. The furoquinoline alkaloids dictamnine (XII), γ-fagarine (XIII), and skimmianine (XIV) have been found in *C. edulis*.[2b]

EXPERIMENTAL

NMR spectra were measured at 100 Mc/s with approximately 0·3 M solns in $CDCl_3$, using a Varian HA-100 spectrometer equipped with a spin-decoupler. Chemical shifts, δ, are quoted in ppm from TMS used as an internal standard. Mass spectra were determined on an Atlas CH-4 spectrometer, by direct insertion of the sample into the ion source; the ionizing energy was 70 eV, and a 3 KV accelerating potential was used.

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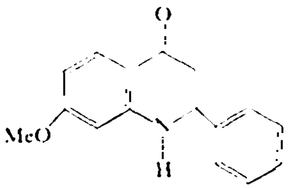
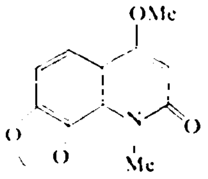
[9] *Vide* H. Budzikiewicz, C. Djerassi and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds*. Holden-Day, San Francisco (1964).

[10] S. Goodwin, J. N. Shoolery and L. F. Johnston, *J. Am. Chem. Soc.* **81**, 3065 (1959).

[11] E. A. Clarke and M. F. Grundon, *J. Chem. Soc.* 438 (1964).



I



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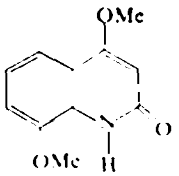

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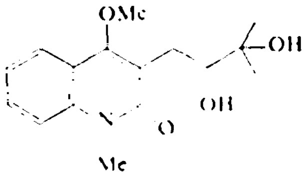

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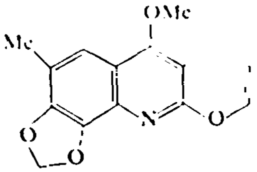

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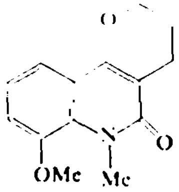

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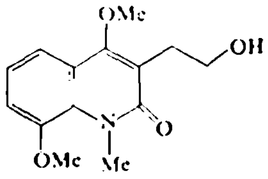

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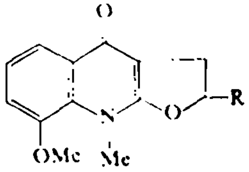
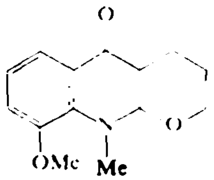


VIII, R = H

X, R = $-CH(CH_3)_2$



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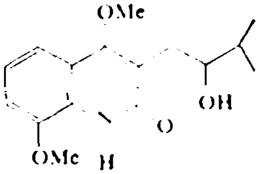
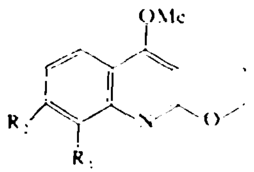


XI



XII, $R_1 = R_2 = H$

XIII, $R_1 = OMe, R_2 = H$

XIV, $R_1 = R_2 = OMe$

2-*Methoxyquinoline*. 2-Chloroquinoline (5 g) was heated overnight at 150–160° with a large excess of MeONa. The product was distilled from the reaction mixture to furnish a mobile liquid which gave a single peak on VPC.

N-*methyl-2-quinolone*. Carbostyril (1 g) in benzene (30 ml) was heated at 60° for 15 min with NaH (5 equivs; 50% in oil). The soln was taken to dryness under reduced press and dissolved in DMF (15 ml). MeI (5 ml) was added cautiously, with cooling, and the reaction mixture allowed to stand for 48 hr at 20°. Water was added and the soln extracted with benzene. The product was crystallized from hexane at 0°, m.p. 71° (lit.[18] 74°).

[18] L. Knorr, *Ber. Dtsch. Chem. Ges.* **30**, 929 (1897).