Experiments on the Synthesis of Santonin. Part IV. The Preparation of the Lactone of* 1 : 2 : 3 : 4 : 7 : 10-*Hexahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (*Norsantonin*) *and of* 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-1-*hydroxy*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid.*

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[Reprint Order No. 5966.]

The two compounds named in the title (IV; R = Me, R′ = H) and (VIII; R = H) respectively, both closely related to santonin, have been prepared.

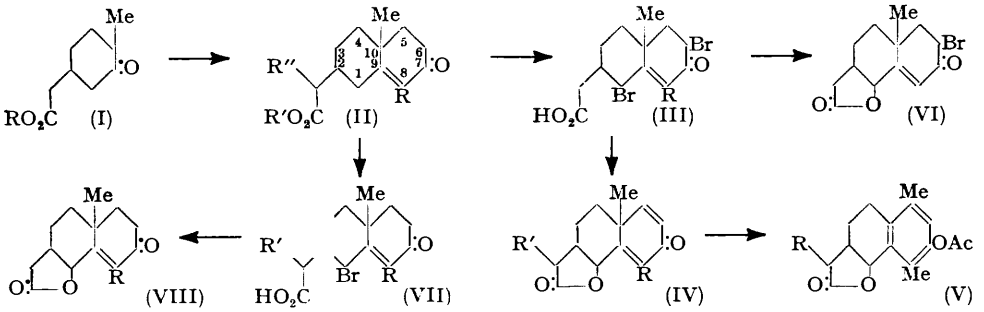
In earlier papers in this series we described compounds required in attempts to synthesise santonin (IV; R = R′ = Me) but whilst this work was in progress Japanese workers reported the synthesis of santonin and some of its stereoisomers (Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1952, **28**, 425; 1953, **29**, 113; 1954, **30**, 116, 119; *J. Amer. Chem. Soc.*, 1953, **75**, 2567; Matsui, Toki, Kitamura, Suziki, and Humura, *Bull. Chem. Soc. Japan*, 1954, **27**, 7). Accordingly we transferred our attention to the synthesis of compounds closely related to santonin and we now report the synthesis of two lactones (IV; R = Me, R′ = H) and (VIII; R = H); the first differs from santonin only in the absence of the side-ring (α) methyl group whilst the latter is without the 8- and the α-methyl group and is hydrogenated at the 5 : 6-position.

Preparation of Norsantonin (IV; R = Me, R′ = H).—Methyl 4-methyl-3-oxo*cyclo*hexyl acetate (I; R = Me) was readily obtained from ethyl 1-methyl-2-oxo*cyclo*hex-3-ene-1-carboxylate (Mukherjee, *J. Indian Chem. Soc.*, 1948, **25**, 155; cf. Gunstone and Tulloch, *J. Appl. Chem.*, 1954, **4**, 291) by Michael condensation with diethyl malonate followed by hydrolysis, decarboxylation, and methylation. The corresponding acid (I; R = H) should exist in two racemic forms but the product appeared to be almost entirely one isomer which was easily isolated; the alternative form was not obtained pure. Condensed with 1-diethylaminopentan-3-one methiodide this keto-ester (I; R = Me) afforded methyl 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-octahydro-8 : 10-dimethyl-7-oxo-2-naphthylacetate (II; R = R′ = Me, R″ = H) (cf. Gunstone and Tulloch, *loc. cit.* and references there cited) and gave the corresponding acid when hydrolysed. With bromine in ether–acetic acid in the presence of a little hydrogen bromide this gave a dibromo-acid assigned the structure (III; R = Me) on account of many analogous reactions in the steroid series (see, *e.g.*, Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534) and of its subsequent reactions. This result differs slightly from that of Abe *et al.* (*loc. cit.*, 1953) who, working with trimethyl compounds (II; R = R″ = Me, R′ = H), obtained directly a monobromo-lactone; on the other hand, Matsui *et al.* (*loc. cit.*), using the same acid, isolated like us the dibromo-acid. When heated with collidine under strictly controlled conditions this dibromo-acid (III; R = Me) was converted into the lactone (IV; R = Me, R′ = H) which is a norsantonin. That the compound has this structure follows from the facts that it is neutral, that its ultra-violet absorption curve shows a single peak at 243 mμ characteristic of dienones of this type (for references see Gunstone and Heggie, *J.*, 1952, 1437), and that, when submitted to the conditions of a dienone-phenol rearrangement, it affords the acetylated phenol (V; R = H) with ultra-violet spectrum almost identical with that of the analogous product prepared from santonin (see p. 1134). Additional evidence follows from the infra-red spectra which are discussed below.

The acid (II; R = Me, R′ = R″ = H) with *N*-bromosuccinimide gave a monobromo-acid (VII; R = Me, R′ = H) in good yield but this afforded only a small quantity of impure lactone when treated with sodium ethoxide. We have shown in our earlier papers

* Part III, *J. Appl. Chem.*, 1954, **4**, 291.

that under these conditions bromination occurs in the 1-position and Abe *et al.*, working with the trimethyl acid, obtained the lactone directly by this means.



Preparation of the Lactone (VIII; R = H).—The experiments now to be described were carried out in an attempt to prepare the santonin analogue (IV; R = R′ = H); this however was not achieved and only the dihydro-compound (VIII; R = H) could be obtained. Methyl 4-methyl-3-oxo*cyclo*hexyl acetate (I; R = Me) condensed with 1-diethylaminobutan-2-one methiodide to give the octalone (II; R = R″ = H, R′ = Me) which served as the starting point for attempts to prepare the lactone (IV; R = R′ = H).

The method used for the conversion of the dimethyl acid (II; R = Me, R′ = R″ = H) into the lactone (IV; R = Me, R′ = H) was applied to the monomethyl acid (II; R = R′ = R″ = H) without success. Hydrolysis of the ester (II; R = R″ = H, R′ = Me) gave the acid (II; R = R′ = R″ = H), one isomeric form of which was readily obtained. Bromination then afforded the dibromo-acid but dehydrobromination yielded only a small quantity of a bromo-lactone, probably (VI). Attempts to remove the second bromine atom failed.

Monobromination (*N*-bromosuccinimide) of the acid (II; R = R′ = R″ = H) gave the bromo-acid (VII; R = R′ = H) which, without purification, was lactonised in good yield. We have not been able to introduce an additional double bond into this compound which would convert it into (IV; R = R′ = H). The structure assigned to the lactone (VIII; R = H) is in accord with the ultra-violet and infra-red spectra.

Infra-red Spectra.—The infra-red spectra of natural santonin and of the two related lactones now synthesised have been measured and compared (4% solution in $CHCl_3$; model 13 Perkin-Elmer infra-red spectrometer, fitted with a sodium chloride prism) (see

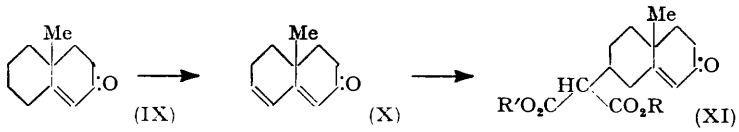
Santonin (IV; R = R′ = Me)			Norsantonin (IV; R = Me, R′ = H)			Lactone (VIII; R = H)		
3020 (m)	1780 (s)	1608 (m)	3020 (m)	1780 (s)	1170 (ms)	3020 (m)	1780 (s)	1170 (ms)
2920 (m)	1664 (s)	990 (ms)	2920 (m)	1660 (s)	835 (m)	2920 (m)	1666 (s)	875 (w)
2850 (sh.w)	1636 (ms)	835 (m)	2850 (w)	1628 (ms)		2850 (w)	1636 (sh.w)	

Table, where figures are cm.$^{-1}$, s = strong, m = medium, w = weak, and sh. = shoulder). As expected, all show comparable bands at 3020, 2920, and 2850 cm.$^{-1}$, due to C–H stretching in :CH and $\cdot CH_2$, a strong band at 1780 cm.$^{-1}$ characteristic of the C:O stretching in a five-membered lactone, and a band at 1660—1666 cm.$^{-1}$ due to the C:O stretching in the ·C:C·C:O system. The bands in the 1608—1636-cm.$^{-1}$ region are considered to arise from the C:C stretching of the ·C:C·C:O system; in the lactone (VIII; R = H) there is only one such ethylenic bond and absorption is accordingly weak, in the norsantonin (IV; R = Me, R′ = H) there are two such ethylenic bonds leading to stronger absorption which appears as a twin peak in santonin itself; the non-separation of the peaks in the norsantonin spectrum, which is not unusual, may be due to steric factors. The two synthetic compounds have a fairly intense band at 1170 cm.$^{-1}$ replaced in santonin by one at 990 cm.$^{-1}$: these peaks are considered to be due to the C–O stretching of the lactone which is reported to be variable within the range 1300—1000 cm.$^{-1}$ (Bellamy, " Infra-Red Spectra of Complex Molecules," Methuen, London, 1954). The differences

observed here may be related to the fact that santonin is believed to have its lactone ring *trans*-fused (Barton, *J. Org. Chem.*, 1950, **15**, 466) whilst our synthetic compounds probably have the lactone ring *cis*-fused (Abe *et al.*, *loc. cit.*, 1954; Cocker and McMurry, *Chem. and Ind.*, 1954, 1199). The band at 835 cm.$^{-1}$ shown by the two diunsaturated ketones but not by the lactone (VIII; R = H) is probably due to the *cis*-olefinic C–H out-of-plane bending in the system ·CH:CH·CO which is only present in these two, but there is no information available at present to confirm this suggestion. The weak band at 875 cm.$^{-1}$ shown by (VIII; R = H) probably arises from the deformation of the solitary C–H bond in the conjugated 1 : 9-double bond which is absent from the other two compounds.

Alternative Route to the Acid (II; R = R′ = R″ = H).—Ralls (*J. Amer. Chem. Soc.*, 1953, **75**, 2123), working in the steroid field, reported the first example of 1 : 6 Michael addition to an unsaturated ketone. As we had already described the preparation of extended dienones similar to (X) (Gunstone and Heggie, *J.*, 1952, 1437) we decided to exploit this in the preparation of the octalone (XI; R = R′ = Et). Whilst the work was in progress other workers applied this reaction to the preparation of homologues of (XI) (Matsui, Toki, Kitamura, Suziki, and Hamura, *Bull. Chem. Soc. Japan*, 1954, **27**, 7; Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1954, **30**, 116; McQuillin, *Chem. and Ind.*, 1954, 311).

The octalone (IX), prepared by the method previously described (du Feu, McQuillin, and Robinson, *J.*, 1937, 53; Gunstone and Heggie, *loc. cit.*) but with sodium methoxide in place of sodamide, was brominated with *N*-bromosuccinimide and dehydrobrominated with collidine. The product was mainly the dienone (X) contaminated with a little unchanged



starting material; this dienone has been prepared before (Yanagita and Tahara, *J. Org. Chem.*, 1953, **18**, 792) but on a small scale and in low yield. Michael addition, effected with one equivalent of sodium ethoxide, gave the substituted octalone (XI; R = R′ = Et) which was readily hydrolysed to the corresponding malonic acid (XI; R = R′ = H). Decarboxylation then gave the monobasic acid (II) (R = R′ = R″ = H) but, whereas the compound previously obtained melted at 113—115°, this sample had m. p. 85—88° and is probably an isomer. Unfortunately we have been unable to prepare an analytically pure sample of this material despite several attempts and the fact that compounds prepared from it gave satisfactory analyses. Abe *et al.* (*loc. cit.*, 1954) obtained different isomers when preparing the homologue (II; R = R″ = Me, R′ = H) by these two routes. The malonic ester (XI; R = R′ = Et) was also hydrolysed with one equivalent of alkali to the half-ester (XI; R = H, R′ = Et); this was decarboxylated and the monoester subsequently hydrolysed to the same low-melting monobasic acid (II; R = R′ = R″ = H). Bromination of this gave a dibromo-acid (III; R = H) again isomeric with that previously obtained, but this, like its isomer, gave a product which could not be freed from bromine-containing impurities when dehydrobrominated. The two dibromo-acids differ somewhat in their ultra-violet spectra ($\lambda_{max.}$ at 238 and 249 mμ) but the configuration of the bromine atom has been reported to have an unexpectedly large influence on the absorption spectrum (Djerassi *et al.*, *loc. cit.*; Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066).

Experimental

Absorption spectra were determined with a Unicam quartz spectrophotometer, ethanol being the solvent unless otherwise stated.

Methyl 4-Methyl-3-oxocyclohexylacetate (I; R = Me).—This was prepared by a modification of the procedure described previously (Mukherjee, *loc. cit.*; Gunstone and Tulloch, *loc. cit.*): Ethyl 1-methyl-2-oxo*cyclo*hexane-1-carboxylate (368 g.) was stirred during addition of bromine (110 ml.) at 0° during 3 hr. With continued stirring, quinoline (350 ml.) was then added and

the mixture heated at 150—160° (bath) for 30 min., during which the temperature of the solution rose to 190°. Worked up as before, the ester (231 g., 64%), b. p. 124—128°/15 mm., absorption max. at 225 mμ (log ε 3·89), was obtained along with lower- and higher-boiling fractions both of which treated as subsequently described for the main fraction gave additional quantities of the acid (I; R = H).

Michael condensation of 1-methyl-2-oxo*cyclo*hex-3-ene-1-carboxylate with diethyl malonate in the presence of catalytic quantities of sodium ethoxide gave after 40 hr. a 74% yield.

Hydrolysis of this substituted malonic ester with concentrated hydrochloric acid (40 hr.) gave the *keto-acid* (I; R = H), b. p. 146—148°/0·4 mm., m. p. 67—88° raised to 88—97° by one crystallisation from carbon tetrachloride. Further crystallisation from this solvent hardly raised the m. p., and a second isomer could not be obtained. The acid crystallised from ether as colourless prisms, m. p. 95—99° (Found: C, 63·8; H, 8·3. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%); it gave a *semicarbazone*, m. p. 193—195° (decomp.), colourless prisms from methanol (Found: C, 53·0; H, 7·4; N, 18·7. $C_{10}H_{17}O_3N_3$ requires C, 52·9; H, 7·5; N, 18·5%), and a p-*bromophenacyl ester*, m. p. 93—95°, colourless leaflets from aqueous ethanol (Found: C, 55·9; H, 5·3; Br, 21·9. $C_{17}H_{19}O_4Br$ requires C, 55·6; H, 5·2; Br, 21·8%).

The acid, esterified by refluxing methanol and concentrated sulphuric acid for 16 hr., gave the *ester* (I; R = Me) (95%), b. p. 136—137°/13 mm., n_D^{18} 1·4627 (Found: C, 65·3; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·8%).

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (II; R = Me, R′ = R″ = H).—A benzene solution of the keto-ester (I; R = Me) (50 g. in 250 ml.) was added to 1-diethylaminopentan-3-one methiodide (from 42·7 g. of the Mannich base and 38·6 g. of methyl iodide) at 0° and the mixture stirred at 0° under a stream of nitrogen during the dropwise addition of sodium (6·3 g.) dissolved in methanol (250 ml.) and subsequently for 2 hr. whilst the temperature rose to 20°. Next day the solution was heated with stirring on the steam-bath for 2 hr., then cooled and acidified (acetic acid, 16 ml.). After removal of most of the solvent under reduced pressure at room temperature, the solution was diluted with water and extracted with ether; acidic material was removed, re-esterified, combined with the main bulk, and distilled. A fore-run of starting material (31·7 g.) was followed by the ester (II; R = R′ = Me, R″ = H) (10·5 g.), b. p. 110—148°/0·3 mm., n_D^{20} 1·510—1·515, absorption max. at 250 mμ (log ε 3·94); the 2 : 4-*dinitrophenylhydrazone*, m. p. 176—177°, formed scarlet leaflets from acetic acid (Found: C, 58·7; H, 6·1; N, 13·1. $C_{21}H_{26}O_6N_4$ requires C, 58·6; H, 6·1; N, 13·0%).

Alkaline hydrolysis (5% sodium hydroxide solution, 3 hr.) gave a gum, approximately one half of which crystallised from ether. This *acid* (II; R = Me, R′ = R″ = H), recrystallised from ether–light petroleum (b. p. 40—60°), had m. p. 130—135°, absorption max. at 248 mμ (log ε 4·22) (Found: C, 71·3; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

1 : 6-*Dibromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (III; R = Me).—Bromine (1·02 g.) in acetic acid (10 ml.) was added dropwise with swirling during 1 hr. to a solution of the acid (II; R = Me, R′ = R″ = H) (0·75 g.) in ether (60 ml.) containing two drops of 4N-hydrogen bromide in acetic acid. The solvent was then removed at 25° under reduced pressure and the residue triturated with ether. The *dibromo-acid* (0·76 g.) solidified [m. p. 123—125° (decomp.)], and formed colourless prisms from benzene–light petroleum (b. p. 60—80°), soluble in 5% sodium carbonate solution, absorption max. at 253 mμ (log ε 4·04) (Found: C, 42·6; H, 4·7; Br, 40·6. $C_{14}H_{18}O_3Br_2$ requires C, 42·7; H, 4·6; Br, 40·6%).

Lactone (IV; R = Me, R′ = H) *of* 1 : 2 : 5 : 6 : 7 : 10-*Hexahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid*.—The dibromo-acid (III; R = Me, 700 mg.) was heated in collidine (20 ml.) to 170° during 30 min. and kept thereat for 90 min., then cooled. Benzene was added and the precipitate of collidine hydrobromide (88%) removed. The solution was then extracted with ice-cold 2N-hydrochloric acid and 5% sodium carbonate solution, and the neutral material (298 mg.) remaining after removal of the solvent was chromatographed on silica gel; the desired *lactone* (93 mg.) was eluted with chloroform. This crystallised from methanol–ether as colourless diamond-shaped prisms, m. p. 122—123°, absorption max. at 243 mμ (log ε 4·05), (cf. santonin, absorption max. at 242 mμ, log ε 4·14; Ruzicka, Cohen, Furter, and van der Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735) (Found: C, 72·3; H, 6·7. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

Lactone (V; R = H) *of* 7-*Acetoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*hydroxy*-5 : 8-*dimethyl*-2-*naphthylacetic Acid*.—After being kept at room temperature for 4·5 hr. a mixture of the ketone (IV; R = Me, R′ = H) (44 mg.), acetic anhydride (2·2 ml.), and concentrated sulphuric acid (9 mg.)

was shaken with water (8 ml.), and the chloroform extract washed with water and with 5% sodium carbonate solution. The gum (38 mg.) remaining after removal of the solvent, when treated with ether, gave crystals (27 mg.) which, after recrystallisation from methanol–ether, afforded the desired *acetate* as colourless prisms, m. p. 148—149°, absorption max. at 273—280 mμ (log ε 3·23), min. at 246 mμ (log ε 2·70), and rising absorption below 210 mμ (log ε 4·32 at 206 mμ) [cf. values for (−)-α-desmotroposantonin acetate given below] (Found: C, 69·8; H, 6·7. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%).

(−)-α-*Desmotroposantonin Acetate* (V; R = Me).—Santonin (50 mg.) was converted into (−)-α-desmotroposantonin acetate, m. p. 154—156° (Huang-Minlon, Lo, and Chu, *J. Chinese Chem. Soc.*, 1943, **11**, 126 give 156—157°), absorption max. at 273—281 mμ (log ε 3·10), min. at 248 mμ (log ε 2·32), and rising absorption below 210 mμ (log ε 4·36 at 206 mμ).

1-*Bromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (VII; R = Me, R′ = H).—A solution of the unsaturated keto-acid (II; R = Me, R′ = R″ = H) (150 mg.) in carbon tetrachloride (25 ml.) was refluxed with *N*-bromosuccinimide (120 mg.) and a trace of benzoyl peroxide for 2 hr. Succinimide was filtered from the cooled solution, the solvent removed at room temperature, and the residue treated with ether, yielding the *monobromo-acid* (115 mg.), m. p. 126—129° after crystallisation from ether–methanol–light petroleum (b. p. 40—60°) (colourless prisms), soluble in cold bicarbonate solution, absorption max. at 246 mμ (log ε 4·12) (Found: C, 53·0; H, 6·1. $C_{14}H_{19}O_3Br$ requires C, 53·3; H, 6·1%). After this had been refluxed with a solution from sodium (50 mg.) in ethanol (20 ml.) for 4 hr. a small amount of neutral product (m. p. 146—153°) was isolated, having an absorption max. at 246 mμ (log ε 4·02). This may have been the lactone (VIII; R = Me) but neither crystallisation nor chromatography gave an analytically pure specimen.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (II; R = R′ = R″ = H).—This octalone ester was also prepared by using sodium methoxide as already described. Methyl iodide (39 g.), 1-diethylaminobutan-3-one (39 g.), keto-ester (I; R = Me) (50 g.), and sodium (6·3 g.) in the same solvents as before gave recovered keto-ester (28 g.) and the octalone ester (8·0 g.), b. p. 144—158°/0·4 mm., absorption max. at 239 mμ (log ε 4·11).

Less conveniently, the keto-ester (I; R = Me) (50 g.) was added dropwise during 30 min. to a stirred suspension of sodamide (from 15·6 g. of sodium) in dry ether (1 l.) at 10° under nitrogen. Stirring was continued for 1 hr. at 10° and for 5 hr. at room temperature and then a solution of 1-diethylaminobutan-3-one methiodide (Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469) [from 1-diethylaminobutan-3-one (39 g.) and methyl iodide (39 g.) in ethanol (45 ml.)] was added at 5° during 90 min. After a further hour's stirring the mixture was left over-night, then heated at 45° for 6 hr., decomposed with 2N-hydrochloric acid, and extracted with ether. The product which was entirely acidic was re-esterified and distilled. The octalone ester (II; R = R″ = H, R′ = Me) (7·7 g.), b. p. 152—180°/0·5 mm., n_D^{21} 1·5220, absorption max. at 239 mμ (log ε 4·05) [*semicarbazone*, m. p. 190—196° (Found: C, 61·4; H, 7·6; N, 14·2. $C_{15}H_{23}O_3N_3$ requires C, 61·4; H, 7·9; N, 14·3%)], was accompanied by a fore-run of starting material (I; R = Me) (25·2 g.).

Hydrogenated over 5% palladium–charcoal this ester gave methyl decahydro-10-methyl-7-oxo-2-naphthylacetate, n_D^{18} 1·4900 [*semicarbazone*, m. p. 188—191° (Found: C, 61·3; H, 8·2; N, 14·3. $C_{15}H_{25}O_3N_3$ requires C, 61·0; H, 8·5; N, 14·2%)]. Attempts to convert this into the ketone (IV; R = R′ = H) were unsuccessful (cf. Gunstone and Heggie, *J.*, 1952, 1437).

Alkaline hydrolysis of the octalone ester by the procedure described above gave the corresponding *acid* (II; R = R′ = R″ = H), m. p. 113—115°, absorption max. at 240 mμ (log ε 4·17) (Found: C, 70·4; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%). Other low-melting samples were obtained but a pure second isomer could not be isolated.

1 : 6-*Dibromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (III; R = H).—Bromination of the foregoing acid as described on p. 1133 gave the *dibromo-acid* (59% yield), m. p. 130—132° (decomp.), absorption max. at 238 mμ (log ε 4·06) (Found: C, 40·9; H, 4·5; Br, 42·5. $C_{13}H_{16}O_3Br_2$ requires C, 41·1; H, 4·2; Br, 42·1).

This dibromo-acid, with refluxing collidine, gave a *monobromo-lactone* (VI), m. p. 115—118° (decomp.), absorption max. at 240 mμ (log ε 4·06) (Found: C, 51·9; H, 5·1. $C_{13}H_{15}O_3Br$ requires C, 52·2; H, 5·1%). When heated with collidine to 170° during 1 hr. and at 170° for a further hour the neutral product (m. p. 168—172°) could not be obtained free from bromine-containing impurities.

Lactone (VIII; R = H) *of* 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-1-*hydroxy*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid*.—The acid (II; R = R′ = R″ = H) (1·24 g.) was treated with *N*-bromosuccinimide (1·1 g.) and the crude monobromo-acid [m. p. 133—135° (decomp.)] was refluxed

with a solution of sodium (124 mg.) in ethanol (15 ml.) for 4 hr. The product, extracted with chloroform and washed with 5% sodium carbonate solution, crystallised from ether. This crude product (600 mg.) was crystallised from ether–methanol and chromatographed on silica gel; elution with benzene–chloroform (1 : 1) removed bromine-containing impurities, followed by the desired *lactone*, m. p. 136—137° after crystallisation from ether–methanol; it had an absorption max. at 235 mμ (log ε 4·14) (Found : C, 70·7; H, 7·4. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

Attempts to brominate this lactone with bromine or with *N*-bromosuccinimide gave only intractable gums. Reaction of the dibromo-acid with sodium ethoxide also gave uncrystallisable products.

2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-*Octahydro*-10-*methyl*-2-*oxonaphthalene* (IX).—This was prepared (19·6 g.) by condensation of 1-diethylaminobutan-3-one methiodide (from 110 g. each of the ketone and of methyl iodide) with 2-methyl*cyclo*hexanone (86 g.) in the presence of sodium methoxide (from 16·5 g. of sodium) by the method already given.

2 : 3 : 4 : 5 : 6 : 10-*Hexahydro*-10-*methyl*-2-*oxonaphthalene* (X).—Bromination of the octalone (33 g.) with *N*-bromosuccinimide in the presence of benzoyl peroxide and subsequent dehydrobromination with collidine at 145° (cf. Gunstone and Tulloch, *loc. cit.*) gave the ketone (X) (15 g.), b. p. 80—86°/0·25 mm., n_D^{18} 1·5630, absorption max. at 281 mμ (log ε 4·22); this gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 187—190°, lustrous deep crimson plates from acetic acid, absorption max. at 267, 307, and 401 mμ (log ε 4·20, 4·12, and 4·53) in $CHCl_3$ (Found : C, 59·7; H, 5·0; N, 16·4. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·4%).

Diethyl 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylmalonate* (XI; R = R′ = Et).—Diethyl malonate (19 g.) in ethanol (25 ml.) was added to sodium (2·42 g.) dissolved in anhydrous ethanol (35 ml.) under a stream of nitrogen, followed by the ketone (X) (17 g.) also in ethanol (25 ml.). The mixture was refluxed for 75 min., cooled, acidified (acetic acid, 6·5 ml.), and poured into brine (50% saturated; 300 ml.); the products were extracted with chloroform and washed with sodium hydrogen carbonate solution and with brine. Distillation gave the keto-ester (11·1 g.), b. p. 174—180°/0·2 mm., n_D^{20} 1·5105, absorption max. at 239 mμ (log ε 4·21), yielding a red 2 : 4-*dinitrophenylhydrazone*, m. p. 146—150° (from ethanol) (Found : C, 57·6; H, 5·8; N, 11·3. $C_{24}H_{30}O_8N_4$ requires C, 57·4; H, 6·0; N, 11·2%).

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylmalonic Acid* (XI; R = R′ = H).—The ester (8 g.) hydrolysed with 3N-alcoholic potassium hydroxide (75 ml.) for 4 hr. after acidification, extraction with chloroform, and crystallisation from ether gave the *dibasic acid* (1·76 g.) which formed colourless prisms, m. p. 165—168° (decomp.) (from water), absorption max. at 239 mμ (log ε 4·24) (Found : C, 63·1; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). The aqueous solution which had been extracted with chloroform deposited more acid (1·54 g.) when concentrated.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (II; R = R′ = R″ = H).—The dibasic acid (2·44 g.) was decomposed at 205°/0·2 mm. during 10 min. The residue, treated with ether, gave an acid, m. p. 85—88° after crystallisation from ether–light petroleum (b. p. 60—80°), having an absorption max. at 240 mμ (log ε 4·19). The m. p. was unchanged when the acid was distilled *in vacuo*. Its p-*bromophenacyl ester* had m. p. 123—124° (Found : C, 59·7; H, 5·5. $C_{21}H_{23}O_4Br$ requires C, 60·1; H, 5·5%).

The same acid was obtained from the diester *via* the acid-ester thus : The diester (860 mg.) was refluxed with 0·5N-ethanolic potassium hydroxide (5·3 ml., 1 equiv.) for 2 hr. and worked up as described. Crystallised from ether at −20° and subsequently from benzene–light petroleum (b. p. 60—80°), the product gave *monoethyl* 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-10-*methyl*-7-*oxo*-2-*naphthylmalonate* (XI; R = H, R′ = Et) (115 mg.), m. p. 142—145° (decomp.), absorption max. at 240 mμ (log ε 4·22) (Found : C, 65·0; H, 7·1. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). When this was distilled at 160° (bath)/0·5 mm., decarboxylation occurred with formation of the ester (II; R = R″ = H, R′ = Et) [*semicarbazone*, m. p. 187—190°, needles from methanol (Found : C, 62·7; H, 8·0; N, 13·8. $C_{16}H_{25}O_3N_3$ requires C, 62·5; H, 8·2; N, 13·7%)]. The 2 : 4-*dinitrophenylhydrazone* of the methyl ester (II; R = R″ = H, R′ = Me) was obtained when prepared from the ethyl ester in methanol solution in presence of concentrated sulphuric acid, and had m. p. 76—78° (Found : C, 57·9; H, 5·7. $C_{20}H_{24}O_6N_4$ requires C, 57·7; H, 5·8%). The non-crystalline portion of the acid-ester was similarly decarboxylated and then hydrolysed to give the monobasic acid (II; R = R′ = R″ = H), m. p. 84—86°.

1 : 6-*Dibromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (III; R = H).—The low-melting isomer of the acid (II; R = R′ = R″ = H) gave a *dibromo-acid*, m. p. 142—145° (decomp.), absorption max. at 249 mμ (log ε 4·03) (Found : C, 40·7; H, 4·4.

$C_{13}H_{16}O_3Br_2$ requires C, 41·1; H, 4·2%). Attempts to dehydrobrominate this acid with collidine again gave impure material containing bromine.

We are indebted to the D.S.I.R. for a Maintenance Allowance (to A. P. T.), to Miss C. E. A. Smith for assistance with early experiments in the alternative route to the acid (II; R = R′ = R″ = H), to Dr. G. Eglinton for the measurement and interpretation of the infra-red spectra, and to Mr. J. M. L. Cameron and Miss M. W. Christie for the microanalyses.

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