## 248. *Experiments on the Synthesis of Santonin. Part I. The Preparation of the Lactone of α-(2-Hydroxy-3-ketocyclohexyl)propionic Acid.*

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The lactone of α-(2-hydroxy-3-keto*cyclo*hexyl)propionic acid, an intermediate required for the synthesis of santonin, has been prepared. It has not been possible to relate this lactone to any known compound but indirect evidence suggests that the crystalline product has, in fact, the structure stated.

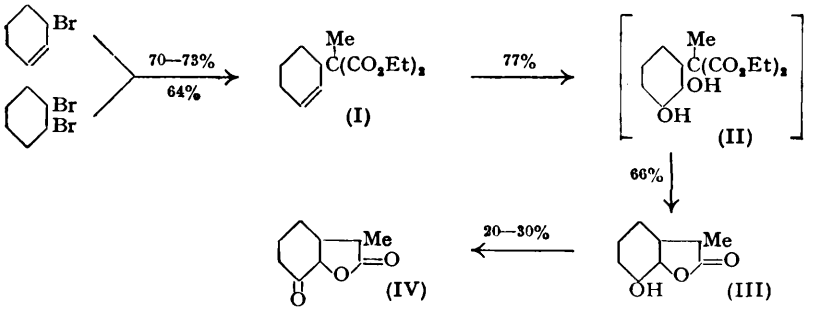
Mitchell and his co-workers (*J.*, 1939, 889; 1947, 686) suggested that *rac.*-parasantonide would be suitable for asymmetric photochemical work with wave-lengths around 3000 Å. It was concluded (Mitchell and Scott, unpublished work) that since racemisation of santonin, santonic acid, or parasantonide is impracticable, *rac.*-parasantonide could be best obtained from *rac*-santonin, the synthesis of which is the object of the present work. The structure of santonin is known from the work of Clemo *et al.* (*J.*, 1930, 1110, 2579).

The synthesis of santonin and related compounds claimed by Paranjape, Phalnikar, Bhide, and Nargund (*Rasayanam*, 1943, I, 233; *Chem. Abs.*, 1944, **38**, 4266; *Proc. Ind. Acad. Sci.*, 1944, A, **19**, 381; *Nature*, 1944, **153**, 141) has been much criticised for various reasons (Clemo, Cocker, and Hornsby, *J.*, 1946, 616; Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1715; Martin and Robinson, *J.*, 1949, 1867; Cornforth, Cornforth, and Dewar, *Nature*, 1944, **153**, 317; O'Gorman, *J. Amer. Chem. Soc.*, 1944, **66**, 1041; Woodward and Singh, *ibid.*, 1950, **72**, 494; Heggie, Thesis, Glasgow, 1951). So far as the authors are aware no reply has been made. Another report of a projected synthesis of santonin (Banerjea, *Science and Culture*, 1948, **13**, 347; *Chem. Abs.*, 1948, **42**, 5890) describes work which has not been completed.

The present attempt to synthesise santonin is being developed in three stages, *viz.*, (i) synthesis of the lactone (IV) of α-(2-hydroxy-3-keto*cyclo*hexyl)propionic acid, (ii) an investigation into methods of preparing the dienone system present in santonin, and (iii) an attempt to apply these methods to the appropriate methylated keto-lactone required to yield santonin. This paper is an account of the preparation of the keto-lactone (IV).

The claim by Paranjape *et al.* (*loc. cit.*) to have prepared (IV) in " fairly moderate yield " by condensation of 3-chloro*cyclo*hex-2-enone with ethyl methylmalonate and subsequent hydrolysis has been questioned by Clemo, Cocker, and Hornsby (*loc. cit.*) and by Carruthers and Mitchell (private communication), each of whom obtained 3-ethyl*cyclo*hex-2-enone in high yield by this procedure.

The preparation described in this paper is illustrated in the annexed scheme. Diethyl α-*cyclo*hex-2-enyl-α-methylmalonate (I) was obtained by condensation of 1 : 2-dibromo-




*cyclo*hexane with diethyl methylmalonate in presence of 2 mols. of sodium ethoxide (Mousseron and Winternitz, *Bull. Soc. chim.*, 1946, **13**, 604), or from 3-bromo*cyclo*hexene (Ziegler, Späth, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 109) in a similar condensation using 1 mol. of sodium ethoxide. The former method was preferred, despite the lower yield, because the dibromide was more readily available. The two products gave the same substituted malonic acid [m. p. 158° (decomp.)] on hydrolysis. Mousseron and Winternitz (*loc. cit.*) however give 137° as the melting point of this compound, and Kon and Speight

(*J.*, 1926, 2727) have described α-*cyclo*hex-1-enyl-α-methylmalonic acid (m. p. 155°) which they prepared by condensation of *cyclo*hexanone with malonic ester with subsequent methylation and hydrolysis. The condensation used by Mousseron and Winternitz and by us has been utilised by many authors for the preparation of substituted malonic esters containing the *cyclo*hex-2-enyl or other similar cyclic group (Eikmann, *Chem. Centr.*, 1909, II, 2146; Miescher and Hoffmann, *Helv. Chim. Acta*, 1941, **24**, 458; Buu-Hoï and Cagniant, *Bull. Soc. chim.*, 1942, **9**, 99; Moffett, Hart, and Hoehn, *J. Amer. Chem. Soc.*, 1947, **69**, 1849, 1854; Fieser *et al.*, *ibid.*, 1948, **70**, 3195). We have repeated the experiments of Kon and Speight (*loc. cit.*) and have shown that the product so obtained differs from ours by comparison of the barbiturates, the substituted malonic acids, and the amides of the corresponding monobasic acids. We therefore conclude that the figures given by Mousseron and Winternitz are in error.

Performic acid (Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786; English and Gregory, *ibid.*, 1947, **69**, 2120) was the most convenient reagent for oxidation of the unsaturated ester to the glycol (II) (or a partly formylated derivative). This product was not purified but immediately hydrolysed and decarboxylated to the hydroxy-lactone (III) which was satisfactorily oxidised by chromium trioxide in acetic acid solution to the desired keto-lactone (IV). All yields are fairly good except for the final oxidation. The product was an oil, purified by distillation, and obtained in reasonable yield (65—75%), but proved to be a mixture from which (IV) was obtained as a crystalline solid (20—30%) leaving a liquid residue which has not been identified. Attempts have been made at each stage to determine optimum reaction conditions.

Our keto-lactone (IV) was a stable, colourless, crystalline, sharp-melting solid which could be distilled *in vacuo* (the Indian workers report a thick syrup decomposing during distillation under reduced pressure). Analysis indicated the formula $C_9H_{12}O_3$, the presence of a carbonyl function is shown by the ready formation of a mono-2 : 4-dinitrophenylhydrazone and monosemicarbazone (the latter differing in m. p. from that described by Paranjape *et al.*), and a lactone group is indicated by the behaviour with alkali. Values for the equivalent were consistently low, possibly owing to the formation of an acidic enediol (cf. ascorbic acid). The hydroxy-lactone (III) which cannot behave in this way gave satisfactory results. The spectrum of (IV) indicated the absence of any conjugated chromopheres.

Attempts to reduce (IV) to the known lactone of α-2-hydroxy*cyclo*hexylpropionic acid (which may be oxidised to the solid α-2-keto*cyclo*hexylpropionic acid) or to decarboxylate (IV) to 3-ethyl*cyclo*hex-2-enone were unsuccessful.

The method of synthesis is such that the only structural question remaining about (IV) is whether it is the γ- or the δ-lactone. The keto-group in the γ-lactone has one adjacent methylene group whilst in the δ-lactone it is flanked by two bridgehead positions. Although it has not been possible to prepare a benzylidene derivative in virtue of the reactive methylene group the presence of such a group has been indicated. The keto-lactone reacted readily with *N*-bromosuccinimide, or with bromine in acetic acid, to form a bromo-compound which was easily dehydrobrominated. The product has not been adequately characterised but was probably phenolic. Such a compound could result by bromination, dehydrobromination, lacto-enoic tautomerism, and dienone-phenol rearrangement, the last two reactions being catalysed by hydrogen bromide. Neither bromination nor subsequent dehydrobromination would occur very readily with the δ-lactone since this would involve bromination of tertiary hydrogen atoms and then the formation of double bonds at bridgehead positions in a bicyclic structure, the latter contrary to Bredt's rule (cf. Fawcett, *Chem. Reviews*, 1950, **47**, 219). (IV) was readily converted into a crystalline enol-acetate when heated with acetic anhydride and toluene-*p*-sulphonic acid (Bedoukian, *J. Amer. Chem. Soc.*, 1945, **67**, 1430). The γ-lactone should readily form an enol-acetate but the δ-lactone could only yield such a compound as an exception to Bredt's rule. It could be argued that under the acid conditions of this reaction the δ-lactone would undergo lacto-enoic tautomerism and then yield an enol-acetate [α-(2-acetoxy*cyclo*hexa-1 : 3-dienyl)propionic acid]. Such a compound would have the characteristic absorption of a conjugated diene shown to be absent from the compound actually obtained.

Thus, whilst it has not been possible to relate the keto-lactone to any known compound, indirect evidence suggests that it has the structure (IV).

## Experimental

M. p.s are uncorrected. Absorption spectra were determined with a Unicam quartz spectrophotometer, ethanol being used as solvent.

*Diethyl Methylmalonate.*—Diethyl methylmalonate was prepared from malonic ester and methyl iodide. Unchanged malonic ester was removed by shaking the product for exactly one minute with (30%) sodium hydroxide solution.

*Condensation of* 3-*Bromo*cyclo*hexene with Diethyl Methylmalonate.*—3-Bromo*cyclo*hexene (Ziegler *et al.*, *loc. cit.*) was added to diethyl sodiomethylmalonate prepared from diethyl methylmalonate (44 g.) and sodium (6·5 g.) in ethanol (120 ml.). A fairly vigorous reaction ensued. After refluxing (30—60 minutes), alcohol was removed, water added, and the product extracted with ether. Diethyl *cyclo*hex-2-enylmethylmalonate (52 g., 73%) (I), b. p. 144—150°/12 mm., was obtained.

*Condensation of* 1 : 2-*Dibromo*cyclo*hexane with Diethyl Methylmalonate.*—1 : 2-Dibromo*cyclo*hexane (242 g.) (*Org. Synth.*, Coll. Vol. 1, 2nd Edn. p. 171) was added dropwise to diethyl methylmalonate (174 g.) in sodium ethoxide solution (from 48 g. of sodium and 800 ml. of ethanol) and the whole refluxed for 12 hours. This gave diethyl *cyclo*hex-2-enylmethylmalonate (163 g., 64%), b. p. 156—160°/16 mm., $n_D^{17}$ 1·4670. (Lower yields were obtained after shorter or longer reflux periods.)

cyclo*Hex*-2-*enylmethylmalonic Acid.*—The ester (I) was hydrolysed (4N-ethanolic potassium hydroxide for 6 hours) to *cyclo*hex-2-enylmethylmalonic acid, obtained as a white microcrystalline solid (from benzene), m. p. 158° (decomp.) (lit., 137°) (Found : C, 60·8; H, 7·3. Calc. for $C_{10}H_{14}O_4$ : C, 60·6; H, 7·1%).

α-cyclo*Hex*-2-*enylpropionamide.*—The above malonic acid, heated at 165—170° for 30 minutes, gave α-*cyclo*hex-2-enylpropionic acid (91%), b. p. 140—147°/10 mm., $n_D^{18\cdot5}$ 1·4831. Treated with thionyl chloride and subsequently with ammonia this yielded α-*cyclo*hex-2-enylpropionamide, m. p. 129—134° (softens at 116°) (probably a mixture of racemates; Mousseron and Winternitz, *loc. cit.*, give m. p. 112—113°).

5-cyclo*Hex*-2-*enyl*-5-*methylbarbituric Acid.*—Urea (1·5 g.) in ethanol (12·5 ml.) was added to diethyl *cyclo*hex-2-enylmethylmalonate (6·4 g.) and sodium ethoxide solution [from sodium (0·58 g.) in ethanol (12·5 ml.)], the mixture was refluxed (7 hours), and hot water and concentrated hydrochloric acid were added. 5-cyclo*Hex*-2-*enyl*-5-*methylbarbituric acid* separated on cooling. Crystallised from ethanol, white needles, m. p. 208°, were obtained (Found : C, 59·8; H, 6·2; N, 12·6. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%).

cyclo*Hex*-1-*enylmethylmalonic Acid.*—Diethyl *cyclo*hex-1-enylmalonate was prepared and subsequently methylated to give diethyl *cyclo*hex-1-enylmethylmalonate and then hydrolysed, yielding *cyclo*hex-1-enylmethylmalonic acid according to the procedure of Kon and Speight (*loc. cit.*). The disubstituted malonic acid melted at 150—152° (decomp.) (lit., 155°) but this fell to 137—142° (decomp.) when the sample was mixed with the $\Delta^2$-isomer obtained above. Decarboxylation was effected at 170° (15 minutes) and the residue converted into α-*cyclo*hex-1-enylpropionamide, m. p. 89—90° (Kandiah and Linstead, *J.*, 1929, 2139, cite 90°).

5-cyclo*Hex*-1-*enyl*-5-*methylbarbituric Acid.*—This acid was prepared from diethyl *cyclo*hex-1-enylmethylmalonate (1 g.) by the method described above, and crystallised from hot water as white needles, m. p. 190—194° (Found : C, 59·4; H, 6·0; N, 12·7. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%).

γ-*Lactone* (III) *of* α-(2 : 3-*Dihydroxy*cyclo*hexyl*)*propionic Acid.*—The diester (I) (63·5 g.), added to a mixture of 98—100% formic acid (265 g.) and 30% hydrogen peroxide (32·5 g.), was kept at 40—45° for 16 hours. (Similar yields were obtained at 40—45° for 4—24 hours and at 65—70° for 1—4 hours, but the longer heating was conveniently effected overnight.) Formic acid and unchanged diester (I) were removed by steam-distillation, leaving the partly formylated glycol [55 g., 77% (calc. as glycol)] (Found : equiv., 123·0. Calc. for free glycol : equiv., 144·2. Calc. for monoformyl derivative : equiv., 105·4), which was hydrolysed by 3N-methanolic potassium hydroxide (300 ml.) for 5 hours. Methyl alcohol was removed, and the residue mixed with hydrochloric acid and then evaporated to dryness. The resulting sticky solid, admixed with anhydrous sodium sulphate, was extracted with acetone in a Soxhlet extractor and distilled *in vacuo*, the γ-lactone (III) of α-(2 : 3-dihydroxy*cyclo*hexyl)propionic acid distilling at 154—156°/1 mm. (22 g., 66%) (Found : equiv., 173·2. Calc. for $C_{10}H_{14}O_3$ : equiv., 172). This lactone solidified after several days at 0° but melted at room temperature ;

attempts to crystallise it failed. Reaction with 3 : 5-dinitrobenzoyl chloride gave the 3 : 5-*dinitrobenzoate* as colourless platelets, m. p. 184—185°, after crystallisation from methanol (Found : C, 53·1; H, 4·5; N, 7·8. $C_{16}H_{16}O_8N_2$ requires C, 52·7; H, 4·4; N, 7·7%).

*Lactone* (IV) *of* α-(2-*Hydroxy*-3-*keto*cyclo*hexyl*)*propionic Acid.*—Attempts to oxidise the hydroxy-lactone (III) by the Oppenauer procedure were unsuccessful and the reaction was effected by chromium trioxide in acetic acid.

The hydroxy-lactone (21 g.) in acetic acid (85 ml.) was slowly stirred into a solution of chromium trioxide (9 g.) in water (9 ml.), diluted with acetic acid (85 ml.), at 10—15°. After 10 days at room temperature the reaction mixture was diluted (water) and continuously extracted (ether; 36 hours). The oily residue obtained on removal of the solvent was distilled. The distillate (b. p. 144—158°/1 mm.), dissolved in ether, slowly deposited crystals (m. p. 80—82°) at 0°. The yield of solid was 4·3—5·0 g. (20—24%) and of liquid 8·5—8·9 g. In some experiments, using 15% excess of chromium trioxide, these values were 6·5 g. (30%) and 7·5—8·0 g., respectively.

The liquid product (equiv., 145·5) gave a mixture of 2 : 4-dinitrophenylhydrazones from which no pure compounds were isolated.

The crystalline *lactone*, m. p. 86—87°, colourless prisms from ether or ethanol (Found : C, 64·3; H, 7·1%; equiv., 149—158. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%; equiv., 168·2), gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 168—170°, yellow plates from acetic acid (Found : N, 15·9. $C_{15}H_{16}O_6N_4$ requires N, 16·1%), and a *semicarbazone*, m. p. 195—197° (decomp.) (Paranjape *et al.*, give m. p. 150°), colourless prisms from ethanol (Found : C, 53·6; H, 6·5; N, 18·4. $C_{10}H_{15}O_3N_3$ requires C, 53·3; H, 6·7; N, 18·7%). In the early stages of this work before the keto-lactone was crystallised, carbonyl derivatives were obtained from the liquid distillate. These differed in m. p. from those already described : 2 : 4-*dinitrophenylhydrazone*, m. p. 206—210° (Found : C, 51·4; H, 4·6; N, 16·2. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·6; N, 16·1%); *semicarbazone*, m. p. 202—203° (Found : C, 53·4; H, 6·6; N, 18·6%).

The thioacetal prepared from the keto-lactone (Wolfram and Karabinos, *J. Amer. Chem. Soc.*, 1944, **66**, 909) was refluxed with Raney nickel in ethanol but only traces of material could be obtained from the alcohol solution or from the nickel by extraction with acetone.

Reduction of the keto-lactone (2 g.) by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1946, **68**, 2457) gave a liquid (0·43 g.), b. p. 135—145°/8 mm. (bath-temp.), $n_D^{20}$ 1·4760. This on oxidation (potassium permanganate) afforded an oil (0·27 g.) which could not be induced to crystallise.

Reduced by the Clemmensen procedure, the keto-lactone (2 g.) gave a liquid (0·47 g.), b. p. 140—150°/8 mm. (bath-temp.), which was oxidised (potassium permanganate) to a solid (0·21 g.) which could be purified only by repeated precipitation with acid from an alkaline solution, and then had m. p. 59—60° (Found : C, 68·3; H, 10·1. Calc. for $C_{17}H_{30}O_4$ : C, 68·4; H, 10·6%); it has not been possible to suggest any structure for this substance.

Heated with aqueous hydrobromic–acetic acid (cf. Johnson, Peterson, and Schneider, *J. Amer. Chem. Soc.*, 1947, **69**, 74), the keto-lactone (1 g.) gave a crude solid (0·61 g.), of m. p. 105—125°, raised by extraction with light petroleum (b. p. 80—100°) and crystallisation of the extract from benzene–light petroleum (b. p. 80—100°) to m. p. 128—130° (Found : C, 65·9; H, 5·3%), which could not be identified.

When treated with ethanolic sulphuric acid according to the directions of Clemo, Cocker, and Hornsby (*loc. cit.*), the keto-lactone (1 g.) gave unchanged starting material (0·25 g.) and a liquid (0·037 g.), b. p. 140—155°/15 mm. (bath-temp.), which gave a small quantity of a yellow 2 : 4-dinitrophenylhydrazone accompanied by a dark red oil.

Unsuccessful attempts were made to prepare a benzylidene derivative by interaction of the keto-lactone with benzaldehyde in the presence of (*a*) 5N-sodium hydroxide, (*b*) sodium in toluene, and (*c*) piperidine acetate. The last reagent led to 2 : 6-dibenzylidene*cyclo*hexanone (33%) when refluxed for 24 hours with the required components.

*Bromination of the Keto-lactone* (IV).—(a) *Action of* N-*bromosuccinimide.* *N*-Bromosuccinimide (1·25 g.), heated under reflux with a solution of keto-lactone (1 g.) in carbon tetrachloride, produced, after a short induction period, a vigorous reaction with copious evolution of hydrogen bromide and separation of a brown oil. No succinimide crystallised on cooling. The solvent was removed by distillation under reduced pressure and the residue refluxed with pyridine (10 ml.) for 70 minutes. The solution, extracted with chloroform and washed with 6N-hydrochloric acid, afforded, on distillation, a liquid (0·61 g.), b. p. 120—140°/0·15 mm. (bath-temp.). This gave almost no 2 : 4-dinitrophenylhydrazone, was soluble in sodium hydroxide solution (blood-red colour) and sodium hydrogen carbonate solution (yellow colour), gave an indefinite

azo-dye test with aniline, and a dark brown precipitate with ferric chloride. The absorption spectrum of this liquid showed a maximum at 278 mμ (log ε 3·25) and a minimum at 253 mμ (log ε 3·10), probably due to a phenol (cf. Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 990), and an inflexion at 220 mμ (log ε 3·60), probably due to a trace of unsaturated ketone.

(b) *Bromine in acetic acid.* Bromination with bromine in acetic acid at room temperature and subsequent dehydrobromination with collidine afforded an oil (0·55 g.) similar in properties to that obtained above.

*Enol-acetate of the Keto-lactone* (IV).—Toluene-*p*-sulphonic acid (0·5 g.), the keto-lactone (1 g.), and acetic anhydride (50 ml.) were refluxed for 1·5 hours. Acetic acid was removed by slow distillation through a short column for a further 2 hours, most of the acetic anhydride was then distilled off, and the remainder hydrolysed by shaking it with water (10 ml.). The product, extracted with chloroform, decolorised with charcoal, and further purified by dissolution in light petroleum (b. p. 80—100°) and removal of a small insoluble portion, was finally crystallised from light petroleum (b. p. 80—100°), giving the α-(3-*acetoxy*-2-*hydroxy*cyclo*hex*-3-*enyl*)*propionic lactone* (0·79 g., 63%), m. p. 124—126° (Found: C, 62·8; H, 6·3. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%).

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