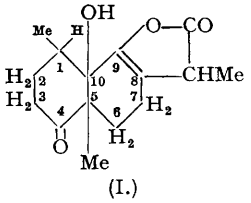
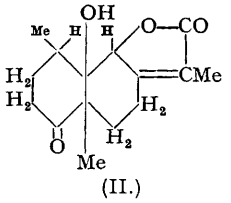
11. *The Constitution of ψ-Santonin. Part I.*

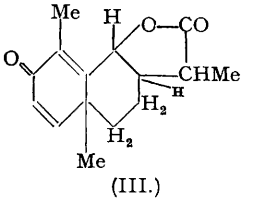
By G. R. Clemo and Wesley Cocker.

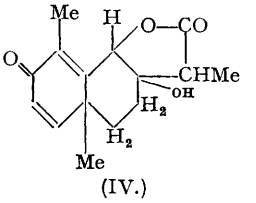
In addition to *l*-santonin and β-santonin a further compound, $C_{15}H_{20}O_4$, has been isolated from certain species of *Artemesia*. Its chemistry is now discussed, but no final structure can yet be given to the new *compound*, which is named *ψ-santonin*.

In the course of an examination of a number of species of *Artemesia* collected from the N.W. frontier of India, Messrs. T. and H. Smith, Ltd., of Edinburgh discovered a further crystalline compound in addition to *l*-santonin (III; Clemo, Haworth, and Walton, *J.*, 1929, 2368; 1930, 1110; Clemo and Haworth, *J.*, 1930 2570) and β-santonin (Clemo, *J.*, 1934, 1343).


(I.)


(II.)


(III.)


(IV.)

The new compound, $C_{15}H_{20}O_4$, termed *ψ-santonin*, is *lævo*-rotatory. Whilst *l*- and β-santonin impart little colour to concentrated sulphuric acid, ψ-santonin gives an immediate dark brown coloration. Further, *l*- and β-santonin and artemisin (IV; Tettweiler, Engel, and Wedekind, *Annalen*, 1932, **492**, 105) are unaffected by alkaline sodium nitroprusside, but ψ-santonin gives a deep red coloration when the test is performed according to Jacobs and Hoffmann (*J. Biol. Chem.*, 1925, **67**, 333). When, however, the test is modified according to Paist, Blout, Uhle and Elderfield (*J. Org. Chem.*, 1941, **6**, 273) the latter compound gives a pink coloration after the addition of the third drop of sodium hydroxide when the solution is still acid to Congo red, and this colour shows little fading. When the fourth drop of alkali is added and the solution is faintly alkaline to phenolphthalein a deep red coloration is produced which fades after three or four minutes. Addition of further drops of nitroprusside again produce the deep red coloration, which changes to blue-green on acidification. Potassium ferrocyanide has no effect. These results strongly suggest the presence of a β—γ unsaturated lactone.

Tollens' reagent is unaffected by either *l*- or β-santonin, but, like the cardiac aglycones and other α—β unsaturated lactones, a silver mirror is very slowly produced by ψ-santonin. Immediate reduction of the reagent usually takes place with a β—γ lactone (Jacobs, Hoffmann, and Gustus, *J. Biol. Chem.*, 1926, **70**, 1).

ψ-Santonin gives no colour reaction with tetranitromethane, but the absence of ethylenic bonds cannot be concluded from this, since protected or α—β double bonds very often fail to give a reaction with this reagent (Haworth, *Ann. Reports*, 1937, **34**, 328).

Tested side by side, tincture of digitalis and an aqueous-alcoholic solution of ψ-santonin of comparable strength give similar cardiac effects. Depression of conduction and cardiac inhibition take place similarly in each case, but neither *l*- nor β-santonin shows similar reactions. In the latter cases there is slight augmentation of the heart beat, probably due to the alcohol used as solvent. These results point to the existence of an un-

saturated lactone in ψ-santonin (compare Kraft, *Arch. Pharm.*, 1912, **250**, 126; Windhaus, Bohne, and Schwieger, *Ber.*, 1924, **57**, 1388).

ψ-Santonin gives an oxime and a 2 : 4-dinitrophenylhydrazone, but all attempts to prepare a piperonylidene or *p*-nitrobenzylidine derivative have so far failed. Recently, however, it has been possible to obtain a nitrogenous compound, $C_{22}H_{23}O_3N$, presumably a 2 : 3-substituted quinoline by condensation with *o*-aminobenzaldehyde, thereby showing the probable existence of the $-CO-CH_2-$ system. ψ-Santonin has, so far, failed to yield an osazone.

ψ-Santonin is not immediately soluble in sodium hydroxide, but, on shaking, it slowly passes into solution from which it is reprecipitated unchanged even on careful neutralisation with dilute acetic acid. In addition, several attempts to prepare a methyl ester from the sodium salt yielded a substance which gradually lost methyl alcohol and yielded ψ-santonin. The evidence therefore points to the existence of a relatively stable γ-lactone and together with the carbonyl group accounts for three of the four oxygen atoms present in the molecule.

ψ-Santonin yields a monoacetyl derivative with difficulty and in poor yields and this together with Zerewitinoff determinations points to the probable presence of one tertiary hydroxyl group. Incidentally, when the above-mentioned monoacetate is hydrolysed with sodium hydroxide and the solution acidified, a *lactone*, $C_{15}H_{20}O_4$, isomeric but not identical with ψ-santonin is obtained. The structure of this lactone has not been established, but in view of the mobility of tertiary hydroxyl groups it would not be surprising if a molecular rearrangement were to take place during acetylation. No change in structure has yet been encountered when ψ-santonin is treated with potassium hydroxide under a variety of conditions (compare Paist, Blout, Uhle, and Elderfield, *loc. cit.*).

A point of interest is that whilst *l*- and β-santonin are soluble in cold water to the extent of only one part in four hundred and one part in six hundred respectively, ψ-santonin is soluble to the extent of one part in forty, a property which may be due to the hydroxyl group in the last compound.

Catalytic reduction of ψ-santonin by hydrogen in the presence of palladised charcoal and at 1 atm. yields a *dihydro*-compound, $C_{15}H_{22}O_4$, which dissolves readily in sodium bicarbonate with evolution of carbon dioxide and is reprecipitated unchanged even on warming with mineral acid. This dihydro derivative possesses a carbonyl group and it is evident that its preparation involves the hydrogenolysis of the lactone ring. Treatment of the acid with acetic anhydride yields a δ-lactone. Further hydrogenation using Adams' catalyst (PtO_2,H_2O) yields an acid *hexahydro-ψ-santonin*, $C_{15}H_{26}O_4$, which is also produced by reduction of ψ-santonin itself under the same conditions. The latter acid has no carbonyl group and yields a *monoacetyl* compound which is also a δ-lactone. It appears therefore that two of the four additional hydrogen atoms are used in the reduction of the carbonyl group to the corresponding alcohol.

When the reduction of ψ-santonin with Adams' catalyst is carried out quantitatively, it is found that the absorption of the first molecular equivalent of hydrogen is rapid and the second and third equivalents progressively slower.

Dihydro-ψ-santonin is readily reduced with sodium amalgam to an acid *tetrahydro-ψ-santonin*, $C_{15}H_{24}O_4$, which fails to give the reactions of carbonyl compounds but is readily converted to a *monoacetate*, also a δ-lactone. The tetrahydro compound is slowly reduced to the hexahydro compound by Adams' catalyst, and there appears to be no doubt that the reduction of the tetrahydro to the hexahydro compound corresponds to the third (slow) stage in the reduction of ψ-santonin itself. It appears therefore that the first stage in the catalytic reduction is the hydrogenolysis of the lactone ring, the second is the reduction of the carbonyl group, and the third is probably the reduction of the unsaturated lactone.

The hydrogenolysis of unsaturated γ-lactones has been widely investigated by Jacobs and his co-workers and more recently by Elderfield and his co-workers, and it now appears certain that the cardiac aglycones and other β-substituted α—β butenolides undergo hydrogenation by uptake of one molecule of hydrogen to give saturated lactones (Paist, Blout, Uhle, and Elderfield, *loc. cit.*). On the other hand β—γ unsaturated lactones yield varying amounts of deoxy acids on catalytic reduction (Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601) with uptake of two molecules of hydrogen. ψ-Santonin, however, takes up one molecule of hydrogen to yield an unsaturated carboxylic acid, the double bond of which is only hydrogenated with difficulty. This evidence favours the existence of a β—γ double bond, as in structure (I), in which compound there is a "protected" β—γ double bond which might be expected to be resistant to hydrogenation.

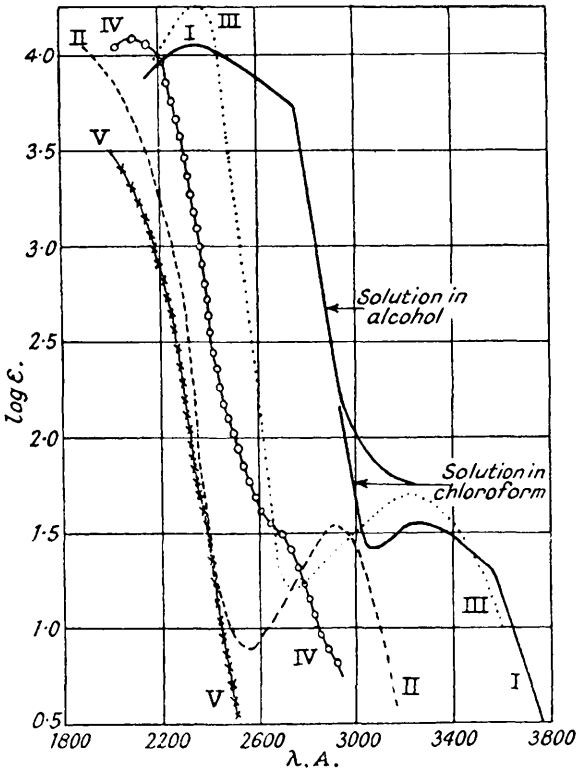
In view of the ready hydrogenation of the double bonds in *l*-santonin using palladised charcoal (Wienhaus and Oettingen, *Annalen*, 1913, **397**, 219; Asahina, *Ber.*, 1913, **46**, 1775), the possibility that the third molecule of hydrogen absorbed in the reduction of ψ-santonin is taken up by a double bond similarly placed to either of those in *l*-santonin is remote, but as α—β double bonds are frequently inert or sluggish towards catalytic reduction (compare Haworth, *loc. cit.*) the evidence cited does not rule out the possibility that this grouping is present in ψ-santonin. Its absence is, however, indicated by spectroscopic studies.

Compounds with such a grouping have an absorption band due to the carbonyl group in the neighbourhood of 3000—3200 A. and a much more intense band ($\log \varepsilon = 3{\cdot}8$ to $4{\cdot}2$) between 2200 and 2500 A. Isolated carbonyl groups absorb near 2800 A. (Gillam and West, *J.*, 1945, 95). *l*-Santonin has absorption bands at 2360 A. ($\log \varepsilon = 4{\cdot}05$) and 3250 A. ($\log \varepsilon = 1{\cdot}54$), corresponding to a carbonyl group conjugated with an α—β double bond (compare Gillam and West, *loc. cit.*, who show that piperitone has bands at 2350 A.; $\log \varepsilon = 4{\cdot}25$, and 3210 A.; $\log \varepsilon = 1{\cdot}73$). On the other hand ψ-santonin shows the band at 2900 A. ($\log \varepsilon = 1{\cdot}56$) charac-

teristic of the isolated carbonyl group, but it has much stronger absorption (no maximum) at 2000—2200 A. ($\log \varepsilon = 2{\cdot}2$—$4{\cdot}0$) than would be expected in this case. This spectrum has some similarity to those of β-*cyclo*hexyl-Δ^{α}-butenolide and vinyl acetate (see fig.), supporting the conclusion that ψ-santonin possesses an unsaturated lactone ring.

When ψ-santonin is treated with one molecule of bromine it yields a *monobromo* compound, $C_{15}H_{19}O_4Br$, which is readily reduced with zinc and alcohol to ψ-santonin. Three to four molecules of bromine yield a *tribromo* compound, $C_{15}H_{19}O_4Br_3$, which is a lactone and which is reduced in the presence of palladised charcoal to the monobromo compound. Titration by the method of Winkler (*Pharm. Zentr.*, 1924, **65**, 385) gives a bromine uptake of four atoms which with the above evidence points to the substitution of one bromine atom and the addition of two others to a double bond. Bromination under the conditions of titration points to β—γ rather than α—β unsaturation in the lactone ring.

Dihydro-ψ-santonin on titration by Winkler's method also shows a bromine uptake of four atoms, and it appears that the double bond is preserved during the hydrogenation of ψ-santonin with palladised charcoal, thus supporting the view that only hydrogenolysis of the lactone ring takes place under these conditions of hydrogenation.



I, l-*Santonin* II, pseudo-*Santonin*. III, *Piperitone*. IV, β-cyclo*Hexyl*-Δ^{α}-*butenolide*. V, *Vinyl acetate*.

When ψ-santonin is treated with 55% sulphuric acid or with anhydrous formic acid at 50°, a dark red solution is quickly produced from which a crystalline compound, $C_{15}H_{18}O_3$, is obtained as the main product. This compound now called *desmotropo-ψ-santonin* is *dextro*-rotatory and like the *dextro*-rotatory derivatives of *l*-santonin is phenolic. It fails to couple with diazotised *p*-nitroaniline and gives only a dull red-brown colour, but it is readily benzoylated and methylated in alkaline solution. It does not give a satisfactory Legal reaction nor is it reduced with palladised charcoal and hydrogen.

Attempts to obtain a fully aromatised compound from desmotropo-ψ-santonin by heating with selenium were unsuccessful; the compound sublimed unchanged. Aromatisation is, however, readily effected by fusion with potassium hydroxide at 320° (cf. Andreocci, *Gazzetta*, 1895, **25**, 545). The compound obtained has the formula $C_{12}H_{12}O$, corresponding to a dimethylnaphthol, and by analogy with the naphthol obtained from *l*-santonin it was anticipated that it would be a dimethyl-β-naphthol with the methyl groups in the same ring as the phenolic group. It is not identical, however, with 1 : 4-dimethyl-2-naphthol (Cannizzaro and Carnelutti, *Ber.*, 1879, **12**, 1575), which is obtained from *l*-santonin, or with 1 : 3-dimethyl-2-naphthol or with 3 : 4-dimethyl-2-naphthol, both of which have now been synthesised (see Part II, following paper). It was finally shown to be identical with 2 : 4-dimethyl-1-naphthol (Cornforth, Cornforth, and Robinson, *J.*, 1943, 168), and we are indebted to these workers for a sample of their compound for comparison. It is clear, therefore, that in ψ-santonin there is a carbonyl group at position 4.

When ψ-santonin is treated with cold concentrated hydrochloric acid a *dextro*-rotatory *compound*, $C_{15}H_{22}O_5$, quickly separates. This compound is readily soluble in sodium bicarbonate with evolution of carbon dioxide and is converted into desmotropo-ψ-santonin on treatment with sulphuric acid. Attempts to obtain an oximino derivative gave a high-melting compound which contained nitrogen and apparently also sodium. Further work on the new compound is necessary; the fact that it is *dextro*-rotatory is significant.

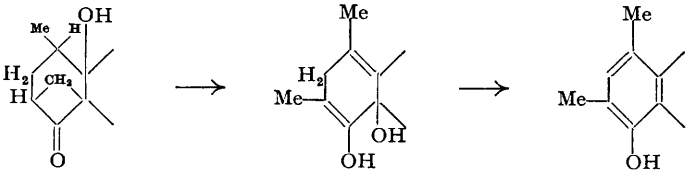
When ψ-santonin, or its dihydro derivative, is distilled with selenium an intractable syrup is produced, but after reduction with amalgamated zinc and hydrochloric acid the dihydro compound yields a gum which, on distillation with selenium, yields an oil whose picrate is identical with that obtained from 1-methyl-7-ethylnaphthalene. This hydrocarbon is also obtained from *l*-santonin (Clemo, Haworth, and Walton, *loc. cit.*) and artemisin (Tettweiler, Engel, and Wedekind, *loc. cit.*). It appears therefore that ψ-santonin possesses a similar carbon skeleton to the compounds named, and that in all three compounds the α-propionyl group is at position 8.

It should be noticed that in the production of 1-methyl-7-ethylnaphthalene a methyl group is lost, which is characteristic of compounds containing angular methyl groups or derivatives of these. This evidence, together with the fact that 2 : 4-dimethyl-1-naphthol may be obtained as indicated above, shows that in ψ-santonin there is a methyl group at position 1 and a methyl group or a derivative of this at either position 5 or 10 and that, during the treatment with acid, the latter methyl group migrates in some way to position 3.

Evidence is presented below to show that the hydroxy group is at position 10 and therefore the angular methyl group is at 5.

The migration of the methyl group from position 5 to position 3 during the treatment of ψ-santonin with sulphuric or formic acids is difficult to explain, as there appears to be no analogy. Migration of methyl groups on treatment of ψ-quinols with mineral acid is well known (cf. Clemo, Haworth, and Walton, *loc. cit.*, who give references to earlier work), but migration takes place to an adjacent position in all the cases mentioned by these workers. In the case of ψ-santonin the methyl group migrates to a position two carbon atoms away.

This difficulty could be overcome by the postulation of a methylene bridge between carbon atoms 3 and 5, in which case simple hydrolysis and dehydration would lead to the required naphthol according to the following scheme.



With such a methylene bridge it would be necessary to postulate a saturated lactone ring, against which there is considerable evidence. The suggested tertiary hydroxyl group may be at positions 1, 5, or 10. It cannot be at 8, as in artemisin, since the lactone is unsaturated, nor can it be at 9 (only possible in the α—β unsaturated lactone structure) because of the ready re-formation of the ψ-santonin after hydrolysis. Furthermore, dihydro-ψ-santonin does not undergo acetylation, but readily gives a theoretical yield of a *lactone*, $C_{15}H_{20}O_3$, on being heated with acetic anhydride, and is regenerated on warming with either dilute sodium hydroxide or dilute hydrochloric acid.

The new lactone is much less stable than ψ-santonin. It gives a *monoxime* on treatment with one equivalent of hydroxylamine, but, with an excess of this reagent, a compound, $C_{15}H_{24}O_4N_2$, is produced which combines the properties of an oxime and a hydroxamic acid. It is also obtained by further treatment of the monoxime with excess of hydroxylamine, and it appears that the lactone ring is opened during this reaction.

Observations on the effect of hydroxylamine on a limited number of γ and δ lactones indicated that the δ-lactones were converted to hydroxamic acids, whilst the γ-lactones were unaffected. Thus, *N*-*p*-toluenesulphonyl-6 : 6-dimethyl-2-morpholone (Cocker, *J.*, 1943, 373) readily gave *N*-*p*-toluenesulphonyl-*N*-β-hydroxy*iso*butylacethydroxamic acid. Coumarin gave β-2-hydroxy-phenylacrylhydroxamic acid, and anhydro-2-hydroxy*cyclo*hexyl-β-propionic acid gave a small yield of a nitrogenous, hygroscopic substance which gave the usual hydroxamic acid reactions. All attempts to obtain a compound containing nitrogen from anhydro-2-hydroxy*cyclo*hexyl-α-propionic acid were unsuccessful and of course ψ-santonin itself gave no hydroxamic acid.

The above evidence supports the view that the lactone, $C_{15}H_{20}O_3$, mentioned above is of the δ-type which could only be the case if the tertiary hydroxy group were at 10. Therefore the angular methyl group is at 5. It should be mentioned that the lactone, $C_{15}H_{20}O_3$, is unaffected by catalytic hydrogenation using palladised charcoal.

The evidence so far presented gives a good picture of the carbon skeleton of ψ-santonin with methyl groups at positions 1 and 5, the keto group at 4, the α-propionyl group at 8 and the hydroxy group at position 10. The position of the double bond in the lactone ring is, however, uncertain, since there is evidence in favour of each possibility, nor is it certain whether fusion of the lactone ring takes place at 9 as in (I) and (II) or in the alternative position 7. On biogenetic grounds and analogy with ψ-santonin, etc., the former is favoured.

Further work in this field is in hand.

Experimental.

ψ-Santonin crystallised from alcohol in colourless rhombic prisms, m. p. 183—184° (Found: C, 68·0; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·5%); $[\alpha]_D^{20°}$ — 169° (*c* = 2·49 in chloroform); cell dimensions: *a* = 8·40 A., *b* = 10·1 A., *c* = 15·9 A.; *d* 1·245. The available atomic models did not permit the setting up of accurate scale models of the structures (I) and (II), but measurements made on rough models showed that these structures agreed fairly well with the crystal measurements.

ψ-Santonin dissolved slowly in aqueous sodium hydroxide and was recovered on neutralisation with dilute acetic acid at 0° (Found: equiv. wt. (by titration), 251, 253, 245; *M* (Rast), 275; active hydrogen 1·2—1·3 atoms per molecule. $C_{15}H_{20}O_4$ requires equiv. wt., 264). The *oxime* crystallised from boiling water in long, pointed prisms, m. p. 203—204° (Found: C, 64·8; 64·9; H, 7·5, 7·8; N, 5·0. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·5; N, 5·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from a large volume of alcohol as bright yellow prisms, m. p. 257° (Found: C, 57·3; H, 5·4. $C_{21}H_{24}O_7N_4$ requires C, 56·8; H, 5·4%).

Condensation with o-Aminobenzaldehyde.—ψ-Santonin (0·2 g.), *o*-aminobenzaldehyde (0·1 g.), alcohol (1 c.c.) and sodium hydroxide (0·4 g.; 20%) were shaken together until a clear solution was obtained and then set aside for 48 hours at room temperature. The liquid was diluted with water, extracted thrice with ether and the aqueous portion carefully neutralised with dilute acetic acid. The precipitate was collected, washed with water, dried and recrystallised from dilute alcohol, giving colourless needles, m. p. 210° (Found: C, 75·4; H, 6·4. $C_{22}H_{23}O_3N$ requires C, 75·6; H, 6·6%). This *condensation product* was readily soluble in dilute mineral acid and insoluble in cold dilute sodium hydroxide. It dissolved in the latter on warming and was reprecipitated on neutralisation. The condensation product was undoubtedly a quinoline containing a lactone ring.

Acetyl-ψ-santonin. ψ-Santonin (0·5 g.) was refluxed with acetic anhydride (3 c.c.) and anhydrous sodium acetate

(1·0 g.) for 3 hours. Excess acetic anhydride was removed under reduced pressure and the residue extracted with water and crystallised twice from dilute acetic acid as colourless plates (0·15 g.), m. p. 187°, $[\alpha]_D^{20°}$ — 69·2° (*c*, 2·24 in chloroform) (Found: C, 66·6; H, 7·0. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%). On hydrolysis with dilute sodium hydroxide and crystallisation from dilute alcohol colourless needles were deposited, m. p. 205—207° (Found: C, 67·95; H, 7·59. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·5%). This new *compound* was not identical with ψ-santonin. *Oxime of acetate*, prepared in alcohol in presence of sodium acetate, crystallised from dilute alcohol as colourless prisms, m. p. 196—197° (Found: C, 63·9; H, 7·1. $C_{17}H_{23}O_5N$ requires C, 63·6; H, 7·1%).

Hydrogenation Experiments.—(a) *Using palladised charcoal.* ψ-Santonin (169·45 mg.) in glacial acetic acid absorbed 17·2 c.c. hydrogen at 16°/755 mm., equivalent to 1·1 mols. hydrogen per mol. In a second experiment, ψ-santonin (4·05 mg.) absorbed 0·50 c.c. hydrogen at 19°/766 mm. equivalent to 1·2 mols. hydrogen per mol. The absorption was complete in 1 hour in each case. (b) *Using Adams' catalyst.* ψ-Santonin (4·56 mg.) absorbed 1·40 c.c. hydrogen at 20°/760 mm. in 1 hour, equivalent to 3·4 mols. hydrogen per mol. In this experiment, a large excess of catalyst was employed. In a second experiment, using a smaller quantity of catalyst, ψ-santonin (327 mg.) absorbed 88·5 c.c. hydrogen at 16°/770 mm. equivalent to 3 mols. hydrogen per mol. of ψ-santonin. The absorption of the first 28·5 c.c. (1 mol.) hydrogen ook 15 minutes, the second mol. took 3½ hours and the third mol. took 36 hours.

Dihydro-ψ-santonin. A mixture of ψ-santonin (1 g.), palladised charcoal (0·1 g.) and glacial acetic acid (10 c.c.) was shaken for 20 hours in hydrogen at a pressure slightly greater than one atmosphere. After removal of catalyst and solvent, the residue was crystallised from dilute alcohol as colourless needles (0·9 g.), m. p. 188—189°, $[\alpha]_D^{20°}$ — 239° (*c*, 0·96 in glacial acetic acid), completely soluble with effervescence in dilute sodium carbonate (Found: C, 67·4; 68·1; H, 7·8, 8·0; *M* (Rast) 282. $C_{15}H_{22}O_4$ requires C, 67·7; H, 8·3%; *M*, 266). The same *dihydro* compound was obtained by hydrogenation in alcohol at 100 lbs./sq. in. using palladised charcoal. The quantitative experiments described above using palladised charcoal gave the same compound. The dihydro compound was also obtained by refluxing a mixture of ψ-santonin (0·3 g.), sodium hydroxide (8%, 4 c.c.), ammonia (*d* 0·88, 1 c.c.), water (2 c.c.) and activated copper (2 g.) for 12 hours, cooling and acidifying with dilute acetic acid when, after removal of some brownish flocculent material, the dihydro compound was deposited as well-formed prisms, m. p. 182—184°, raised to 189° by crystallisation from dilute alcohol (Found: C, 67·8; H, 8·8%).

The dry sodium salt of the above acid (2 g.) and methyl iodide (20 c.c.) were refluxed for 24 hours. Excess methyl iodide was removed and the residue extracted with ether and distilled. The fraction b. p. 175—180°/1 mm. was again distilled and collected (1 g.) at 181°/1 mm. On standing, the *methyl ester* solidified and crystallised from ligroin in long, transparent needles, m. p. 77° (Found: 68·6; H, 8·1. $C_{16}H_{24}O_4$ requires C, 68·6; H, 8·6%).

The *oxime of dihydro-ψ-santonin* crystallised from alcohol in short stout prisms, m. p. 229—230° (Found: C, 64·6; H, 7·8; N, 5·0. $C_{15}H_{23}O_4N$ requires C, 64·1; H, 8·2; N, 5·0%). The same compound resulted from the catalytic reduction of ψ-santoninoxime and it reverted to dihydro-ψ-santonin on treatment with hydrochloric acid.

Anhydro-dihydro-ψ-santonin. A mixture of dihydro-ψ-santonin (0·2 g.), acetic anhydride (3 c.c.) and anhydrous sodium acetate (0·5 g.) was heated for 2 hours, excess acetic anhydride removed, the residue extracted with water and crystallised from dilute alcohol, forming colourless needles (0·1 g.), m. p. 158° (Found: C, 72·65; H, 7·8. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%). It was insoluble in sodium carbonate, but slowly dissolved in sodium hydroxide from which dihydro-ψ-santonin was recovered on acidification. The lactone was also obtained by heating dihydro-ψ-santonin for a few minutes at 190—200°.

Oximes of anhydro-dihydro-ψ-santonin. A mixture of the above lactone (0·2 g.), hydroxylamine hydrochloride (0·2 g.; 4 mols.), anhydrous sodium acetate (0·5 g.) and alcohol (3 c.c.) was shaken for 12 hours. The alcohol was removed under reduced pressure and the residue was extracted with water and crystallised from aqueous alcohol as colourless prisms, m. p. 209—210° (decomp.). It gave an insoluble copper salt with ammoniacal copper sulphate, and was insoluble in sodium bicarbonate and, generally, gave reactions of a *hydroxamic acid* (Found: C, 60·7; H, 7·9; N, 9·3. $C_{15}H_{24}O_4N_2$ requires C, 60·8; H, 8·1; N, 9·5%). Using only one molecule of hydroxylamine hydrochloride the true *oxime* was obtained, and this crystallised from benzene–ligroin as colourless needles, m. p. 188° (Found: C, 68·3; H, 7·9. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·0%).

Hexahydro-ψ-santonin. A mixture of ψ-santonin (0·5 g.), glacial acetic acid (15 c.c.) and Adams' catalyst (0·1 g.) was shaken in hydrogen at 15 atm. for 24 hours and the product was crystallised from dilute acetic acid as long needles, m. p. 191—192° (Found: C, 66·5; H, 9·8. $C_{15}H_{26}O_4$ requires C, 66·6; H, 9·6%). It readily dissolved in sodium carbonate with effervescence, and was regenerated unchanged on acidification. It did not yield an oxime. *Acetyl-anhydro-hexahydro-ψ-santonin* was obtained by refluxing the hexahydro compound with an excess of acetic anhydride. It crystallised from alcohol as colourless needles, m. p. 125° (Found: C, 69·9; H, 8·75. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·8%). It was insoluble in sodium hydroxide and was hydrolysed to hexahydro-ψ-santonin with 13% methanolic potash.

Tetrahydro-ψ-santonin. To dihydro-ψ-santonin (0·3 g.) in alcohol (4 c.c.) alcohol-washed 4% sodium amalgam (11 g.) was added in portions. The mixture was refluxed for 5 hours and left overnight. Alcohol was removed and the residue dissolved in water and acidified. The precipitate was crystallised twice from water and obtained as colourless prisms, m. p. 189—190° (Found: C, 67·3; H, 8·8. $C_{15}H_{24}O_4$ requires C, 67·2; H, 9·0%). All attempts to obtain an oximino derivative failed. *Acetyl-anhydro-tetrahydro-ψ-santonin* crystallised from dilute alcohol in colourless prisms, m. p. 104° (Found: C, 70·4; H, 8·3. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·2%). It yielded the acetyl anhydro-hexahydro compound described above when submitted to hydrogenation in presence of Adams' catalyst.

Tribromo-ψ-santonin. Bromine (1 g., 3 mols.) was added dropwise to a stirred solution of ψ-santonin (0·5 g.) in chloroform (10 c.c.) at room temperature. Stirring was continued for half an hour and the chloroform and excess bromine were removed under reduced pressure. The residue was crystallised from alcohol as long, colourless needles (0·6 g.), m. p. 243° (Found: C, 36·0; H, 3·6; Br, 48·3. $C_{15}H_{19}O_4Br_3$ requires C, 35·8; H, 3·8; Br, 47·7%). *Monobromo-ψ-santonin*, obtained in a similar manner, using 1·2 mols. of bromine, crystallised from ligroin (b. p. 80—100°) as colourless needles or prisms, m. p. 198—199° (Found: C, 52·3; H, 5·5. $C_{15}H_{19}O_4Br$ requires C, 52·4; H, 5·5%). The same monobromo compound was obtained when a solution of the tribromo compound in glacial acetic acid was submitted at 35° to hydrogenation at one atmosphere using palladised charcoal. When these bromo compounds were refluxed with zinc and alcohol for 3 to 4 hours, a product, m. p. 184°, was obtained in each case which gave no depression of m. p. when mixed with ψ-santonin.

Monobromo-ψ-santonin oxime crystallised from dilute alcohol as colourless plates, m. p. 251° (decomp.) (Found: C 50·4; H, 5·4. $C_{15}H_{20}O_4NBr$ requires C, 50·3; H, 5·6%). Attempts to obtain the oxime of the tribromo compound were unsuccessful.

ψ-Santonin (0·1058 g.), titrated by Winkler's method (*loc. cit.*), required 15·84 c.c. 0·1004N-sodium bromate, equivalent to 0·127 g. bromine (four atoms of bromine = 0·127 g.). Similarly, 0·0684 g. dihydro-ψ-santonin required 10·06 c.c. 0·1004N-sodium bromate, equivalent to 0·081 g. bromine (four atoms of bromine = 0·082 g.).

Action of Mineral Acids on ψ-Santonin.—(a) *Sulphuric acid* (55%). Finely powdered ψ-santonin (0·25 g.) was introduced with stirring into a mixture of conc. sulphuric acid (2·5 c.c.) and water (3·7 c.c.), and the mixture was warmed

to 48—55° for 24 hours. After a short time the ψ-santonin passed into solution with the production of a bright red colour and shortly afterwards a crystalline solid was deposited. This was crystallised twice from 80% alcohol, when *desmotropo-ψ-santonin* was deposited as colourless needles (0·06 g.), m. p. 185—186°, $[\alpha]_D^{20°}$ + 67·9° (*c*, 2·461 in chloroform) (Found: 73·2, 73·3; H, 7·4, 7·3. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). It was soluble in sodium hydroxide, insoluble in sodium carbonate, gave a red coloration with neutral ferric chloride and a deep pink nitroso compound. It gave a dull red coloration with *p*-nitrobenzenediazonium chloride. The *benzoate* prepared in alkaline solution crystallised from dilute alcohol as long needles, m. p. 164° (Found: C, 74·8; H, 6·2. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%). The *acetate* crystallised from dilute alcohol as colourless plates, m. p. 233° (Found: C, 70·5; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%). This compound was not readily hydrolysed, but hydrolysis was effected by the use of concentrated methanolic potash when desmotropo-ψ-santonin was regenerated. This resistance to hydrolysis is characteristic of phenyl esters. The *methyl ether*, prepared by using methyl sulphate in alkaline solution, crystallised from dilute alcohol in tufts of silvery needles, m. p. 159—160° (Found: C 73·3; H, 7·4. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). Thionyl chloride had no action on desmotropo-ψ-santonin. Attempts to reduce the desmotropo compound by palladised charcoal were unsuccessful.

From the mother liquors obtained during the crystallisation of the desmotropo compound, an amorphous solid was obtained from which a crystalline *acetate* (needles, m. p. 239°) was obtained in small quantity. This compound has not yet been identified (Found: C, 71·4; H, 7·1. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%).

(b) *Formic acid.* The desmotropo compound was also obtained by refluxing ψ-santonin (0·5 g.) with formic acid (4 c.c.; 98%) for 2 hours. Excess formic acid was removed under reduced pressure and the residue was crystallised from alcohol as colourless plates (0·2 g.), m. p. and mixed m. p. 186°.

(c) *Concentrated hydrochloric acid.* Powdered ψ-santonin (1 g.) was stirred into conc. hydrochloric acid (5 g.). The solution quickly became yellow, and in a short time a crystalline solid was deposited. After 1 hour, this was collected, washed with a little concentrated hydrochloric acid and then with water, leaving a colourless crystalline solid (0·7 g.), m. p. 172—173°. It was crystallised twice from dilute acetic acid as fine colourless needles, m. p. 175—176°, $[\alpha]_D^{20°}$ + 25·2° (*c* 1·8 in chloroform), readily soluble in sodium carbonate with effervescence and recovered on acidification (Found: C, 63·9; H, 7·5; *M*, 286. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·8%; *M*, 282). Oximation in alcohol using sodium acetate gave a nitrogenous compound which was readily soluble in water and contained sodium. By crystallisation from the minimum quantity of water, it was obtained in clusters of needles which darkened at 200° and did not melt below 400° (Found: N, 4·3. $C_{15}H_{22}O_5NNa$ requires N, 4·4%). Attempts to acetylate the compound m. p. 175—176° gave inconclusive results, but on treatment with 55% sulphuric acid it gave desmotropo-ψ-santonin.

Dihydro-ψ-santonin and its anhydro compound were both unaltered by conc. hydrochloric acid and 55% sulphuric acid.

Attempted dehydrogenation of the desmotropo compound by selenium failed, since the compound sublimed too readily. Dehydrogenation was effected by heating gradually and with stirring a solution of the desmotropo compound (0·5 g.) in potassium hydroxide (0·5 g.) and water (2 c.c.). Fusion commenced at 220° and gas evolution took place at 240°. The temperature was then raised gradually to 310—320° and kept there for about 10 minutes, until gas evolution had ceased. The cooled melt was extracted with water and the violet solution shaken with a little charcoal and filtered. The filtrate was acidified and on steam-distillation a colourless crystalline solid (0·15 g.), m. p. 76—78°, was obtained. It was crystallised thrice from ligroin as colourless needles, m. p. 81—82°. It was found impossible to raise the m. p. above this value, but the product did not depress the m. p. of authentic 2:4-dimethyl-1-naphthol (Cornforth, Cornforth, and Robinson, *loc. cit.*, give m. p. 84—85°) (Found: C, 83·4; H, 7·1. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 7·0%). Its *carbanilate* crystallised from ligroin (80/100°) as clusters of colourless needles, m. p. 174—175°. The m. p. when mixed with the carbanilate prepared from 2:4-dimethyl-1-naphthol, obtained according to Cornforth, Cornforth, and Robinson, showed no depression (Found: C, 78·0; H, 6·3. $C_{19}H_{17}O_2N$ requires C, 78·4; H, 5·8%). Its picrate crystallised from aqueous alcohol as deep red needles giving m. p. and mixed m. p. with authentic material 143—144° (Found: C, 54·2; H, 3·8. Calc. for $C_{12}H_{12}O,C_6H_3O_7N_3$: C, 53·9; H, 3·7%).

Clemmensen reduction of dihydro-ψ-santonin. The dihydro compound (0·4 g.), amalgamated zinc (4 g.) and concentrated hydrochloric acid (7 c.c.) were refluxed for 18 hours; then a further quantity of the acid (3 c.c.) was added and the boiling continued for 8 hours. After cooling, the odoriferous oil was extracted with ether, dried over sodium sulphate and the ether removed. As the resulting colourless gum (0·07 g., b. p. 140°/1 mm.) showed no signs of crystallisation after standing for a fortnight, it was subjected to selenium dehydrogenation. The product from several such experiments (1·55 g.) was heated with selenium (4 g.) at 280—340° for 48 hours and finally at 340—350° for a further 12 hours. The residue was extracted with ligroin (b. p. 60—80°) and the solvent removed. The residue was distilled from sodium giving an oil (0·25 g., b. p. 80°/1 mm.). This residue (0·15 g.) in alcohol was treated with picric acid (0·18 g.) in alcohol and the orange prisms collected. On crystallisation from alcohol the picrate was obtained as long, orange needles, m. p. 96°. The m. p. was not depressed on admixture with the picrate of 1-methyl-7-ethylnaphthalene (Harvey, Heilbron, and Wilkinson, *J.*, 1930, 423).

Ozonolysis experiments. A number of experiments were performed in which ψ-santonin (1 g.) dissolved in purified chloroform (20 c.c.) was submitted to the action of 6% ozonised oxygen for periods of 6 to 9 hours at 0—5°. The solvent was removed and the syrupy residue was steam distilled into an aqueous alcoholic solution of "dimedon," from which the formaldehyde condensation product (0·06 g.), m. p. 190° (cp. Vorlander, *Z. anal. Chem.*, 1929, **74**, 241) was obtained The residue, remaining after steam distillation, was an intractable syrup.

Efforts to convert desmotropo-ψ-santonin to a ψ-santonous acid were unsuccessful. Sodium amalgam, hydriodic acid and red phosphorus, and zinc and acetic acid were employed, but the compound was either recovered unchanged or it gave an intractable syrup.

All attempts to dehydrate ψ-santonin were fruitless. It distilled unchanged from anhydrous sodium sulphate, copper sulphate and calcium oxide.

Some Experiments on the Opening of Lactone Rings with Hydroxylamine.—(i) *Action of hydroxylamine on* p-*toluenesulphonyl*-6:6-*dimethyl*-2-*morpholone.* This compound (0·5 g.) in alcohol (5 c.c.) was refluxed for 1 hour with hydroxylamine hydrochloride (0·5 g.) and anhydrous sodium acetate (1·8 g.). Alcohol was distilled away and the residue was washed with water and crystallised from alcohol. Two crops of crystals were obtained. The first had m. p. 132° and was identical with the starting material, the second was crystallised twice from dilute alcohol as long, colourless prisms, m. p. 105° (decomp.). It was readily soluble in sodium hydroxide and gave a blood-red coloration with neutral ferric chloride, and a sparingly soluble copper salt with ammoniacal copper sulphate. Its properties, generally, conformed with those expected of N-p-*toluenesulphonyl*-N-β-*hydroxy*iso*butylacethydroxamic acid* (Found: C, 48·9; H, 6·4. $C_{13}H_{20}O_5N_2S$ requires C, 49·4; H, 6·3%).

(ii) *Action of hydroxylamine on coumarin.* Coumarin (0·5 g.), hydroxylamine hydrochloride (0·4 g.), sodium acetate (0·5 g.) and alcohol (5 c.c.) were refluxed for 2 hours. The product was isolated as in (i) and crystallised twice from alcohol when β-2-*hydroxyphenylacrylhydroxamic acid* was obtained as colourless prisms (0·1 g.), m. p. 252° (decomp.) (Found: C, 60·4; H, 5·2. $C_9H_9O_3N$ requires C, 60·3; H, 5·0%).

(iii) *Action of hydroxylamine on the lactone of* cyclo*hexanol-2-β-propionic acid* (Cook and Lawrence, *J.*, 1937, 823). From this lactone (2 g.) a very small quantity of a very hygroscopic nitrogenous material was obtained which, on crystallisation from alcohol and ether, was obtained as colourless plates, m. p. 115—116°. There was insufficient material for analysis.

(iv) *Lactone of* cyclo*hexanol-2-α-propionic acid.* Ethyl *cyclo*hexanone-2-carboxylate (40 g.), ethyl α-bromopropionate (42 g.) and sodium ethoxide (from 5·4 g. sodium and 120 c.c. alcohol) were refluxed overnight. The alcohol was removed and the residue extracted with ether and fractionated, giving *ethyl* cyclo*hexanone-2-carboxylate-2-α-propionate* (25 g.) as a colourless oil, b. p. 158—163°/6—8 mm. (Found: C, 62·6; H, 8·0. $C_{14}H_{23}O_5$ requires C, 62·2; H, 8·1%). Attempts to hydrolyse this compound with hydrochloric acid (compare Robinson and Openshaw, *J.*, 1937, 944) gave poor results, but hydrolysis with baryta gave somewhat higher yields than with aqueous methanolic potassium hydroxide (compare Haworth and Mavin, *J.*, 1933, 1015). The ester (25 g.) was added to barium hydroxide (50 g. of monohydrate) in a mixture of methanol (250 c.c.) and water (250 c.c.) and the whole heated with shaking for 2 hours. Methanol was distilled away and the residue acidified and extracted with ether; the extract was dried with sodium sulphate and fractionated. Two fractions were obtained: (*a*) 2 g., b. p. 94—96°/0·25 mm., (*b*) 6 g., b. p. 153—156 (0·25 mm.). Fraction (*b*) solidified on cooling and was crystallised from ligroin as rosettes of needles, m. p. 135° (Found: C, 63·61, H, 8·4. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%). This was the required cyclo*hexanone-2-α-propionic acid.* Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as orange needles, m. p. 244° (Found: C, 51·7; H, 5·2. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·1%), and its *semicarbazone* from water as prisms, m..p. 185—186° (decomp.) (Found: C, 51·1; H, 7·5. $(C_{10}H_{17}O_3N_3)_2H_2O$ requires C, 50·8; H, 7·6%).

Reduction of the above acid. The acid (1·7 g.) in alcohol (50 c.c.) was refluxed with sodium (3 g.) until all the sodium had dissolved. Alcohol was removed, water was added and the mixture was acidified and extracted with ether. The extract was fractionated and a colourless liquid (1 g.), b. p. 106—108/0·5 mm., was collected. This was the required *lactone* (Found: C, 69·7; H, 9·0. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). All attempts to obtain a nitrogen containing compound from this lactone by treatment with hydroxylamine failed, as did all attempts at hydrogenolysis using palladised charcoal.

Fraction (*a*), b. p. 94—96/0·25 mm., dissolved slowly in sodium hydroxide, readily decolorised bromine water and gave a 2 : 4-*dinitrophenylhydrazone* which crystallised from alcohol as golden-yellow plates, m. p. 154°, insoluble in sodium carbonate (Found: C, 51·3, 51·8; H, 5·5, 4·9. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·1%). This compound was not investigated further.

The authors desire to thank Messrs. T. and H. Smith, Ltd., for gifts of ψ-santonin.

KING'S COLLEGE, UNIVERSITY OF DURHAM, NEWCASTLE-UPON-TYNE. [*Received, July* 31*st*, 1945.]