Simple Methods to Find the Stereochemistry of the Side Chain of γ-Lactones[1,2]

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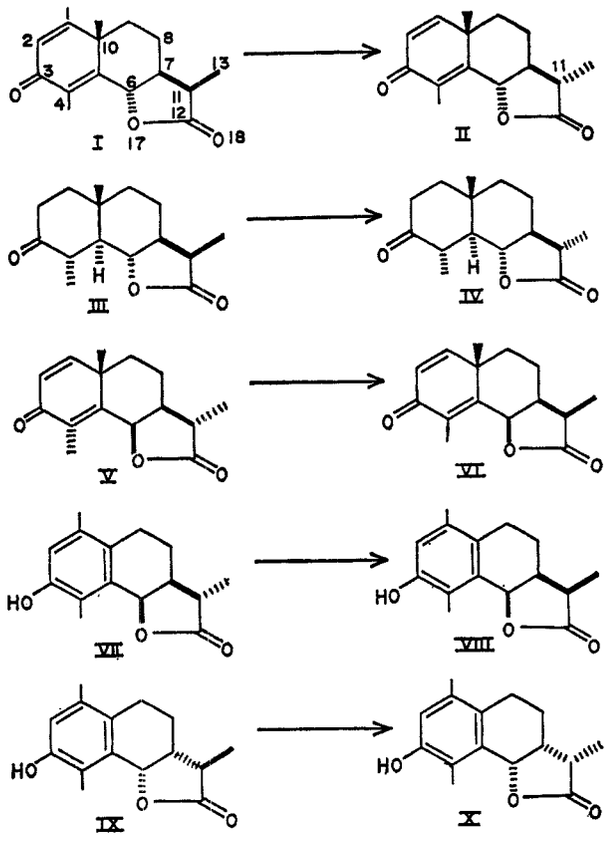
The preferred conformation of the side chain C_{11}–CH_3 in γ-lactones on the eudesmane skeleton is discussed in the light of thermodynamic studies recently conducted on some of these compounds. Reasons are advanced to justify the results, which are contrary to earlier assumptions. Two simple methods, one depending on solvent shifts and the other on coupling constants, are presented to find directly the stereochemistry of this methyl group in any γ-lactone.

A variety of γ-lactones fused to cyclohexane systems such as santonin, artemisin, alantolactone, etc.,[4] has been known for a long time and new ones are also being found or made. All of these have a methyl side chain next to the lactone carbonyl. There is no simple or direct chemical method, nor was there any physical method to find the stereochemistry of this side chain.

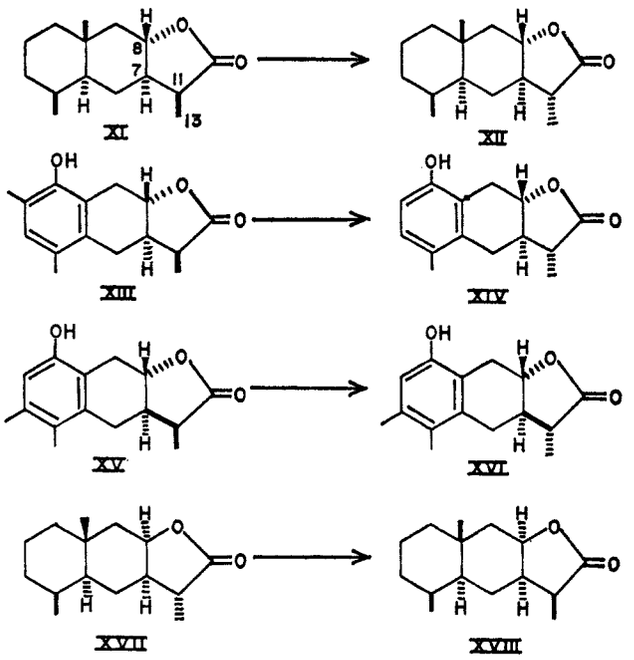
The C_{11}–CH_3 in α-santonin (II, Scheme I) was deduced to be β oriented, because of stability considerations, based on equilibration reactions of this methyl group in the lactone.[5,6] Subsequently, all other related γ-lactones were assigned stereochemistry at C_{11}, either by chemically relating them to an α-santonin derivative or by equilibrating the methyl group and applying the stability considerations referred to above. A series of rules[7] detailing the particular type of lactone and the relation of C_{11}–CH_3 with C_7–H, etc., in each case has been proposed to describe the above assumed stability order and these were applied to assign the stereochemistry at C_{11} of newly found lactones.[8]

However, more recent X-ray studies of 2-bromodihydroisophoto-α-santonic lactone acetate[9] and 2-bromo-α-santonin[10] and independent chemical studies[11,12] have conclusively shown that α-santonin has its C_{11}-methyl group actually α oriented. Hence the previous stereochemical assignment at C_{11}, for all santonin derivatives and related lactones, had to be reversed. The present assignments are given in Schemes I and II.

SCHEME I
STABLE CONFIGURATION OF THE C_{11}–CH_3 IN γ-LACTONES, ANGULARLY FUSED (C_6,C_7)



SCHEME II
STABLE CONFIGURATION OF THE C_{11}–CH_3 IN γ-LACTONES, LINEARLY FUSED (C_7,C_8)



It follows that the stereochemical changes involved in the isomerizations, and the order of stabilities as-

(1) Stereochemical Studies by PMR Spectroscopy. Part VII. Part VI: *Indian J. Chem.*, **5**, 218 (1967).

(2) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Lett.* 5865 (1966), preliminary communication.

(3) To whom all correspondence should be addressed in Nigeria.

(4) See, *e.g.* (a) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, 1952, pp 249–322. (b) D. H. R. Barton in "Chemistry of Carbon Compounds," E. H. Rodd, Ed., Vol. II, Elsevier Publishing Co., Amsterdam, 1953, pp 676–687.

(5) R. B. Woodward and P. Yates, *Chem. Ind.* (London), 1391 (1954).

(6) E. J. Corey, *J. Amer. Chem. Soc.*, **77**, 1044 (1955).

(7) N. M. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurry, and E. R. Stuart, *J. Chem. Soc.*, 1828 (1956).

(8) See, *e.g.*, W. G. Dauben, W. K. Hayes, J. S. Schwarz, and J. W. McFarland, *J. Amer. Chem. Soc.*, **82**, 2232 (1960).

(9) J. D. Asher and G. A. Sim, *J. Chem. Soc.*, 1584 (1965).

(10) J. D. Asher and G. A. Sim, *ibid.*, 6041 (1965).

(11) Y. Abe, T. Micki, M. Sumi, and T. Toga, *Chem. Ind.* (London), 953 (1956).

(12) M. Nakazaki and H. Arakama, *Bull. Chem. Soc. Jap.*, **37**, 464 (1964).

TABLE I

MEASUREMENTS OF THE HEAT OF COMBUSTION AND THE HEAT OF SOLUTION OF α- AND β-SANTONINS AND DESMOTROPOSANTONINS[a]

Compound[b]	$-H_c$[c]	$-H_f$ (s)[c]	E (soln)[c,d]	$-H_f$ (soln)[c]
α-Santonin (II)	1884.40 ± 0.54	141.22 ± 0.54	+0.44	140.78 ± 0.5
β-Santonin (I)	1885.23 ± 0.43	141.39 ± 0.43	+0.01	140.38 ± 0.4
6-Epi-α-santonin (V)	1885.80 ± 0.36	139.82 ± 0.36	−1.09	140.91 ± 0.4
6-Epi-β-santonin (VI)	1881.47 ± 0.56	144.15 ± 0.56	+0.09	144.06 ± 0.6
(−)α-DTS* (VII)	2073.95 ± 0.64	208.08 ± 0.64	−0.36	208.44 ± 0.6
(+)α-DTS* (X)	2071.88 ± 0.43	210.15 ± 0.43	−1.06	211.21 ± 0.4
(−)α-DTS$^+$ (VII)	2031.24 ± 0.52	156.74 ± 0.52	+1.54	155.20 ± 0.5
(+)α-DTS$^+$ (X)	2028.27 ± 0.45	159.71 ± 0.45	+0.33	159.38 ± 0.5

[a] Enthalpy data measure thermochemical rather than thermodynamic stability, but it is unlikely that the standard molar entropies of each pair of isomers differ significantly.[23] [b] *, acetate; $^+$, methyl ether. [c] Kilocalories per mole. [d] E (soln) refers to measurements made on 0.01 M solutions in $CHCl_3$ at 25°.

sumed before, have also now to be reversed. These developments, in the light of the present knowledge of the correct stereochemistry of these sesquiterpene lactones at C_{11}, can now be summarized as follows.

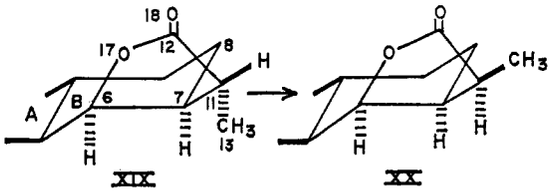
β-Santonin I and tetrahydro-β-santonin III, which have a *trans*-lactone system, isomerize to α-santonin II and tetrahydro-α-santonin IV, respectively,[13,14] showing thereby that the C_{11}–CH_3 is more stable in the α configuration in these systems, but in 6-epi-α-santonin V, 6-epi-β-santonin VI, (−)-α-desmotroposantonin VII, and (−)-β-desmotroposantonin VIII (DTS), which have the lactone ring 6,7-β-*cis*, the C_{11}–CH_3 prefers the β configuration.[15,16] In (+)-β-desmotroposantonin IX and (+)-α-desmotroposantonin X, which have a C_6,C_7 α-*cis*-lactone fusion, the C_{11} side chain is seen to be more stable[16] in the α configuration (Scheme I). Similarly in the case of the linear *trans*-lactone, tetrahydroepialantolactone[17] XI or the desmotropopseudosantonins[8,18] XIII to XVI, the C_{11}-methyl group is found to be more stable in the α configuration, but in the C_7,C_8 β-*cis*-lactone XVII, derived from alantolactone, it is the β configuration of the C_{11}–CH_3 (XVIII) that is found to be preferred[19] (Scheme II).

Some of the isomerization procedures leading to the above conclusions have been criticized,[20] but these criticisms have subsequently been met,[21,22] these and other experiments have been repeated, and the original conclusion, that (−)-β-desmotroposantonins are more stable than (−)-α-desmotroposantonins, has been confirmed. Accurate measurements of the heat of combustion and the heat of solution of α-santonin II, β-santonin I, 6-epi-α-santonin V, 6-epi-β-santonin VI, and those of the acetates and methyl ethers of (−)-α- and (+)-α-desmotroposantonins VII and X have been carried out.[23] The data obtained as given in Table I clearly show that the thermodynamic stabilities arrived at earlier[24] are indeed correct.

The authors of the above measurements,[22,23] however, conclude from these results that the order of stabilities arrived at is difficult to reconcile with the configurations presently assigned to the *cis*-lactones from X-ray studies. We, however, find that a detailed study of these systems fully justifies the above order of stabilities.

Nmr spectral studies of the lactones (section A) show that ring B in santonin and derivatives exists in the chairlike conformation in both the *cis*- and *trans*-lactones.[2] Solvent shift studies of the C_{11}-methyl group (section A) in the lactones independently confirm the stereochemistry assigned to them after the X-ray studies on 2-bromodihydroisophoto-α-santonic lactone acetate[9] and 2-bromo-a-santonin.[10] Hence an explanation for the present stability orders is called for. For this it becomes essential to go into some detail about the reasons why certain stereochemical relations in the stability orders were considered correct before,[5,6] and whether adequate grounds can be found at present to reverse these stereochemical relationships to fit the experimental facts now obtained.

The stability relationship now found for the *cis*-lactones can be represented by XIX, which isomerizes to the more stable form XX, whether ring A is aromatic or nonaromatic, whereas it was originally considered[5,6] that XIX should be the more stable form and that on equilibration XX should isomerize to XIX. (It will be



XIX XX

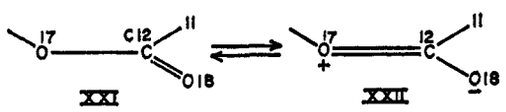
shown in section A that ring B retains the same chair or half-chair conformation in the *cis*-lactones with ring A aromatic or not as was present in the original *trans*-lactone of the ring-A nonaromatized santonin derivative, from which the *cis*-lactone is made.) This led to the wrong assignment of stereochemistry for santonin at C_{11}, and subsequently for all the related lactones.[24] The reasons why XIX should be more stable than XX have not been spelled out. It is only stated that "it may scarcely be doubted that XIX will be

(13) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955).
(14) W. Cocker, N. J. Dodds, and T. B. H. McMurry, *Tetrahedron*, **8**, 160 (1958).
(15) D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962).
(16) N. M. Chopra, W. Cocker, and J. T. Edward, *Chem. Ind.* (London), 41 (1955).
(17) W. Cocker, T. B. H. McMurry, and L. U. Hopkins, *J. Chem. Soc.*, 1998 (1959).
(18) W. Cocker, B. E. Cross, and C. Lipman, *ibid.*, 959 (1949).
(19) C. Asselineau, S. Bory, and E. Lederer, *Bull. Soc. Chim. Fr.*, 1524 (1954).
(20) J. W. Huffman, *J. Org. Chem.*, **28**, 601 (1963).
(21) N. K. Venkatasubramanian, Ph.D. Thesis, Poona University, 1966.
(22) A. J. N. Bolt, M. S. Carson, W. Cocker, L. O. Hopkins, T. B. H. McMurry, M. A. Nisbet, and S. J. Shaw, *J. Chem. Soc., Sect.* C, 261 (1967).
(23) W. Cocker, T. B. H. McMurry, M. A. Frisch, T. McAllister, and H. Mackle, *Tetrahedron Lett.*, 2233 (1964).
(24) See, for a review, W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

strongly favored in stability to XX, on obvious steric reasons" [5] and "clearly XX is the unstable and XIX, the stable arrangement." [6]

The instability attributed to XX should apparently be due to the nearly eclipsed interaction between the C_{11}-β-CH_3 and the methylene at 8, since they are on the same side of the C_7,C_{11} bond, whereas, in XIX, they are on opposite sides. Although this apparently looks very reasonable, a consideration of all the possible interactions on the methyl group in the two alternate configurations and the actual conformation of the lactone ring may show that this need not necessarily be true. Those factors that reduce the instability of XX but increase that of XIX are given below.

i.—Recent X-ray studies[9,10,25,26] have shown that in γ-lactones resonance structure XXII makes an important contribution with the result that the O_{17},C_{12} bond acquires considerable double-bond character. As



XXI XXII

a consequence, the lactone group consisting of C_6, C_{11}, C_{12}, O_{17}, and O_{18} [C—O—C(=O)—C] becomes planar, with C_7 out of the plane. It is now recognized that a carbanion,[27] or the lone pair of electrons on the nitrogen[28,29] or the oxygen[30,31] atom, can exert an appreciable steric effect. In XIX, the lone pair of electrons on the oxygen atom or the π electrons, which are in a plane perpendicular to the lactone ring, could be expected to exert a steric effect on the pseudo-axial, α-methyl group at C_{11}, besides the strong nonbonded interaction on this methyl group by the α-hydrogen atoms at C_6 and C_5. These are absent in XX.

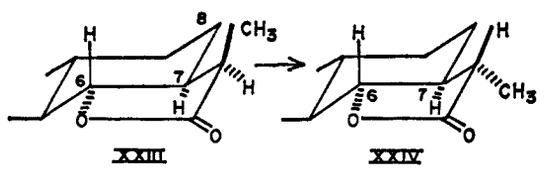
ii.—Models indicate that, in XX, the double-bond character of the O_{17},C_{12} bond, with buckling at C_7, increases the dihedral angle between the planes made by $C_{13}C_{11}C_7$ and $C_{11}C_7C_8$. This will move C_{13} a little further away from C_8.

iii.—X-Ray work on 2-bromo-α-santonin[10] shows that the $C_6C_7C_{11}$ and $C_7C_{11}C_{12}$ angles are much smaller (99 and 102°, respectively) and the $C_8C_7C_{11}$ and $C_7C_{11}C_{13}$ angles are much larger (122 and 115°, respectively) than normal, and the C_{11},C_{13} bond longer (1.63 Å) than usual. These angle distortions are largely brought about by the fusion of the five-membered lactone ring to the rigid cyclohexane ring B. Distortions of bond angles and bond lengths are also found to take place to accommodate steric strain, as in the case of ring A of the normal triterpenes with a *gem*-dimethyl group at C_4.[32] Hence, if we make the reasonable assumption that these distortions take place at least to the same extent in the *cis*-lactones as well, all these factors will help to move C_{13} away from C_8.

iv.—If the angles at C_6 are also distorted as is true at C_8, in the case of the *cis*-lactone in the guaianolide bromogeigerin acetate,[25] the plane of the lactone ring in the *cis*-lactone will be so bent and twisted from the plane of ring B, that C_{13} is quite away from 8 (further support for this is given at the end of section B).

This would minimize the interaction between C_{11}-β-CH_3 on the one hand, and the carbon atom 8 and the protons on it on the other. At the same time the change in the plane of the lactone ring brings C_{11}-α-CH_3 closer to C_6 and C_7-α-H in XIX, thus increasing its instability. These factors thus appear to tilt the equilibrium in the *cis*-lactones in favor of the pseudo-equatorial β-methyl group of XX over the pseudo-axial one in XIX.

In the *trans*-lactones, the pseudo-axial methyl group at C_{11} in XXIII, being destabilized by the axial hydrogen atoms at C_6 and C_8 and the lone pair of electrons on the oxygen or the π electrons of the lactone ring as mentioned before, would readily isomerize to the pseudo-equatorial conformation as in XXIV. Thus the side-chain C_{11}-CH_3 prefers the pseudo-equatorial orientation over the pseudo-axial one in the *trans*- as well as the *cis*-fused γ-lactones.



XXIII XXIV

Two Simple Methods to Find the Stereochemistry at C_{11}.—Two simple methods are now presented by which the stereochemistry of the side chain of sesquiterpene lactones can be directly and independently determined.

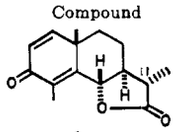
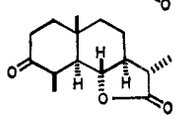
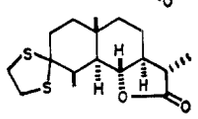
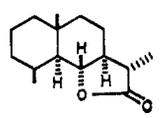
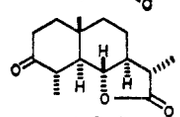
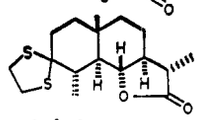
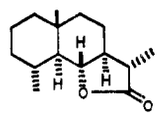
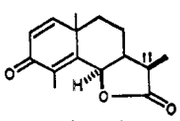
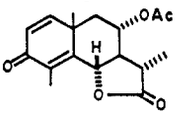
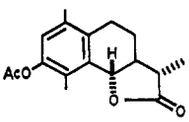
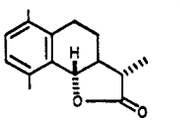
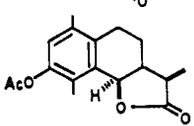
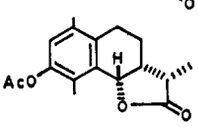
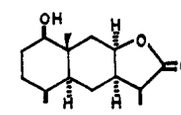
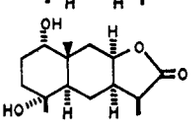
A.—In *trans*-lactones like α- or β-santonins (XXV, XL, Tables II and III) or their hydrogenation products (XXVI, XXIX, XLI, XLII), the B ring has no flexibility and is rigidly held owing to the *trans* fusion of the lactone ring. In 6-epi-α-santonin (XLIV) and its hydrogenation products (XLV, XLVI) the B ring is capable of existing in a boat conformation, but, if it were so, models show that the lactone carbonyl should strongly shield the C_{10}-angular methyl group. However, the angular methyl group shows virtually the same chemical shifts of about 1.33 ppm in α- and 6-epi-α-santonin (XXV, XLIV) and of about 1.20 ppm in tetrahydro-α- and tetrahydro-6-epi-α-santonin (XXIX, XLVI). This shows that the B ring is in the chair conformation in the *cis*-lactones as well as in the *trans*-lactones. Hence in the *trans* angular (XXV to XXXI, XXXIII to XXXV, XL to XLIII) or linear (XLVIII) lactones, the C_{11}-β-CH_3 would be pseudo-axial and C_{11}-α-CH_3 pseudo-equatorial. In the *cis* angular (XXXII, XXXVI, XLIV to XLVII) and linear lactones (XXXVIII, XXXIX) the opposite relations would hold; *viz.*, C_{11}-β-CH_3 would be pseudo-equatorial and the C_{11}-α-CH_3 pseudo-axial. Lactone XXXVII is the optical antipode of XXXVI.

It has recently been observed that axial and equatorial methyl groups adjacent to ester carbonyl groups show different types of solvent shifts in benzene, when compared with those in chloroform.[33] This difference should be much more prominent with respect to the

(25) J. A. Hamilton, A. T. McPhail, and G. A. Sim, *J. Chem. Soc.*, 708 (1962).
(26) I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *ibid.*, 4133 (1962).
(27) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).
(28) K. Brown, A. R. Katrizky, and J. A. Waring, *Proc. Chem. Soc.*, 257 (1964).
(29) J. B. Lambert and R. G. Keske, *J. Amer. Chem. Soc.*, **88**, 620 (1966).
(30) R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 335 (1965).
(31) E. L. Eliel and M. C. Knober, *J. Amer. Chem. Soc.*, **88**, 5347 (1966).
(32) S. R. Hall and E. N. Masler, *Acta Cryst.*, **18**, 265 (1965).
(33) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Lett.*, 3639 (1965).

TABLE II

PSEUDO-EQUATORIAL METHYL GROUP

No.	Compound	Chemical shift of —the C_{11}–CH_3 in— $CDCl_3$	Benzene (pyridine)[a]	$\delta_{CDCl_3} - \delta_{C_6H_6}$ ($\delta_{CDCl_3} - \delta_{C_5H_5N}$)[b]	Ref
XXV		1.28	0.99 (1.23)	+0.29 (+0.05)	4
XXVI		1.25	1.05 (1.19)	+0.20 (+0.06)	*c*
XXVII		1.18	0.97 (1.15)	+0.21 (+0.03)	*d*
XXVIII		1.21	1.04 (1.18)	+0.17 (+0.03)	*d*
XXIX		1.24	1.03 (1.16)	+0.21 (+0.08)	*d*
XXX		1.18	0.96 (1.13)	+0.22 (+0.05)	*d*
XXXI		1.19	1.02 (1.16)	+0.17 (+0.03)	*d*
XXXII		1.26	0.98 (1.21)	+0.28 (+0.05)	15
XXXIII		1.28	1.06 (1.34)	+0.22 (−0.06)	*e*
XXXIV		1.28	1.03 (1.23)	+0.05 (+0.05)	13
XXXV		1.26	1.01 (1.21)	+0.05 (+0.25)	4
XXXVI		1.27	1.02 ...	+0.25 ...	4
XXXVII		1.27	1.02 ...	+0.25 ...	4
XXXVIII		1.21	1.03 (1.19)	+0.18 (+0.02)	*f*
XXXIX		1.23	... (1.18)	... (+0.25)	*g*

[a] The figures given in parentheses are the chemical shifts in pyridine solution. [b] The figures in parentheses are the chemical shifts in $CDCl_3$ minus those in pyridine solution. [c] J. B. Hendrickson and T. L. Bogard, *J. Chem. Soc.*, 1678 (1962). [d] O. Kovacs, V. Herout, M. Horak, and F. Šorm, *Coll. Czech. Chem. Commun.*, **21**, 225 (1956). [e] M. Sumi, *J. Amer. Chem. Soc.*, **80**, 4869 (1958). [f] W. Herz and N. V. Viswanathan, *J. Org. Chem.*, **29**, 1022 (1964). [g] W. Herz, G. Högenauer, and A. Romo de Vivar, *ibid.*, **29**, 1700 (1964).

side-chain methyl of γ-lactones, wherein both the carbonyl and the methyl groups are held rigidly in a cyclic structure. To determine this, 24 γ-lactones of different types were prepared and their nmr spectra scanned in chloroform, benzene, and pyridine solutions. The chemical shifts of C_{11}–CH_3 in these compounds are tabulated in Tables II and III.

The tables show that the signals of the pseudo-equatorial methyl groups exhibit an upfield shift of about 0.23 ± 0.06 ppm in benzene relative to chloroform solution (Table II), whereas the pseudo-axial ones exhibit a very large upfield shift of 0.46 ± 0.06 ppm (Table III). The difference between the solvent shifts of the two categories is so large that the conformation of this methyl group could not be mistaken. Interestingly, these shifts are somewhat different in magnitude and direction from those observed for methyl groups adjacent to ketones.[34]

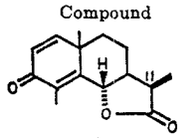
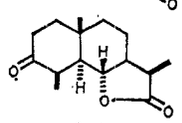
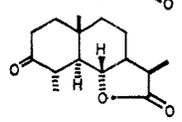
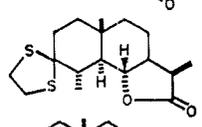
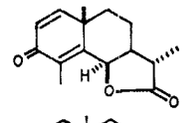
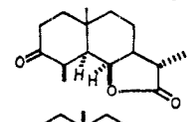
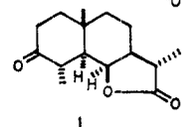
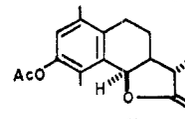
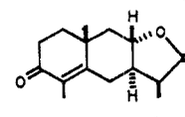
The tables show that chemical shifts of the C_{13} protons (in $CDCl_3$) are affected by the carbonyl group and double bonds in ring A (compare XXV with XXXI in column 3). The C_3 carbonyl group alone deshields the C_{13} protons by 0.05 ppm, although they are seven bonds (six carbon–carbon and one carbon–hydrogen single bonds) away (compare XXVI with XXVIII, or XXIX with XXXI, in column 3). When this distant methyl group comes a little closer in space to the C_3 carbonyl, by becoming pseudo-axial, the deshielding is more, *ca.* 0.10 ppm (compare XLIII with XLI or XLII, column 3), and when it is still nearer the deshielding rises to +0.16 ppm (compare XLIII with XLV or XLVI). Since in these cases the separation of seven single bonds is maintained, the downfield shift of these distant protons is probably to be attributed to the field effect of the carbonyl, rather than to its inductive effect. It is interesting to note that in XXIX the distance between the two groups on Dreiding models is over 7 Å. Similarly an aromatized ring A deshields the pseudo-equatorial C_{11}–CH_3 by about 0.08 ppm (compare XXXI, column 3, with XXXIV to XXXVII, column 9) and pseudo-axial C_{11}–CH_3 by about 0.18 ppm (compare XXXI, column 3, with XLVII, column 3).

The solvent shifts (columns 5 and 11) do not seem to be very much affected by the presence of a C_3 ketone or double bonds. Thus between XLIII and XLIV which show the largest difference of 0.23 ppm in their chemical shifts in chloroform (column 3) the difference in $\delta_{CHCl_3} - \delta_{C_6H_6}$ is only 0.03 ppm (column 5) and between XXVI and XXVII or XXIX and XXX having

(34) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).

TABLE III

PSEUDO-AXIAL METHYL GROUP

No.	Compound	Chemical shift of —the C_{11}–CH_3 in— $CDCl_3$	Benzene (pyridine)[a]	$\delta_{CDCl_3} - \delta_{C_6H_6}$ ($\delta_{CDCl_3} - \delta_{C_6H_5N}$)[b]	Ref
XL		1.26	0.71 (1.16)	+0.55 (+0.10)	4
XLI		1.27	0.79 (1.14)	+0.48 (+0.13)	14
XLII		1.26	0.78 (1.10)	+0.48 (+0.16)	14
XLIII		1.16	0.76 ...	+0.40 ...	3
XLIV		1.39	0.96 (1.29)	+0.43 (+0.10)	*c*
XLV		1.31	0.84 (1.18)	+0.47 (+0.13)	*d*
XLVI		1.32	0.88 (1.23)	+0.44 (+0.09)	*d*
XLVII		1.37	1.00 (1.28)	+0.37 (+0.09)	4
XLVIII		1.26	0.81 (1.18)	+0.45 (+0.08)	*e*

[a] The figures in parentheses are the chemical shifts in pyridine solution. [b] The figures in parentheses are the chemical shifts in $CDCl_3$ minus those in pyridine solution. [c] H. Ishikawa, *J. Pharm. Soc. Jap.*, **76**, 504 (1956). [d] W. Cocker, B. Donnelly, H. Gobinsingh, T. B. H. McMurry, and M. A. Nisbet, *J. Chem. Soc.*, 1262 (1963). [e] W. Cocker and M. A. Nisbet, *ibid.*, 534 (1963).

a difference of 0.06–0.07 ppm in chloroform (column 3) there is practically no difference in $\delta_{CDCl_3} - \delta_{C_6H_6}$ (column 5). Thus these large shifts appear to be mostly brought about by the lactone group alone.

Pseudo-equatorial methyl groups seem to be too far away from the benzenoid A ring to be seriously affected by it (*e.g.*, XXXIV to XXXVII), but a pseudo-axial methyl group appears to be affected; *e.g.*, in compound XLVII the signal of the C_{13} protons is slightly brought down from its normal value of 0.46 ± 0.06 ppm (column 5).

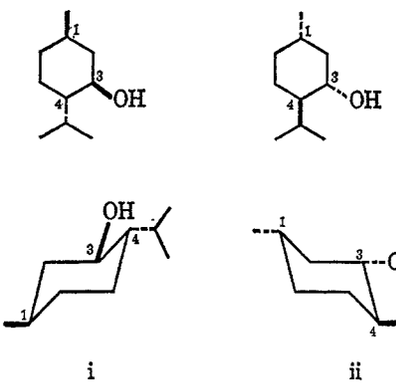
Since the *cis* or *trans* nature of the lactone will be easily revealed from the J values of C_6– or C_8–H, as the case may be,[35,36] determination of these solvent shifts would directly lead to the stereochemistry of the C_{11}–CH_3. Spectra in pyridine solution also show similar shifts, though of small magnitude (about +0.05 ppm for pseudo-equatorial and about +0.10 ppm for pseudo-axial ones), and could be used when the compound is insoluble in benzene, as is the case with XXXIX.

These results clearly show that C_{11}–CH_3, in either of the two possible configurations in any of the γ-lactone rings, assumes a pseudo-axial or pseudo-equatorial position, as the case may be, with respect to the lactone ring. If the methyl group were equally inclined to the plane of the lactone ring as in simple methylcyclopetenes or -pentanes (which have an average planar form), a marked solvent shift in the two different configurations would not be expected. Comparable solvent shifts have recently been observed for similarly located methyl groups in axial and equatorial conformations of fused δ-lactones.[37]

The present results also show that ring B in all desmotroposantonins except XXXVII retains the same chair or half-chair conformation as that of its parent santonin, since the C_{11}–CH_3 has the corresponding conformation in both. Since XXXVII also displays the solvent shift characteristic of a pseudo-equatorial C_{11}–CH_3 as XXXVI, models would show that ring B in XXXVII should exist in the alternate half-chair conformation to that in XXXVI (or the parent santonin). This is to be expected since the two have enantiomeric structures.[38]

B.—Another approach can also be made in suitable cases to determine the stereochemistry of C_{11}–CH_3. This depends on finding the C_{11}–H—C_7–H coupling constant. As the γ-lactones can be fused *cis* or *trans*, and in each case the C_{11}–H can have an α or β orientation, there are four possible situations that can arise. When these four different situations and the coupling pattern of the C_{11}–H in each of them are examined, the following results are obtained.

i.—***trans*-Lactones, Pseudo-Axial C_{11}–H.**—The C_{11}–β-H in α-santonin[36] (XXV) and 6-epidesmotroposantonin acetate (XXXIV) is found split into a doublet of



i ii

quartets. Double irradiation at the signal of the C_{11}–CH_3 on a 100-Mc nmr spectrometer shows the C_{11}–H as a doublet centered at δ 2.47 in XXV and at δ 2.43 in XXXIV, $J_{11\beta,7\alpha}$ being 12.5 cps.

ii.—***trans*-Lactones, Pseudo-Equatorial C_{11}–H.**—The C_{11}–α-H in β-santonin (XL) on the other hand is split into a quintet, J = 7.5 cps, showing thereby that the

(35) C. R. Narayanan and N. K. Venkatasubramanian, *Indian J. Chem.*, **2**, 274 (1964).

(36) J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).

(37) G. Di Maio, P. A. Tardella, and C. Iavarone, *Tetrahedron Lett.*, 2825 (1966).

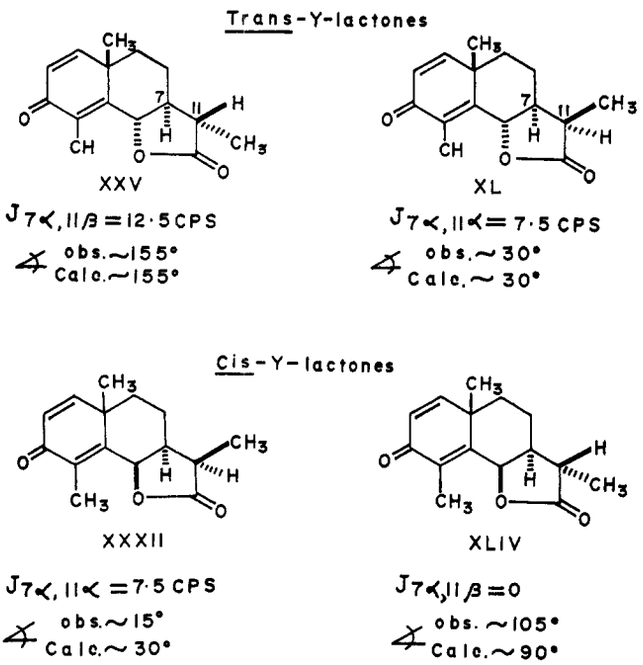
(38) See for example the enantiomeric menthols i and ii. The chair form of i has to be flipped to form the alternate chair in the case of ii so as to retain the conformations of the substituents which are the same in both.

C_{11}–H in this case makes equal coupling with the C_7–H and the C_{11}–CH_3.

iii.—*cis*-Lactones, Pseudo-Axial C_{11}–H.—In 6-epi-β-santonin (XXXII) and (−)-β-desmotroposantonin acetate (XXXVI), the C_{11}–α-H again shows up as a quintet, J = 7.5 cps, the C_{11}–H having in this case also equal coupling with the C_{11}–CH_3 and the C_7–H.

iv.—*cis*-Lactones, Pseudo-Equatorial C_{11}–H.—In 6-epi-α-santonin (XLIV) and (−)-α-desmotroposantonin acetate (XLVII) the C_{11}–β-H shows up as a quartet, J = 7 cps, showing thereby that the C_7–α-H has no appreciable coupling with the C_{11}–β-H. This is confirmed by spin decoupling of the C_{11}–CH_3, which shows the C_{11}–β-H as a sharp singlet at δ 2.57 in XLIV and at δ 2.52 in XLVII.

These distinctive coupling patterns of the C_{11}–H, wherever they are identifiable, can also be used to find the stereochemistry of the C_{11}–CH_3 and also that of the lactone fusion. In ii and iii where the pattern is the same, the coupling constant of the C_6–H (in the case of angular lactones) or C_8–H (in the case of linear lactones) as the case may be, with the 7-H, can show whether the lactone is *trans* or *cis* fused, and the coupling pattern of the C_{11}–H would then give the configuration of the C_{11}–CH_3.



The J values of 12.5 cps in α-santonin (XXV) and 7.5 cps in β-santonin (XL) which have the *trans*-lactone system (i and ii) would require a dihedral angle of about 155° in the former and about 30° in the latter.[39] Models show that these are nearly as required, but with the *cis*-lactones (iii and iv) the situation is somewhat different. In the case of 6-epi-β-santonin (XXXII), where there is a coupling constant of about 7.5 cps, one expects a dihedral angle of about 30° between 11α-H and 7α-H, but Dreiding models of the molecule show a dihedral angle of about 15° only. Similarly in the case of 6-epi-α-santonin (XLIV) there is no observable coupling between H_7 and H_{11}. This would indicate a dihedral angle of about 90° between them. However, models show only a dihedral angle of 105°. A bending and twisting of the lactone plane, away from ring B, at C_7–C_{11} (and probably at C_6–O_{17}), by about 15° or more so as to move C_{11}–CH_3 further away from C_8 would be needed in the case of both the *cis*-lactones to give the dihedral angles corresponding to the J values observed. This thus gives strong support to the argument advanced in the earlier section that in the case of the *cis*-lactones the plane of the lactone ring is so bent and twisted that the α- and β-C_{11}–CH_3 is considerably farther away from the C_8 protons than would be expected from models.

Making a rough energy calculation, a dihedral angle of 30° in (XXXII) between the 7α-H and 11α-H would mean that the angle between the planes $C_8C_7C_{11}$ and $C_7C_{11}C_{13}$ is 30°, *i.e.*, midway between an eclipsed and skew interaction[27,40] between C_8 and C_{13}. Making allowance for the larger angles $C_7C_{11}C_{13}$ (115°), $C_8C_7C_{11}$ (122°), and longer bond length of C_{11}–C_{13} (1.63 Å)[10] the energy of the interaction between C_8 and C_{13} should be expected to be less than 2 kcal (eclipsed, 4.4–6.1, and skew, 0.8 kcal/mol). Similarly in XLIV whose lactone is found to make the same angle as XXXII with ring B, the C_{11}–α-CH_3 is much closer to the two α-hydrogen atoms at C_6 and C_7 than 2.55 Å, the normal distance between an axial methyl group and the 1,3-*cis*-diaxial hydrogen atoms in a cyclohexane ring[41] ($C_6C_7C_{11}$ angle is 99° and $C_7C_{11}C_{12}$ angle 102°).[10] This alone would considerably raise the energy of XLIV.[42] Added to this is also the small interaction of the lone pair of electrons on O_{17}. All of these together may therefore be expected to give an energy of over 2 kcal (two normal axial CH_3–H interactions alone, 1.8 kcal/mol)[43] for the C_{11}–αCH_3, thus giving XLIV a significantly higher energy than XXXII, as observed by actual measurements,[23] and thus leading to the isomerization of this methyl group[15,24] from the pseudo-axial to the pseudo-equatorial conformation in the *cis*-lactones. As this is largely brought about by angle distortions needed for the fusion of the five-membered lactone ring to a rigid cyclohexane ring, such a ready isomerization of a methyl group or bond from a pseudo-axial to a pseudo-equatorial conformation should be expected as a general feature of such systems, although this might appear to involve an eclipsed butane interaction.

Experimental Section

Melting points are uncorrected and were taken on a Gallenkamp melting point apparatus. Optical rotations were determined in 1% chloroform solution in a Perkin-Elmer spectrophotometer or a Carl Zeiss polarimeter. Nmr spectra were recorded on a Varian A-60 spectrometer in 10% solution in the solvents given. The signals were recorded in δ (parts per million) using TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrometer. Chromato-

(39) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

(40) K. S. Pitzer, *Discussions Faraday Soc.*, **10**, 66 (1951).

(41) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 43.

(42) Some idea of the energy involved in nonbonded interactions between two hydrogen atoms when they come too close can be gained from the following data [the internuclear distance is given in angstroms and the potential energy (in parentheses) is given in kilocalories per mole]: 2.6 (0.7), 2.4 (1.4), 2.2 (2.7), 2.0 (5.0), 1.8 (9.1). In the present case, the energy involved would be about three times those given, since the interaction involved is that between one hydrogen atom and the three hydrogen atoms on a methyl group: E. A. Mason and M. M. Kreevoy, *J. Amer. Chem. Soc.*, **77**, 5808 (1955); L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 825.

(43) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, **69**, 2488 (1947).

grams were run on neutral Brockmann grade II alumina. Thin layer chromatography was carried out on silica gel mixed with plaster of Paris (15%) as binder. The plates were sprayed with concentrated H_2SO_4. Petroleum ether refers to fraction boiling between 60 and 80°.

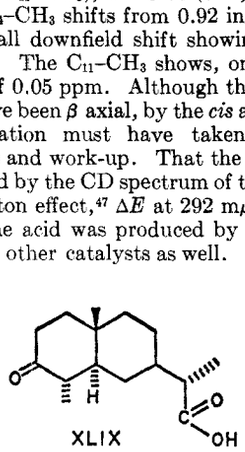
All known compounds were prepared according to the procedures given in the literature as cited in the references and identified by their melting points, specific rotations, and infrared spectra. The homogeneity of the compounds was often checked by thin layer chromatography on silica gel.

Thio Ketal of 4 α-Methyltetrahydro-β-santonin (XLIII).—To a solution of 100 mg of 4α-methyltetrahydro-β-santonin in 3 ml of acetic acid was added 0.1 ml of ethanedithiol and 0.2 ml of BF_3 etherate and kept at room temperature for 5 hr. The solution was poured into water and worked up. The product was crystallized from alcohol and recrystallized from the same solvent to yield 90 mg of XLIII: mp 155°; $[\alpha]D$ +75° (*c* 1.2); ν_{max} 1754 cm^{-1} (γ-lactone). *Anal.* Calcd for $C_{17}H_{26}O_2S_2$: C, 62.56; H, 8.03. Found: C, 62.50; H, 8.16.

4β-Methyltetrahydro-6-epi-α-santonin (XLV).—Considerable difficulty was experienced in preparing this compound. Hydrogenation of 6-epi-α-santonin on 10% Pd–$CaCo_3$, 2% Pd–$SrCo_3$, or 5% Pd–C gave almost exclusively an acid, by the hydrogenolysis of the 6β-ether oxygen function. In α-santonin, where the C_6–O bond is quasi-equatorial, practically no hydrogenolysis was encountered under these conditions, showing thereby that the quasi-axial alcoholic oxygen is more prone to hydrogenolysis. The title compound was, however, prepared in about 20% yield by the following procedure.

6-Epi-α-santonin (1 g) in 30 ml of ethyl acetate was hydrogenated over 200 mg of 10% Pd–C[44,45] until no more hydrogen was absorbed (2 hr). The solution was filtered and extracted with 5% sodium bicarbonate solution. The ethyl acetate solution was further washed with water, dried over sodium sulfate, and evaporated. The solid was crystallized from ethyl acetate to give 225 mg of the compound: mp 196° (lit.[46] mp 196–197°); $[\alpha]D$ −133° (*c* 1.4) (lit.[46] −135°); ν_{max} 1770 (lactone) and 1710 cm^{-1} (cyclohexanone).

The bicarbonate extract was acidified and extracted with ether to give 700 mg of an acid. It was esterified with diazomethane to give a liquid which was chromatographed over 30 g of alumina grade II. Elution with 25% petroleum ether–75% benzene (250 ml) and removal of solvent gave 650 mg of a viscous liquid. It was distilled under vacuum: bath temperature, 160–165° (0.2 mm); $[\alpha]D$ +44° (*c* 1.5); ν_{max} (liquid film) 1750 (ester) and 1725 cm^{-1} (cyclohexanone). *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.20; H, 9.32. The nmr spectrum showed signals at δ 0.92 (3 H, doublet, J = 7 cps, C_4–CH_3), 1.06 (3 H, singlet, C_{10}–CH_3), 1.07 (3 H, doublet, J = 7 cps, C_{11}–CH_3), and 3.63 (3 H, singlet, $COOCH_3$). The signal of the C_4–CH_3 shifts from 0.92 in chloroform to 0.99 in benzene, the small downfield shift showing that the methyl group is equatorial. The C_{11}–CH_3 shows, on the other hand, a small upfield shift of 0.05 ppm. Although the C_4–CH_3 originally produced should have been β axial, by the *cis* addition of hydrogen at C_4,C_5, epimerization must have taken place during the acidification process and work-up. That the A/B rings are *trans* locked was confirmed by the CD spectrum of the compound which gave a positive Cotton effect,[47] ΔE at 292 mμ = +0.78 (solvent dioxane). The same acid was produced by hydrogenolysis and hydrogenation with other catalysts as well. It should thus have structure XLIX.



XLIX

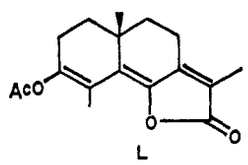
(44) This catalyst in its preparation had to be finally reduced by hydrogen.[45] That prepared by reduction with formaldehyde in the final stage completely hydrogenolyzed the lactone.

(45) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1964, p 950.

(46) See Table III, footnote *d*.

(47) We are indebted to Professor G. Snatzke, University of Bonn, for the CD measurements.

6-Epidesmotroposantonin acetate (XXXIV) could be prepared only twice.[48] Treatment of α-santonin with acetyl chloride and acetic anhydride gave a 20% yield of this substance,[13] a reaction which was able to be repeated only once. Purification of the reagents or addition of small amounts of aqueous hydrochloric acid did not improve the situation. The product invariably obtained, either as the main product or as the sole product, was the enol lactone for which structure L has been proposed.[13]



L

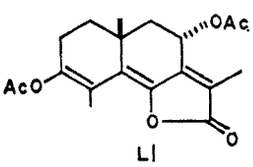
The nmr spectrum of this compound confirmed the proposed structure. It showed the acetate methyl at δ 2.23, C_4-vinyl methyl at 1.89, C_{10}–CH_3 at 1.17, and C_{11}–CH_3 as a clear triplet (J = 1.5 cps) centered at 2.00 (probably due to long-range coupling with the two protons at C_8, or an axial proton at C_8 and another axial proton at C_2[49,50]), and no vinyl proton signal.

Registry No.—I, 13927-50-9; II, 481-06-1; III, 13902-55-1; IV, 13902-54-0; V, 1618-78-6; VI, 1618-77-5; VII, 13743-88-9; acetate of VII, 14794-71-9; methyl ether of VII, 13743-90-3; VIII, 13743-89-0; IX, 13743-96-9; X, 16963-59-0; acetate of X, 16963-60-3; methyl ether of X, 16963-61-4; XI, 16963-62-5; XII, 16963-63-6; XIII, 16963-64-7; XIV, 16963-65-8; XV, 16963-66-9; XVI, 16963-31-8; XVII, 16963-32-9; XVIII, 15797-9-30; XXVI, 14804-46-7; XXVII, 16963-35-2; XXVIII, 2221-83-2; XXX, 14804-50-3; XXXI, 14804-52-5; XXXIII, 1618-76-4; XXXIV, 16963-40-9; XXXV, 14794-97-9; XXXVI, 6339-71-5; XXXVIII, 16963-43-2; XXXIX, 14794-72-0; XLI, 14804-47-8; XLIII, 16963-46-5; XLV, 14987-66-7; XLVI, 14794-68-4; XLVIII, 10208-52-3; methyl ester of XLIX ($C_{16}H_{26}O_3$), 3717-63-3.

Acknowledgment.—We are indebted to Professor W. Cocker for samples XXXII, XXXIII, and XL, Professor Werner Herz for samples XXXVIII and XX, Shri N. R. Bhadane for the data on XXVII, and Dr. U. Scheidegger of Varian AG, Switzerland, for the decoupling experiments.

(48) We are indebted to Professor W. Cocker for kindly informing us that he also could prepare this compound only twice or thrice.

(49) To ascertain which of these two possibilities was the correct one, an enol lactone was prepared under the same conditions from artemisin acetate XXXIII. This compound, after chromatography on silica gel in benzene, showed a single spot in thin layer chromatography (solvent 5% ethyl acetate, 95% benzene) and had $[\alpha]D$ −132° (*c* 1.2), but could not be induced to crystallize. Its infrared spectrum was similar to that of L and hence should have the structure LI. Its nmr spectrum showed signals at δ 2.20



LI

(singlet, C_3 and C_8 acetate methyl signals), 1.27 (singlet, C_{10}–CH_3), 1.97 (singlet, C_4–CH_3), and at 2.05 (doublet, J = 1 cps, C_{11}–CH_3). Hence the triplet signal of the C_{11}–CH_3 in L is due to long-range coupling of the C_{11}–CH_3 with the C_8 α and β protons. (Such biallylic couplings[35] between both the protons of the allylic ring methylene group on the one side, and the protons of the vinyl methyl group on the other side, has recently been reported.[50]

(50) M. D. Nair and R. Mehta, *Indian J. Chem.*, **5**, 123 (1967).