The Chemistry of Santonin. Part I. Some Rearrangement Products of the Santonins.

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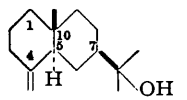
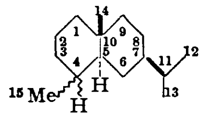
The acetates of two new desmotroposantonins (*trans*-fused lactones) have been prepared by the reaction of santonin and 11β(H)-santonin * with a mixture of acetyl chloride and acetic anhydride. The constitutions of the other products of these reactions are discussed. 11β(H)-Santonin has been converted into santonin.

Although the absolute configurations of the two known naturally occurring santonins have not yet been rigidly established, it is most probable from molecular-rotation data (Corey, *J. Amer. Chem. Soc.*, 1955, **77**, 1044; Abe and Sumi, *Chem. and Ind.*, 1955, 253) that their configurations at $C_{(7)}$ and $C_{(10)}$ are as in eudesmol (I) (Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313), and that santonin (III) and 11β(H)-santonin (IV) have the configurations shown (Corey, *loc. cit.*; Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1953, **75**, 2567; *Proc. Japan Acad.*, 1952, **28**, 425; 1953, **29**, 113; 1954, **30**, 119; Matsui, Toki, Kitamura, Suzuki, and Hamuro, *Bull. Chem. Soc. Japan*, 1954, **27**, 7; Cocker and McMurry, *Chem. and Ind.*, 1954, 1199; Cocker, *Ann. Reports*, 1954, **51**, 209). The acid-catalysed isomerisation of these two santonins under mild conditions involves inversion at $C_{(6)}$ so that the desmotropo-compounds so produced, namely, (V) and (VI), respectively, are *cis*-fused lactones (Huang-Minlon, *J. Amer. Chem. Soc.*, 1948, **70**, 611) with the absolute configurations shown. These desmotropo-compounds can be isomerised by various treatments so that of the eight possible isomeric forms, all four *cis*-fused lactones (V—VIII) have been described (Huang-Minlon, *loc. cit.*; Chopra, Cocker, and Edward, *Chem. and Ind.*, 1955, 41, who also give references to earlier work).

(I)





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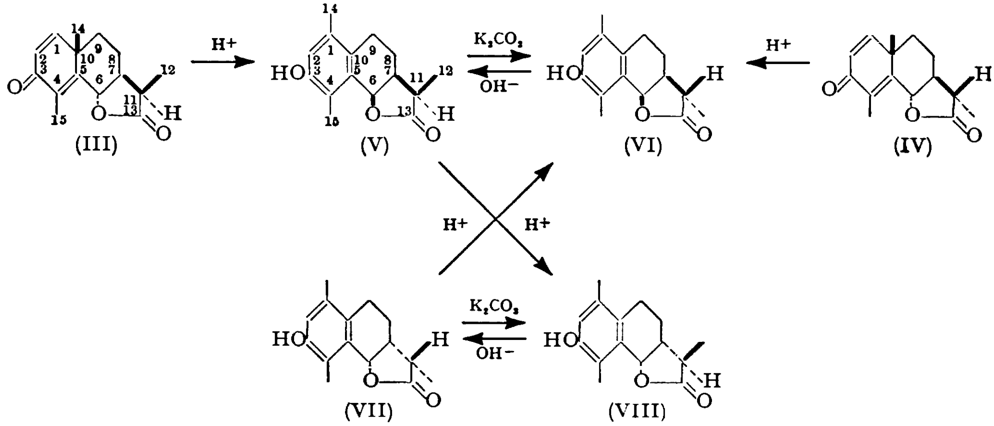

(III) (V) (VI) (IV) (VII) (VIII)

Nomenclature of the Desmotroposantonins.—The nomenclature of these compounds is

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* The nomenclature and numbering are as suggested by Cocker and Cahn (*Chem. and Ind.*, 1955, 384). The root name, desmotroposantonin, is retained for the butanolides obtained from the santonins with acidic reagents. The non-aromatic compounds lacking a butanolide ring are named after the parent hydrocarbon, eudesmane (II), with the absolute configuration shown.

confused, but in the more rational system of Huang-Minlon (*loc. cit.*; cf. Simonsen "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 263), the primary rearrangement products (V) of santonin, and (VI) of 11β(H)-santonin, are respectively named (—)α- and (—)β-desmotroposantonin. Their enantiomorphs (VII) and (VIII) are (+)α- and (+)β-desmotroposantonin, respectively. It is now proposed to name the desmotropo-compounds according to their absolute configuration as shown below.

(—)α-Desmotroposantonin (V) = 6α(H),7α(H),11α(H)-Desmotroposantonin
(—)β-Desmotroposantonin (VI) = 6α(H),7α(H),11β(H)- ,,
(+)α-Desmotroposantonin (VII) = 6β(H),7β(H),11β(H)- ,,
(+)β-Desmotroposantonin (VIII) = 6β(H),7β(H),11α(H)- ,,

The proposed system, whilst it does not state the direction of optical rotation of the desmotropo-compounds, otherwise gives a full description of their stereochemistry.

New Desmotroposantonins.—We have now obtained under mildly acidic conditions the acetates of two of the four remaining isomeric desmotroposantonins, in which the lactone rings are *trans*-fused. Treatment of santonin (III) with a mixture of acetyl chloride and acetic anhydride (cf. Westphal, *Ber.*, 1937, **70**, 2128; Inhoffen, *Ber.*, 1936, **69**, 2141) afforded a mixture of two isomeric compounds, $C_{17}H_{20}O_4$, which proved to be the acetate (IX) of 6β(H),7α(H),11α(H)-desmotroposantonin and an unsaturated enol acetate (XI) discussed below.

The assignment of the structure of the new desmotropo-compound (IX) is based on the following facts. (1) Its ultraviolet absorption maxima are at 2720 (log ε 2·89) and 2800 Å (log ε 2·91). Gunstone and Tulloch (*J.*, 1955, 1130) record absorption in the range 2730—2810 Å (log ε 3·10) for the acetate of (V). (2) A 6β(H)-configuration is likely because the new lactone is dextrorotatory. The *cis*-fused dextrorotatory lactones (VII) and (VIII), and *hypo*santonin (IX; H for OAc) all have the 6β(H)-configuration (cf. Huang-Minlon, *loc. cit.*). (3) The compound (IX) displays the butanolide (>C=O) maximum at 1788 cm.$^{-1}$ (in $CHCl_3$) whilst we have found for the *cis*-fused lactone (V) a maximum at 1766 cm.$^{-1}$ (in $CHCl_3$). All the *cis*-fused butanolides we have examined exhibit >C=O stretching frequency at about 1765 cm.$^{-1}$ (in $CHCl_3$); many, but not all, *trans*-butanolides exhibit a >C=O band at 1785—1790 cm.$^{-1}$. (4) The *trans*-fusion of the lactone ring is proved by isomerisation of the compound to the acetate of the more stable *cis*-lactone (V) by the action of sulphuric acid in acetic anhydride (cf. Huang-Minlon, *loc. cit.*; Huang-Minlon, Lo, and Chu, *J. Amer. Chem. Soc.*, 1943, **65**, 1780). Similarly, hydrolysis of the acetate (IX) with methanolic potassium hydroxide and acidification of the solution affords the phenol (V). Inversion at $C_{(6)}$ occurs during acidification, a reaction analogous to the conversion of *hypo*santonic acid into *isohypo*santonin (V; H for OH) (cf. "Encyclopædia of Organic Chemistry," Elsevier Publ. Co., Amsterdam, Vol. XIIB, p. 3458). This is confirmed by the widely different molecular rotations of the potassium salts of the acids derived from (IX) and (V) (see Table 1). (5) The molecular-rotation contribution of the lactone ring in (IX) is *positive* (Table 1), due allowance being made for the contribution of the acetate residue. Klyne's rule (*Chem. and Ind.*, 1954, 1198) then indicates a 6β(H)-configuration when the molecule is orientated as in (IX).

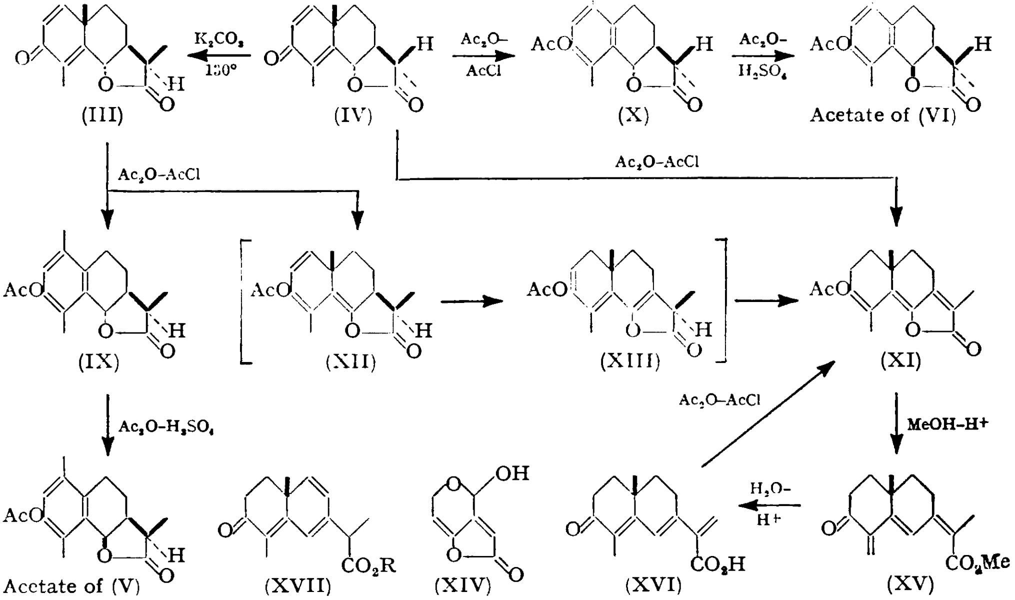
Treatment of 11β(H)-santonin (IV) with acetyl chloride and acetic anhydride affords a small quantity of the acetate of the *trans*-lactone (X) together with larger quantities of the acetate of the *cis*-lactone, 6α(H),7α(H),11β(H)-santonin (VI), into which the isomer (X) is converted with the greatest ease. The new lactone (X), like the acetates of the other desmotropo-compounds, displays maximum absorption at 2720 (log ε 3·02) and 2800 Å (log ε 3·03). In the infrared region, however, it shows butanolide carbonyl stretching frequency at 1766 cm.$^{-1}$, rather than in the 1785—1790 cm.$^{-1}$ range expected of a *trans*-lactone. On treatment with acetic anhydride–sulphuric acid, it is transformed into the acetate of 6α(H),7α(H),11β(H)-santonin (VI). The instability of the lactone (X) serves to indicate the lower stability of the 11β(H)-configuration in the *trans*-fused lactone system in which $C_{(7)}$ has the α(H)-configuration. This fact is further demonstrated by the conversion of 11β(H)-santonin (IV) into santonin (III) by treatment of the former with anhydrous potassium carbonate in boiling xylene (cf. Chopra, Cocker, and Edward, *loc. cit.*). Whilst this conversion takes place in 45% yield only, similar treatment of santonin leads to 45%

recovery, and in both cases charring accounts for the losses. In the *cis*-lactones the reverse order of stabilities is found (Woodward and Yates; also Chopra, Cocker, and Edward, *locc. cit.*). Examination of molecular models shows that in a *cis*-fused lactone such as (V) with 11α(H)-configuration the 11-methyl group directly opposes the 8-methylene group, and further that in this arrangement the 11-methyl group is *cis* with respect to the non-hydrogen substituent atoms at $C_{(6)}$ and $C_{(7)}$. Obviously this is a less stable arrangement than that with the 11β(H)-configuration. In the *trans*-fused lactones there is no direct opposition between the groups attached to $C_{(11)}$ and the 8-methylene group. There is however greater interference between the 11-methyl and the carbonyl group when $C_{(11)}$ has the β- than when it has the α-configuration.

TABLE 1. *Molecular-rotation contributions of lactone rings.*

Substance	Lactone, $[M]_D$	Acid, $[M]_D$	$\Delta[M]_D$	Ref.
Santonin (III)	−425° (EtOH)	−68° (EtOH)	−357°	*a*
11β(H)-Santonin (IV)	−342 (MeOH)	−234 (K salt in MeOH)	−108	
(V)	−344 (EtOH)	+186 (EtOH) −130 (K salt in MeOH)	−530 −214	*b*
Acetate of (V)	−376 ($CHCl_3$)	—	—	
(VI)	−261 (EtOAc)	+134	−395	*b*
(VII)	+320 (EtOH)	−184	+504	*b*
(VIII)	+261 (EtOH)	−213	+393	*b*
(IX)	+247 ($CHCl_3$)	−132 —	—	
(IX, OH for OAc) (est.)	+243	+ 95 (K salt in MeOH)	+148	

(*a*) Hesse, *Annalen*, 1875, **176**, 89, 125. (*b*) Chopra, Cocker, and Edward, *loc. cit.* Klyne's rule (*loc. cit.*) confirms the configuration shown for lactones (V—VIII); it cannot be applied to santonin (III) and 11β(H)-santonin (IV); presumably the dienone system interferes.



The second product of the action of acetyl chloride and acetic anhydride on santonin was a yellow compound which we formulate as the unsaturated enol acetate, 3-acetoxyeudesma-3 : 5 : 7(11)-trien-6 : 13-olide (XI). The same compound was obtained in small yield by the action of carefully purified acetyl chloride and acetic anhydride on 11β(H)-santonin (IV). This second mode of preparation serves to exclude formulations such as (XII) and (XIII), since in these the original asymmetry at $C_{(11)}$ is retained. Since the preparation of the enol acetate takes place under conditions unlikely to epimerise $C_{(11)}$, structures (XII) and (XIII) would necessitate different products from santonin and 11β(H)-santonin. Structure (XI) is supported by spectroscopic evidence. Thus the enol acetate exhibits ultraviolet maxima at 3300 (log ε 4·46) and 2190 Å (log ε 3·63) and an infrared peak at 1764 cm.$^{-1}$ (lactone and acetate-carbonyl), and a triplet around 1639 cm.$^{-1}$ which can be attributed to the triene system. It is interesting that the carbonyl frequency of the αβ-unsaturated lactone is increased rather than decreased by the extended conjugated system. However Grove (*J.*, 1951, 883) has shown that the carbonyl frequency of patulin (XIV), with a similar unsaturated system, is at 1768 cm.$^{-1}$.

The enol-acetate is unaffected by a mixture of sulphuric acid and acetic acid whereas a compound of structure (XII), and perhaps (XIII), would be expected to be rearranged to a desmotropo-compound by this reagent. Again these structures may be eliminated on spectroscopic grounds. If probable hypsochromic effects of the oxygen-substituents are neglected (Briggs and Cain, *J.*, 1954, 4182), a compound (XII) would be expected to show maximum absorption at 3080 Å and a compound (XIII) at about 3130 Å (cf. Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 185).

Reaction of the enol acetate (XI) with N-methanolic hydrogen chloride affords a methyl ester, $C_{16}H_{20}O_3$ (XV), hydrolysed by aqueous mineral acid to an acid, $C_{15}H_{18}O_3$ (XVI). The last is reconverted into (XI) on being treated with acetyl chloride and acetic anhydride. Thus the three compounds have the same carbon skeleton. Further, the mild conditions of the reactions rule out very extensive migrations of the double bonds. The methyl ester, however, cannot have the disposition of the double bonds shown in (XVI) or (XVII) since it does not show a low-intensity maximum in the region 4700 Å due to a carbonyl group conjugated with a triene. Again the large difference in molecular rotation between the ester and acid (Table 2) indicates that the two cannot have the same disposition of double bonds. By exclusion the ester must be methyl 3-oxoeudesma-4(15) : 5 : 7(11)-trien-13-oate (XV), and in this structure the low-intensity maximum of the carbonyl group in the neighbourhood of 3200 Å is masked by the higher absorption of the conjugated triene-ester chromophore.

TABLE 2.

Substance	Enol acetate (XI)	Me ester (XV)	Acid (XVI)
$[M]_D$	−697°	−1082°	−659°

The extended unsaturated system would be expected to give high negative values for $[M]_D$.

The acid obtained by hydrolysis of the ester shows a low-intensity absorption band at 4740 Å, indicative of a conjugated trienone, either (XVI) or (XVII). The latter formulation is however excluded since it is that of a βγ-unsaturated acid, which should readily be decarboxylated, and the acid does not behave in this fashion. The acid is thus 3-oxoeudesma-4 : 6 : 11-trien-13-oic acid (XVI).

Table 3 sets out the spectroscopic characteristics of ester (XV), acid (XVI), and ethyl methyleneacetoacetate, a vinylogue of (XV and XVI), and likewise a " crossed " enedione system.

TABLE 3.

	Ultraviolet max. (Å) (and log ε)					Infrared bands (cm.$^{-1}$)
Ester (XV)	3650	2940	2780	2375	—	1728 (br., s), αβ-unsat. ester & CO
	(4·5	3·58	3·59	3·60)	—	1631 (m), 1600 (m) triene
Acid (XVI)	4740	3725	2875	2755	2350	1730 (br., s), CO_2H & CO
	(1·60	4·50	3·65	3·67	3·65)	1630 (m), 1593 (m) triene
$CH_2{:}C(CO{\cdot}CH_3){\cdot}CO_2Et$ ...	3070 (infl.)		2390	—	—	1741 (s), CO_2Et
	(1·5		3·24)			1712 (s), CO
						1632 (m), $>C{:}CH_2$

It is interesting that the infrared absorptions of the ester and the acid are similar, but this is not surprising since one system is electronically the reverse of the other. It is also interesting that in all three systems the infrared spectra display carbonyl stretching frequencies at positions expected of isolated carbonyl groups. Indeed the frequencies appear to be somewhat enhanced. It might have been expected that the " crossed " ene-dione systems, like the " crossed " dienone system found in santonin, would have behaved as two separate αβ-unsaturated carbonyl systems; in the ultraviolet region this appears to be the case, but the infrared spectra of both ester and acid are strongly reminiscent of those of an α-keto-ester and -acid.

EXPERIMENTAL

Ultraviolet spectra were measured for EtOH solutions with a Beckmann D.U. instrument, and the infrared spectra in $CHCl_3$ with a Hilger 800 Double-beam instrument. $[\alpha]_D$ refer to $CHCl_3$ solutions.

Acetate of 6β(H),7α(H),11α(H)-*Desmotroposantonin* (IX) *and* 3-*Acetoxyeudesma*-3 : 5 : 7(11)-*trien*-6 : 13-*olide* (XI).—A mixture of santonin (10 g.), acetic anhydride (20 c.c.), and acetyl chloride (20 c.c.) was refluxed for 2·5 hr. The reagents were then removed under reduced pressure, and the product was crystallised from ethanol, giving a mixture of well-formed needles and rhombs. These were separated by hand-picking, and each crystallised from ethanol, thus affording 6β(H),7α(H),11α(H)-*desmotroposantonin acetate* (5·4 g.) as colourless needles, m. p. 180°, $[\alpha]_D^{18}$ +85·8° (*c* 0·91) (Found : C, 70·4; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%), and the "*enol acetate*" (XI) (2·5 g.) as yellow rhombs, m. p. 135°, $[\alpha]_D^{20}$ −242·0° (*c* 1·9) (Found : C, 70·3; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

Action of Acetic Anhydride–Sulphuric Acid on 6β(H),7α(H),11α(H)-*Desmotroposantonin Acetate*.—The preceding compound (0·5 g.) was dissolved in acetic anhydride (8 c.c.), sulphuric acid (2 drops) was added, and the mixture was heated on the water-bath for 20 min. The product was poured into water, giving crude (0·46 g.) acetate of 6α(H),7α(H),11α(H)-desmotroposantonin (V) which after recrystallisation from ethanol had m. p. 155—156°, undepressed by an authentic specimen of this desmotropo-compound.

Hydrolysis of 6β(H),7α(H),11α(H)-*Desmotroposantonin Acetate* (IX).—A solution of this compound (1·0 g.) and potassium hydroxide (0·4 g.) in methanol (15 c.c.) was set aside for 24 hr. at room temperature. The product on acidification was 6α(H),7α(H),11α(H)-desmotroposantonin (V) (0·62 g.), m. p. and mixed m. p. 194°.

Methyl 3-*Oxoeudesma*-4(15) : 5 : 7(11)-*trien*-13-*oate* (XV).—The enol acetate (XI) (1 g.) was heated with methanolic hydrochloric acid (N; 10 c.c.) until it dissolved and the solution was set aside for 1 hr. The solid which had been deposited was collected (0·65 g.) and crystallised from methanol, giving the *ester* (XV) as pale yellow needles, m. p. 150—151°, $[\alpha]_D^{20}$ −416·1° (*c* 0·92) [Found : C, 74·3; H, 7·8; OMe, 12·1%; *M* (Rast), 267. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7; OMe, 11·9%; *M*, 260].

3-*Oxoeudesma*-4 : 6 : 11-*trien*-13-*oic Acid* (XVI).—A solution of the above ester (0·1 g.) in 50% aqueous-methanolic hydrogen chloride (0·5N; 10 c.c.) was warmed at 50° for 1 hr. and cooled. The *acid* (0·07 g.; m. p. 170—171°) was collected and crystallised from ethanol as pale yellow needles, m. p. 176—177°, $[\alpha]_D^{20}$ −268° (*c* 0·52) (Found : C, 72·8; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

Reconversion of 3-*Oxoeudesma*-4 : 6 : 11-*trien*-13-*oic Acid* (XVI) *into the Enol Acetate* (XI).—The acid (XVI) (0·5 g.) was refluxed with acetic anhydride (5 c.c.) and acetyl chloride (5 c.c.) for 3·5 hr. The product (0·46 g.), m. p. 134°, was the enol acetate (XI).

Experiments with 11β(H)-*Santonin*.—*Santonin from* 11β(H)-*santonin*. 11β(H)-Santonin (1 g.), anhydrous potassium carbonate (1 g.), and xylene (12·5 c.c.) were refluxed for 24 hr. (cf. Cocker, Cross, and Lipman, *J.*, 1949, 959). After refluxing with charcoal, filtration, and removal of solvent, the product (0·45 g.) had m. p. 158—165°. Crystallisation from ethanol gave santonin, m. p. and mixed m. p. 169—171°, $[\alpha]_D^{17}$ −171·5° (*c* 1·35).

6β(H),7α(H),11β(H)-*Desmotroposantonin acetate* (X). (*a*) A solution of 11β(H)-santonin (5 g.) in acetic anhydride (10 c.c.), and acetyl chloride (10 c.c.) were refluxed for 3·5 hr. The main product was 6α(H),7α(H),11β(H)-desmotroposantonin acetate (VI) (4·3 g.), m. p. and mixed m. p. 155—156°, together with unchanged 11β(H)-santonin (0·35 g.).

(*b*) In a similar experiment but with purified acetyl chloride, 11β(H)-santonin (4·2 g.) was recovered together with the enol acetate (XI) (0·13 g.), m. p. and mixed m. p. 134—135°.

(*c*) In a further experiment 6α(H),7α(H),11β(H)-desmotroposantonin acetate (3·4 g.) was isolated, together with 6β(H),7α(H),11β(H)-*desmotroposantonin acetate* (X) (0·6 g.) as plates, m. p. 116°, $[\alpha]_D^{21}$ +12·6° (*c* 1·2) (Found : C, 70·6; H, 6·9. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%). Crystallisation of this compound from alcohol gave a second form (needles), m. p. 124—125° (Found: C, 70·9; H, 7·1%). A mixture of the two forms had m. p. 116—117°. Light absorption max. of both forms : 2800, 2720 Å (log ε 3·03, 3·02).

Rearrangement of the acetate (X). The acetate (0·15 g.) was heated with acetic anhydride

(2 c.c.) and concentrated sulphuric acid (1 drop) for 20 min. The product was the crude acetate (0·12 g.) of 6α(H),7α(H),11β(H)-desmotroposantonin (VI) and after crystallisation from ethanol had m. p. and mixed m. p. 154—155°.

Ethyl Methyleneacetoacetate.—Ethyl acetoacetate (10 g.) was added to a mixture of formaldehyde (10 c.c., 40%), and crystalline sodium acetate (2 g.). Alcohol was then added, dropwise, with cooling, until the mixture was homogeneous (cf. Nakazawa and Matsuura, *J. Pharm. Soc. Japan*, 1951, **71**, 178, who give no physical constants for the product). After 1 hr. the product was poured into water and extracted with ether, and the extract washed several times with water. After drying, the product was twice distilled, giving a colourless oil (2·5 g.), b. p. 176—177°/38 mm., $n_D^{18\cdot8}$ 1·4522 (Found: C, 58·7; H, 7·5. $C_7H_{10}O_3$ requires C, 59·1; H, 7·1%).

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