

X-Ray Structure Determination of Methoxynepetaefolin and Nepetaefolinol, Labdane Diterpenoids from *Leonotis nepetaefolia* R.Br.¹

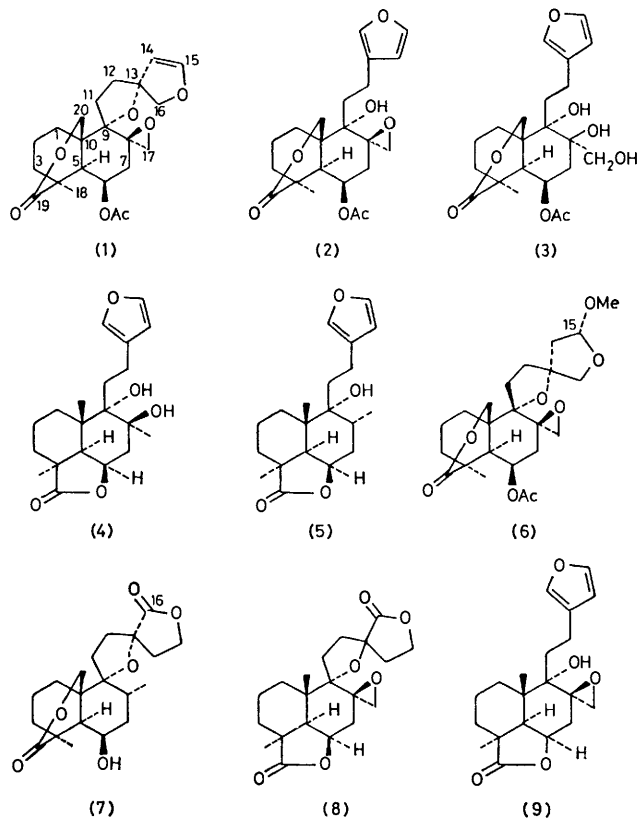
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The gross structures previously assigned to methoxynepetaefolin (6) and nepetaefolinol (7) have been confirmed by X-ray crystallography, which also defined the stereochemistry at C-13 as (*R*) in (6) and (*S*) in (7). Crystals of (6) are monoclinic, space group $P2_1$, with $a = 6.769(1)$, $b = 11.551(2)$, $c = 13.812(2)$, $\beta = 96.15(1)^\circ$, and $Z = 2$. Crystals of (7) are orthorhombic, space group $P2_12_12_1$ with $a = 8.910(2)$, $b = 10.520(1)$, $c = 19.527(2)$, and $Z = 4$. The structures were refined by least-squares to R 0.041 for (6) and 0.044 for (7).

Leonotis nepetaefolia R.Br. (Labiatae)^{2,3} is a widely distributed tropical plant whose leaves have been used in the treatment of a variety of diseases.³ Smoking of the dried leaves ('dagga') is also a common practice in certain parts of Africa.^{3,4} Although ethanol extracts of

diterpenes from this source included nepetaefuran (2),⁷ nepetaefuranol (3),⁷ and leonotin (4).⁶ The absolute stereochemistry of these substances follows from correlation of leonotin (4) with marrubiin (5),⁹ and correlation of the former with nepetaefolin.

In a further examination of the extract *L. nepetaefolia*, we encountered a minor constituent, methoxynepetaefolin, for which structure (6) was suggested,⁸ but without stereochemical assignments at C-13 and C-15. This structure was adduced from spectral evidence and was substantiated by the acid-catalysed conversion of (6) into a mixture containing (2) and (3). Our reason for placing the methoxy-group at C-15 rather than C-16, was based primarily on the ¹H n.m.r. spectrum which displayed a pair of doublets at δ 4.96 and 5.02 (J 6 and 3 Hz), which were attributed to the proton on C-15. An



L. nepetaefolia collected in Puerto Rico exhibited confirmed antitumour activity in the National Cancer Institute's Walker carcinoma 256 (intramuscular, WM) screening system,⁵ and despite extensive isolation studies on this species,⁶⁻⁸ the biologically active constituents of this plant have yet to be identified.

Extracts of the leaves of *L. nepetaefolia* collected in Trinidad have yielded a number of related labdane diterpenoids of which nepetaefolin (1), the major constituent, was shown by chemical⁷ and X-ray crystallographic studies⁵ to possess structure (1). Other

TABLE I
Crystal data and details of X-ray crystallographic analyses for (6) and (7)

Compound	(6)	(7)
Space group	$P2_1$	$P2_12_12_1$
	Monoclinic	Orthorhombic
$a/\text{\AA}$	6.769(1)	8.910(2)
$b/\text{\AA}$	11.551(2)	10.520(1)
$c/\text{\AA}$	13.812(2)	19.527(2)
$\beta/^\circ$	96.15(1)	
Z	2	4
$D_s/\text{g cm}^{-3}$	1.349	1.322
$\mu(\text{Cu-K}\alpha)/\text{cm}^{-1}$	8.5	8.1
Crystal size/mm	$0.64 \times 0.59 \times 0.12$	$0.50 \times 0.30 \times 0.20$
$\theta_{\text{max}}/^\circ$	57	57
Total reflectns.	1 546	1 436
Obs. reflectns.	1 525	1 348
Final R	0.041	0.044
Final R'	0.054	0.059
Final Δ map, largest peak/ \AA^{-3}	$< \pm 0.2$	$< \pm 0.2$

AB quartet at δ 3.53 and 3.78 (J 8 Hz) was ascribed to the protons on C-16.

Subsequent to our investigations in this area, Connolly and co-workers reported¹⁰ the isolation of three related diterpenes from *L. nepetaefolia* of Indian origin. These were: nepetaefolinol (7), the major component, dilactone (8), and leonotinin (expoxyleonotin, 9). The structures of these substances were based on cogent interpretation of various spectral and chemical data, but the stereochemistry at C-13 in (7) and in (8) was not determined. In nepetaefolinol (7) the substitution pattern formulated for rings A and B was similar to that in (1)–(3) and (6),

but the γ -lactone carbonyl was surprisingly placed at C-16 rather than at C-15 as would be expected by analogy with (6) and with another related labdane diterpene isolated from *L. leonurus*.¹¹

This surprising difference in the location of the oxygen

parameters, and bond lengths and angles are given in Tables 2–7. An attempt to establish the absolute stereochemistry of (6), based on the anomalous scattering of oxygen, failed. There was no significant difference in the weighted *R* values for the two antipodes of (6).

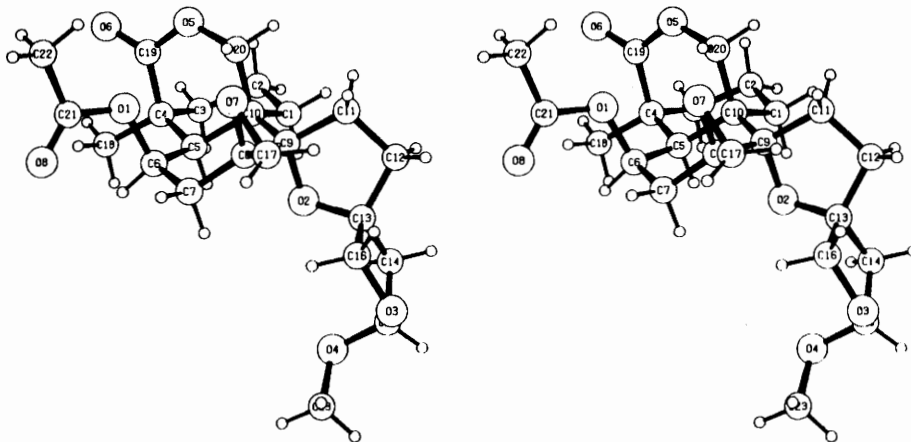


FIGURE 1 A stereoscopic drawing of methoxynepetaefolin (6)

functions, *i.e.* at C-15 in (6) and at C-16 in (7), prompted us to investigate the structures of these compounds by X-ray crystallography. In addition, although the number of diterpenes possessing the 9,13-oxy-bridge has increased rapidly in recent years,¹² in only four cases (nepetaefolin, lasiocoryin,^{12, 13} lagochilin,^{12, 14} and

The stereochemistry at C-13 in (6) is the same as that found in nepetaefolin (1) and prerotundifuran,¹⁵ whereas that for nepetaefolinol (7) is as reported for lasiocoryin^{12, 13} and lagochilin.^{12, 14}

It has been demonstrated that the prefuranoid diterpenoids nepetaefolin⁷ and premarrubiin¹⁶ are readily

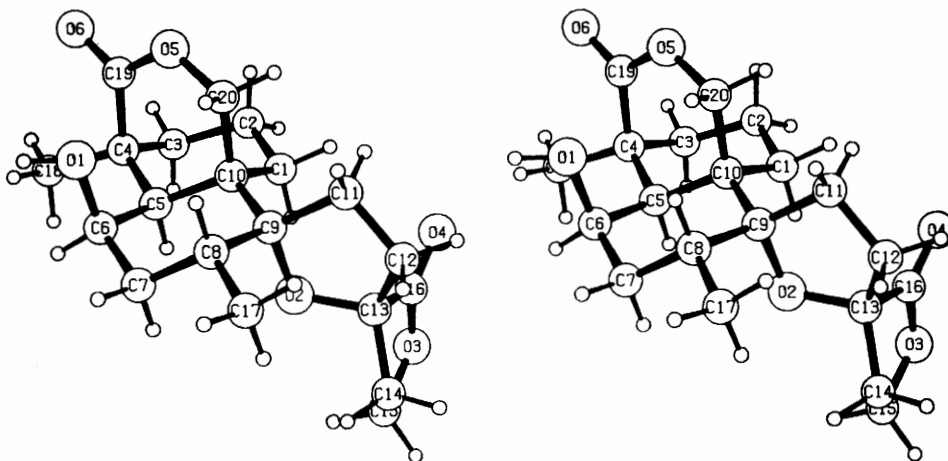


FIGURE 2 A stereoscopic drawing of nepetaefolinol (7)

prerotundifuran¹⁵) has the stereochemistry at C-13 been established unambiguously.

As a result of X-ray crystallographic studies, using direct methods, we have confirmed the gross structures originally suggested for methoxynepetaefolin (6) and nepetaefolinol (7), and have defined the stereochemistry at C-13 in these compounds as (*R*) and (*S*), respectively. Stereoscopic drawings of (6) and (7) as determined from the X-ray crystallographic analyses are depicted in Figures 1 and 2. Details of the crystal data and experimental results are given in Table 1, and final atomic

converted into nepetaefuran (2) and marrubiin (5), respectively. However, the biogenetic processes leading to the dihydrofuran moiety and the 9,13-oxy-bridge in the former substances are not known. McCrindle has suggested¹⁶ (see Scheme 1) that the 9,13-oxy-bridge is formed *via* Michael addition of a 9 α -hydroxy-group to an α,β -unsaturated aldehyde (*D* \rightarrow *E*), and that subsequently a derived hemiacetal undergoes elimination to the dihydrofuran moiety (*E* \rightarrow *F*).

McCrindle's proposal readily accommodates structures such as nepetaefolin and methoxynepetaefolin, but not

TABLE 2

Final atom parameters for (6), with standard deviations in parentheses

Atom	X	Y	Z
O(1)	0.0482(4)	0.9509	0.2167(2)
O(2)	0.2052(3)	0.5721(3)	0.2572(2)
O(3)	0.1630(4)	0.3296(3)	0.1090(2)
O(4)	0.4811(4)	0.4067(4)	0.1198(2)
O(5)	0.0276(4)	0.9258(3)	0.4261(2)
O(6)	0.1990(5)	1.0853(4)	0.4243(2)
O(7)	-0.2441(4)	0.7506(3)	0.1880(2)
O(8)	0.1138(6)	1.0425(4)	0.0813(2)
C(1)	0.2689(6)	0.6808(4)	0.4394(3)
C(2)	0.3614(6)	0.7705(4)	0.5114(3)
C(3)	0.4764(6)	0.8614(5)	0.4611(3)
C(4)	0.3592(5)	0.9150(4)	0.3692(3)
C(5)	0.2798(5)	0.8175(4)	0.2997(3)
C(6)	0.1937(6)	0.8624(4)	0.1997(3)
C(7)	0.0949(6)	0.7682(4)	0.1362(3)
C(8)	-0.0491(6)	0.6980(4)	0.1860(3)
C(9)	0.0440(5)	0.6434(4)	0.2823(2)
C(10)	0.1417(5)	0.7380(4)	0.2526(2)
C(11)	-0.0969(6)	0.5608(5)	0.3293(3)
C(12)	-0.0117(7)	0.4407(5)	0.3186(3)
C(13)	0.1410(6)	0.4536(4)	0.2444(3)
C(14)	0.3197(6)	0.3731(5)	0.2614(3)
C(15)	0.3523(6)	0.3302(4)	0.1616(3)
C(16)	0.0618(7)	0.4297(5)	0.1388(3)
C(17)	-0.2231(6)	0.6494(5)	0.1290(3)
C(18)	0.4969(6)	0.9966(5)	0.3213(3)
C(19)	0.1897(6)	0.9833(4)	0.4051(3)
C(20)	-0.0244(5)	0.8102(4)	0.3889(3)
C(21)	0.0217(7)	1.0359(4)	0.1497(3)
C(22)	-0.1342(8)	1.1171(5)	0.1732(5)
C(23)	0.5079(8)	0.3805(7)	0.0218(3)
H(1)A	0.181	0.628	0.474
H(1)B	0.376	0.634	0.414
H(2)A	0.252	0.811	0.543
H(2)B	0.450	0.731	0.564
H(3)A	0.602	0.823	0.443
H(3)B	0.519	0.924	0.511
H(5)	0.399	0.769	0.289
H(6)	0.305	0.899	0.167
H(7)A	0.026	0.803	0.076
H(7)B	0.202	0.714	0.117
H(11)A	-0.102	0.580	0.400
H(11)B	-0.236	0.565	0.295
H(12)A	-0.120	0.386	0.295
H(12)B	0.054	0.414	0.383
H(14)A	0.443	0.418	0.290
H(14)B	0.299	0.308	0.306
H(15)	0.411	0.205	0.166
H(16)A	-0.086	0.416	0.132
H(16)B	0.088	0.498	0.097
H(17)A	-0.242	0.658	0.057
H(17)B	-0.280	0.574	0.149
H(18)A	0.419	1.035	0.263
H(18)B	0.610	0.954	0.300
H(18)C	0.546	1.060	0.369
H(20)A	-0.131	0.818	0.333
H(20)B	-0.077	0.765	0.443
H(22)A	-0.074	1.181	0.216
H(22)B	-0.236	1.075	0.210
H(22)C	-0.205	1.152	0.113
H(23)A	0.601	0.438	-0.004
H(23)B	0.378	0.382	-0.020
H(23)C	0.568	0.301	0.018

TABLE 3
Bond lengths (Å) in (6)

O(1)-C(6)	1.456	C(4)-C(5)	1.539
O(1)-C(21)	1.347	C(4)-C(18)	1.526
O(2)-C(9)	1.439	C(4)-C(19)	1.518
O(2)-C(13)	1.442	C(5)-C(6)	1.532
O(3)-C(15)	1.404	C(5)-C(10)	1.548
O(3)-C(16)	1.426	C(6)-C(7)	1.508
O(4)-C(15)	1.407	C(7)-C(8)	1.492
O(4)-C(23)	1.418	C(8)-C(9)	1.545
O(5)-C(19)	1.340	C(8)-C(17)	1.457
O(5)-C(20)	1.460	C(9)-C(10)	1.562
O(6)-C(19)	1.208	C(9)-C(11)	1.541
O(7)-C(8)	1.456	C(10)-C(20)	1.527
O(7)-C(17)	1.440	C(11)-C(12)	1.515
O(8)-C(21)	1.189	C(12)-C(13)	1.539
C(1)-C(2)	1.524	C(13)-C(14)	1.524
C(1)-C(10)	1.547	C(13)-C(16)	1.524
C(2)-C(3)	1.519	C(14)-C(15)	1.503
C(3)-C(4)	1.552	C(21)-C(22)	1.473

Estimated standard deviation for a typical C-C bond length 0.010 Å.

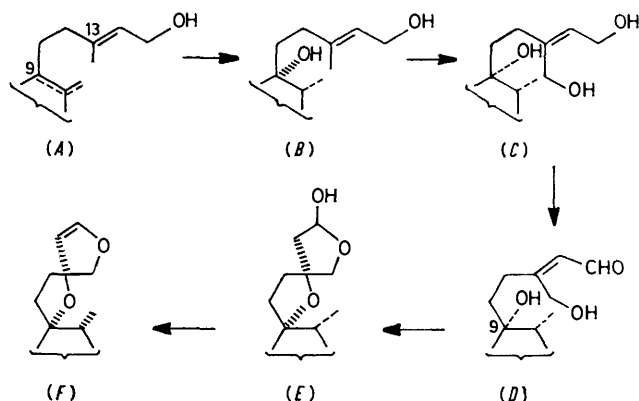


TABLE 4

Bond angles (°) in (6)

C(6)-O(1)-C(21)	116.3	C(8)-C(9)-C(10)	110.9
C(9)-O(2)-C(13)	110.3	C(8)-C(9)-C(11)	113.7
C(15)-O(3)-C(16)	106.7	C(10)-C(9)-C(11)	114.3
C(15)-O(4)-C(23)	114.0	C(1)-C(10)-C(5)	107.7
C(19)-O(5)-C(20)	123.3	C(1)-C(10)-C(9)	110.3
C(8)-O(7)-C(17)	60.4	C(1)-C(10)-C(20)	110.3
C(2)-C(1)-C(10)	111.8	C(5)-C(10)-C(9)	111.0
C(1)-C(2)-C(3)	111.5	C(5)-C(10)-C(20)	109.5
C(2)-C(3)-C(4)	114.0	C(9)-C(10)-C(20)	108.0
C(3)-C(4)-C(5)	109.4	C(9)-C(11)-C(12)	105.4
C(3)-C(4)-C(18)	108.6	C(11)-C(12)-C(13)	105.4
C(3)-C(4)-C(19)	106.2	O(2)-C(13)-C(12)	103.1
C(5)-C(4)-C(18)	111.7	O(2)-C(13)-C(14)	109.7
C(5)-C(4)-C(19)	111.0	O(2)-C(13)-C(16)	111.1
C(18)-C(4)-C(19)	109.8	C(12)-C(13)-C(14)	114.7
C(4)-C(5)-C(6)	112.9	C(12)-C(13)-C(16)	115.3
C(4)-C(5)-C(10)	109.1	C(14)-C(13)-C(16)	103.2
C(6)-C(5)-C(10)	115.9	C(13)-C(14)-C(15)	104.6
O(1)-C(6)-C(5)	106.9	O(3)-C(15)-O(4)	111.2
O(1)-C(6)-C(7)	109.5	O(3)-C(15)-C(14)	105.1
C(5)-C(6)-C(7)	112.5	O(4)-C(15)-C(14)	109.1
C(6)-C(7)-C(8)	113.3	O(3)-C(16)-C(13)	107.0
O(7)-C(8)-C(7)	114.9	O(7)-C(8)-C(8)	60.3
O(7)-C(8)-C(9)	116.2	O(5)-C(19)-O(6)	117.4
O(7)-C(8)-C(17)	59.3	O(5)-C(19)-C(4)	118.5
C(7)-C(8)-C(9)	113.1	O(6)-C(19)-C(4)	123.7
C(7)-C(8)-C(17)	119.4	O(5)-C(20)-C(10)	117.2
C(9)-C(8)-C(17)	122.6	O(1)-C(21)-O(8)	123.4
O(2)-C(9)-C(8)	106.0	O(1)-C(21)-C(22)	111.0
O(2)-C(9)-C(10)	105.6	O(8)-C(21)-C(22)	125.6
O(2)-C(9)-C(11)	105.5		

Estimated standard deviation for a typical C-C-C bond angle 0.7°.

TABLE 5

Final atom parameters for (7), with standard deviations in parentheses

Atom	X	Y	Z
O(1)	-0.0074(4)	0.5765(3)	0.0536(2)
O(2)	0.2325(3)	0.2298(3)	0.1473(1)
O(3)	0.5034(4)	0.0587(3)	0.1765(2)
O(4)	0.5282(4)	0.2307(3)	0.2409(2)
O(5)	0.2481(4)	0.6977(3)	0.1191(2)
O(6)	0.2819(4)	0.7989(3)	0.0240(2)
C(1)	0.4302(5)	0.4367(4)	0.1349(2)
C(2)	0.5243(5)	0.5364(5)	0.0988(3)
C(3)	0.4787(6)	0.5508(5)	0.0242(3)
C(4)	0.3076(5)	0.5724(4)	0.0163(2)
C(5)	0.2245(5)	0.4606(4)	0.0495(2)
C(6)	0.0565(6)	0.4576(5)	0.0321(2)
C(7)	-0.0165(5)	0.3469(5)	0.0670(3)
C(8)	0.0003(5)	0.3531(4)	0.1445(2)
C(9)	0.1693(5)	0.3525(4)	0.1656(2)
C(10)	0.2579(5)	0.4574(4)	0.1268(2)
C(11)	0.1883(5)	0.3604(4)	0.2445(2)
C(12)	0.2037(6)	0.2234(5)	0.2680(2)
C(13)	0.2769(5)	0.1572(4)	0.2067(2)
C(14)	0.2474(6)	0.0178(4)	0.1944(3)
C(15)	0.3807(6)	-0.0206(4)	0.1521(3)
C(16)	0.4470(5)	0.1582(4)	0.2111(2)
C(17)	-0.0950(5)	0.2498(5)	0.1790(3)
C(18)	0.2714(8)	0.5877(6)	-0.0598(2)
C(19)	0.2748(6)	0.6970(4)	0.0519(3)
C(20)	0.2161(5)	0.5860(4)	0.1590(2)
HO(1)	-0.075	0.605	0.022
H(1)A	0.454	0.441	0.187
H(1)B	0.459	0.350	0.119
H(2)A	0.633	0.508	0.101
H(2)B	0.514	0.618	0.123
H(3)A	0.533	0.628	0.004
H(3)B	0.511	0.475	-0.004
H(5)	0.272	0.382	0.030
H(6)	0.050	0.444	-0.019
H(7)A	0.030	0.267	0.051
H(7)B	-0.124	0.351	0.054
H(8)	-0.047	0.436	0.161
H(11)A	0.276	0.412	0.258
H(11)B	0.094	0.399	0.267
H(12)A	0.270	0.218	0.310
H(12)B	0.104	0.184	0.280
H(14)A	0.150	0.006	0.169
H(14)B	0.241	-0.031	0.238
H(15)A	0.404	-0.116	0.159
H(15)B	0.363	-0.008	0.102
H(17)A	-0.053	0.166	0.166
H(17)B	-0.201	0.257	0.165
H(17)C	-0.088	0.261	0.231
H(18)A	0.158	0.596	-0.065
H(18)B	0.296	0.501	-0.084
H(18)C	0.325	0.654	-0.081
H(20)A	0.105	0.584	0.169
H(20)B	0.270	0.592	0.204

TABLE 6

Bond lengths (Å) in (7)

O(1)-C(6)	1.437	C(4)-C(19)	1.513
O(2)-C(9)	1.453	C(5)-C(6)	1.536
O(2)-C(13)	1.445	C(5)-C(10)	1.538
O(3)-C(15)	1.456	C(6)-C(7)	1.498
O(3)-C(16)	1.343	C(7)-C(8)	1.523
O(4)-C(16)	1.201	C(8)-C(9)	1.561
O(5)-C(19)	1.332	C(8)-C(17)	1.534
O(5)-C(20)	1.439	C(9)-C(10)	1.554
O(6)-C(19)	1.204	C(9)-C(11)	1.552
C(1)-C(2)	1.516	C(10)-C(20)	1.538
C(1)-C(10)	1.558	C(11)-C(12)	1.519
C(2)-C(3)	1.520	C(12)-C(13)	1.531
C(3)-C(4)	1.548	C(13)-C(14)	1.509
C(4)-C(5)	1.533	C(13)-C(16)	1.519
C(4)-C(18)	1.531	C(14)-C(15)	1.502

Estimated standard deviation for a typical C-C bond length 0.007 Å.

TABLE 7

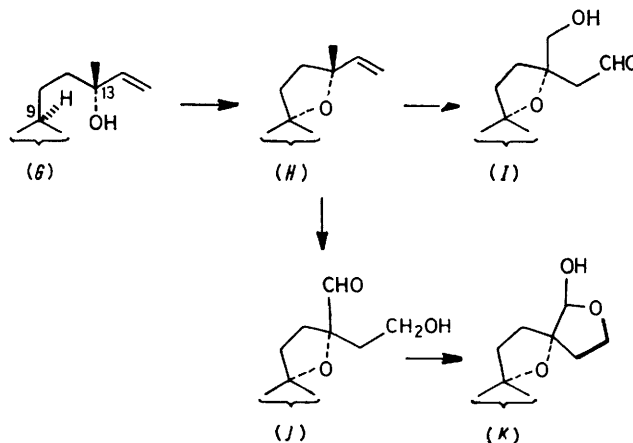
Bond angles (°) in (7)

C(9)-O(2)-C(13)	112.2	C(8)-C(9)-C(11)	111.5
C(15)-O(3)-C(16)	109.3	C(10)-C(9)-C(11)	113.0
C(19)-O(5)-C(20)	124.3	C(1)-C(10)-C(5)	107.0
C(2)-C(1)-C(10)	113.7	C(1)-C(10)-C(9)	110.6
C(1)-C(2)-C(3)	111.5	C(1)-C(10)-C(20)	108.6
C(2)-C(3)-C(4)	111.9	C(5)-C(10)-C(9)	113.3
C(3)-C(4)-C(5)	108.8	C(5)-C(10)-C(20)	109.5
C(3)-C(4)-C(18)	108.6	C(9)-C(10)-C(20)	107.6
C(3)-C(4)-C(19)	105.8	C(9)-C(11)-C(12)	105.0
C(5)-C(4)-C(18)	112.9	C(11)-C(12)-C(13)	103.5
C(5)-C(4)-C(19)	112.1	O(2)-C(13)-C(12)	105.7
C(18)-C(4)-C(19)	108.3	O(2)-C(13)-C(14)	109.7
C(4)-C(5)-C(6)	113.1	O(2)-C(13)-C(16)	108.3
C(4)-C(5)-C(10)	109.8	C(12)-C(13)-C(14)	119.6
C(6)-C(5)-C(10)	114.0	C(12)-C(13)-C(16)	112.2
O(1)-C(6)-C(5)	107.6	C(14)-C(13)-C(16)	100.9
O(1)-C(6)-C(7)	111.8	C(13)-C(14)-C(15)	102.2
C(5)-C(6)-C(7)	109.8	O(3)-C(15)-C(14)	105.1
C(6)-C(7)-C(8)	112.1	O(3)-C(16)-O(4)	120.9
C(7)-C(8)-C(9)	110.9	O(3)-C(16)-C(13)	109.9
C(7)-C(8)-C(17)	110.5	O(4)-C(16)-C(13)	129.2
C(9)-C(8)-C(17)	114.5	O(5)-C(19)-O(6)	116.7
O(2)-C(9)-C(8)	108.2	O(5)-C(19)-C(4)	119.4
O(2)-C(9)-C(10)	108.3	O(6)-C(19)-C(4)	123.6
O(2)-C(9)-C(11)	104.5	O(5)-C(20)-C(10)	116.7
C(8)-C(9)-C(10)	111.0		

Estimated standard deviation for a typical C-C-C bond angle 0.5°.

that of nepetaefolinol. An alternative pathway (see Scheme 2), based on the recent observation¹⁷ that oxidation of manool with a mixture of SeO₂ and H₂O₂ effects formation of the 9,13-oxy-bridge, has been discussed elsewhere.¹⁸ In Scheme 2 the 13-OH group present in the labdanoid precursor (*G*) is apparently incorporated stereospecifically into the 9,13-ether linkage present in (*H*). The latter may be transformed either into (*I*), which would give acetal (*E*) of Scheme 1, or into (*J*), which would give acetal (*K*). Oxidation of (*K*) would give the γ -lactone moiety present in nepetaefolinol.

Although we were unable to detect nepetaefolinol in our extract, albeit an old one, we were able to isolate crystalline leonotinin (*9*). The latter substance was also isolated by Zelnik¹⁹ from Brazilian *L. nepetaefolia*. Since a direct comparison of Indian and West Indian *L. nepetaefolia* has not been performed, we cannot yet assess the taxonomic significance of the variation in the diterpenoid content of this plant.



SCHEME 2

EXPERIMENTAL

M.p.s were determined in capillaries and are uncorrected. I.r. and ^1H n.m.r. (100 MHz) spectra were determined in chloroform and deuteriochloroform, respectively. Chemical shifts are expressed in p.p.m. from tetramethylsilane and coupling constants J in Hz. Mass spectra were recorded at 70 eV; m/e values are given with relative intensities in parentheses. Thin-layer chromatography (t.l.c.) was carried out on silica gel (Pfl₂₅₄, Merck) plates and spots were made visible by spraying the plates with 10% ceric sulfate in 10% H_2SO_4 followed by heating to ca. 120 °C.

Isolation of Methoxynepetaefolin (6).—An acetone extract (20.3 g)⁷ of *Leonitis nepetaefolia* R.Br. (Labiatae) was crystallized from ethanol to give nepetaefolin (1) (1.74 g). The filtrate was evaporated and a portion (5 g) of the residue, which contained nepetaefolin (1), nepetaefuran (2), leonotin (4), and (6), was chromatographed on 100 g of neutral alumina (Grade II) with 40% ethyl acetate in hexane as eluant. The progress of the separation was monitored by t.l.c. (50% ethyl acetate in benzene): (4) had R_F 0.75, (2) 0.56, (1) 0.50, and (6) 0.41. Fractions containing (6) were combined and crystallized from ethyl acetate–hexane to give 41 mg of (6), m.p. 275–278 °C; $[\alpha]_D^{25}$ –35.8 (c 1.2 CHCl_3); ν_{max} 1737 (OAc), 1725 (δ -lactone), and 1031 (OMe); δ 1.16 (3 H, s, CH_3 -4), 2.02 (3 H, s, OCOCH_3), 3.38 (3 H, s, OCH_3), 2.30 and 2.62 (2 H, q, J 3.5, CH_2 -17), 3.53 and 3.78 (2 H, q, J 8, CH_2 -16), 4.00 and 5.10 (2 H, q, J 11, CH_2 -20), and 4.96 and 5.02 (1 H, d of d, J 6 and 3, CH-15); m/e 436.1985 (M^+ 0.1), 405 (35, M^+ –OMe), 376 (100, M^+ – $\text{CH}_3\text{-CO}_2\text{H}$), and 361 (30, M^+ – $\text{CH}_3\text{-CO}_2\text{-H} - \text{CH}_3$).

Conversion of (6) into (2).—A solution of (6) (15 mg) in methanol (10 ml) was cooled to 5 °C and treated with 2% H_2SO_4 (10 ml) in methanol (v/v). The mixture was stirred at room temperature for 3.5 h, diluted with water (35 ml) and extracted with ethyl acetate (2 × 35 ml). The extract was washed with saturated brine, dried (MgSO_4), and evaporated to give a gum, which was shown by t.l.c. (55% ethyl acetate in benzene) to consist of nepetaefuran, R_F 0.58, isonepetaefuran,⁷ R_F 0.50, and nepetaefuranol, R_F 0.31. Preparative-scale t.l.c. (50% benzene in ethyl acetate; for the purpose of visualization a strip of the plate was sprayed with ceric sulphate) afforded, after extraction into ethyl acetate, 12 mg of (2), m.p. 237–241 °C, identical with an authentic sample (mixed m.p., mixed t.l.c., m.s.).

Isolation of Leonotin (9).—Chromatography of *L. nepetaefolia* extract⁷ (10 g) with 25% ethyl acetate in benzene gave a fraction (3 g) whose t.l.c. (55% ethyl acetate in benzene) revealed (4) (R_F 0.60), (2) (R_F 0.58), (9) (R_F 0.50), and nepetaefolin (R_F 0.41). This fraction was dissolved in methanol (30 ml) and the mixture stirred at room temperature for 5 h and filtered to give nepetaefolin (300 mg). The filtrate was then left at 0 °C overnight and crude (9) (428 mg) was collected by filtration. Repeated crystallizations from dichloromethane–ether gave 214 mg of (9), m.p. 190–192 °C; $[\alpha]_D^{25}$ +62° (c 2.0 CHCl_3); ν_{max} 3560, 1770, 1025, and 875 cm^{-1} ; δ 1.06 (3 H, s, CH_3 -20), 1.27 (3 H, s, CH_3 -18), 2.44 and 2.95 (2 H, q, J 4 Hz CH_2 -17), 4.90 (1 H, m, H-6), 6.27 (1 H, br s, H-14), 7.22 (1 H, s, H-16), and 7.33 (1 H, br s, H-15); m/e 346 (M^+ , 9), base peak at m/e 109 (Found: C, 69.50; H, 7.77). Calc. for $\text{C}_{20}\text{H}_{26}\text{O}_5$: C, 69.35; H, 7.50%.

X-Ray Crystallography.—Crystallographic data for (6) and (7) were collected on a fully-automated Hilger-Watts diffractometer ($\text{Cu-K}\alpha$ radiation, θ –2 θ scans, pulse-height

discriminations, no absorption corrections applied), and are summarized in Table 1. Final atom parameters, and bond lengths and angles are given in Tables 2–7. The structure and relative stereochemistry of (6) and (7) were solved by a multiple-solution procedure²⁰ and refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms and isotropic factors for hydrogen atoms. Hydrogen atoms were included in the structure-factor calculation but their parameters were not refined. Observed and calculated structure factors and atom thermal parameters for (6) and (7) are listed in Supplementary Publication No. SUP 22589 (13 pp.).*

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* For details of Supplementary Publication, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1979, Index issue.

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