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

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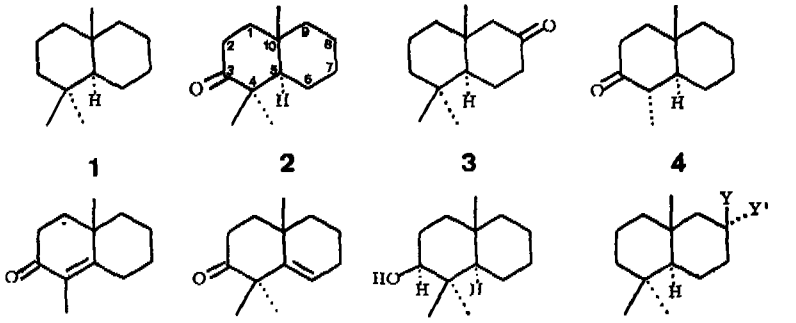
(16. V. 75)

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



[1]) For part XXXIV see [1].
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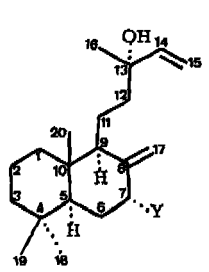
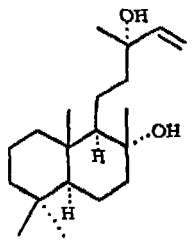
carbon shift assignment of models 1,1,10-trimethyl-*trans*-decalin **1**[3]), decalones **2**, **3**, **4**, **5** and **6** and trimethyl-*trans*-decalols **7**, **8a** and **8b** [4] as well as of manool **9a**, 7α-hydroxymanool **9b**, sclareol **10**, methyl copaiferate **11**, dimethyl agathate **12**, manoyl oxide **13a**, 2-ketomanoyl oxide **13b**, 19-hydroxy-2-ketomanoyl oxide **14**.



9a, Y = H
9b, Y = OH



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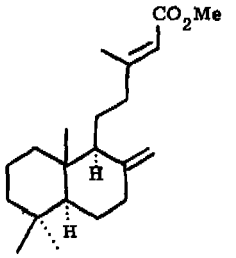

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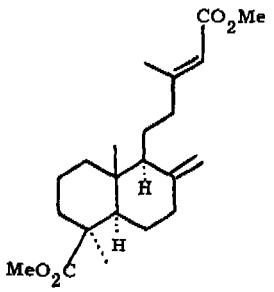

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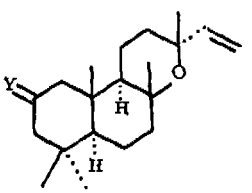
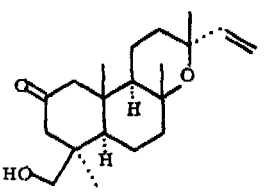


13a, Y = H_2
13b, Y = O



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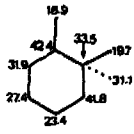
Shift assignment. – Proton noise-decoupled spectra and off-resonance spectra at single frequencies (sford) were recorded for each of the above substances and analyses of ketones **5** and **6** as well as manool **9a**, its 7α-hydroxy derivative **9b** and 2-ketomanoyl oxide **13b** with the aid of the shift agents Eu(DPM)$_3$ and Yb(DPM)$_3$ were executed. The carbon shifts of models **1**–**8** are listed in Table 1, while those of the natural systems **9**–**14** in Table 2.

The shift assignment of hydrocarbon **1** and saturated ketones **2**–**4** is based on multiplicities in the sford spectra, comparison of the shifts of the four compounds with each other and comparison with the δ values recorded for 1,1,2-trimethylcyclohexane (**15**) [5], 9-methyl-*trans*-decalin (**16**) [6] and tricarbocyclic diterpenes [2] [3]. The analysis of olefinic ketones **5** and **6** required an Yb(DPM)$_3$ shift study, the $\Delta\delta$ values from which are depicted on formulas **17** and **18**, respectively. The carbon shifts of ketone **5** are in accord with those reported recently for 10-methyl-1,2,3,6,7,8,9,10-octahydronaphthalene-3-one [7] and those of the olefinic ring of **6** with the shifts of 10-methyl-1,2,3,6,7,8,9,10-octahydronaphthalene [7]. The ^{13}C-NMR. data for **1** and recognition of proper substituent effects permit the full shift designation for alcohols **7** and **8** [8].

[3]) Despite the name of this hydrocarbon the numbering system for **1** and the other decalin derivatives in the discussion and the Tables is based on the diterpene nomenclature for sake of clarity.



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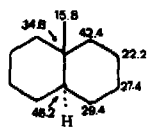

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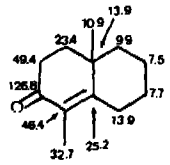

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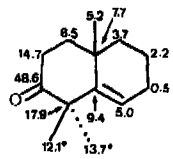

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Table 1. *Carbon Shifts of Decalin Models*[a])

	1[b])	2[c])	3[b])	4[c])	5[b])	6[b])	7[c])	8a[b])	8b[b])
C(1)	42.6[d])	40.3	41.0[e])	41.0	37.5	34.7	40.3	42.4[g])	42.4
C(2)	18.7	34.3	18.0	38.2	33.6	33.3	27.4	18.5	18.2
C(3)	42.9[d])	215.3	41.5[e])	213.0	199.3	214.6	79.4	41.9[g])	42.4
C(4)	33.1	47.2	32.4	45.6	128.0	48.0	38.8	32.7	33.0
C(5)	54.1	52.9	51.2	51.5	162.8	147.6	52.7	53.0	54.2
C(6)	22.1	22.4	22.2	25.9	27.6	123.4	21.7	20.9	17.0
C(7)	28.1	26.5	41.5[c])	26.3	26.7	24.7	27.4	36.7	33.0
C(8)	22.1	21.2	209.2	21.4	21.3	17.5	21.7	66.8	67.6
C(9)	45.8	43.6	58.6	41.9	42.0	38.1	45.2	54.1	51.2
C(10)	34.3	33.5	37.4	33.9	36.1	33.2	34.1	35.1	34.2
4α-Me	33.1	24.7	32.4	11.3	10.7	26.6[f])	27.4	33.0	33.0
4β-Me	21.4	20.7	20.6			28.3[f])	15.2	20.9	21.3
10β-Me	19.2	17.7	18.5	16.3	22.3	23.7	19.4	19.8	21.3

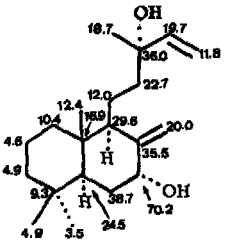
[a]) The δ values are in ppm downfield from TMS. [b]) In deuteriochloroform solution; δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm. [c]) In chloroform solution; δ(TMS) = $\delta(CHCl_3)$ + 77.2 ppm. [d]) [e]) [f]) [g]) Signals in any vertical column may be reversed.

Table 2. *Carbon Shifts of Diterbenic Substances*[a])

	9a	9b	10	11[b])	12[c])	13a	13b	14
C(1)	39.0	38.6	39.4	39.0	39.0	38.9	54.5	54.8
C(2)	19.3	19.3	18.2[d])	19.1	19.8	18.4	210.4	211.7
C(3)	42.1	42.0	41.7	42.0	38.0	41.9	56.2	50.4
C(4)	33.5	33.0	33.0	33.3	44.2	32.5	38.5	42.9
C(5)	55.5	47.6	55.8	55.3	56.1	55.5	55.5	56.0
C(6)	24.4	30.9	18.7[d])	24.4	26.1	19.8	19.9	20.0
C(7)	38.3	73.9	44.7[e])	38.1	38.5	42.6	42.5	42.9
C(8)	148.4	149.5	74.5	148.3	147.4	74.9	74.4	74.4
C(9)	57.2	51.1	61.5	56.1	55.2	56.2	55.0	55.3
C(10)	39.8	39.9	38.9	39.5	40.1	36.7	42.1	41.8
C(11)	17.6	17.2	20.1	21.2	21.5	15.2	15.4	15.5
C(12)	41.3	40.7	43.8[e])	39.6	39.6	35.5	35.3	35.4
C(13)	73.4	73.5	73.1	161.0	160.5	73.0	73.1	73.2
C(14)	144.9	144.8	146.6	114.9	114.7	147.8	147.3	147.4
C(15)	111.4	111.5	110.5	167.2	166.9	110.0	110.2	110.4
C(16)	27.9	28.0	26.0	19.1	19.0	28.4	28.4	28.3
C(17)	106.2	109.5	23.9	106.2	106.2	25.4	24.8	24.8
C(18)	33.5	33.2	33.0	33.3	28.6	32.5	33.3	27.0
C(19)	21.7	21.5	21.2	21.1	177.3	21.3	22.8	65.4
C(20)	14.4	13.4	15.1	14.4	12.4	16.6	16.4	16.6

[a]) The δ values are in ppm downfield from TMS: δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm. [b]) The OMe shift is 50.5 ppm. [c]) The OMe shifts are 50.5 and 50.9 ppm. [d]) [e]) Signals may be reserved.

Application of chemical shift theory, use of the ^{13}C-NMR. data for hydrocarbon **1** and a Eu(DPM)$_3$ study for the verification of the differences of shifts of C(1) or C(3), C(2) and C(5) from those of C(12), C(11) and C(9), respectively, lead to the complete assignment of δ values for manool **9a**, from which all shifts can be allotted to 7α-hydroxymanool **9b** and methyl copaiferate **11**. An Yb(DPM)$_3$ shift study of diol **9b** confirmed the signal assignment and, as the $\Delta\delta$ values on formula **19** indicate, revealed an expected stronger association of the lanthanide complex with the secondary hydroxyl than the tertiary hydroxy function. The shifts of dimethyl agathate **12** are based on those of monoester **11** and the known effects of the substitution of a 4β-methyl group by a methoxycarbonyl unit on tricarbocyclic diterpenes [3]. The ^{13}C-NMR. data of manool **9a** allow the shift allocation for sclareol **10** and hence for manoyl oxide **13a**. The difference of the vinyl carbon shifts of **9a** and **10** may be due to concentration effects [9]. An Yb(DPM)$_3$ shift study on 2-ketomanoyl oxide **13b** ($\Delta\delta$ values on **20**) confirms the deduction of the shifts of **13b** from those of **13a**. Finally, the shift designation of 19-hydroxy-2-oxo-manoyl oxide (**14**) follows that of **13b** and consideration of the known shift perturbations on modification of the C(4) substitution pattern [3].



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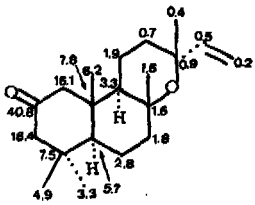

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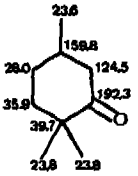
Discussion. – A variety of interesting facts emerge from the ^{13}C-NMR. data of the models and the labdanic diterpenes. The small shift difference of C(5) between ketones **4** and **2** is analogous to the highly reduced β-effect imposed on the methine of *trans*-1,2-dimethylcyclohexane on conversion into 1,1,2-trimethylcyclohexane **15** [5]. Comparison of the C(2) shifts of *trans*-decalin (27.2 ppm) [6], 9-methyl-*trans*-decalin (**16**) and hydrocarbon **1** indicates the previously noted decrease of the ca. 5 ppm γ-shift imposed by an axial methyl group to a ca. 4 ppm shielding effect upon the introduction of another 1,3-diaxial interaction by a methyl function on the same carbon site. As the C(2) shift difference of ketones **4** and **2** reveals, the same phenomenon is observed in cyclohexanones, even when the 1,3-diaxial interaction takes place at the α-ketocarbon sites. The similarity of the C(2) $\Delta\delta$(**2**–**4**) and $\Delta\delta$(**1**–**16**) points to the conformational identity of the ketonic rings of **2** and **4**. The shift likeness of the methyl group of methylcyclohexane (23.3 ppm) [5] and of the olefinic methyl functions of 1-methylcyclohexene (23.8 ppm) [8] and enone **21** reveals the imperturbability of the methyl shift toward neighboring double bonds of varying polarity. The amazing similarity of the 4-methyl shifts of ketones **4** and **5** is in accord with this fact. Comparison of the δ values of ketones **2** and **6**, especially those of C(1) and the methyl groups, shows that the introduction of the $\Delta^{5,6}$ linkage causes a dramatic conformational change in the bicyclic olefin. The dissimilarity of the angular methyl shift

difference between **22** [7] and **16** (8.6 ppm) *vs.* **6** and **2** (6.0 ppm) strongly confirms this argument and the difference of the C(7), C(8) and C(9) shifts of olefins **22** and **6** indicates the conformational alteration of ketone **6** to affect both rings[4]).



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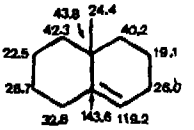

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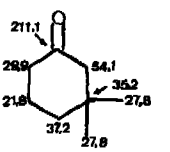

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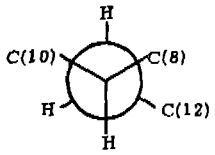
The alcohols **7** and **8a** exhibit the recently described *γ-anti*-periplanar hetero-atom effect [12]. Thus C(1) and C(5) of the former and C(6) of the latter resonate distinctly upfield from comparable sites of hydrocarbon **1**. Comparison of the ring carbon shifts of dimethyl agathate **12** with those of methyl copaiferate **11** and manool **9a** shows C(2) nearly unaffected, C(3) to be shielded and C(6) to be deshielded on substitution of an axial 4*β*-methyl group by a carbomethoxy function. These facts suggest that the 4-methoxycarbonyl unit of **12** possesses a preferred rotamer population in a plane parallel to the C(3)–C(5)–H(5) plane. In contrast to the known minor shift perturbation of *β* ring methylenes and methines on introduction of a keto group into a cyclohexane unit [8] the heretofore undescribed effect on a *β* quaternary site is striking. Thus C(10) of ketone **3** and C(10) and C(4) of ketone **13b** are deshielded by 3.1, 5.4 and 6.0 ppm, respectively. This unpredicted phenomenon occurs to the extent of 4.6 ppm in model **23**.

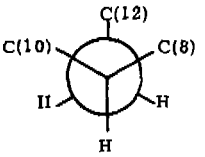
The shifts of C(1), C(8) and C(20) of manool **9a** shed some light on the conformation of the sidechain of **9a** and **11**, and hence also of **9b** and **12**, with respect to the C(11)–C(12) bond orientation. Comparison of **9a** with model **1** shows C(1) to be shielded in the natural product by 3.6 ppm, a value similar to the average for a *γ*-effect induced by a *peri*, diequatorial methyl-hydrogen interaction in the *trans*-decalin system [6], *e.g.* $\Delta\delta$(**16–4**) = 3.5 ppm and $\Delta\delta$(*trans*-decalin – *trans-anti*-1-methyldecalin) = 3.7 ppm. The C(1) shift, therefore, supports rotamer **24a** or **24b** for manool **9a** and related substances. Comparison of the angular methyl shifts of selinene **25** [3] and *trans*-9-methyldecalin **16** indicates that the *γ*-effect of the *π* bond of the exocyclic methylene group is barely different from that of an axial hydrogen. As a consequence, the C(20) $\Delta\delta$(**9a–1**) = 4.8 ppm reflects and added *γ*-effect on C(20) from C(11) without a *δ*-effect from C(12). This argument militates against rotamer **24b** and is supported by the absence of a *γ*-shift imposed by C(12) on C(8), as revealed by the similarity of the *δ* value of C(8) in manool **9a** with that of the like carbon in selinene **25** [3]. Hence **24a** represents the preferred C(11)–C(12) bond rotamer of manool **9a**.

The *trans*-decalin models and the diterpenic compounds exhibit a multitude of *δ*-effects, first noted among methyldecalols incorporating 1,3-diaxial, methyl-hydroxyl, non-bonded interactions [13]. The existence of such interaction in alcohol **8b** is reflected by a *δ*-effect of $\Delta\delta$(**8b–1**) = 2.1 ppm on the angular methyl group and

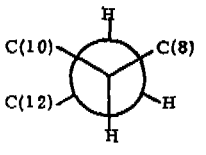
[4]) The 2-bromo derivatives of 4,4-dimethyl-5-cholesten-3-one [10] and the triterpenoid substance cedrelone [11], all compounds with structure patterns as those of ketone **6**, have been shown to possess non-chair ketonic ring conformations.



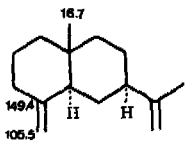
24a



24b



24c



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a similar effect of 2.6 ppm on C(8), calculated from the axial oxymethine shift of 65.0 ppm for 4-*t*-butylcyclohexanol [8]. Comparison of the angular methyl shift of *trans*-9-methyldecalin (**16**) with that of **1**, **7** and **8a** reveals δ-effects of 3.4, 3.6 and 4.0 ppm, respectively, for 1,3-diaxial, methyl-methyl, non-bonded interactions. Reciprocal δ-effects of 1.7 and 1.2 ppm on the 4β-methyl group of **1** and **8a**, respectively, can be calculated from the 19.7 ppm axial methyl shift of 1,1,2-trimethylcyclohexane **15** [5]. The influence of the 4β-methyl group of ketone **2** on its angular methyl function is $\Delta\delta$(**2**–**4**) = 1.4 ppm. The imposition of a second 1,3-diaxial interaction of a methyl group by another leads to an attenuation of the δ-effect, *e.g.* the C(20) $\Delta\delta$(**10**–**9a**) = 0.7 ppm. The 1.5 ppm C(20) shift perturbation on conversion of sclareol **10** into manoyl oxide **13a** may be a consequence of a δ shift enhancement due to a transmission of the C(16)–C(17) buttressing onto C(20). The 2.0 ppm difference of the angular methyl shift of esters **11** and **12** shows the decrease of the δ-effect of a 'flat' methoxycarbonyl group. The buttressing of two methyl groups 1,3-diaxial to each ether induces deshielding of the geminal, 1,3-diequatorial carbon sites, *e.g.* the C(9) $\Delta\delta$(**2**–**4**) = 1.7 ppm and the shift difference of 3.1 ppm for the 4α-methyl group of ketones **2** and **4**, calculated from the $\Delta\delta$(**15**-*trans*-1,2-dimethylcyclohexane) value of 10.3 ppm for the geminal, equatorial methyl group [5]. This effect is shown by the 4α-methyl groups of **1**, **3**, **8**, **9**, **10**, **11** and **13**, all of which are deshielded by ca. 2 ppm from the 31.1 ppm shift of the 1-equatorial methyl function of 1,1,2-trimethylcyclohexane [5] and by C(9) of **1**, **7** and **8** which is deshielded by ca. 3 ppm.

Experimental Part

The ^{13}C-NMR. spectra were recorded on *Varian* DP-60 and XL-100-15 spectrometers operating in the *Fourier* transform mode at 15.08 and 25.20 MHz, respectively. The lanthanide shift values denoted on formulas **17**, **18**, **19** and **20** and the carbon shifts indicated on **21** and **23** were determined on samples in deuteriochloroform solution; δ(TMS) = δ($CDCl_3$) + 76.9 ppm. The stars on **18** show permissible signal reversal. The $\Delta\delta$ values depicted on **17**, **18**, **19** and **20** fit equation $\Delta\delta_{Yb} = \delta_{complex} - \delta_o$ wherein complex = 1:1 Yb(DPM)$_3$/substrate.

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174. ^{13}C-Kernresonanzspektroskopische Untersuchung der Komplexierung von synthetischen «Carrier»-Molekeln mit Ca^{2+}-Ionen

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Summary. The complex formation between $CaCl_2$ and the ion carrier ligands **1** and **2** was investigated with ^{13}C-NMR. spectroscopy. In methanol as solvent, the ligands form complexes with both 1:2- and 1:1-stoichiometry (Ca^{2+}/ligand). In the latter case, apart from solvent molecules, the ligand's two amide carbonyl groups and two ether oxygenatoms probably take part in the coordination of the metal cation. In contrast, when using a non polar solvent ($CDCl_3$), **2** forms only a complex with 1:2-stoichiometry, whereas **1** may also form a 1:1-complex in which the ester carbonylgroups participate in the coordination too.

1. Einleitung. – Seit der Entdeckung der Fähigkeit elektrisch neutraler, synthetischer [1] [2] oder natürlich vorkommender [3] Liganden mit Alkali- und Erdalkali-Metallionen Komplexe zum Teil beachtlicher Stabilität [4] zu bilden, entwickelte sich ein grosses Interesse an derartigen Liganden seitens der Biochemie [5] [6], der organischen [7] sowie der analytischen Chemie [6] [8] [9]. In den letzten Jahren wurden eine Reihe von acyclischen, lipophilen, elektrisch neutralen Liganden für Alkali- und Erdalkali-Ionen hergestellt [9–12], die in künstlichen Membranen als selektive Ionen-«Carrier» wirken [13] und dementsprechend [14] in ionenselektiven Membranelektroden als selektive Komponente eingesetzt werden können. Je nach Konstitution des Liganden und Zusammensetzung der Membranphase wurden bisher Elektroden mit Selektivitäten für Ca^{2+}-[15], Ba^{2+}-[16], Li^{+}-[17] und Na^{+}-Ionen [18] gefunden (vgl. auch [9] [19]).

Die ^{13}C-Kernresonanzspektroskopie wurde bei der Untersuchung der Komplexierung verschiedener ionenselektiver Antibiotika mit Alkali- und Erdalkali-Ionen eingesetzt [20–24]. Sie weist gegenüber den anderen spektroskopischen Methoden den Vorteil auf, dass für die meisten Zentren, auch in komplexen Molekeln, isolierte Signale beobachtet werden können, deren Lage durch Konformationsänderungen der Molekeln im allgemeinen stark beeinflusst wird [25]. In den untersuchten Anti-