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SYNTHESIS OF DITERPENOID ACIDS—VIII[1]

NUCLEAR MAGNETIC RESONANCE SPECTRA AND CONFORMATIONS OF SOME LACTONES OF OCTA- AND DECAHYDRO-8-HYDROXYNAPHTHOIC ACIDS

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Abstract—The NMR spectra of 11 lactones (**1a**–**7d**) are described. The width of the peak due to the C_8 proton has been related to the stereochemistry of the decalin ring junction. The following conformations are proposed: ring B in **4**–**6** is a twist; ring B of **7a**–**7d** is a chair; and in **1a**–**3** the C_8—O bond is axial and probably ring A is a twist and ring B a chair.

Recently NMR spectroscopy has been used to deduce the conformations of molecules containing γ-lactone functions.[3] We now report our studies of the lactones **1a**–**7d** prepared in work on diterpenoid synthesis.[4–8] The spectra confirm previous assignments of structures.[4–6, 8]

The lactones can be divided into three stereochemical types: those with a *cis* fused ring junction, compounds **1a**–**3**; those with the ring junction *trans* and the lactone fusion *trans* to the C_{8a} hydrogen, compounds **4**–**6**; and those with the ring junction *trans* and the lactone fusion *cis* to the C_{8a} hydrogen, compounds **7a**–**7d**. Inspection of Table 1 shows that the three stereochemical types can be distinguished by their W and $W_{\frac{1}{2}}$ values. These results have been applied in other work.[1, 8]

Conformations of lactones. With all the lactones except **1b**, the C_8 proton is considered as the X proton of an ABCX system.[9, 10] In none of these spectra was the peak of the C_8 proton sufficiently well resolved so that the individual coupling constants could be deduced.

We calculated theoretical line spectra for a number of possible conformations of **2**, **6**, and **7a**, each of which is taken as an example of its stereochemical class. In these calculations the X shift was the measured shift for the C_8 proton; the A (C_7 axial), B (C_7 equatorial) and C (C_{8a}) protons were assigned arbitrary values of 100, 125 and 150 c/s downfield from tetramethylsilane; J_{AB} was put equal to −13 c/s; and values for J_{AX}, J_{BX}, and J_{CX} were assigned from a standard curve,[11b] using dihedral angles obtained from Dreiding models of the particular conformation being studied (see below). In all the conformations we considered, the atoms C_1, C=O, —O—, and C_8 were assumed planar.[12, 13] Inspection of the calculated spectra confirmed that the combination lines were very weak and may be ignored[10] and that the extreme lines of the X portion of the spectrum were separated by a distance equal to $J_{AX} + J_{BX} + J_{CX}$; thus the width of the X peak gives a reliable guide to the sum of the coupling constants $J_{AX} + J_{BX} + J_{CX}$.

Table 2 gives the possible conformations for **2**, **6** and **7a** and the corresponding

TABLE 1. NMR SIGNALS CORRESPONDING TO C_8 PROTONS ($CDCl_3$ SOLUTIONS)

Compound	δ (ppm)[a]	$W_{\frac{1}{2}}$[b] (c/s)	W[c] (c/s)
1a[d,e]	5·07	10–11	16
1b	4·63 (triplet)	12	15
2[d,f]	4·82	10	17
3[d,f]	4·45	9	18
4[d]	4·87	12	25
5[d]	5·10	15	22
6[d,f]	4·75	12	27
7a[g]	3·95	17	35
7b[h]	4·42	23	38
7c[h]	3·97[i]	26[i]	44[i]
7d[h]	3·87	20	32

[a] Peak appears as broad unresolved multiplet for all compounds except 1b

[b] Width at half height

[c] Width at base of peak

[d] Reference[5]

[e] Reference[6]

[f] Reference[8]

[g] Reference[4]

[h] Reference[7]

[i] The peaks due to the C_5 and C_8 hydrogens appear as one broad and one narrow peak superimposed on each other. On acetylation (to 7d) the narrow peak moves to 5·01; hence the broad peak is assigned to the C_8 proton.

TABLE 2. RELATION OF CALCULATED SUM $J_{AX} + J_{BX} + J_{CX}$ TO POSSIBLE CONFORMATIONS

Compound	Conformation Ring A	 Ring B	$J_{AX} + J_{BX} + J_{CX}$ (c/s)	
6	chair	chair		9
	chair	twist		29
7a	chair	chair		34
2	chair	twist	C_8—O axial	15
	twist	chair		
	boat	boat		
	chair	twist	C_8—O equatorial	27–28
	twist	chair		
	boat	boat		

sums $J_{AX} + J_{BX} + J_{CX}$ which were derived using Dreiding models and the Johnson-Williamson curve.[11a] Although the dihedral angles are difficult to measure accurately and coupling constants are not specified exactly by the Johnson-Williamson or similar curves,[14] the differences between sums derived from possible conformations are sufficiently large to make the conclusions reached below safe. Two conformations (both with ring A chair) are considered for the *trans* lactone **6**: ring A could also be a twist but this would have little effect on the dihedral angles at C_8 (with B either in the chair or twist form).

In the *cis*-lactone **2** the lactone oxygen can be either axial or equatorial to ring B and so six conformations are possible; two with both rings in the boat form; two with ring A chair and ring B twist; and two with ring A twist and ring B chair. The sum of the coupling constants for each of the three conformations in which the C_8—O bond is axial is 15: the sums for those with the bond equatorial vary from 27–28. These latter values are minimum values because they do not allow for the increase in the coupling constant between an axial and equatorial proton resulting from the equatorially substituted oxygen at C_8.[15] The three smaller values (15) are larger than the sum (9) of the coupling constants calculated for the *trans* lactone **6** on the basis of a two chair conformation. As the peak for the C_8 proton in **6** is broader than that for **2**, ring B in the *trans* compound must be in the twist conformation, (sum of coupling constants = 29), and the correct conformation for the *cis* compound must be one of the three in which the C_8—O bond is axial. Of the three possible conformations the boat–boat is unlikely, because it corresponds to the conformation in *cis*-decalin which has a conformational energy about 8 kcal/mole greater than that of the twist-chair form.[16] To distinguish between the two remaining possibilities we consider the C_5 proton signal in the hydroxy lactone **3**. This has $W_{\frac{1}{2}} = 18$ which corresponds better with B a chair (sum of coupling constants is 17) than with A a chair (sum is 8). Consideration of the methoxy lactone **1b** confirms this conclusion. The shifts of the C_7 and C_8 protons are separated by about 45 c/s and so the C_8 proton is the X proton of an AMX set. As it appears as a triplet the coupling constants J_{AX} and J_{MX} must be equal. This fits for the C_8—O axial, ring B a chair and the methoxyl configuration assigned as in **1b**. Further in this conformation the dihedral angles between the protons on C_7 and C_8, and C_8 and C_{8a} correspond to coupling constants of about 6 c/s, in good agreement with the observed splitting 5·5 c/s.

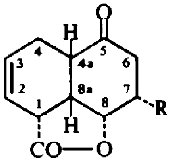
The sum given for the chair–chair form of **7a** is a minimum: it was calculated on the basis that $J_{8,7e} = 2$ c/s; but as the lactone oxygen is equatorial $J_{8,7e}$ may be closer to 4–5 c/s.[15] Changing the conformations of either or both the rings does not change the sum $J_{AX} + J_{BX} + J_{CX}$ much. In the spectrum of **7c** the C_5 proton appears as a band superimposed on (but distinguishable from) the signal for the C_8 proton: it has $W_{\frac{1}{2}} = 8$ c/s. In **7d** this peak (shifted 1 ppm downfield) has $W_{\frac{1}{2}} = 7$ c/s. These widths show that the α-hydroxyl and acetoxyl are axial and therefore that ring B in **7c** and **7d** (and presumably in **7a** and **7b**) is a chair. In agreement with Table 2 the C_8 proton in **7a**–**7d** gives a broader peak than that in the lactones related to **2** and **6**.

In the conformations we suggest, the C_8 proton is axial in **7a**–**7d**, equatorial in **1a**–**3** and intermediate between axial and equatorial in **4**–**6**. These conclusions are consistent with the chemical shifts of this proton in **2** ($\delta = 4{\cdot}83$), **6** ($\delta = 4{\cdot}75$) and **7b** ($\delta = 4{\cdot}40$ ppm). Also with these conformations the theoretical spectra for the C_8 peaks in **2**, **3**, **6** and **7b** and the C_5 peak in **3** have widths agreeing well with the experimental ones. In addition the shapes of the peaks (except for the C_5 in **3**) agree fairly well with experiment. The lack of complete agreement is not surprising since the discussion ignored the effect of virtual coupling[17] on the 8a proton.

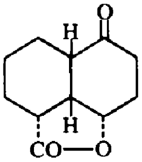
Studies of models show that with rings A and B in chair forms closure of the lactone in **6** and **7a** involves bending the C_1-carbonyl and C_8-oxygen bonds towards each other by about 15°. In **6** the overall strains which are lessened in part by bending and twisting in the molecule, must be at least 5 kcal/mole, since they cause ring B to change to the twist form; this allows the lactone to close with little strain at C_1 and

C_8. In **7a** however the bonds bent in closing the lactone are in the plane of the rings; the strains are set up along the ring bonds and are not relieved by changing the conformation of either ring. Even in **7d** ring B is still in the chair conformation, in spite of the fact that this puts the acetoxyl group axial.

The suggestion,[1] based on our results with **6**, that ring B in marrubiin, **8**, is in a twist form has been confirmed,[18-20] In addition, Hanson[3c] established that ring B in the kaurenolides (**9**), is a twist. In both the marrubiin and kaurenolide compounds the presence of the angular Me group reinforces the tendency for the chair conformation to change to twist when the lactone is closed. The interest of our present results is that the lactone itself is sufficient to bring about the change.



1a: R = H
1b: R = OCH_3



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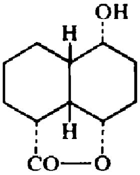

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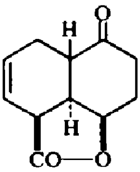

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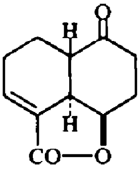

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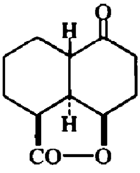

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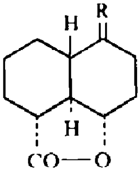
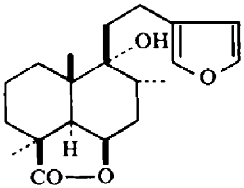


7a: R = H_2
7b: R = O

,OH
7c. R
||
,OCOCH$_3$
7d: R =
H



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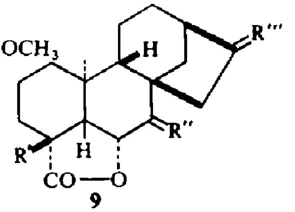
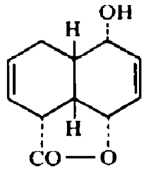


9



10

EXPERIMENTAL*

cis-1,4,4a,5,6,7,8,8a-*Octahydro-8α-hydroxy-7α-methoxy-5-oxonaphthalene-*1*α-carboxylic acid lactone* (**1b**). This compound was obtained as a by-product from the oxidation of **10** with chromic acid.[5, 21] An oxidation of **10** (36·0 g) was carried out and the excess of chromic acid removed by addition of MeOH. After crystallization of the keto lactone corresponding to **10** the material (12·0 g) from the mother liquors was divided into neutral (3·0 g) and acidic (7·9 g) fractions. The neutral material in ethyl acetate was shaken with charcoal and filtered through Florisil. Crystallization from EtOAc gave the keto methoxy lactone **1b** (0·319 g) with m.p. 187–188°. (Found: C, 64·75; H, 6·39. $C_{12}H_{14}O_4$ requires: C, 64·85; H, 6·35%), ν_{max}: 1776, 1721, 1466, 1434, 1416, 1379, 1356, 1326, 1295, 1265, 1219, 1184, 1150, 1100, 1018, 992, 963, 905 and 892 cm^{-1}; NMR peaks at δ = 1·50–3·30 (m, 7H), 3·42 (s, 3H), 3·55–4·13 (m, 1H), 4·63 (tr, J = 5·5 c/s, 1H, $W_{1/2}$ = 12, W = 15) and 5·66–5·96 (d, 2H) ppm; and (CF_3COOH) at δ = 1·87–3·4 (m, 6H), 3·60 (s, 1H), 3·68 (s, 3H), 3·93–4·63 (m, 1H), 5·03 (tr, J = 5 c/s, 1H, $W_{1/2}$ = 13, W = 18), 5·7–6·03 (d, 2H).

The following NMR spectra were obtained.

cis-1,4,4a,5,6,7,8,8a-*Octahydro-8α-hydroxy-5-oxonaphthalene-*1*α-carboxylic acid lactone* (**1a**)[5, 6] δ = 1·6–3·0 (m, 7H) 3·0–3·8 (m, 2H), 4·9–5·25 (broad unresolved m—at least two peaks, 1H, $W_{1/2}$ = 10–11, W = 16), and 5·5–6·3 (m, 2H) ppm.

cis-*Decahydro-8α-hydroxy-5-oxonaphthalene-*1*α-carboxylic acid lactone* (**2**)[5, 8] δ = 0·8–3·5 (m, 13H), and 4·70–4·95 (broad unresolved peak, 1H, $W_{1/2}$ = 10, W = 17) ppm.

cis-*Decahydro-5α,8α-dihydroxynaphthalene-*1*α-carboxylic acid γ-lactone* (**3**)[5, 8] δ = 1·0–3·1 (m, 14H), 3·5–4·0 (broad unresolved m, 1H), and 4·3–4·6 (broad unresolved m, 1H, $W_{1/2}$ = 9, W = 18) ppm.

trans-1,4,4a,5,6,7,8,8a-*Octahydro-8α-hydroxy-5-oxonaphthalene-*1*α-carboxylic acid lactone* (**4**)[5] δ = 1·6–2·9 (m, 8H), 3·1–3·6 (broad unresolved m, 1H), 4·65–5·10 (broad unresolved m, 1H, $W_{1/2}$ = 12, W = 25) and 5·85–6·10 (s, with slight splitting, 2H) ppm.

trans-3,4,4a,5,6,7,8,8a-*Octahydro-8α-hydroxy-5-oxonaphthalene-*1*-carboxylic acid lactone* (**5**)[5] δ = 1·4–3·0 (m, 9H), 3·2–3·7 (broad m, 1H) 4·9–5·3 (broad m, contains at least two peaks, 1H, $W_{1/2}$ = 15, W = 22), 6·7–7·0 (m, probably qu, 1H) ppm.

trans-*Decahydro-8α-hydroxy-5-oxonaphthalene-*1*α-carboxylic acid lactone* (**6**)[5, 8] δ = 0·6–3·1 (m, 13H), and 4·5–5·0 (broad unresolved m, 1H, $W_{1/2}$ = 12, W = 27) ppm. The spectrum of **6** was examined down to −60° without detecting any significant changes.

trans-*Decahydro-8β-hydroxynaphthalene-*1*β-carboxylic acid lactone* (**7a**)[4] δ = 0·8–2·5 (m, 15H), and 3·7–4·2 (broad unresolved m, 1H, $W_{1/2}$ = 17, W = 35) ppm.

The preparation and spectra **7b**–**7d** will be reported in full elsewhere.[7]

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* For nomenclature see Ref. 4. The NMR spectra were determined in deuteriochloroform solutions on an A-60 spectrometer. $W_{1/2}$ is width of peak at half-height and the W the width at the base; both are expressed in c/s. In the calculations the spin Hamiltonian was solved exactly using the Jacobi method of diagonalising the matrix.

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