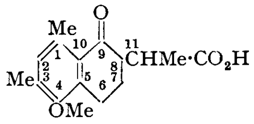
206. *The Constitution of ψ-Santonin. Part V. Further Studies of the Chemistry of Desmotropo-ψ-santonin.*

By WESLEY COCKER, B. E. CROSS, and CYRIL LIPMAN.

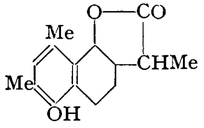
It has been shown that desmotropo-ψ-santonin is a saturated lactone best represented by structure (II) (compare Clemo and Cocker, *J.*, 1946, 30; Cocker and Lipman, *J.*, 1947, 533). The desmotropo-ψ-santonin described by Clemo and Cocker is now named $(+)\beta$-desmotropo-ψ-santonin (compare the nomenclature suggested by Huang-Minlon, Lo, and Chu, *J. Amer. Chem. Soc.*, 1943, **65**, 1780, for the desmotropo-santonins).* A second desmotropo-compound $(+)\alpha$-iso*desmotropo-ψ-santonin* has been isolated from the mother-liquors obtained from the crystallisation of $(+)\beta$-desmotropo-ψ-santonin. Two further dextrorotatory desmotropo-compounds, $(+)\beta$-iso- and $(+)$*α-desmotropo-ψ-santonin* have been obtained by heating $(+)\alpha$-*iso*- and $(+)\beta$-desmotropo-ψ-santonin, respectively, with anhydrous potassium carbonate in anhydrous xylene. All the four possible dextrorotatory desmotropo-ψ-santonins are now known. A mechanism for the conversion of ψ-santonin into its desmotropo-compounds is suggested.

IN an earlier paper Cocker and Lipman (*loc. cit.*) suggested that $(+)\beta$-desmotropo-ψ-santonin was an unsaturated phenolic lactone. The methyl ether of the corresponding acid was considered to be (I), but comparison with a synthetic compound of this structure was impossible owing to an inability to racemise the former acid.

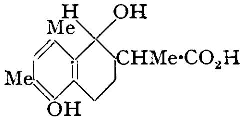
Active-hydrogen determinations on the methyl ether of desmotropo-ψ-santoninic acid (III) gave consistent results indicative of the presence of only one active hydrogen, and could be considered to support the suggestions of Cocker and Lipman. It is, however, possible that a hydroxyl group at C_9 might be undetectable by the Zerewitinoff method, owing to steric hindrance. Efforts made to reach a decision, by chemical methods, on the saturated or unsaturated character of the lactone ring in $(+)\beta$-desmotropo-ψ-santonin have been fruitless. This compound was not reduced by catalytic methods, by zinc and hydrochloric acid, or by sodium amalgam, nor could it be oxidised by permanganate, hypobromite, hydrogen peroxide, or potassium *tert.*-butoxide.



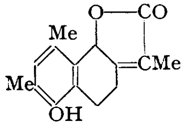
(I.)



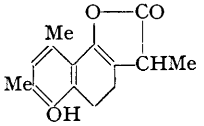
(II.)



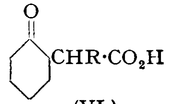
(III.)



(IV.)



(V.)



(VI.)

Failure to oxidise the desmotropo-compound may be parallelled in the santonin series, since so far as we are aware none of the desmotropo-santonins has been oxidised to the corresponding unsaturated lactones or keto-acids. It is probable that, owing to steric hindrance, oxidation at C_9 in compounds of type (II) and (III) is difficult or impossible.

The earlier views of Clemo and Cocker (*loc. cit.*) on the structure of desmotropo-ψ-santonin were eventually confirmed by analysis of a number of different specimens of this compound, its methyl ether, its acetate, its benzoate, and its *carbanilate*.

Spectroscopic evidence lends support to the analytical data. Fig. 1 shows that $(+)\beta$-desmotropo-ψ-santonin has a light-absorption curve similar to that of phenol (Wolf and Herold, *Z. physikal. Chem.*, 1931, *B*, **13**, 201) and the saturated acid, γ-(6-methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthyl)butyric acid (Stork, *J. Amer. Chem. Soc.*, 1947, **69**, 2936). Structures (II) and (III) would be expected to show such light-absorption characteristics. A compound of structure (IV)—an $\alpha\beta$-butenolide—would be expected to absorb like eugenol, whilst its $\beta\gamma$-isomeride (V) would be expected to absorb like *iso*eugenol (Fig. 2). *iso*Eugenol absorbs quite differently from phenol both qualitatively and quantitatively, and although eugenol (Paersch, Diss., Berlin, 1932) is qualitatively like phenol, eugenol shows a higher intensity of absorption at the maximum.

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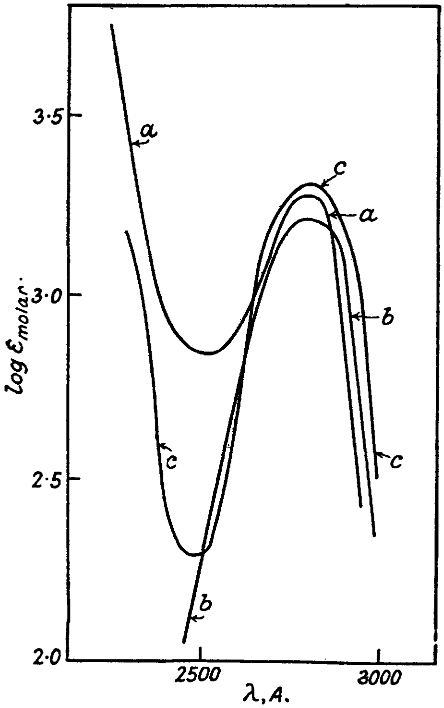
* On this nomenclature the lower-melting isomers are of the α-series, and the higher-melting isomers of the β-series.

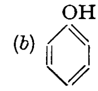
Fig. 2 also shows that the lactone of 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-α-propionic acid (Cocker and Lipman, *loc. cit.*) has a light-absorption curve similar to that of eugenol, which agrees with the suggestion made by Cocker and Hornsby (*J.*, 1947, 1157) that keto-acids of the type (VI) cyclise to give αβ-butenolides.

Fig. 1.

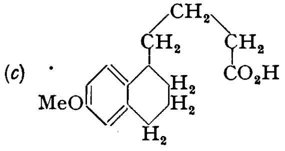


(a) (+) *β-Desmotropo-ψ-santonin.*

(*b*)

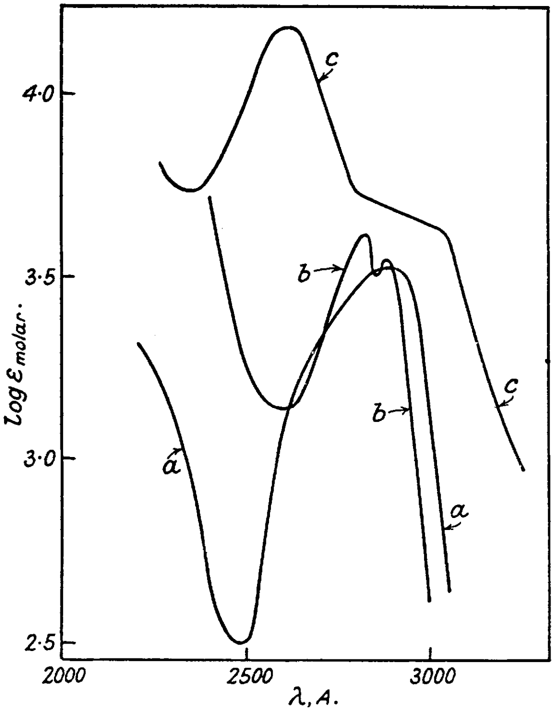


(*c*)

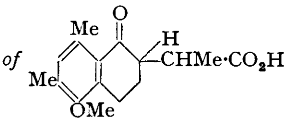


(*All in alcohol.*)

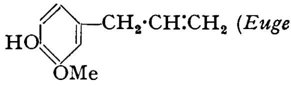
Fig. 2.



(a) *Lactone of*

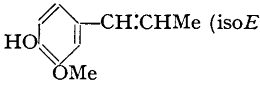


(b)



(*Eugenol*)

(c)



(iso*Eugenol*)

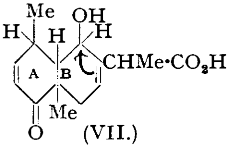
(*All in alcohol.*)

The existence of a saturated lactone ring in (+)β-desmotropo-ψ-santonin is confirmed by the isolation of three other dextrorotatory desmotropo-compounds, which can be represented by structure (II).

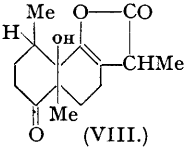
When ψ-santonin is treated with *cold* concentrated hydrochloric acid or 50% sulphuric acid, a dextrorotatory carboxylic acid is produced (Clemo and Cocker, *loc. cit.*) to which we now give the name ψ-santonic acid. The chemistry of this compound will be dealt with in a later communication but the evidence, chemical and spectroscopic, which we possess leads us to suggest the tentative structure (VII). It possesses two double bonds, one of which is conjugated with the keto-group while the other is in the second ring. This acid is an intermediate in the formation of the desmotropo-compounds since on being heated at 50° with 50% sulphuric acid, ψ-santonic acid gives the desmotropo-ψ-santonin (II).

The two structures (VIII) and (IX) have already been advanced for ψ-santonin (see earlier publication in this series) but structure (X) is a further possibility.

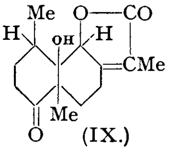
If structure (VII) is correct for ψ-santonic acid, then the formation of this acid from ψ-santonin involves the loss of water from C_1–C_{10} and migration of the double bond so formed to the αβ-position with respect to the keto-group. The second double bond in ψ-santonic acid is probably that associated with the lactone ring in ψ-santonin. The conversion of ψ-santonic acid into desmotropo-ψ-santonin (II) may involve the migration of the double bond of ring B to ring A in the direction shown by the arrow to give a form such as (XI), the angular methyl group of which might be expected to migrate to C_3 with consequent aromatisation of ring A. These changes will have far-reaching stereochemical implications. The asymmetric centres at C_1, C_5, and C_{10} are destroyed and a structure is obtained in which all the centres in the lactone ring are asymmetric. The conversion of structures (VIII) and (X) through (VII) into desmotropo-ψ-santonin would probably lead to a mixture of two pairs of diastereoisomers in both of which the configuration at C_{11} should be the same. This is possible, since it is most unlikely that C_{11} is affected by acid reagents [compare Huang-Minlon *et al.*, *loc. cit.*; *J. Chinese Chem. Soc.*, 1943, **10**, 126; *J. Amer. Chem. Soc.*, 1948, **70**, 611, who made the same assumption for the conversion of *l*-santonin into (–)α-desmotroposantonin]. Unless the diastereoisomers form diastereo-compounds or solid solutions, separation into four desmotropo-compounds should be possible. Two of the latter compounds should have the *cis*- and the other two the *trans*-configuration at C_8–C_9.



(VII.)

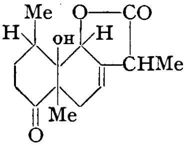


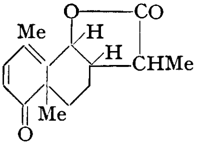
(VIII.)



(IX.)

(X.)





(XI.)

Experimentally, we find that when ψ-santonin is heated with 55% sulphuric acid a dark red solution is produced from which a mixture of at least two desmotropo-compounds separates. Crystallisation of this mixture from dilute alcohol yields (+)β-desmotropo-ψ-santonin (m. p. 189°, $[\alpha]_D^{15^\circ}$ + 68°), already described, and a second desmotropo-compound, (+)α-iso*desmotropo-ψ-santonin* which after several crystallisations melts at 251—253°, $[\alpha]_D^{20^\circ}$ + 68·5°. The latter compound may not be quite optically pure, since the yields of this material are very small, and it is possible that the specific rotation should be slightly higher. Nevertheless, it is significant that the rotations of the two desmotropo-compounds are almost identical. This may be due to a small optical contribution by one of the centres C_8 or C_9. Another alternative is that the two compounds are pairs of diastereoisomers in solid solution or existing as diastereo-compounds, so that C_{11} is the only optically effective centre, but this is unlikely in view of the transformations to be described below. Finally, (+)β-desmotropo-ψ-santonin and (+)α-*iso*desmotropo-ψ-santonin can only differ in configuration at C_8 or C_9, otherwise (+)*α-desmotropo-ψ-santonin* (below) would be the enantiomorph of (+)α-*iso*desmotropo-ψ-santonin and (+)β-iso*desmotropo-ψ-santonin* would be the enantiomorph of (+)β-desmotropo-ψ-santonin.

On dilution of the red solution from which the two desmotropo-compounds separate, a gum is produced which so far has proved intractable. This gum may contain a mixture of the still unknown lævorotatory compounds, (–)β-*iso*desmotropo-ψ-santonin and (–)α-desmotropo-ψ-santonin.

When (+)β-desmotropo-ψ-santonin is heated with sodium hydroxide at 200°, it yields a small quantity of a further desmotropo-compound, (+)*α-desmotropo-ψ-santonin*, m. p. 171—172°, $[\alpha]_D^{20^\circ}$ + 153°. The same compound is produced in good yield when (+)β-desmotropo-ψ-santonin is heated in boiling xylene with anhydrous potassium carbonate. Under the latter conditions it is likely that C_{11} is inverted, whilst C_8 and C_9 are unaffected (compare Huang-Minlon *et al.*, *loc. cit.*). The lactone ring is not opened in this reaction when the potassium carbonate is perfectly anhydrous, since the inverted lactone can be isolated from the xylene without the use of mineral acid. The same inverted lactone is obtained even when some of the lactone is hydrolysed. Inversion probably occurs through the enol. Further, all the available evidence (compare Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 689; *Ann. Reports*, 1946, **43**, 165, where references to the work of Kenyon *et al.* are given) goes to show that oxygen–alkyl fission is the exception rather than the rule in the hydrolysis of esters and this mechanism is favoured by ionising conditions which are absent in the experiments described. As the specific rotation is increased by inversion of C_{11}, this centre in (+)β-desmotropo-ψ-santonin and in ψ-santonin itself must be lævorotatory. However, a true assessment of the value of the rotatory power of C_{11} in these compounds cannot be made since vicinal effects from C_8 and C_9 are likely to operate (compare Kauzmann, Walter, and Eyring, *Chem. Reviews*, 1940, **26**, 339).

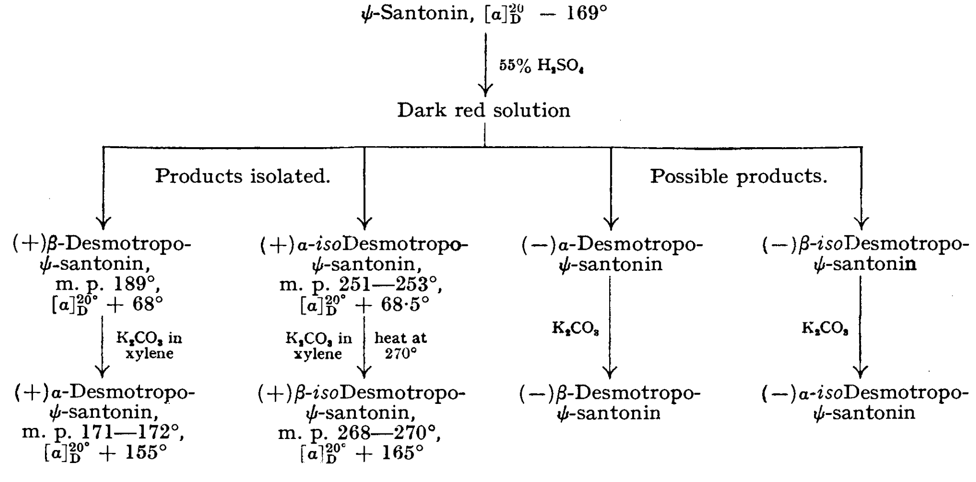
In addition to (+)α-desmotropo-ψ-santonin a further product was isolated (in varying yield) from the alkaline inversion described. After several crystallisations the latter melted at 188—189° ($[\alpha]_D^{20°}$ + 113°). It gave no depression in melting point with a synthetic mixture of equal amounts of (+)α- and (+)β-desmotropo-ψ-santonin, and the specific rotation of this mixture was +113°. This mixture could be crystallised without change in rotation or melting point and, like the product of the inversion described, was probably a solid solution of the two compounds.

By a similar treatment with potassium carbonate in xylene, (+)α-*iso*desmotropo-ψ-santonin is inverted at C_{11} to yield the fourth, and only remaining, possible dextrorotatory desmotropo-ψ-santonin, namely, (+)β-iso*desmotropo-ψ-santonin*, m. p. 268—270°, $[\alpha]_D^{20°}$ + 165°. This compound is also obtained in excellent yield when (+)α-*iso*desmotropo-ψ-santonin is heated above its melting point, although no such inversion takes place on heating either (+)α- or (+)β-desmotropo-ψ-santonin. Inversion of C_{11} most likely takes place by enolisation of the carbonyl group in the lactone ring, a process which need not involve the opening of the lactone ring. As expected, the specific rotation is increased by roughly the same value during the inversion of (+)α-*iso*- and (+)β-desmotropo-ψ-santonin.

The following new derivatives of the above desmotropo-compounds have been prepared: *methyl ether* and *acetate* of (+)α-desmotropo-ψ-santonin, the *acetate* of (+)β-*iso*desmotropo-ψ-santonin, and the *acetate* of (+)α-*iso*desmotropo-ψ-santonin. The specific rotations of these compounds are roughly in agreement with the expected values, indicating the absence of stereochemical changes during acetylation and methylation. The acetate of (+)β-desmotropo-ψ-santonin is the chief product obtained when ψ-santonin is warmed at 50° with acetic anhydride and concentrated sulphuric acid.

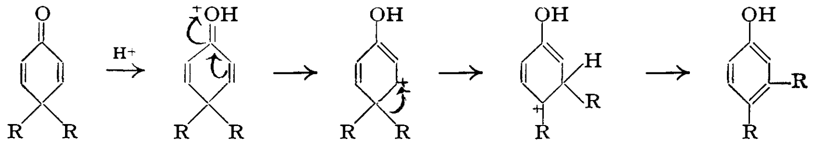
Attempts to produce the lævorotatory desmotropo-compounds by inversion of C_8 and C_9, by acidic reagents, in any of the dextrorotatory desmotropo-compounds described (compare Huang-Minlon *et al.*, *loc. cit.*) have so far failed, but further investigations are in hand. As already stated, two of the lævorotatory desmotropo-compounds may be found in the red solution described, and this is also being investigated. We hope to study the relative stability of the lactone ring in the two series of desmotropo-compounds (normal and *iso*) with a view to arrive at the configurations of C_8 and C_9.

Many of the reactions described are summarised in the accompanying scheme.

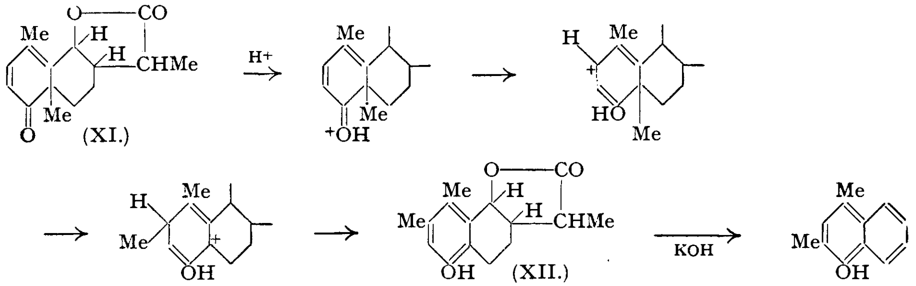


The formation of the desmotropo-compounds from ψ-santonic acid may take place through an unstable intermediate compound such as (XI). This could undergo rearrangement. But the migration of methyl from C_5 to C_3 in such a compound is unusual.

The migration of methyl in semiquinones has been studied by Arnold, Buckley, and Richter (*J. Amer. Chem. Soc.*, 1947, **69**, 2322) who advance the mechanism given below. This mechanism has been used by Huang-Minlon (*J. Amer. Chem. Soc.*, 1948, **70**, 611) to explain the conversion of santonin into desmotropo-santonin (see also Clemo, Haworth, and Walton, *J.*, 1929, 2368, who also give earlier references).

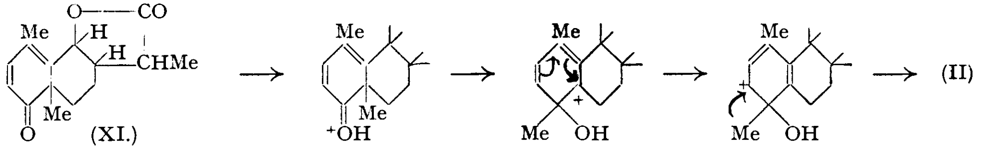


Such a series of changes is not directly applicable to the partial aromatisation of (XI), but it is possible that (XI) could be converted into the form (XII), and that during dehydrogenation, which Clemo and Cocker (*loc. cit.*) effected by fusion of (+)β-desmotropo-ψ-santonin with potash, further migration of the methyl to give 2 : 4-dimethyl-1-naphthol might take place. On this view (XII) would represent desmotropo-ψ-santonin.



In order to test the above hypothesis, 3 : 4-dimethyl-5 : 6 : 7 : 8-tetrahydro-1-naphthol and 3 : 4-dimethyl-1-naphthol * were fused with potassium hydroxide under the conditions employed by Clemo and Cocker. No migration of the methyl group took place and it is now considered that (II) correctly represents desmotropo-ψ-santonin, particularly in view of the fact that this compound fails to couple with diazonium compounds. It may be added that *o*-4-xylenol is also recovered unchanged after fusion with potassium hydroxide.

The production of desmotropo-ψ-santonin from a compound such as (XI) might, however, proceed along the following lines :—



It was stated above that the conversion of ψ-santonic acid into desmotropo-ψ-santonin probably takes place by bond migration. Another, less likely alternative is that the desmotropo-compounds are formed by an oxidation–reduction mechanism in which ring A of ψ-santonic acid is dehydrogenated and the second double bond becomes reduced. The desmotropic change was carried out in presence of benzoquinone as a hydrogen acceptor, but there was no evidence of the production of quinol.

EXPERIMENTAL.

(+)α-iso*Desmotropo-ψ-santonin.*—ψ-Santonin (6 g.) was treated with 50% sulphuric acid as described by Clemo and Cocker (*loc. cit.*). The crude product (1·9 g.) was crystallised (charcoal) from a mixture of alcohol (35 c.c.) and water (12 c.c.), yielding a compound (*A*) (1·3 g.), m. p. 182—186°. The mother-

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* The preparation of these compounds from *o*-4-xylenol and succinic anhydride will be described in a separate publication on certain substituted naphthols.

liquor from (*A*) was concentrated, and a second fraction (*B*) (0·4 g.), m. p. 165—230°, was obtained. Crystallisation of (*A*) from dilute alcohol yielded (+)β-desmotropo-ψ-santonin, m. p. 188—189°.

Phenylhydrazide of (+)*β-Desmotropo-ψ-santoninic Acid.*—A mixture of (+)β-desmotropo-ψ-santonin (0·1 g.) and phenylhydrazine (0·3 g.) was heated at 140—150° for 9 hours. On cooling, the *phenylhydrazide* was collected, washed with a little ice-cold alcohol, and crystallised twice from dilute alcohol, forming colourless needles, m. p. 228—229° (Found : C, 70·6; H, 7·3. $C_{21}H_{26}O_3N_2$ requires C, 71·2; H, 7·3%). Its *methyl ether*, prepared in the same manner from the methyl ether of (+)β-desmotropo-ψ-santonin, crystallised from dilute alcohol in silky needles, m. p. 212—213° (Found : N, 7·4. $C_{22}H_{28}O_3N_2$ requires N, 7·6%).

The mother-liquor from which the (+)β-desmotropo-ψ-santonin separated was mixed with a dilute alcoholic solution of (*B*) (see above) and the mixture was passed through a column of activated alumina, the effluent from which was concentrated. On cooling, this yielded a fraction (about 100 mg.), m. p. 215—230°, rich in (+)α-iso*desmotropo-ψ-santonin*. The combined crops of crystals from several such processes were crystallised several times alternately from benzene and dilute alcohol, yielding needles, m. p. 251—253°, $[\alpha]_D^{20^\circ}$ + 68·5° (*c* 0·71, in alcohol) (Found : C, 72·9; H, 7·45. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Its *acetate* crystallised from absolute alcohol in needles, m. p. 244·5—245·5°, $[\alpha]_D^{20^\circ}$ + 64·1° (*c* 0·4, in chloroform) (Found : C, 70·5; H, 6·95. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%).

(+)*α-Desmotropo-ψ-santonin.*—(+)β-Desmotropo-ψ-santonin (0·5 g.) in anhydrous xylene (10—15 c.c.) was refluxed for 24 hours with freshly ignited potassium carbonate (0·8 g.). The hot mixture was filtered, giving a residue (*A*) and a filtrate (*B*). The latter was evaporated in a vacuum and warmed with concentrated hydrochloric acid, and the *α-desmotropo-ψ-santonin* (0·35 g.), m. p. 164°, was crystallised several times from dilute alcohol and obtained as colourless rosettes of needles, m. p. 171—172°, $[\alpha]_D^{20^\circ}$ + 155° (*c* 0·7, in chloorform) (Found : C, 73·4; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Its *acetate* crystallised from absolute alcohol as needles or prisms, m. p. 214°, $[\alpha]_D^{18^\circ}$ + 121° (*c* 0·55, in chloroform) (Found : C, 71·3; H, 7·2. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%); on deacetylation with alcoholic potash, (+)α-desmotropo-ψ-santonin was recovered. Its *methyl ether* crystallised from dilute alcohol in silvery plates, m. p. 150° (Found : C, 73·5; H, 7·8. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%).

When the residue (*A*) (above) was warmed with concentrated hydrochloric acid, a product (0·1 g.), m. p. 183°, was obtained. Several crystallisations from dilute alcohol yielded colourless rhombs, m. p. 189—190°, $[\alpha]_D^{18^\circ}$ + 113° (*c* 0·9, in chloroform) (Found : C, 73·1; H, 7·5. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). This molecular *compound* depressed the m. p. of (+)β-desmotropo-ψ-santonin, but did not depress the m. p. of the colourless rhombs obtained by crystallising a mixture of equal quantities of (+)α- and (+)β-desmotropo-ψ-santonin from dilute alcohol; this mixture gave $[\alpha]_D^{19^\circ}$ + 112·6° (*c* 0·1, in chloroform).

(+)β-iso*Desmotropo-ψ-santonin.*—A mixture of (+)α-*iso*desmotropo-ψ-santonin (0·21 g.), freshly ignited potassium carbonate (0·63 g.), and anhydrous xylene (25 c.c.) was heated under reflux for 22 hours. The xylene was removed in a vacuum, the residue heated with concentrated hydrochloric acid, and the β-iso*desmotropo-ψ-santonin* collected (0·2 g.), m. p. 245—250°; $[\alpha]_D^{20^\circ}$ + 135·5° (*c* 0·5, in chloroform). It was crystallised several times from absolute alcohol and obtained as slender, colourless needles, m. p. 268—270°, $[\alpha]_D^{18^\circ}$ + 165° (*c* 0·4 in chloroform) (Found : C, 73·1; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Its *acetate* crystallised from dilute acetic acid in fine, colourless needles, m. p. 223—224°, $[\alpha]_D^{14^\circ}$ + 135° (*c* 0·3, in chloroform) (Found : C, 71·0; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%). (+)β-*iso*Desmotropo-ψ-santonin was also obtained when (+)α-*iso*desmotropo-ψ-santonin (200 mg.) was heated in a sealed tube at 250—270° for 60—70 minutes. The crystalline product, m. p. 256—262°, was recrystallised from absolute alcohol and obtained (90—100 mg.) as colourless needles, m. p. 268—270°, $[\alpha]_D^{18^\circ}$ + 165° (Found : C, 73·6; H, 7·1. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

The *carbanilate* of (+)*β-desmotropo-ψ-santonin* crystallised from alcohol as silvery plates, m. p. 222—223° (Found : C, 71·8, 71·5; H, 6·3, 6·5. $C_{22}H_{23}O_4N$ requires C, 72·3; H, 6·3%).

Acetate of (+)*β-Desmotropo-ψ-santonin* (compare Clemo and Cocker, *loc. cit.*).—A mixture of ψ-santonin (0·1 g.), acetic anhydride (5·0 g.), and concentrated sulphuric acid (5 g.) was heated at 50° for 20 minutes, cooled, and diluted. The solid product was crystallised twice from alcohol, giving the required acetate, m. p. 230—231° undepressed by authentic acetate.

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