^{13}C Fourier Studies. The Configurational Dependence of the Carbon-13 Chemical Shifts in Santonin Derivatives

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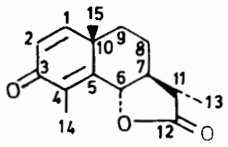
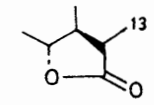
The carbon-13 chemical shifts in α, β, α-*epi*-, and β-*epi*-santonin have been measured. The data provide a simple method of determining the stereochemistry of the lactone ring fusion as well as configuration of the methyl group at C-11.

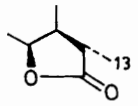
THE determination of the molecular structure of santonin has long been the subject of chemical investigation.[1] Apart from chemical studies the molecular framework of α-santonin and its derivatives has been investigated



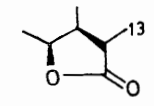
α-Santonin (I)



β-Santonin (II)



α-episantonin (III)

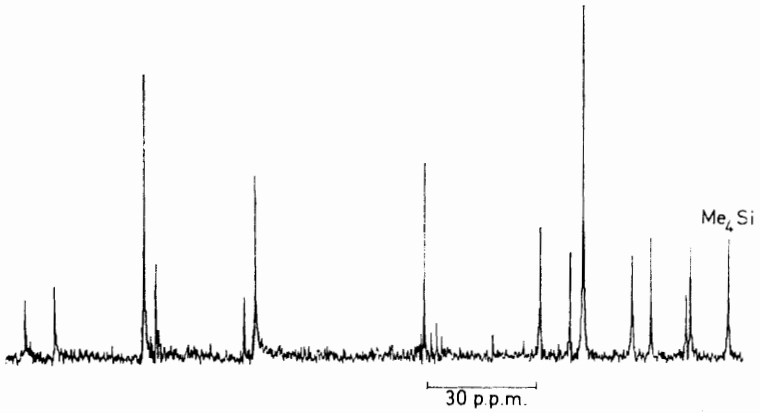


β-episantonin (IV)

using a number of physical techniques including mass [2] and ^1H n.m.r. spectroscopy.[3] We present here a simple, but elegant, method of assigning the stereochemistry of the 6,7-fusion in the santonins (I)—(IV) as well as the configuration of the methyl group at C-11.

The natural-abundance proton-decoupled carbon-13 n.m.r. spectrum of β-santonin (II) is shown in the accompanying Figure while the resonance positions are listed in Table 1. The spectrum may be divided conveniently into two sections: those absorptions associated with sp^2 and sp^3 carbon atoms respectively with the former appearing in the region +120 to +180 p.p.m. (downfield from the carbon resonance of internal tetramethylsilane) and the latter between +9 and +80 p.p.m.

The low-field position of sp^2 carbon relative to sp^3 is thought to be involved with the relatively low-lying excited states (*i.e.* $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$) available to this grouping. A consideration of those factors affecting carbon chemical shifts may be found in several reviews.[4] Within the sp^2 grouping the lowest field resonances (excepting carbonium ion carbons) are the carbonyl carbons. The positions of a variety of carbonyl absorptions have been documented by Stothers and Lauterbur [5] with ketone carbonyls found generally in the region +190 to +220 p.p.m. while ester carbonyls fall at +160 to +180 p.p.m. Thus the resonance at +186·1 p.p.m. is assigned to C-3 and that at +178·3 to C-12.

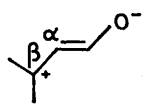


Natural-abundance proton-decoupled ^{13}C n.m.r. spectrum of β-santonin (II)

The four vinyl carbon signals may be divided into two categories: those bearing a vinyl proton and those which have no directly bonded protons. Assignment of these resonances was made utilizing single-frequency

[1] Sir John Simonsen and D. H. R. Barton, 'The Terpenes,' Cambridge University Press, 1952, vol. 3.
[2] N. Woseda, T. Tsuchiya, E. Yoshii, and E. Watanabe, *Tetrahedron*, 1967, **23**, 4623.
[3] J. T. Pinhey and S. Sternhell, *Austral. J. Chem.*, 1965, **18**, 543.
[4] E. F. Mooney and P. H. Winson, *Ann. Rev. N.M.R.*, 1969, **2**, 153; P. S. Pregosin and E. W. Randall, in 'Determination of Organic Structures by Physical Methods,' eds. F. C. Nachod and J. J. Zucherman, Academic Press, vol. **4**, ch. 6, to be published.
[5] J. B. Stothers and P. C. Lauterbur, *Canad. J. Chem.*, 1964, **42**, 1563.

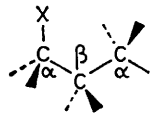
off-resonance (s.f.o.r.) techniques, alkyl substituent effects,[6] and the recognized [7] deshielding of the β-carbon in αβ-unsaturated ketones resulting from contributions of the type (V). The use of s.f.o.r. techniques allows



(V)

the observation of reduced $^1J(^{13}C-H)$ values, and has been found to be exceptionally valuable in allowing the observation of the multiplicity of a given carbon signal due to a residual one-bond coupling while retaining some Overhauser enhancement of the signal.

The assignments in the high-field set were made using inductive and aliphatic [8] substituent effects as well as s.f.o.r. techniques. Of particular value in assigning the signals in this region was the known sterically induced and sterically dependent upfield shift at a γ carbon [see (VI)] resulting from either methyl [9] or hydroxy- [10] substitution at an α carbon. Using these techniques the resonances at +80·3, +49·5, and +38·2 p.p.m. were assigned to carbons 6, 7, and 11 (C-9 co-



(VI)

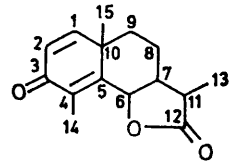
incides with C-11) respectively. The large downfield shift (>40 p.p.m.) observed when oxygen is substituted for hydrogen has been noted previously [10] and unambiquously allows the identification of the C-6 resonance. In similar fashion the remaining signals were assigned.

The carbon-13 chemical shifts of α-, β-, α-epi-, and β-epi-santonin are shown in Table 1. Since the differences in these molecules are centred in the lactone ring it might be expected that the dienone ring should be relatively unaffected and to a large extent this is observed. The effects, Δδ, of changing the configuration at C-11 whilst maintaining the stereochemistry of the lactone fusion are shown in the first two columns of Table 2, while the last two columns reveal the effects of changing the ring fusion for a given configuration at C-11.

It is readily seen that the resonances for C-6 fall into two sets depending upon the steochemistry at the ring junction: one upfield set at *ca.* 76·5 p.p.m. for α-epi- and β-epi-santonins, and one set at *ca.* 81 p.p.m. for the α- and β-santonins, the exact differences being 5·0 p.p.m. for the α-cases and 3·9 p.p.m. for the β-cases.

TABLE 1

Carbon-13 chemical shifts * of the santonins



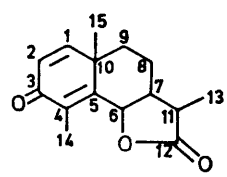
Carbon no.

Compound	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
α-Santonin	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	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	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	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

* Solutions were measured as 10—15% solutions by weight containing *ca.* 5% C_6F_6 (w/w). Values are in p.p.m. downfield from internal Me_4Si and are estimated to be correct to ±0·2 p.p.m.

TABLE 2

Carbon-13 chemical shift differences,* Δδ for the santonins as a function of configuration



Carbon no.	$\alpha - \beta$	$\alpha_{epi} - \beta_{epi}$	$\alpha - \alpha_{epi}$	$\beta - \beta_{epi}$
1	0·1	−0·1	−2·4	−2·6
2	−0·1	~0	−0·2	−0·1
3	−0·1	−0·1	−0·2	−0·2
4	−0·4	0·2	−9·4	−8·8
5	−0·4	−0·3	2·5	2·6
6	0·7	−0·4	5·0	3·9
7	4·5	2·0	10·2	7·7
8	3·0	5·1	0·1	2·0
9	0·1	0·2	3·4	3·5
10	0·2	−0·1	2·3	2·5
11	3·0	2·9	−3·0	−3·1
12	−0·9	0·6	−2·2	−0·7
13	2·6	5·3	−2·4	0·3
14	−0·1	~0	−0·1	~0
15	0·1	0·3	0·1	0·3

* Values are in p.p.m. A positive value signifies that the resonance for the α-isomer appears at lower field.

A similar dependence of carbon-13 chemical shifts on group orientation has been observed in methyl-

[6] R. A. Friedel and H. L. Retcofsky, *J. Amer. Chem. Soc.*, 1963, **85**, 1300.

[7] D. H. Marr and J. B. Stothers, *Canad. J. Chem.*, 1965, **43**, 510.

[8] D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, 1964, **86**, 2984.

[9] D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 1967, **89**, 6612.

[10] J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, 1970, **92**, 1338.

cyclohexanes [9] and cyclohexanols.[10] Specifically a comparison of the chemical shifts at C-1 between *cis*- and *trans*-2-methylcyclohexanol reveals a difference of 5·8 p.p.m. with the *trans* being downfield. It follows therefore that the α- and β-santonins have *trans*-ring fusion whereas their epimers have a *cis*-fusion. This obvious dependence of the position of C-6 on configuration combined with the relative uniqueness of this chemical shift provide an efficient probe into the nature of the lactone ring in these systems. This may be extended to other santonins. Thus the observation of the C-6 resonances at +75·6 and +75·5 p.p.m. in α- and β-desmotroposantonin acetates,[11] confirms the *cis*-orientation of the lactone rings in these compounds.

The conclusions reached above for the parent santonins may be confirmed by a consideration of the shifts for C-9 and C-10. In these instances a change from the *trans*- to the *cis*-fusion induces an upfield shift of between 2 and 4 p.p.m. at each centre. The magnitudes and direction are consistent with an expected γ-alkyl substituent effect brought about, at C-9, by the change in configuration at C-7 and, at C-10, by the change at C-6. The upfield shifts at these carbons are consistent only with a ring fusion which permits sterically induced perturbations from remote centres. Thus the conclusions reached above regarding the nature of the ring fusion are obtained by a somewhat more circuitous route.

For a given stereochemistry at carbons 6 and 7 a similar analysis of the relative positions at C-8, C-11, and C-13 permits the assignment of the isomer whose resonances are at the lowest field to the α-isomer. The first two columns in Table 2 reveal the situation at carbons 8 to 13 to be a complementary one. Inversion of the methyl group at C-11 results in an increased γ-alkyl substituent effect at C-8 due to the new proximate C-13 methyl, and at C-13 due to the new relative position of C-8. The situation at C-11 represents another example of the dependence of the α-methyl substituent effect on configuration. Inversion from equatorial to axial substitution at C-1 (α position) in cyclohexanols,[10] methylcyclohexane,[9] and simple sugars [12] has been shown to shield C-1 by *ca.* 4—5 p.p.m. *X*-Ray crystallography [13] suggests that the C-11 methyl group in α-santonin occupies a pseudo-equatorial position; thus inversion to the β-isomer produces the expected upfield shift (*ca.* 3 p.p.m.) of C-11 and provides us with an additional method of assigning the configuration at this centre.

The changes in position of carbons 4 (−9·4 and −8·8 p.p.m.) and 7 (+10·2 and +7·7 p.p.m.) as a function of the lactone fusion are worthy of note. The former may result from relief of a relatively large γ-substituent effect at C-4, although it seems reasonable that if this were the case, it should be mirrored by a significant change at C-14, which is not observed. Alternately, this change at C-4 may be related to the orientation of the C-6 oxygen lone-pairs. Carbon-13 chemical-shift dependences on the orientation of nitrogen lone-pairs, and of similar magnitude, have been observed.[14,15] The change at C-7 may well be the cumulative effect of changing several substituent effects (*i.e.* α-effect at C-7, β-effect at C-6) simultaneously.

The positions of the lactone carbonyl carbons are not significantly different from those of other lactones (see Table 3). We note that this resonance appears at slightly lower field in the *cis*-fused santonins than in *trans*-ones.

TABLE 3

Some carbon-13 chemical shifts [a] in lactones

Compound [b]	Chemical shift OC=O	C–O
β-Propiolactone	169·9	59·4
γ-Butyrolactone	178·3	69·0
α-Methyl-γ-butyrolactone	180·6	66·7
γ-Valerolactone	177·4	77·5
ε-Caprolactone	175·9	69·2

[a] Values are downfield from internal Me_4Si and are estimated to be correct to ±0·2 p.p.m. [b] The samples were measured as *ca.* 50% (v/v) solutions in chloroform.

EXPERIMENTAL

^{13}C Fourier spectra were recorded on a Bruker HFX multinuclear spectrometer operating at 22·63 MHz. The spectra were obtained by storing the free induction decays produced by a series of 6 μs Rf pulses in a Fabritek 1074 computer of average transients. The interferograms which result were then Fourier transformed by a Digital PDP 8I computer.

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). The lactones were measured as *ca.* 50% solution (v/v) in chloroform. The data recorded are in p.p.m. downfield 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 postdoctoral fellowship (to P. S. P.).

[1/1543 *Received*, 24*th August*, 1971]

[11] P. S. Pregosin and E. W. Randall, unpublished results.
[12] L. D. Hall and L. F. Johnson, *Chem. Comm.*, 1969, 509; D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, 1970, **92**, 1355.
[13] J. D. M. Asher and G. A. Sim, *J. Chem. Soc.*, 1967, *B*, 107.
[14] P. S. Pregosin and E. W. Randall, *Chem. Comm.*, 1971, 399.
[15] P. S. Pregosin, E. W. Randall, and A. I. White, *J.C.S. Perkin II*, 1972, 1.