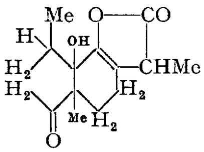
216. *The Constitution of ψ-Santonin. Part IV. A Study of the Butenolide System.*

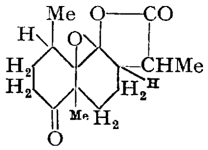
By Wesley Cocker and Stanley Hornsby.

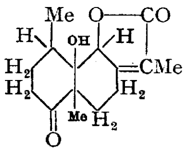
The speeds of bromination and hydrogenation, and the products of the latter, of ψ-santonin and a number of *αβ*- and *βγ*-butenolides have been compared. Spectroscopic observations have also been made. Possible structures for ψ-santonin are discussed.

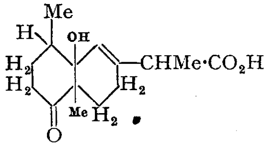
Experiments with dihydro-ψ-santonin suggest that this compound can be represented as (III).

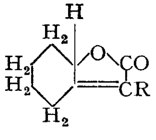
In Part I of this series Clemo and Cocker (*J.*, 1946, 30) discussed the chemistry of ψ-santonin and suggested that one of the structures (I*a*) and (II) represented the constitution of this compound, but it was not then possible to decide which was the more likely.

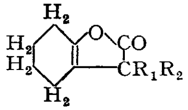

(I*a*.)


(I*b*.)


(II.)


(III.)


(IV; R = H; V; R = Me.)

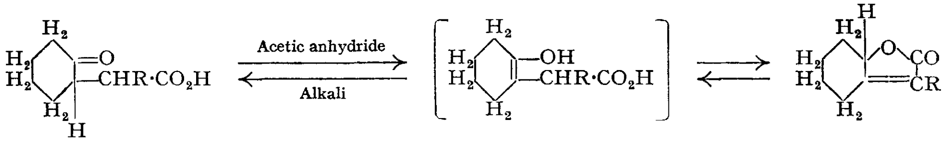

(VI.)

Colour reactions with sodium nitroprusside (cf. Jacobs and Hoffmann, *J. Biol. Chem.*, 1925, **67**, 333; Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, 1941, **6**, 273) strongly suggested the presence of a βγ-butenolide, whilst the slow reduction of ammoniacal nitrate suggested an αβ-butenolide (cf. Jacobs, Hoffmann, and Gustus, *J. Biol. Chem.*, 1926, **70**, 1).

In view of these opposing reactions it was felt desirable to study the properties of a number of butenolides of both the αβ- and the βγ-type in which, as in ψ-santonin, the butenolide is fused in the βγ-position to a *cyclo*hexane ring.

Although various α- and β-substituted butenolides have been studied in which the substituent was *cyclo*hexyl (Elderfield *et al.*, *J. Org. Chem.*, 1941, **6**, 289) and a few of the above mentioned fused lactones have been prepared, no systematic study of the properties of the latter compounds seems to have been undertaken. We have therefore prepared and studied the properties of the lactones of the following acids, namely, 2-hydroxy*cyclo*hexylideneacetic acid (IV), 2-hydroxy*cyclo*hexylidene-α-propionic acid (V), and *2-hydroxy*cyclo*hex-1-enyl-α-*iso*butyric acid* (VI; $R_1 = R_2 = Me$).

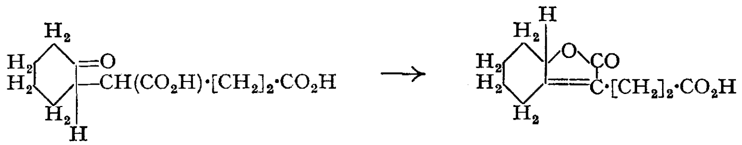
The αβ-butenolides (IV and V) were prepared by the cyclisation of 2-keto*cyclo*hexylmalonic or 2-keto*cyclo*hexyl-α-propionic acid with acetic anhydride; the reactions are apparently as follows:



(R = H or Me.)

That the product of the cyclisation is an αβ-butenolide is shown by the fact that when the lactone obtained from 2-keto*cyclo*hexylmalonic acid was submitted to ozonolysis in chloroform, 2-keto*cyclo*hexanol was obtained. Although neither glyoxylic nor oxalic acid was obtained in this reaction, yet when the same lactone was oxidised with neutral permanganate a mixture was obtained from which, in addition to some unchanged lactone, an unidentified carbonyl compound, adipic acid, and oxalic acid were isolated. We do not consider that the isolation of adipic acid and oxalic acid is necessarily of diagnostic value, but together with the evidence from the ozonolysis experiments there is adequate proof of the αβ-butenolide structure. The lactone from 2-keto*cyclo*hexyl-α-propionic acid also gave 2-keto*cyclo*hexanol on ozonolysis. Furthermore, Kendal and Osterberg (*J. Amer. Chem. Soc.*, 1927, **49**, 2047) showed conclusively by ozonolysis experiments on the product that when 2-keto*cyclo*hexyl-α-glutaric acid (VII) is cyclised it yields the αβ-butenolide (VIII), a result which is analogous to those we obtained.

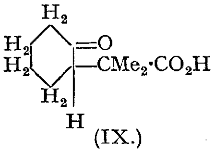
(VII.)



(VIII.)

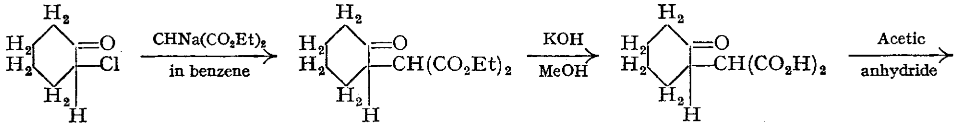
Other workers, *e.g.*, Grewe (*Ber.*, 1939, **72**, 426), have concluded that when γ-keto-acids of the type already mentioned are cyclised the result is a βγ-lactone. This worker assumed that the product of cyclisation of 2-keto*cyclo*hexyl-α-benzylacetic acid was (VI; $R_1 = H$; $R_2 = CH_2Ph$). He found, however, that on catalytic hydrogenation the butenolide system was unaffected, whereas the aromatic nucleus suffered reduction. This resistance to hydrogenation was similar to that shown by lactone (V), and we believe that Grewe's lactone was actually of the αβ-butenolide type.

The production of an αβ-butenolide in the manner stated does not appear to be in accordance with the work of Kon and Speight (*J.*, 1926, 2727) who showed that, presumably as a result of the tendency of the six membered ring to acquire a double bond, the equilibrium between *cyclo*hex-1-enylacetic acid and its esters and *cyclo*hexylideneacetic acid and its esters lies on the side of the former compounds. By analogy we should have expected the equilibrium between the βγ- and αβ-butenolides under discussion to lie on the side of the former, but it appears that in these lactones the tendency of the double bond to conjugate with the carbonyl group predominates. It was obvious, therefore, that a βγ-butenolide of type (VI) could only be prepared if the tautomeric system were blocked, *i.e.*, if R_1 and R_2 were groups other than H. We therefore prepared and cyclised 2-keto*cyclo*hexyl-α-*iso*butyric acid (IX) which yielded the required *lactone* (VI; $R_1 = R_2 = Me$).



(IX.)

The lactone of 2-hydroxy*cyclo*hexylideneacetic acid (IV) was prepared by McCrae, Charlesworth, and Alexander (*Canadian J. Res.*, 1943, **21***B*, 1) who oxidised the lactone of 2-hydroxy*cyclo*hexylacetic acid (Coffey, *Rec. Trav. chim.*, 1923, **42**, 382) with bromine and magnesium hydroxide. The keto-acid so obtained was then cyclised by heating at 200° in a vacuum, and the butenolide was obtained as a solid, m. p. 7—8°. We preferred to use a more economical method for the preparation of this lactone. 2-Chloro*cyclo*hexanone was condensed with ethyl sodiomalonate and the ester obtained was saponified with methyl-alcoholic potash to give 2-keto*cyclo*hexylmalonic acid, which was simultaneously lactonised and decarboxylated by refluxing with an excess of acetic anhydride.

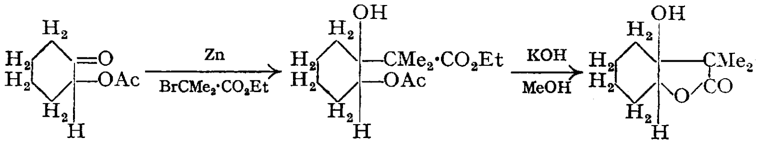


(IV)

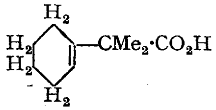
By this method we obtained the butenolide as a crystalline solid, m. p. 29—30°. Lactone (V) was prepared in a similar manner, and we found this to be preferable to the method of Clemo and Cocker (*loc. cit.*) who started from 2-carbethoxy*cyclo*hexanone and ethyl α-bromopropionate.

The preparation of the lactone of 2-hydroxy*cyclo*hex-1-enyl-α-*iso*butyric acid was troublesome and a number of routes were tried before a satisfactory one was found. The first was by the condensation of 2-carbethoxy*cyclo*hexanone in presence of sodium with ethyl α-bromo*iso*butyrate, and the product, which gave only poor analysis results, was hydrolysed with 8% methyl-alcoholic potash. Unfortunately this gave only pimelic acid and a hygroscopic acid which gave no carbonyl reactions. In the second method 2-acetoxy*cyclo*hexanone was condensed in presence of zinc with ethyl α-bromo*iso*butyrate to give *ethyl 1-hydroxy-2-acetoxy*cyclo*hexyl-α-*iso*butyrate* (X) in fair yield. All attempts to dehydrate this ester failed. It was boiled with acetic anhydride, with and without anhydrous sodium acetate; it was heated at 160° with potassium hydrogen sulphate; and finally it was heated under reflux with pyridine and phosphoryl chloride: all these treatments left it unchanged. Torrey, Kuck, and Elderfield

(*J. Org. Chem.*, **1941**, **6**, 289) found similar difficulty in the dehydration of certain tertiary alcohols, but all their compounds yielded to the dehydrating action of a boiling mixture of pyridine and phosphoryl chloride.



(X.) (XI.)



(XII.)

When the ester (X) was hydrolysed with alcoholic potash and the mixture acidified, a lactone $C_{10}H_{16}O_3$ was obtained which presumably was (XI). Attempts to dehydrate this lactone were again unsuccessful, but it was found that on heating it with 30% alcoholic sulphuric acid a very small yield of a carbonyl compound was obtained, and this gave a *2 : 4-dinitrophenylhydrazone* which proved to be identical with that obtained from 2-keto*cyclo*hexyl-α-*iso*butyric acid. The ketone was probably produced from (XI) by a pinacol–pinacolone rearrangement. The method was, however, of little preparative value.

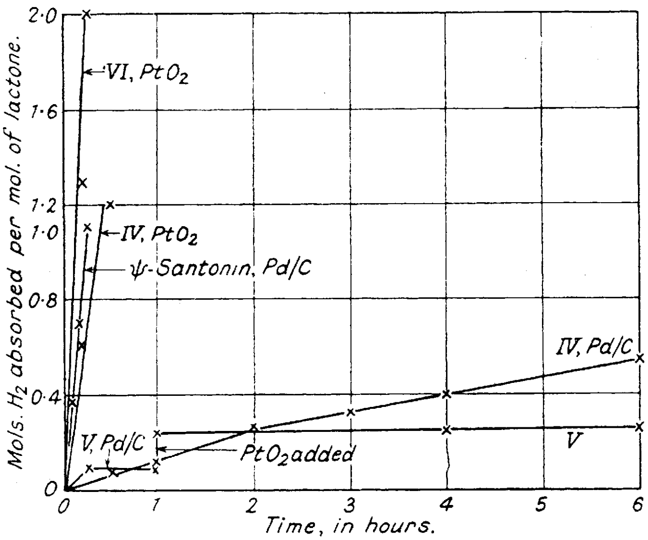
Finally the required lactone (VI; $R_1 = R_2 = Me$) was obtained by a method similar to that used by McCrae, Charlesworth, and Alexander (*loc. cit.*) for the preparation of (IV). Ethyl 1-hydroxy*cyclo*hexyl-α-*iso*butyrate (Wallach and Mallinson, *Annalen*, 1908, **360**, 68) was obtained by the condensation of *cyclo*hexanone with ethyl α-bromo*iso*butyrate in presence of zinc, and it was dehydrated and then saponified to yield *cyclo*hex-1-enyl-α-*iso*butyric acid. Von Braun and Münch (*Annalen*, 1928, **465**, 55) effected the lactonisation of this acid with hydrogen bromide in acetic acid. We performed the lactonisation with 50% sulphuric acid, and the product was oxidised to 2-keto*cyclo*hexyl-α-*iso*butyric acid. The lactonisation of *cyclo*hex-1-enyl-α-*iso*butyric acid mentioned above was, however, accompanied by the production of 1-*iso*propyl*cyclo*hexene. Wallach and Mallinson (*loc. cit.*) showed that this compound could be obtained from *iso*propylidene*cyclo*hexane by heating with sulphuric acid. Lactone (VI; $R_1 = R_2 = Me$) was finally obtained by the cyclisation of 2-keto*cyclo*hexyl-α-*iso*butyric acid with acetic anhydride.

Various attempts were made to prepare the lactone of 1-hydroxy-3 : 4-dihydronaphthalene-2-*iso*butyric acid, but these were unsuccessful.

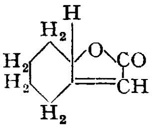
Hydrogenation Experiments.—ψ-Santonin and the lactones (IV), (V), and (VI; $R_1 = R_2 = Me$) were separately submitted to catalytic hydrogenation at 1 atmosphere pressure of hydrogen, at room temperature using (*a*) palladised charcoal and (*b*) Adams's platinic oxide catalyst. The results of these experiments are shown in Fig. 1 and Table I. It can readily be seen that, of all the lactones employed, only ψ-santonin was hydrogenated with any rapidity when palladised charcoal was employed, and here absorption ceased when one molecule of hydrogen had been taken up. The product of the reaction was dihydro-ψ-santonin (III), an unsaturated carboxylic acid. With the same catalyst the αβ-butenolide (IV) absorbed one molecule of hydrogen in about 16 hours and the product was the saturated lactone of 2-hydroxy*cyclo*hexylacetic acid. On the other hand the αβ-butenolide (V), in which the αβ-double bond is further protected, absorbed about 0·1 molecule of hydrogen in fifteen minutes in presence of palladised charcoal after which no further absorption took place. The addition of Adams's catalyst at this stage effected no further absorption apart from that expected in the reduction of the catalyst. On working up the reaction mixture only (V) was isolated. The βγ-butenolide (VI; $R_1 = R_2 = Me$) was unaffected by hydrogen and palladised charcoal, but in presence of Adams's catalyst absorption took place at a very rapid rate and 2 molecules of hydrogen were taken up in 15 minutes with the production of *cyclo*hexyl-α-*iso*butyric acid, identical with the acid obtained from the hydrogenation of *cyclo*hex-1-enyl-α-*iso*butyric acid (XII) in presence of Adams's catalyst. In presence of the same catalyst ψ-santonin absorbed one molecule of hydrogen at a speed very similar to that of (VI), but further hydrogenation was slower and was complicated by the reduction of the keto-group. Under similar conditions (IV) was reduced rapidly, but not so rapidly as either ψ-santonin or (VI), and again a saturated lactone was obtained. Finally we found that *cyclo*hex-1-enyl-α-*iso*butyric acid (XII) was unaffected by hydrogen and palladised charcoal, which falls into line with the absence of reactivity of dihydro-ψ-santonin (III) towards the same reagents, and it is of interest to record that Thakur (*J.*, 1933, 1481) found that *cyclo*hex-1-enyl-α-propionic acid was only slowly reduced with Adams's catalyst.

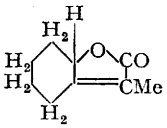
These results clearly indicate that ψ-santonin and the βγ-lactone behave alike in the production of a deoxy-acid on hydrogenation; a result which is similar to that found by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601) in the investigation of a number of simple βγ-butenolides. These workers and Paist, Blout, Uhle, and Elderfield (*loc. cit.*) also found that simple αβ-butenolides are reduced to the corresponding saturated lactones. Both ψ-santonin and (VI; $R_1 = R_2 = Me$) are more rapidly hydrogenated than the αβ-butenolides (IV) and (V), but it is well known that αβ-double bonds, and particularly protected αβ-double bonds, are very often sluggish or resistant to hydrogenation (Haworth, *Ann. Reports*, 1937, **34**, 328).

FIG. 1.



Hydrogenation of ψ-santonin and the synthetic lactones.

IV =


V =


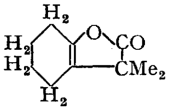
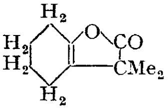
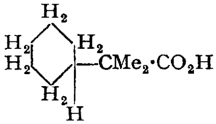
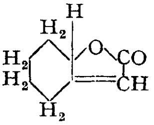
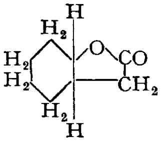
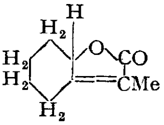
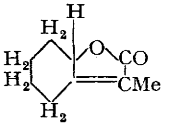
VI =


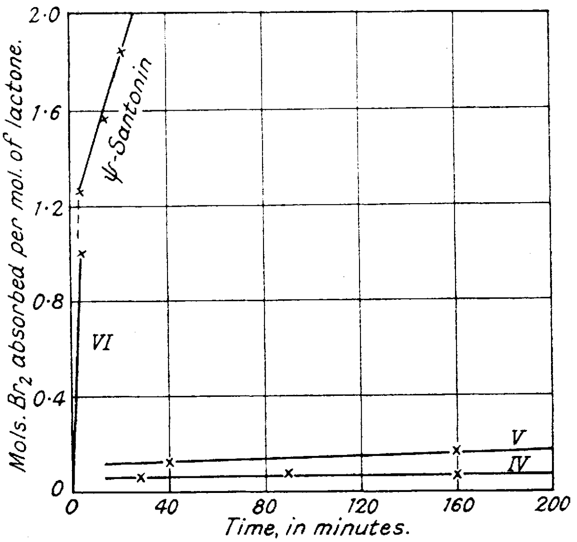
TABLE I.

Hydrogenation Experiments on the Lactones at 1 *atm.*/18°±3°.

Lactone.	Catalyst.	Time for uptake of hydrogen. 1 mol.	2 mols.	Product.
ψ-Santonin	Pd/C PtO_2,H_2O	15 minutes 10 ,,		Dihydro ψ-santonin (III)
	Pd/C PtO_2,H_2O	No absorption	15 minutes	
	Pd/C PtO_2,H_2O	16 hours 30 minutes		
	Pd/C PtO_2,H_2O	0·1 mol. in 15 mins. No further absorption		

Halogenation Experiments. (With C. Lipman.)—It is well known that αβ-unsaturated acids and esters absorb bromine less rapidly than their βγ-isomerides (Sudborough and Thomas, *J.*, 1910, **97**, 715, 2450) and this method was used by Linstead (*J.*, 1927, **355**) for determination of the position of equilibrium in mixtures of isomeric unsaturated acids. By a method similar to that advocated by Linstead we have studied the comparative speeds of bromination of ψ-santonin and the three other lactones. For this purpose equivalent quantities (1/1200 g.-mol.) of the lactones in N/60-solution in carbon tetrachloride, containing 30% acetic acid necessary to obtain solution, were treated with 2 mols. of N/15-solution of bromine in carbon tetrachloride, the final concentration of the bromine in the mixture being N/30, and the carefully stoppered vessels were placed in a dark container at 16—17°. Aliquot portions of the solutions were withdrawn at intervals and after treatment with potassium iodide the liberated iodine was titrated with N/40-thiosulphate. 2 Mols. of bromine were employed because ψ-santonin brominates first to give a monobromo-compound by substitution and then one molecule of bromine adds to give a tribromo-compound (Clemo and Cocker, *loc. cit.*). Fig. 2 and Table II show that ψ-santonin and the βγ-butenolide (VI; $R_1 = R_2 = Me$) absorb bromine at approximately the same rate, although it should be remembered that it is the upper part of the graph of ψ-santonin which must be compared with that of (VI), since the lower part of the ψ-santonin graph, which lies upon that of (VI), represents the substitution reaction. When monobromo-ψ-santonin was brominated using one molecule of bromine its rate of bromination was similar to that found for the absorption of the second molecule of bromine in ψ-santonin itself, so that the influence of the hydrogen bromide produced in the substitution reaction in ψ-santonin need not be considered. When (VI) was brominated with 1 mol. of bromine there was no change in the rate of reaction. The absorption of bromine by the αβ-butenolides (IV and V) is very slow, but the initial rapid absorption is interesting and is paralleled by a similar absorption in the hydrogenation of (V). This is probably due to the presence of some βγ-butenolide in (IV) and (V).

Fig. 2.



Bromination of ψ-santonin and the synthetic lactones.
(IV, V, *and* VI *as for Fig.* 1.)

Table II.

	Bromine absorption in mols. in x minutes.										
Lactone	$x = 5$	10	15	20	30	40	90	160	320	**420**	**900**
ψ-Santonin	1·242	—	1·54	1·82	1·99	—	—	—	—	—	—
(VI)	1·11	1·06	—	—	—	—	—	—	—	—	—
(IV)	—	—	—	—	0·04	—	0·06	0·05	—	—	**0·15**
(V)	—	—	0·11	—	—	0·14	—	0·17	0·19	**0·21**	—

(IV, V, and VI as for Fig. 1.)

Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1946, **68**, 2332) used Hanus solution (IBr) as a reagent for differentiating between αβ- and βγ-lactones. They found that the latter reacted much more rapidly than the former with this reagent.

The bromination and hydrogenation results seem to be evidence in favour of the adoption of structure (I*a*) for ψ-santonin.

Spectroscopic Evidence.—Spectroscopic studies do not appear to support the βγ-structure, and in fact, neglecting the absorption due to the carbonyl group, there is a striking resemblance between the absorptions of ψ-santonin and the αβ-lactone (V). In each case there is high intensity absorption at the extreme end of the usual ultra-violet range, and in neither is a maximum discernible. This is similar to the experience noted by other workers such as Haynes and Jones (*J.*, 1946, 954) and Ruzicka *et al.* (*Helv. Chim. Acta*, 1942, **25**, 435; 1944, **27**, 186) with a number of simple αβ-unsaturated lactones. The βγ-lactone (VI) absorbs with a much smaller intensity than either ψ-santonin or lactone (V) at comparable wave-lengths.

TABLE III.

Light-absorption Data for Unsaturated Lactones.

(In alcoholic solutions.)

	λ, A.	ε.
ψ-Santonin ...	2900 *	35
	2000 †	14,000
(V)	2200 †	12,000
(VI)	2200 †	3,851

* Maximum characteristic of the isolated >C=O group.
† Maximum not discernible.

Colour Reactions and Reactions with Tollens's Reagent.—Lactones (IV) and (V) both instantaneously reduced Tollens's reagent whilst ψ-santonin and (VI; $R_1 = R_2 = Me$) gave a silver mirror only after twelve hours. These reactions were carried out as follows. A solution of 10 mg. of lactone in 1 c.c. of purified pyridine was treated with 1 c.c. of Tollens's reagent, prepared from equal volumes of 10% sodium hydroxide and 10% silver nitrate to which 10% ammonia was added dropwise until the precipitated silver oxide had disappeared.

The results are interesting since they appear to show that ψ-santonin and lactone (VI; $R_1 = R_2 = Me$) are alike in the position of the double bond (*i.e.*, they are βγ-butenolides), but the slowness of reduction of the reagent by these butenolides is contrary to the experience of Jacobs, Hoffmann, and Gustus (*loc. cit.*) who found that the βγ-butenolides they investigated gave immediate reduction of Tollens's reagent, whereas the αβ-butenolides were very sluggish. It must be remembered, however, that Jacobs and his co-workers were not investigating lactones fused to a *cyclo*hexane ring, and it is more than likely that this is the explanation of the differing results.

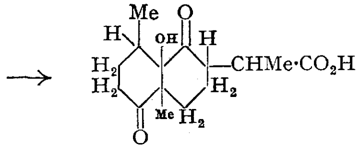
The Legal tests when applied to all the synthetic lactones in the manner recommended by Paist, Blout, Uhle, and Elderfield (*loc. cit.*) were most unsatisfactory. There was little change in colouration with sodium nitroprusside until the solution became distinctly alkaline to phenolphthalein and it is felt that as applied to these particular lactones the Legal test has little diagnostic value.

Cardiac Activity of the Lactones.—The effect on the isolated frog heart of ψ-santonin, the lactones (IV), (V), (VI), and the lactone of 2-hydroxy*cyclo*hexylacetic acid was tried through the courtesy of the late Dr. J. Secker of the Department of Physiology of King's College. The concentration of lactone used was 1 mg. per c.c. of 10% aqueous alcohol and it was found that 1 drop of solution of all the butenolides produced cardiac inhibition, whilst the saturated lactone was ineffective. It appears, therefore, that the unsaturated lactone system has some cardiac effect, but it is not specific for either the αβ- or the βγ-type. No experiments were performed on cats but it is highly unlikely that any of the lactones would have important effects (cf. Swain, Todd, and Waring, *J.*, 1944, 548).

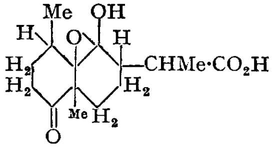
If the βγ-butenolide structure (I) for ψ-santonin is adopted there are certain experimental results which require an explanation. In the first place when ψ-santonin is saponified with methyl-alcoholic potash a solution is obtained from which the starting material is regenerated even on acidification at 0°. Many experiments were performed but in none of these was there any evidence for the production of a diketo-acid on saponification of ψ-santonin, whereas the diketo-acid (XIII) would be expected from structure (I*a*). All the synthetic butenolides give keto-acids on saponification. One possible explanation could be that on hydrolysis the keto-acid undergoes isomeric change with the formation of the cyclic alcohol (XIV), in the same way that Bergmann and Gierth (*Annalen*, 1926, **448**, 48) found that 2-keto*cyclo*hexanol can exist in the oxido-form (XV). It is possible that on acidification (XIV) could lactonise and undergo isomeric change with the formation of (I*a*).

A further difficulty in the way of acceptance of structure (I*a*) lies in the fact that it has been shown that in the butenolides fused to the *cyclo*hexane ring, unless tautomeric change is impossible as in (VI), the double bond is found in the αβ-position. Why then should ψ-santonin be a βγ-butenolide? We believe that the hydroxyl group is somehow connected with this problem and it may be that structure (I*b*) is more acceptable than (I*a*), but until we have succeeded in synthesising certain hydroxylated butenolides it would be well to withhold further comment.

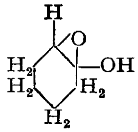
(I*a*)



(XIII.)

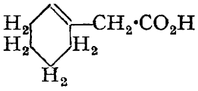


(XIV.)

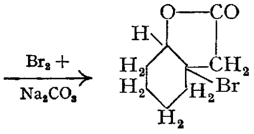


(XV.)

Some Experiments with Dihydro-ψ-santonin.—This compound readily decolourises bromine water, and in quantitative experiments performed under identical conditions with those already described it was found that one mol. of bromine was completely absorbed per mol. of acid in less than 5 minutes. This result is strongly suggestive of a βγ-unsaturated acid. Moreover such βγ-acids readily form bromo-lactones on treatment, in sodium carbonate, with bromine water. Thus Harding, Haworth, and Perkin (*J.*, 1908, **95**, 1963) obtained a bromo-lactone, to which they assigned the structure (XVII), when *cyclo*hex-1-enylacetic acid (XVI) was brominated in sodium carbonate. In a similar manner when dihydro-ψ-santonin was treated in sodium carbonate with bromine water a white crystalline solid was obtained. This was a bromo-lactone, $C_{15}H_{21}O_4Br$, and to this compound by analogy we assign structure (XVIII).

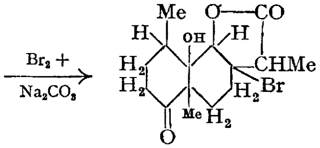


(XVI.)



(XVII.)

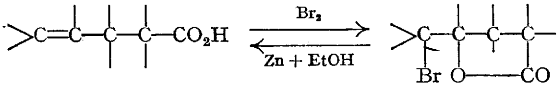
(III)

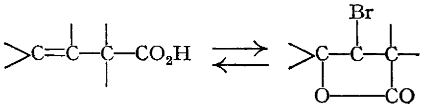


(XVIII.)

The possibility that the bromo-lactone is a β-lactone may be ruled out, since we have shown already that the αβ-double bond is resistant to attack of bromine and the mechanism of addition of hypobromous acid is undoubtedly similar to that of bromine itself.

Such bromo-lactones as those mentioned above should be capable of reduction to the corresponding unsaturated acids. Thus Winterstein and his co-workers (*Z. physiol. Chem.*, 1931, **199**, 25, 37, 46, 56, 64, 75) have shown that βγ- and γδ-unsaturated acids can be converted into crystalline bromo-lactones from which the unsaturated acids are regenerated by reduction with zinc and alcohol or zinc and acetic acid.





When the bromo-lactone (XVIII) was refluxed with zinc dust in alcohol it was smoothly reconverted into dihydro-ψ-santonin. In an analogous manner *cyclo*hex-1-enyl-α-*iso*butyric acid was converted into a bromo-lactone, $C_{10}H_{15}O_2Br$, from which the unsaturated acid was again obtained by reduction with zinc and alcohol.

We consider that the above evidence strongly supports the structure (III) suggested for dihydro-ψ-santonin.

EXPERIMENTAL.

*Lactone of 2-Hydroxy*cyclo*hexylideneacetic Acid* (IV). *2-Keto*cyclo*hexylmalonic Acid.*—Ethyl malonate (63·4 g.) was added dropwise to a stirred and boiling suspension of powdered sodium (9·1 g.) in benzene (300 c.c.) and the reaction was continued until all the sodium had disappeared. The cooled mixture was then slowly treated, with stirring, with 2-chloro*cyclo*hexanone (63 g.). After 1 hour in the cold the mixture was heated on the water-bath and refluxed, with stirring, for 8 hours. It was then cooled and acidified with dilute acetic acid, and the benzene layer was separated, washed with water, and dried. On distillation *ethyl 2-keto*cyclo*hexylmalonate* (49 g.) was collected as a colourless oil, b. p. 150—151°/3 mm. (Found: C, 61·5; H, 7·9. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·8%). This ester was hydrolysed by heating for 2 hours under reflux with a solution of potassium hydroxide (34 g.) in methyl alcohol (500 c.c.) and water (50 c.c.). Methyl alcohol was then removed and the residue was diluted with water, shaken with charcoal, and filtered. The filtrate was acidified, saturated with ammonium sulphate, and extracted several times with ethyl acetate from which the required 2-keto*cyclo*hexylmalonic acid was obtained (19 g.), m. p. 160°. It crystallised from water as colourless needles, m. p. 168—169° (decomp.). McCrae, Charlesworth, and Alexander (*loc. cit.*) give m. p. 163° (Found: C, 54·1; H, 6·0; equiv., 105·1. Calc. for $C_9H_{12}O_5$: C, 54·0; H, 6·0%; equiv., 100). Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as yellow needles, m. p. 218—219° (decomp.) (Found: C, 48·0; H, 4·5. $C_{15}H_{16}O_8N_4$ requires C, 47·4; H, 4·2%).

The above acid (19 g.) was gently refluxed for 2 hours with acetic anhydride (80 g.) and the acetic anhydride was then removed under reduced pressure. The residual oil was dissolved in ether, washed several times with sodium hydrogen carbonate solution, dried, and distilled. The product distilled almost completely at 131—133°/3—4 mm. and on cooling it solidified to a mass of colourless needles of (IV), m. p. 29—30° (Found: C, 69·3; H, 7·3. Calc. for $C_8H_{10}O_2$: C, 69·6; H, 7·25%). On hydrolysis with 10% methyl-alcoholic potash the lactone yielded 2-keto*cyclo*hexylacetic acid, m. p. 73°, undepressed by admixture with an authentic specimen prepared by heating 2-keto*cyclo*hexylmalonic acid (cf. McCrae *et al., loc. cit.*) (Found: equiv., 150. Calc. for $C_8H_{12}O_3$: equiv., 156). *2-Keto*cyclo*hexylacetic acid 2 : 4-dinitrophenylhydrazone* crystallised from dilute alcohol as yellow needles, m. p. 193—194° (Found: C, 50·5; H, 4·8. $C_{14}H_{16}O_6N_4$ requires C, 50·0; H, 4·8%).

Oxidation of the Lactone.—(a) *With neutral potassium permanganate.* The lactone (1·0 g.) in water (10 c.c.) containing magnesium sulphate (3 g.) was slowly treated, with shaking, with 1% permanganate (75 c.c.). The mixture was then further shaken for 30 minutes. It was made alkaline to phenolphthalein and filtered. The filtrate was warmed for 30 minutes on the water-bath and extracted with ether from which unoxidised lactone, m. p. 29—30°, was obtained. The alkaline residue was evaporated to a very small bulk, acidified with sulphuric acid, and extracted many times with ether from which adipic acid (crude, m. p. 140°) was isolated. The aqueous residue was freed from sulphate ions, buffered with sodium acetate, and treated with calcium chloride; calcium oxalate was produced, soluble in hydrochloric acid and capable of reducing acid potassium permanganate.

(b) *With ozone.* The lactone (0·5 g.) in purified chloroform (25 c.c.) was subjected to ozonised oxygen (0·009 g.-mol. O_3/hr.) for 30 minutes. The solvent was then removed in a vacuum at room temperature and the residue was shaken thoroughly with water and left overnight. The solution was treated with sodium carbonate (0·5 g.) and steam distilled. The distillate yielded a 2 : 4-dinitrophenylhydrazone which on crystallisation from alcohol gave m. p. 231—232° undepressed by an authentic specimen of the 2 : 4-dinitrophenylhydrazone of 2-keto*cyclo*hexanol. Neither glyoxylic acid nor oxalic acid was, however, identified in the residue from the steam distillation.

Hydrogenation.—The above lactone (1·0002 g.) in glacial acetic acid (20 c.c.) containing palladised charcoal (0·5 g.) absorbed 166·4 c.c. of hydrogen at 15·5°/761 mm. This is equivalent to 0·98 mols. of hydrogen per mol. of lactone. The reaction was complete in 16 hours. The glacial acetic acid was removed under reduced pressure and the residue was distilled to give the lactone of 2-hydroxy*cyclo*hexylacetic acid (0·9 g.), b. p. 110—111°/3—4 mm. (Found: C, 68·3; H, 8·6. Calc. for $C_8H_{12}O_2$: C, 68·6; H, 8·6%). Its *phenylhydrazide* crystallised from dilute acetic acid in colourless plates, m. p. 168° (Found: C, 67·7; H, 8·2. $C_{14}H_{20}O_2N_2$ requires C, 67·7; H, 8·1%). No acid products were isolated from the reduction, and when the reduced lactone was hydrolysed by alkali and the solution acidified it was regenerated unchanged.

When (IV) (0·3070 g.) was hydrogenated in acetic acid (20 c.c.) containing Adams's platinic oxide catalyst (0·05 g.) at 20°/769 mm. hydrogen was rapidly absorbed and absorption was complete (1·17 mols. of hydrogen per mol. lactone) in 30 minutes. When the acetic acid was removed the residue was found to be insoluble in sodium carbonate, and it gave a phenylhydrazide identical with that described above.

*Lactone of 2-Hydroxy*cyclo*hexylidene-α-propionic Acid* (V). *2-Keto*cyclo*hexyl-α-propionic Acid.*—The following method was found to be more convenient than that described by Clemo and Cocker (*loc. cit.*). Ethyl methylmalonate (27 g.) in dry benzene (20 c.c.) was added dropwise to powdered sodium (3·55 g.) in dry benzene (50 c.c.), and the reaction was continued until the sodium had disappeared. Then 2-chloro*cyclo*hexanone (20 g.) was slowly added with stirring, and the mixture was stirred and refluxed for 8 hours. It was diluted with water and the benzene layer was separated, dried, and distilled. The ester (18 g.) was collected at 158—162°/3—4 mm., but all attempts to get a good analytical specimen failed. It was therefore hydrolysed under reflux for 2 hours with a mixture of potassium hydroxide (12 g.), methyl alcohol (90 c.c.), and water (30 c.c.). Methyl alcohol was removed under reduced pressure, and the cooled residue was acidified with dilute sulphuric acid and extracted with ether from which 2-keto*cyclo*hexyl-α-propionic acid (5 g.) was obtained, m. p. 133—134°. It crystallised from water (charcoal) as colourless plates, m. p. 134·5—135·5° (Found: equiv., 172. Calc. for $C_9H_{14}O_3$: equiv., 170). Its 2 : 4-dinitrophenylhydrazone crystallised from alcohol as yellow needles, m. p. 244° (decomp.) (Found: C, 51·3; H, 5·5. Calc. for $C_{15}H_{18}O_6N_4$: C, 51·4; H, 5·1%).

Lactone (V).—The above keto-acid (17·5 g.) was heated under reflux for 2 hours with acetic anhydride (60 c.c.). Acetic anhydride was removed under reduced pressure and the residue was extracted with ether. The extract was washed several times with sodium hydrogen carbonate solution, dried, and distilled, to give the required lactone as a highly refractive liquid, b. p. 133—134°/3 mm. (Found: C, 70·5; H, 7·8. $C_9H_{12}O_2$ requires C, 71·0; H, 7·9%). This lactone was somewhat less soluble in water than its lower homologue, but it was readily and quantitatively saponified with 5—10% methyl-alcoholic potash to 2-keto*cyclo*hexyl-α-propionic acid, m. p. and mixed m. p. 135°.

Attempted hydrogenation. The above lactone (0·9763 g.) in glacial acetic acid (20 c.c.) containing palladised charcoal (0·5 g.) was hydrogenated at 15°/745 mm. 17·5 C.c. of hydrogen were absorbed in about 15 minutes, and then absorption ceased. Adams's catalyst (0·1 g.) just previously reduced was later introduced and a further 30·0 c.c. of hydrogen was absorbed, but even after further shaking overnight no appreciable further absorption took place. On removal of the acetic acid and alkaline hydrolysis of the residue, 2-keto*cyclo*hexyl-α-propionic acid (0·7 g.), m. p. 135°, was recovered.

2-*Hydroxy*cyclo*hex*-1-*enyl*-α-iso*butyrolactone* (VI; $R_1 = R_2 = Me$).—(*a*) *From* 2-*acetoxy*cyclo*hexanone*. Clean and bright zinc wool (3·2 g.; 2·1 g.-atoms) was added in portions to 40 c.c. of a mixture of 2-acetoxy*cyclo*hexanone (3·5 g.; Bergmann and Gierth, *Annalen*, 1926, **448**, 48), ethyl α-bromo*iso*butyrate (4·4 g.), iodine (0·05 g.), and dry benzene (85 c.c.), and the whole was brought to the boil, under reflux, with stirring. Reaction set in, and after 10 minutes the remainder of the benzene solution was added dropwise to the stirred mixture. Stirring and refluxing were then continued for 3 hours. The mixture was cooled and added to 10% sulphuric acid and ice, and, after shaking, the benzene layer was separated, washed with 5% sodium hydrogen carbonate solution, dried, and distilled, the fraction b. p. 139—140°/6 mm. being collected. This was again distilled and the *ester* collected as a colourless viscous liquid (4·6 g.), b. p. 127—130°/3—4 mm. (Found: C, 62·4; H, 8·9. $C_{14}H_{24}O_5$ requires C, 61·8; H, 8·8%). The ester (3·55 g.) was hydrolysed by heating under reflux for 3 hours with potassium hydroxide (2·5 g.) and methyl alcohol (50 c.c.). Methyl alcohol was removed, and the residue was dissolved in water, clarified with charcoal, and acidified with 20% sulphuric acid. The solution was then saturated with ammonium sulphate and extracted with ether from which a solid, m. p. 69—73°, was obtained. It was crystallised from ligroin (b. p. 40—60°), and the *lactone* of 1 : 2-dihydroxy*cyclo*hexyl-α-*iso*butyric acid (XI) was obtained as colourless needles, m. p. 107—108° (Found: C, 65·6; H, 8·3. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). Attempted dehydration of the ester (3·2 g.) was carried out by boiling for 3 hours with acetic anhydride (6 g.) and fused sodium acetate (3 g.). On hydrolysis of the product only (XI) was obtained. Again dehydration was attempted by heating the ester (2·0 g.) with pyridine (20 c.c.) and phosphoryl chloride (7 c.c.) at 150—160° for 4 hours. The reaction mixture was then cooled and poured into ice and sulphuric acid and the mixture was exhaustively extracted with ether. From the extract a small quantity of oil, b. p. 100—130°/3 mm., was obtained, from which by hydrolysis (XI) was produced. The lactone (XI; 0·5 g.) was heated on the water-bath with 30% sulphuric acid in 50% alcohol (10 c.c.) for 3½ hours. The product was an oil which was immediately saponified with 10% sodium hydroxide and the small amount of acidic product was extracted with ether. It yielded a 2 : 4-dinitrophenylhydrazone which had m. p. 250°, undepressed by that of authentic 2-keto-*cyclo*hexyl-α-*iso*butyric acid prepared as described below (*c*).

(*b*) *From* 2-*carbethoxy*cyclo*hexanone*. 2-Carbethoxy*cyclo*hexanone (13 g.) was added dropwise to sodium ethoxide from sodium (1·76 g.) and alcohol (48 c.c.). The solid sodio-derivative was cooled and with stirring ethyl α-bromo*iso*butyrate (15 g.) was slowly added and the mixture was refluxed for 24 hours. Alcohol was then removed and the residue was diluted with water and extracted with ether, from which by distillation a fraction, b. p. 155—180°/2—3 mm., was obtained. On redistillation a fraction (5·3 g.) was collected at 170—178°/2—3 mm. This fraction was refluxed for 3 hours with a solution of potassium hydroxide (4 g.) in methyl alcohol (50 c.c.), methyl alcohol was distilled off, and the residue, after acidification was saturated with ammonium sulphate and extracted many times with ether. From this extract pimelic acid, m. p. 103—104° (Found: C, 52·5; H, 7·5; equiv., 73·2. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·5%; equiv., 80), and another solid product were isolated. The latter consisted of hygroscopic needles. It was strongly acid but gave no carbonyl reactions. It was not investigated further.

(*c*) *From* 1-*hydroxy*cyclo*hexyl*-α-iso*butyric acid*. This compound was previously prepared by Wallach and Mallinson (*loc. cit.*) but experimental details were scanty. We adopted the following procedure. Clean and bright zinc wool (32 g.) was added in five equal portions to a stirred boiling mixture of *cyclo*hexanone (40 g.), ethyl α-bromo*iso*butyrate (80 g.), iodine (0·05 g.), and benzene (150 c.c.). The mixture was heated with stirring for 3 hours, then cooled, poured on crushed ice, and shaken with 20% sulphuric acid (300 c.c.). The benzene layer was removed and the aqueous layer was further extracted with benzene and the combined benzene extracts were dried. The extract was distilled and the fraction, b. p. 134—136°/10—12 mm. (32 g.), collected. This consisted of ethyl 1-hydroxy*cyclo*hexyl-α-*iso*butyrate. The above ester (30 g.) was heated for 2½ hours at 150—160° with freshly fused potassium hydrogen sulphate (60 g.). The mixture was cooled and the paste extracted several times with ether. The ether extract was distilled and the fraction (13 g.), b. p. 130—136°/10—12 mm., collected. This was substantially ethyl *cyclo*hex-1-enyl-α-*iso*butyrate. An earlier fraction (13 g.), b. p. 120—130°/10—12 mm., was the undehydrated ester. A mixture of the unsaturated ester (13 g.), potassium hydroxide (7·2 g.), and methyl alcohol (120 c.c.) was refluxed for 3 hours. The methyl alcohol was distilled off and the residue diluted with water and extracted with ether. The aqueous layer was then clarified with charcoal, acidified, and extracted with ether from which by distillation *cyclo*hex-1-enyl-α-*iso*butyric acid (4·5 g.) was obtained as a viscous liquid, b. p. 154—160°/10—12 mm. It solidified on being kept, and crystallised from dilute alcohol as long colourless needles, m. p. 71—72° (v. Braun and Münch, *Annalen*, 1928, **465**, 52, give m. p. 69—71°). The acid (0·1 g.) in 10% sodium carbonate (20 c.c.) was treated at room temperature with saturated bromine water in excess. The opalescent liquid was then extracted with ether from which an oil was obtained which slowly solidified. It was purified by sublimation in a vacuum and the *bromo-lactone* was obtained as long prisms, m. p. 59—60° (Found: C, 49·2; H, 6·3. $C_{10}H_{15}O_2Br$ requires C, 48·6; H, 6·1%). This lactone had a strong camphoraceous odour; it was insoluble in cold sodium hydroxide but on being warmed with this reagent it rapidly decomposed giving a solution containing sodium bromide.

The above unsaturated acid (13·5 g.) was stirred and gently refluxed with 50% sulphuric acid (135 g.) for 6 hours. The dark gum which was produced on dilution with water was extracted with ether, and the extract was washed with 5% sodium carbonate and dried. On distillation two fractions were obtained: (i) b. p. 50°/10—12 mm. (4 g.), and (ii) b. p. 136—140°/10—12 mm. (4·3 g.). Fraction (i) was distilled at atmospheric pressure and collected at 155—157°. It was undoubtedly 1-*iso*propyl-*cyclo*hexene (Found: C, 86·6; H, 12·3. Calc. for C_9H_{16}: C, 87·1; H, 12·9%). It gave a nitrosochloride which crystallised from benzene–ligroin as needles, m. p. 143—144°. Wallach and Mallinson (*loc. cit.*) give m. p. 129—130° (Found: C, 57·3; H, 8·4. Calc. for $C_9H_{16}ONCl$: C, 56·9; H, 8·4%). Fraction (ii) was the lactone of 2-hydroxy*cyclo*hexyl-α-*iso*butyric acid; it solidified on standing and had m. p. 48°. It was considered to be sufficiently pure for the further stages of the synthesis. The lactone (4·3 g.) was hydrolysed by boiling with sodium hydroxide (2 g.) in water (20 c.c.) for 30 minutes. The clear solution was treated with a boiling solution of magnesium sulphate (6 g. of the heptahydrate) in water (40 c.c.). It was cooled, shaken thoroughly, and treated dropwise at 0° with bromine (5 g.). The mixture was then shaken for 24 hours, further portions of sodium hydroxide being added at intervals to ensure very slight alkalinity to phenolphthalein. The mixture was acidified and exhaustively extracted with ether, from which, after drying, a dark red solid was obtained. This was dissolved in a slight excess of sodium carbonate solution, boiled with charcoal, and filtered, and the hot solution was acidified with concentrated hydrochloric acid. The buff-coloured acid (2·7 g.) had m. p. 149—150° and was considered sufficiently pure for further work. A portion recrystallised from water (charcoal) was deposited as colourless prisms, m. p. 151—152°. This was undoubtedly 2-*keto*cyclo*hexyl-α-*iso*butyric acid* (Found: C, 64·6; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·6%). Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as yellow needles, m. p. 255—256° (decomp.) (Found: C, 52·3; H, 6·0. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·5%). The above keto-acid (2·7 g.) dissolved in acetic anhydride (15 g.) was heated under reflux for 2 hours. The acetic anhydride was then removed under reduced pressure and the residue was extracted with ether. The extract was washed with sodium carbonate, dried, and distilled, and 2-*hydroxy*cyclo*hex*-1-*enyl-α-*iso*butyrolactone* (1·8 g.) was collected at 119—120°/10—11 mm. (Found: C, 71·5; H, 8·3. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%). On alkaline hydrolysis the keto-acid was regenerated.

Hydrogenation of the Lactone (VI; $R_1 = R_2 =$ Me).—When the lactone (0·1996 g.) in glacial acetic acid (10 c.c.) mixed with palladised charcoal (0·2 g.) was submitted to hydrogenation at 16°/755 mm. no hydrogen was absorbed, but in a second experiment when lactone (0·1514 g.) in acetic acid (10 c.c.) mixed with Adams's platinic oxide catalyst (50 mg.) was reduced at 18°/758 mm., 7—8 c.c. of hydrogen were absorbed in 3 minutes and two molecules (43 c.c.) in 15 minutes. The acetic acid was then removed in a vacuum and a solid residue was obtained which was completely soluble in sodium carbonate with effervescence. The alkaline solution was shaken with charcoal, filtered, and acidified to give *cyclo*hexyl-α-*iso*butyric acid as silvery plates, m. p. 77—78°, raised only to 80° on two crystallisations from dilute alcohol. This compound was identical with that obtained when *cyclo*hex-1-enyl-α-*iso*butyric acid (0·2 g.) was hydrogenated in glacial acetic acid (15 c.c.) mixed with Adams's catalyst (0·06 g.) at 15°/751·5 mm. The total absorption, which took 15 minutes to complete, was 28·4 c.c., equivalent to 1 mol. of hydrogen per mol. of unsaturated acid. No hydrogenation took place with palladised charcoal as catalyst.

Attempts to Prepare 1-*Hydroxy*-3 : 4-*dihydronaphthalene*-2-α-iso*butyrolactone*.—The method adopted was the attempted condensation of ethyl α-bromo*iso*butyrate with ethyl 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylate. α-Tetralone was prepared by the ring closure of γ-phenylbutyric acid with a mixture of phosphoric acid and phosphoric oxide (cf. Birch and Robinson, *J.*, 1945, 582); this method was more economical than the usual one involving the ring closure of γ-phenylbutyryl chloride (*Org. Synth.*, Coll. Vol. II, 569). α-Tetralone was converted into ethyl 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene-2-glyoxylate by a method similar to that employed by Hückel and Goth (*Ber.*, 1924, **57**, 1288), but decomposition of this compound to give the carboxylate was improved as follows. A mixture of the glyoxylate (7·5 g.) and finely powdered glass (7 g.) was heated in an oil-bath maintained at 190—195° for 2 hours. On cooling, the paste was extracted several times with ether from which the required ester (6 g.) was obtained as a colourless liquid, b. p. 153—155°/2 mm. (Found: C, 71·9; H, 6·5. Calc. for $C_{13}H_{14}O_3$: C, 71·6; H, 6·4%). The keto-ester (11·3 g.) was slowly added to a suspension of finely powdered potassium (2·1 g.) in xylene (50 c.c.) and the mixture was stirred and refluxed until all the potassium had dissolved. The bromo-ester (10·1 g.) was slowly added and the stirred mixture was heated under reflux for 24 hours. It was then cooled and poured into water, and the xylene layer separated and distilled. Five fractions were obtained, namely: (i) 60—70°/3 mm., (ii) 105—145°/3 mm., (iii) 155—160°/3 mm., (iv) 170—175°/3 mm., and (v) 180—185°/3 mm. Of these (i) was unchanged bromo-ester and (iii) was almost pure keto-ester. Fractions (iv) and (v) were separately hydrolysed for 5 hours with 8% methyl alcoholic potassium hydroxide, and from each a very small quantity of solid was obtained which by several crystallisations from dilute alcohol, was obtained as needles, m. p. 191—192° (Found: C, 69·5; H, 4·0%). It did not give a precipitate with 2 : 4-dinitrophenylhydrazine and was recovered unchanged after boiling with acetic anhydride for 2 hours. Its investigation was therefore abandoned.

Experiments with Dihydro-ψ-santonin.—All attempts to reduce dihydro-ψ-santonin in presence of palladised charcoal were unsuccessful, but it can be reduced in presence of Adams's catalyst (cf. Clemo and Cocker, *loc. cit.*).

Bromination. Dihydro-ψ-santonin (0·2 g.) in water (10 c.c.) containing sodium carbonate (0·5 g.) was slowly treated, with stirring, with bromine water (0·12 c.c. of bromine in 15 c.c. of water). On the addition of the first drop of bromine water a white precipitate was formed, and this was ultimately collected. It was washed with 10% sodium carbonate, then with water, and dried. On crystallisation from dilute alcohol the *bromo-lactone* was deposited as colourless prisms, m. p. 180° (decomp.) (Found: C, 52·6; H, 6·15; Br, 22·6. $C_{15}H_{21}O_4Br$ requires C, 52·2; H, 6·1; Br, 23·2%). This compound was readily decomposed on boiling with water yielding a solution containing hydrobromic acid.

Reduction of the bromo-lactone. Bromo-lactone (0·3 g.) in alcohol (5 c.c.) was refluxed with zinc dust (1·0 g.) for 4 hours. The hot mixture was filtered and the filtrate was evaporated to dryness. An oily residue was left and this was rubbed with 10% hydrochloric acid to remove zinc; a solid was thus obtained which, after being washed, was recrystallised from dilute alcohol; it separated as needles (0·2 g.), m. p. 187—188° undepressed with authentic dihydro-ψ-santonin. This compound was again obtained when the bromo-lactone was heated on the water-bath with zinc dust and acetic acid for 3 hours.

One of us (S. H.) desires to thank the Council of King's College for a Post-Graduate Scholarship. We also desire to thank Messrs. T. and H. Smith for a gift of ψ-santonin.

King's College, University of Durham,
Newcastle-upon-Tyne.

[*Received, November* 18*th*, 1946.]