102. *The Constitution of ψ-Santonin. Part III. Some Synthetical Experiments.*

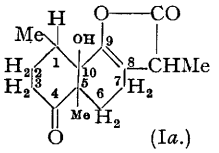
By Wesley Cocker and Cyril Lipman.

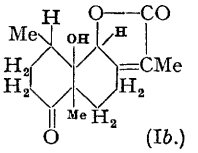
The synthesis of 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-α-*propionic acid* and its *lactone* is described. It is possible that the latter is identical with inactive desmotropo-ψ-santonin methyl ether. Attempts to obtain the inactive material from *d*-desmotropo-ψ-santonin have so far failed.

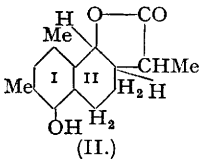
When ψ-santonin (I*a* or I*b*) is treated with 55% sulphuric acid or anhydrous formic acid it undergoes dehydration and rearrangement, and a dextrorotatory desmotropo-ψ-santonin is obtained (Clemo and Cocker, Part I, *J.*, 1946, 30). Desmotropo-ψ-santonin was given the empirical formula $C_{15}H_{18}O_3$, and it was believed that its structure was best represented by (II), the isomeric compound in which the lactone is fused at position 7 being less acceptable on biogenetic grounds [cf. the structure of *l*-santonin (Clemo, Haworth, and Walton, *J.*, 1929, 2368; 1930, 1110; Clemo and Haworth, *J.*, 1930, 2570)].

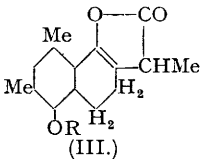
Evidence obtained since the publication of Part I of this series has led us to doubt the accuracy of the saturated structure (II) previously advanced for the desmotropo-compound. There is in fact some evidence which suggests that the butenolide structure (III; R = H) is a better representation of the compound. If this is correct its empirical formula is $C_{15}H_{16}O_3$.

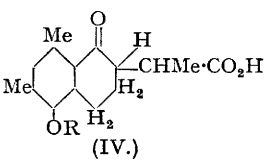
We have therefore synthesised a lactone of structure (III; R = Me) to compare with the material obtained from ψ-santonin itself with a view to proving the position at which the lactone ring in the latter is fused, and also whether desmotropo-ψ-santonin is unsaturated. We have also synthesised the *keto-acid* (IV; R = Me).


(I*a*.)


(I*b*.)


(II.)


(III.)


(IV.)

The evidence for and against the unsaturated character of the lactone ring is as follows. When desmotropo-ψ-santonin is methylated in alkaline solution and the mixture is acidified and heated for several minutes the dextrorotatory methyl ether described by Clemo and Cocker (*loc. cit.*) is obtained in good yield, and this compound is undoubtedly a lactone. However, if

the alkaline solution is carefully neutralised in the cold, another dextrorotatory methyl ether is obtained which dissolves with effervescence in sodium carbonate solution. Moreover, the former methyl ether can by converted, by alkaline hydrolysis and careful neutralisation, into the same acid. This acid may be a mixture of enantiomorphic forms but by crystallisation a highly crystalline acid is obtained which is stable at ordinary temperatures, but when heated above its melting point or refluxed with acetic anhydride rapidly loses water and yields the lactone previously described. Similarly desmotropo-ψ-santonin itself may be hydrolysed to an acid which is reconverted to desmotropo-ψ-santonin on heating above its melting point. The stability of these acids towards mineral acid and the fact that they can be lactonised only under energetic conditions appears to indicate that they are keto-acids.

On the other hand we have, so far, been unable to obtain ketone derivatives from the acids obtained from either desmotropo-ψ-santonin or its methyl ether, but this is not necessarily evidence that the keto-group is absent since we have also been unable to obtain evidence of carbonyl activity in the synthetic 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-α-*propionic acid* where the keto-group is " protected ". Similar experiences were encountered by Cagniant and Buu-Hoï (*Bull. Soc. chim.*, 1942, **9**, 841) who had the greatest difficulty in obtaining carbonyl activity in 1-keto-2-ethyl-7-*tert.*-butyl-1 : 2 : 3 : 4-tetrahydronaphthalene and found none in 1-keto-6-methoxy-5-methyl-2-ethyl-8-*iso*propyl-1 : 2 : 3 : 4-tetrahydronaphthalene. In fact it may be that the absence of carbonyl activity indicates the presence of the C=O group at 9 rather than at 7 in the acids under discussion, and hence for the fusion of the lactone ring at 9 rather than at 7.

Furthermore, we have been unable to oxidise either desmotropo-ψ-santonin or its methyl ether either with bromine and sodium hydroxide in presence of magnesium sulphate or with potassium permanganate, both of which methods have given good results in our hands when applied to the oxidation of the lactone of 2-hydroxy*cyclo*hexyl-α-*iso*butyric acid. By both methods 2-keto*cyclo*hexyl-α-*iso*butyric acid was obtained in good yields.* Alexander, Charlesworth, and McCrae (*Canadian J. Res.*, 1943, **21**, *B*, 1) also found these reagents successful in the oxidation of the lactone of 2-hydroxy*cyclo*hexylacetic acid.

If the above results are taken to mean that the lactones are unsaturated contrary evidence is provided by the fact that we have so far failed to reduce desmotropo-ψ-santonin either with sodium in alcohol (cf. Part I, p. 36) or with sodium amalgam in alcohol (cf. Clemo, Haworth, and Walton, *J.*, 1930, 1110).

All efforts to racemise desmotropo-ψ-santonin or its methyl ether or the acids derived from these compounds have failed, although they were subjected for long periods to the action of boiling pyridine, aqueous and alcoholic potash, and acetic anhydride. This failure to racemise is not difficult to explain if the lactones are saturated, but, if they are unsaturated, autoracemisation would be expected to take place, especially if they were of the αβ type since racemisation would then be immediate on hydrolysis to the corresponding keto-acid. Racemisation would, however, be more difficult if the lactones were of the βγ type, and this structure is not impossible in view of the possible conjugation of the butenolide double bond with the aromatic system.

We have, therefore, as yet been unable to obtain an inactive specimen of desmotropo-ψ-santonin or its methyl ether to compare with the synthetic lactone, although the properties of the synthetic and natural specimens are very similar. The problem of whether the lactone is or is not unsaturated must remain open for the time being.

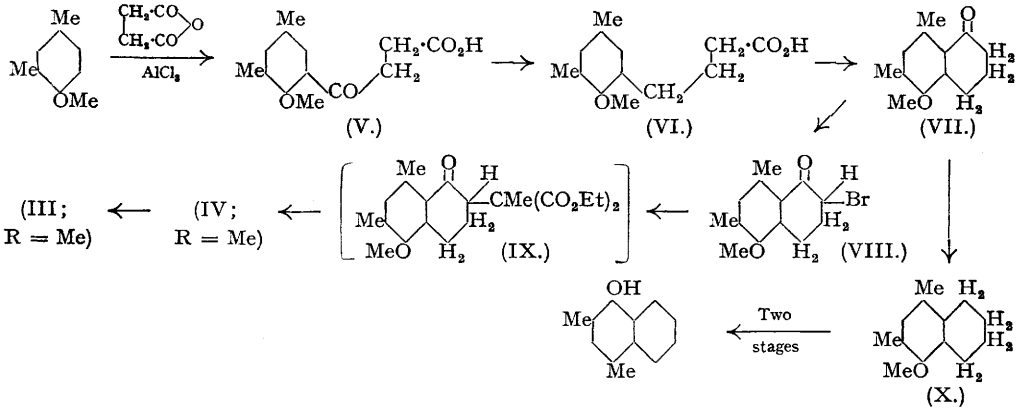
More work is in progress, but we feel that that already performed is of sufficient interest to warrant a report at this stage.

The keto-acid (IV; R = Me) and its lactone (III; R = Me) has been synthesised by three routes, each starting from *m*-4-xylenol. Only one route is of real preparative value.

Route A.—The xylyl methyl ether was condensed with succinic anhydride to give β-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*propionic acid* (V) which was reduced with amalgamated zinc to the corresponding butyric *acid* (VI). This was ring-closed with 80% sulphuric acid to 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII) which was brominated in ether to give 2-*bromo*-1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII). All these reactions proceeded satisfactorily, but the reaction of ethyl sodiomethylmalonate with (VIII) was very inefficient and most of the bromo-ketone was recovered unchanged. Only small quantities of the keto-acid (IV; R = Me) were obtained, but it was identical with the material produced by the alternative routes. The yield of (IV) was only slightly improved by the use of ethyl potassiomethylmalonate even when the reaction was performed in boiling

* Unpublished work to be communicated shortly in Part IV of this series.

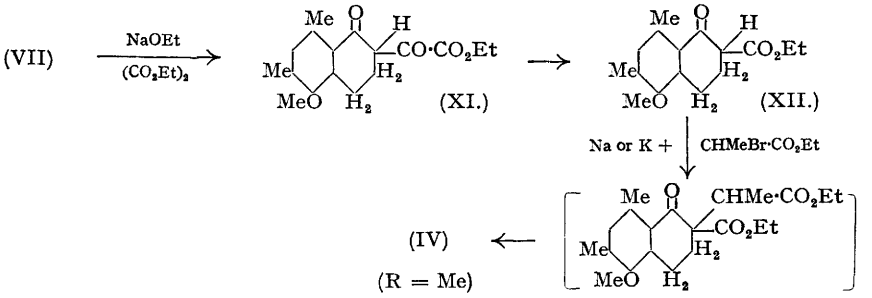
xylene. It appears that the bromine in (VIII) is only feebly reactive, a fact that was confirmed by its slow rate of hydrolysis with boiling alkali.



All attempts to isolate the malonic ester (IX) were unsuccessful. Even in the molecular still it apparently decomposed and it was therefore directly hydrolysed to (IV; R = Me) with alcoholic potash.

The orientation of the substituents in compounds (V) to (VII) was proved by the fact that (VII) was readily reduced by amalgamated zinc to 5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (X) which was dehydrogenated and demethylated to give 2 : 4-dimethyl-1-naphthol (Cornforth, Cornforth, and Robinson, *J.*, 1943, 168; Clemo and Cocker, *loc. cit.*).

Route B.—The tetralone (VII) was condensed with ethyl oxalate in presence of sodium ethoxide to give *ethyl* 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*glyoxylate* (XI) which was heated with powdered glass to give good yields of *ethyl* 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylate* (XII). The sodio-derivative, and later the potassio-derivative, was then condensed in boiling xylene with ethyl-α-bromopropionate (cf. B.P. 341,402 for a similar preparation of desmotropo-santonin). A large proportion of the starting materials was recovered unchanged, but small amounts of a thick red oil were isolated which on hydrolysis with alcoholic potash yielded traces of the required keto-acid (IV; R = Me).

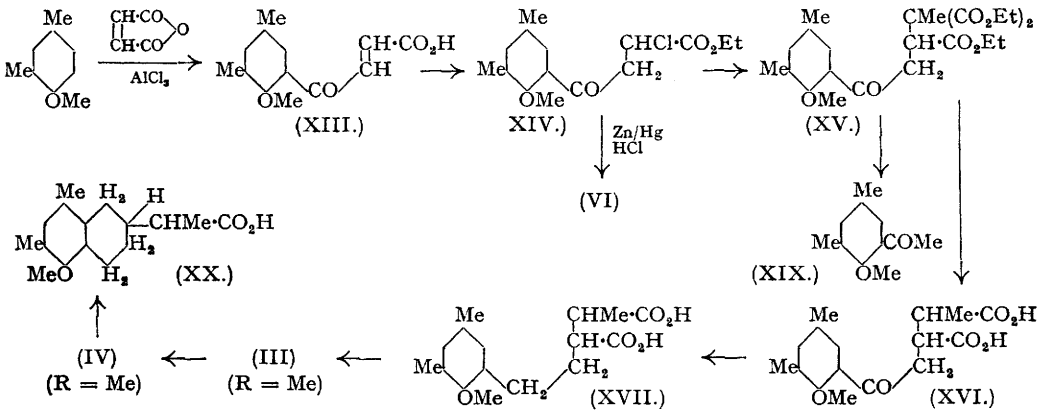


In view of the poor yields obtained in the conversion of (XII) into (IV) this route was abandoned.

Route C.—This was similar to the method used by Clemo, Haworth, and Walton (*J.*, **1929**, 2368) for the synthesis of desmotroposantonin. *m*-4-Xylyl methyl ether was condensed in ligroin with maleic anhydride to give β-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*acrylic acid* (XIII). This was condensed with hydrogen chloride in alcohol at 0° to give *ethyl* α-*chloro*-β-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*propionate* (XIV). The direction of addition of the hydrogen chloride must obviously be in the manner stated since the final stage of the synthesis yields a compound identical with that obtained from routes A and B (compare Clemo, Haworth, and Walton, *loc. cit.*). The chloro-ester was then condensed with ethyl sodiomethylmalonate to give *ethyl* α-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*butane*-βγ-*tricarboxylate* (XV). This was hydrolysed with alcoholic potash and gave α-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*butane*-βγ-*dicarboxylic acid* (XVI) as a mixture of racemates of which at least a partial separation was effected by crystallisation first from ligroin and then from water. During the alkaline hydrolysis a neutral compound

was produced which was shown to be identical with 2-*methoxy*-3 : 5-*dimethylacetophenone* (XIX) prepared directly from *m*-4-xylyl methyl ether and acetic anhydride. On reduction with amalgamated zinc the acid (XVI) was converted into α-(β-2-*methoxy*-3 : 5-*dimethylphenylethyl*)-α′-*methylsuccinic acid* (XVII) which was again a mixture of racemates. A partial separation of these was effected by trituration with benzene followed by crystallisation from dilute alcohol. The lactone (III) was finally obtained by treatment of the above acid (XVII) with sulphuric acid, and the keto-acid (IV) was obtained, by hydrolysis of the lactone, as a mixture of racemates which were separated only with difficulty.

A further link between routes C and A was established by the reduction of the chloro-ester (XIV) to the butyric acid (VI).



The keto-acid (IV; R = Me) was reduced by amalgamated zinc to a mixture of acidic substances (XX) which probably corresponded to a mixture of racemates of ψ-santonous acid methyl ether, but the yield was too small to effect a purification.

Experimental.

m-4-*Xylenol*.—(*a*) *m*-Xylene-4-sulphonyl chloride (Ullmann, *Ber.*, 1909, **42**, 2057; Pollak and Lustig, *Annalen*, 1923, **433**, 199) (50 g.) was refluxed for 6 hours with potassium hydroxide (50 g.) in methyl alcohol (150 c.c.). Methyl alcohol was removed, more potassium hydroxide (30 g.) was added, and the mixture was slowly raised to 280° at which it was maintained with stirring for 1 hour. The melt was poured into water, acidified, and steam distilled to yield the required xylenol which was further purified by distillation. It was collected (10 g.) at 208—211°.

(*b*) The following procedure for the preparation of 4-nitro-*m*-xylene was adopted in preference to the methods described in the literature.* *m*-Xylene (50 g.) was stirred with a mixture of concentrated sulphuric acid (55 c.c.) and water (25 c.c.) whilst nitric acid (3·6 c.c., *d* 1·42) was added at such a speed that the temperature was retained at 20°. The mixture was stirred for 1 hour longer, and poured into water, and the oil was separated, washed with sodium carbonate solution, dried, and distilled. Some unchanged *m*-xylene distilled first, and the desired compound (30 g.) was collected at 235—240°. Dinitroxylenes were not obtained.

4-Nitro-*m*-xylene (60 g.) in methyl alcohol (40 c.c.) containing Raney nickel (1 g.) was reduced at 100—110°/100 atm. to yield *m*-4-xylidine (43 g.), b. p. 214—216°. Its acetyl derivative had m. p. 125—126° (cf. Hofman, *Ber.*, 1876, **9**, 1295, who gives m. p. 127—128°). *m*-4-Xylidine (33 g.) in concentrated hydrochloric acid (99 c.c.) and water (99 c.c.) was added to finely powdered ice (500 g.) and the stirred mixture was kept at − 5° whilst a concentrated solution of sodium nitrite (24·5 g.) was added over ½ hour. Stirring was continued at − 5° for a further ½ hour and the solution was then added dropwise to a boiling solution of hydrated copper sulphate (11 g.) in 50% sulphuric acid (46 g.), the xylenol being removed by steam as it was produced. The aqueous distillate was extracted with ether yielding the xylenol (14 g.), b. p. 210—214°.

(*c*) A mixture containing approximately equal quantities of *p*-xylenol and *m*-4-xylenol which distilled at 205—215° was obtained from Messrs. R. Graesser, Ltd. Attempts to separate the xylenols through their sulphonic acids (cf. Brüchner, *Z. anal. Chem.*, 1928, **75**, 289) were not uniformly successful and were abandoned in favour of the following method. The mixture was cooled in ice and salt, and seeded with a crystal of *p*-xylenol, and after ½ hour the mass of crystals was collected at the pump on an ice-cold filter and thoroughly pressed. The filtrate, rich in *m*-4-xylenol, then had a setting point of 8·7° (pure *m*-4-xylenol melts at 25°), but it was considered to be sufficiently pure for further work. Bromination by the method of Francis and Hill (*J. Amer. Chem. Soc.*, 1942, **46**, 2503) gave an uptake of 1·16 atoms of bromine per mol. of xylenol, indicating the presence of 16% of *p*-xylenol.

1-*Keto*-5-*methoxy*-6 : 8-*dimethy* -1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-α-*propionic Acid and its Lactone*.—*Route A*. β-(2-*Methoxy*-3 : 5-*dimethylbenzoyl*)*propionic acid* (V). *m*-4-Xylenol (63 g.) was methylated

* We are indebted to Mr. S. Hornsby, B.Sc., for this preparation.

by methyl sulphate (140 g.) in excess of sodium hydroxide solution, and the methyl ether (45 g.) was collected at 188—191°.

A mixture of this ether (17·4 g.), succinic anhydride (13·0 g.) and dry benzene (50 c.c.) was stirred vigorously, and finely powdered aluminium chloride (18·0 g.) was added in small portions. In the early stages of the addition a gel was repeatedly produced. This was stirred until fluid before more aluminium chloride was added. The addition took 3 hours, after which the mixture was stirred overnight. It was then poured into a mixture of ice and excess of hydrochloric acid, and the white solid which separated was collected, washed with further amounts of dilute acid, then with water, dissolved in dilute sodium carbonate, and reprecipitated from the filtered solution. It finally crystallised from dilute acetic acid as long needles (7·4 g.), m. p. 129—130° (Found: C, 65·9; H, 6·6. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

γ-(2-Methoxy-3 : 5-dimethylphenyl)butyric acid (VI). A mixture of the above *keto-acid* (7·4 g.), water (37·5 c.c.), concentrated hydrochloric acid (50 c.c.), and amalgamated zinc (50 g.) was shaken at room temperature for 1 hour and then refluxed for 8 hours. More acid (25 c.c.) and amalgamated zinc (25 g.) were then added and the mixture was refluxed for a further 16 hours. On cooling, the required *acid* separated as a cake on the surface. It was collected, washed, dried, and crystallised from ligroin (b. p. 60—80°) as colourless needles, m. p. 92—93° (Found: C, 70·0; H, 7·9. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). In one experiment, using more concentrated hydrochloric acid, a compound, m. p. 116—117°, was also obtained. This was identical with *γ-(2-hydroxy-3 : 5-dimethylphenyl)butyric acid* obtained by heating the above methoxy-compound with hydriodic acid. This substance crystallised from benzene–ligroin as small needles, m. p. 116—117° (Found: C, 69·1; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

1-Keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (VII). The above methoxybutyric acid (4 g.) was heated on the water-bath for 2 hours with a mixture of concentrated sulphuric acid (16·4 c.c.) and water (8 c.c.). After being poured into water, the mixture was extracted with ether, and the ethereal solution was washed with sodium carbonate, dried, and fractionated. The required *ketone* (2·0 g.) was collected at 170°/3 mm. It solidified on standing and was crystallised from ligroin (b. p. 40—60°) as colourless plates, m. p. 61·5—62° (Found: C, 76·0; H, 7·45; OMe, 14·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8; OMe, 15·2%). Its *semicarbazone* crystallised from alcohol as needles, m. p. 192—193° (Found: C, 63·9; H, 7·2. $C_{14}H_{19}O_2N_3$ requires C, 64·4; H, 7·3%). Its *2 : 4-dinitrophenylhydrazone* crystallised from benzene–alcohol as scarlet needles with a violet reflex, m. p. 204° (Found: C, 59·5; H, 5·0. $C_{19}H_{20}O_5N_4$ requires C, 59·4; H, 5·2%). Its *2-piperonylidene* derivative prepared in alcoholic sodium hydroxide crystallised from dilute alcohol in canary yellow prisms, m. p. 132—133° (Found: C, 74·0; H, 5·7. $C_{21}H_{20}O_4$ requires C, 75·0; H, 5·9%).

5-Hydroxy-1-keto-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. The methoxytetralone (1 g.) was gently refluxed with hydriodic acid (15 c.c., *d* 1·7) for 2 hours and the mixture was poured into water, extracted with ether, and the extract washed with sodium hydrogen sulphite solution. From the ether a pale yellow solid was obtained which crystallised from ligroin (charcoal) as colourless needles, m. p. 145°, which on methylation gave the methyl ether (VII).

2-Bromo-1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (VIII). The tetralone (VII) was brominated (*a*) in carbon disulphide, (*b*) in acetic acid (cf. Bergs, *Ber.*, 1930, **63**, 1292), (*c*) in carbon tetrachloride, and (*d*) in ether (cf. Wilds, *J. Amer. Chem. Soc.*, 1942, **64**, 1424). Method (*d*) gave the best results and was performed as follows. The tetralone (2 g.) in anhydrous ether (20 c.c.) was cooled, stirred, and treated drop-wise with bromine (0·5 c.c.) at such a speed that the temperature was maintained at 10°, each drop of bromine being decolourised before the addition of the next. After a further 1 hour's stirring the solid which had separated was collected and washed with a little ether; the *bromo-ketone* crystallised from ligroin (b. p. 100—120°) as colourless needles (1·75 g.), m. p. 140—141° (Found: C, 54·5; H, 5·2. $C_{13}H_{15}O_2Br$ requires C, 55·1; H, 5·3%).

5-Methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (X). The tetralone (VII, 5 g.) was refluxed with amalgamated zinc (25 g.), concentrated hydrochloric acid (25 c.c.), and water (16 c.c.) for 8 hours, after which a further equal quantity of acid and amalgam was added and refluxing was continued for a further 16 hours. On cooling, the *tetralin* was extracted with ether, distilled, and collected at 128°/3 mm. It solidified on standing, giving long colourless needles (Found: C, 81·7; H, 9·4. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

2 : 4-Dimethyl-1-naphthol. The above compound (1·0 g.) was heated with selenium (0·7 g.) for 4 hours at 300—350° and then extracted with methyl alcohol from which a pale yellow oil (0·2 g.) b. p. 140/3 mm. was obtained. This was gently refluxed with hydriodic acid (2 c.c., *d* 1·7) for 90 minutes, and then poured into water. The required naphthol was extracted with ether which was washed with sodium hydrogen sulphite. On removal of the ether a solid, m. p. 79—84°, was obtained which crystallised from ligroin (b. p. 80—100°) as colourless needles, m. p. 84° (cf. Cornforth, Cornforth, and Robinson, *loc. cit.*). Its picrate crystallised from aqueous alcohol and had m. p. and mixed m. p. with authentic material 143—144°.

Condensation of the bromo-ketone (VIII) *with ethyl methylmalonate.* Ethyl methylmalonate (4·7 g.) was added slowly to a stirred suspension of powdered potassium in dry benzene (30 c.c.), and the mixture was heated and stirred until all potassium had dissolved. The bromo-ketone (5 g.) in benzene (20 c.c.) was slowly added, and the mixture was stirred and refluxed for 10 hours after which it was poured into water and the benzene layer was separated, washed with water, and dried. Benzene and excess of ethyl methylmalonate were removed under reduced pressure. Since the residue appeared to decompose even in a molecular still, it was refluxed for 3 hours with potassium hydroxide (4 g.) in methyl alcohol (70 c.c.) and water (10 c.c.). Methyl alcohol was then removed under reduced pressure and the residue was poured into water, filtered (charcoal), and acidified. The reddish oil which separated was extracted with ether and the required acid was extracted from the ethereal solution with dilute aqueous sodium carbonate. The alkaline extract was filtered and acidified; a red solid (0·7 g.), m. p. 95—98°, was thus obtained. It gave no depression of m. p. with the crude 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-α-propionic acid (IV; R = Me) prepared by Routes B and C described below.

Route B. Ethyl 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*glyoxylate* (XI). The tetralone (VII; 10·2 g.) was dissolved in freshly distilled ethyl oxalate (7·1 g.) and cooled to − 5°. Sodium ethoxide [from sodium (1·15 g.) and alcohol (20 c.c.)] was cooled to 0° and added slowly with stirring to the above mixture, the temperature being kept at − 5—0°. A violet solution was obtained which was kept in a slowly melting ice-bath and finally at room temperature for 24 hours. The solid product was then poured into ice-water and acidified to give an oil which rapidly solidified, and was collected, washed, and dried. It crystallised from alcohol as red-yellow needles (2·5 g.), m. p. 92—94°, and was then considered sufficiently pure for further work. A sample for analysis, recrystallised from alcohol, had m. p. 93—94° (Found : C, 66·9; H, 6·6. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

Ethyl 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylate* (XII). A mixture of the above *glyoxylate* (2·4 g.) and finely powdered glass (2·4 g.) was heated in an oil-bath at 190—195° for 2 hours. On cooling, the mixture was extracted with ether from which the required *compound* was obtained. It crystallised from ligroin (b. p. 60—80°) as silky needles (2 g.), m. p. 100—101°. In alcohol it gave a violet colouration with ferric chloride (Found : C, 69·0; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2%).

Condensation with ethyl α-bromopropionate. The carbethoxy-compound was recovered unchanged when its sodio-derivative was refluxed in alcohol with excess of ethyl α-bromopropionate for 24 hours. A little of the required propionic acid (IV; R = Me) was, however, obtained as follows. The carbethoxy-compound (1·4 g.) was slowly added with stirring to finely powdered potassium (0·21 g.) in xylene (20 c.c.) and the mixture was stirred and refluxed for 3½ hours. Ethyl α-bromopropionate (1·4 g.) in xylene (10 c.c.) was then added slowly, and stirring and refluxing were continued for 30 hours. The yellow solution was then poured into water, the xylene layer was separated and dried, and the solvent was removed under reduced pressure. The gummy residue, which still gave a faint enol reaction with ferric chloride, was hydrolysed for 2 hours with a mixture of potassium hydroxide (1 g.), methyl alcohol (15 c.c.), and water (5 c.c.). The mixture was concentrated under reduced pressure, diluted, and filtered (charcoal). On acidification with dilute acetic acid a gum was obtained which after being dissolved in sodium carbonate solution, filtered, and re-acidified, gave a semi-solid product which solidified on rubbing with ligroin. It then had m. p. 80—90° and behaved in a similar manner to the mixture of racemates obtained by routes A and C. After many crystallisations from dilute alcohol it had m. p. 138—140°.

Route C. β-(2-*Methoxy*-3 : 5-*dimethylbenzoyl*)*acrylic acid* (XIII). A mixture of *m*-4-xylyl methyl ether (23 g.), maleic anhydride (17 g.) and ligroin (b. p. 80—100°; 100 c.c.) was stirred and slowly treated with finely powdered aluminium chloride (23 g.). The deep red syrup was then agitated at room temperature overnight. It was poured into ice and hydrochloric acid, and the yellow solid was collected, washed with more acid, then with water, and dried; it then crystallised from dilute acetic acid as very pale yellow needles (3·5 g.), m. p. 144—145° (Found : C, 67·2; H, 6·2. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

Ethyl α-chloro-β-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*propionate* (XIV). A solution of the *acid* (XIII; 7 g.) in absolute alcohol (30 c.c.) was saturated at 0° with hydrogen chloride and then kept in a stoppered bottle for 12 hours. The deposited solid was collected, washed with a little absolute alcohol, and crystallised from ligroin (b. p. 80—100°), from which it separated as colourless prisms (6·0 g.), m. p. 88—89° (Found : C, 60·7; H, 6·6. $C_{15}H_{19}O_4Cl$ requires C, 60·3; H, 6·4%). This substance did not depress the m. p. (91—92°) of ethyl α-chloro-β-(4-methoxy-2 : 5-dimethylbenzoyl)propionate (Clemo, Haworth, and Walton, *J.*, 1929, 2383), but the identity of the new *ester* was verified by reduction with amalgamated zinc to γ-(2-methoxy-3 : 5-dimethylphenyl)butyric acid (VI), m. p. and mixed m. p. 92—93°.

Ethyl α-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*butane*-βγ-*tricarboxylate* (XV). Ethyl methylmalonate (2·5 g.) was slowly added to a stirred suspension of powdered sodium (0·4 g.) in benzene (35 c.c.), and the stirred mixture was refluxed for 1½ hours. Then the above chloro-compound (XIV; 4·1 g.) in benzene (10 c.c.) was slowly added in the cold, and the reaction was completed by refluxing for 3½ hours. Water was added to the mixture, the benzene layer was separated, and the aqueous layer was extracted twice with benzene. The combined extracts were dried and evaporated under reduced pressure, and the gummy residue was rubbed with ligroin (b. p. 40—60°), whereby it rapidly became crystalline (2·3 g., m. p. 93—95°). It crystallised from ligroin (b. p. 80—100°) as colourless prisms, m. p. 96—97° (Found : C, 63·6; H, 7·5. $C_{23}H_{32}O_8$ requires C, 63·3; H, 7·3%).

α-(2-*Methoxy*-3 : 5-*dimethylbenzoyl*)*butane*-βγ-*dicarboxylic acid* (XVI). A mixture of the above *ester* (XV; 1·5 g.), methyl alcohol (15 c.c.), and potassium hydroxide (3 g.) was refluxed for 2½ hours. The deep red solution was then diluted with water, and methyl alcohol was distilled off. On cooling, the precipitated solid (XIX; 0·25 g.) was collected and the filtrate acidified and extracted with ether. After being dried, the extract yielded an oil which slowly solidified (1·1 g.); m. p. 125—135°. This was undoubtedly a mixture of racemates. However, on trituration with a mixture of ether and ligroin it gave a solid which crystallised from water (charcoal) in colourless leaflets, m. p. 157—162° (Found : C, 61·8; H, 6·6. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%). The solid (XIX) obtained above was crystallised thrice from ligroin (b. p. 40—60°), and so obtained as colourless needles, m. p. 75—76° (Found : C, 74·4; H, 8·2. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). Its *semicarbazone* crystallised from dilute alcohol as prisms, m. p. 200° (Found : C, 61·4; H, 7·3. $C_{12}H_{17}O_2N_3$ requires C, 61·3; H, 7·2%). The ketone (XIX) proved to be identical with 2-*methoxy*-3 : 5-*dimethylacetophenone* prepared directly as follows. A mixture of *m*-4-xylyl methyl ether (4 g.), ligroin (12 c.c.), and acetic anhydride (4 g.) was slowly treated with powdered aluminium chloride (5 g.). The mixture was gently warmed and then kept at room temperature for 3 hours. It was then decomposed with ice and hydrochloric acid, and extracted with ether. The extract was dried and distilled, to yield a yellow oil, b. p. 145°/1 mm., which slowly solidified. The solid crystallised from a very small quantity of ligroin (b. p. 40—60°) as colourless needles, m. p. and mixed m. p. 74—75°.

α-(β-2-*Methoxy*-3 : 5-*dimethylphenylethyl*)-α′-*methylsuccinic acid* (XVII). The above *dicarboxylic acid* (XVI; 2·25 g.) was refluxed for 15 hours with a mixture of hydrochloric acid (50 c.c.) and amalgamated zinc (50 g.). The mixture was then cooled, diluted, and extracted with ether from which

a yellow oil was obtained. This solidified on standing, and was stirred with benzene; it then had m. p. 154—160°. Crystallisation from dilute alcohol yielded small prisms (0·3 g.), m. p. 170—172° (Found: C, 64·9; H, 7·4. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). The crude acid was undoubtedly a mixture of racemates.

Lactone of 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*α*-*propionic acid* (III; R = Me). The above succinic acid (XVII; 0·3 g.) was dissolved in concentrated sulphuric acid (5 c.c.) and heated for 3 minutes at 80°. After being cooled, the mixture was added to ice-water and the solid was collected, stirred with sodium bicarbonate solution, collected again, and crystallised from dilute alcohol; the *lactone* formed slender needles (0·2 g.), m. p. 159—160° (Found: C, 74·4; H, 6·9. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

0·20 G. of the lactone was boiled with 20 c.c. of 3N-sodium hydroxide until a clear solution was obtained (35 minutes). The solution was boiled with charcoal, cooled, filtered, and carefully acidified in the cold. A gum was obtained—a mixture of racemates—but this solidified overnight. It was extracted with sodium carbonate solution and filtered, and the filtrate was again acidified. The gummy material obtained was separated, desiccated, and rubbed with benzene–ligroin; a crystalline substance, m. p. 105—107°, was thereby obtained. After many recrystallisations a mixture, m. p. 134—138°, was obtained, but the yield was very small.

5-*Methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-*α*-*propionic acid* (XX).—The above keto-acid was reduced for 15 hours with amalgamated zinc and hydrochloric acid, and the mixture was extracted with ether. The oil obtained from the dried extract was stirred with ligroin (b. p. 40—60°). Colourless leaflets, m. p. 57—63°, were thereby obtained, but this mixture of racemates was insufficient for further purification.

Desmotropo-ψ-santonin Methyl Ether.—This was obtained by shaking desmotropo-ψ-santonin, in excess of hot sodium hydroxide solution, with methyl sulphate. The hot solution was filtered, immediately acidified with hot concentrated hydrochloric acid, and heated on the water-bath for a few minutes. The methyl ether was then obtained from dilute alcohol as silvery needles, m. p. 159—160° (cf. Clemo and Cocker, *loc. cit.*), $[\alpha]_D^{18°}$ + 61·3° (*c*, 2·092 in glacial acetic acid) (Found: C, 74·4; H, 7·5. Calc. for $C_{16}H_{18}O_3$: C, 74·4; H, 7·0%).

Hydrolysis of Desmotropo-ψ-santonin Methyl Ether.—The lactone (0·1 g.) was heated with 2N-sodium hydroxide (10 c.c.) until it dissolved. The mixture was filtered and acidified in the cold, and the solid which separated was extracted with cold 10% sodium carbonate from which the *keto-acid* was obtained by acidification in the cold. It was crystallised several times from dilute alcohol and obtained as colourless needles, m. p. 141—142°, $[\alpha]_D^{18°}$ + 108·5° (*c*, 1·518 in pyridine) (Found: C, 69·7; H, 7·8. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2. $C_{16}H_{22}O_4$ requires C, 69·0; H, 7·9%). Prolonged boiling of the pyridine solution did not measurably reduce the specific rotation. The acid forms a somewhat sparingly soluble sodium salt.

Re-lactonisation. The above acid was heated at 190—200° for 10 minutes, cooled, and extracted with cold dilute sodium carbonate in which most of the product was insoluble. The residue was crystallised from dilute alcohol; it then had m. p. 157·5—158°, not depressed on admixture with desmotropo-ψ-santonin methyl ether.

Hydrolysis of Desmotropo-ψ-santonin.—This substance (Clemo and Cocker, *loc. cit.*) was hydrolysed with 2N-sodium hydroxide and the product isolated in the same way as its methyl ether. The keto-acid crystallised from dilute alcohol as colourless needles, m. p. 229—230°. It was reconverted into desmotropo-ψ-santonin on heating at its m. p. for 10 minutes.

One of us (C. L.) thanks the Council of King's College for the award of a post-graduate Scholarship.

UNIVERSITY OF DURHAM,
KING'S COLLEGE, NEWCASTLE-UPON-TYNE, 1.

[*Received, July 23rd,* 1946.