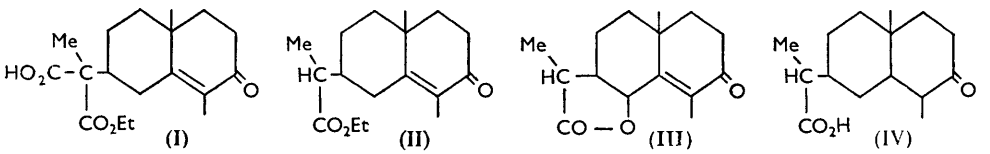
1012. *Synthetic Studies in the Santonin Series.*

By J. R. MAHAJAN, P. DUTT, and P. C. DUTTA.

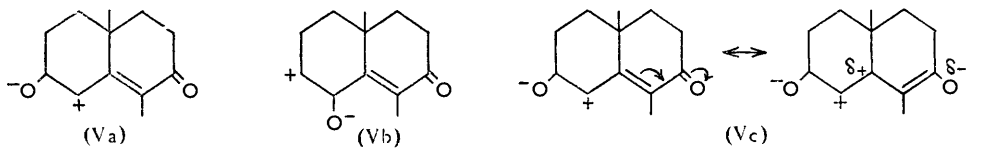
Synthesis of a dihydrosantonin related to santonin C is described, along with studies of new methods designed for synthesis of other isomers.[1]

A PREVIOUS paper [2] reported the synthesis of an isomer of a dihydrosantonin related to santonin D. The present paper reports synthesis of a dihydrosantonin related to santonin C, and related exploratory experiments designed to develop new routes to other isomers.

The half-ester [3] (I) was thermally decarboxylated to the ester [2,3] (II) which was converted, as in previous work,[2] into a mixture (III) of dihydrosantonins C and D. Attempts to obtain a pure component by heating the mixture [4] with collidine having failed, dihydrosantonin D and a smaller amount of its C isomer were separated by laborious fractional crystallisation. The structure of the former was established by bromination and dehydrobromination to santonin C, and identity was established by direct comparison with an authentic sample [3] through the kindness of Dr. Abe. Catalytic reduction of dihydrosantonin D led to an acid [5] (IV) and a trace of a neutral material.



Attempts were next directed to synthesise dihydrosantonins related to santonin A and B containing an axial propionic acid residue and *cis*-lactone ring.[6] For this purpose, advantage was taken of the diaxial [7] opening of an epoxide with the anion of ethyl methylmalonate, leading to the possibility of the formation of a γ-lactone.[8] Our interest in the present investigation centred round the unsaturated epoxide (IX), which could undergo displacement reactions with nucleophilic reagents through one of the polar forms (Va and b). The former would not be energetically favoured because polarisation of the $\alpha\beta$-unsaturated carbonyl group would place two positive charges on vicinal carbon atoms



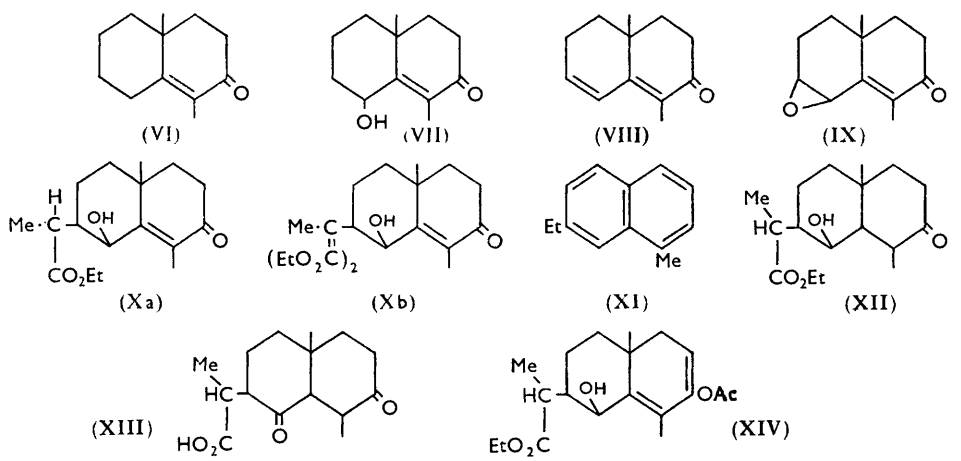
(see Vc). Consequently the form (Vb) should take part in the reaction, affording the esters (Xa and b).* Steric considerations [10] also favour the attachment of the chain at $C_{(7)}$ because of the presence of the 1-methyl group. The isolation of the hydroxy-ester (Xa)

* Van Tamelen *et al.*[9] condensed ethyl methylmalonate with 3 : 4-dihydronaphthalene 1 : 2-oxide with a view to synthesising hyposantonin, but this led to the *trans*-lactone of the β-hydroxy-α-carboxylic acid. The resonance hybrid (analogous to Va) took part in this reaction because of the participation of π-electrons in stabilising the incipient positive charge.

[1] For a preliminary communication see *Chem. and Ind.*, 1955, 170.
[2] Chakrabarti, Dutt, and Dutta, *J.*, 1956, 4978.
[3] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1416.
[4] Cocker and McMurry, *J.*, 1955, 4430.
[5] Cf. Barton and Elad, *J.*, 1956, 2085, 2090.
[6] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1953, **75**, 2567.
[7] Cookson, *Chem. and Ind.*, 1954, 1512.
[8] Traube and Lehman, *Ber.*, 1901, **34**, 1977.
[9] Van Tamelen, Van Zyl, and Zuidema, *J. Amer. Chem. Soc.*, 1950, **72**, 488.
[10] Brown and Eldred, *ibid.*, 1949, **71**, 445.

from the reaction mixture and the poor tendency exhibited by it or the related hydroxy-acid to lactonise under thermal conditions [11] ruled out the possibility of isolating the isomeric dihydrosantonins with a *trans*-fusion of the lactone-ring and involving two vicinal axial bonds. This also appeared to be improbable from steric considerations as the *cyclo*hexane ring in the bicyclic compound would preferably not exist in an energetically less favoured boat configuration.[12]

For synthesis of the esters (X), a considerable quantity of the doubly unsaturated ketone [13] (VIII) was needed. The ketone [2,13] (VI) was converted into the enol acetate and then oxidised with monoperphthalic acid. The resulting epoxide was converted by potassium carbonate in refluxing aqueous methanol into the hydroxy-ketone (VII) which was dehydrated by a catalytic amount of toluene-*p*-sulphonic acid in boiling benzene to the ketone (VIII). Perbenzoic acid in chloroform or monoperphthalic acid in ether then afforded the epoxide (IX) in a moderate yield. In analogy with well-known cases,[14] it is assumed that the $\gamma\delta$-double bond was epoxidised and this was confirmed by disappearance of ultraviolet absorption at longer wavelengths and appearance of the characteristic absorption of the $\alpha\beta$-unsaturated carbonyl group. Attempts to isolate the analytically pure epoxide (IX) by distillation or crystallisation failed but the final product was 85—90% pure as estimated by analysis and by the intensity of the ultraviolet absorption, account being taken of the hypsochromic effect of the oxygenated function at the γ-position to the $\alpha\beta$-unsaturated carbonyl system.[15] This epoxide with ethyl methylmalonate in presence of sodium ethoxide gave two products (Xa [16] and b) in satisfactory yield: in presence of potassium *tert.*-butoxide, the condensation gave only the monoester (Xa), with an unidentified low-boiling product. To confirm the point of attachment of the side-chain, the ester (Xa) was reduced with sodium borohydride, and the hydroxy-acid obtained on hydrolysis of the reduced acid was dehydrogenated with selenium: this afforded 7-ethyl-1-methylnaphthalene (XI) as expected.



It was expected that under more vigorous acidic conditions the hydroxy-ester (Xa) could perhaps lactonise with inversion, thus forming a dihydrosantonin corresponding to santonin A or B. However, it gave the ketone (VIII), arising by elimination of the axial propionic acid residue and of the hydroxyl group. The hydroxy-ester (Xa) was

[11] Newman and Vanderwerf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.
[12] Cocker and McMurry, *Chem. and Ind.*, 1954, 1199.
[13] Gunstone and Heggie, *J.*, 1952, 1437.
[14] (*a*) Karrer and Sturzinger, *Helv. Chim. Acta*, 1946, **29**, 1829; (*b*) Narres, Schwarzkopf, and Lewis, *ibid.*, 1947, **30**, 880.
[15] Amendolla, Rasenkranz, and Sondheimer, *J.*, 1954, 1227.
[16] Skinner, Stokes, and Spiller, *J. Amer. Chem. Soc.*, 1947, **69**, 3083.

then reduced catalytically and the hydroxy-acid corresponding to the reduced ester (XII) was subjected to vigorous acid treatment, but it failed to yield any lactonic material.

In connection with the synthesis of naturally occurring santonins, the importance of the diketo-acid (XIII), which was isolated in an extremely poor yield and characterised through a yellow dinitrophenylhydrazone, has already been indicated.[17,18] Experiments with dihydrosantonin D (III) and the hydroxy-ester (Xa), for their eventual conversion into this diketo-acid (XIII), were without success. Attempts to shift the αβ-unsaturated linkage by formation of a ketal with ethylene glycol or ethyl orthoformate failed.[19] The lactone (III) with potassium *tert.*-butoxide did not give a useful product, and the hydroxy-ester (Xa) afforded an isomeric ester with retention of the αβ-unsaturated linkage. Attempts to oxidise the hydroxy-ester (Xa) with manganese dioxide,[15] *N*-bromosuccinimide,[20] and the chromic acid–pyridine complex [21] also failed. Refluxing the ketone (Xa) with acetyl chloride and acetic anhydride yielded the enol acetate (XIV) [characterised by $\lambda_{max.}$ 280 mμ (log ε 4·32) in hexane and by slow formation of the dinitrophenylhydrazone corresponding to (Xa)]. The extremely inert nature of the hydroxyl group in this compound (Xa) was evidently due to steric hindrance, which was indeed evident in models.

Experimental

Dihydrosantonins C, D (III).—The half-ester (I) (135 g.), obtained from the Michael condensation product, was decarboxylated at 190—195° for 1 hr., giving the ester (II), b. p. 165—170°/0·6 mm. (88 g.). This was converted into the enol acetate (95 g.) when refluxed under nitrogen with acetyl chloride (350 c.c.) and acetic anhydride (350 c.c.) for 3 hr. This acetate was oxidised with cold ethereal monoperphthalic acid, and a crude epoxide (91 g.) was obtained. This (30 g.) was converted into a mixture of dihydrosantonins (*ca.* 6 g.), m. p. 114—120°, which on fractional crystallisation from ethyl acetate and then methanol gave dihydrosantonin D[3] (3 g.), m. p. 136—137°. The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethyl acetate as orange-red needles, m. p. 250—251° (Found: C, 59·0; H, 5·6. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6%).

From the mother-liquor, a fraction of m. p. 110—115° was obtained, which on repeated crystallisation from methanol afforded *dihydrosantonin C* (0·5 g.), m. p. 125° (mixed m. p. with dihydrosantonin D 111—114°) (Found: C, 72·7; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·0%). The 2 : 4-*dinitrophenylhydrazone* separated as orange-yellow needles (from chloroform–ethyl acetate), m. p. 236—237° (Found: C, 59·1; H, 5·8. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6%). Its monobromo-derivative melted at 144° (lit., 143°). This was dehydrohalogenated by collidine: santonin C, on crystallisation from methanol, had m. p. and mixed m. p. 178—179°.

α-(*Decahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthyl*)*propionic Acid* (IV).—Dihydrosantonin D (2 g.) in dry acetone (12 c.c.) was hydrogenated in presence of palladium–strontium carbonate (100 mg.). Absorption (2 mols.) was complete in 40 min. After removal of the catalyst and solvent, the residue was taken up in ether and the acid removed in 5% sodium carbonate solution. Acidification afforded isomer acids (1·8 g.). Repeated crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) and finally from ethyl acetate afforded the pure *acid*, m. p. 120—121° (Found: C, 71·0; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%). A small amount of the neutral material was repeatedly crystallised from ether–light petroleum and melted at 162—163°. Tahara [18a] described a tetrahydrosantonin having a *cis*-lactone ring and melting at 162—163°, but direct comparison was not possible.

1-*Hydroxy*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-8 : 10-*dimethyl*-7-*oxonaphthalene* (VII).—The ketone (VI) (30 g.), acetyl chloride (120 c.c.), and acetic anhydride (120 c.c.) were refluxed under nitrogen for 6 hr. The enol acetate (32·3 g.), b. p. 120—125°/2 mm., $\lambda_{max.}$ 238 mμ (log ε 4·2 in EtOH), was oxidised with cold ethereal 0·63N-monoperphthalic acid (525 c.c.) for 24 hr. The solution was repeatedly washed with 10% sodium carbonate solution, and the solvent was

[17] (*a*) Dutta, *Science and Culture*, 1953, **19**, 164; (*b*) Dutta and Ghosh, *J. Indian Chem. Soc.*, 1955, **32**, 741.
[18] (*a*) Tahara, *J. Org. Chem.*, 1956, **21**, 442; (*b*) Cocker and McMurry, *J.*, 1956, 4549.
[19] Sondheimer, Mancera, and Rosenkranz, *J. Amer. Chem. Soc.*, 1954, **76**, 5020.
[20] Fieser, Herz, Klohs, Romero, and Utne, *ibid.*, 1952, **74**, 3309.
[21] Poos, Arth, Beyler, and Sarett, *ibid.*, 1953, **75**, 422.

removed. The residue was refluxed under nitrogen with potassium carbonate (20 g.) in water (180 c.c.) and methanol (900 c.c.) for 0·5 hr., then cooled and neutralised with acetic acid. Methanol was removed from a boiling-water bath. The product was diluted with water and extracted with ether. On removal of the solvent, the *hydroxy-ketone* boiled at 140—145°/3 mm. (18 g.) and had $\lambda_{max.}$ 249 mμ (log ε 3·9 in EtOH) (Found: C, 74·0; H, 9·2. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·2%). The 2 : 4-*dinitrophenylhydrazone* melted at 214—215° alone or mixed with the derivative from the ketone (VIII) (see below).

2 : 3 : 4 : 5 : 6 : 10-*Hexahydro*-1 : 10-*dimethyl*-2-*oxonaphthalene* (VIII).—A solution of the hydroxy-ketone (25 g.) in dry benzene (400 c.c.) containing toluene-*p*-sulphonic acid (4 g.) was refluxed and water formed during the reaction was separated continuously. The doubly unsaturated ketone (16 g.) was obtained with b. p. 120—125°/3 mm., $\lambda_{max.}$ 286 mμ (log ε 4·1 in EtOH). The 2 : 4-dinitrophenylhydrazone melted at 215—216° alone or mixed with an authentic sample (Found: N, 15·7. $C_{18}H_{20}O_4N_4$ requires N, 15·7%).

Ethyl α-(1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthyl*)-*propionate* (Xa) *and* -*methylmalonate* (Xb).—To the ketone (VIII) (10 g.) in chloroform (20 c.c.), cooled in ice, was added a chloroform solution of perbenzoic acid (68 c.c.; 0·66N) and the whole was kept overnight, and repeatedly washed with an ice-cold 10% sodium carbonate solution and finally water. After removal of the solvent, a fraction (3·4 g.), b. p. 120—124°/1 mm., $\lambda_{max.}$ 244 mμ (log ε 3·9 in EtOH), corresponded to the epoxide (IX).

(*a*) Sodium (4·9 g., 1·2 atom-equivs.) was dissolved in alcohol (100 c.c.), and ethyl methylmalonate (90 g., 3 mols.) was added, and then the epoxide (34 g.). The mixture was kept overnight at room temperature, acidified, diluted with water, and extracted with ether. The ethereal extract was washed with 10% sodium carbonate solution, water, and very dilute hydrochloric acid. Distillation gave fractions (i) b. p. 145—150°/0·8 mm. (2 g.), (ii) b. p. 185—195°/0·8 mm. (16 g.) (Xa), and (iii) b. p. 210—215°/0·8 mm. (10 g.) (Xb). Fraction (ii), on redistillation, gave the *ester*, b. p. 168—172°/0·1 mm., $\lambda_{max.}$ 247 mμ (log ε 4·0 in EtOH) (Found: C, 69·3; H, 8·5. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·8%). Its 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate as red needles, m. p. 127° (Found: C, 58·3; H, 6·5. $C_{23}H_{30}O_7N_4$ requires C, 58·2; H, 6·3%). Fraction (iii), on redistillation, gave *ester* (Xb), b. p. 200—205°/0·5 mm. (Found: C, 65·8; H, 7·9. $C_{20}H_{30}O_6$ requires C, 65·5; H, 8·1%).

(*b*) To a solution of potassium *tert.*-butoxide [from potassium (5·1 g., 0·5 atom-equiv.) in *tert.*-butyl alcohol (250 c.c.)] was added ethyl methylmalonate (136 g., 3 mols.). After 0·5 hr., the epoxide (50 g.) was added and the mixture was refluxed in nitrogen for 4 hr., then cooled in ice, acidified with dilute hydrochloric acid, and extracted with ether. On distillation it afforded fractions, b. p. 140—160°/0·6 mm. (6·5 g.) and 165—185°/ 0·6 mm. (6·5 g.). The second fraction corresponded to the ester (Xa) (Found: C, 69·0; H, 8·7%) (dinitrophenylhydrazone, m. p. 126°). The first fraction redistilled at 140—145°/0·1 mm., had $\lambda_{max.}$ 248 mμ (log ε 3·9 in EtOH) (Found: C, 72·3, 72·5; H, 8·4, 8·4%), and gave no dinitrophenylhydrazone.

7-*Ethyl*-1-*methylnaphthalene* (XI).—The hydroxy-ester (Xa) (0·82 g.) was reduced with sodium borohydride (110 mg.) in methanol (2 c.c.). The dihydroxy-ester (0·8 g.) was hydrolysed with potassium hydroxide (0·64 g.) in methanol (6 c.c.) and water (1 c.c.) on the water-bath for 4 hr. The acidic product (0·6 g.) was dehydrogenated with selenium (3 g.) at 300—350° for 40 hr. in a sealed tube. The hydrocarbon, isolated in the usual way and distilled over sodium, was directly converted into a picrate, orange-yellow needles (from methanol), m. p. 95° alone or mixed with that (m. p. 96—97°) of 7-ethyl-1-methylnaphthalene.

Reactions of the Hydroxy-ester (Xa).—(a) *With hydrochloric–acetic acid.* The hydroxy-ester (3 g.) was refluxed in nitrogen with acetic acid (20 c.c.), concentrated hydrochloric acid (20 c.c.), and water (20 c.c.) for 12 hr. The dark brown solution was diluted with water and extracted with ether. The ethereal extract was washed with water, ice-cold dilute 5% potassium hydroxide solution, and water, and dried (Na_2SO_4). On removal of the solvent, the residue was distilled, the major fraction distilling at 120—125°/1·5 mm. Its 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark-red shining flakes, m. p. 214—215° alone or mixed with the derivative of the ketone (VIII) (Found: N, 15·6. Calc. for $C_{18}H_{20}O_4N_4$: N, 15·7%).

(b) *With potassium in* tert.-*butyl alcohol.* The hydroxy-ester (1 g.) was refluxed in nitrogen with a solution of potassium (1 g.) in *tert.*-butyl alcohol (50 c.c.) for 8 hr. The mixture was acidified with acetic acid, and after removal of the solvent was treated with hydrochloric acid and extracted with ether. The ether solutions gave on evaporation a residue which was refluxed

on the water-bath with potassium hydroxide (2 g.) in methanol (20 c.c.) and water (5 c.c.) for 3 hr. The acidic material was isolated in the usual way and esterified with diazomethane. The methyl ester had b. p. 180°/1 mm. $\lambda_{max.}$ 247 mμ (log ε 3·9 in EtOH). This was converted into a 2 : 4-*dinitrophenylhydrazone*, orange flakes (from ethyl acetate) or red needles (from benzene–ethyl acetate), m. p. 190—191°, $\lambda_{max.}$ 390 mμ (log ε 4·3 in EtOH) (Found: C, 57·1; H, 6·1. $C_{22}H_{28}O_7N_4$ requires C, 57·3; H, 6·0%).

Ethyl α-(*Decahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthyl*)*propionate* (XII).—The hydroxy-ester (Xa) (2 g.) was slowly hydrogenated in acetic acid (15 c.c.) in presence of platinic oxide (100 mg.). The *product* distilled at 170—175°/0·2 mm. (Found: C, 68·7; H, 9·0. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·4%). It readily formed a yellow dinitrophenylhydrazone, which melted over a wide range.

Ethyl α-(7-*Acetoxy*-1 : 2 : 3 : 4 : 5 : 10-*hexahydro*-1-*hydroxy*-8 : 10-*dimethyl*-2-*naphthyl*)-*propionate* (XIV).—The hydroxy-ester (0·5 g.) was refluxed in nitrogen with acetyl chloride (2 c.c.) and acetic anhydride (5 c.c.) for 1·5 hr. Low-boiling products were removed at a water-pump. The residual *ester* (XIV) was taken up in ether, washed with 2% sodium carbonate solution, and distilled. It boiled at 180°/0·5 mm. (Found: C, 67·9; H, 8·2. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·3%). It afforded the dinitrophenylhydrazone of (Xa) when kept for 0·5 hr. at room temperature with a solution of the reagent.

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INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE, JADAVPUR,
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