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OCOTEA ALKALOIDS: THE CHARACTERIZATION AND STRUCTURES OF FOUR NEW APORPHINE BASES

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The genus Ocotea (Lauraceae) produces a variety of alkaloids derivable from benzylisoquinoline units. Thus, Ocotea puberula yields the aporphine ocoteine,[1] O. glaziovii the proaporphine glaziovine,[2] and O. rodiei a number of bisbenzyltetrahydroisoquinoline alkaloids.[3] This paper describes the isolation and characterization of four new aporphines (I, II, III, and IV) from two additional Ocotea species.

Ocotea macropoda[4] affords a mixture of aporphine bases, three of which have been isolated and identified. The first is the alkaloid dicentrine (V); the second and third are the new aporphines dehydrodicentrine (I) and ocopodine (II).

Dehydrodicentrine (I), $C_{20}H_{19}NO_4$, is crystallized from chloroform in golden yellow needles, m.p. 218°, and is optically inactive. Its ultraviolet spectrum [λ_{max}^{EtOH} 263 mμ (log ε 4.74), 302 (3.85), 340 (4.10)] indicates a highly conjugated system similar to that of dehydronuciferine (VI)[5,6]. Its NMR spectrum reveals an N-methyl group (3.04 δ), two methoxyls (4.00), a methylenedioxy group (singlet at 6.18) and four unsplit aromatic protons (6.51, 6.87, 7.02, and 8.41); the aromatic proton at low field and the unusually deshielded N-methyl group are typical of a C-11 proton and an N-methyl of a dehydroaporphine[5]. Identification of the new base as dehydrodicentrine (I) was obtained by using mild permanganate oxidation[7] to prepare it from dicentrine (V) in 50% yield. Dehydrodicentrine (I) represents the first simple dehydroaporphine to be isolated from natural sources[8].

Ocopodine (II), $C_{21}H_{23}NO_5$, forms needles from ethanol, m.p. 116°; $[\alpha]_D^{25}$ + 87° (c 0.82) EtOH); λ_{max}^{EtOH} 223 mμ (log ε 4.57), 281 (4.30), 305 (4.08). Its NMR spectrum shows a methylenedioxy group (close doublets at 5.86 and 6.03), an N-methyl group (2.52), three methoxyl groups (3.82, 3.85, 3.87), and two aromatic protons (6.48 and 7.47). The most deshielded aromatic proton must be at C-11. The position of the three methoxy groups was determined as follows: strong acid hydrolysis of ocopodine, followed by permanganate oxidation of the resulting catechol derivative, produced an acid fraction. Conversion of this acid fraction to its N-ethylimide produced N-ethyl-3,4,5-trimethoxyphthalimide (VII), m.p. 90-92°, identical (IR, mixed m.p.) with an authentic synthetic sample[9]. Ocopodine is unusual in that it is the first *naturally occurring* aporphine to have three substituents attached to ring D[10]. The racemic form of ocopodine was synthesized several years before isolation from natural sources[12]. A direct comparison of natural ocopodine and the synthetic *dl*-base (infrared spectra in chloroform solution) showed the compounds to be identical[13].

An incompletely identified *Ocotea* species, collected in the vicinity of Manaus, Brazil[14], yielded three bases, which were separated by combined column and thin layer chromatography. The first base proved to be the alkaloid isocorydine (VIII); the second and third bases were new aporphines which were named ocokryptine (III) and oconovine (IV).

Ocokryptine (III) forms crystals from ether, m.p. 160-161°, $[\alpha]_D^{27}$ + 164° (*c* 0.4 $CHCl_3$), mol. wt. (mass spec.) 355. Its ultraviolet spectrum [λ_{max}^{EtOH} 222 mμ (log ε 4.53), 284 (4.08), 299 sh (3.42)] is consistent with its formulation as an 11-substituted aporphine[15]; its NMR spectrum reveals the presence of two aromatic protons (both at 6.77), one methylenedioxy group (close doublets at 5.92 and 5.98), two methoxyls (both at 3.91) and an N-methyl group (2.50). Ocokryptine is cryptophenolic; it is insoluble in aqueous base, but exhibits a bathochromic ultraviolet shift in alkaline ethanol solution. A positive Gibbs test is indicative of a free position para to the phenol. These facts, and the absence of a low field C-11 proton signal in its NMR spectrum[16], place the phenolic function at C-11. Ocokryptine very slowly reacts with diazomethane to give O-methylocokryptine (IX), m.p. 170-171°, $[\alpha]_D^{27}$ + 156° (*c* 1.1 $CHCl_3$). The NMR spectrum of O-methylocokryptine shows in addition to the N-methyl group (2.49), the methylenedioxy group (close doublets at 5.88 and 5.91), three methoxyls (3.63, 3.84, and 3.97), and two ortho aromatic protons as an AB-type quartet centered at 6.82 ($\Delta\nu$ = 13, J = 8 cps). A study of the NMR spectra of other aporphines has shown that the ortho protons at C-8 and C-9 appear as an AB quartet when methoxy substituents are present at both C-10 and C-11, but the same protons appear as a *singlet* when either the C-10 or C-11 oxygen is present as a free phenol function.[11,16] On the basis of this evidence, ocokryptine must be either 1,10-dimethoxy-2,3-methylenedioxy-11-hydroxyaporphine (III) or 1,2-methylenedioxy-3,10-dimethoxy-11-hydroxyaporphine X. Structure X was eliminated by direct comparison (IR, NMR: see Table I) of O-methylocokryptine IX and O,N-dimethylhernandine (XI)[17], which were distinctly different. Ocokryptine is therefore assigned structure III; it is unusual in that it is the first known aporphine bearing a methylenedioxy group between C-2 and C-3.

Oconovine (IV), $[\alpha]_D^{27}$ + 156° (c 0.2 $CHCl_3$) was amorphous but was characterized as its crystalline methiodide, $C_{22}H_{28}NO_5I$, m.p. 204-205°, $[\alpha]_D^{27}$ + 70° (c 0.2 $CHCl_3$). The ultraviolet spectrum of oconovine [λ_{max}^{EtOH} 222 mμ (log ε 4.54), 276 (4.15), 310 sh (3.70)] is similar to that of ocokryptine (III). Like ocokryptine, oconovine is cryptophenolic, and gives a positive Gibbs test, suggesting the same substitution pattern in the lower ring (ring D) of both alkaloids. The NMR spectrum of oconovine shows two aromatic protons (both at 6.84), four methoxyls (see Table I for assignments) and an N-methyl group (2.50). Diazomethane slowly reacts with oconovine to give the amorphous O-methyloconovine (XII), the NMR spectrum of which shows the ortho protons at C-8 and C-9 as an AB quartet characteristic of a 10,11-dimethoxyaporphine (center at 6.87, $\Delta\nu$ = 11.5, J = 8.5 cps). Oconovine is therefore assigned structure (IV); no other permutation of a phenolic hydroxyl and four methoxyls is in accord with the data just described.

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4. Ocotea macropoda (H.B.K.) Mez. was collected by Dr. Aparicio Duarte in the state of Guanabara, Brazil. A voucher specimen, under no. Ap. 9687, is deposited in the herbarium of the Botanical Garden, Rio de Janeiro. This assistance in collection and identification of the material is gratefully acknowledged.

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6. All molecular formulae indicated in this paper were supported by acceptable elemental analyses. Melting points are uncorrected. All NMR spectra were run in deuteriochloroform with tetramethylsilane as internal standard and are reported in δ (delta units).

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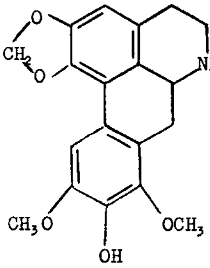

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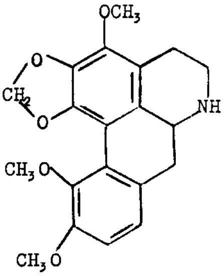

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13. We are grateful to Prof. M. Tomita for a sample of synthetic dl-1,2-methylenedioxy-8,9,10-trimethoxyaporphine.

14. This material was collected by Drs. G. Hatchbach and R. Raffauf, whose assistance is hereby acknowledged. The speciman was sterile and could not be identified as to species.

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17. We are grateful to Prof. F. N. Lahey (University of Queensland) for a generous gift of N-methylhernandine, from which O,N-dimethylhernandine was prepared by reaction with diazomethane.

TABLE I NMR DATA (δ UNITS)

Compound	N-Methyl Protons	Methoxyl Protons							Methylene-dioxy Protons		Aromatic Protons				
		1	2	3	8	9	10	11	(doublets)		3	7	8	9	11
Dehydrodicentrine (I)	3.04					4.00			6.18[a]		6.51	7.02	6.87		8.41
Ocopodine (II)	2.52				3.87[b]	3.82[b]	3.85[b]		6.03	5.86	6.48				7.47
Ocokryptine (III)	2.50	3.91					3.91		5.98	5.92			6.77	6.77	
O-Methylocokryptine (IX)	2.49	3.86					3.97	3.63	5.91	5.88			6.82[c]		
O,N-Dimethylhernandine (XI)	2.52			4.04	3.87	3.77			6.03	5.87			6.87[d]		
Oconovine (IV)	2.50	3.76	3.92	3.98			3.92						6.84	6.84	
O-Methyloconovine (XII)	2.50	3.71	3.86	3.92			3.92	3.71					6.87[e]		

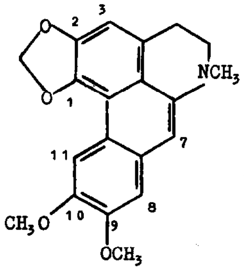
a Singlet

b Assignments may be interchanged

c AB quartet, $\Delta\nu = 13$, $J = 8$ cps

d AB quartet, $\Delta\nu = 18$, $J = 8$ cps

e AB quartet, $\Delta\nu = 11.5$, $J = 8.5$ cps



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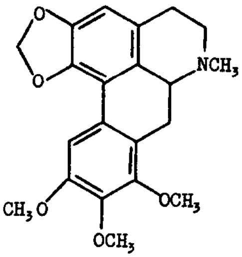

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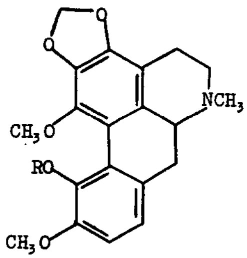

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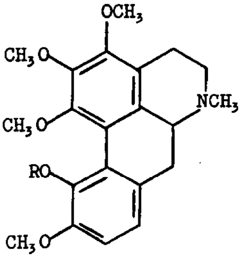
IX: R = CH$_3$



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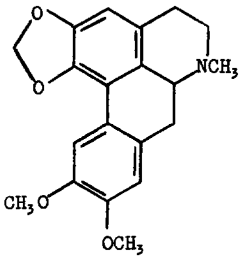

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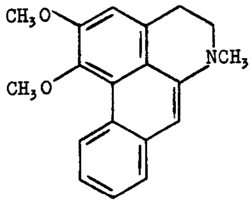

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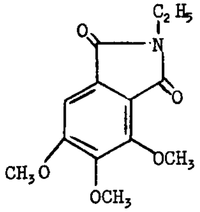

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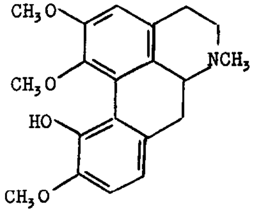

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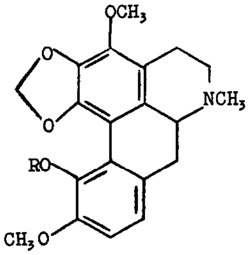

X: R = H

XI: R = CH$_3$