The Absolute Configuration at C_{11} of Santonin[1]

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Although the syntheses of (−)-α-santonin (Ia) and all its possible stereoisomer have been accomplished[2] and although the absolute configurations of the asymmetric centers of C_{10}[3] and C_7[4] have been established unambiguously, that of C_{11} is still in dispute.[4] Deducing mainly from the relative stability of epimeric α- (II) and β-desmotroposantonin (III),[5] Woodward and Yates,[6] Corey[7] and Cocker et al.[4] assigned the (R)-configuration to the C_{11} asymmetric center. The same conclusion was reached by Mitsuhashi[8] after a consideration of the molecular models of santonin and its derivatives as well as of their relative rates of hydrolyses.

Assuming that the stereochemistry of the lactone ring of santonin and the D ring of steroid are isosteric, Miki[9] reached the opposite conclusion, that in santonin the methyl group at C_{11} must have a quasi-equatorial conformation (i. e., the (R)-configuration) and the less stable β-santonin (the C_{11} epimer of Ia) the (S)-configuration. Prelog's atrolactic acid method[10] applied to the alcohol IV derived from santonin added conclusive evidence to support this view.[11] However, the opinions[4] of Cocker et al. have appeared to tend to favor the (R)-configuration at this asymmetic

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1) For a preliminary account of this work, see M. Nakazaki and H. Arakawa, *Proc. Chem. Soc.*, **1962**, 151.

2) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *Proc. Japan Acad.*, **28**, 427 (1952); **29**, 113 (1953); **30**, 116, 119 (1954), *J. Am. Chem. Soc.*, **75**, 2567 (1953); **78**, 1416, 1422 (1956).

3) H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1954); B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, *J. Am. Chem. Soc.*, **76**, 313 (1954)).

4) For a relevant review, see W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

5) The correlation of desmotroposantonin series and (−)-α-santonin has not been necessarily established, and this point was discussed in a short communication, M. Nakazaki, This Bulletin, **35**, 1904 (1962).

6) R. B. Woodward and P. Yates, *Chem. & Ind.*, **1954**, 1391.

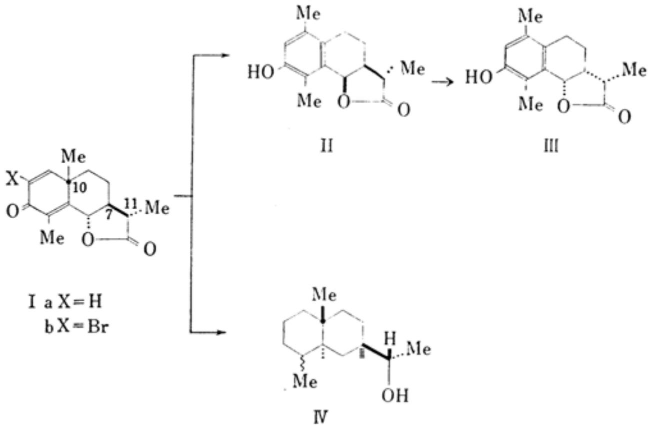
7) E. J. Corey, *J. Am. Chem. Soc.*, **77**, 1044 (1955).

8) H. Mitsuhashi, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **71**, 1115 (1951).

9) T. Miki, ibid., **75**, 416 (1955).

10) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

11) Y. Abe, T. Miki, M. Sumi and T. Toga, *Chem. & Ind.*, **1956**, 953.



I a X=H
b X=Br

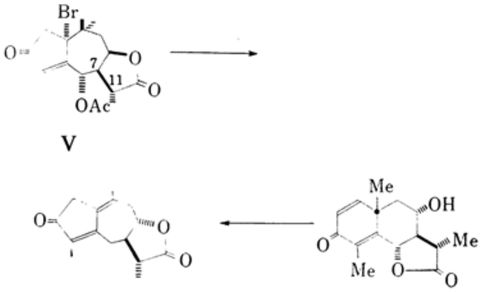
II

III

IV

center. Moreover, Bose and Chatterjee,[12] formulating a generalized rule permitting the prediction of the absolute configuration of an asymmetric center, have shown that the lactones of the santonin series possess the configuration assigned previously on the basis of thermodynamical studies.

The crystal structure of acetylbromogeigerin (V) determined by the Glasgow group[13] also point to this (R)-configuration when their results are combined with the chemical correlation (via anhydrogeigerin (VI)) between acetylbromogeigerin and artemisin (VII), the relative configuration of which to santonin has been elegantly established by Sumi.[11]



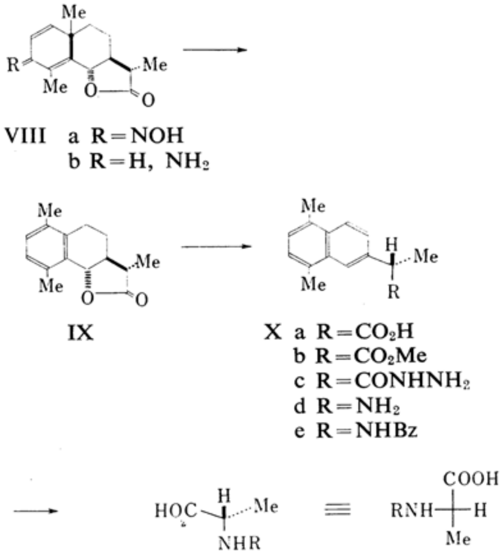
V

VI

VII

In this communication we will report findings which prove the (s)-configration around this center.

Hyposantonin (IX),[14,15] prepared from santonin oxime (VIIIa) through the dienamine VIIIb by dienamine-benzene rearrangement, was refluxed with iodine in an acetic acid solution for 3 hr., giving santinic acid (Xa),[16] which, after chromatography on silica gel, had an m.p. of 125~127°C ($[\alpha]_D$ +57.3° (in ethanol)).



VIII a R=NOH
b R=H, NH_2

IX

X a $R=CO_2H$
b $R=CO_2Me$
c $R=CONHNH_2$
d $R=NH_2$
e R=NHBz

XI a R=H
b R=Bz

Santinic acid with diazomethane gave the methyl ester Xb, which was converted into the hydrazide Xc. The amine Xd, obtained from this hydrazide by the Curtius rearangement

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[12] A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958); A. K. Bose, Abstracts of XVth International Congress of Pure and Applied Chemistry, Paris 1957, p. 141. W. G. Dauben, W. K. Hayes, J. S. P. Schwarz and J. W. Farland, *J. Am. Chem. Soc.*, **82**, 2232 (1960) applied this method to ψ-santonin which has the same configuration around C_{11} as artemisin (VII) and santonin (M. Sumi, *J. Am. Chem. Soc.*, **80**, 4869 (1958); M. Sumi, W. G. Dauben and W. K. Hayes, ibid., **80**, 5704 (1958)) and assigned the (R)-configuraton to this asymmetric center,

[13] J. A. Hamilton, A. T. McPhail and G. A. Sim, *Proc. Chem. Soc.*, **1960**, 278. For the chemical correlation between artemisin and geigerin, see D. H. R. Barton and J. T. Pinhey, *Proc. Chem. Soc.*, **1960**, 279.

[14] M. Nakazaki, This Bulletin, **35**, 1387 (1962); *Chem. & Ind.*, **1962**, 413. D. Gucci, *Gazz. chim. ital.*, **19**, 367 (1889) (*Chem. Zentr.*, **1889**, II, 595); G. Grassi-Cristaldi, ibid., **19**, 382 (1889) (*Chem. Zentr.*, **1889**, II, 597).

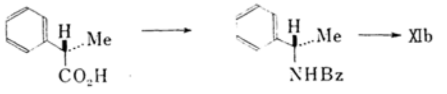
[15] Elsevier's "Encyclopedia of Organic Chemistry," Series III, Vol. 12B, Elsevier Pub. Co. Inc., New York-Amsterdam (1948), pp. 3326, 3456.

[16] D. Gucci and G. Grassi-Cristaldi, *Gazz. chim. ital.*, **22**, I 35 (1892); J. Simonsen and D. H. R. Barton, "The Terpenes," II Ed., Vol. III, Cambridge Univ. Press (1952), p. 253.

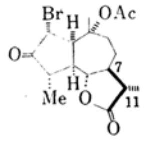
(retention of configuration)[17] was directly benzoylated to the amide Xe (m. p. 172～174°C, $[\alpha]_D$ $-12.7°$ (in chloroform)), which was dissolved in chloroform and exhaustively ozonized for 9 hr. Acetic acid (90%) was added to the remaining solution, and ozonolysis was continued for an additional 12 hr. After oxidation with peracetic acid and concentration, the reaction mixture was hydrolyzed by hot 20% hydrochloric acid and the chloride ion was removed by Amberite IR-4B resin, giving a solution which showed the presence of alanine (XIa) on paper chromatography. The alanine was then converted into (+)-benzoyl-L-alanine (XIb), which showed, after recrystallization from benzene, an m. p. of 148～151°C ($[\alpha]_D$ $+7.4°$ ($\pm 4°$) (in N potassium hydroxide)) and an infrared spectrum (in dioxane) superimposable on that of an authentic sample.

These facts show that (+)-α-santinic acid (Xa) has the (s)-configuration. Further, since, from a mechanistic standpoint, epimerization at position 11 is inconceivable during the conversion of santonin into the acid, (−)-α-santonin must also have the (s)-configuration at this center, thus confirming the assignment made by Abe et al.[11]

It is of interest to note that during their studies of the stereochemistry of pinacolic deamination, Bernstein and Whitmore[18] converted (+)-hydratropic acid[19] (XII), a phenyl analog of stantinic acid, into (−)-benzoyl-α-phenyl-α-phenylethylamine (XIII), the absolute configration of which was established by the conversion into (+)-benzoyl-L-alanine (XIb) through a sequence of degradations.[20] Eventually, the (s)-configuration was given to (+)-hydratropic acid by this correlation, and the observed parallel shift of the optical rotations between these two series of compounds (Xa→Xe and XII→XIII) also confirms the (s)-configuration of santinic acid.[21] The X-ray crystal analysis of bromodihydroiso-α-photosantonic lactone acetate (XIV) by Asher and Sim[22] demonstrated that (−)-α-santonin has the stereo-chemistry Ia with reference to that of the asymmetric carbon atom 7, the absolute configuration of which has been established by a long series of inter-correlations.[4]



XII XIII



XIV

The seemingly inconsistent result of Barton et al.[13] (vide supra) could be interpreted by assuming the feasible inversion at C_{11} demonstrated clearly in their synthetic studies of deoxygerin from 8-epiartemisin.[23]

Finally the whole problem was settled by the X-ray analysis of 2-bromo-α-santonin[24] (Ib), which defined its constitution and relative stereochemistry as Ib. Since the absolute configuration at the asymmetric center C_{10} has been firmly established,[3] this result indicates that (−)-α-santonin has the (s)-configuration at C_{11}, confirming the results obtained by chemical methods.[1,11]

Experimental*

(+)-Santinic Acid (Xa).—A solution of 3 g. of hyposantonin (IX)[14,15] and 6 g. of iodine in 55 cc. of acetic acid was refluxed for 3 hr. After 50 cc. of water had been added, the reaction mixture was concentrated under reduced pressure to remove the excess iodine; this process was repeated twice. The residue was dissolved in 200 cc. of ether and washed with water, aqueous sodium thiosulfate and saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. The removal of the solvent gave a viscous oil, which was sublimed at 3 mmHg. The sublimate began to condense at 160°C (bath temperature), and the main fraction came over at 180～220°C. The condensate (2.6 g.) was dissolved in chloroform and chromatographed on a column of 70 g. of silica gel. Elution with chloroform and the removal of the solvent gave 1.5 g. of crystals (m. p. 120～125°C). Recrystallization from aqueous ethanol raised the m. p. to 125～127°C $[\alpha]^{20}_D$ $+57.3°$ (*c* 1.22 in ethanol). (Lit.[16]: m. p. 132～132.5°C, $[\alpha]^{16}_D$ $+64.37°$ (in ethanol)).

(+) Methyl Santinate (Xb).—To an ether solution of diazomethane prepared from 25 g. of nitrosomethylurea, 6.1 g. of (+)-santinic acid were added, and the reaction mixture was allowed to stand overnight. The usual work-up gave 6.1 g. of

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[17] P. A. S. Smith, "Organic Reactions," Vol. III, 337 (1946); C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, New York (1953), p. 495; D. J. Cram, "Intramolecular Rearrangements," in M. S. Newman, "Steric Effects in Organic Chemistry," John-Wiley and Sons, Inc., New York (1955), p. 253.

[18] H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1325 (1939).

[19] On the absolute configuration of hydratropic acid, see W. Klyne, "Progress in Stereochemistry," Vol. I., Butterworth Scientific Pub., London (1954), pp. 187, 195 196.

[20] W. Leithe, *Ber.*, **64**, 2827 (1931).

[21] This can be predicted also by employing Brewster's model of optical activity, J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5478 (1959).

[22] J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, **1962**, 111.

[23] D. H. R. Barton, T. Miki, J. T. Pinhey and R. J. Wells, ibid., **1962**, 112.

[24] J. D. Asher and G. A. Sim, ibid., **1962**, 335.

* All melting and boiling points are uncorrected. The analyses were performed in the Microanalytical Laboratory of the Institute of Polytechnics, Osaka City University.

methyl santinate (b. p. 155～157°C/2 mmHg, $[\alpha]_D^{20}$ +70.1° (*c* 1.49 in ethanol)).

Found: C, 78.9; H, 7.6. Calcd. for $C_{16}H_{18}O_2$: C, 79.39; H, 7.49%

The Hydrazide (Xc) of (+)-Santinic Acid.—Six grams of the methyl santinate was stirred into 2.5 g. of hydrazine hydrate (b. p. 117～119°C) at 80°C over a period of 1/2 hr. After a mixture of absolute ethanol and 2 cc. of hydrazine had been added, the reaction mixture was allowed to stand in a refrigerator overnight. The crystals which deposited were filtered and washed with ethanol to yield 1.8 g. of the hydrazide Xc. The filtrate and washing were combined and were refluxed on a water bath for 6 hr. Upon the mixture had cooled in an ice-salt bath, 3.2 g. of crystals were obtained. Recrystallization of the combined crude products from ethanol afforded 4.0 g. of partiallly-racemized hydrazide, which melted at 136°C after sintering at 127～130°C. $[\alpha]_D^{18}$ +25.5° (*c* 1.45 in 95% ethanol).

Found: C, 74.4; H, 7.5; N, 11.8. Calcd. for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49; N, 11.56%.

Concentration of the mother liquor gave the second crop which was seemingly optically pure and which weighed 0.4 g. (m. p. 151～152°C, $[\alpha]_D^{18}$ +73.2° (*c* 1.01 in ethanol)).

Found: C, 74.4; H, 7.5; N, 11.7. Calcd. for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49; N, 11.56%.

(−)-*N*-Benzoyl-*α*-(5, 8-dimethyl-2-naphthyl)ethylamine (Xe).—A mixture of 3.5 g. of the hydrazide Xc ($[\alpha]_D^{18}$ +25.5°), 25 cc. of acetic acid and 50 cc. of benzene was chilled (2～4°C) in an ice bath, and then a solution of 1.2 g. of sodium nitrite in 15 cc. of water was stirred in over a 10 min. period. After water was added, the benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene extracts were washed with water, aqueous sodium hydrogen carbonate and water successively. After drying over calcium chloride, the benzene solution was heated on a water bath to decompose the acyl azide. Nitrogen was observed to begin to evolve at 50°C, and a vigorous reaction occurred at 60～75°C. After the mixture was refluxed for 15 min., 18 cc. of concentrated hydrochloric acid was added and the mixture was refluxed for 2.5 hr. The crystalline product which deposited was filtered, washed with water and ether, and dried to give 2.1 g. of the hydrochloride of the amine Xd. The hydrochloride of the amine (2.1 g.) was benzoylated with 40 cc. of 10% aqueous sodium hydroxide and 5 cc. of benzoyl chloride. The crude crystalline product was recrystallized from ethanol to afford 2.3 g. of crystals (m. p. 166～172°C). A portion of the benzoyl derivative, after recrystallization from 95% ethanol, melted at 172～174°C, $[\alpha]_D^{19}$ −12.7° (*c* 1.02 in chloroform).

Found: C, 83.0; H, 7.2; N, 4.9. Calcd. for $C_{21}H_{21}ON$: C, 83.13; H, 6.98; N, 4.62%.

The Exhaustive Ozonolysis of the Benzoyl Derivative (Xe).—A stream of ozone was passed into a solution of 2.5 g. of the benzoyl derivative Xe in 60 cc. of chloroform at room temperature. After 9 hr., the solvent evaporated, leaving a residue which was dissolved in 50 cc. of 90% acetic acid; the ozonolysis was then resumed for 13 hr. To the mixture was added 8 cc. of 30% hydrogen peroxide, and the solution was allowed to stand at room temperature for 20 hr. After 50 cc. of water was added, the excess hydrogen peroxide was decomposed by heating it with a small amount of palladium on a carbon catalyst on a water bath for 4.5 hr. After the catalyst had been filtered, the filtrate was freed from the solvent under reduced pressure. The syrup was dissolved in 50 cc. of water and concentrated under reduced pressure; this process was repeated four times. The syrup was dissolved in 20 cc. of water, and an insoluble, brown, viscous material was filtered off. The filtrate was concentrated again under reduced pressure to give a viscous residue which was then dried in a vacuum dessicator over concentrated sulfuric acid overnight. The residue (2.0 g.) was dissolved in 10 cc. of 20% hydrochloric acid and refluxed for 5 hr. The solution was filtered through a layer of Hyflo super cell and treated with Norit. The filtrate was freed from chloride ions with Amberite IR-4B until its pH became about 7. Upon concentration under reduced pressure, a crystalline material deposited which was dissolved in 15 cc. of water and filtered through a layer of Hyflo super cell. A paper chromatogram (acetic acid: butanol: water) exhibited only a single spot corresponding to alanine. After 5 g. of sodium hydrogen carbonate had been added to the aqueous solution, 3.2 g. of benzoyl chloride was added drop by drop over 2 hr. with vigorous shaking at room temperature The turbid reaction mixture was filtered through a layer of Hyflo super cell and made acidic with concentrated hydrochloric acid, and then the mixture was continuously extracted with ether. The removal of the solvent gave a crystalline solid which was dried in a vacuum dessicator. The solid was extracted with four portions of 5 cc. of boiling ligroin to remove the benzoic acid. The insoluble material left in the flask was dissolved in 12 cc. of benzene. Cooling and scratching induced crystallization to afford 10 mg. of (+)-benzoyl-L-alanine (m. p. 148～151°C, $[\alpha]_D^{24}$ +7.4° (±4°) (*c* 0.597 in N potassium hydroxide)). The infrared spectra of this compound and an authentic (+) benzoyl-L-alanine[25] (m. p. 144～146°C, $[\alpha]_D^{15}$ +23.2° (*c* 1.01 in N potassium hydroxide) (Lit.:[25] m. p. 146～148°C, $[\alpha]_D^{20}$ +33.0° (in N potassium hydroxide))) were indistinguishable.

Found: C, 61.9; H, 6.0; N, 7.3. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25%.

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[25] E. Fischer, *Ber.*, 32, 2451 (1899).