The Constitution of ψ-Santonin. Part IX. Investigations into the Position of the Double Bond.*

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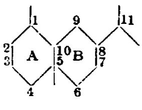
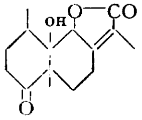
Evidence is presented which indicates that the sesquiterpene, ψ-santonin, has the structure (V).

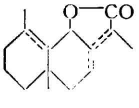
Previous investigations in this series have shown that ψ-santonin, $C_{15}H_{20}O_4$, has almost certainly the carbon skeleton (I) (Clemo and Cocker, *J.*, 1946, 30). The sesquiterpene has a lactone ring, a ketone group, a hydroxyl group, and a double bond, and the formula (II) has been advanced as being most in harmony with all the experimental data (Cocker, Cross, and Hayes, *Chem. and Ind.*, 1952, 314). The evidence for the skeleton (I) came from dehydrogenation experiments on compounds derived from ψ-santonin, affording 7-ethyl-1-methylnaphthalene, and from application of the isoprene rule indicating the position of the two carbon atoms eliminated as derived from the angular methyl group and the carbonyl group of the lactone ring. Further evidence has now been provided by the dehydrogenation of ψ-santonin itself by palladised charcoal in a sealed tube. The reaction affords 7-ethyl-1-methylnaphthalene and a dextrorotatory phenol $C_{15}H_{18}O_3$. Like the desmotropo-ψ-santonins (Clemo and Cocker, *loc. cit.*; Cocker, *J.*, 1946, 36), the phenol on fusion with potassium hydroxide yields 2 : 4-dimethyl-1-naphthol, and so is probably a molecular compound of two of the desmotropo-ψ-santonins. These compounds are produced by the action of acids on ψ-santonin (Clemo and Cocker, *loc. cit.*; Cocker, Cross, and Lipman, *J.*, 1949, 959); in the present case the palladised charcoal is evidently acting as a source of protons (cf. Schmidt, *Chem. Rev.*, 1933, 12, 363).



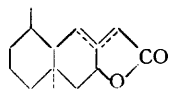
(I)



(II)



(III)



(IV)

It was postulated by Clemo and Cocker (*loc. cit.*) that the lactone ring of ψ-santonin is fused to the perhydronaphthalene nucleus to form the angular (III) rather than linear (IV) polycyclic compound, by analogy with santonin and other terpenes. The lactone

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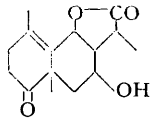
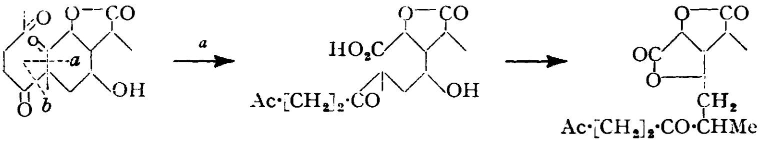
* Part VIII, *J.*, 1951, 929; cf. *Chem. and Ind.*, 1952, 314.

ring undergoes ready hydrogenolysis to give dihydro-ψ-santonin (Clemo and Cocker, *loc. cit.*), and so the double bond must be in the allyl position with respect to the lactone oxygen atom as shown in (III; $\Delta^{1(10)}$, Δ^{7}, or $\Delta^{8(11)}$) and (IV; Δ^{8} or $\Delta^{8(11)}$).

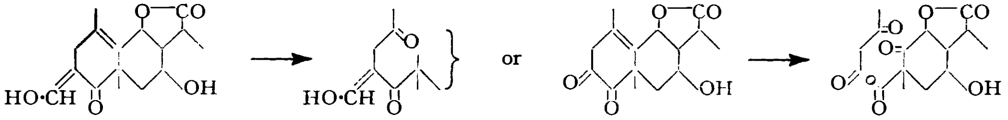
The double bond has now been shown to be in the 1 : 10-position, and ψ-santonin is (V). Ozonolysis of ψ-santonin and reduction of the ozonide with palladised charcoal afford a crystalline solid (A = VI), $C_{15}H_{20}O_6$, m. p. 108°; this results from the cleavage of the double bond, as shown by the absence of the infra-red absorption band of ψ-santonin (1652 cm.$^{-1}$ in Nujol; 1658 cm.$^{-1}$ in $CHCl_3$) due to the double bond. Hydrolysis of (A) with cold aqueous barium hydroxide yields lævulic acid, indicating the presence of the Ac·$[CH_2]_2$·CO group, derived from the decomposition (*b*) of the β-diketone system shown in (VI). The relative positions of the double bond and the keto-group are further demonstrated by ozonolysis of hydroxymethylene-ψ-santonin (IX) in methyl acetate containing methyl alcohol, which affords methyl acetoacetate and acetone: blank experiments show that these are not derived from the solvent, but must have arisen by methanolysis of an oxidation product, probably (XI) (cf. Johnson, Bannister, Bloom, Kemp, Pappo, Rogier, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2275). Again, the base-catalysed reaction of ψ-santonin with butyl nitrite gives a mononitroso-compound which is not the monoxime of (X) since it shows a single absorption maximum at 2830 Å (log ε 4·21) different from that shown by *iso*nitrosocamphor (2410 Å; log ε 3·57) and dihydro*iso*nitrosoumbellulone (2390 Å; log ε 4·08) (Eastman and Selover, *J. Amer. Chem. Soc.*, 1954, **76**, 4118). It is obvious that the double bond contributes to the absorption of the ψ-santonin derivative.



(V)



(VI = A) (VII) (VIII = B)



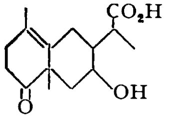
(IX) (X) (XI)

From the evidence given above there can be no doubt that the double bond and the keto-group are in ring A, as shown in (V).

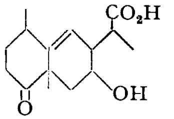
The location of the double bond at 1 : 10 makes it tetrasubstituted and is in harmony with its ultra-violet spectrum (Cocker, Cross, and Hayes, *loc. cit.*) and with the difficulty of its hydrogenation (Clemo and Cocker, *loc. cit.*).

The hydroxyl is thus displaced from $C_{(10)}$, as suggested by Clemo and Cocker (*loc. cit.*), and indeed from ring A, as shown by the production of lævulic acid during the fragmentation of this ring. We have now shown that the hydroxyl group is quantitatively formylated in the cold, and hence is not tertiary, and we place it at position 7 for the following reasons. Under mild alkaline conditions the ozonolysis product (A) gives an isomeric product (B), m. p. 144°. Compound (A) is also converted into (B) and an unidentified compound (C) by boiling water. The properties of (B) are those of a diketo-di-γ-lactone (VIII). In the infra-red region, the product (B) shows peaks at 1704 (Nujol and $CHCl_3$), 1723 (Nujol), and 1732 cm.$^{-1}$ ($CHCl_3$) due to keto-groups, and at 1782 (Nujol) and 1790 cm.$^{-1}$ ($CHCl_3$) due to the butanolide systems. Titration with alkali shows the presence of two lactone systems, one being more stable than the other. We picture the formation of this dilactone as a hydrolysis by route (*a*) of the β-diketone system in (VI), and hence the hydroxyl must be at position 7.

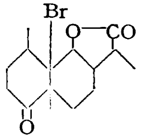
Further evidence for the position of the hydroxyl group of ψ-santonin is derived from the properties of dihydro-ψ-santonin (XIII). Dihydro-ψ-santonin loses water on being melted or heated in acetic anhydride to furnish anhydrodihydro-ψ-santonin (XV); from this lactone dihydro-ψ-santonin can be recovered by alkaline hydrolysis (Clemo and Cocker, *loc. cit.*). Anhydrodihydro-ψ-santonin in Nujol absorbs at 1777 (butanolide) and 1698 cm.$^{-1}$ (ketone), but shows no hydroxyl absorption. It must, consequently be the lactone (XV), and its characterisation as a butanolide serves to locate the hydroxyl group in dihydro-ψ-santonin (XIII) and in ψ-santonin (V).



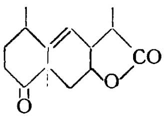
(XII)



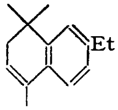
(XIII)



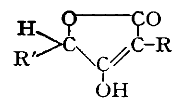
(XIV)



(XV)



(XVI)

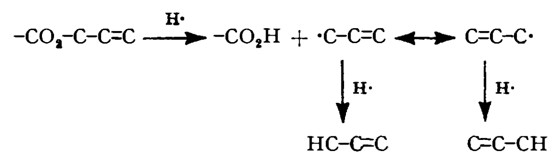


(XVII)

Other methods of degradation have been applied to ψ-santonin, but with less fruitful results. By using permanganate in acetone, the required dihydroxy-derivative was obtained, but in poor yield. This resisted benzoylation and acetylation, as expected if ψ-santonin has the formula (V) since the glycol would be ditertiary. It was oxidised by lead tetra-acetate to the compound (B = VIII), the compound (VI) probably being formed initially and undergoing its ready transformation into (B); the poor yield in this reaction is not surprising in view of the ease with which the product (B) is oxidised further.

Oxidation of ψ-santonin with perbenzoic acid in chloroform gave the epoxide, m. p. 156° (cf. Cocker, and Lipman, *J.*, 1949, 1170). By use of hydrogen peroxide in acetic or formic acids two polymorphic forms of the epoxide, m. p. 156° and 143°, have been obtained. In experiments with formic acid the formyl epoxide was also obtained; this compound was also prepared by the reaction of formyl-ψ-santonin with perbenzoic acid, or by the formylation of the epoxide, m. p. 156°, with anhydrous formic acid. Although the epoxide was obtained in good yield, it did not provide a useful starting material for further degradative work, because of its stability (cf. Herout and Šantavý, *Coll. Czech. Chem. Comm.*, 1954, **19**, 120). Attempted hydrolysis under acid or alkaline conditions and reduction over platinum or palladium led to recovery of the epoxide. Reaction with methylmagnesium iodide (cf. Gaylord and Becker, *Chem. Rev.*, 1951, **49**, 413) took place only after prolonged heating of the reactants in boiling xylene and afforded a product which on dehydrogenation over palladised charcoal gave a dihydronaphthalene, $C_{15}H_{20}$. The most probable formula for this compound is (XVI), in which the *gem*-dialkyl group prevents complete aromatisation (cf. Clemo and Dickenson, *J.*, 1937, 255; Cocker *et al.*, *J.*, 1950, 1781).

The ready hydrogenolysis of allyl compounds is possible because of the ease of formation of an intermediate mesomeric radical :



$$\begin{array}{ccccc} -CO_2\text{-}C\text{-}C{=}C \xrightarrow{H\cdot} -CO_2H + & \cdot C\text{-}C{=}C & \longleftrightarrow & C{=}C\text{-}C\cdot \\ & \downarrow{\scriptstyle H\cdot} & & \downarrow{\scriptstyle H\cdot} \\ & HC\text{-}C{=}C & & C{=}C\text{-}CH \end{array}$$

Accordingly dihydro-ψ-santonin might have its double bond in its original position, as in (XII), or shifted to the adjacent position as in (XIII). The latter appears more probable since the bromo-lactone (XIV) formed on treatment of dihydro-ψ-santonin with bromine in sodium carbonate solution (Cocker and Hornsby, *J.*, 1947, 1157) is a butanolide (1763 cm.$^{-1}$; Nujol mull). The compound (XII) cannot readily give a butanolide, whilst (XIII) would be expected to give a butanolide rather than a pentanolide (van Tamelen and Shamma, *J. Amer. Chem. Soc.*, 1954, **76**, 2315). Further dihydro-ψ-santonin shows the light-absorption characteristics of a trisubstituted double bond (cf. Bladon, Henbest, and Woods, *Chem. and Ind.*, 1951, 866; Halsall, *ibid.*, p. 867) as required by (XIII).

Several tetronic acids (XVII) were studied as model compounds at a time when the possibility that the ozonolysis product (A) might be derived from (III; Δ^7) or (IV; Δ^8) was being considered. Tetronic acid and α-methyl-, α-ethyl-, and αγ-dimethyl-tetronic acid were prepared from acetoacetic ester or its appropriate derivative (cf. Freer, *Amer. Chem. J.*, 1895, **17**, 779; Wolff and Schwabe, *Annalen*, 1896, **292**, 231; Clutterbuck, Raistrick, and Reuter, *Biochem. J.*, 1935, **29**, 316, 1308). For tetronic acid it was preferable to reduce the intermediate bromotetronic acid in methyl alcohol with palladised charcoal, rather than in alkali as recommended by Clutterbuck, Raistrick, and Reuter. In other cases it was found that intensive drying of the bromo-esters before cyclisation improved the yield of the tetronic acids.

The Table summarises some of the properties of the tetronic acids, various β-keto-esters and β-diketones, and the compounds (A), (B), and (C) obtained from ψ-santonin. One of the interesting facts which then emerges is that compounds capable of enolisation to the –C(OH)=CMe–C=O system give a positive iodoform reaction. That iodoform arises *via* the enol is shown by the negative response of the keto-form of 1 : 1-dibenzoylethane. The results also emphasise that the production of iodoform is not an exclusive characteristic of the Me·CO or Me·CH(OH) groups (cf. Booth and Saunders, *Chem. and Ind.*, 1950, 824.).

EXPERIMENTAL

ψ-Santonin shows the following infrared bands in Nujol mull: 3484 and 909 (OH), 1706 (keto), 1753 (1764 in CHCl$_3$) (butanolide), and 1658 cm.$^{-1}$ (C=C). For ultraviolet characteristics, see Cocker, Cross, and Hayes (*loc. cit.*). Dihydro-ψ-santonin shows the following characteristics (without max.) at low wavelength: 2150 Å, ε = 2500; 2200 Å, ε = 2000.

Expoxide of ψ-Santonin.—(*a*) When prepared by Cocker and Lipman's method (*loc. cit.*) with perbenzoic acid the epoxide had m. p. 145—146°, $[\alpha]^{11}_{D}$ −51·5° (*c*, 2·0 in CHCl$_3$). (*b*) ψ-Santonin (2·64 g.) was kept for a week in a mixture of acetic acid (30 c.c.) and hydrogen peroxide (100-vol.; 12 c.c.). The solvent was removed under reduced pressure, water was added to the residue, and the product was extracted with chloroform from which a solid (2·05 g.; m. p. 131—132°) was obtained Crystallisation from ethyl acetate–light petroleum yielded the above epoxide, m. p. 145°, and from the mother-liquors a second form, m. p. 155—156° (Found: C, 64·1; H, 6·4. Calc. for C$_{15}$H$_{20}$O$_5$: C, 64·3; H, 7·1%). A mixture of the two forms melted at 155° and when an alcoholic solution of the lower-melting form was evaporated to dryness it gave the higher-melting form. (*c*) ψ-Santonin (5 g.) was kept for 36 hr. with a mixture of 98% formic acid (25 c.c.) and hydrogen peroxide (200-vol.; 2·11 c.c.) (cf. Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786). The mixture was poured into water and neutralised with sodium hydrogen carbonate. The collected solid (3·25 g.; m. p. 145—165°) crystallised from dilute alcohol gave the *formyl-ψ-santonin epoxide* (1 g.) as needles, m. p. 189—190°, $[\alpha]^{16}_{D}$ −18·9° (*c*, 7·365 in CHCl$_3$) (Found: C, 62·2; H, 6·4. C$_{16}$H$_{20}$O$_6$ requires C, 62·3; H, 6·5%). From the mother-liquors ψ-santonin epoxide, m. p. 156° (1·3 g.), was obtained.

Formylation of ψ-Santonin.—ψ-Santonin (0·5 g.) was kept in anhydrous formic acid (2·3 c.c.) for 72 hr., giving the required *formyl* compound (0·5 g.), m. p. 176—177·5° (needles from ethyl acetate), $[\alpha]^{16}_{D}$ −118·7° (*c*, 1·35 in CHCl$_3$), $\lambda_{max.}$ 2925 Å (log ε 1·68) (Found: C, 65·4; 65·6; H, 6·8, 7·1. C$_{16}$H$_{20}$O$_5$ requires C, 65·8; H, 6·8%). When this compound (0·2 g.) was kept with perbenzoic acid (50 mol.) in chloroform it gave the formyl epoxide (0·2 g.; m. p. 188—189°) described above. The latter compound was also obtained (0·15 g.) when ψ-santonin epoxide (0·2 g.; m. p. 155—156°) was kept for 48 hr. with anhydrous formic acid (1 c.c.).

Reaction of ψ-Santonin Epoxide with Methylmagnesium Iodide.—The epoxide (5 g.) in anhydrous xylene (175 c.c.) was added dropwise during 30 min. to a boiling solution of Grignard reagent from magnesium (14·3 g.) in xylene (100 c.c.). The mixture was refluxed for 48 hr. (oil-bath, 170°). The xylene was removed under reduced pressure, and the residue was decomposed with ice and sulphuric acid. The mixture was extracted with ether, and the extract washed with dilute sodium hydrogen carbonate solution, then dried and evaporated, yielding a brown gum (5·5 g.). This was refluxed for 24 hr. in benzene (120 c.c.) with amalgamated zinc (70 g.) and hydrochloric acid (20 c.c.). The reduced compound, a viscous brown oil (5 g.), was passed in a slow stream of hydrogen over 10% palladised charcoal mixed with its own weight of asbestos, at 320—340°, yielding a pale yellow oil (2·2 g.). This was distilled over sodium and the fraction of b. p. 140—160°/14 mm. (0·85 g.) again distilled over sodium, giving a colourless oil (0·25 g.), b. p. 127—130°/2—4 mm., $\lambda_{max.}$ 2320, 2620, (2750), and (2920) [log ε 4·06, 3·23, (3·18), and (3·0) respectively; parentheses denote inflexions]

(Found: C, 89·4; H, 9·6. Calc. for $C_{14}H_{18}$: C, 90·3; H, 9·7. Calc. for $C_{15}H_{20}$: C, 90·0; H, 10·0%). It failed to give an addition compound with picric acid or trinitrobenzene. Heating with selenium for 3 hr. at 335—340° had no effect.

Reduction of ψ-Santonin Epoxide with Lithium Aluminium Hydride.—The epoxide (6·7 g.) was reduced in a Soxhlet apparatus with lithium aluminium hydride (7 g.) in anhydrous ether (300 c.c.) for 6 hr. after all the epoxide had been carried from the thimble (*ca.* 24 hr. in all). The ethereal solution was decomposed with ice and sulphuric acid, the ethereal layer was separated, and the aqueous layer extracted several times with ethyl acetate. The combined extracts were washed with sodium hydrogen carbonate solution, dried, and evaporated, yielding a brown gum (6·0 g.), which when rubbed with light petroleum became solid. After several crystallisations from ethyl acetate the *product* was obtained as rosettes of needles (1 g.), m. p. 179—180°, $[\alpha]_D^{15}$ $+51·3°$ (*c*, 0·77 in EtOH) (Found: C, 62·7; H, 9·4. $C_{15}H_{28}O_5$ requires C, 62·5; H, 9·7%). It gave a negative boric acid test for glycols, and was recovered unchanged on attempted oxidation with lead tetra-acetate.

Dihydroxy-ψ-santonin.—A solution of potassium permanganate (4·1 g.) in acetone (300 c.c.) and water (10 c.c.) was added dropwise to a stirred solution of ψ-santonin (4 g.) in acetone (200 c.c.), and the mixture was stirred for 3 hr. It was filtered, and the filtrate concentrated to 10 c.c., saturated with ammonium sulphate, and extracted with ethyl acetate from which a solid (2·65 g.) was obtained. After several crystallisations from ethyl acetate–light petroleum, the *glycol* was obtained as prisms, m. p. 245—246°, $[\alpha]_D^{16}$ $+22·4°$ (*c*, 2·46 in EtOH) (Found: C, 60·6; H, 7·6%; *M*, 315. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4%; *M*, 298). Its 2 : 4-*dinitrophenylhydrazone* (yellow prisms from alcohol) had m. p. 274—276° (Found: C, 53·5; H, 5·6. $C_{21}H_{26}O_9N_4$ requires C, 52·7; H, 5·4%).

Oxidation of the Glycol.—This compound (1 g.) in a mixture of anhydrous benzene (50 c.c.), acetic acid (5 c.c.), and methyl alcohol (10 c.c.) was treated with lead tetra-acetate (2 g.), and the mixture was warmed to 50°. It was then set aside for 48 hr. and finally warmed at 50° for 3 hr., after which water was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were evaporated to a yellow gum (0·7 g.). This was triturated with ether, a solid (0·1 g.), m. p. 120—128°, being obtained. Crystallisation from ethyl acetate–light petroleum gave the *compound* (*B*) as needles, m. p. 140—141° (Found: C, 61·0; H, 6·7. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·75%).

Ozonolysis of ψ-Santonin to Compound (*A*).—ψ-Santonin (5 g.) in methyl acetate (100 c.c.) was ozonised at $-30°$ to $-40°$ until the ozone was in excess. The solution was then hydrogenated over palladised charcoal (0·2 g.), and after filtration the solvent was removed in a vacuum at room temperature. The gummy product was then kept overnight with water (10 c.c.), needles of *compound* (*A*) (5·1 g.), m. p. 105°, being obtained. Crystallisation from water gave material of m. p. 108—109°, $[\alpha]_D^{17}$ $-125°$, (*c*, 0·9784 in EtOH), $\lambda_{max.}$ 2830 Å (ε 70) in EtOH (Found: C, 61·0; H, 6·9. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·75%). It gave a positive iodoform test, strongly reduced ammoniacal silver nitrate, Tollens's reagent, Fehling's solution, and alkaline methylene-blue, and consumed one mol. of periodate in alkaline solution. However, the Schiff and the Angeli–Rimini test for aldehydes were negative. When tested on paper with a spray containing sodium nitroprusside and piperazine, it gave a pink colour instead of the blue colour characteristic of the pyruvyl group (Acklin, *Biochem. Z.*, 1925, **164**, 312; Edward and Waldron, *J.*, 1952, 3631). With a spray of alkaline 3 : 5-dinitrobenzoic acid it gave a yellow, while pyruvic acid gave a purple, colour.

Hydrolysis of (*A*) *to Lævulic Acid.*—(*a*) The compound (A) (0·7 g.) was dissolved in 2·8% aqueous barium hydroxide (20 c.c.) at room temperature. After 3 hr. the barium was exactly precipitated with sulphuric acid, and the solution freed from barium sulphate was submitted to chromatography on Whatman No. 1 filter paper. Zones having R_F values similar to that of lævulic acid were obtained with the solvent systems butanol–pyridine–ethanol–water (66 : 12 : 4 : 18 by vol.) (R_F 0·64—0·68) or butanol saturated with aqueous 0·75N-ethylamine (R_F 0·74—0·80). The sprays used were Tollens's reagent, 2 : 4-dinitrophenylhydrazine, and aqueous alkaline sodium nitroprusside.

(*b*) The compound (A) (10 g.) was treated as above with 3·9% barium hydroxide solution (200 c.c.). One-fifth of the barium-free solution was distilled at 30 mm., first on a water-bath and then from an oil-bath, the strongly acidic fraction (0·6 g.; 60% of lævulic acid, by titration; about 45% of theory), b. p. 136—138°, being collected. Its 2 : 4-dinitrophenylhydrazone had m. p. 205° (from alcohol) undepressed by the corresponding derivative of lævulic acid (Braude and Jones, *J.*, 1945, 498), and its semicarbazone had m. p. and mixed m. p. 188° (decomp.) (Perkin and Simonsen, *J.*, 1907, **91**, 827).

Isomerisation of Compound (*A*) *to* (*B*).—When a solution of (A) in chloroform was slowly passed through a column of alumina and the issuing solution evaporated to dryness it gave the product (B), m. p. 126—140°, which after crystallisation from water was obtained as needles, m. p. 144°, $[\alpha]_D^{15}$ $-2°$ (*c*, 3·355 in $CHCl_3$), $\lambda_{max.}$ 2780 Å (ε = 37) in EtOH (Found: C, 60·85; H, 6·65. Calc for $C_{15}H_{20}O_6$: C, 60·8; H, 6·75%). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 205—207° (decomp.) (Found: C, 52·65; H, 5·2. $C_{21}H_{24}O_9N_4$ requires C, 52·9; H, 5·0%). The same 2 : 4-dinitrophenylhydrazone was afforded by (A), which apparently isomerised to (B) under the acidic conditions of the reaction. The compound (B) gave a pink colour with nitroprusside–piperazine and a yellow colour with alkaline 3 : 5-dinitrobenzoic acid. Oxidation of (B) (0·25 g.) with sodium hypoiodite (10 g.) gave iodoform (0·12 g., 0·3 mol.) and oxalic acid (0·036 g., 0·5 mol.).

Conversion of (*A*) *into* (*B*) *and* (*C*).—When compound (A) (1 g.) in water (10 c.c.) was boiled for 6 hr. and the aqueous solution extracted with chloroform it gave compound (B) (0·25 g.) and from the aqueous solution by evaporation a *product* (*C*) which on crystallisation from water was obtained as rhombs, m. p. 186°, $[\alpha]_D^{17}$ $-217·4°$ (*c*, 1·85 in acetone), $\lambda_{max.}$ 2870 Å (ε = 60) in EtOH (Found: C, 57·3; H, 7·35. $C_{15}H_{20}O_6,H_2O$ requires C, 57·3; H, 7·0%). The infrared absorption in a Nujol mull shows peaks at 1712 (ketone), 1754 (lactone carbonyl), and 3400, 3200, and 900 cm.$^{-1}$ (hydroxyl). The compound gave a yellow colour with nitroprusside–piperazine and a lilac colour with alkaline 3 : 5-dinitrobenzoic acid solution.

Chromatographic Examination of Compounds (*A*), (*B*), *and* (*C*).—These compounds were boiled with water and with dilute acid and alkali, and the solutions examined for pyruvic acid by chromatography on Whatman No. 1 filter paper with developing solvents: (1) ethanol–pyridine–water (80 : 12 : 8 by vol.), and (2) ethanol–water (1 : 1 by vol.) with a trace of formic acid. Zones were shown by spraying with Tollens's reagent and acidic 2 : 4-dinitrophenylhydrazine solution ; R_F values were :

	Compound A	Compound B	Compound C	Pyruvic acid
Solvent 1	0·81	0·80—0·81	0·77—0·81	0·40—0·41
Solvent 2	0·82—0·85	0·82—0·85	0·63—0·64	0·73—0·76

The absence of pyruvic acid from these compounds and from the crude ozonolysis product was clearly shown by using solvent (1). Separations with solvent (2) were uncertain and erratic and the zone attributed to pyruvic acid in a preliminary communication (Cocker, Cross, and Hayes, *loc. cit.*) was probably due to compound (B) or (C). Compound (A) probably isomerised to (B) in the solvent systems employed.

Hydroxyimino-ψ-santonin.—ψ-Santonin (2·4 g.) was added to a solution of sodium (0·5 g.) in absolute alcohol (40 c.c.) and the solution was cooled to −5°. Butyl nitrite (0·9 g.) in alcohol (5 c.c.) was added and the mixture was kept at −5° for 2 hr. and then overnight at 0°. Solvent was removed in a vacuum at 40°, and the residue was dissolved in water and acidified. The gummy product (1·1 g.) was extracted with sodium hydrogen carbonate solution, and the extract was acidified, giving a semisolid material which when rubbed with ether gave a product, m. p. 234—238°. Crystallisation from dilute methyl alcohol gave the required *hydroxyimino-compound*, m. p. 238° (decomp.), as pale yellow needles giving a red ferric reaction, $\lambda_{max.}$ 2830 Å (log ε 4·21) in EtOH (Found: C, 61·6; H, 6·8; N, 4·85. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·8%).

2 : 6-*Di*(*hydroxyimino*)cyclo*hexanone*, prepared by a similar method (but cf. Pezold and Shriner, *J. Amer. Chem. Soc.*, 1932, **54**, 4710), had m. p. 233° (cf. Borsche, *Chem. Zent.*, 1909, 1549, who gives an indefinite m. p. over 200°), $\lambda_{max.}$ 2710 Å (log ε 4·153) (Found: C, 46·2; H, 5·2; N, 18·5. $C_6H_8O_3N_2$ requires C, 46·2; H, 5·1; N, 18·0%).

Hydroxymethylene-ψ-santonin.—Finely powdered ψ-santonin (2 g.), suspended in ethyl formate (7 c.c.), was added to dry sodium methoxide (from sodium, 0·4 g.), and the mixture was chilled to 0°, shaken until solution was obtained, and kept overnight at room temperature. Solvent was removed in a vacuum at room temperature and the solid residue was dissolved in the minimum of water, filtered, and added to a stirred mixture of ice and hydrochloric acid. The resultant oil quickly solidified on stirring, and the solid (2·1 g.), m. p. 185°, was collected and crystallised from ethyl acetate, yielding the *hydroxymethylene-compound* as pale yellow needles (1·5 g.), m. p. 195°. It gave a deep violet ferric reaction (Found: C, 66·1; H, 6·8. $C_{16}H_{20}O_5$ requires C, 65·8; H, 6·8%). Its *acetate*, made in alkali, consisted of colourless plates, m. p. 164—165° (Found: C, 64·6; H, 6·71. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%). These compounds were hydrolysed by alkali to ψ-santonin.

Ozonolysis of Hydroxymethylene-compound.—This compound (4·9 g.) in methyl acetate

(15 c.c.; dried over Na_2SO_4, and distilled, but containing a little methyl alcohol) was ozonised at −40° to −50° until the solution became deep blue. The product was hydrogenated over palladised charcoal and, after filtration, the solvent was removed in a vacuum at room temperature, formaldehyde being trapped in 2 : 4-dinitrophenylhydrazine hydrochloride. The oily residue was then distilled in steam into a solution of 2 : 4-dinitrophenylhydrazine hydrochloride. From this solution methyl acetoacetate 2 : 4-dinitrophenylhydrazone (0·2 g.), m. p. 105°, was obtained which after crystallisation from methyl alcohol had m. p. and mixed m. p. 119° (cf. Johnson, *J. Amer. Chem. Soc.*, 1951, **73**, 5888), $\lambda_{max.}$ 2225, (2500), and 3570 Å [log ε = 4·36, (4·07), 4·21 respectively] (Braude and Jones, *J.*, 1945, 498, give 3580 Å, log ε 4·31, for the acetoacetic acid derivative (Found : C, 44·4; H, 4·0; N, 19·6. Calc. for $C_{11}H_{12}O_6N_4$: C, 44·6; H, 4·1; N, 18·9%). The aqueous mother-liquors, which gave a red-yellow ferric reaction, were evaporated to dryness and refluxed for 2 hr. with chloroform (100 c.c.), formic acid (90%; 100 c.c.), and hydrogen peroxide (100-vol.; 15 c.c.) (cf. Prelog and Kocór, *Helv. Chim. Acta*, 1947, **31**, 237) but gave no further volatile carbonyl compound. An intractable gum was left when the solvents were removed.

In a second experiment in which one mol. of methyl alcohol was added to the methyl acetate, and the 2 : 4-dinitrophenylhydrazones of the products separated by chromatography on alumina with benzene and benzene–ethanol as eluants, the derivatives of methyl acetoacetate, formaldehyde, and acetone (m. p. 118°, 167°, and 128° respectively) were obtained, the last in greatest amount.

Dehydrogenation of ψ-Santonin (cf. Clemo and Cocker, *loc. cit.*).—ψ-Santonin (2·5 g.) was heated at 250—270° for 72 hr. with palladised charcoal. The product was then powdered and extracted with chloroform, which was washed first with sodium carbonate and then with sodium hydroxide solution. Three fractions were thus obtained. The carboxylic acid fraction proved intractable, but from the sodium hydroxide solution a phenolic fraction was obtained and from the chloroform a neutral fraction.

The phenol was obtained as a dark solid, which on sublimation in a vacuum gave a yellow solid, m. p. 158—168°. Crystallised several times from a mixture of benzene and light petroleum and then dilute alcohol the *phenol* (0·5 g.) was obtained as needles, m. p. 210—212°, $[\alpha]_D^{18}$ +138° (*c*, 0·51 in EtOH) (Found : C, 72·7; H, 6·9. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Fused with potash it gave 2 : 4-dimethyl-1-naphthol, m. p. 78—79° (cf. Clemo and Cocker, *loc. cit.*; Cornforth, Cornforth, and Robinson, *J.*, 1943, 168), characterised as its picrate, m. p. 143°.

The combined neutral fractions (3·3 g.) from several experiments, when distilled from sodium, gave an oil (0·2 g.), b. p. 80—100°/10 mm., from which the picrate of 7-ethyl-1-methylnaphthalene, m. p. 90°, was obtained.

ψ-Santonin hydrazone was obtained as colourless plates (from dilute alcohol), m. p. 249—250° (Found : C, 63·9; H, 7·9. $C_{15}H_{22}O_3N_2$ requires C, 64·7; H, 7·9%). Repeated heating with dilute alcohol leads to decomposition.

Deoxy-ψ-santonin.—(*a*) A mixture of ψ-santonin (2·4 g.), potassium hydroxide (1·75 g.), ethylene glycol (15 c.c.), and hydrazine hydrate (1·3 c.c.; 100%) was refluxed for 1·5 hr. Heating was continued whilst the temperature rose to 187°, at which it was maintained for 4 hr. The *product* (0·2 g.) crystallised from dilute alcohol as needles, m. p. 250°, $[\alpha]_D^{18}$ +30° (*c*, 0·606 in $CHCl_3$) (Found : C, 72·1; H, 9·2%; *M*, 264. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%; *M*, 250). (*b*) ψ-Santonin (2 g.) was refluxed for 43 hr. with hydrazine hydrate (20·5 c.c.; 100%) and a solution of sodium (4 g.) in ethylene glycol (65 c.c.). The *product* (0·2 g.) crystallised from dilute alcohol as needles, m. p. 204—205° (Found : C, 72·8; H, 8·8%), which gave no carbonyl reactions. The two forms are polymorphic.

Reduction of Anhydrodihydro-ψ-santonin.—This compound (0·1 g.) was reduced in glacial acetic acid (10 c.c.) over palladised charcoal at slightly above 1 atm. The *lactone* (0·1 g.) crystallised from dilute alcohol in leaflets, m. p. 157—158°, depressed to 140° by anhydrodihydro-ψ-santonin (Found : C, 72·0; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%).

Tetronic Acids.—*Tetronic acid.* Ethyl acetoacetate was brominated and cyclised to α-bromotetronic acid by the methods of Wolff and Schwabe and of Clutterbuck, Raistrick, and Reuter (*loc. cit.*). The crude bromo-compound (6 g.) was reduced in methyl alcohol (50 c.c.) over palladised charcoal (0·5 g.), yielding tetronic acid as sticky solid, which was crystallised from water, giving the pure acid (2 g.), m. p. 139—140° (softens at 136°).

α-Methyltetronic acid had m. p. 190—191° (cf. Freer, *loc. cit.*), $\lambda_{max.}$ 2315 Å (log ε 4·09), absorption max. at 1758 (in $CH_2Cl{\cdot}CH_2Cl$), 1751, and 1676 cm.$^{-1}$ (in $CHCl_3$) (Found : C, 52·6; H, 5·3. Calc. for $C_5H_6O_3$: C, 52·6; H, 5·3%).

α-Ethyltetronic acid, prepared by a similar method from ethyl α-ethylacetoacetate (40 g.), crystallised from water as needles (10 g.), m. p. 126°, $\lambda_{\text{max.}}$ 2330 Å (log ε 4·12) in HCl–EtOH (Found: C, 55·9; H, 6·1. Calc. for $C_6H_8O_3$: C, 56·25; H, 6·25%).

Ethyl α-propionylpropionate (10 g.) similarly gave *αγ-dimethyltetronic acid* (2·5 g.) which crystallised from water as needles, m. p. 120—121°, $\lambda_{\text{max.}}$ 2310 Å (log ε 3·998) in EtOH, absorption bands at 1756, 1690 (in $CH_2Cl{\cdot}CH_2Cl$), 1738, 1673 (in $CHCl_3$), 1725, 1664, and 2720 cm.$^{-1}$ (in Nujol) (Found: C, 56·1; H, 6·1. $C_6H_8O_3$ requires C, 56·25; H, 6·25%).

	(XVII; R=R′=H)	(XVII; R=Me, R′=H)	(XVII; R=R′=Me)	(XVII; R=Et, R′=H)	Et·CO·CHMe·CO$_2$Me
Fe^{+++} reaction ...	Orange-red	Violet-red	Red	Red	Violet
CHI$_3$ reaction (cold)	–	+	+	–	+
Reduction of Tollens's reagent ...	–	–	–	–	+
Reduction of Fehling's soln.	–	–	–	–	+
Reaction with NaHCO$_3$	+	+	+	+	–
p*K* (water) (±0·1)	3·6	3·6	4·0	4·0	

	Et·CO·CHMe·COEt	Ph·CO·CH$_2$·COPh	Ph·CO·CHMe·COPh	Ph·C(OH):CMe·COPh
Fe^{+++} reaction ...	Violet	Violet	–	Violet
CHI$_3$ reaction (cold)	+	–	–	+
Reduction of Tollens's reagent ...	+	–	–	–
Reduction of Fehling's soln.	+	–	–	–
Reaction with NaHCO$_3$	–	–	–	–
p*K* (water) (±0·1)				

	Pr^n·CO·CHEt·CO$_2$Me	Ph·CO·CHEt·COPh	A	B	C
Fe^{+++} reaction ...	Red	–	–	–	–
CHI$_3$ reaction (cold)	–	–	++	++	++
Reduction of Tollens's reagent ...	–	–	++	++	++
Reduction of Fehling's soln.	–	–	++	++	++
Reaction with NaHCO$_3$	–	–	–	–	–
p*K* (water) (±0·1)			*	7·0	

* No p*K* value obtainable since the change A ⟶ B takes place even in weak alkali.
++ = Rapid reaction. – = No reaction.

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