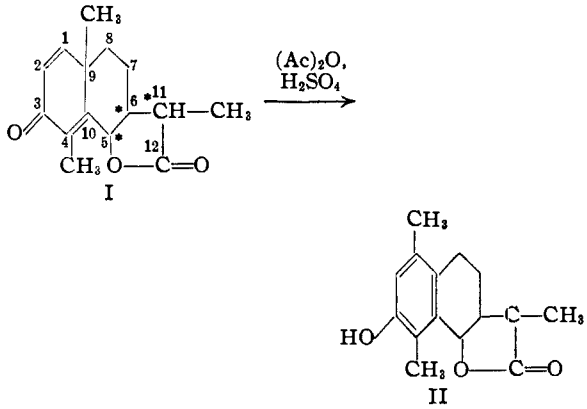
[CONTRIBUTION OF THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Studies in the Santonin Series. IV.[1,2,3] The Stereochemistry of Santonin and its Derivatives

BY HUANG-MINLON[3a]

The relative configuration of santonin and of various transformation products has been discussed briefly in an earlier paper.[1] In the meantime sufficient experimental facts have accumulated to extend this discussion.

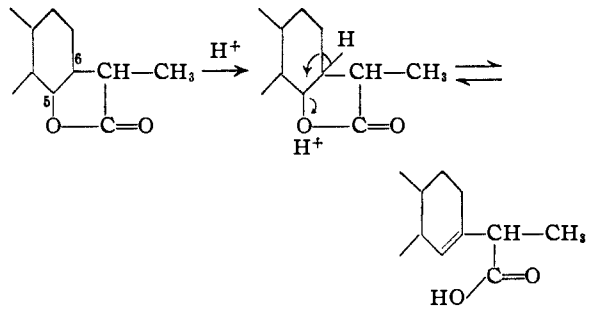
The almost quantitative rearrangement of santonin (I) into the aromatic *l*-α-desmotroposantonin (II)[3b] induced by acetic anhydride and a trace of sulfuric acid was originally considered as an enol acylation reaction.[1] The enolization, however, is unusual in that, in addition to the prototropic change, an alkylotropy occurs also. This acid-catalyzed rearrangement is similar to a Wagner–Meerwein rearrangement and the mechanism can be formulated as



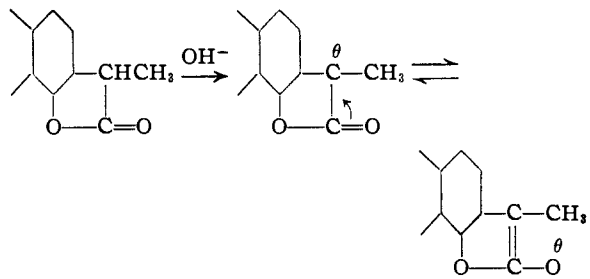
Of particular interest is the interconversion of the four isomeric desmotroposantonins by successive treatment with acid and with alkali[1] (see chart[3c]), since this is probably the first instance of a cycle in which the configurations of three asymmetric carbon atoms are changed and then restored to the original state.

Plausible mechanisms for the conversions observed with acid and with alkali can now be advanced. Support for the postulated acid-catalyzed reaction is furnished by the formation of the ethyl ester of dihydrosantinic acid (IV) from isohyposantonin (III) by the action of alcoholic hydrochloric acid.[6] Isohyposantonin is *levo*-rotatory; it contains three asymmetric carbon atoms that have the same configuration as that of *l*-α-desmotroposantonin, A (see conversion of III into A, below). The β,γ-unsaturated ester, which contains only one asymmetric carbon atom, is dextrorotatory. The reaction is comparable to the transformation of A to B, but in this case the β,γ-un-

(a) Acid conversion:



(b) Alkaline conversion



(1) Huang-Minlon, Lo and Chu, THIS JOURNAL, **65**, 1780 (1943); for experimental part see: *J. Chinese Chem. Soc.*, **10**, 126 (1943).

(2) Huang-Minlon, Lo and Chu, THIS JOURNAL, **66**, 1954 (1944).

(3) Huang-Minlon and Cheng, *ibid.*, **70**, 449 (1948).

(3a) On leave of absence from the National Research Institute of Chemistry, Academia Sinica.

(3b) The nomenclature is discussed in Paper I.[1]

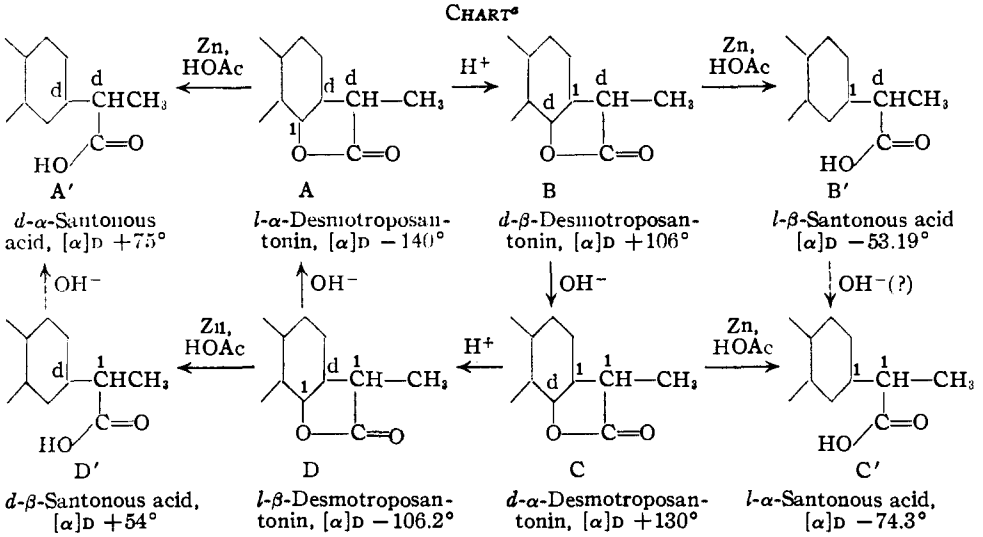
(3c) The transformations indicated by the dotted lines in the chart, D′ → A′ and B′ → C′, have probably been accomplished. In the latter case, the experimental conditions have not been clearly defined[4]; in the former, the investigators[5] did not realize the true nature of the observed change. They did observe, however, that treatment of *d*-β-santonous acid (D′) with barium hydroxide followed by alkali fusion led to a more dextrorotatory acid ([α]D +64), undoubtedly A′

(4) Andreocci, *Atti R. Accad. dei Lincei Roma*, [5] **4**, 259 (1894); *Chem. Zentr.*, **66**, I, 1069 (1895).

(5) Clemo, *J. Chem. Soc.*, 1343 (1934).

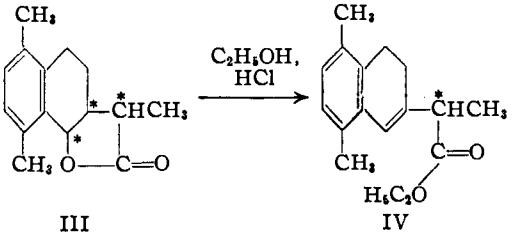
(6) Gucci and Grassi-Cristaldi, *Gazz. chim. ital.*, **22**, I, 24 (1892).

CHART[a]



[a] All data of the specific rotations given in this paper are taken from the work of: (a) Huang-Minlon, see refs. 1 and 3; (b) Clemo, see ref. 5; (c) Asahina, see ref. 10; (d) Andreocci, *Gazz. chim. ital.*, **23**, II 477, 478 (1893); **25**, I, 486 (1895); (e) Grassi-Cristaldi, see refs. 6, 13 and 14.

saturated acid postulated in the acid-catalyzed reaction above is tied down by esterification.



III IV

According to the postulated reactions with acid and with base the configurations of C-5 and of C-6 are inverted by acid treatment, whereas the configuration of C-11 is inverted by alkali. Unfortunately, the rule of optical superposition[7] is not obeyed strictly in the case under discussion because the asymmetric centers are adjacent to one another and conseqently vicinal effects are to be expected.[7] However, the [α]D values do correspond with proposed formulations with the exception of B → C and D → A. Furthermore, it is assumed in the following discussion that inversion of one asymmetric center does not cause inversion of another asymmetric center.

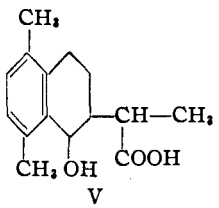
The reduction of each optically active desmotroposantonin results in an optically active santonous acid[8] of opposite optical rotation[1] as shown above. In the reduction one center of asymmetry is destroyed (C-5) and, since this loss results in a marked change in the optical rotatory power in all four cases, it can be assumed that this asymmetric center (C-5) makes the largest contribution to the total rotatory power. For this reason the asymmetric center C-5 in 1-α-desmotroposantonin (A) for example, must be levorotatory; the two remaining asymmetric centers (C-6 and C-11) must be dextrorotatory since the corresponding santonous acid (A′) is the most dextrorotatory of the four possible santonous acids. Since treatment with acid and then with alkali (for example, A → B → C) or treatment with alkali and then with acid (B → C → D) converts a desmotroposantonin into the antipode, either acid or alkali must change simultaneously the configuration of two carbon atoms. Acid converts one desmotroposantonin into an isomer of opposite rotation (A → B or C → D); when the asymmetry (C-5) of the isomer (B or D) is destroyed by reduction (*e. g.*, B → B′) an acid is obtained that is not identical with the acid obtained from the starting material (*i. e.*, B′ ≠ A′). These facts are explainable only on the assumption that acid treatment changes the direction of rotation of two asymmetric centers. The postulated acid reaction (a) results in inversion at C-5 and at C-6 and the alkaline reaction (b) results in inversion at C-11, and thus they fit the experimental facts.

According to the above formulation the desmotroposantonins are all either *cis* or *trans* compounds with reference to the linkage of the lactone ring to the cyclohexyl ring, and are not *cis–trans* isomers. Various experimental facts indicate that the linkage is *cis*. When the lactone ring of a desmotroposantonin is opened by dilute alkali and the basic solution is acidified, the starting material is recovered immediately. The equally instantaneous ring closure of either the α- or the β-form suggests a *cis*-configuration of both forms. From a consideration of molecular models Clemo[5] concludes that the *cis* linkage is the more stable. The physical and chemical properties of the open compounds, (V), of the lactone, (III), hyposanto-

(7) For a discussion of the modern theories of optical rotatory power see Kauzmann, Walter and Eyring, *Chem. Rev.*, **26**, 339 (1940).

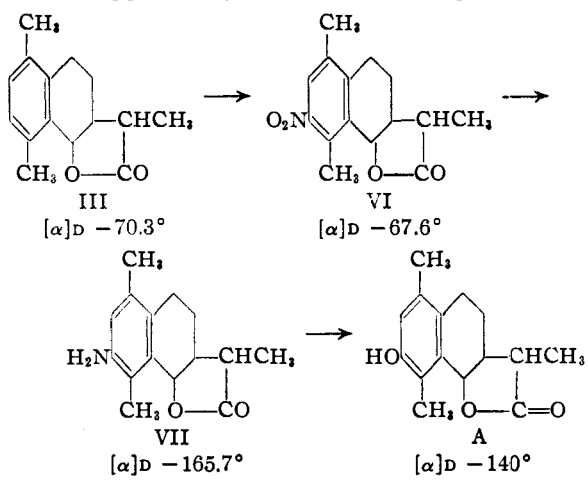
(8) For the sake of convenience the desmotroposantonous acids are named simply santonous acids.

ninic acid (*trans*) and isohyposantoninic acid (*cis*), indicate that the isomerism is geometrical.[9]



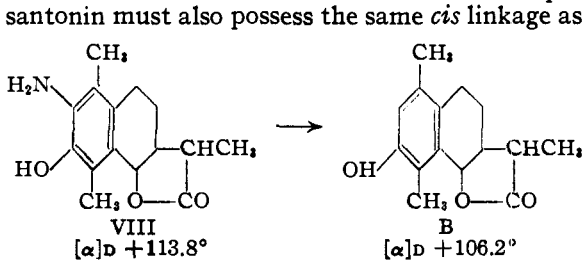
V

Accordingly, hyposantonin (III) is probably the *trans* form because the lactone ring opens readily with the formation of hyposantoninic acid. Isohyposantoninic acid is not stable and even on standing reverts to the lactone, isohyposantonin[9] (III). This *cis* lactone can be converted into *l*-α-desmotroposantonin (A) by the procedure of Asahina,[10] who converted the *trans* lactone in A. The series of transformations, shown in the formulas, do not involve the lactone ring and probably do not affect the mode of juncture. This assumption is supported by the fact that the optical rotation is not affected to any significant extent by the transformation. Furthermore, the transformation of 2-amino-*d*-β-desmotroposantonin (VIII), which is prepared by analogous reaction, into *d*-β-desmotroposantonin (B)[3] demonstrates unequivocally that nitro and amino derivatives retain the configuration of the parent desmotroposantonin. It follows then that *l*-α-desmotroposantonin must also possess the same *cis* linkage as in isohyposantonin and that the other desmotroposantonins are also *cis*.



III [α]D −70.3° VI [α]D −67.6°

VII [α]D −165.7° A [α]D −140°



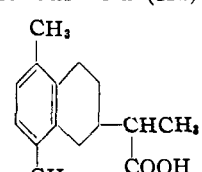
VIII [α]D +113.8° B [α]D +106.2°

(9) Grassi-Cristaldi, *Gass. chim. ital.*, **23**, I, 67 (1893).

(10) Asahina and Momose, *Ber.*, **71**, 1421 (1938).

The assumption that the so-called *l*-desmotropo-β-santonin[11] prepared by Clemo[1] from β-santonin is identical with *l*-β-desmotroposantonin (D)[1] has now been established by a direct comparison of crystalline form, of solubility, and of melting point (m. p. 259–260°). The two substances show no depression of melting point on admixture. Equal quantities of Clemo's material and of *d*-β-desmotroposantonin (B) form a racemic product which exhibits no optical activity, melts at 230–231°, and shows no depression in melting point on admixture with *dl*-β-desmotroposantonin.[1] The acetate of the racemic product was likewise compared with the known *dl*-compound[1] and found to be identical. The racemic product on zinc and acetic acid reduction yields an inactive acid (m. p. 181°), which is identical with *dl*-β-santonous acid.[1] The identity of Clemo's compound and D was further confirmed by transformation of both substances into the same santonous acid (D′) (m. p. 175–176°).

Santonin (I) itself probably does not have the *cis* configuration of the lactone ring, even though the aromatization reaction proceeds so readily as to suggest[1] that the steric arrangement is not affected in the transformation into 1-α-desmotroposantonin (A). Santonin oxime is transformed by mild reducing agents mainly into hyposantonin,[12] which has a *trans* configuration and which changes readily into isohyposantonin (*cis*).[13] Hyposantonin and isohyposantonin frequently produce the same reaction products, and many of the derivatives obtained by chemical treatment of hyposantonin, particularly in the presence of acids, are probably in reality derivatives of isohyposantonin. For example, hyposantonin and isohyposantonin form the same nitro product (VI).[10] The rotation of VI and of the amino derivative (VII) is comparable to that of isohyposantonin ([α]D −70.3°) and not to that of hyposantonin ([α]D +32.7°), and therefore nitric acid treatment probably induces isomerization of hyposantonin. Furthermore the so-called aminohyposantonous acid[10] obtained by reduction of the amino derivative (VII) ([α]D −165.7°) is dextrorotatory ([α]D +62.5°) and in this respect is comparable to the changes observed in the reduction of the desmotroposantonins (A → A′, etc.). Similarly, the so-called hyposantonous acid (IX)[14] obtained from



IX [α]D +75.95°

(11) I am indebted to Prof. Clemo for a sample of this material and of *d*-β-santonous acid.

(12) Gucci, *Gass. chim. ital.*, **19**, 378 (1889).

(13) Grassi-Cristaldi, *ibid.*, **19**, 393 (1889).

(14) Grassi-Cristaldi, *ibid.*, **26**, II, 456 (1896).

both hyposantonin and isohyposantonin by reduction should be designated isohyposantonous acid because it is dextrorotatory, and reductive opening of the lactone ring causes reversal in the direction of rotation.

I am indebted to Prof. L. F. Fieser for his encouragement in the persuance of this investigation and to Mrs. Mary Fieser for help in the preparation of this manuscript.

Summary

The mechanism of the acid-catalyzed rearrangement of santonin to desmotroposantonin and that of the interconversion of the four isomers of desmotroposantonins by acid and alkali has been postulated. The relative configurations of all the known desmotroposantonins have been formulated. *l*-Desmotropo-β-santonin of Clemo has been found to be identical with *l*-β-desmotroposantonin. The spacial configurations of santonin, hyposantonin and isohyposantonin have also been discussed.

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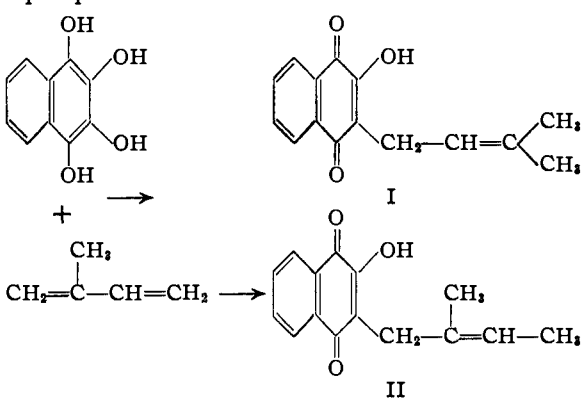
[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY, BRYN MAWR COLLEGE, AND THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Syntheses in the Lapachol Series

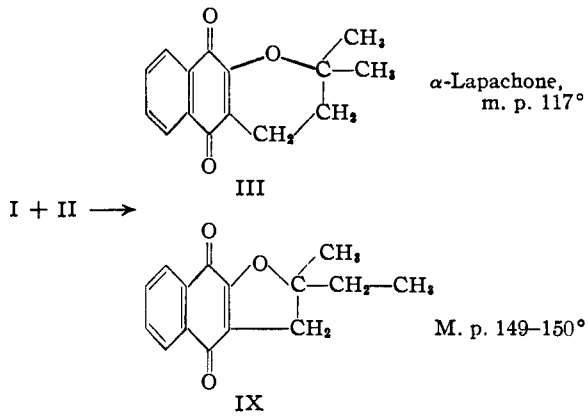
BY MARSHALL GATES AND DOROTHY L. MOESTA[1]

In an extension of the condensation reaction between allylic alcohols and hydroxyhydroquinones reported by Fieser and Gates,[2] we have investigated the condensation of leucoisonaphthazarin with isoprene and with several allylic alcohols related to isoprene. As in earlier examples[2] yields are low, but the inaccessibility of the products by other methods may warrant consideration of this method for the preparation of small amounts.

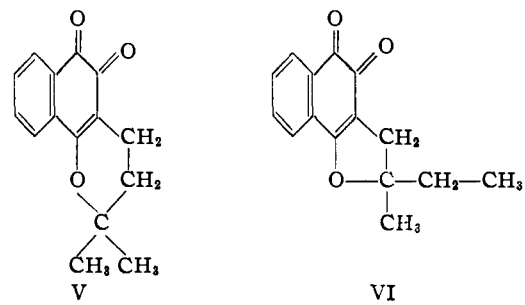
Isoprene condenses with leucoisonaphthazarin in the presence of oxalic acid to yield, after oxidation, a mixture of lapachol (I)[3] and an isomer of lapachol, presumably 2-hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II), in roughly equal parts.



Separation of the two was achieved by fractional crystallization, although the more soluble isomer II was obtained pure only in small amounts by this method. Additional material containing the side-chain carbon skeleton of II could be obtained from the filtrate by cyclization to a mixture of the α-lapachone type isomers III and IV in which the solubility relationships are reversed.



The hydroxynaphthoquinones I and II were further characterized by cyclization with concentrated sulfuric acid to β-lapachone (V) and its isomer, α-methyl-α-ethyldihydrofurano-1,2-naphthoquinone (VI),[4] respectively.



2-Hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II) also results from the condensation

(1) Mrs. George Hain.

(2) Fieser and Gates, THIS JOURNAL, 63, 2948 (1941).

(3) Earlier syntheses of lapachol have been reported by Fieser, *ibid.*, 49, 857 (1927), and by Hooker, *ibid.*, 58, 1181 (1936).

(4) Structure VI is one, although not the preferred one, of three structures originally considered possible for dunnione by Price and Robinson (*J. Chem. Soc.*, 1525 (1939)). If the structure assigned above is correct, VI is eliminated as a possible structure for dunnione since its physical properties do not agree with those of dunnione. Later work by Price and Robinson (*J. Chem. Soc.*, 1493 (1940)) continues to support their original preference (α,α,β-trimethyldihydrofurano-1,2-naphthoquinone) for the structure of this substance.