[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, IMPERIAL COLLEGE]

THE STEREOCHEMISTRY OF SANTONIN, β-SANTONIN, AND ARTEMISIN

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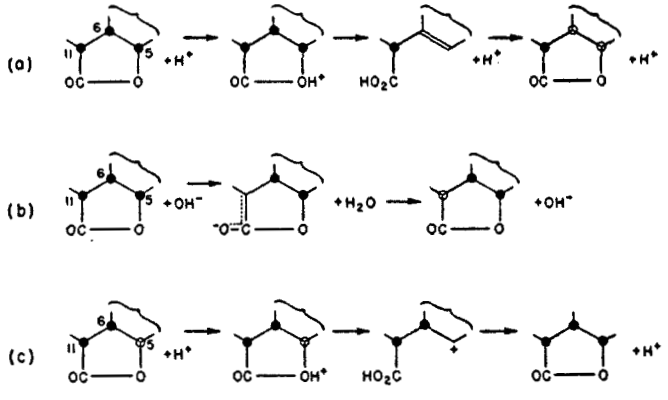
Huang-Minlon (1) has recently discussed the stereochemistry of the desmotroposantonins (I; R = H). The arguments advanced in his paper seem, for the most part, very plausible and are accepted in the present article. Huang-Minlon showed that treatment of an α-desmotroposantonin (2) with acidic reagents led to inversion at the asymmetric centers 5 and 6, whilst fusion of a β-desmotroposantonin with potassium hydroxide caused inversion at C_{11}. The isomerisation caused by acid was formulated in accordance with mechanism (a), whilst inversion by alkali was suggested to proceed as in (b). It is the purpose of the present article to show that, for appropriate compounds, there must be a third mechanism, (c), for acid-induced stereochemical rearrangement at C_5.



I II III

As Huang-Minlon pointed out it seems to be satisfactorily established that the desmotroposantonins must have the lactone ring fused in the more stable *cis*-position at C_5 and C_6. This must also be the case in *iso*hyposantonin (II). In contrast, the isomeric hyposantonin must be *trans*-fused at these positions as indeed was first recognised many years ago (3). The existence of mechanism (c) can only be detected in compounds where the fusion of the lactone ring is *trans*.

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Huang-Minlon, by a consideration of the molecular rotations of the desmotroposantonins and of the related santonous and desmotroposantonous acids, proposed tentatively, according to the Principle of Optical Superposition, signs for the contributions of the various asymmetric centers. In actual fact the additivity of the molecular rotations is not very satisfactory and it would seem preferable to discuss the stereochemistry on the following basis. Let the configurations at C_5, C_6, and C_{11} in (−)-α-desmotroposantonin be denoted by X, Y, and Z and let the alternative configurations at these centers be X′, Y′, and Z′ respectively. On this nomenclature the conclusions on relative configuration reached by Huang-Minlon can be conveniently summarised as in Table I.

When santonin (IV; R = H) is treated with acidic reagents under mild conditions it is isomerized, with loss of the asymmetric center at C_9, to (−)-α-desmotroposantonin. Under more drastic conditions (+)-β-desmotroposantonin is the product of this reaction. Although this might be taken to imply that the configurations at C_5, C_6, and C_{11} are the same in both santonin and (−)-α-desmo-

TABLE I

SUMMARY OF RELATIVE CONFIGURATIONS; AFTER HUANG-MINLON

SUBSTANCE	Configurations relative to (−)-α-desmotroposantonin[a]		
	C_5	C_6	C_{11}
(−)-α-Desmotroposantonin	X	Y	Z
(+)-β-Desmotroposantonin	X′	Y′	Z
(+)-α-Santonous acid	—	Y	Z
(−)-β-Santonous acid	—	Y′	Z

[a] The lactone ring is *cis*-fused in both types of desmotroposantonin.

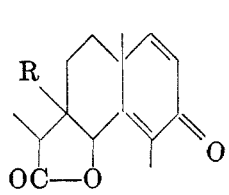
troposantonin, as Huang-Minlon has already mentioned, this is not so. Santonin β-oxime, its acetate, and the phenylhydrazone can all be transformed under very mild reducing conditions to hyposantonin (4). Santonin must, therefore, have the lactone ring fusion *trans* and be either $C_5(X'):C_6(Y):C_{11}(Z)$ or $C_5(X):C_6(Y'):C_{11}(Z)$. The fact that the transformation of santonin (*trans*-fused) to the acid-stable configuration of (+)-β-desmotroposantonin (*cis*-fused) proceeds *via* (−)-α-desmotroposantonin (also *cis*-fused) proves that santonin must be $C_5(X'):C_6(Y)$; $C_{11}(Z)$ and that there must be a mechanism (c) for the inversion of C_5 without altering C_6.[2] Santonin is strongly levorotatory ($[\alpha]_D$ −172° in chloroform). Since the asymmetric centers at C_5, C_6, and C_{11} make relatively small contributions to the molecular rotation (1) the strong levorotation must be due to the asymmetry induced by the center at C_9 in the closely neighboring and very unsaturated dienone system. For convenience the configuration at C_9 in santonin may be denoted as W (alternative configuration would be W′).

That these views with regard to the stereochemistry of santonin are correct is

[2] The alternative is that there is a mechanism for inverting C_6 without affecting C_5. This would mean that santonin was $C_5(X):C_6(Y'):C_{11}(Z)$. Such a mechanism is inherently improbable and, indeed, is excluded by the evidence discussed later.

shown by several other pieces of published evidence. First, both hyposantonin and *iso*hyposantonin are reduced, under conditions not likely to lead to inversion at C_6, to hyposantonous acid (5) (III; R = H), which, from its rotation ($[\alpha]_D$ +76° in alcohol) must correspond to (+)-α-santonous acid ($[\alpha]_D$ +75° in alcohol) and have $C_6(Y):C_{11}(Z)$. Hyposantonin and *iso*hyposantonin differ therefore only in configuration at C_5 being $C_5(X'):C_6(Y):C_{11}(Z)$ and $C_5(X):C_6(Y):C_{11}(Z)$ respectively.

Second, we may invoke the chemistry of artemisin (IV; R = OH). Treatment of artemisin under fairly drastic acid conditions causes dehydration with formation of artemisic acid (6) (V; R = OH) which has $[\alpha]_D$ +70.4° (in alcohol) and is clearly analogous to santinic acid $[\alpha]_D$ +64.4° in alcohol) (V; R = H) obtained by dehydration and mild oxidation of hyposantonin. The configuration of artemisin at C_{11} must therefore be (Z). Now when santonin is electrolytically reduced in aqueous acetic acid solution it gives a dilactone, santonone (7) (VI; R = H) presumably formed *via* the corresponding pinacol (VII). Santonone, which has $[\alpha]_D$ +130° in benzene, is readily isomerised to *iso*santonone, $[\alpha]_D$ −265° in acetic acid, and the two compounds are related to each other in the



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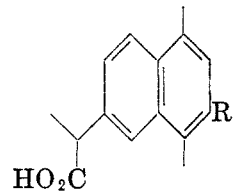

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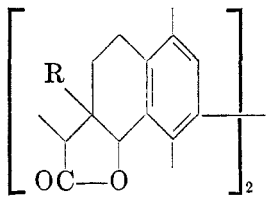

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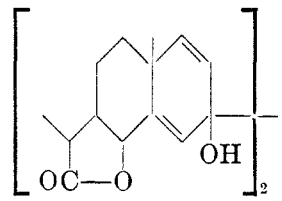

VII

same way, as hyposantonin ($[\alpha]_D$ +33° in benzene) and *iso*hyposantonin ($[\alpha]_D$ −70° in benzene). On similar reduction using zinc dust in aqueous acetic acid Bertolo and Ranfaldi (8) obtained artemisone (VI; R = OH) ($[\alpha]_D$ +159° in acetic acid) from artemisin. Like santonone, artemisone was readily isomerised to *iso*artemisone ($[\alpha]_D$ −153° in acetic acid.) It must be concluded, therefore, that the lactone ring in artemisin is *trans*-fused as in santonin, and that artemisone and *iso*artemisone are isomeric about C_5 and C_5'. Treatment of artemisin under mild acid conditions, such as cause the isomerisation of santonin to (−)-α-desmotroposantonin (see above), leads to the formation of desmotropoartemisin (I; R = OH) ($[\alpha]_D$ −84° in alcohol) having the lactone ring *cis*-fused. The formation of this compound provides a further proof of the existence of isomerisation mechanism (c) formulated above. Assuming that the substitution of a hydroxyl group for a hydrogen atom does not alter the sign of the molecular

rotation contribution of an asymmetric centre possessing a particular spatial configuration, then reference to the isomeric desmotroposantonins shows that desmotropoartemisin must be analogous to (−)-α-desmotroposantonin and must therefore be formulated as $C_5(X):C_6(Y):C_{11}(Z)$. Since the conversion of artemisin to desmotropoartemisin cannot involve a change at C_6, artemisin must be $C_5(X'):C_6(Y):C_{11}(Z)$ and, by reason of its strong levorotation (compare above), $C_9(W)$.

Knowing the configurations for santonin it is possible to deduce the stereochemical nature of β-santonin (9). On treatment with acidic reagents the latter affords (−)-β-desmotroposantonin (1) and therefore it must be $C_{11}(Z')$. The change in molecular rotation from β-santonin ($[M]_D$ −337° in chloroform) to (−)-β-desmotroposantonin ($[M]_D$ −261° in alcohol) is +76 units. This is almost exactly the same as the change in molecular rotation (+79 units) on going from santonin ($[M]_D$ −423° in chloroform) to (−)-α-desmotroposantonin ($[M]_D$ −344° in alcohol), and implies a similarity in stereochemistry at C_5, C_6, and C_9. β-Santonin must, therefore, be $C_5(X'):C_6(Y):C_{11}(Z'):C_9(W)$.

TABLE II

SUMMARY OF RELATIVE CONFIGURATIONS; PRESENT PAPER

SUBSTANCE	LACTONE RING FUSION	Configurations relative to (−)-α-desmotroposantonin			
		C_5	C_6	C_{11}	C_9
Santonin	*trans*	X′	Y	Z	W
Hyposantonin	*trans*	X′	Y	Z	—
*iso*Hyposantonin	*cis*	X	Y	Z	—
Desmotropoartemisin	*cis*	X	Y	Z	—
Artemisin	*trans*	X′	Y	Z	W
β-Santonin	*trans*	X′	Y	Z′	W

The conclusions on stereochemical relationships reached here are summarised in Table II.

The mechanism (c), established above by stereochemical arguments, constitutes an interesting example analogous to alkyl-oxygen fission (10).

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SUMMARY

The discussion of Huang-Minlon (1) on the stereochemistry of santonin derivatives is extended. Relative configurations are assigned *inter alia*, to santonin, desmotropoartemisin, artemisin, and β-santonin.

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(2) For nomenclature see HUANG-MINLON, LO, AND CHU, *J. Am. Chem. Soc.*, **65**, 1780 (1943).

(3) GRASSI-CRISTALDI, *Gazz. chim. ital.*, **23** I, 67 (1893).
(4) GUCCI, *Gazz. chim. ital.*, **19**, 378 (1889); GUCCI AND GRASSI-CRISTALDI, *Gazz. chim. ital.*, **22** I, 3, 24, 35, 44 (1892); *Atti reale accad. Lincei.*, [4]7 II, 35 (1891).
(5) GRASSI-CRISTALDI, *Gazz. chim. ital.*, **26** II, 459 (1896).
(6) The chemistry of artemisin quoted here is due to BERTOLO: *Atti reale accad. Lincei.*, [5] **11** I, 486 (1902); *Atti reale accad. Lincei.*, [5] **12** II, 273 (1903); *Gazz. chim. ital.*, **50**, I, 114 (1920); *Gazz. chim. ital.*, **53**, 867 (1923); *Gazz. chim. ital.*, **56**, 856 (1926); *Atti congr. naz. chim. pura applicata., 4th Congr.*, 1932, 396 (1933).
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(9) CLEMO, *J. Chem. Soc.*, 1343 (1934).
(10) Compare DAY AND INGOLD, *Trans. Faraday Soc.*, **37**, 686 (1941); BALFE, *et al.*, *J. Chem. Soc.*, 797 (1946).