30 ml. of 2 *N* sodium hydroxide and finally with water. After the organic layer was dried overnight with magnesium sulfate, the solvent was removed by distillation. The residue was recrystallized three times from a mixture of chloroform and petroleum ether to yield 0.18 g. (40%) of 1,2-dimethyl-1,2-di-(benzoxymethyl)-3,5-cyclohexadiene (III), m.p. 102.5–103.5°.

Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.59; H, 6.39. Found: C, 76.70; H, 6.28.

Treatment of III with benzoyl peroxide in benzene produced only a very low molecular weight substance.

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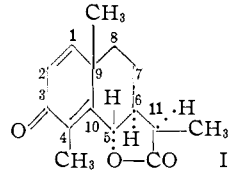
The Stereochemistry of Santonin, β-Santonin and Artemisin

BY E. J. COREY

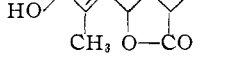
RECEIVED OCTOBER 25, 1954

Although the Clemo–Haworth–Walton structure for santonin[1] has been confirmed beyond doubt by numerous chemical studies and, more recently, by total synthesis,[2] the stereochemistry of santonin has remained an unsolved problem.[3] The purpose of the present note is to adduce evidence in favor of stereoformula I for (−)-santonin[4] and IX and X for the related β-santonin and artemisin.



I

The first important evidence on the stereochemistry of santonin was obtained by a study of the well-known (−)-α- and (+)-β-desmotroposantonins (II) (obtained by the action of acids on santonin) and two of their stereoisomers, (−)-β- and (+)-α-desmotroposantonins (II). The stereochemical relationships between these four isomeric desmotroposantonins, which are of key importance



II

to the stereochemistry of santonin, have been elucidated elegantly by Huang-Minlon[5] and are summarized in Table I. As has been pointed out by Huang-Minlon the six-membered-alicyclic and lactone rings are *cis* locked in all four known desmotroposantonins. The *cis* fusion, which is the more stable one in the desmotroposantonins and the hyposantonins and which is the only one encountered in the desmotropo series, is not present in santonin itself which possesses a *trans* juncture of the lactone and six-membered alicyclic rings.[5,6]

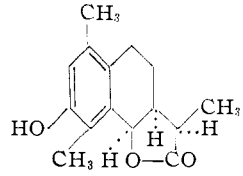
TABLE I

RELATIVE CONFIGURATIONS OF THE DESMOTROPOSANTONINS[a]

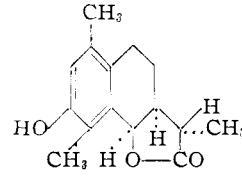
Compound	$[\alpha]_D$	Configuration at $C_{(5)}$	$C_{(6)}$	$C_{(11)}$
(−)-α-Desmotropo	−140	(−)	(+)	(+)
(+)-α-Desmotropo	+130	(+)	(−)	(−)
(−)-β-Desmotropo	−106	(−)	(+)	(+)
(+)-β-Desmotropo	+106	(+)	(−)	(−)

[a] The symbol (+) refers to the more dextrorotatory configuration and the symbol (−) to the opposite configuration.

(−)-α-Desmotroposantonin is unstable relative to (+)-β-desmotroposantonin and can be converted to it by isomerization in 50% sulfuric acid.[7] During this transformation the configuration at $C_{(11)}$ remains unchanged, but the configurations at $C_{(5)}$ and $C_{(6)}$ are both inverted. As a consequence, in one isomer the methyl substituent at $C_{(11)}$ is *cis* to the carbons attached to $C_{(5)}$ and $C_{(6)}$, whereas in the other isomer the methyl group at $C_{(11)}$ is *trans* to the carbons attached to $C_{(5)}$ and $C_{(6)}$. Clearly, the former is the unstable and the latter is the stable arrangement. Thus, the methyl group at $C_{(11)}$ in (−)-α-desmotroposantonin (III) is *cis* to the carbons attached to $C_{(5)}$ and $C_{(6)}$ and the methyl group at C_{11} in (+)-β-desmotroposantonin (IV) is *trans* to the carbons attached to $C_{(5)}$ and $C_{(6)}$. As is to



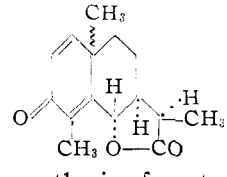
+ mirror image
III, α-series



+ mirror image
IV, β-series

be expected from the Huang-Minlon assignments (Table I) (+)-α-desmotroposantonin can be isomerized to (−)-β-desmotroposantonin.[8]

The configurations at $C_{(6)}$ and $C_{(11)}$ in santonin are known to be the same as in (−)-α-desmotroposantonin whereas the configuration at C_5 is opposite in two compounds.[5,9] Thus, santonin must be represented by expression V or its mirror image.



V

The recent synthesis of santonin[2] permits correlation of the configurations at $C_{(6)}$ and $C_{(9)}$ as follows. The intermediate from which santonin was synthesized is the bicyclic malonic ester VII which was prepared by the Michael addition of methylmalonic ester to the dienone VI. Since the

(1) G. R. Clemo, R. D. Haworth and E. Walton, *J. Chem. Soc.*, 2368 (1929).

(2) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *Proc. Japan Acad.*, **30**, 116, 119 (1954).

(3) For a recent discussion see W. Cocker and T. B. H. McMurray, *Chem. and Ind.*, 1199 (1954).

(4) *I.e.*, naturally occurring, (−)-α-santonin.

(5) Huang-Minlon, THIS JOURNAL, **70**, 611 (1948).

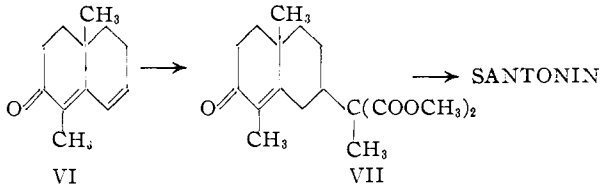
(6) The *trans* structure for the desmotropo- and hyposantonins involves strong steric interaction between the lactonic oxygen and the nearby methyl substituent at $C_{(4)}$ whereas the *cis* locked structure which has the a′ orientation of oxygen is free of this interaction.

(7) G. Bargellini and A. Mannino, *Gazz. chim. ital.*, **39**, II, 101 (1909).

(8) Huang-Minlon, C. Lo and L. Chu, THIS JOURNAL, **65**, 1780 (1943); *J. Chinese Chem. Soc.*, **10**, 126 (1943).

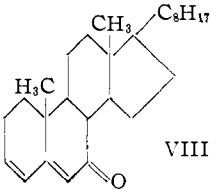
(9) D. H. R. Barton, *J. Org. Chem.*, **15**, 466 (1950).

Michael adduct VII was transformed into santonin by reactions which do not affect the configurations



VI VII

of $C_{(6)}$ and $C_{(9)}$, the relative configurations at these carbon atoms are the same in the Michael adduct VII as in santonin. It is probable that the malonic ester substituent at $C_{(6)}$ and the angular methyl group at $C_{(9)}$ are *cis* in the Michael adduct (malonic ester group equatorial) because in the very closely analogous addition of malonic ester to cholesta-3,5-diene-7-one (VIII) the malonic ester substituent assumes the equatorial (β) orientation, *cis* to the angular methyl group.[10-12] The equatorial arrangement is the more stable one and would

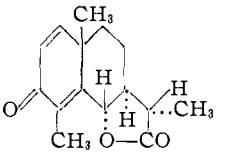


VIII

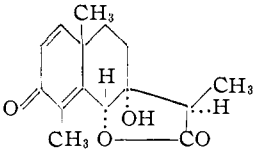
result either if the Michael addition proceeded to give the stable epimer more rapidly or if the addition were sufficiently rapidly reversible to allow equilibration.[13] There is, therefore, a good basis for formulating santonin as I or its mirror image.

Evidence for the absolute configuration of (−)-santonin can be deduced using the method of molecular rotation differences.[14] The molecular rotation difference between (−)-santonin (M_D −426[15]) and its 1,2-dihydroderivative (M_D +187[15]) is +613° which is comparable to that between $\Delta^{1,4}$-cholesta-diene-3-one (M_D +107) and Δ^4-cholestenone (M_D +342), ΔM_D +235°. The ΔM_D value for santonin and either of its tetrahydroderivatives[15] (the two tetrahydroderivatives which are probably epimeric at C_{10} have approximately the same rotation) is *ca.* +450° and that for $\Delta^{1,4}$-cholestadiene-3-one and cholestanone is +245°. The large positive values of ΔM_D in all cases indicates that (−)-santonin is related stereochemically to the steroids and, hence, is correctly represented by stereoformula I and *not* its mirror image.

On the basis of formula I for (−)-santonin and previously derived relationships,[9] it is now possible to assign formula IX to β-santonin and formula X to artemisin.



IX



X

NOTE ADDED JANUARY 8.—Since the submission of this manuscript for publication, R. B. Woodward and P. Yates [*Chem. and Ind.*, 1319 (1954)] have proposed structure I for santonin on the basis of arguments similar to those presented herein.

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(10) J. W. Ralls, THIS JOURNAL, **75**, 2123 (1953).

(11) C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.*, 2230 (1954).

(12) E. J. Corey and R. A. Sneen, THIS JOURNAL, **75**, 6234 (1953). The assigned configuration given in this paper must be changed from α to β in view of the correction made in ref. 11 of the erroneous results [R. H. Baker and Q. R. Petersen, *ibid.*, **73**, 4080 (1951)] from which the α-assignment was derived.

(13) For another example in which the thermodynamically stable product is formed in a Michael reaction (with 4-phenylcyclohexenone) see E. D. Bergmann and J. Szmuszkovicz, *ibid.*, **75**, 3226 (1953).

(14) W. Klyne, *J. Chem. Soc.*, 2916 (1952); 3072 (1953).

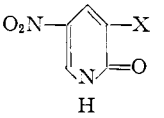
(15) J. Simonsen and D. H. R. Barton, "The Terpenes," 2nd edition, Cambridge University Press, Cambridge, 1952, Vol. 3, pp. 249-292.

The Condensation of Sodium Nitromalonaldehyde with Cyanoacetamide[1]

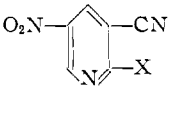
BY PAUL E. FANTA AND ROBERT A. STEIN

RECEIVED OCTOBER 27, 1954

The condensation of sodium nitromalonaldehyde with cyanoacetamide in the presence of Triton B gave a 93% yield of 3-cyano-5-nitro-2-pyridone (I). This is the first reported synthesis of a nitropyridone by the use of sodium nitromalonaldehyde.



I, X = CN
II, X = CO_2H
III, X = H



IV, X = Cl
V, X = OC_2H_5

The cyanopyridone I was hydrolyzed in strong aqueous sulfuric acid to give the corresponding carboxylic acid II. Degradative evidence for the presence of the nitropyridone ring in I and II was provided by the decarboxylation of II to give the 5-nitro-2-pyridone (III) previously reported by Chichibabin.[2]

The pyridone I was converted in good yield to the chloropyridine (IV) by treatment with an excess of phosphorus pentachloride in phosphorus oxychloride solution. The ethoxypyridine V was obtained by treatment of IV with sodium ethoxide in ethanol. All attempts to hydrolyze the nitrile group of V resulted in the hydrolysis of both the nitrile and ethoxy group to give the pyridone II.

Experimental[3]

3-Cyano-5-nitro-2-pyridone (I).—To a solution of 31.4 g. (0.2 mole) of sodium nitromalonaldehyde and 16.4 g. (0.2 mole) of cyanoacetamide in 400 ml. of water at 20° was added 4 ml. of 40% aqueous Triton B (trimethylbenzylammonium hydroxide, technical). The solution became deep red and set to a mass of fine yellow needles as the temperature rose to 33° during the next 15 minutes. The reaction mixture was allowed to stand for another 5 minutes and

(1) This work was supported by a grant from the Office of Ordnance Research. For the previous paper in the series, see P. E. Fanta, THIS JOURNAL, **75**, 737 (1953).

(2) A. E. Chichibabin, *Ber.*, **58B**, 1707 (1925).

(3) All melting points are corrected. Analyses are by Micro-Tech Laboratories, Skokie, Ill.