

Determination of the Configuration and Conformation of γ -Metasantonin¹

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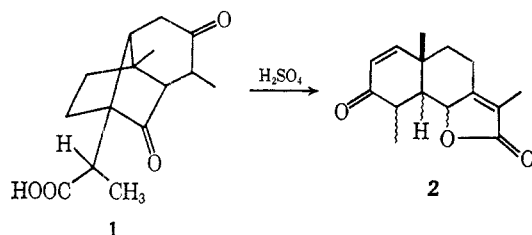
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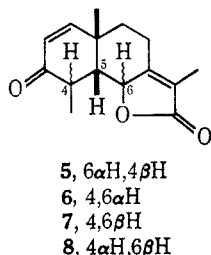
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γ -Metasantonin, the product obtained in 29% yield by treatment of santonin (1) with warm concentrated sulfuric acid, possesses structure 2.² A *cis* ring fusion in 2 was considered likely, since the bridgehead methyl and hydrogen substituents would have the same orientation relative to one another as in the precursor molecule 1; however, the possibility of *trans* ring fusion in 2 was not excluded.³



In the following discussion it will be demonstrated that from a study of the nmr spectrum of γ -metasantonin it is possible to define the stereochemistry at the ring fusion as well as at all the other asymmetric centers in this compound, and furthermore, to define the preferred conformation of γ -metasantonin in solution.

At the outset, six possible structures with completely defined stereochemistry were considered for γ -metasantonin, *viz.*, two *trans*-fused isomers, 3 (5,6 α H,4 β H) and 4 (5 α H,4,6 β H),⁴ and the four possible *cis*-fused isomers, 5-8.



The nmr spectrum (100 MHz) of γ -metasantonin exhibited several characteristic features (see Table I). The appearance of an AB pattern with doublets ($J = 10.1$ Hz) centered at δ 6.63 and δ 5.95 was in accord with the reported² position of the double bond at C-1-C-2. H-1 was also coupled to one other proton with

$J = 2.0$ Hz; spin-decoupling studies confirmed that this other proton was H-5. This observation served to exclude the *trans*-fused isomers 3 and 4 as possible structures for γ -metasantonin since it has been demonstrated that long-range spin coupling between protons at C-1 and C-5 does not occur in such *trans*-fused conjugated ketones in the decalin series [*e.g.*, only simple AB patterns are observed for *trans*-4,5-dihydrosantonin ($J_{1,2} = 9.5$ Hz),^{5a} tuberiferine ($J_{1,2} = 9.9$ Hz),^{5b} and farinosin ($J_{1,2} = 10$ Hz)^{5c}].

TABLE I
NMR SPECTRAL DATA FOR γ -METASANTONIN^a

Proton(s)	Chemical shift ^b	Multiplicity ^c	Observed coupling constants ^d
H-1	6.63	d, d (four lines)	$J_{1,2} = 10.1, J_{1,5} = 2.0$
H-2	5.95	d	$J_{1,2} = 10.1$
H-4	3.12	q, d (eight lines)	$J_{4,15} = 6.8, J_{4,5} = 3.7$
H-5	1.88	d, d, d (eight lines)	$J_{5,6} = 9.5, J_{4,5} = 3.7, J_{1,5} = 2.0$
H-6	4.48	d, q (eight lines, broadened)	$J_{5,6} = 9.5, J_{6,12} = 1.8$
H-12	1.78	d (broadened)	$J_{6,12} = 1.8$
H-14	1.37	s	
H-15	1.32	d	$J_{4,15} = 6.8$

^a The nmr spectrum was measured in CDCl₃ solution with a Varian HA-100 spectrometer. ^b Chemical shifts are relative to internal tetramethylsilane at δ 0.00. ^c Abbreviations are s, singlet; d, doublet; q, quartet (1:3:3:1); d, d, doublet of doublets; q, d, quartet of doublets. ^d Coupling constants are in hertz and were obtained from spectra run at 60 MHz; estimated accuracies are 0.1 Hz.

Thus it could be established at this point that only the *cis*-fused structures 5-8 need be considered, and also that γ -metasantonin probably exists in a preferred conformation in which the H-1-C-1-C-10-C-5-H-5 portion of the molecule is in the zigzag (W) coplanar configuration generally associated with long-range coupling phenomena.⁶⁻⁸

A slightly broadened doublet of quartets (d, q) appeared at δ 4.48 and was assigned to H-6. Spin-decoupling experiments proved that H-6 was coupled to H-5 ($J_{5,6} = 9.5$ Hz) and to the C-12 methyl hydrogens ($J_{6,12} = 1.8$ Hz); the signal for the latter hydrogens appeared as a slightly broadened three-proton doublet ($J_{6,12} = 1.8$ Hz) at δ 1.78. Comparison of the coupling constant $J_{5,6} = 9.5$ Hz with those observed for H-6 in several rigid systems in the santonin series [*e.g.*, *trans*-

(5) (a) E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, **87**, 5736 (1965); (b) J. B. Barrera, J. L. Bretón, M. Fajardo, and A. G. González, *Tetrahedron Lett.*, 3475 (1967); (c) T. A. Geissman and R. Mukherjee, *J. Org. Chem.*, 656 (1968).

(6) For a review see N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(7) Particularly relevant to this latter suggestion is the observation of similar long-range coupling between H-1 and H-5 ($J_{1,5} = 2.2$ Hz) in the *cis*-fused noreudesmanoid sesquiterpene, chamaecynone, which has led Nozoe, Cheng, and Toda to conclude (with the additional support of optical rotatory dispersion spectral data) that this compound exists in a nonsteroidal, rather than a steroidal, conformation.⁸

(8) T. Nozoe, Y. S. Cheng, and T. Toda, *Tetrahedron Lett.*, 3663 (1966); see also T. Nozoe, T. Asao, M. Ando, and K. Takase, *ibid.*, 2821 (1967).

(1) This work was partially supported by Public Health Service Research Grant 5-R01-GM-13441-03.

(2) R. B. Woodward and P. Yates, *J. Amer. Chem. Soc.*, **85**, 551 (1963).

(3) See footnote 15 in ref 2.

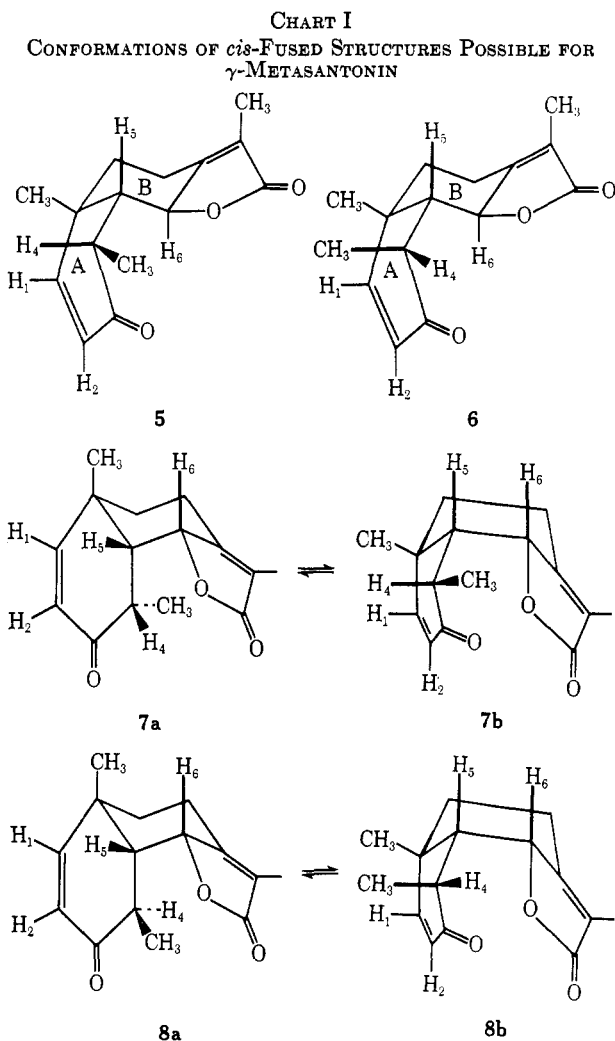
(4) The 4 α -H epimers of 3 and 4 were not considered likely to be present in significant concentration under acidic conditions which would allow formation of 3 and 4 from 1.

4,5-dihydrosantonin ($J_{5,6}$ or $J_{6,7} = 9.5, 10.5$ Hz),⁹ 5 α H, 6,11 β H-eudesm-1,3-dien-6,13-olide ($J_{5,6}$ or $J_{6,7} = 9.5, 11.5$ Hz),^{5a} and 10-*epi*-5 α H,6,11 β H-eudesm-1,3-dien-6,13-olide ($J_{5,6} = J_{6,7} = 10$ Hz)^{5a}] indicates that the value of $J_{5,6} = 9.5$ Hz observed for γ -metasantonin is compatible with the predominant existence in solution of only one highly preferred conformer of this compound which must have approximate dihedral angles between H-5 and H-6 of either $\theta \sim 0^\circ$ or $\theta \sim 180^\circ$.¹⁰⁻¹²

The signal due to H-5 appeared as a multiplet of eight lines of equal intensity (d,d,d) centered at δ 1.88. Spin-decoupling experiments demonstrated that, besides being coupled to H-1 and H-6, the H-5 proton was further coupled with H-4 ($J_{4,5} = 3.7$ Hz). The signal due to H-4 appeared as a quartet of doublets (q, d; 1:1:3:3:3:3:1:1) at δ 3.12; decoupling experiments indicated that H-4 was splitting the protons of the C-15 methyl group (doublet at δ 1.32, $J_{4,15} = 6.8$ Hz) and further confirmed that H-4 was split by H-5 with $J_{4,5} = 3.7$ Hz.

The magnitude of the vicinal coupling constant between H-4 and H-5 indicates¹¹ that the dihedral angle between these protons is in the vicinity of either 50 or 130°. Thus, at this point it can be concluded from the $J_{1,5}$, $J_{4,5}$, $J_{5,6}$ values that, of the B ring chair conformers of the *cis*-fused structures possible for γ -metasantonin (see Chart I), only **5** ($\theta_{5,6} \sim 170^\circ$, $\theta_{4,5} \sim 60^\circ$) and **6** ($\theta_{5,6} \sim 170^\circ$, $\theta_{4,5} \sim 60^\circ$) need be seriously considered.^{13,14} Of these, **5** would probably be favored under the acidic conditions of formation since the 1,3 interaction between the C-15 methyl and the lactonic oxygen at C-6 would be smaller than the 1,3 "diaxial" interaction between the C-14 and C-15 methyl groups in **6**, assuming no distortion of ring A in the latter case.¹⁵

Of the remaining structures, **7** and **8**, only the B ring boat conformers **7b** and **8b** could exhibit the observed $J_{4,5}$ and $J_{5,6}$ values and long-range coupling between



H-1 and H-5. Under the conditions employed for the formation of γ -metasantonin, **7b** might be expected to be preferred to its C-4 epimer, **8b** for the same reasons outlined above for preferring **5** to **6**. However, although **7b** might also be preferred to **7a** (in which there is a strong interaction between the C-15 methyl and the axial hydrogen at C-9), there does not appear to be any reason *a priori* to favor **7b**, having nonbonded eclipsing interactions associated with the B ring-boat form,¹⁶ over **8a** in which these interactions are non-existent.

Finally, since long-range spin coupling commonly occurs between α and α' hydrogens in approximately planar zigzag $H_\alpha-C_\alpha-CO-C_{\alpha'}-H_{\alpha'}$ systems,^{12,17} the absence of long-range spin-coupling interactions between H-2 and H-4 in γ -metasantonin suggests that H-4 is not oriented pseudo-equatorially to ring A and thus provides additional support for eliminating **8b** from consideration, and also for favoring **5** over **6**.

Thus, γ -metasantonin very probably has structure **5**, since this is the only structure having a preferred

(9) A. G. Hortmann, unpublished results.

(10) These conclusions follow from (a) the fact that for any given type of carbocyclic system the observed spin-coupling interaction between two hydrogens on adjacent carbon atoms having a dihedral angle $\theta \sim 0^\circ$ is always of approximately the same magnitude, but consistently somewhat less than that between hydrogens having $\theta \sim 180^\circ$;^{6,11} (b) the observation (see above) that 9.5 to 11.5 Hz is the approximate range of maximum values possible for $J_{5,6}$ in eudesman-6,13-olide systems; and (c) the consequence that for any given mobile conformational equilibrium involving **5-8**, any significant amount of a conformer other than **5** ($\theta_{5,6} \sim 170^\circ$), **6** ($\theta_{5,6} \sim 170^\circ$), **7b** ($\theta_{5,6} \sim 0-20^\circ$), or **8b** ($\theta_{5,6} \sim 0-20^\circ$) (see Chart I), respectively, would result in the prediction of a value for $J_{5,6}$ which would be markedly less than the value of 9.5 Hz observed for γ -metasantonin.¹²

(11) H. Conroy, *Advan. Org. Chem.*, **2**, 311 (1960).

(12) Cf. Y.-H. Pan and J. B. Stothers, *Can. J. Chem.*, **45**, 2943 (1967).

(13) For the purposes of this analysis, Dreiding models of **5-8** were built. The dihedral angles (θ) between hydrogens on adjacent carbon atoms were measured and estimates of the expected coupling constants^{6,11,14} $J_{4,5}$ and $J_{5,6}$ were made for comparison with the observed values. The estimates were made using models in which the B ring of each structure was in the chair form (see Chart I); for isomers **7** and **8** the possibility of the existence of the mobile conformational equilibria $7a \rightleftharpoons 7b$ and $8a \rightleftharpoons 8b$ was also considered (*vide infra*).

(14) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963), and references cited therein.

(15) If **6** were capable of existence in preference to **5** under these conditions it would seem (from inspection of Dreiding models) that distortion of ring A with a consequent increase of $\theta_{4,5}$ to ca. 90° and decrease of $J_{4,5}$ to ca. 0 Hz would result from the process of lessening the 1,3 diaxial interaction between the C-14 and C-15 methyl groups.

Furthermore, if a structure such as **6** could be favored over **5** it would be difficult to explain the observation of Nozoe, *et al.*,⁸ that base-induced equilibration at C-4 of chamaecynone (the favored conformation of which is similar to that depicted by **5**)⁷ favors *chamaecynone* over *isochamaecynone*, its epimer at C-4. This epimer, in contrast to the relative rigidity of **6** in the situation $5 \rightleftharpoons 6$, has the additional possibility of flipping into a seemingly more stable steroidal conformation having both the 7-ethynyl group and the C-15 methyl group equatorially oriented.

(16) These nonbonded interactions would be less severe in a conformation **7b** in which the B ring exists in a twist-boat form. However, $J_{5,6}$ for this form would be expected to be considerably less than the observed value of 9.5 Hz.

(17) Such $H_\alpha H_{\alpha'}$ coupling has been noted in at least two systems structurally analogous to γ -metasantonin: (a) aristolone ($J = 0.5$ Hz), H. Takeda, *Dissertation Abstr.*, **27**, 2303-B (1967); (b) 1-methyltricyclo-[4.4.0.0^{2,7}]dec-9-ene ($J = 2.0$ Hz), C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

conformation which could be expected to exhibit all the observed vicinal and long-range proton spin-coupling interactions.¹⁸

Registry No.— γ -Metasantonin (5), 17335-57-8.

(18) The authors wish to thank Dr. J. B. DeRoos for several of the spin-decoupling data.

Reaction of 3,4-Dihydro-2H-pyran with Methyl α -D-Glucopyranoside¹

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The use of 3,4-dihydro-2H-pyran² (2) as a hydroxyl blocking group in various synthetic reactions is well established.³ It has been determined⁴ that 3,4-dihydro-2H-pyran reacts unselectively with axial and equatorial hydroxyl groups in partially acetylated *myo*-inositol derivatives. In an attempt to determine how selectively alkyl vinyl ethers might react with an array of hydroxyl groups, methyl α -D-glucopyranoside was shown to form methyl 6-O-(1-alkoxyethyl)- α -D-glucopyranoside preferentially. The product was then readily convertible into methyl 4,6-O-ethylidene- α -D-glucopyranoside.⁵ It was thought that this latter process should not occur with a cyclic vinyl ether such as 3,4-dihydro-2H-pyran and thus this reagent might be preferred for such a preferential or selective reaction.

Equimolar quantities of methyl α -D-glucopyranoside (1) and 3,4-dihydro-2H-pyran (2) were brought into reaction, in *N,N*-dimethylformamide solution and under catalysis by *p*-toluenesulfonic acid, for different reaction periods. The products obtained were fully methylated and the acetal group was later removed from them by mild acid hydrolysis. Identification of the resulting methyl ethers of methyl α -D-glucopyranoside or D-glucose indicated the location of the acetal attachment. From these data it was determined that the reaction of 3,4-dihydro-2H-pyran with methyl α -D-glucopyranoside gave rise to a mixture of tri- and di-*O*-methyl-D-glucose. Conversion of these into the corresponding methyl glucosides allowed their separation and isolation by preparative vapor phase chromatography. The ratio of tri- to di-*O*-methyl glycoside was 5:1. The separated tri-*O*-methyl glycoside fraction liberated a tri-*O*-methyl-D-glucose having optical rotatory, chromatographic, and electrophoretic properties identical with an authentic sample of 2,3,4-tri-*O*-methyl-D-glucose.

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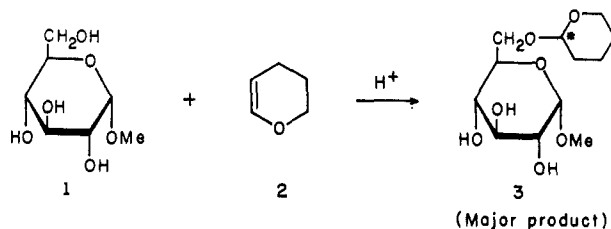
(2) R. Paul, *C. R. Acad. Sci., Paris*, **196**, 1409 (1933); *Bull. Soc. Chim. Fr.*, [5] **1**, 971 (1934).

(3) H. J. E. Lowenthal, *Tetrahedron*, **6**, 303 (1959); J. F. W. McOmie, *Advan. Org. Chem.*, **3**, 218 (1963).

(4) S. J. Angyal and S. D. Gero, *J. Chem. Soc.*, 5255 (1965).

(5) M. L. Wolfrom, A. Beattie, and S. S. Bhattacharjee, *J. Org. Chem.*, **33**, 1067 (1968).

In another experiment, the crude reaction product resulting from the reaction of equimolar amounts of 3,4-dihydro-2H-pyran with methyl α -D-glucopyranoside was fractionated by thin layer chromatography. The major component, obtained in a yield of 58% of the crude reaction product, was identified as methyl 6-*O*-tetrahydro-2H-pyran-2-yl- α -D-glucopyranoside on the basis of the following observations. On methylation and subsequent hydrolysis, the above compound gave 2,3,4-tri-*O*-methyl-D-glucose identified by conversion into the known crystalline *N*-phenyl-2,3,4-tri-*O*-methyl- β -D-glucopyranosylamine; this major component is chromatographically identical with a compound obtained from methyl 2,3,4-tri-*O*-acetyl- α -D-glucopyranoside by its reaction with 3,4-dihydro-2H-pyran followed by deacetylation. In some experiments a portion (25%) of the syrupy reaction product crystallized. The low yield of crystals was probably due to the syrup being a mixture of diastereoisomers since the acetal carbon (see 3) is asymmetric. It is accordingly estab-



lished that the cyclic 3,4-dihydro-2H-pyran and the acyclic vinyl ethers used previously⁵ react preferentially with the C-6 hydroxyl group of methyl α -D-glucopyranoside. In the case of the acyclic vinyl ethers, the acetal formed then readily reacts further with an available hydroxyl group to give an ethylidene cyclic acetal. With 3,4-dihydro-2H-pyran, however, some distribution of the acetal group takes place (Table I) instead of any further reaction of the *O*-tetrahydro-2H-pyran-2-yl group. Reaction of 3,4-dihydro-2H-pyran with methyl α -D-glucopyranoside is, therefore, not as selective as is the tritylation reaction.⁶

Experimental Section⁷

Reaction of Methyl α -D-Glucopyranoside with 1 Molar Equiv of 3,4-Dihydro-2H-pyran.—Methyl α -D-glucopyranoside (1, 15 g) was dispersed in dry *N,N*-dimethylformamide (30 ml) over Drierite (calcium sulfate as soluble anhydrite, 2 g). 3,4-Dihydro-2H-pyran (2, 6.5 g) was added, followed by a catalytic quantity

(6) B. Helferich and J. Becker, *Ann.*, **440**, 1 (1924).

(7) Paper chromatography was effected on Whatman No. 1 paper in the solvent systems 1-butanol-ethanol-water (4:1:5 v/v, solvent A), 1-butanone-1% ammonium hydroxide (10:1 v/v, solvent B) with indication by *p*-anisidine hydrochloride solution [L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1702 (1950)] or with silver nitrate and alkali [W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950)]. Solutions were concentrated under reduced pressure. Melting points were determined in a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained with a Perkin-Elmer Infracord infrared spectrometer. Ascending thin layer chromatography was effected on 0.25–1.25 mm layers of silica gel G (E. Merck, Darmstadt, Germany), activated at 110°, using the solvent systems benzene-ethanol-water-10 *N* ammonium hydroxide (200:47:15:1 v/v, solvent C) and chloroform-acetone (1:1 v/v, solvent D) with indication by iodine vapor (preparative) or sulfuric acid. Vapor phase chromatography was effected with a Beckman GC 2A gas chromatograph containing a thermal conductivity detector with helium as the carrier gas. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data, interplanar spacing, Å, Cu K α radiation, λ 1.539 Å, Ni filter, camera diameter 114.6 mm, photographic recording, are expressed as relative intensities, estimated visually: vs, very strong; s, strong; m, medium; w, weak; vw, very weak. Parenthetical numerals indicate the order of the most intense lines; 1, most intense.