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CARIOCAL, A NEW SECO-ABIETANE DITERPENE FROM THE LABIATE *Coleus barbatus*

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Abstract : cariocal is a new seco-diterpene isolated from a cardioactive fraction of the false boldo, *Coleus barbatus*. The structure was deduced from chemical and spectral data.

The hexane and dichloromethane crude extracts of stems of the Labiate *Coleus barbatus* Bentham induce, in anaestezised rats, small lowering of blood pressure and discrete bradycardia. This activity was shown to be associated with a fraction containing several abietane diterpenes[1], some of whose structures were reported in previous communications[2-4]. Common features to all these diterpenes are a catechol in the C-ring and a substituted C-20 methyl group[2-4]. In this paper, we wish to report on the structure of cariocal (1), a new diterpene obtained from the hexane crude extract by a combination of gel permeation and silica gel chromatography.

Cariocal (1)[5] was isolated as a colorless crystalline solid (m.p. 186-189°, $|\alpha|_D^{25}$ = +39°) in 0.08% yield from dry plant material (stems). Elementary analysis together with low resolution MS (M^+ m/z 346) and ^{13}C NMR data established molecular formula $C_{20}H_{26}O_5$. The IR and UV spectra[5] were characteristic of a substituted *p*-hydroxybenzaldehyde moiety[6], and allowed identification of two of the five oxygen atoms of 1. ^1H and ^{13}C NMR spectra (see Tables 1 and 2) indicated the presence of a pentasubstituted aromatic ring, of four methyl groups, two of which are on quaternary carbon and two that are part of an isopropyl group attached to the aromatic nucleus. These preliminary data together with the absence of any other unsaturated carbon in the ^{13}C NMR spectrum suggested that 1 was a tetracyclic diterpene. Biogenetic considerations and similarities between the ^{13}C NMR spectra of 1 and carnosolone (2)[7] (see Table 2) pointed to an aromatic abietane with an unsubstituted A-ring. Acetylation (Ac_2O/Py, r.t., 3 hr) of 1 gave diacetate 3[8] and methylation (CH_3I/K_2CO_3-acetone, r.t., 4.5 hr) of 1 gave monomethyl ether 4 (IR : 3350 cm^{-1})[9] followed by acetylation to 5[10] established the presence of one phenolic OH and of one secondary OH group. The small upfield shift ($\Delta\delta$ -0.23 ppm) of H-15 and the non-equi-

valency of the iPr methyl groups observed on acetylation showed that the phenolic OH and the iPr were in an *ortho* relationship to each other. Moreover, the absence of effects on H-14 during acetylation or methylation proved that the aromatic hydrogen was *meta* to the phenolic OH. Finally, since the oxygen substituted aromatic carbon was observed at *ca* 145 ppm, an oxygen function was suspected to exist *ortho* to the phenolic OH. In the abietane skeleton, all these considerations allowed only one arrangement for the aromatic substituents. Hence the aldehydic carbon in 1 is C-7 of the abietane frame and 1 is a 6,7-*seco* diterpene, closely related to the recently described rosmadial (6)[11]. Comparison of the ^{13}C NMR spectra of 1 and 6 (see Table 2) confirmed this conclusion and showed main differences at C-6 and C-20. These carbons appear in the ^{13}C NMR spectrum of 1 as two doublets at δ 114.81 and 101.82 (the latter shielded to δ 99.72 on acetylation). These data and the low field positions of the 1H singlet at *ca* δ 5.9 (attributed to H-20) and of the carbinol hydrogen at δ 5.32 in 1 (deshielded to δ 6.00 on acetylation) indicated the presence of one acetal and one hemiacetal functions envolving C-6, C-20 and the three remaining oxigen atoms, and originating two heterocycles. Two alternative structures, 1 and 7, satisfy all the above requirements. Experimental support for structure 1 came from PCC oxidation (PCC 2 eq., CH_2Cl_2, r.t., 2 hr) of cariocal methyl ether 4 to lactone 8 which showed in its ^1H NMR spectrum deshielding effects on H-5 ($\Delta\delta$ +0.45), H-20 (+0.27) and Me-18 (+0.18)[12] comparable to those observed on oxidation of acetyl enmein 9 to lactone 10[13]. Introduction of a Δ^5 double bond should be an elegant method to distinguish between structures 1 and 7. However, all our attempts to dehydrate 4 or to pyrolyse ester 5 failed showing the unfavorable orientations of H-5 and the oxygen function at C-6. This result and also the rather upfield position of the methyl of the secondary acetate in 3 or 5 (at *ca* δ 1.45) fixed the stereochemistry at C-6 with the OH pointing towards the aromatic nucleus. Final proof for structure 1 came when 4 was refluxed in dry toluene for 1 hr in the presence of an excess of TsOH. Again no dehydration occurred and the only product formed was tosylate 11[14]. The ^1H NMR spectrum of 11 indicated deshielding effects on H-5 ($\Delta\delta$ +0.38), H-20 (+0.10) and Me-19 (+0.09) and shielding effects on H-7 (-0.31), H-14 (-0.55), H-15 (-0.15) and Me-16 & 17 (-0.12) only compatible with structure 1. The absence of coupling between H-5 and H-6 indicates that the dihedral angle between these two hydrogens is about 90°, probably due to strong steric interaction between Me-18 and H-6. Absolute configuration and chemical correlation of cariocal (1) with rosmadial (6) will be reported elsewhere.

To our knowledge, very few 6,7-*seco*-abietanes have been reported[11]. We have now isolated two other *seco*-abietanes ; the structures of these compounds are still under investigation.

TABLE 1 : ^{1}H-NMR data (100 MHz) of cariocal (1) and derivatives.

assignment	1	3	4	5	8	11
H - 5	2.76 s	2.75 s	2.77 s	2.78 s	3.23 s	3.15 bs
H - 6	5.32 d[1,3]	6.00 s	5.24 bs[3,2]	6.00 s	-	5.12 bs
H - 7	9.85 s	9.98 s	9.89 s	9.88 s	9.82 s	9.54 s
H - 14	7.34 s	7.36 s	7.30 s	7.28 s	7.32 s	6.75 s
H - 15	3.34 h[4]	3.11 h[4]	3.32 h[4]	3.34 h[4]	3.33 h[4]	3.17 h[4]
H - 20	5.91 s	5.92 s	5.90 s	5.92 s	6.17 s	6.00 s
Me- 16	1.27 d[4]	1.19*d[4]	1.24 d[4]	1.20*d[4]	1.24 d[4]	1.12 d[4]
Me- 17	1.27 d[4]	1.26*d[4]	1.24 d[4]	1.27*d[4]	1.24 d[4]	1.12 d[4]
Me- 18	1.09 s	1.13 s	1.13 s	1.15 s	1.31 s	1.08*s
Me- 19	0.91 s	0.93 s	0.91 s	0.95 s	0.99 s	1.00*s
OR- 12	8.71 b[5,6]	2.36 s	4.07 s	4.06 s	4.10 s	4.09 s
OR'- 6	4.67 d[1,6]	1.45 s	n.o.	1.42 s	-	see[7]

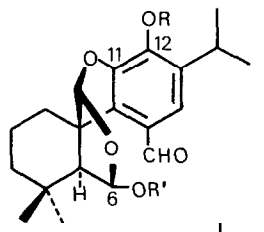
* signals in any vertical column may be reversed ; h = heptuplet, s = singlet, d = doublet and b = broad ; n.o. = not observed.

[1] J = 3.9 Hz ; [2] $W_{1/2}$ = 9.0 Hz ; [3] s on D_2O addition ; [4] J = 7.0 Hz ; [5] $W_{1/2}$ = 17 Hz ; [6] disappear on D_2O addition ; [7] tosyl signals shielded by the C-ring : 2.09 (3H, s) and 6.64 (2H d J=8Hz), 6.78 (2H d J=8Hz).

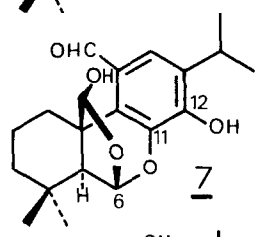
TABLE 2 : ^{13}C-NMR (25.2 MHz) data of 1,2,3 and 6

C Nº	1	3	2[7]	6[11]
1	29.69 t	28.15 t	30.0	31.5
2	19.39 t	18.49 t	18.9	16.5
3	38.37 t	37.46 t	41.8	40.1
4	31.08 s	30.67 s	32.7	33.9
5	56.72 d	54.94 d	58.6	61.1
6	101.82 d	99.72 d	105.4	201.9
7	191.50 d	191.32 d	192.8	191.9
8	124.66 s	129.10 s	121.6	123.9
9	136.11*s	137.81*s	141.2	135.9
10	56.90 s	55.85 s	51.8	48.3
11	145.63 s	150.00 s	139.1	142.5
12	144.88 s	141.56 s	150.0	141.0
13	135.17*s	135.43*s	133.9	131.6
14	128.55 d	126.70 d	119.7	131.1
15	27.47 d	27.38 d	27.2	26.9
16	22.86●q	23.11●q	22.6	22.0
17	22.58●q	22.62●q	22.7	22.1
18	32.39 q	32.05 q	34.0	33.2
19	23.31 q	23.11 q	22.5	23.7
20	114.81 d	114.45 d	72.3	176.9

*●signals may be reversed in any vertical column



	R	R'
1	H	H
3	Ac	Ac
4	Me	H
5	Me	Ac
11	Me	Ts



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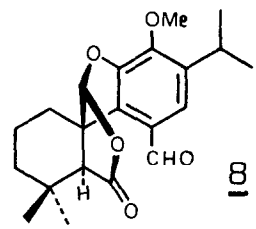

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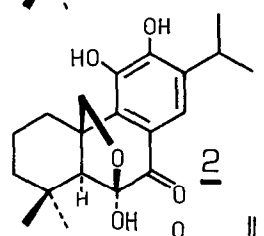

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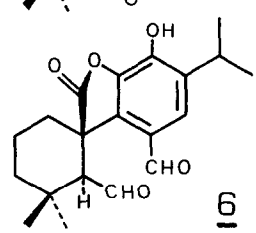

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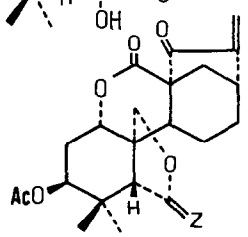

9 Z = H, OH

10 Z = O

Acknowledgements.

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2. A. KELECOM, *Tetrahedron* 39, 3603 (1983).
3. A. KELECOM, *Química Nova* 6, 117 (1983).
4. A. KELECOM, *Phytochemistry* 23, 1677 (1984).
5. cariocal (1) : m.p. 186-189º ; analysis : C, 65.8 and H, 7.5 calculated for $C_{20}H_{26}O_5.H_2O$ C, 65.93 and H, 7.69% ; $|\alpha|$ = +39º (589), +41º (578), +45º (546) and +42º (436nm ; c=1.00 MeOH) ; UV λ_{max}^{MeOH} nm(ε)= 234 (7180), 288 (7600) & 315 (sh 4090) in neutral MeOH and 228 (5730), 254 (7460), 286 (3760) & 358 (14770) in alkaline MeOH ; IR_{KBr} cm^{-1} = 3410, 3215, 2717, 1672, 1613 1577 1230, 1164, 1117 ; MS m/z (rel. int.) = M^+ 346 (100, $C_{20}H_{26}O_5$), 331 (5), 328 (86), 318(22), 313(26), 300(62), 299(47), 285(95), 271(43), 258(61), 243(40), 231(66), 229(37), 217(31), 215(32), 205(43), 181(29) ; ^{1}H NMR (CD_3COCD_3) : see Table 1 ; ^{13}C NMR (CD_3COCD_3) : see Table 2.
6. A.I. SCOTT in "Interpretation of the Ultraviolet Spectra of Natural Products" chap 3, pp109 & 113, Pergamon Student Edition, Oxford (1964),
7. F. YOSHIZAKI, P. RÜEDI & C.H. EUGSTER, *Helvetica Chimica Acta* 62, 2754 (1977).
8. diacetate (3): gum ; $|\alpha|_D$ = +38º (c = 0.45 $CHCl_3$) ; UV λ_{max}^{MeOH} nm = 226, 263 & 319 ; IR_{film} cm^{-1} = 2732, 1770, 1742, 1689, 1618, 1580, 1277, 1186, 1110 ; MS m/z (rel. int.) = no molecular ion, 328 (53, M^+-42,-60), 300(19), 299(11), 292(8), 285(9), 271 (5), 259(9), 257(8), 244(7), 231(7), 218(8), 182(11), 43(100) ; ^{1}H NMR ($CDCl_3$) : see Table 1 ; ^{13}C NMR ($CDCl_3$) : see Table 2, acetate signals : 20.40(2C,q), 167.34(s) & 169.25(s).
9. methyl ether (4): m.p. 141-144º ; $|\alpha|_D$ = +46.5 (c=1.00 $CHCl_3$) ; UV λ_{max}^{MeOH} nm = 228, 282 & 315(sh) ; IR_{film} cm^{-1} = 3350, 2747, 1667, 1610, 1570, 1277, 1115, 1007 ; MS m/z (rel.int.) M^+ 360 (88, $C_{21}H_{28}O_5$), 342 (100), 327(29), 314(26), 313(37), 299(54), 285(17), 271(26), 257(21), 245(26), 243(20) ; ^{1}H NMR ($CDCl_3$) = see Table 1.
10. acetate (5): m.p. 119-123º ; $|\alpha|_D$ = +38º (c=0.50 $CHCl_3$); UV λ_{max}^{MeOH} nm= 231, 280 & 322 ; IR_{film} cm^{-1} = 2740, 1742, 1689, 1610, 1575, 1277, 1115; MS m/z (rel.int.)= M^+ 402 (95, $C_{23}H_{30}O_6$), 342 (100), 327(26), 313(44), 299(24), 285(11),273(10),271(12),257(13) ; ^{1}H NMR ($CDCl_3$) : see Table 1.
11. N. NAKATANI & R. INATANI, *Agricultural Biological Chemistry* 47, 353 (1983).
12. lactone (8): m.p. 143-145º ; $|\alpha|_D$= +40.2º(c=0.44 $CHCl_3$); UV λ_{max}^{MeOH}nm =232, 280 & 314;IR_{film} cm^{-1}=2740,1786,1686,1610,1570,1272,1109; MS m/z(rel.int.)= M^+ 358(100,$C_{21}H_{26}O_5$), 343(11), 340(4),330(15),329(11),313(8),301(21),297(20),...;^{1}H NMR($CDCl_3$): see Table 1.
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14. tosylate (11): m.p.118-120º; $|\alpha|_D$= +62.7º(c=0.30 $CHCl_3$); UV λ_{max}^{MeOH}nm= 231,284 & 322; IR_{film} cm^{-1}=2732,1686,1605,1570,1270.1112.1060,1010,966,853,805; MS m/z(rel.int.)= no mol. ion, 440(100),423(4),407(9),391(4),373(4),351(4),314(37),301(21),299(49);^{1}HNMR($CDCl_3$):Table 1.

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