874. *The Chemistry of Santonin. Part III.* The Stereochemistry of Some Reduction Products of Santonin.*

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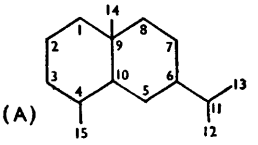
Absolute configurations, which differ from those suggested by Yanagita and Tahara,[1] are assigned to the known tetrahydrosantonins. Several hexahydrosantonins have been prepared.

RECENTLY three papers [1,2,3] have focused attention on the hydrogenation products of santonin (I). Early workers [4] recorded the preparation of two of the four possible tetrahydrosantonins, the so-called α-isomer, m. p. 155—156°, and the β-isomer, m. p. 105°. Yanagita and Tahara [1] recently described the reduction of santonin in acetone over palladised charcoal, and the isolation of α-tetrahydrosantonin and two other tetrahydrocompounds. One of these, m. p. 143—144°, a new compound, was confusingly named the β-isomer, whilst the other, m. p. 96—97°, which we believe to be substantially identical with the β-isomer of earlier workers, was named the γ-isomer. The isomer, m. p. 143—144°, could be converted into α-tetrahydrosantonin by treatment with mineral acid, and hence was assumed to have an axial methyl group at $C_{(4)}$. The γ-isomer is unaffected by acid.

Kovács, Herout, Horák, and Sorm [2] reduced santonin over a palladium–barium carbonate catalyst in methanol and obtained α-tetrahydrosantonin, which they renamed 3-ketosantan-5 : 12-olide-a,† and an isomeric compound, 3-ketosantan-5 : 12-olide-b,

* Part II, *J. Pharm. Pharmacol.*, 1956, in the press.

† The numbering used by Kovács *et al.* is as shown in (A) and differs from our convention (I).



[1] Yanagita and Tahara, *J. Org. Chem.*, 1955, **20**, 959.

[2] Kovács, Herout, Horák, and Sorm, *Chem. Listy*, 1955, **49**, 1856; *Coll. Czech. Chem. Comm.*, 1956, **21**, 225.

[3] Tahara, *J. Org. Chem.*, 1956, **21**, 422.

[4] Simonsen, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 256; Weinhaus and von Oettingen, *Annalen*, 1913, **397**, 219; Weinhaus, *Ber.*, 1913, **46**, 2839; Wedekind and Beniers, *Annalen*, 1913, **397**, 246; Asahina, *Ber.*, 1913, **46**, 1775.

m. p. 103—105°, believed to be identical with the β-isomer of earlier workers.[4] A third tetrahydro-compound, 3-ketosantan-5 : 12-olide-c, m. p. 145—146°, was obtained by oxidation of the hexahydrosantonin, 3-hydroxysantan-5 : 12-olide-c, formed by reduction of santonin over a platinum catalyst in methanol. This tetrahydrosantonin was isomerised by mineral acid to 3-ketosantan-5 : 12-olide-a, and hence is probably identical with the β-tetrahydrosantonin of the Japanese workers.

Yanagita and Tahara [1] conclude that their α- and β-isomers have *cis*-A/B ring-fusion, whilst their γ-isomer is *trans*-fused. These assignments are based upon a comparison of the molecular rotations of the α- and the γ-isomer with the *cis*- and *trans*-A/B ring-fused steroidal 3-ketones, and on the fact that, like corresponding *cis*- and *trans*-A/B fused steroids, the α-isomer gives a 2 : 4-dibromo-derivative whilst the γ- gives a 2 : 2-dibromo-derivative, which rearranges to the 2 : 4-isomer. The latter argument is of doubtful value. In a recent paper,[3] Tahara has shown that the keto-acid (II) derived from the so-called γ-tetrahydrosantonin equilibrates at $C_{(5)}$ (our numbering) with alkali to a mixture containing a predominating quantity of the keto-acid derived from α-tetrahydrosantonin, the latter thus appearing to have the more stable *trans*-decalin system.

Our own investigations support this revision. We have related the three tetrahydrosantonins, and the hydroxy-acid corresponding to the fourth, to six of the eight possible hexahydrosantonins; considerations of molecular rotations and of the known stereochemical course of reductions enable structures to be assigned to the hexa- and hence to the tetra-hydrosantonins.

In this paper we employ the nomenclature suggested by Cocker and Cahn,[5] which avoids trivial names and gives a rigid description of the compounds in question. The alternative names previously given to these compounds are set out in Table 1. It is now known [6,7,8,9] that santonin has the absolute configuration shown in (I). Eudesmol,[10] carissone,[11] and α-cyperone [12] have the same configuration at $C_{(7)}$ and $C_{(10)}$.

TABLE 1. *Alternative names used for the reduced santonins.*

Present authors	Yanagita and Tahara	Kovács *et al.*	Earlier workers
3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII)	α-Tetrahydrosantonin	3-Ketosantan-5 : 12-olide-a	α-Tetrahydrosantonin
3-Oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV)	γ-Tetrahydrosantonin	3-Ketosantan-5 : 12-olide-b	β-Tetrahydrosantonin
3-Oxo-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (VII)	β-Tetrahydrosantonin	3-Ketosantan-5 : 12-olide-c	—
3α-Hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = H)	—	3-Hydroxysantan-5 : 12-olide-c	—
3β-Hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III)	—	3-Hydroxysantan-5 : 12-olide-b	—

(A) *Compounds having* trans-A/B *Ring-fusion.*—We have found that when santonin was hydrogenated in acetic acid over a platinum catalyst a compound believed to have the *cis*-A/B ring-fusion, 3β-hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide [2,13] (III), discussed below, was obtained in low yield and a mixture from which, by acetylation, 3α-acetoxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = Ac) was obtained in good yield. Hydrolysis gave the alcohol (IV; R = H), which was obtained in two crystalline forms; the higher-melting form is probably identical with 3-hydroxysantan-5 : 12-olide-c. The negative shift in molecular rotation on acetylation and the negative molecular-rotation contribution of the hydroxyl group (Table 2) indicate, according to the rule of Klyne and Stokes,[14] that the hydroxyl is α-orientated. The conditions of reduction make it

[5] Cocker and Cahn, *Chem. and Ind.*, 1955, 384; Cocker and McMurry, *J.*, 1955, 4430.
[6] Bruderer, Arigoni, and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858.
[7] Chopra, Cocker, and Edward, *Chem. and Ind.*, 1954, 41.
[8] Abe and Sumi, *ibid.*, 1955, 253.
[9] Corey, *J. Amer. Chem. Soc.*, 1955, **77**, 1044.
[10] Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313.
[11] Barton and Tarlton, *J.*, 1954, 3492; Ayer and Taylor, *J.*, 1955, 3027.
[12] Howe and McQuillin, *J.*, 1955, 2423.
[13] Ruzicka and Eichenberger, *Helv. Chim. Acta*, 1930, **13**, 1117.
[14] Klyne and Stokes, *J.*, 1954, 1979; Stokes and Bergmann, *J. Org. Chem.*, 1952, **17**, 1194; Mills, *Chem. and Ind.*, 1953, 218; Barton and Holness, *J.*, 1954, 4665.

probable that the hydroxyl group is axial and hence the rings A/B are *trans*-fused; this involves 1 : 2-α-addition of hydrogen to the Δ^4-double bond and consequently an axial 4-methyl group. Catalytic hydrogenation of 3-keto-Δ^4-steroids usually gives the *cis*-decal-3-one system,[15] but cases are known where the *trans*-decal-3-one system is obtained.

TABLE 2.

Compound	$[M]_D$ of alcohol	$[M]_D$ of acetate	$[M]_D$ of corresponding deoxy-compound [a]	ΔOH [b]	Δ_1 [b]
3β-Hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III)	− 21°	+ 96°	− 64°	+ 43°	+117°
3α-Hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV; R = H)	+ 91	+ 45	+218	−127	− 46
3α-Hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (X; R = H)	+ 42	− 83	+ 63	− 21	−125
3β-Hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = H)	+128	+186	+ 63	+ 65	+ 58
3α-Hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XVI)	− 96	− 94	− 64	− 32	+ 2
3β-Hydroxy-4 : 11α(H),5 : 6β(H)-eudesman-6 : 13-olide (XIX)	+ 92	+208	—	—	+116

TABLE 3.

Compound	$[M]_D$ of chloro-compound	$[M]_D$ of corresponding dechloro-compound	ΔCl
3α-Chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XII)	−60°	+63°	−123°
3β-Chloro-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XVIII)	+83	−64	+147

[a] From Kovács *et al.*[2] [b] ΔOH and Δ_1 are defined as suggested by Klyne and Stokes.[14]

Treatment of the hexahydrosantonin (IV; R = H) with phosphorus oxychloride and pyridine gave a mixture of 4 : 5 : 11α(H),6β(H)-eudesm-2-en-6 : 13-olide (V) and 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI). The 3 : 4-position of the double bond in the latter compound follows from its infrared absorption at 1774 (lactone) and 851 cm.$^{-1}$ (trisubstituted olefin), and from its ozonolysis to a gummy product exhibiting peaks at 2790 (aldehyde), 1779 (lactone), and 1721 cm.$^{-1}$ (carbonyl), and giving positive Schiff's and Tollens's tests and a positive iodoform reaction. The gummy product from the ozonolysis of the other olefin (V), on the other hand, gave tests for aldehyde groups but no iodoform, showing it to be the Δ^2-isomer.

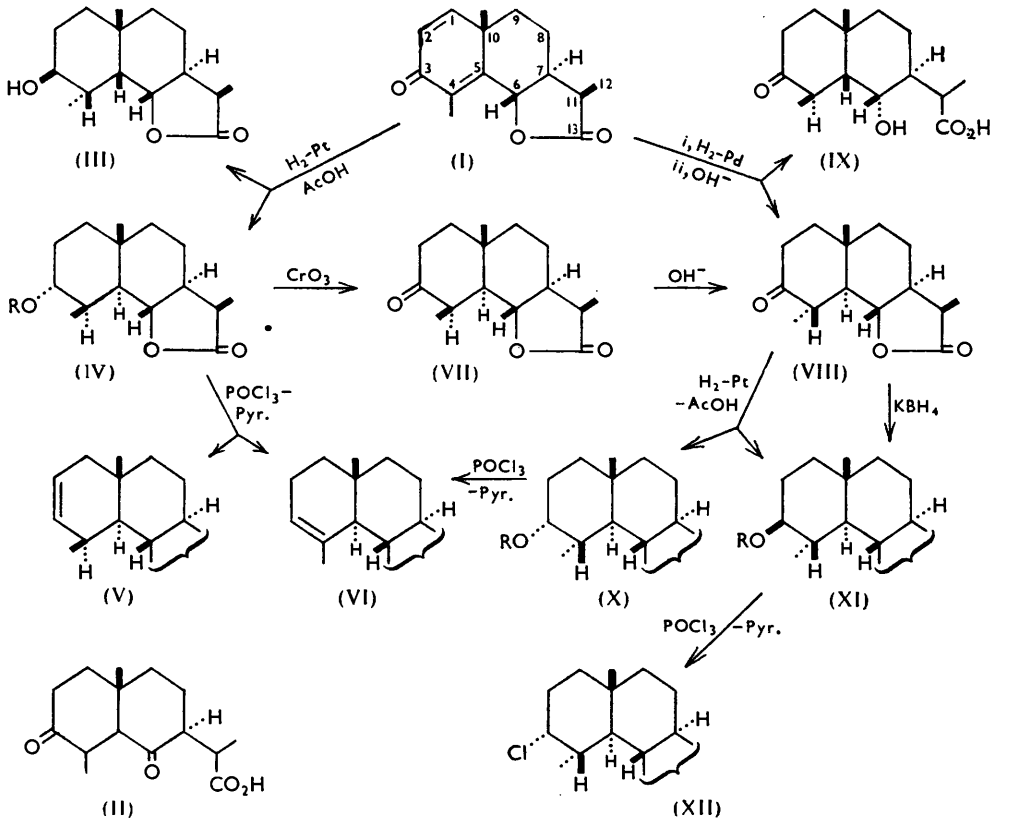
The factors which influence the relative stability of the 2- and 3-enes are (*a*) the *trans*-ring fusion which favours the 2-ene,[16] and (*b*) the greater stability of a tri- than a di-substituted olefin which favours the 3-ene.[17] The former would be the kinetically controlled product on account of diaxial elimination [18] of water from the alcohol (IV). The formation of the 3-ene indicates at least some dehydration by a carbonium-ion mechanism.

Oxidation of the hexahydrosantonin (IV) affords the known tetrahydrosantonin (VII; Table 1), which is epimerised at $C_{(4)}$ by alkali to 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII; Table 1). These ketones must accordingly have *trans*-fused A/B rings. The carbonyl stretching frequency of both occurs at 1703 cm.$^{-1}$, the configuration of the 4-methyl group having no effect.[19]

The ketone (VIII) may also be obtained by hydrogenation of santonin in acetone over palladised charcoal and treatment of the product with alkali;[4] a second compound formed in smaller yield is shown later to have the formulation (IX). These compounds arise from α- and β-addition respectively of hydrogen to the 4 : 5-double bond and subsequent epimerisation at $C_{(4)}$.

[15] Halder, *Experientia*, 1955, **11**, 175; Lewis and Shoppee, *J.*, 1955, 1365.
[16] Taylor, *Chem. and Ind.*, 1954, 250; Dreiding, *ibid.*, p. 1419.
[17] Ingold, "Structure and Reactivity in Organic Chemistry," Cornell Univ. Press, Ithaca, 1954, p. 468—472.
[18] Grand and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 344; Berner, Lardon, and Reichstein, *ibid*, 1947, **30**, 1542.
[19] Cf. Lukes, Poos, Beyler, Johns, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 1707; Braude and Waight, "Progress in Stereochemistry," Butterworths, London, 1954, Vol. I, p. 170 (ed. Klyne).

When the ketone (VIII) was reduced with potassium borohydride it gave a good yield of 3β-hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = H), which on acetylation showed a positive shift in molecular rotation and must therefore have a β-hydroxyl group,[14] which from the method of preparation must also be equatorial. Reaction of this alcohol (XI; R = H) with phosphorus oxychloride and pyridine afforded 3α-chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XII), the α-orientation of the chlorine following from its negative molecular-rotation contribution [14] (Table 3). This reaction involves an



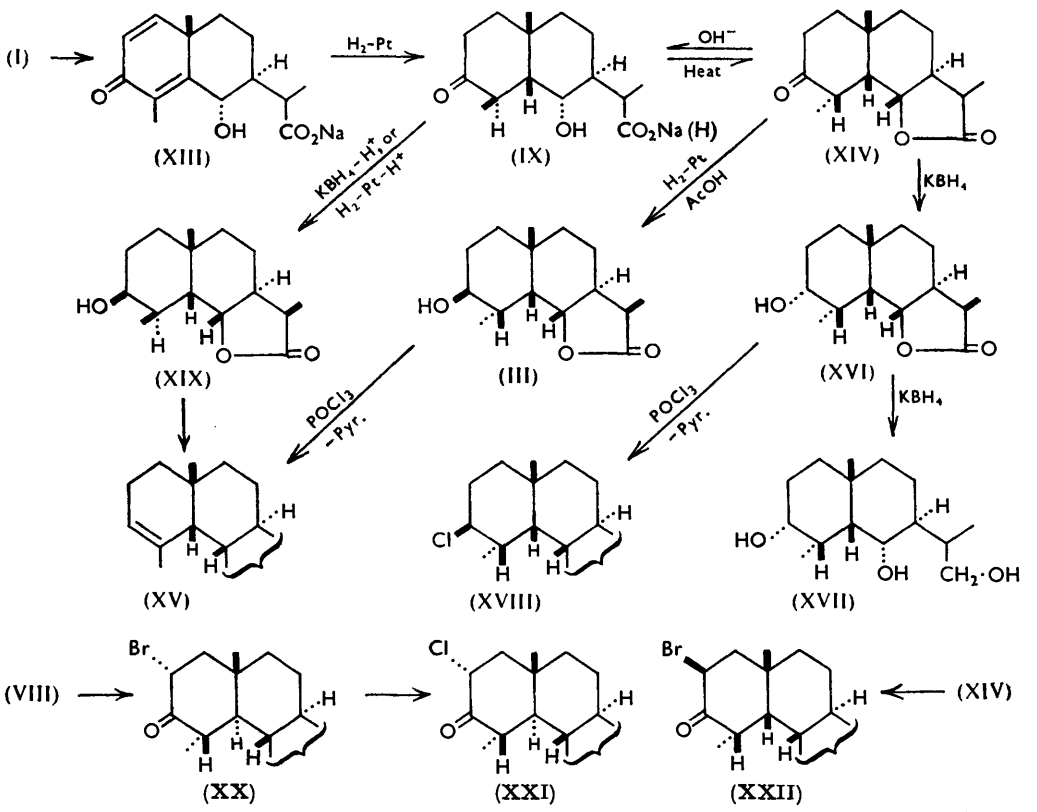
S_N2 replacement with inversion, analogous to the similar reaction of sterols with phosphorus pentachloride.[20] *

Hydrogenation of the ketone (VIII) with platinic oxide in acetic acid and acetylation of the product gave a mixture of the acetate (XI; R = Ac) and of a new acetate, 3α-acetoxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (X; R = Ac). The latter on alkaline hydrolysis gave the corresponding 3α-alcohol (X; R = H). The negative shift in molecular rotation on acetylation of the alcohol and the negative molecular-rotation contribution of the hydroxyl group (Table 2) show [14] that the latter is α-orientated and hence axial. Reaction of the alcohol (X; R = H) with phosphorus oxychloride and pyridine gave a complex of the corresponding 3 : 4-unsaturated and 3-chloro-compounds from which by chromatography on alumina 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI) was obtained in a pure condition. The formation of the latter is to be expected of the alcohol (X) : the formation of the chloro-compound is surprising.

* Fieser, Fieser, and Chakravarti (*J. Amer. Chem. Soc.*, 1949, **71**, 2226) have recorded the replacement of an equatorial hydroxyl group by chlorine using phosphorus oxychloride in pyridine. They suggest that no inversion occurs, because the product is stable in boiling pyridine. The same conversion, however, can be carried out by using phosphorus pentachloride (Wintersteiner and Moore, *ibid.*, 1943, **65**, 1507), a reaction known to cause inversion (Shoppee, *J.*, 1946, 1138).

[20] Shoppee, *J.*, 1946, 1138.

(B) *Compounds having a* cis-A/B *Ring-fusion.*—When sodium santoninate (XIII) was hydrogenated over platinum black in aqueous solution [21] it gave the *cis*-A/B-fused keto-acid (IX), also obtained (see above) by the direct hydrogenation of santonin. The acid can be lactonised either by heating [4] or with toluene-*p*-sulphonic acid in acetic acid,[2] to give 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV), this reaction being reversed by treatment



of the lactone with alkali. The axial configuration of the 4-methyl group in the ketone (XIV) is required since on hydrogenation in acetic acid over platinum it gave 11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III), which as mentioned above can also be obtained, in low yield, by hydrogenation of santonin under the same conditions. In the latter case, the 1 : 2-β-addition of hydrogen to the double bond requires the 4- and the 5-hydrogen atom to be *cis* with respect to each other, and hence the 4-methyl to be axial. 1 : 4-Addition of hydrogen to the enone system could lead to the equatorial configuration for the 4-methyl group : this is regarded as less likely, since 1 : 2-addition, to give the *trans*-A/B-fused hexahydrosantonin (IV), in which the 4-methyl group is known to be axial, has already been demonstrated (IV ⟶ VII ⟶ VIII).

Dehydration of the alcohol (III) with phosphorus oxychloride in pyridine gave 11α(H),5 : 6β(H)-eudesm-3-en-6 : 13-olide (XV). This is an unexpected *cis*-elimination, and it is significant that none of the 2-ene, arising from the normal *trans*-diaxial elimination, was formed. Of the two 3-enes, (VI) and (XV), the former is the more dextrorotatory, as would be expected from a comparison with the corresponding 3-methyl*cyclo*hexenes.[22]

Ozonolysis of the olefin (XV) gave a gum with the properties of an aldehyde and a methyl ketone. In the infrared spectrum it exhibited peaks at 2780 (aldehyde), 1785 (lactone), and 1730—1766 cm.$^{-1}$ (carbonyl).

[21] Cusmano, *Atti R. Accad. Lincei*, 1913, V, **22**, 507.
[22] Mills, *J.*, 1952, 4976.

Reduction of 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV) with a slight excess of potassium borohydride gave the equatorial alcohol, 3α-hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XVI). The molecular-rotation shift on acetylation of this alcohol (Table 2) is very small and has no diagnostic value. When the reduction was performed with a large excess of borohydride, the lactone ring was also reduced, thus affording the triol (XVII). Reaction of the alcohol (XVI) with phosphorus oxychloride and pyridine gave the chloro-compound (XVIII) with inversion, as shown by the large positive molecular-rotation contribution of the chlorine atom (Table 3). Reduction of 6α-hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid (IX) [the acid from which the lactone (XIV) is derived] with borohydride and lactonisation of the product afforded 3β-hydroxy-4 : 11α(H),5 : 6β(H)-eudesman-6 : 13-olide (XIX), the β-configuration of the hydroxyl group being demonstrated by the positive molecular-rotation shift on acetylation (Table 2). The hydroxyl group must consequently be orientated axially, an unexpected result from a borohydride reduction. The same alcohol (XIX) was obtained when the acid (IX) was reduced over platinum in acetic acid. The reduction of the keto-acid (IX) to give a hexahydrosantonin, different from either of those derived from the lactone (XIV), indicates that the former differs from the latter in the configuration of the 4-methyl group. Klyne has discussed the factors influencing the stability of various configurations of *cyclo*hexanones.[23] The stability of the axial 4-methyl group in the lactone (XIV) and of the equatorial methyl group in the hydroxy-acid (IX) must be attributed to the effect of the release of strain on opening of the lactone ring, and to the different sizes of the hydroxyl and the lactone groupings.

Treatment of the alcohol (XIX) with phosphorus oxychloride and pyridine afforded 11α(H),5 : 6β(H)-eudesm-3-en-6 : 13-olide (XV) in better yield than from (III), as expected since in (XIX) the elements of water are disposed in the most favourable arrangement for their elimination.

Bromination of 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) gave the 2α-bromo-compound (XX), having equatorial bromine,[1] whilst bromination of the corresponding *cis*-A/B-fused ketone (XIV) gave the 2β-bromo-compound (XXII).[1]

Treatment of the bromo-compound (XX) with lithium chloride in dimethylformamide gave 2-α-chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XXI). This has equatorial chlorine as shown by the hypsochromic shift of 15 Å and increase in intensity of the carbonyl maximum ($\lambda_{max.}$ 2775, log ε 1·53) in going from the corresponding tetrahydrosantonin (VIII) to the chloro-compound.[25] The halogen replacement is very probably an S_N1 reaction which would be favoured by the highly polar solvent : the alternative, an S_N2 reaction followed by inversion, is less likely.

Experimental

Ultraviolet spectra were measured for EtOH solutions with a Beckman DU instrument, and the infrared spectra in $CHCl_3$ with a Hilger 800 double-beam instrument. $[\alpha]_D$ refer to $CHCl_3$ solutions unless otherwise stated.

Hydrogenation of Santonin at a Platinum Catalyst.—Santonin (5·0 g.) in acetic acid (150 c.c.) was stirred with platinic oxide catalyst (0·2 g.) in hydrogen for 5 hr. After removal of the catalyst and solvent, the product was treated with ether (50 c.c.). The undissolved solid was collected and recrystallised from ethanol, to give 3β-hydroxy-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (III) (0·46 g.) as needles, m. p. 210—212°, $[\alpha]_D^{16}$ −8·5° (*c* 0·77) (Found : C, 71·7; H, 9·5. Calc. for $C_{15}H_{24}O_3$: C, 71·5; H, 9·6%). Ruzicka and Eichenberger[13] record m. p. 210—211°; Kovács *et al.*[2] give m. p. 213—215°, $[\alpha]_D$ −8·5°, for 3-hydroxysantan-5 : 12-olide-b.

The ethereal solution was evaporated and the residue was heated on a water-bath with pyridine (5 c.c.) and acetic anhydride (5 c.c.). Removal of the solvents gave 3α-*acetoxy*-4 : 5 : 11α(H),6β(H)-*eudesman*-6 : 13-*olide* (IV; R = Ac, 4·0 g.) as needles (from ethanol), m. p. 199—200°, $[\alpha]_D^{20}$ +15·4° (*c* 0·72) (Found : C, 69·4; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

[23] Klyne, *Experientia*, 1956, **12**, 119.
[24] Holysz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432.
[25] Cookson, *J.*, 1954, 282.

3α-*Hydroxy*-4 : 5 : 11α(H),6β(H)-*eudesman*-6 : 13-*olide* (IV; R = H).—The preceding compound (2·0 g.) was refluxed for 2 hr. with potassium hydroxide (1·0 g.) in methanol (50 c.c.). The product obtained on acidification was 3α-*hydroxy*-4 : 5 : 11α(H),6β(H)-*eudesman*-6 : 13-*olide* (IV; R = H) (1·55 g.), forming fine needles (from alcohol), m. p. 108—110°, $[\alpha]_D^{20}$ +36·0° (*c* 0·95) (Found: C, 71·0; H, 9·8. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). On one occasion, a second crystalline modification (also needles), m. p. 130—131°, was obtained. Kovács *et al.*[2] record m. p. 135°, $[\alpha]_D$ +42·7°, for 3-hydroxysantan-5 : 12-olide-c.

Action of Phosphorus Oxychloride in Pyridine on 3α-*Hydroxy*-4 : 5 : 11α(H),6β(H)-*eudesman*-6 : 13-*olide* (IV).—A mixture of the above hydroxy-compound (IV) (5 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·75 c.c.) was set aside at room temperature for 24 hr. The solid obtained on dilution with water was collected, dried, and extracted with boiling light petroleum (b. p. 60—80°). Chromatography of the extract on "Woelm" brand acid alumina gave 5 : 11α(H),6β(H)-*eudesm*-3-*en*-6 : 13-*olide* (VI) (0·27 g.) as plates, m. p. 136—137°, $[\alpha]_D^{20}$ +90·6° (*c* 0·13) (Found: C, 77·3; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%), and 4 : 5 : 11α(H),6β(H)-*eudesm*-2-*en*-6 : 13-*olide* (V) (0·21 g.) as plates, m. p. 107—108°, $[\alpha]_D^{21}$ +98·0° (*c* 0·55) (Found: C, 77·0; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

Ozonolysis of 4 : 5 : 11α(H),6β(H)-*Eudesm*-2-*en*-6 : 13-*olide* (V).—Excess of ozone was passed into a solution of the unsaturated compound (V) (1·0 g.) in methyl acetate (30 c.c.). Hydrogenation of the ozonide over 10% palladised charcoal (0·2 g.) gave an oil which rapidly restored the colour to Schiff's reagent and reduced Tollens's reagent. It failed to give iodoform with sodium hypoiodite.

Ozonolysis of the isomer (VI) in a similar manner gave a gum which gave iodoform with sodium hypoiodite, reduced Tollens's reagent, and restored the colour to Schiff's reagent.

3-*Oxo*-4 : 5 : 11α(H),6β(H)-*eudesman*-6 : 13-*olide* (VII).—A mixture of 3α-hydroxy-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide (IV) (0·52 g.), chromium trioxide (0·14 g.), and acetic acid (30 c.c.) was set aside for 3 days at room temperature. Removal of the acetic acid gave 3-oxo-4 : 5 : 11α(H),6β(H)-eudesman-6 : 13-olide as fine needles, m. p. 141—142° (from aqueous ethanol), $[\alpha]_D^{16}$ +71·5° (*c* 0·64) (Found: C, 71·3; H, 8·9. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9%). Yanagita and Tahara[1] record m. p. 143—144°, $(\alpha)_D$ +64·5°, for β-tetrahydrosantonin; Kovács *et al.*[2] give m. p. 145—146°, $[\alpha]_D$ +77·5° for 3-oxosantan-5 : 12-olide-c.

3-*Oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (VIII) *from* 3-*Oxo*-4 : 5 : 11α(H),6β(H)-*eudesman*-6 : 13-*olide* (VII) (cf. refs 1, 2).—The ketone (0·10 g.) was heated on the water-bath for 15 min. with sodium hydroxide (0·5 g.) in water (10 c.c.), and the solution was then acidified. The product was 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) (0·07 g.), m. p. and mixed m. p. 152—153° (see below).

Hydrogenation of Santonin in Acetone over Palladised Charcoal.—(a) 3-*Oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (VIII). Santonin (25 g.) and 10% palladised charcoal (2·5 g.) in acetone (300 c.c.) were shaken for 24 hr. in an atmosphere of hydrogen. The resulting solid was dissolved by heating it with 10% sodium hydroxide solution. The mixture was filtered. The product formed on acidification of the filtrate was recrystallised several times from ethanol, to give 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (12·2 g.), m. p. 154—155°, $[\alpha]_D^{15}$ +27·9° (*c* 2·1).

(b) 6α-*Hydroxy*-3-*oxo*-4α(H),5β(H)-*eudesman*-13-*oic acid* (IX).—The mother-liquors from which the ketone (VIII) was deposited were combined, evaporated to a small bulk, and treated with ethanol (100 c.c.) containing potassium hydroxide (2·5 g.). The solid potassium salt was collected, washed with ethanol, dissolved in water, and acidified. The resulting solid was recrystallised from aqueous ethanol, to give 6α-hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid (IX; see also below) (1·4 g.), m. p. 191—192°, $[\alpha]_D^{10}$ +2·2° (*c* 1·16 in MeOH). Cusmano[21] records m. p. 190°, $[\alpha]_D^{10}$ +2°. Kovács *et al.*[2] record m. p. 190—192°, $[\alpha]_D$ +20·7°, for 3-keto-5-hydroxysantanic acid-b.

Hydrogenation of 3-*Oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (VIII) *at a Platinum Catalyst.*—A mixture of the ketone (2·5 g.), platinic oxide (0·1 g.), and acetic acid (30 c.c.) was stirred in hydrogen for 2 hr. The resulting mixture of alcohols was heated with acetic anhydride (10 c.c.) and pyridine (10 c.c.) on the water-bath for 1 hr. Fractional crystallisation of the product from ethyl acetate–light petroleum (b. p. 60—80°) gave 3α-*acetoxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (X; R = Ac) (0·7 g.) as rhombs, m. p. 153—154°, $[\alpha]_D^{17}$ −28·3° (*c* 0·7) (Found: C, 69·5; H, 8·8. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%), and 3β-acetoxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = Ac) (1 g.), m. p. 143° undepressed by a sample prepared by the alternative method given below.

3α-*Hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (X; R = H).—The corresponding

acetate (0·4 g.) was refluxed for 1·5 hr. with a solution of potassium hydroxide (0·2 g.) in methanol (20 c.c.), and the solution then acidified. The product, 3α-*hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (X; R = H) (0·24 g.) was obtained as needles (from ethanol), m. p. 142—143°, $[\alpha]_D^{25}$ +16·6° (*c* 0·66) (Found : C, 72·2; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

Action of Phosphorus Oxychloride in Pyridine on 3α-*Hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (X; R = H).—The hydroxy-compound (0·42 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·5 c.c.) were set aside at room temperature for 24 hr. The solid obtained on dilution with water was collected and recrystallised from ethanol, to give a molecular complex of 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI) and 3-chloro-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide, as plates, m. p. 127—128°, $[\alpha]_D^{17}$ +84·1° (*c* 1·05) (Found : C, 72·1; H, 9·1. $C_{15}H_{22}O_2$,$C_{15}H_{23}O_2Cl$ requires C, 71·7; H, 9·0%). Chromatography on " Woelm " brand acid alumina afforded 5 : 11α(H),6β(H)-eudesm-3-en-6 : 13-olide (VI), m. p. and mixed m. p. 134—135°. The chloro-compound could not be obtained pure.

Reduction of the Ketone (VIII) *with Borohydride.* 3β-*Hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XI; R = H).—3-Oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) (1·0 g.) in methanol (20 c.c.) was treated with potassium borohydride (0·70 g.) in water (5 c.c.). After 1 hr., the mixture was acidified, and water (100 c.c.) was added. The product obtained was recrystallised from ethanol, to give 3β-*hydroxy*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XI; R = H) (0·78 g.), as needles, m. p. 171—172°, $[\alpha]_D^{15}$ +50·7° (*c* 0·56) (Found : C, 71·5; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The *acetate* (XI; R = Ac), prepared by heating the alcohol with acetic anhydride and pyridine, crystallised from ethanol as needles, m. p. 143°, $[\alpha]_D^{17}$ +63·1° (*c* 1·27) (Found : C, 69·1; H, 9·0. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

3α-*Chloro*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XII).—A mixture of 3β-hydroxy-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XI; R = H) (1 g.), phosphorus oxychloride (0·5 c.c.), and pyridine was set aside for 24 hr. The mixture was diluted with water and the solid was collected. Crystallisation from ethanol gave 3α-*chloro*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XII) (1·04 g.), as plates, m. p. 147—148°, $[\alpha]_D^{17}$ −22·2° (*c* 1·02) (Found : C, 66·9; H, 8·6. $C_{15}H_{23}O_2Cl$ requires C, 66·5; H, 8·5%).

Hydrogenation of Sodium Santoninate (XIII) *over Platinum.* 6α-*Hydroxy*-3-*oxo*-4α(H),5β(H)-*eudesman*-13-*oic acid* (IX).—A solution of sodium santoninate [from santonin (25 g.) and sodium hydroxide (4·0 g.)] in water (300 c.c.) and platinum black (1 g.) were stirred in hydrogen for 60 hr. Acidification of the filtered solution gave 6α-hydroxy-3-oxo-4α(H),5β(H)-eudesman-13-oic acid (IX; 16 g.), m. p. 190—191° after recrystallisation from aqueous ethanol.

3-*Oxo*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIV).—The above acid (IX) (2·5 g.) was heated at 195° for 30 min. The resulting solid was recrystallised from ethyl acetate–light petroleum, to give 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (1·8 g.), m. p. 100—101°, $[\alpha]_D^{15}$ +10·1° (*c* 0·77). Cusmano [21] records m. p. 105°, $[\alpha]_D$ +9·3°, Yanagita and Tahara,[1] m. p. 96—97°, $[\alpha]_D$ +7·3°, and Kovács *et al.*,[2] m. p. 103—105°, $[\alpha]_D$ +11·3°.

Hydrogenation of the Ketone (XIV) *over Platinum.* 3β-*Hydroxy*-11α(H),4 : 5 : 6β-(H)-*eudesman*-6 : 13-*olide* (III).—A mixture of 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV) (1·0 g.), platinum oxide (0·1 g.), and acetic acid (20 c.c.) was shaken in hydrogen for 2 hr. The product (III), after crystallisation from ethanol, was obtained as needles (0·75 g.), m. p. and mixed m. p. with an authentic sample 210—211° (see above). The *acetate* was obtained as needles, (from ethanol), m. p. 129—130°, $[\alpha]_D^{16}$ +32·7° (*c* 0·46) (Found : C, 69·5; H, 8·6. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

11α(H),5 : 6β(H)-*Eudesm*-3-*en*-6 : 13-*olide* (XV).—A mixture of the preceding compound (III) (1·0 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·3 c.c.) was set aside for 24 hr. at room temperature. The mixture was diluted with water, and the product collected and crystallised from light petroleum followed by aqueous ethanol, giving 11α(H),5 : 6β(H)-*eudesm*-3-*en*-6 : 13-*olide* (XV) as plates (0·32 g.), m. p. 118—119°, $[\alpha]_D$ −61·2° (*c* 1·2) (Found : C, 76·4; H, 9·2. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

Ozonolysis of 11α(H),5 : 6β(H)-*eudesm*-3-*en*-6 : 13-*olide* (XV).—The unsaturated compound (0·50 g.) in methyl acetate (50 c.c.) was treated with ozone at −20° for 1 hr., and the ozonide was decomposed by hydrogenation at a palladium–charcoal catalyst. No volatile carbonyl compound was found, but the residual oil gave positive reactions with Tollens's and Schiff's reagents, and also iodoform with sodium hypoiodite.

Reduction of the Ketone (XIV) *with Borohydride.*—(a) *In slight excess.* 3α-*Hydroxy*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XVI). A solution of 3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV) (2·5 g.) in methanol (30 c.c.) was treated with potassium

borohydride (0·14 g.) in water (5 c.c.). After 1 hr. at room temperature the mixture was acidified, and diluted with water, giving a solid product. Crystallisation from ethanol afforded 3α-*hydroxy*-11α(H),4 : 5 : 6β-*eudesman*-6 : 13-*olide* (XVI) as needles (1·9 g.), m. p. 143—144°, $[\alpha]_D$ −38·0° (*c* 0·62) (Found: C, 71·6; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The *acetate* crystallised from ethanol as needles, m. p. 181—182°, $[\alpha]_D^{15}$ −31·9° (*c* 1·06) (Found: C, 68·8; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

(b) *In large excess.* 11α(H),4 : 5β(H)-*Eudesmane*-3 : 6α : 13-*triol* (XVII). 3-Oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (1·0 g.) in methanol (10 c.c.) was treated with potassium borohydride (0·5 g.) in water (10 c.c.). After 24 hr. at room temperature the mixture was acidified and diluted with water, thus affording the *triol* which on recrystallisation from ethanol was obtained as needles (0·54 g.), m. p. 220°, $[\alpha]_D$ −42·6° (*c* 0·77 in MeOH) (Found: C, 70·0; H, 10·8. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·0%).

3β-*Chloro*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XVIII).—A mixture of 3α-hydroxy-11α(H),4 : 5 : 6β-eudesman-6 : 13-olide (XVI) (0·6 g.), pyridine (5 c.c.), and phosphorus oxychloride (0·3 c.c.) was kept for 24 hr. at room temperature, then poured into water. The product was collected and crystallised from ethyl acetate–light petroleum (60—80°), giving 3β-*chloro*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XVIII) as plates (0·31 g.), m. p. 160°, $[\alpha]_D^{15}$ +30·5° (*c* 0·43) (Found: C, 67·1; H, 8·6. $C_{15}H_{23}O_2Cl$ requires C, 66·5; H, 8·5%).

Reduction of 6α-*Hydroxy*-3-*oxo*-4α(H),5β(H)-*eudesman*-13-*oic Acid* (IX).—(a) *With borohydride.* 3β-*Hydroxy*-4 : 11α(H),5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIX). A solution of the acid (IX) (2·7 g.), potassium hydroxide (0·55 g.), and potassium borohydride (0·25 g.) in aqueous methanol (30 c.c.; 50%) was set aside for 24 hr., then was acidified and heated on a water-bath for 1 hr. Recrystallisation of the product from ethanol gave 3β-*hydroxy*-4 : 11α(H),5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIX) as needles (1·8 g.), m. p. 153—154°, $[\alpha]_D^{14}$ +36·6° (*c* 1·07) (Found: C, 71·0; H, 9·5. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). A second form (rhombs), m. p. 153—154°, was obtained in one experiment. The *acetate* (from ethanol) had m. p. 151—152°, $[\alpha]_D^{17}$ +70·6° (*c* 0·9) (Found: C, 69·5; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

(b) *With platinic oxide.* A mixture of the acid (IX) (1·0 g.), platinic oxide (0·1 g.), and acetic acid (50 c.c.) was stirred in hydrogen for 48 hr., giving 3β-hydroxy-4 : 11α(H),5 : 6β(H)-eudesman-6 : 13-olide (0·60 g.), m. p. and mixed m. p. 153—154°.

Dehydration of 3β-*Hydroxy*-4 : 11α(H),5 : 6β(H)-*eudesman*-6 : 13-*olide* (XIX).—This compound (1·1 g.) on treatment with pyridine (6 c.c.) and phosphorus oxychloride (0·33 c.c.) gave 11α(H),5 : 6β(H)-eudesm-3-en-6 : 13-olide (XV) (0·6 g.), m. p. 117—118°, undepressed by admixture with a sample prepared as above.

2α-*Bromo*-3-*oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XX).—Bromine (1·6 g.) in acetic acid (16 c.c.) was added slowly to 3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (VIII) (2·5 g.) in acetic acid (12·5 c.c.) containing 30% hydrobromic acid (0·5 c.c.) at 40°. The product, recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), afforded 2α-bromo-3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (XX) (2·8 g.) as needles, m. p. 147—148°, $[\alpha]_D^{17}$ +9·4° (*c* 1·33) Yanagita and Tahara[1] record m. p. 145—147°, $[\alpha]_D^{20}$ +8·3° (Found: C, 55·0; H, 6·7. Calc. for $C_{15}H_{21}O_3Br$: C, 54·7; H, 6·4%).

2α-*Chloro*-3-*oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XXI).—2α-Bromo-3-oxo-5 : 11α(H),4 : 6β(H)-eudesman-6 : 13-olide (3·5 g.), lithium chloride (1·5 g.), and dimethylformamide (25 c.c.) were heated at 100° for 2 hr. under nitrogen. The product obtained by dilution with water crystallised from ethanol, to give 2α-*chloro*-3-*oxo*-5 : 11α(H),4 : 6β(H)-*eudesman*-6 : 13-*olide* (XXI) as plates, m. p. 178—179° (variable), $[\alpha]_D^{23}$ +19·3° (*c* 0·4) (Found: C, 62·2; H, 7·6. $C_{15}H_{21}O_2Cl$ requires C, 63·2; H, 7·4%).

2β-*Bromo*-3-*oxo*-11α(H),4 : 5 : 6β(H)-*eudesman*-6 : 13-*olide* (XXII).—3-Oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XIV) (2·5 g.) on treatment with bromine (1·6 g.) in acetic acid (15 c.c.) gave 2β-bromo-3-oxo-11α(H),4 : 5 : 6β(H)-eudesman-6 : 13-olide (XXII) as needles (3·1 g.) (from ethyl acetate–light petroleum), m. p. 146° [depressed on admixture with (XX)], $[\alpha]_D^{13}$ −7·6° (*c* 1·2) Yanagita and Tahara[1] record m. p. 147—149°, $[\alpha]_D$ −7·55° (Found: C, 54·7; H, 6·6. Calc. for $C_{15}H_{21}O_3Br$: C, 54·7; H, 6·4%).

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