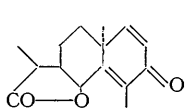
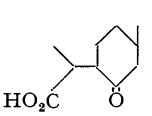
734. *Synthesis in the Santonin Series. Part I. Some Oxidation Products of α-(2-Keto-4-methylcyclohexyl)propionic Acid.*

By G. R. Clemo and F. J. McQuillin.

Oxidation of α-(2-keto-4-methyl*cyclo*hexyl)propionic acid (II) by selenium dioxide yields a lactone (IV) having the same chemical properties as the autoxidation product of menthofuran (V) (cf. Treibs, *Ber.* 1937, **70**, 1021; Woodward and Eastman, *J. Amer. Chem. Soc.*, 1950, **72**, 399). Oxidation of α-(3-carboxy-2-keto-4-methyl*cyclo*hexyl)propionic acid (VII; R = H) by nitrous acid and subsequent hydrolysis involve aromatisation, to give the catechol lactone (X); aromatisation is prevented by hydrolysis in the presence of formaldehyde leading to the diketo-acid (IX).

In experiments directed towards the synthesis of santonin (I) and related compounds, the oxidation of α-(2-keto-4-methyl*cyclo*hexyl)propionic acid (II) has been examined with the aim of introducing a hydroxy- or keto-group at position 3.


(I)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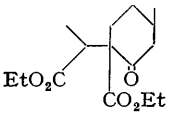
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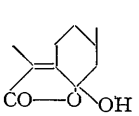
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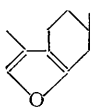
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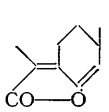

(VI)

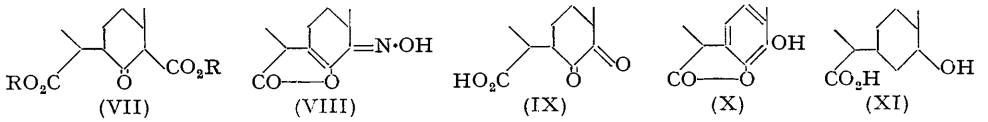
α-(2-Keto-4-methyl*cyclo*hexyl)propionic acid (II), obtained by acid hydrolysis of the keto-dicarboxylic ester (III) (Ruzicka and Steiner, *Helv. Chim. Acta*, 1934, **17**, 614), largely crystallised in one racemic form, m. p. 117°, in good yield. Both the acid and its methyl ester were oxidised only slowly by selenium dioxide in neutral solvents and led to inhomogeneous non-crystalline products. In aqueous acetic acid, however, oxidation of the acid was rapid, leading to a crystalline product, $C_{10}H_{14}O_3$, m. p. 150°, in good yield. This substance, which was readily purified by vacuum-sublimation, was non-ketonic, saturated to bromine in carbon tetrachloride, but attacked fairly rapidly by cold potassium permanganate solution. There was no strong absorption above 220 mμ. Towards alkali the substance behaved as a remarkably stable lactone; although freely soluble in cold aqueous alkali it could not be titrated with alkali nor could its alkaline solution be back-titrated to a definite end-point. On oxidation with alkaline potassium permanganate it gave (±)-2-methyladipic acid in good yield.

These chemical properties coincide closely with those described for the autoxidation product, $C_{10}H_{14}O_3$, m. p. 188°, obtained from menthofuran (V), for which Woodward and Eastman (*J. Amer. Chem. Soc.*, 1950, **72**, 399) proposed structure (IV). Our material in alcoholic alkali showed strong ultra-violet absorption at 265 mμ (log ε 3·93) (cf. Fig. 1), and for the autoxidation product of menthofuran under similar conditions Woodward and Eastman found $\lambda_{max.}$ 265 mμ (log ε 3·72). Also, in agreement with these authors, our material was found to undergo ready dehydration to a product $C_{10}H_{12}O_2$ on distillation from potassium hydrogen sulphate. This showed the strong absorption [$\lambda_{max.}$ 276 mμ (log ε 4·14)] expected of the conjugated system present in (VI). For patulin, which contains essentially the same chromophore as (VI), Bergel, Morrison, Moss, and Rindeknecht (*J.*, 1944, 417) give $\lambda_{max.}$ 276·5 mμ (log ε 4·22); for deoxypatulin, Woodward and Singh (*J. Amer. Chem. Soc.*, 1949, **71**, 758) give $\lambda_{max.}$ 273 mμ (log ε 4·17).

The rapid oxidation of (II) in aqueous acetic acid is clearly due to acid-catalysed enolisation and oxidation of the enolic lactone form at the " allyl " 1'-position, which is further activated by the adjacent carbonyl group. Concomitant acid-catalysed oxotropic rearrangement leads to (IV) which also is the only structure consistent with the ultra-violet absorption and chemical properties.

This result may be taken as synthetical verification of the structure of the menthofuran autoxidation product, the difference in melting point being due to our material being a racemic mixture.

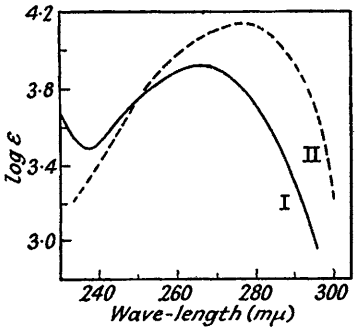
In view of this behaviour of α-(2-keto-4-methyl*cyclo*hexyl)propionic acid, the carbethoxy-derivative (VII) (R = Et) was prepared, so as to facilitate oxidation at the activated position 3. This was readily obtained by alcoholysis of the intermediate (III) and re-cyclisation. In an analogous case Openshaw and Robinson (*J.*, 1937, 941; 1946, 912) were able to effect a rearrangement of this type in one operation by means of alcoholic



sodium ethoxide. In our case these conditions led to much high-boiling material, and isolation of the intermediate triethyl 2-methylheptane-1 : 5 : 6-tricarboxylate was found to be necessary. Acid hydrolysis of the recyclised product gave the same keto-acid (II), m. p. 117°, as was obtained directly from (III).

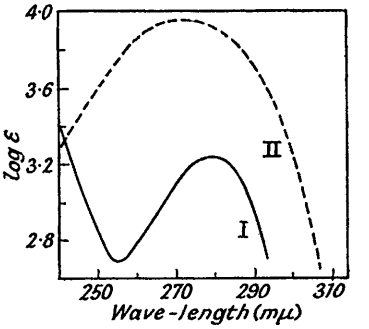
Oxidation was effected by treatment of the corresponding dicarboxylic acid (VII; R = H) with nitrous acid (cf. Kötz and Wunstorf, *J. pr. Chem.*, 1913, **88**, 528; Kötz, Nussbaum, and Takens, *ibid.*, 1914, **90**, 378), leading to a product $C_{10}H_{13}O_3N$ regarded as the oximino-

FIG. 1.



I, *The hydroxy-lactone* (IV) *in alcoholic potassium hydroxide.*
II, *The unsaturated lactone* (VI).

FIG. 2.



I, *The lactone* (X).
II, *The diketo-acid* (IX).

enol-lactone (VIII) or the related oximino-αβ-butenolide. This material which was soluble in caustic alkali, but insoluble in sodium hydrogen carbonate solution, gave a characteristic green colour with alcoholic ferric chloride. Acid hydrolysis of the oximino-lactone afforded as main product a crystalline lactone, m. p. 107°, showing no ferric chloride colour when pure, but an intense green colour when freshly liberated from its alkaline solution. Its alkaline solution rapidly became deep red, this commencing at the air interface. The substance gave no carbonyl derivative. It was saturated to bromine in carbon tetrachloride and with bromine in acetic acid gave a red derivative decolorised by sulphurous acid, which is typical of *o*-quinone formation. These reactions were clearly not those of the diketone (IX) to be expected from simple hydrolysis of (VIII), nor of a derived enol lactone. Analyses indicated a formula, $C_{10}H_{10}O_3$, corresponding to the catechol derivative (X), and the substance was found to couple with diazotised *p*-nitroaniline. The catechol structure was supported by the ultra-violet absorption [$\lambda_{max.}$ 279 mμ (log ε 3·23) (cf. Fig. 2)]. For catechol Morton and Stubbs (*J.*, 1940, 1347) found $\lambda_{max.}$ 278 mμ (log ε 3·42), and closely similar figures are given for a number of catechol derivatives (Adams, Cain, and Wolff, *J. Amer. Chem. Soc.*, 1940, **62**, 732). Corresponding α-diketones in general absorb at somewhat shorter wave-lengths, but are characterised more particularly by extinction values of the order of log $\varepsilon_{max.}$ 4. For diosphenol, Gillam, Lynas-Gray, Penfold, and Simonsen (*J.*, 1941, 62) found $\lambda_{max.}$ 274 mμ (log ε 4·04). In the sterol series, for a 2 : 3-dione Rosenheim and Steiner (*J.*, 1938, 353) found $\lambda_{max.}$ 270 mμ (log ε 3·70 and 3·93 for isomeric forms); for a 6 : 7-diketo-sterol Heilbron, Jones, and Spring (*J.*, 1937, 801) found $\lambda_{max.}$ 274·5 mμ (log ε 4·03).

The substance $C_{10}H_{10}O_3$, m. p. 107°, was not hydrogenated over palladised charcoal in alcohol, but in presence of Adams's platinum oxide in acetic acid rather more than four molecular equivalents of hydrogen were absorbed, to give a hydroxy-acid, $C_{10}H_{18}O_3$, which is unchanged on distillation and therefore regarded as the δ-hydroxy-acid (XI). The hydrogen uptake is consistent only with the catechol structure (X), and hydrogenolysis of the lactone ring provides an example in the aromatic series of the behaviour of βγ-butenolides noted by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601).

In the formation of (X), aromatisation apparently occurs through oxidation during hydrolysis of the oximino-lactone. By hydrolysis in the presence of formaldehyde (cf. Kötz, Nussbaum, and Takens, *loc. cit.*) it was possible to obtain a substance, $C_{10}H_{14}O_4$, m. p. 155—156°, corresponding to the diketone (IX), but not in good yield. This substance which also showed a deep green colour reaction with alcoholic ferric chloride, gave, however, a stable yellow solution in alkali. The ultra-violet absorption (cf. Fig. 2) showed the expected maximum at 272 mμ (log ε 3·95) in agreement with the data noted above.

In view of the structural analogy between (VI) and patulin, this substance was tested but found to have no antibiotic activity; (III) and (VII) were similarly inactive.

Experimental

*Ethyl 2-Keto-4-methyl*cyclo*hexanecarboxylate*.—This was obtained, with b. p. 127—128°/17 mm., n_D^{18} 1·4763, in 60% yield by the general method of *Org. Synth.*, Coll. Vol. II, p. 532, but without isolation of the intermediate glyoxylic ester (cf. Kötz and Hesse, *Annalen*, 1905, **342**, 321).

Diethyl α-(1-*Carboxy*-2-*keto*-4-*methyl*cyclo*hexyl*)*propionate*.—This ester was obtained, with b. p. 105°/0·1 mm., n_D^{18} 1·4737, in 55% yield from ethyl 2-keto-4-methyl*cyclo*hexanecarboxylate with an equivalent of ethyl α-bromopropionate in dry ethyl-alcoholic sodium ethoxide (Ruzicka and Steiner, *Helv. Chim. Acta*, 1934, **17**, 614).

Hydrolysis of Diethyl α-(1-*Carboxy*-2-*keto*-4-*methyl*cyclo*hexyl*)*propionate*.—(i) Gentle refluxing with concentrated hydrochloric acid for 2 hours gave as the main acid product a viscous colourless oil, b. p. 135—140°/0·04 mm., n_D^{19} 1·4778, corresponding to α-(1-*carbethoxy*-2-*keto*-4-*methyl*-cyclo*hexyl*)*propionic acid* (Found: C, 61·2; H, 8·1. $C_{13}H_{20}O_5$ requires C, 61·0; H, 7·8%).

(ii) Hydrolysis of the diethyl ester (6·9 g.) in glacial acetic acid (25 c.c.) with concentrated hydrochloric acid (25 c.c.) on the steam-bath for 6 hours afforded α-(2-*keto*-4-*methyl*cyclo*hexyl*)-*propionic acid*, b. p. 145—150°/0·1 mm. (2·2· g.), which largely crystallised. Separation of the crystalline material by means of benzene–light petroleum (b. p. 40—60°) gave, after recrystallisation from the same solvent, α-(2-*keto*-4-*methyl*cyclo*hexyl*)*propionic acid*, m. p. 117°, as rosettes of fine prisms (Found: C, 65·1; H, 8·9. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). The 2 : 4-*dinitrophenylhydrazone* formed orange yellow prisms, m. p. 219°, from ethyl alcohol–ethyl acetate (Found: C, 53·0; H, 5·7. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·4%).

Oxidation of α-(2-*Keto*-4-*methyl*cyclo*hexyl*)*propionic Acid with Selenium Dioxide*.—α-(2-Keto-4-methyl*cyclo*hexyl)propionic acid (9·2 g.) and selenium dioxide (5·6 g.) in acetic acid (40 c.c.) and water (5 c.c.) were heated under reflux for 2 hours. Removal of precipitated selenium, and of solvent, gave a brown viscous oil which was taken into warm sodium carbonate solution. Acidification gave a brown solid (5·5 g.) which was recrystallised from benzene–light petroleum and further purified by vacuum–sublimation at 100—110°/0·1 mm., to give the colourless *lactone*, m. p. 150°, of α-(2 : 2-dihydroxy-4-methyl*cyclo*hexylidene)propionic acid (Found: C, 66·2; H, 8·0. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·7%), insoluble in aqueous sodium carbonate solution in the cold, slowly soluble on warming, but rapidly soluble in sodium hydroxide solution.

Further oxidation. This lactone (0·4 g.) in sodium hydroxide solution (15 c.c. of 6%) was oxidised with potassium permanganate (1 g.) in water (75 c.c.), and the solution then treated with sulphur dioxide and concentrated *in vacuo*. The residue, acidified and thoroughly extracted with ether, gave a viscous oil (0·4 g.) which largely crystallised. The crystals, separated by means of ether–light petroleum, were purified by vacuum-sublimation and obtained as a colourless crystalline powder, m. p. 89° undepressed on admixture with authentic (±)-2-methyladipic acid.

Dehydration. α-(2 : 2′-Dihydroxy-4-methyl*cyclo*hexylidene)propionic lactone (0·3 g.) with a few crystals of potassium hydrogen sulphate was gently refluxed for a few minutes in a partial vacuum and then twice distilled, to give a colourless mobile oil, b. p. 90°/0·01 mm., d_D^{17} 1·5471 (Found: C, 72·8; H, 7·6. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·3%), this being the *lactone* (VI) of α-(2-hydroxy-4-methyl*cyclo*hex-2-enyl)propionic acid.

Triethyl 2-Methylheptane-1 : 5 : 6-*tricarboxylate*.—Diethyl α-(1-carboxy-2-keto-4-methyl*cyclo*hexyl)propionate (22·8 g.) in dry alcohol (15 c.c.) was added to a solution of sodium ethoxide [from sodium (1·8 g.) in dry alcohol (40 c.c.)], cooled in ice. After 3 days under nitrogen, the solution was treated with ice and acidified with dilute hydrochloric acid, the liberated oil taken into ether, and the solution washed with water and dried. Distillation afforded a small fraction, b. p. 80—100°/0·4 mm., showing a red-violet ferric chloride colour, and a main fraction (13·3 g.), b. p. 135—145°/0·3 mm., n_D^{22} 1·4463; of *triethyl 2-methylheptane*-1 : 5 : 6-*tricarboxylate* (Found: C, 61·7; H, 9·4. $C_{17}H_{30}O_6$ requires C, 61·8; H, 9·1%).

Diethyl α-(3-*Carboxy*-2-*keto*-4-*methyl*cyclo*hexyl*)*propionate*.—Sodium powder (1·4 g.) under benzene (35 c.c.) was treated with trimethyl 2-methylheptane-1 : 5 : 6-tricarboxylate (20 g.) in benzene (30 c.c.) and a little dry alcohol, and reaction completed on the steam-bath during 3½ hours. After being kept overnight the reaction mixture was treated with ice-water and acidified with dilute acetic acid, and the benzene solution was separated. The aqueous layer was re-extracted and the combined extracts were dried and distilled, giving a main fraction (9·8 g.), b. p. 131—137°/0·4 mm., n_D^{21} 1·4618, of *diethyl* α-(3-*carboxy*-2-*keto*-4-*methyl*cyclo*hexyl*)-*propionate*, giving a red-violet ferric chloride colour (Found: C, 63·1; H, 8·8. $C_{15}H_{24}O_5$ requires C, 63·3; H, 8·5%).

Hydrolysis of this ester (2·5 g.) in glacial acetic acid (5 c.c.) with concentrated hydrochloric acid (15 c.c.) on the steam-bath for 6 hours afforded α-(2-keto-4-methyl*cyclo*hexyl)propionic acid (1·2 g.), b. p. 140—150°/0·1 mm., from which the crystalline acid, m. p. 117°, was obtained in good yield.

Reaction of α-(3-*Carboxy*-2-*keto*-4-*methyl*cyclo*hexyl*)*propionic Acid with Nitrous Acid*.—Diethyl α-(3-carboxy-2-keto-4-methyl*cyclo*hexyl)propionate (5·65 g.) was shaken mechanically with a cold solution of potassium hydroxide (2·5 g.) and sodium nitrite (1·4 g.) in water (57 c.c.) for 24 hours. A small amount of oil was then removed by ether, and the yellow aqueous layer separated and cooled to 0°. Concentrated sulphuric acid (1·5 c.c.) was then added dropwise with stirring during 15 minutes. After some hours the liquid was thoroughly extracted with ether, to yield, after drying and removal of solvent, 4·7 g. of red-brown oil (A). On attempted distillation this partly decomposed, but a fraction could be collected, having b. p. 120—125°/0·05 mm. and giving analytical figures corresponding to α-(2-*hydroxy*-4-*methyl*-3-*oximino*cyclo*hex*-1-*enyl*)*propionic lactone* ((Found: C, 61·7; H, 7·1; N, 7·4. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%). This was a viscous oil showing a dark green ferric chloride colour reaction in alcohol. It was insoluble in sodium hydrogen carbonate solution, but soluble in warm sodium hydroxide solution.

Hydrolysis. The above crude material (A) (19 g.) was heated with acetic acid (25 c.c.), concentrated hydrochloric acid (40 c.c.), and water (80 c.c.) on the steam-bath for 2 hours. It was then diluted somewhat, cooled, saturated with ammonium sulphate, and extracted thoroughly with ether. Distillation of the recovered oil gave material (6·6 g.), b. p. 130—170°/0·5 mm. This was separated by means of sodium hydrogen carbonate solution into an acid fraction [isolated as a colourless crystalline solid, m. p. 117° (3 g.) after distillation and recrystallisation from light petroleum (b. p. 40—60°)], and a neutral fraction. The latter on distillation gave material (1·7 g.), b. p. 115—120°/0·2 mm., which crystallised at once and was obtained as colourless prisms, m. p. 107°, by recrystallisation from light petroleum (b. p. 40—60°). The acid fraction gave no m. p. depression on admixture with α-(2-keto-4-methyl*cyclo*hexyl)propionic acid. The neutral material 2 : 3-*dihydro*-7-*hydroxy*-2-*keto*-3 : 6-*dimethylbenzofuran*, which could also be very conveniently purified by vacuum-sublimation (80—90°/0·2 mm.) (Found: C, 67·2; H, 5·6. $C_{10}H_{10}O_3$ requires C, 67·3; H, 5·7%), was insoluble in sodium hydrogen carbonate solution, but in strong alkali it at once gave a solution which rapidly developed a bright red colour at the air interface. It showed no colour with ferric chloride in alcohol, but when it was liberated into ether from its alkaline solution the ethereal solution gave with alcoholic ferric chloride an intense green colour. It gave no carbonyl derivatives.

On hydrogenation in glacial acetic acid with Adams's platinum oxide rather more than four mols. of hydrogen were rapidly absorbed by the benzofuran without a break in the rate curve. The resultant α-(3-*hydroxy*-4-*methyl*cyclo*hexyl*)*propionic acid* formed a gum, b. p. 145°/0·02 mm. (Found: C, 64·7; H, 10·0. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%).

The crude material (A) (5·65 g.) was stirred vigorously with 30% aqueous formaldehyde (15 c.c.) and treated gradually with concentrated hydrochloric acid (10 c.c.). After 1½ hours the solution was neutralised with aqueous ammonia and extracted with ether, yielding a brown oil (1·6 g.) which partly crystallised. Separation of the solid by means of benzene–light petroleum (b. p. 40—60°) and recrystallisation from the same solvents gave α-(2 : 3-*diketo*-4-

*methyl*cyclo*hexyl*)*propionic acid*, m. p. 155—156° (Found : C, 60·3; H, 7·3. $C_{10}H_4O_4$ requires C, 60·6; H, 7·2%).

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