Assignments in the Carbon-13 Fourier Spectra of Eudesmanolides

By **Gerard P. Moss, Paul S. Pregosin,** and **Edward W. Randall,*** Department of Chemistry, Queen Mary College, Mile End Road, London E1 4NS

The ^{13}C n.m.r. spectra of some eudesmanolides have been measured, and the influence of stereochemistry on chemical shifts has been examined. The stereochemistry of pseudosantonin has been confirmed. The influence of the lone electron pair of an oxime group on ^{13}C shifts is noted.

We have reported the ^{13}C n.m.r. spectra of the santonins (1)—(4).[1] We concluded that the stereochemistry at C-6, C-7, and C-11 could be determined readily from the ^{13}C shifts of carbon atoms 6—9 and 11—13. A number of related eudesmanolides (5)—(10) are considered in this paper and the influence of oxygen-containing substituents is discussed.

The ^{13}C resonance positions of the eudesmanolides examined are shown in Table 1. Assignments in each case were made by utilising the expected substituent effects, the technique of single frequency off-resonance decoupling (which separates the resonances into four groups arising from carbon nuclei with three, two, one, and no attached protons), and comparisons between spectra of related structures. Most of the variations in structure occur in ring A, but some examples involve substitution at C-8. The stereochemistry of the lactone ring in each case was reflected in the corresponding resonances, showing the same differences as previously observed.[1]

In the case of the α-santonin derivatives (5) and (6) (Table 2), for C-6 to C-9 and C-11 to C-13, there is less than 1 p.p.m. change in shift from the corresponding α-santonin signals. This variation is significantly less than the differences found between the shifts for α-santonin on the one hand and for compounds (2)—(4) on the other.[1] Thus the configuration of the lactone ring in (5) and (6) is the same as in α-santonin.

Acid-catalysed rearrangement of α-santonin to α-desmotroposantonin acetate (7) results in inversion at C-6 as well as the formation of an aromatic ring A.[2] This result is confirmed by comparison of the ^{13}C spectra of (7) and α-episantonin (3). The difference at C-9 (10·5 p.p.m.) is clearly due to the change of C-10 from

TABLE 1

^{13}C N.m.r. chemical shifts [a] for some eudesmanolides

Compound	Carbon no. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	3-OAc	8-OAc
α-Santonin (1)	155·1	125·9	186·0	128·4	151·5	81·5	54·0	23·3	39·3	41·7	41·2	177·4	12·5	10·9	25·3		
β-Santonin (2)	155·0	126·0	186·1	128·8	151·9	80·8	49·5	20·3	38·2	41·5	38·2	178·3	9·9	11·0	25·2		
α-Episantonin (3)	157·5	126·1	186·2	137·8	149·0	76·5	43·8	23·4	34·9	39·4	44·2	179·6	14·9	11·0	25·2		
β-Episantonin (4)	157·6	126·1	186·3	137·6	149·3	76·9	41·8	18·3	34·7	39·5	41·3	179·0	9·6	11·0	24·9		
Dihydro-α-Santonin (5)	42·1	33·9	198·5	128·5	152·9	82·1	53·4	23·7	38·7 *	38·5 *	41·4	177·6	12·5	11·3	23·4		
Santonin oxime (6)	145·6	112·5	150·7	122·5	139·5	82·3	53·7	23·8	38·5	41·1	41·4	178·0	12·5 *	12·2 *	26·0		
α-Desmotroposantonin acetate (7)	†	124·2	148·1	†	†	75·6	42·1	23·8 *	24·4 *	†	40·8	179·4	14·6	12·1	20·7	169·6, 19·5	
β-Desmotroposantonin acetate	†	124·4	148·1	†	†	75·5	40·0	19·7	25·9	†	40·7	178·7	9·5	11·9	20·8	169·7, 19·4	
Desmotroposantonin diacetate (8)	†	124·0	148·4	†	†	79·6	53·0	70·7	35·5	†	40·5	178·3	14·1 *	13·6 *	20·7	169·7, 19·8	170·9, 21·1
Pseudosantonin (9)	214·3	29·6	35·0	139·4	127·0	77·5	51·0	67·3	39·2	46·7	41·5	180·4	15·6	19·8	25·1		
Deoxypseudosantonin (10)	213·9	30·8 *	35·5	139·3	128·1	76·6	42·8	23·6	31·1 *	46·1	44·4	180·0	15·2	19·5	24·4		

[a] Values in p.p.m. downfield from internal Me_4Si, correct to about ±0·2 p.p.m.

* These pairs of shifts may be interchanged since the assignment is ambiguous. † Signal obscured by C_6F_6.

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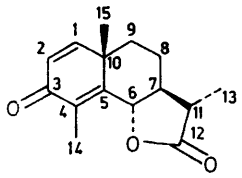
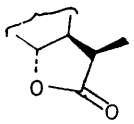
[2] J. W. Huffman, *J. Org. Chem.*, 1963, **28**, 601; and references therein.

sp^3 to sp^2. The effect at C-9 is similar to the corresponding change on aromatisation of a steroid analogue (11·2 p.p.m. for C-9 of prednisolone[3] and estrone



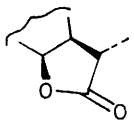
α-santonin

(1)



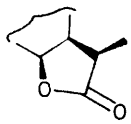
β-santonin

(2)



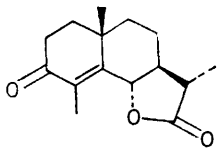
α-episantonin

(3)

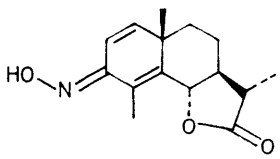


β-episantonin

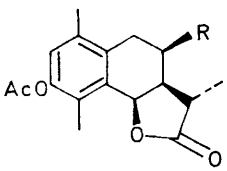
(4)



(5)

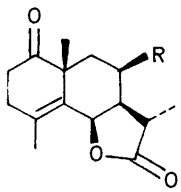


(6)



(7) R = H

(8) R = OAc



(9) R = OH

(10) R = H

acetate[4]). Comparison with α-santonin[1] (Table 2) showed a poor fit. β-Desmotroposantonin acetate was correlated similarly with β-episantonin (4) (Table 2). Furthermore, comparison between α- and β-desmotroposantonin acetates showed close correspondence to the santonin values (ref. 1, Table 2).

The stereochemistry of pseudosantonin (9) was related to that of α-santonin[5] before revision[6] of the latter. The situation at the lactone ring can be deduced partially by ^{1}H n.m.r. studies.[7] Close correspondence of the ^{13}C n.m.r. spectra of deoxypseudosantonin (10) and α-episantonin (3) (Table 2) definitely confirms the lactone stereochemistry. The change at C-9 of 3·8 p.p.m. clearly is due to the oxo-group at C-1 of (10).

TABLE 2

Chemical shift differences

	Carbon no.						
	6	7	8	9	11	12	13
(1) — (5)	−0·6	0·6	−0·4	0·6	−0·2	−0·2	0·0
(1) — (6)	−0·8	0·3	−0·5	0·8	−0·2	−0·6	0·0
(3) — (7)	0·9	1·7	−0·4	10·5	3·4	0·2	0·3
(1) — (7)	5·9	11·9	−0·5	14·9	0·4	−2·0	−2·1
(4) — (11) [a]	1·4	1·8	−1·4	8·8	0·6	0·3	0·1
(2) — (11) [a]	5·3	9·5	0·6	12·3	−2·5	−0·4	0·4
*	2·3	4·8	−4·1	11·2			
(7) — (11) [a,b]	0·1	2·1	4·1	−1·5	0·1	0·7	5·1
(3) — (10)	−0·1	1·0	−0·2	3·8	−0·2	−0·4	−0·3
(8) — (7)	4·0	10·9	46·9	11·1	−0·3	−1·1	−0·5
(9) — (10)	0·9	8·2	43·7	8·1	−2·9	0·4	0·4

* Values from (prednisolone) — (estrone).

[a] Compound (11) is β-desmotroposantonin. [b] *Cf.* ref 1, Table 2.

Natural eudesmanolides frequently contain an oxygen function at C-8. The influence of this group is illustrated by data for pseudosantonin (9) and desmotropoartemesin diacetate (8). The oxygen function produces a downfield shift at C-8 of about 45 p.p.m., and small shifts at C-7 and C-9 of about 10 p.p.m., with negligible changes at C-6 and C-10. These effects are similar to those observed with cyclohexanols,[8] steroids,[4] and other terpenoids.[9] The conformation at C-8 is probably indicated by the shifts of the γ-carbon atoms C-6 and C-10. Thus the oxygen function is, as expected, pseudoequatorial. However the effect of adjacent methyl groups on the magnitude of these substituent effects suggests that some caution is needed in this interpretation in the absence of axially substituted examples. Presumably these differences are due to a vicinal effect analogous to that observed with the methylcyclohexanes.[10]

Shifts of the various types of carbonyl carbon atoms illustrate the effect of an αβ-double bond. Pseudosantonin (9) shows a non-conjugated ketonic ^{13}C shift slightly modified by the βγ-double bond. The one conjugated double bond of dihydrosantonin (5) produces the expected carbonyl deshielding of about 19 p.p.m. With santonin the second αβ-double bond results in a further downfield shift of 12·5 p.p.m. These figures correspond closely to analogous results with steroidal[3,4] and other enones[11,12] and dienones.[13]

[3] G. Lukacs, X. Lusinchi, E. W. Hagaman, B. L. Buckwalter, F. M. Schell, and E. Wenkert, *Compt. rend.*, 1972, **274***C*, 1458.

[4] H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigart, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 7445.

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[13] R. Hollenstein and W. von Philipsborn, *Helv. Chim. Acta*, 1972, **55**, 2030.

The results for santonin oxime (6) show that the carbon atom of the oxime group is less influenced by the two αβ-double bonds: the ^{13}C signal is deshielded by only 10·1 p.p.m. However the oxime group does effect the shifts of the adjacent carbon atoms. This effect may be transmitted through the π-system in part, but the α-carbon atoms are affected in all oximes in a way dependent on the stereochemistry of the C=N system. In acetone and cyclohexanone oximes, the carbon atom *cis* to the hydroxy-group is shielded more than the *trans*-carbon atom by 6·7 and 7·6 p.p.m., respectively. Clearly santonin oxime has the *E*-stereochemistry. After correction for the differences between C-2 and C-4 of santonin, its oxime also shows a difference of 7·5 p.p.m. Presumably the principal cause of this difference is the hydroxy-group.[14]

EXPERIMENTAL

^{13}C Fourier spectra were recorded with a Bruker HFX multinuclear spectrometer operating at 22·63 MHz and employing wide band noise decoupling techniques. The spectra were obtained by storing the free induction decays produced by a series of 6 μs r.f. pulses in a Fabritek 1074 computer of average transients (4K points). The power conditions were determined by optimisation of the free induction decays (16 or more) of a sample of ethylbenzene. The interferograms which resulted were then Fourier-transformed by a Digital PDP 8I computer, to yield magnitude spectra in 2K points.

The santonins were measured as 10—15% (w/w) solutions in deuteriochloroform containing *ca.* 5% C_6F_6 and *ca.* 5% Me_4Si (w/w). Typical spectra were obtained in an hour or less. The data are quoted in p.p.m. downfield (positive) from the carbon resonance of internal tetramethylsilane and are thought to be accurate to ±0·2 p.p.m.

We thank the S.R.C. for the spectrometer and for a post-doctoral fellowship (to P. S. P.).

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[14] See also G. C. Levy and G. L. Nelson, *J. Amer. Chem. Soc.*, 1972, **94**, 4897; N. Gurudata, *Canad. J. Chem.*, 1972, **50**, 1956; Z. W. Wolkowski, E. Vautier, B. Gonbeau, H. Sauvaitre, and J. A. Musso, *Tetrahedron Letters*, 1972, 565.