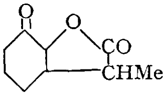
127. *The Constitution of Santonin. Part IV.*

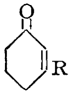
By G. R. Clemo, Wesley Cocker, and Stanley Hornsby.

All attempts to prepare the lactone of 2-hydroxy-3-keto*cyclo*hexyl-α-propionic acid (I) by the method of Paranjape, Phalnikar, Bhide, and Nargund (*Current Science*, 1943, **12**, 150; *Rasayanam*, 1943, **1**, 233) from 3-chloro-Δ^2-*cyclo*hexen-1-one and ethyl sodiomethylmalonate followed by cyclisation of the ester with sulphuric acid were unsuccessful; 3-ethyl-Δ^2-*cyclo*hexen-1-one (IV) was invariably obtained.

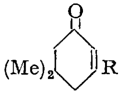
In view of the work done in these laboratories since 1929 on santonin and related sesquiterpenes we were interested in the asymmetric synthesis of *l*-santonin claimed by Paranjape, Phalnikar, Bhide, and Nargund (*Nature*, 1944, **153**, 141). Fuller details of the synthesis were given later and lactone (I) was stated to be obtained at an early stage of the synthesis. Unfortunately we have been unable to consult the second paper referred to in the summary above, but the abstract (*Chem. Abs.*, 1944, **38**, 4266) gives sufficient information to enable a repetition of the work to be attempted.



(I.)



[II., R = $CMe(CO_2Et)_2$.
III., R = $CHMe\cdot CO_2Et$.
IV., R = Et.]



[V., R = $CH_2\cdot CO_2Et$. VI., R = $CH(CO_2Et)_2$.
VII., R = $CHMe\cdot CO_2Et$. VIII., R = $CMe(CO_2Et)_2$.
IX, R = Et.]

In the method described by the Indian workers 3-chloro-Δ^2-*cyclo*hexen-1-one (Crossley and Haas, *J.*, **1903**, **83**, 498) was condensed in benzene with ethyl sodiomethylmalonate to give ethyl Δ^2-*cyclo*hexen-1-one-3-methylmalonate (II) and this, on treatment with 6N-sulphuric acid in 50% aqueous alcohol, was stated to cyclise to the lactone (I).

Several attempts by the present authors to repeat this work have failed to yield (I) and in every case an almost quantitative yield of 3-ethyl-Δ^2-*cyclo*hexen-1-one (IV) was obtained.

A similar result was reported by Crossley and Gilling (*J.*, 1909, **95**, 24), who obtained *iso*phorone by the hydrolysis of ethyl 5 : 5-dimethyl-Δ^2-*cyclo*hexen-1-one-3-acetate (V) with alcoholic potash, and 5 : 5-dimethyl-3-ethyl-Δ^2-*cyclo*hexen-1-one (IX) from ethyl 5 : 5-dimethyl-Δ^2-*cyclo*hexen-1-one-3-α-propionate (VII) under similar conditions.

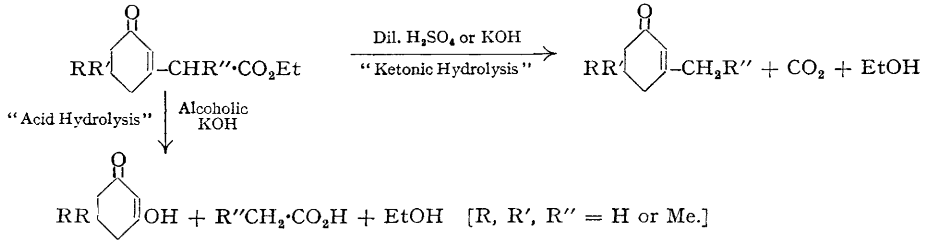
We have repeated and confirmed this work and similar results were obtained by hydrolysis of compounds (V) and (VII) with 6N-aqueous-alcoholic sulphuric acid. In addition, compounds (III), (VI), and (VIII) respectively gave 3-ethyl-Δ^2-*cyclo*hexen-1-one, *iso*phorone, and 5 : 5-dimethyl-3-ethyl-Δ^2-*cyclo*hexen-1-one on treatment with either acid or alkali.

Decarboxylation in varying degree took place during the attempted cyclisation of all these esters with ice-cold 60%, 80%, or concentrated sulphuric acid, a proportion of the starting material being recovered. There was no evidence of the formation of any lactone.

Attempts made to prepare the acids corresponding to the esters (III), (V), and (VII) by hydrolysis with cold 6% alcoholic potash were unsuccessful. In every instance decarboxylation to a greater or less extent was experienced and we must conclude that even the potassium salts of the required acids are extremely labile. When, however, these esters are refluxed with 10% alcoholic potash small amounts of dihydroresorcinol and dimedon are respectively isolated in addition to the ketones already mentioned.

Compounds (II), (VI), and (VIII) were never obtained pure. On condensation of 3-chloro-Δ^2-*cyclo*hexen-1-one or 3-chloro-5 : 5-dimethyl-Δ^2-*cyclo*hexen-1-one with ethyl sodiomalonate or ethyl sodiomethylmalonate in dry benzene partial decarboxylation always appeared to take place and difficultly separable mixtures of compounds (II) and (III), (V) and (VI), and (VII) and (VIII) were obtained. If the condensations were carried out in alcohol the principal products were compounds (III), (V), and (VII), since under these circumstances alcoholysis took place with the formation of ethyl carbonate (compare Crossley and Gilling, *Proc.*, 1908, **24**, 130; 1909, **25**, 96).

The total decarboxylation of all these esters on hydrolysis is not surprising since in every case there is a system similar to that of a β-keto-ester, for the double bond α : β to the keto group is virtually a second carbonyl group, and hence, on hydrolysis with acid or dilute alkali, " ketonic hydrolysis " takes place. In addition, however, some " acid hydrolysis " also takes place under alkaline conditions, thus completing the analogy with the β-keto-esters.



EXPERIMENTAL.

Ethyl Δ^2-cyclo*Hexen*-1-*one*-3-*methylmalonate* (II).—As no details of the preparation of this compound are given in the abstract its preparation is described. Ethyl methylmalonate (5·3 g.) was added drop by drop to a stirred suspension of sodium (0·7 g.) in boiling benzene (50 c.c.) and the mixture was refluxed until no metallic sodium remained. Then 3-chloro-Δ^2-*cyclo*hexene-1-one (4·0 g.) was slowly added, and stirring and boiling continued for 5 hours. The benzene was distilled off, and the residue acidified with cold dilute acetic acid and extracted thrice with ether. The dried extract was distilled and collected at 184—190°/2 mm. On redistillation it had b. p. 174°/2 mm. (1·4 g.) (Found: C, 64·0; H, 7·5. Calc. for $C_{14}H_{20}O_5$: C, 62·7; H, 7·5%).

3-*Ethyl*-Δ^2-cyclo*hexen*-1-*one*.—The above compound was heated for 6 hours with 6N-sulphuric acid in 50% aqueous alcohol (14 c.c.), the alcohol was removed in a vacuum, and the residue was poured into water and extracted with ether. The extract after drying was distilled, giving 0·55 g. (84% of theory), b. p. 73—75°/1—2 mm. (Blaise and Maire, *Bull. Soc. chim.*, 1908, **4**, 419, give b. p. 83°/8 mm.) (Found : C, 76·8; H, 9·6. Calc. for $C_8H_{12}O$: C, 77·4; H, 9·7%). The *semicarbazone* prepared in the usual way crystallised from aqueous alcohol as plates, m. p. 191—192°; this is possibly a stereoisomeric form of that described by Blaise and Maire (*loc. cit.*) who give m. p. 240° (Found : C, 59·8; H, 8·2. $C_9H_{15}ON_3$ requires C, 59·7; H, 8·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as scarlet needles, m. p. 133—134° (Found : C, 55·5; H, 5·5. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·3%).

Ethyl 5 : 5-*Dimethyl*-Δ^2-cyclo*hexen*-1-*one*-3-*malonate* (VI).—3-Chloro-5 : 5-dimethyl-Δ^2-*cyclo*hexene-1-one (5 g., Crossley and Le Sueur, *J.*, 1903, **83**, 117) was added to a stirred suspension of ethyl sodiomalonate (from ethyl malonate (5·1 g.) and sodium (0·73 g.)), in benzene (25 c.c.), and the mixture was refluxed overnight. The reaction mixture was treated as described above and a colourless oil (3·5 g., b. p. 168—170°/3 mm.) was isolated.

iso*Phorone*.—The above ester (1·7 g.) was refluxed for 6 hours with 30% aqueous-alcoholic sulphuric acid (17 g.). *iso*Phorone (0·8 g., 95% of theory), b. p. 78°/3 mm., was obtained. Its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in scarlet plates, m. p. 129—130° (Found : C, 56·5; H, 5·2. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·6%).

Ethyl 5 : 5-*Dimethyl*-Δ^2-cyclo*hexen*-1-*one*-3-*methylmalonate* (VIII).—This was obtained as a colourless oil, b. p. 170°/4 mm. (Found : C, 65·9; H, 8·4. $C_{16}H_{24}O_5$ requires C, 64·9; H, 8·1%), by a method similar to those described above. On hydrolysis with 6N-sulphuric acid in 50% alcohol it gave 5 : 5-dimethyl-3-ethyl-Δ^2-*cyclo*hexen-1-one, b. p. 105—106°/5 mm., in almost quantitative yield. It gave a semicarbazone, m. p. 197°, identical with that obtained by Crossley and Gilling (*loc. cit.*).

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