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THEORETICAL

Recent investigations by Abe et al (J. Amer. Chem. Soc., 1956, 78, 1416) have resulted in the total synthesis of the six out of the eight possible stereoisomers of santonin, the other two being sterically impossible because these involve formation of the Y-lactone moiety through vicinal diaxial valencies in a six-membered ring. In this laboratory, synthesis of santonin C and santonin D has been completed with special emphasis on the stereospecificity of the reactions in order to have a better knowledge of the stereoisomerism of the final products. With a view to synthesising α and β santonins, it was realised quite early (Dutta, Sci. & Cult., 1953, 19, 164; Dutta and Ghosh, J. Ind. Chem. Soc., 1955, 32, 741) that the diketo-acid (I) would be emminently suited for the purpose because through chemical reduction of the more hindered carbonyl group, an equatorial hydroxyl group could be introduced and eventually to the formation of the trans-lactone system present in natural santonins. We were evidently anticipated by Tahara (J. Org. Chem., 1956, 21, 442), who has synthesised santonins α and β from the diketo-acid (I), which in its turn was obtained from α-santonin. Another interesting fact was that all the asymmetric centres in (I), excepting the carbon atom carrying the angular methyl group, are
epimerisable under usual conditions as being adjacent to a functional group and hence the final product was subject to stereochemical control. With this end in view, experiments were carried out to synthesise the acid (I) and the formation of this acid in an extremely poor yield could be demonstrated through a yellow monodinitrophenylhydrazone (Dutta and Ghosh, loc. cit.). Recently our knowledge about the stereochemistry of \( \alpha \)-decalones has undergone unexpected modifications and the presence of the \( \alpha \)-carbonyl group will no longer ensure the trans-juncture of the ring-system. This is specially so in presence of the angular methyl group, which lowers to a considerable extent the energy difference between \textit{cis} and \textit{trans} forms of 9-methyldecalins (Turner, J. Amer. Chem. Soc., 1952, 74, 2118). The bicyclic ketone (II), synthesised in this laboratory (Ghatak, Saha and Dutta, \textit{ibid}, 1957, 79, 4487) has been found to be a mixture of \textit{cis} and \textit{trans} forms (Sondheimer and Rosenthal, \textit{ibid}, 1958, 80, 3995) and the keto-acid (I) was also present as a mixture of two stereoisomers epimerisable under mild alkaline conditions (Tahara, loc. cit.; Cocker and McMurry, J. Chem. Soc., 1956, 4549).

As reported in the preceding reprint all attempts to obtain the diketo-acid (I) from the hydroxy-ester (III), synthesised in this laboratory, have failed. The latter was found to be susceptible to acidic conditions leading to a dienone (V) and so also was the hydroxy-ketone (IV). It was next decided to introduce the
propionic acid residue to a suitably substituted bicyclic compound and experiments described in the sequel deal with studies along these lines. The hydroxy-ketone (VI) was considered to be of some use for this purpose. The ketone (VII, Mahajan et al, attached reprint) was reduced with sodium borohydride and the acetylated product (VIII) was subjected to allylic oxidation with N-bromo-succinimide/silver dichromate, t-butyl chromate (Heusler and Wettstein, Helv. Chim. Acta., 1952, 35, 284) or potassium dichromate and acetic acid. N-bromo succinimide/silver dichromate led to (V) as the final product. The other two reagents also did not afford the desired compound and from the products isolated it appears that the oxidation has proceeded too far.

Next series of experiments were concerned with the synthesis of ketone (A) and the following scheme was chalked out.
3-Methyl-$\Delta^2$-cyclohexenone, available in quantities from the hydrolysis of Hagemann's ester, was allowed to condense with ethyl malonate under controlled conditions in order to avoid the formation of secondary products (Farmer and Ross, J. Chem. Soc., 1925, 2359). The formation of the keto-ester (IX) was confirmed through the known semicarbazona. The keto-ester was ketalised and subsequently reduced with sodium and alcohol to afford (X). The tosylate of this alcohol was condensed with ethyl acetoacetate. The product on deketalisation and subsequent hydrolysis with alkali afforded, in addition to a low boiling product having a pronounced camphoric smell, the diketone (XI), which failed to undergo ring-closure even on subsequent treatment with mineral acids.

Next series of studies deals with the synthesis of the diketone (XIII). The hydroxy-ketone (IV) through oxidation with chromic acid in acetone (Bowers et al., J. Chem. Soc., 1953, 2548) gave a highly crystalline solid (XII). This was then reduced with zinc-dust and acetic acid to afford the diketone (XIII) as a viscous liquid evidently due to the presence of stereoisomers. It was expected that of the two positions (3,7), the latter would be more accessible stereochemically and (XIII) was then allowed to react with ethyl α-bromopropionate in presence of potassium t-butoxide.
This led to the formation of a product of the expected boiling point and yielded an acidic material on hydrolysis. This was reduced with sodium borohydride and on subsequent dehydrogenation with selenium afforded a hydrocarbon, characterised by a yellow picrate melting at 132-134°C, the identity of which could not be definitely established.
EXPERIMENTAL


The ketone (VII, 20 g.) dissolved in alcohol (50 c.c.) was reduced with sodium-borohydride (4.3 g.) and the product (ca 20 g.) acetylated in the cold with a mixture of acetyl chloride (16 c.c.) and acetic anhydride (21 c.c.) in the presence of pyridine (45 c.c.) to afford the desired acetate as a colourless liquid, b.p. 135-138°/10 mm. Yield 21 g.

(Found : C, 75.8 ; H, 10.0. C_{14}H_{22}O_{2} requires C, 75.7 ; H, 9.9 per cent).

Oxidation of the acetate (VIII).

t-Butylchromate method.

To the above acetate (5 g.) dissolved in carbon tetrachloride (30 c.c.) was added at room temperature, t-butylchromate solution (65 c.c.), acetic acid (20 c.c.) and acetic anhydride (12 c.c.) with vigorous mechanical stirring. After 1 hour, the reaction mixture was allowed to stand overnight. It was next refluxed with stirring for 2 hours. To the cooled reaction mixture was then added a solution of oxalic acid (12.5 g.) in water (100 c.c.), followed after 10 minutes by a further addition of solid oxalic acid (12.5 g.). Stirring was stopped after 1 hour and the mixture allowed to stand. Carbon tetrachloride layer was separated and washed with sodium carbonate solution followed by water and the solvent removed. The
residual liquid on distillation gave two products: (i) A colourless liquid (2.5 g.), b.p. 115-120°/5 mm. (Found: C, 74.9 %; H, 9.3 %). Its 2,4-dinitrophenylhydrazone crystallised from ethyl acetate, m.p. 191°. (Found: C, 55.1 %; H, 5.3 %; N, 14.4 %). (ii) The high boiling residue left in the distillation flask afforded beautiful crystals from alcohol, m.p. 190°. It did not afford any 2,4-dinitrophenylhydrazone. (Found: C, 68.5 %; H, 8.9 %).

**Potassium dichromate method.**

Potassium dichromate (4 g.) was dissolved in acetic acid (50 c.c.) and a solution of the acetate (4 g.) in acetic anhydride (12 c.c.) was added to it. On stirring for 2 hours, the reaction mixture was allowed to stand overnight. The green reaction mixture was diluted with water, extracted with ether and worked up as usual to afford finally a colourless liquid (2.8 g.), b.p. 120-124°/7 mm. It gave a 2,4-dinitrophenylhydrazone, m.p. 190°, alone or mixed with the same derivative described before. In this case no solid was obtained from the residue in the distillation flask.

**Ethyl (1-methyl-3-ketocyclohexyl)-acetate (IX).**

Ethyl malonate (72 g.) was added in the cold to a solution of sodium (3.5 g.) in ethanol (70 c.c.) followed by 3-methyl-Δ²-cyclohexenone (33 g.). This was allowed to stand at room temperature for about 16 hours. The reaction mixture was decomposed with dilute hydrochloric acid and extracted with ether to afford the desired product (41 g.) as a colourless liquid, b.p. 155-160°/0.8 mm.
This was refluxed for 10 hours with a mixture of hydrochloric acid (125 c.c.) and acetic acid (40 c.c.). The crude product (ca 20 g.) obtained on removal of the low boiling products, was esterified on refluxing for 8 hours with a mixture of alcohol (60 c.c.) and sulphuric acid (4 c.c.) to afford a colourless mobile liquid (9 g.), b.p. 115-117°/2 mm.

(Found : C, 66.8 ; H, 9.0. C₁₁H₁₈O₃ requires C, 66.7 ; H, 9.1 per cent).

The semicarbazone, prepared in the usual way, was crystallised from ether, m.p. 158° (lit. 158-159°).

β-(1-methyl-3-ethylenedioxy cyclohexyl)-ethanol (X).

The above keto-ester (18 g.) was ketalised on refluxing in a constant water-separator for 8 hours with a mixture of ethylene glycol (7 c.c.), p-toluene sulphonic acid (100 mg.) and benzene (100 c.c.) to afford the desired ketal-ester (14.5 g.), b.p. 130-132°/5 mm.

This was reduced with sodium (17 g.) in absolute ethanol (200 c.c.). On the completion of reaction, alcohol was distilled off with steam and product isolated with ether, whereupon the desired ketal-alcohol (9.3 g.) was obtained as a colourless, viscous liquid, b.p. 142-143°/5 mm.

(Found : C, 65.7 ; H, 9.6. C₁₁H₂₀O₃ requires C, 66.0 ; H, 10.0 per cent).
3-Methyl-3-(4-ketopentyl)-cyclohexanone (XI).

The tosyl-derivative prepared in the usual way from the ketone-acetate (9 g.) was added to a suspension of the sodium salt prepared from ethyl acetoacetate (12 g.) and sodium (1.5 g.) under benzene (50 c.c.). This was refluxed on a water-bath for about 12 hours. The cooled reaction mixture was decomposed with dilute hydrochloric acid, the benzene layer separated and washed with water. On removal of the solvent, the crude product (ca 15 g.) was dissolved in alcohol (100 c.c.). Dilute hydrochloric acid (20 c.c.; 1:1) was added and the mixture refluxed for ½ hour. After allowing it to stand overnight, a solution of potassium hydroxide (15 g.) in alcohol (50 c.c.) was added and the mixture refluxed in nitrogen atmosphere for 10 hours. The cooled reaction mixture was acidified with acetic acid and excess alcohol removed. The residue was diluted with water, extracted with ether and worked up as usual. On distillation of the product, two fractions were collected: (i) A colourless liquid with a strong camphoric smell, b.p. 80-82°/12 mm. (1.3 g.). Its 2:4-dinitrophenylhydrazone crystallised from alcohol as orange-yellow silky needles, m.p. 124°.

(ii) A faint yellow liquid (ca 2 g.) b.p. 150-152°/12 mm. It afforded an orange 2:4-dinitrophenylhydrazone which crystallised from ethyl acetate, m.p. 205°.

(Found: C, 51.5; H, 5.5. C\textsubscript{24}H\textsubscript{28}O\textsubscript{8}N\textsubscript{8} requires C, 51.8; H, 5.1 per cent).
To the hydroxy-ketone (IV, 2.7 g.) dissolved in acetone (6 c.c.), 8N-solution of chromic acid was added dropwise with shaking till the colour of the reaction mixture was persistently yellow. On allowing to stand for 15 minutes, it was diluted with water and the product isolated with ether. Solvent was removed and the product crystallised from petroleum ether (40-60°C). Stout laths, m.p. 61-62°C. Yield 2 g.

(Found: C, 75.1; H, 8.5. C_{12}H_{16}O_2 requires C, 75.0; H, 8.3 per cent).

Condensation of ethyl α-bromopropionate with (XIII).

The above diketone (5 g.) was reduced with zink-dust (15 g.) in acetic acid (80 c.c.) and water (3 c.c.) on refluxing for 6 hours. The product was isolated with ether to afford a slightly yellowish liquid (ca 4 g.). The dried diketone was added to a suspension of potassium t-butoxide (potassium 1 g.) in toluene (50 c.c.) under nitrogen atmosphere and thoroughly shaken. The colour of the reaction mixture became dark-brown and a clear solution was obtained. Ethyl α-bromopropionate (6 g.) was introduced and the reaction mixture was allowed to stand overnight, followed by heating on the oil-bath for 6 hours. This was then decomposed with water and dilute hydrochloric acid. On removal of the solvent, the product was distilled to afford three fractions:
(i) Pale-yellow liquid, b.p. 120-140°/0.3 mm (ca 1.2 g.)
(ii) Light-yellow liquid, b.p. 150-155°/0.3 mm (ca 1 g.)
(iii) Yellow liquid, b.p. 160-170°/0.3 mm (ca 1 g.)

Fractions (ii) and (iii) afforded, on redistillation, a light-yellow product at 150-155°/0.2 mm. Yield 0.9 g.

(Found : C, 70.0 ; H, 8.7. C_{17}H_{26}O_{4} requires
C, 69.4 ; H, 8.8 per cent).

0.7 g. of this product was hydrolysed on a boiling water-bath for 6 hours with a solution of potassium hydroxide (0.5 g.) in rectified spirit (5 c.c.). The acidic product was isolated and reduced with sodium borohydride (0.75 g.) in alcohol (10 c.c.). On working up in the usual way, crude product was heated with selenium (2 g.) in a sealed tube at 300° for 30 hours. The hydrocarbon was purified by distillation in vacuum over sodium and the distillate converted into a picrate, which crystallised from alcohol in golden-yellow needles melting at 132-134°.