172. ^{13}C-NMR. Spectroscopy of Naturally Occurring Substances. XXXII. Vincaleucoblastine and Related Alkaloids[1])

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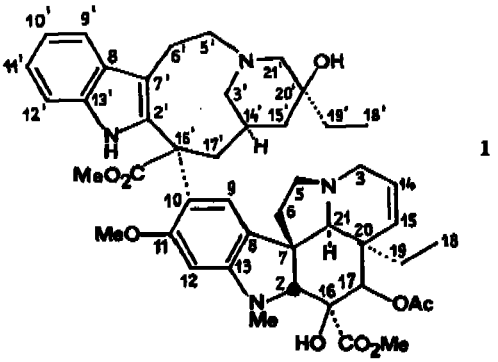
Summary. The total assignment of the ^{13}C-shifts of the complex *Vinca rosea* L. alkaloids vincaleucoblastine, leurosidine and leurosine and of a synthetic isomer of the latter is presented. The structure of leurosidine is corrected and a tentative structure for the acid-catalyzed product of isomerization of leurosine is proposed.

A recent ^{13}C-NMR. spectral analysis of *Aspidosperma* alkaloids [2] included a discussion of vindoline, which not only is a natural base but also represents one half of the complex structures of indole-indoline alkaloids, viz. vincaleucoblastine (VLB), (**1**), leurosidine (**2**) [3] and leurosine (**3**). As a consequence the carbon shifts of the vindoline portion (*i.e.* the indoline portion) of the 'dimeric' alkaloids **1** and **3** were assigned fully, while the velbanamine portion (*i.e.* the indole portion) was described only in terms of the shifts of the indole ring, the methyl group and the non-protonated carbons. The ^{13}C-NMR. analysis of the methylenes and methines of the indole half



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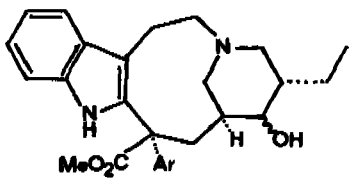

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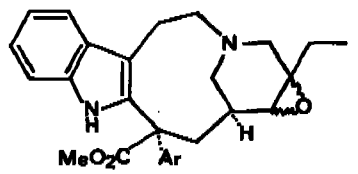

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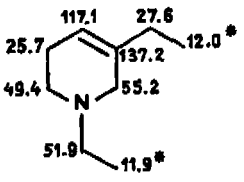
Ar = 10-vindolyl

[1]) For part XXXI see [1].

of these substances had to await higher resolution of the spectra and the acquisition of proper models. The following discussion presents new data which permit complete shift assignment of VLB (**1**) and leurosine (**3**) and correction of the structure **2** for leurosidine.

The piperidine derivatives **5** and **6** were needed for the study and were prepared in the following manner. N-Ethylation of β-ethylpyridine and sodium borohydride reduction of the resultant ethiodide yielded 1,3-diethyl-3-piperideine (**4**). Epoxidation of the perchlorate salt of the latter gave oxide **6**, whose reduction with lithium aluminum hydride afforded 1,3-diethyl-3-piperidinol (**5**), also prepared by the treatment of 1-ethyl-3-piperidone with ethylmagnesium iodide. The proton noise decoupled and single-frequency, off-resonance decoupled (sford) spectra of compounds **4**, **5** and **6**, 1-ethylcyclohexanol (**7**) and 1-ethyl-1,2-oxidocyclohexane (**8**) were recorded. The carbon shifts are denoted on the formulas. The shift assignment of alcohol **7** is based on the expected shift perturbation of ethylcyclohexane [4] on introduction of an axial hydroxy group. The δ values of piperidinol **5** depend on the shifts of alkylpiperidines [5] and the shift parameters evaluated for **7**. The signal allotment of oxide **8** follows from the known shifts of cyclohexene oxide [6] and the shift designation of **6** relies on the shifts of **5** and the shift differences noted between **7** and **8**.



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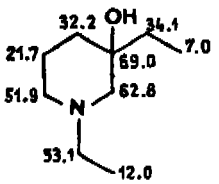

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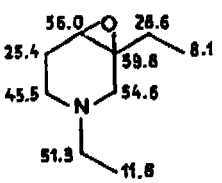

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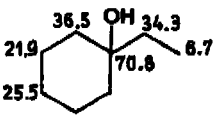

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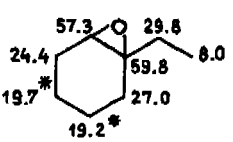

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The earlier ^{13}C-NMR. spectra of VLB (**1**) [2] had exhibited an extraordinary difference of signal clarity between the methylenes and tetrahedral methines of the vindoline half and those of the velbanamine portion of the alkaloid. Thus, while the vindoline lines were sharp, the velbanamine signals were broad and on occasion so diffuse as to prevent their recognition. The difficulty associated with line broadening, presumably due mainly to the conformational flexibility of the large ring in the velbanamine unit and the proximity of the coalescence temperature of the conformer interchanges to that of the ^{13}C-NMR. experiments, was overcome in part by the acquisition of spectra at higher field strength, at 0.10 M concentration and at 33–38°[2]). With all the chemical shifts of VLB (**1**) thus in hand, it is possible to allocate the heretofore ambiguous methylene and methine resonances of the velbanamine unit

[2]) It is difficult to attain perfect conditions since VLB is quite insoluble at low temperatures and decomposes at elevated temperatures.

of the alkaloid[3]). The methine, C(14'), is unique. While C(21') is predictably the most deshielded aminomethylene, differentiation of the remaining aminomethylenes, C(3') and C(5'), rests on the shift data of monomeric, velbanamine-like alkaloids [7]. The C(6') shift is distinguished from the δ values of the other three methylenes by the greater residual coupling exhibited in a sford spectrum in which the decoupler was placed at the upfield end of the proton envelope [8]. The C(15'), responding to many β-effects with few mitigating γ-effects, is expected to be the farthest downfield methylene. The remaining two methylenes, C(17') and C(19'), possess identical chemical shifts. All δ values of VLB (**1**) are listed in the Table.

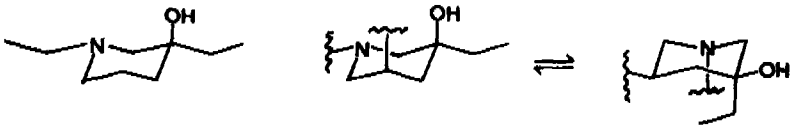
Table. *^{13}C-Chemical Shifts*[a])

	1[b])	**11**	**3**	**17**		**1**[b])	**11**	**3**	**17**
C(2)	83.0	83.1	83.1	83.3	C(2')	130.9	130.2	130.7	132.1[f])
C(3)	50.0	50.2	50.2	50.4[c])	C(3')	47.5	43.9	42.3	
C(5)	50.0	50.2	50.2	50.6[c])	C(5')	55.5	53.9[d])	49.6	
C(6)	44.3	44.5	44.5	43.5	C(6')	28.7	21.4	24.6	
C(7)	52.9	53.1	53.1	52.6	C(7')	115.9	116.8	116.7	108.9
C(8)	122.6	123.0	123.0	124.0	C(8')	129.0	128.9	129.1	128.7
C(9)	123.1	123.4	123.4	122.9	C(9')	118.1	117.9	118.1	117.2
C(10)	120.4	120.4	120.4	118.9	C(10')	122.2	122.0	122.2	121.2
C(11)	157.8	157.6	157.6	157.7	C(11')	118.8	118.6	118.4	118.9
C(12)	93.9	94.0	94.0	92.9	C(12')	110.2	110.2	110.3	110.2
C(13)	152.5	152.8	152.8	153.3	C(13')	134.7	134.5	134.6	134.4
C(14)	124.3	124.3	124.3	124.0	C(14')	29.2	29.8	33.5	
C(15)	129.7	129.7	129.7	129.8	C(15')	40.0	40.4[e])	60.3	
C(16)	79.3	79.5	79.5	79.3	C(16')	55.3	55.4	55.3	133.1[f])
C(17)	76.1	76.2	76.2	76.2	C(17')	34.1	35.1[e])	30.7	142.2
C(18)	8.1	8.3	8.3	6.8	C(18')	6.7	7.1	8.6	6.8
C(19)	30.4	30.7	30.7	30.5	C(19')	34.1	38.5[e])	28.0	
C(20)	42.3	42.6	42.6	42.5	C(20')	68.6	71.8	59.9	73.9
C(21)	65.2	65.5	65.5	66.3	C(21')	63.1	55.5[d])	54.0	
C=O	170.6	170.7	170.7	170.5	C=O	174.6	173.9	174.1	169.0
OMe	51.8	51.9	52.1	51.7	OMe	52.0	52.1	52.3	52.0
Ac C=O	171.4	171.4	171.4	171.5					
Ac Me	20.7	21.0	21.0	20.9					
Ar OMe	55.3	55.7	55.7	55.6					
NMe	38.0	38.2	38.2	38.1					

[a]) In parts per million downfield from TMS; δ(TMS) = δ($CDCl_3$) + 76.9 ppm. [b]) Several δ values differ from and supersede those recorded in the publication cited in [2]. [c]) [d]) [e]) [f]) Signals may be interchanged.

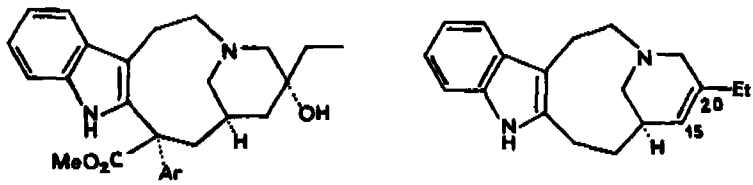
While the velbanamine model **5** possesses conformation **9**, the piperidine ring of the velbanamine half of VLB (**1**) can be represented in principle by conformations **10a** and/or **10b**. The lower basicity of the piperidino nitrogen in VLB (**1**) as compared to the same site in other indole-indoline alkaloids has been considered to reflect intramolecular hydrogen bonding with the HO–C(20') group [3], a phenomenon possible only in conformation **10a**. The close correspondence of the shifts of C(18'), C(19'), C(20') and C(21') of VLB (**1**) and those of like carbons of piperidinol **5** substantiates the strong preponderance of conformation **10a** for the alkaloid.

[3]) The δ values of C(3') and C(15') vary as much as up to 1 ppm under different experimental conditions.



9 **10a** **10b**

In contrast to the ^{13}C-NMR. spectra of VLB (**1**) those of leurosidine (**2**) exhibited no linewidth difference between the signals of its vindoline portion and of its other half. Hence it was possible to recognize unambiguously the multiplicities of all forty-six carbon atoms and their identity with those of VLB, thus making formula **2** untenable. The shifts of all vindoline carbon atoms, the indole moiety and C(16′) and its attached methoxycarbonyl group are nearly identical in leurosidine and VLB (**1**). In view of the presence of a non-protonated oxycarbon atom with shift characteristics similar to those of the equivalent centers in models **5** and **7** as well as in VLB (**1**) and in light of the similarity of the methyl shift of the ethyl group with that in **1**, **5** and **7** leurosidine is the 20′-epimer of VLB (**1**), *i.e.* **11** (*cf.* the Table), a fact substantiated recently by the epimerization of VLB (**1**) into leurosidine **11** [9]. It is noteworthy that the lack of close correspondence of the methylene shifts of the vinrosamine (non-vindoline) portion of leurosidine **11** with those of VLB (**1**) precludes identity of the piperidine conformation in the two alkaloids. As a consequence the methylene shift assignment can be considered to be only tentative except for the identification of C(6′) by the means used for this carbon in VLB (**1**) (*vide supra*) and for the differentiation of aminomethylenes from the remaining methylene pool by the same technique.

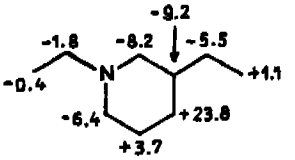


11, Ar = 10-vindolyl **12**

Previous chemical and spectral investigations of leurosine (**3**) have shown the alkaloid to be a dehydro-VLB ether [10], a fact confirmed by the afore-mentioned, partial ^{13}C-NMR. analysis [2]. The formation of cleavamine **12** by a reductive, hydrolytic cleavage of the natural base and the liberation of 15,20-dihydrocleavamine by *Raney*-nickel-reduction of the alkaloid followed by hydrolytic scission [10] indicated that the other oxide terminus besides C(20′) had to be an easily reducible site, requiring the incorporation of a carbinol amine ether, benzyl ether or epoxide unit. The latter functional group was advanced on the basis of the product of the treatment of leurosine (**3**) with acetic acid having been assumed to be a vicinal hydroxy acetate [11]. In the earlier ^{13}C-NMR. study [2] the oxycarbon shift, anomalously upfield of the C(20′) resonance of VLB, was attributed to C(20′) of leurosine (**3**) being part of a small, strained ring system. The present reinvestigation of the ^{13}C-NMR. spectra of the alkaloid showed the remaining oxycarbon to be a methine at 60.3 ppm, an extraordinarily high-field, oxymethine position and hence interpretable only in terms of the oxycarbon being part of an epoxide unit. The latter is confirmed by the

C(15')–H(15') coupling constant of 170 ± 5 Hz[4]), a J value at least 15 Hz greater than the constants for larger cyclic ethers [4] and compatible with $^1J_{C\text{-}H} = 172 \pm 3$ Hz for aliphatic epoxides [4].

The assignment of the as yet undesignated carbon shifts of leurosine (**3**) (*cf.* the Table) is based on the VLB (**1**) shifts and the shift perturbation evaluated from the shift difference of models **5** and **6**. The amazing similarity of the $\Delta\delta$(**6**–**5**) and $\Delta\delta$(**3**–**1**) values, depicted on formulas **13** and **14**, respectively, indicates an equal disposition of the substituent on the piperidino nitrogen in the models and the alkaloids. Since the N-ethyl group of the models must be equatorial, C(5') of leurosine (**3**) has a similar orientation.



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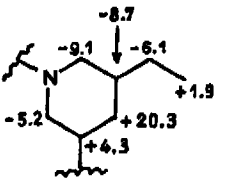

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Repetition of the afore-mentioned treatment of leurosine (**3**) with acetic acid [11] or, more efficiently, short treatment of the alkaloid with sulfuric acid yielded as major product a substance isomeric with leurosine (**3**). The ^{13}C-NMR. spectra of the new compound show the vindoline portion to have remained intact (*cf.* **17** in the Table). A low-frequency carbonyl absorption band and a high-intensity, low-wavelength maximum in the IR. and UV. spectra, respectively, absent from the spectra of leurosine (**3**), reveal the presence of an acrylic ester unit. This chromophore is verified by the high-field ester carbonyl resonance in the ^{13}C-NMR. spectra and the appearance of two new, olefinic signals characteristic of an α,β-disubstituted acrylate moiety [12]. The ^{1}H-NMR. spectrum exhibits the signal of the methyl group of the non-vindoline ethyl group at extraordinarily high field, indicative of the immersion of the methyl group in the shielding cone of a π-bond system. The close similarity of the carbon shift of the same group with the methyl shift of VLB (**1**) and leurosidine (**11**) and the presence of a non-protonated oxycarbon signal in the region of the C(20') resonances of **1** and **11** reflect the presence of an ethyldialkylmethanol unit in the leurosine isomer. The ^{13}C-NMR. data show that the isomerization leaves the indole ring, three aminomethylenes (in the isomer at 51.4, 57.8 and 58.5 ppm) and two methylenes (now at 23.5 and 33.1 ppm) intact, while removing the oxymethine of leurosine (**3**) and generating an additional methine (isomer methine shifts of 33.5 and 47.8 ppm). Furthermore, the distinct aromatic shift changes especially at C(10), C(2') and C(7') indicate that not only has the epoxide suffered dramatic alteration, but also the bonding configuration around C(16') has experienced major modification. All these facts are in agreement with tentative structure **17** for the synthetic isomer

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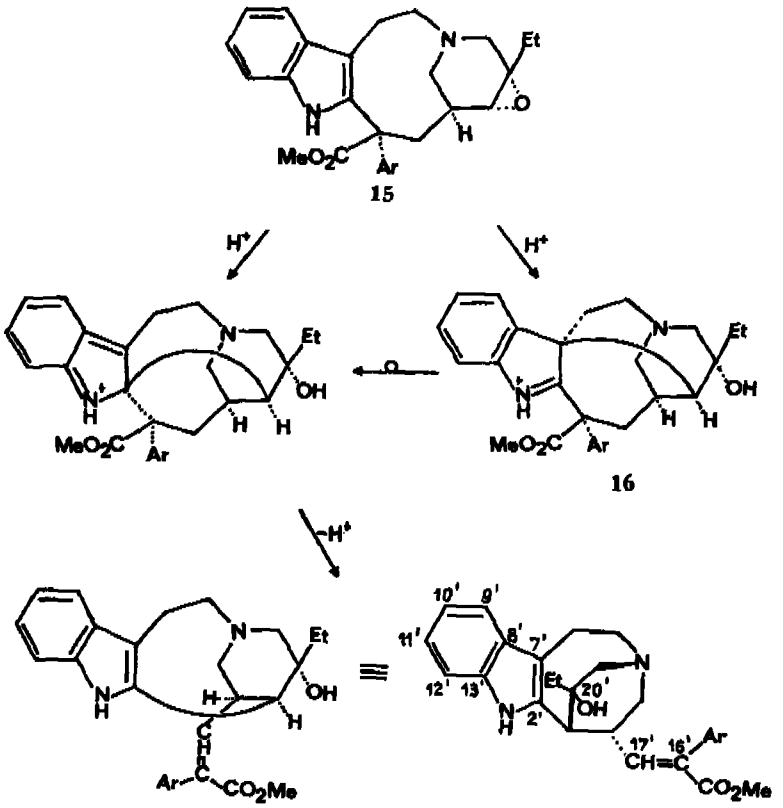
4) The uncertainty of the value stems from the extensive signal widths of the methine doublet components due to two- and three-bond coupling interactions and the partially overlapping multiplet components of the 54.0 and 65.5 ppm signals.

of leurosine (**3**), if it be assumed that the alkaloid possesses an α-epoxide unit (*cf.* **15**) and rearranges according to the following scheme[5]).



Ar = 10-vindolyl **17**

Experimental Part

^{13}C-NMR. Experiments. The carbon shifts denoted on the formulas and in the Table were recorded on a *Varian* XL-100-15 spectrometer operating at 25.20 MHz in the *Fourier* transform mode. The δ values portrayed on formulas **4**–**8** refer to deuteriochloroform solutions; δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm. δ Values are given in ppm, J values in Hz. Stars on the formulas indicate permissible signal reversal. The ^{13}C-NMR. data on leurosidine (**11**), leurosine (**3**) and leurosine isomer **17** were obtained at 25–30° on 0.07 M, 0.1 M and 0.04 M concentration, respectively.

1,3-Diethyl-3-piperideine (**4**) [14]. Ethyl iodide, 40.0 g, was added slowly to a cooling solution of 21.4 g of β-ethylpyridine in 500 ml of ethanol and the mixture then refluxed for 4 h. The mixture was evaporated under vacuum and the residue treated with ether. Crystallization of the resultant precipitate from ethanol/ether yielded 28.0 g of hygroscopic 1,3-diethylpyridinium iodide. Sodium borohydride, 15.0 g, was added slowly to a solution of 18.0 g of the salt in 250 ml of methanol and the mixture stirred at room temperature (RT.) for 12 h. The solvent was evaporated under reduced pressure, saturated brine solution was added and the mixture extracted repeatedly with ether. The extract was dried over sodium sulfate and evaporated under vacuum. Distillation of the residue yielded 11.0 g of air-unstable 1,3-diethyl-3-piperideine (**4**): b.p. 95°/45 Torr. – ^{1}H-NMR. ($CDCl_3$): 1.00 (*t*, 3, J = 7, Me of Et); 1.12 (*t*, 3, J = 7, Me of N-Et); 1.7–2.7 (*m*, 8, methylenes); 2.78 (*d*, 2, J = 2.4, allyl NCH_2), 5.32 (*m*, 1, olefinic H). – Crystallization of its perchlorate from acetone/ether gave colorless crystals: m.p. 71–72°. – ^{1}H-NMR ($CDCl_3$): 1.03

[5]) The deprotonated form of **16** has been shown to be the alkaloid vincathicine as well as another product of the acid treatment of leurosine (**3**) [13].

(*t*, 3, J = 8, Me of Et); 1.44 (*t*, 3, J = 8, Me of N-Et); 2.02 (*q*, 2, J = 8, CH_2 of Et); 2.45 (*m*, 2,5—CH_2); 3.0–3.8 (*m*, 6, methylenes); 5.55 (*m*, 1, olefinic H).

$C_9H_{18}ClNO_4$ Calcd. C 45.9 H 7.50 N 5.84% Found C 45.13 H 7.59 N 5.81%

1,3-Diethyl-3,4-oxypiperidine (**6**). *m*-Chloroperbenzoic acid, 8.0 g, was added slowly to a solution of 8.0 g of **4**-perchlorate in 500 ml of dry chloroform cooled at 0° and the mixture stirred for 12 h. The precipitated *m*-chlorobenzoic acid was filtered off and the filtrate evaporated under vacuum. The residue was washed with ether, treated with sodium hydrogencarbonate in only 1 ml of water and extracted exhaustively with ether. The extract was dried and evaporated under reduced pressure. Distillation of the residual oil gave 4.0 g of colorless, liquid epoxide **6**: b.p. 95°/25 Torr. – ^{1}H-NMR. ($CDCl_3$): 1.05 (*t*, 6, J = 8, Me_2); 0.7–3.1 (*m*, 11, OCH, methylenes). –

$C_9H_{17}NO$ (155.1309) Found 155.1320 (MS., *m/e*)

1,3-Diethyl-3-piperidinol (**5**). A solution of 300 mg of epoxide **6** in 10 ml of dry ether was added slowly to a stirring suspension of 200 mg of lithium aluminum hydride in 20 ml of ether and the mixture stirred at RT. for 12 h. A minimum amount of water for the decomposition of excess hydride was added, the ethereal solution decanted and the aqueous solution extracted with ether. The combined ether solutions were dried and evaporated under reduced pressure. Distillation of the residue at 40°/0.5 Torr produced 200 mg of **5**. – IR. (neat): 3500 *m* cm^{-1} (OH). – ^{1}H-NMR. ($CDCl_3$): 1.03 (*t*, 6, J = 8, Me_2); 1.1–2.9 (*m*, 10, methylenes); 2.38 (*q*, 2, J = 8, CH_2 of N-Et), $C_9H_{19}NO$ (157.1466) Found 157.1469 (MS., *m/e*).

Ethyl iodide, 20.0 g, was added slowly to a stirring suspension of 6.0 g of magnesium turnings in 250 ml of ether. When all magnesium had reacted, the solution of *Grignard* reagent was cooled to 0° and a solution of 5.0 g of 1-ethyl-3-piperidone, freshly prepared from its hydrochloride, in 50 ml of ether added slowly. The mixture was refluxed for 12 h, cold, concentrated, aqueous ammonium chloride added and the mixture extracted exhaustively with ether. The extract was dried, passed through a basic alumina column and evaporated. This yielded 1.0 g of liquid **5**, identical by IR., ^{1}H- and ^{13}C-NMR. analysis with the above preparation.

Leurosine Isomer **17**. A solution of 750 mg of leurosine (**3**) in 10 ml of acetic acid was refluxed for 2 h and then evaporated to dryness under reduced pressure. Preparative TLC. on 2 mm plates of *Merck* silica gel F-254 and development with ethyl acetate/ethanol 3:1 separated bands of products whose major component was extracted with methanol. The extract was evaporated and the residue extracted with methylene chloride. Evaporation of this extract and crystallization of the residual oil from methanol gave 20 mg of colorless **17** (*vide infra*).

A solution of 2.00 g of leurosine (**3**) sulfate and 80 g of concentrated sulfuric acid in 120 ml of water was left standing at RT. for 0.5 h. It then was poured onto ice, made basic with concentrated, aqueous ammonia and extracted exhaustively with methylene chloride. The extract was dried and evaporated under vacuum, leaving 2.0 g of residue. A benzene solution of the total residue from four runs was chromatographed on 240 g of alumina, activity II, and eluted with chloroform/benzene 1:1 to 3:1, yielding 2.6 g of desired product among the central fractions. (The chromatography was monitored by TLC. on silica with ethyl acetate/ethanol 1:1 for development and ceric ammonium sulfate as reagent.) Rechromatography on 75 g of 100–200 mesh *Florisil* and elution with chloroform/ethyl acetate 1:1 yielded 775 mg of amorphous base, homogeneous on TLC. Crystallization from methanol gave leurosine isomer **17**: m.p. 183–187° (dec.); pK_a (66% DMF) 4.65 and 6.60. – IR. ($CHCl_3$) 3400 *w* (OH), 1710 *s* (C=O), 1740 *s* cm^{-1}. – UV. (EtOH): 211 nm (ε 49,700), 220 (48,000), 255 (12,100), 283 (12,000), 291 (12,300), 313 (8,100). – ^{1}H-NMR. ($CDCl_3$): – 0.16 [*t*, 3, J = 7, H—C(18′)]; 0.90 [*t*, 3, J = 7, H—C(18)]. $C_{46}H_{56}N_4O_9$ (808.4030) Found 808.4047 (MS., *m/e*).

$C_{46}H_{56}N_4O_9$ Calc. C 68.30 H 6.98 N 6.93% Found C 68.50 H 7.00 N 6.94%

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173. ^{13}C-NMR. Spectroscopy of Naturally Occurring Substances. XXXV. Labdanic Diterpenes[1])

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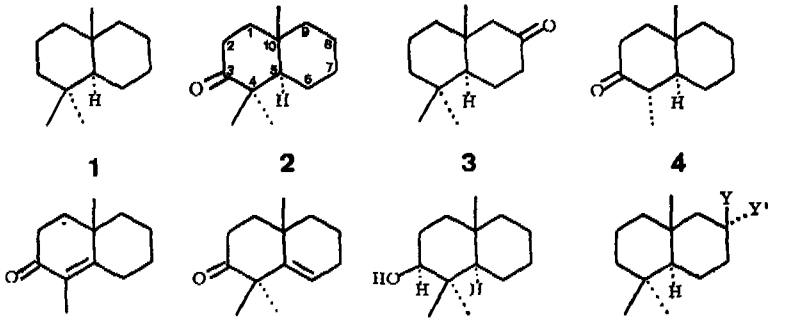
Summary. A total carbon shift analysis of several representatives of the labdane diterpene family of natural products is presented. The shift assignment is based on the prior shift designation of some synthetic *trans*-decalin derivatives.

Introduction. – In continuation of the study of the ^{13}C-NMR. spectra of natural diterpenes [2] [3] an analogous investigation of some diterpenes of the labdane type was undertaken. In this connection a ^{13}C-NMR. analysis of a variety of 9-methyl-*trans*-decalins had to be pursued. The present communication illustrates the total



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