Tetrahedron. Vol. 30, pp. 1073 to 1081. Pergamon Press 1974. Printed in Great Britain

SYNTHESIS OF SOME STEREOISOMERS OF (±) - 1 - DESMETHYLDESMOTROPOSANTONIN METHYL ETHER AND RELATED LACTONES

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(*Received in the UK* 18 *November* 1973; *Accepted for publication* 3 *December* 1973)

Abstract—Alkylation of 7 - methoxy - 8 - methyl - 1 - tetralone (**9**) with α-bromopropionic acid provided a stereoisomeric mixture of the keto-acid (**10**). The isomers (**10a** and **10b**) on sodium borohydride reductions afforded respectively the title compounds (**12** and **13**). Similar reduction of a stereoisomeric mixture of **17**, on the other hand, produced two *cis*-lactones (**19** and **20**), the hydroxy-acid (**30**) and the *trans*-lactone (**22**). Sodium borohydride reduction of the simple keto-acid (**18**) furnished initially the *cis*-lactone (**21**) and a mixture of hydroxy-acids (**31**). This hydroxy-acid on lactonisation gave a separable mixture of **21** and **24**. The steric effect of the peri-Me group on the stereochemical outcome of sodium borohydride reduction of the keto-acid (**10**) has been clearly demonstrated. It has also been pointed out that the difference in the NMR signals for C—6 benzylic protons of the C—11 epimeric *cis*-lactones, reported here and in the literature, may serve as a diagnostic tool for elucidating the stereochemistry of the C—11 Me groups of these lactones.

Partial aromatisation[1] of santonin (**1**) with zinc and dimethylformamide furnished a crystalline phenolic compound fully characterised[2] as 6β (H), 7α (H), 11β (H) - 1 - desmethyldesmotroposantonin (**2**). Pyrolytic aromatisation of α- and β- santonin, on the other hand, produced[3] the isomeric *cis*-lactones (**4** and **6**)† respectively. The first synthesis of *dl*-desmotroposantonin (a *cis*-fused lactone) was reported by Haworth *et al*[4]. A few other syntheses of desmotroposantonins were mostly achieved[5] through the acid-catalysed dienone-phenol rearrangement of synthetic santonins. We initiated[6] a programme aimed at developing facile and practical syntheses of desmotroposantonins and related lactones such as **3** having the *trans*-fused lactone ring. In this paper the syntheses and stereochemical elucidations of (±) - 1 - desmethyl-desmotroposantonin methyl ethers (**12** and **13**) and several related lactones such as **19–21**, **22** and **24** are described.

We planned to utilise 7 - methoxy - 8 - methyl - 1 - tetralone (**9**)[6a] for the synthesis of lactones of the type **3** according to Scheme 1.

The readily available[6a] tetralone derivative (**9**) was converted to **10** following essentially the procedure[7] of Puterbaugh and Readsaw. The tetralone (**9**) on alkylation with α-bromopropionic acid in the presence of lithium amide in liquid ammonia furnished a diastereomeric mixture of the keto-acid (**10**). Fractional crystallisation of this mixture gave predominantly the acid (**10b**), and the epimer (**10a**) as the minor component. The epimeric acid (**10a**) on sodium borohydride reduction in alkaline solution and subsequent acidification provided a pure diastereomeric lactone (**12**), m.p. 159–160°, in excellent yield. The acid (**10b**) on similar reduction furnished the epimeric lactone (**13**), m.p. 109–110°, together with a very small amount of the stereoisomer (**12**) probably arising from the isomeric acid (**10a**) present as impurity in **10b**. Attempted isolation of the intermediate hydroxy-acid (**11**), even under carefully controlled conditions, afforded the lactones mentioned above thereby establishing exclusive *cis*-reduction of the CO group. Incidentally, it may be mentioned that House *et al*[8] reported the isolation of the corresponding *trans*-hydroxy-acid as the predominant component in similar reduction of 1 - keto - 2 - indanylacetic acid. The lactone (**12**) was recovered unchanged on heating with a mixture of acetic anhydride and conc H_2SO_4 thereby establishing the *cis*-ring-fusion of the lactone. That the two lactones (**12** and **13**) differ only in the stereochemistry at C-11 was provided by the well-recognised[9] isomerisation experiment. The epimer (**12**) on refluxing with anhydrous potassium carbonate under xylene afforded an equilibrium mixture from which the epimeric lactone (**13**) could be separated by fractional crystallisations. The lactone (**13**) on similar treatment gave the same equilibrium mixture from which the isomer (**12**) could be iso-

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†The structure XXI and XXII (see page 1391 of ref. 3) respectively for the β-santonin and the *cis*-lactone derived from it need correction. The C-11 methyl group should be β instead of α in both the cases.

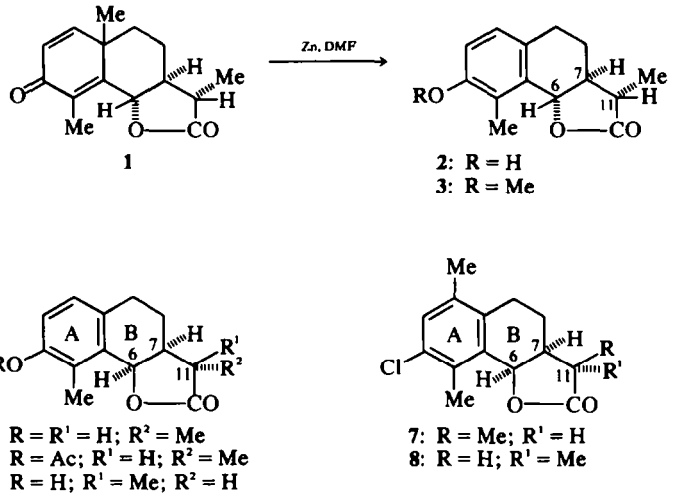
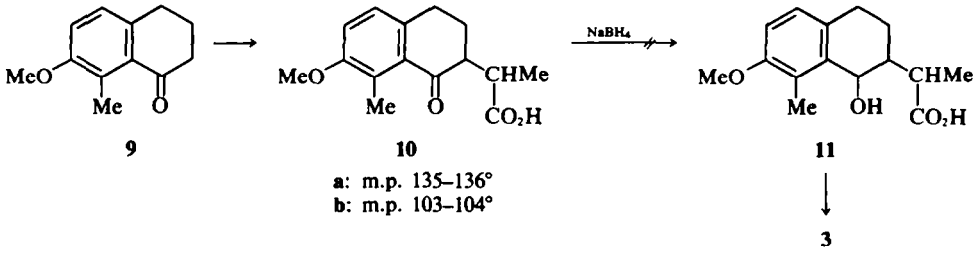


Fig 1.



SCHEME 1

lated in poor yield. The stereochemistry of the C-11 Me with respect to the C-7 hydrogen has been secured from the evidence described in Fig 2.

The diastereomeric mixture of the keto-acids (**10**) on refluxing with acetic anhydride and sodium acetate gave an unsaturated lactone characterised as **14** from its spectral characteristics. This lactone (**14**) on catalytic hydrogenation furnished in excellent yield, a single acid which should be represented by the stereostructure (**15**) from its mode of formation. Catalytic hydrogenolysis of the lactone (**12**) also produced the same acid (**15**) in good yield. From the above chemical as well as from the NMR spectral evidences (Experimental), the stereostructures (**12** and **13**) have been unambiguously established for the higher and lower melting lactones respectively. A recent report by Cocker *et al*[10] also supports the above arguments for the assignment of the stereochemistries of the lactones.

It should be noted that the lactone (**12**) on refluxing with methanolic sodium hydroxide and subsequent acidification provided the epimeric lactone (**13**) as the sole product. Inversion at C-11 asymmetric centre probably is preceded by hydrolysis of the lactone ring, and it could therefore be concluded that the stability of the hydroxy-acid and not that of the lactone which here determines[11] the configuration of the 11-C atom of the lactone obtained through acidification of the alkaline solution.

The mixture of lactones (**12** and **13**) on refluxing with methanol and sulphuric acid furnished an unsaturated ester; and this on saponification produced a crystalline acid, characterised as **16** from spectral properties.

To evaluate the possible effect of the peri-substituent in the aromatic ring on the course of sodium borohydride reduction of γ-keto-acids such as **10**, reductions of the keto-acids (**17** and **18**) were next investigated.

Reduction of a diastereomeric mixture of the keto-acid (**17**)[12] with sodium borohydride in alkaline solution and subsequent acidification afforded a neutral and an acidic components. The neutral material was proved to be a mixture of two *cis*-lactones (**19** and **20**) in a ratio of *ca* 3:7 (from NMR). Repeated fractional crystallisations of this mixture provided a pure *cis*-lactone, m.p. 140–141°, assigned as **19** from the following evidence.

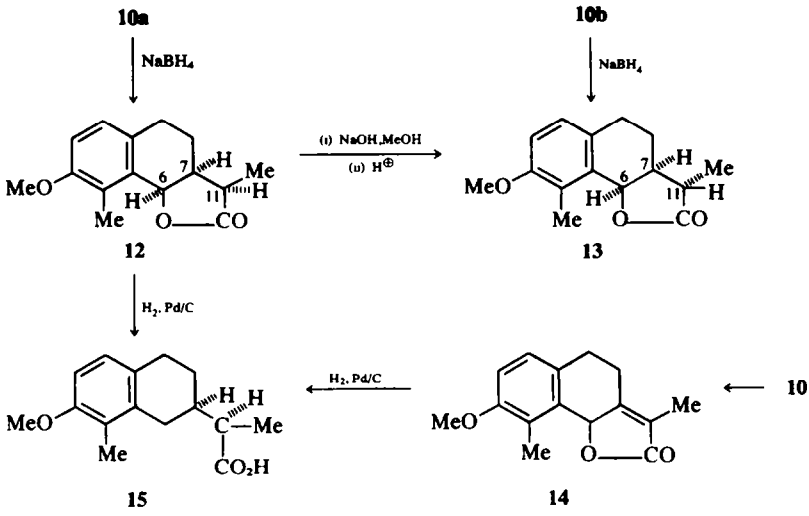


Fig 2.

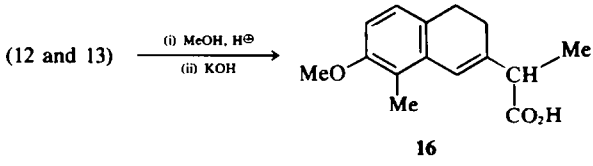


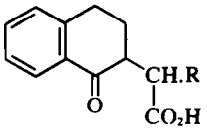
Fig 3.

The *cis*-ring-fusion of the lactone (**19**) was secured from the low coupling constant for the C-6 benzylic proton doublet at τ 4·72 ($J = 5$ Hz) in NMR; and also from the fact that this was practically recovered unchanged on heating with acetic anhydride and conc H_2SO_4. Catalytic hydrogenolysis of the lactone (**19**) provided a single acid (**25**) previously reported by us.[13] The relative stereochemistry of the C-11 Me and C-7 hydrogen in **19** was thus established. Treatment of **19** with hot methanolic sodium hydroxide followed by acidification gave a mixture of **19** and **20**; indicating that the lactone (**20**) is a C-11 epimer of **19**.

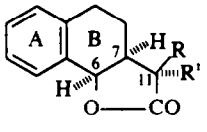
The acidic product obtained from sodium borohydride reduction of **17** was probably a mixture of all possible stereoisomers of *cis*- and *trans*-hydroxy-acids. Careful chromatography of this mixture provided a diastereomeric mixture of *trans*-hydroxy-acids. Lactonisation of this acid by heating at 145–150° under vacuum furnished a neutral and an acidic material. The neutral product on repeated crystallisations afforded the pure lactone (**22**). The assignment of *trans* nature of the lactone ring fusion was followed from the coupling constant of the C-6 proton doublet at τ5·04 (J = 9·8 Hz). The stereochemistry of the C-11 Me group with respect to the C-7 H atom was established from the following transformation. Catalytic or lithium–liquid ammonia induced hydrogenolysis of **22** provided the known[13] acid (**26**) as the only isolable product. Further confirmation for the *trans* nature of the lactone (**22**) was available from the epimerisation of the C-6 asymmetric centre by heating with acetic anhydride and sulphuric acid, producing the epimeric *cis*-lactone (**20**), m.p. 89–90°, which could also be detected in the sodium borohydride reduction product of **17**, and in the epimerisation product of the *cis*-lactone (**19**) as mentioned above. The stereochemistry of this lactone (**20**) was unambiguously confirmed from its NMR spectrum (Experimental). In one experiment, the lactone (**22**) on heating with acetic anhydride and conc H_2SO_4, afforded mainly the known[14] unsaturated acid (**27**).

The unchanged acid obtained during lactonisation of the *trans*-hydroxy-acid (mixture) described above, on crystallisation gave a pure homogeneous sample of the *trans*-hydroxy-acid (**30**) m.p. 158–160°. This acid on heating at 170° followed by sublimation of the residue under vacuum quantitatively transformed to the *trans*-lactone (**22**) mentioned above; and this confirmed the stereostructure (**30**) for the above hydroxy-acid. All attempts at isolation of the other *trans*-lactone (**23**) was futile. The mother liquors, obtained after separation of the pure lactone (**22**) on chromatography

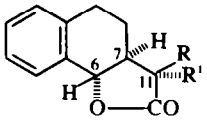
afforded a product, m.p. 62–73° ν_{max} 1779 cm^{-1}; the NMR spectrum of which was, however, practically indistinguishable from that of the lactone (**22**). The spectral evidence indicates that the above product, m.p. 62–73° is a mixture of two isomeric *trans*-lactones (**22** and **23**).



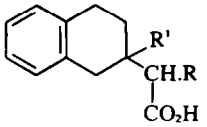
17: R = Me
18: R = H



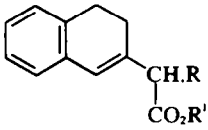
19: R = Me; R' = H
20: R = H; R' = Me
21: R = R' = H



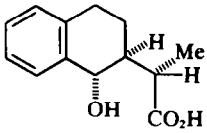
22: R = H; R' = Me
23: R = Me; R' = H
24: R = R' = H



25: β-Me, α-H
26: α-Me, α-H



27: R = Me; R' = H
28: R = Me; R' = Et
29: R = R' = H



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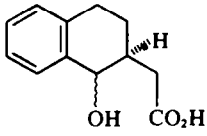

31

Fig 4.

Reduction of the keto-acid mixture (**17**) with sodium borohydride according to the procedure of Dasgupta *et al*[14] furnished a stereoisomeric mixture of *cis*-lactones. Repeated crystallisations of this mixture provided a pure sample of the *cis*-lactone (**19**) mentioned earlier. The lactonic product, m.p. 80–82°, reported by the above authors[14] is in all probability a mixture of the *cis*-lactones (**19** and **20**).

The mixture of the above *cis*-lactones (**19** and **20**) on treatment with thionyl chloride in benzene followed by refluxing with dry ethanol provided initially a chlorine containing product. Repeated evaporative distillation of this product resulted in the isolation of the unsaturated ester (**28**) in good yield. This ester on saponification furnished the unsaturated acid (**27**)[14] reported above.

Lactonisation of the above β,γ-unsaturated acid (**27**)[14] with conc H_2SO_4 in chloroform afforded a mixture of the *cis*-lactones (**19** and **20**) in a ratio of *ca* 5:7 (from NMR). Repeated fractional crystallisation of this mixture finally gave the pure *cis*-lactone (**19**). Two epimers of the lactone of 1-hydroxy-1,2,3,4-tetrahydronaphthalene-2-α-propionic acid with undefined stereochemistry have been previously synthesised.[15] It may also be mentioned in this connection that an attempted stereospecific synthesis of the *trans*-lactone of the type **22** through *trans*-opening of 3,4-dihydronaphthalene-1,2-oxide with the anion of diethyl methylmalonate resulted[16] exclusively in the formation of the structurally isomeric lactone.

We finally turned our attention to the sodium borohydride reduction of the simple keto-acid (**18**).[12] The crude acidic product isolated from the reaction mixture under usual conditions of work-up appeared to be a mixture of hydroxy-acids and lactone. This was redissolved in ether and after usual partition with aqueous sodium carbonate solution afforded a neutral and an acidic product. The neutral fraction on crystallisation provided the pure *cis*-lactone (**21**), m.p. 101–102°. The acidic product on repeated fractional crystallisations afforded a known[15] hydroxy-acid, m.p. 133–135°. This acid was proved to be a stereoisomeric mixture of *cis*- and *trans*-hydroxy acids (**31**) as described below.

The above hydroxy-acid on heating at 170–180° and subsequent sublimation under vacuum produced a mixture of *cis*- and *trans*-lactone, m.p. 87–115° in a ratio of about 11:9 (from NMR). Chromatographic separation of the above mixture provided the pure *cis*-lactone (**21**) mentioned above and the *trans*-isomer (**24**), m.p. 137–138°. The lactone, m.p. 106°, previously reported[15] is in all probability a stereoisomeric mixture of **21** and **24**. The above experiments clearly indicate that the *cis*-hydroxy-acid derived from the keto-acid (**18**) is more stable in comparison with the corresponding acids obtainable from the keto-acids (**17** and **10**).

Treatment of the above *trans*-lactone (**24**) with a mixture of acetic anhydride and sulphuric acid furnished mainly the cyrstalline unsaturated acid (**29**).[17] The *cis*-isomer (**21**) on refluxing with thionyl chloride followed by treatment with ethanol provided an unsaturated ester which on saponification afforded the unsaturated acid (**29**)[17] in excellent yield. Attempted acid-catalysed lactonisation of this acid was unsuccessful.

Previous studies on the stereochemical outcome of sodium borohydride reductions of several γ-keto-acids indicated[8] that the major product formed is the more stable isomer, i.e. the *trans*-hydroxy acid. These results, however, offered no support for the participation of the carboxylate anion on the

stereochemical course of the reductions either by assisting hydride ion transfer or by electrostatic shielding. In the present studies, influence of the peri-Me group on the stereochemical outcome of sodium borohydride reductions of the keto-acids (**10**) is informative. The cumulative steric effect from the peri-Me group and the side chain containing the carboxylate anion probably shields one side of the CO group for the approach of the borohydride ion, and thus facilitates the exclusive formation of the *cis*-lactones *via*- the intermediate *cis*-hydroxy-acids arising from the attack of the hydride ion from the opposite side of the CO group.

NMR spectra of the lactones. Two simple NMR spectroscopic methods based on solvent shifts of C-11 Me group, and the C_{11}-H—C_7—H coupling constant, have been applied[18] to assign the stereochemistry of C-11 Me of santonins and related lactones. Proton chemical shifts of C-6 proton in the *cis*-lactones, described in this paper and for analogous lactones (**4–8**), reported in the literature[3,19] are collected in the Table 1. It is evident from these data that in the *cis*-lactones with C-11 Me *trans* to C-7 H, C-6 H atoms resonate at higher field than those of the isomeric *cis*-lactones with C-11 methyl *cis* to the C-7 H atom. This difference in the NMR signal for H at C-6 may be utilised as a diagnostic tool for elucidating the stereochemistry of the C-11 Me group of these *cis*-lactones. This effect presumably arises in the two epimeric series due to the relative change in geometry of the C-6 proton with respect to the aromatic ring caused by the distortion of the B-ring in the case of the *cis*-lactones with C-11 methyl eclipsed with the C-7 H atom.

Table 1. NMR signals for the C-6 hydrogen atom of some C-11 epimeric *cis*-lactones

Lactones	Stereochemistry of C-11 Me with respect to C-7 H	Signal for C-6 hydrogen doublet (τ)	J values (Hz)
12	*trans*	4·70[a]	6
13	*cis*	4·37[a]	6
19	*trans*	4·72[a]	5
20	*cis*	4·46[a]	6·12
6[3]	*trans*	4·63[b]	5
4[3]	*cis*	4·37[b]	6
5[3]	*cis*	4·45[a]	6
7[19]	*trans*	4·68[a]	6
8[19]	*cis*	4·42[a]	5·9

[a] Spectra measured in $CDCl_3$.
[b] Spectra measured in a mixture of $CDCl_3$ and $(CD_3)_2SO$.

EXPERIMENTAL

The compounds described are all racemic forms. M.ps were determined on a H_2SO_4 bath and are uncorrected. UV spectra (determined in EtOH soln) were measured on Unicam SP 500 spectrophotometer. IR spectra were recorded on a Perkin–Elmer infracord Model 337 (in $CHCl_3$ soln until otherwise stated) and NMR spectra were measured on Varian Associates A60–D spectrophotometer (using $CDCl_3$ as solvent containing TMS as internal standard). Light petroleum refers to the fraction, b.p. 60–80°. Neutral Brockmann alumina (S. Merck and Co.), and silica gel (BDH) were used for column chromatographic experiments. TLC plates were coated with silica gel G (acc. to Stahl) having a thickness of about 0·2 mm and the spots were located by exposing the dried plates in iodine vapour. Extracts were dried over Na_2SO_4.

2 - (*α* - *Carboxyethyl*) - 7 - *methoxy* - 8 - *methyl* - 1 - *tetralone* (**10**). The carboxyalkylation of **9** was carried out according to the procedure of Puterbaugh.[7]

To a stirred suspension of lithium amide prepared from Li (456 mg) in anhyd liquid ammonia (300 ml), a soln of **9** (8 g) in dry ether (20 ml) was added. After the addition, the ammonia was rapidly evaporated and replaced by dry ether (110 ml). To the resulting mixture, a soln of *α* - bromopropionic acid (3·2 g) in dry ether (20 ml) was added over 10 min. The reaction was then completed by refluxing for 10 h. The mixture was then decomposed by cold water (60 ml). The ethereal soln was extracted with water, dried and evaporated to furnish the starting tetralone **9** (4 g), b.p. 125–130°/0·4 mm. The combined aqueous layers were acidified with conc HCl. The resulting turbid soln was extracted with ether, washed with water, dried, and evaporated to furnish **10** (3·52 g, 64% based on the recovery), m.p. 100–106°. The above acid on several recrystallisations from light petroleum furnished an analytical sample of **10a** as star-shaped crystal, m.p. 135–136°, λ_{max} 253 and 319 nm (ϵ 7,762 and 2,511), ν_{max} 1706 and 1679 cm^{-1}. On TLC (benzene–MeOH, 20:80) it gave a single spot. (Found: C, 68·70; H, 7·23; OMe, 11·80. $C_{15}H_{18}O_4$ requires: C, 68·69; H, 6·90; OMe, 11·83%). The mother liquor of the above recrystallisations was chromatographed over silica gel (14 g). Elution with 15% ether–light petroleum afforded **10b** as drops, m.p. 103–104° (from light petroleum), λ_{max} 253 and 319 nm (ϵ 8,239 and 2,474), ν_{max} 1679 and 1710 cm^{-1}. On TLC (benzene–methanol, 20:80) it gave a bright single spot. (Found: C, 68·63; H, 6·76; OMe_3, 11·83. $C_{15}H_{18}O_4$ requires: C, 68·69; H, 6·90; OMe, 11·83%).

Sodium borohydride reduction of the keto-acids (**10**)

Formation of (±) - 6*α* (*H*), 7*α* (*H*), 11*α* (*H*) - 1 - *desmethyldesmotroposantonin methyl ether* (**12**) *and* (±) - 6*α* (*H*), 7*α* (*H*), 11*β* (*H*) - 1 - *desmethyldesmotroposantonin methyl ether* (**13**). (a) To a stirred ice-cold soln of **10a** (320 mg) in 2N NaOH (6 ml) was added $NaBH_4$ (170 mg). The mixture was stirred for 8 h and then allowed to stand at room temp for 16 h. The resulting homogeneous soln was cooled to 0°, carefully acidified with ice-cold dil HCl and extracted with ether. The ethereal extract was washed with sat $NaHCO_3$ aq. The alkaline soln was acidified cautiously with ice-cold dil HCl and the liberated acid was extracted with ether. The ether extract was repeatedly washed with cold water, dried and evaporated to afford colourless silky needles of **12** (230 mg, 76%), m.p. 159–160° (light petroleum–ether), λ_{max} 283 nm (ϵ 2,338), ν_{max} 1768 cm^{-1}, τ 8·80 (3H, d, J 6 Hz), 7·78 (3H, s), 6·80–7·65 (6H, m), 6·23 (3H, s), 4·70 (1H, d, J 6 Hz) and 3·15 (3H, qu, J 8·4 Hz). On TLC (benzene–MeOH, 90:10) it gave a bright single spot. (Found: C, 72·89; H, 7·38. $C_{15}H_{18}O_3$ requires: C, 73·15; H, 7·37%).

(b) To an ice-cold stirred soln of **10b** (130 mg) in 2N

NaOH (5 ml), was added $NaBH_4$ (80 mg). After the complete addition of the borohydride the homogeneous soln was stirred further for 4 h, and then left at room temp for 16 h. This was then worked up as before to afford the isomeric lactones **12** (36 mg) m.p. 159–160°, and **13** (62 mg, 50%), m.p. 109–110°, λ_{max} 282 nm (ϵ 2,230), ν_{max} 1768 cm^{-1}, τ 8·60 (3H, d, *J* 6·5 Hz), 7·70 (3H, s), 6·20 (3H, s) 4·37 (1H, d, *J* 6·0 Hz) and 3·12 (3H, qu, *J* 8·4 Hz). On TLC (benzene–MeOH, 90:10) it gave a bright single spot. (Found: C, 73·26; H, 7·54. $C_{15}H_{18}O_3$ requires: C, 73·15; H, 7·37%).

Action of acetic anhydride and sulphuric acid on (±) - 6α (*H*), 7α (*H*), 11α (*H*) - 1 - *desmethyldesmotroposantonin methyl ether* (**12**). To a soln of **12** (100 mg) in Ac_2O (3 ml), a drop of conc H_2SO_4 acid was added and warmed on the steam bath for 20 min. The mixture was then poured over ice water and the product extracted with ether. The solvent after usual processing afforded the unchanged lactone **12** (60 mg), m.p. and mixed m.p. with the starting material, 159–160°.

Potassium carbonate isomerisation[9] *of the higher melting lactone* (**12**) *and the lower melting lactone* (**13**). (a) A mixture of **12** (136 mg), freshly ignited K_2CO_3 (136 mg) and anhyd xylene (4 ml) was refluxed in an oil bath (150–160°) for 24 h. Xylene was then removed under reduced pressure and the residue extracted with ether. The ether extract was washed with water, dried and evaporated. The residue on fractional crystallisation from ether–light petroleum provided **12** (60 mg), m.p. 159–160°, the isomeric lactone **13** (28 mg), m.p. 109–110°; and a mixture as an oil (50 mg).

(b) A mixture of **13** (100 mg), freshly ignited K_2CO_3 (100 mg) and dry xylene (3 ml) was refluxed for 24 h. The mixture was worked up as described above. The crude mixture thus obtained on fractional crystallisation afforded **12** (20 mg), m.p. 159–160°, the unchanged **13** (30 mg), m.p. 109–110°; and a mixture as an oil (40 mg).

Treatment of the higher melting lactone (**12**), *with methanolic sodium hydroxide solution*

Formation of the lower melting lactone (**13**). To a soln of NaOH (0·16 g) in MeOH (4 ml), the lactone **12** (0·2 g) was added and the mixture was refluxed under N_2 for 5 h. The solvent was then evaporated, diluted with ice water and acidified with calculated amount of cold dil HCl. The turbid soln was extracted with ether, washed with sat $NaHCO_3$ aq, dried, and evaporated to afford the crystalline **13** (158 mg, 79%), m.p. 108–110°.

7 (11) - *Dehydrodesmethyldesmotroposantonin methyl ether* (**14**). A mixture of the crude **10** (500 mg), freshly distilled Ac_2O (4·5 ml) and freshly ignited NaOAc (10 mg) was heated under reflux in an atmosphere of N_2 for 4 h. The volatile material was evaporated under reduced pressure and the solid residue was extracted with ether. The ether extract was washed with sat Na_2CO_3 aq, dried, and evaporated to afford colourless needles (300 mg, 64·4%), which was crystallised to give an analytical sample of **14**, m.p. 163–164° (from ether–light petroleum), λ_{max} 222, 264, 279 and 288 nm (ϵ 19,950, 8,314, 9,772 and 10,230); ν_{max} 1745, 1693 cm^{-1}. (Found: C, 73·68; H, 6·62. $C_{15}H_{16}O_3$ requires: C, 73·75; H, 6·60%).

2 - (α - *Carboxyethyl*) - 7 - *methoxy* - 8 - *methyl* - 1,2,3,4 - *tetrahydronaphthalene* (**15**). (a) A soln of the **14** (152 mg) in 95% EtOH (10 ml) was hydrogenated over 10% Pd-C (50 mg) at room temp and atmospheric pressure. The uptake of theoretical quantity of hydrogen (29 ml) was complete within 15 min. The catalyst was filtered and the solvent evaporated. The acid was dissolved in $NaHCO_3$ aq and acidified. The turbid soln was extracted with ether, and the dry solvent was evaporated to afford crystalline compound (100 mg, 64·5%) which was recrystallised to give an analytical sample of **15**, m.p. 128–129° (from light petroleum), λ_{max} 278 nm (ϵ 1,998); ν_{max} 1708 cm^{-1}. (Found: C, 72·47; H, 8·35. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%).

(b) A soln of **12** (100 mg) in 95% EtOH (10 ml) was hydrogenated over 10% Pd-C (70 mg) at room temp and atmospheric pressure. The theoretical amount of H_2 (8·9 ml) was absorbed during 10 min. The mixture was worked up as above to give **15** (70 mg, 69%), m.p. and mixed m.p. 128–129°.

Action of methanol and sulphuric acid on the mixture of lactones (**12** *and* **13**)

Formation of 7 - *methoxy* - 8 - *methyl* - 3,4 - *dihydro* - 2 - *naphthyl* - α - *propionic acid* (**16**). To a soln of the mixture of **12** and **13** (250 mg) in dry MeOH (15 ml) was added a drop of conc H_2SO_4 and the soln was refluxed for 12 h. The mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed with sat $NaHCO_3$ aq, dried, and evaporated to give a neutral ester (210 mg). The above crude ester was hydrolysed by heating under reflux with a soln of 2% KOH aq (7 ml) for 3 h. The mixture on usual workup furnished **16** (180 mg, 72%) which was crystallised to give an analytical sample, m.p. 119–120° (from ether–light petroleum), λ_{max} 228 and 269 nm (ϵ 27,540 and 12,590); ν_{max} 1711 cm^{-1}. (Found: C, 72·86; H, 7·68. $C_{15}H_{18}O_3$ requires: C, 73·15; H, 7·37%).

Sodium borohydride reductions of the stereoisomeric mixture of the keto-acid (**17**)

Formation of cis- (**19**) *and trans-* (**22**) *lactones of* 1 - *hydroxy* - 1,2,3,4 - *tetrahydro* - 2 - *naphthyl* - α - *propionic acid, and a pure stereoisomer* (**30**) *of the trans-hydroxy-acid.* (a) To a stirred and ice-cold soln of **17** (2·5 g), m.p. 110–115° in 0·2N NaOH aq (150 ml) was added $NaBH_4$ (1·85 g). After complete addition, the resulting homogeneous soln was stirred for 8 h and then left at room temp for 16 h. The mixture was then cooled to 0° and cautiously acidified with cold dil HCl. The product was immediately extracted with ether (3 × 100 ml). The solvent was washed with water and then repeatedly extracted with sat Na_2CO_3 aq (4 × 50 ml). Evaporation of the dry neutral ether gave an oily material (130 mg) which soon solidified. Repeated recrystallisations of this product from ether–light petroleum provided a product, m.p. 80–85° as a mixture of *cis-* **19** and **20**, ν_{max} 1765 cm^{-1} (lactone C=O); two characteristics doublets for C-6 H atoms at τ 4·68 (*J* 5·04 Hz) and 4·46 (*J* 6·12 Hz) indicated the product to be a 3:7 mixture of **19** and **20** respectively. (Found: C, 77·44; H, 6·85. $C_{13}H_{14}O_2$ requires: C, 77·20; H, 6·98%).

The above Na_2CO_3 extract was acidified with calculated amount of dil HCL and the separated product was immediately extracted with ether (3 × 100 ml). Removal of the dry solvent afforded a product (2·24 g) as a mixture. Usual separation of this mixture as before provided a neutral (1·1 g) and an acidic material (1·05 g), ν_{max} 1709 cm^{-1} (acid C=O). The neutral product on one crystallisation from acetone–light petroleum gave a material (1·04 g; 44%), m.p. 135–138°. Three more recrystallisations from the same solvent mixture afforded **19**, m.p. 140–141°; ν_{max} 1762 cm^{-1} (lactone C=O); τ 2·54–2·86 (4H, m), 4·72 (1H, d, *J* 5·0 Hz), 6·85–7·64 (4H, m),

7·92–8·56 (2H, m), τ 8·77 (3H, d, J 7·2 Hz). (Found: C, 77·46; H, 7·11%).

The above acidic product (1·05 g) was chromatographed over activated silica gel (40 g). Ether–light petroleum (30:70) eluted an acidic material (820 mg; 32%), m.p. 110–120°. Crystallisation of this product afforded a product (680 mg; 27%), m.p. 130–132°; the IR absorptions at 1707 (s) and 1778 (v.w.) cm^{-1} indicated the product to be a mixture of hydroxy-acid (major) and lactone (minor). Lactonisation of this product (680 mg) by sublimation at 140–145° (bath)/0·1 mm furnished a neutral (380 mg), m.p. 55–62°, ν_{max} 1778 cm^{-1}; and an acidic product (220 mg) m.p. 152–156°; ν_{max} 1709 cm^{-1}. Repeated crystallisations of the neutral material provided a pure sample of the *trans*-lactone **22**, m.p. 78–79° (ether–light petroleum); ν_{max} 1778 cm^{-1}; τ 2·43–2·98 (4H, m), 5·04 (1H, d, J 9·8 Hz), 6·82–7·04 (2H, m), 7·32–8·43 (4H, m), 8·68 (3H, d, J 6·5 Hz). (Found: C, 77·05; H, 7·16). The oil (340 mg) obtained from the mother liquors of crystallisations of **22** was chromatographed over silica gel (20 g). Ether–light petroleum (5:95) eluted a crystalline material (270 mg); four recrystallisations from the above solvent mixture afforded an analytical sample (62 mg), m.p. 62–73°; ν_{max} 1779 cm^{-1}; NMR spectrum identical with that of the pure **22**. (Found C, 77·17; H, 7·07%).

The acidic material (220 mg), m.p. 152–156° mentioned above on recrystallisation gave a pure sample of the *trans-hydroxy-acid* (**30**), m.p. 159–160°, ν_{max} 1709 cm^{-1} (acid C=O). (Found: C, 70·61; H, 7·58. $C_{13}H_{16}O_3$ requires: C, 70·89; H, 7·32%).

The oily material (700 mg) obtained from the mother liquors of crystallisations of the hydroxy-acids (from chromatography) was lactonised by heating at 155–160° (bath)/0·2 mm to furnish a neutral product (600 mg), ν_{max} 1765 cm^{-1}, probably as a mixture of all possible *cis*- and *trans*-lactones. Several recrystallisations of this mixture afforded a material, m.p. 94–125°, ν_{max} 1766 cm^{-1} (lactone C=O). (Found: C, 77·19; H, 7·09%).

(b) Sodium borohydride reduction of **17** according to the procedure of House *et al*[8] afforded a mixture of *cis*-**19** and **20**; and a mixture of hydroxy-acids in 38 and 30% yields respectively. The mixture of *cis*-lactones could not be resolved into two pure isomers through chromatography or fractional crystallisations.

(c) Reduction of **17** with $NaBH_4$ following exactly the procedure of Dasgupta *et al*[4] provided a mixture of *cis*-**19** and **20** (80%), m.p. 72–76°, ν_{max} 1764 cm^{-1}. Several recrystallisations of the above mixture finally afforded the pure *cis*-**19**, m.p. 140–141° (ether–light petroleum) (Found: C, 77·25; H, 6·91%).

Lactonisation of the trans-hydroxy-acid (**30**). The *trans*-acid **30** (140 mg), m.p. 158–160° was heated for 15 min in an oil bath maintained at 180°. Sublimation of the resulting residue at 140–145° (bath)/0·1 mm gave **22** (100 mg), m.p. 79–80° (ether–light petroleum); IR and NMR spectra identical with those of **22** reported before.

Treatment of the cis-lactone (**19**) *with methanolic sodium hydroxide solution.* To a soln of NaOH (450 mg) in MeOH (11·5 ml) was added the *cis*-**19** (310 mg), m.p. 140–141°. The mixture was heated under reflux for 5 h under N_2. Usual workup of the mixture as before furnished a mixture of *cis*-lactones **19** and **20** (300 mg), m.p. 90–120° (ether–light petroleum), ν_{max} 1764 cm^{-1}. (Found: C, 77·35; H, 7·20%).

A pure stereoisomer of 2 - (α - *carboxyethyl*) 1,2,3,4 - *tetrahydronaphthalene* (**25**). A soln of the *cis*-**19** (270 mg), m.p. 140–141° in EtOH (95% 20 ml) was hydrogenated over Pd-C (10%, 100 mg) at room temp and atmospheric pressure. The theoretical amount of H_2 (32·2 ml) was absorbed within 10 min. The mixture was worked up as before to give an acid (210 mg), m.p. 87–88°. An analytical sample of **25** melted at 91–92° (light petroleum); ν_{max} (Nujol) 1706 cm^{-1}. (Found: C, 76·26; H, 7·98. $C_{13}H_{16}O_2$ requires: C, 76·45; H, 7·90%). Mixed m.p. of this acid with an authentic sample (reported[13] m.p. 91–92°) remained undepressed.

Treatment of the cis-lactone (**19**) *with acetic anhydride and conc sulphuric acid.* To a soln of **19** (100 mg), m.p. 140–141° in Ac_2O (3 ml) was added a drop of conc H_2SO_4; and the mixture was heated on the steam bath for 20 min. The mixture after usual processing afforded the unchanged **19** (72 mg), m.p. 140°.

A pure stereoisomer of 2 - (α - *carboxyethyl*) - 1,2,3,4 - *tetrahydronaphthalene* (**26**)

(a) *By* Na-NH_3 *reduction of the trans-lactone* (**22**). Liquid ammonia (200 ml) was taken in a 3-necked flask. Na metal (50 mg) was divided into 2 parts. One part of the metal was added to the liquid ammonia with stirring. A soln of the *trans*-lactone **22** (100 mg), m.p. 78–79° in dry ether (30 ml) was then added slowly with stirring to the resulting blue-coloured liquid ammonia soln. The remaining part of the Na metal was next added; and the resulting mixture was stirred for 20 min more. Ammonium chloride was then added to discharge the blue colour. After complete evaporation of ammonia, the residue was worked up as usual to furnish the pure crystalline acid (**26**) (56 mg), m.p. 115–117° (ether–light petroleum) ν_{max} 1701 (acid C=O). Mixed m.p. of this acid with an authentic sample (reported[13] m.p. 117–118°) was undepressed.

(b) *By catalytic hydrogenolysis of* (**22**). A soln of **22** (120 mg) in EtOH (95%, 12 ml) was hydrogenated over Pd-C (10%, 70 mg) as before. Theoretical amount of H_2 was not absorbed even after stirring for 8 h. Usual processing of the mixture afforded the recovered **22** (60 mg), m.p. 77–79°; and the desired acid **26** (20 mg), m.p. 115–116° (light petroleum).

Action of acetic anhydride and sulphuric acid on the trans-lactone (**22**)

Formation of the cis-lactone (**20**), *and* 3,4 - *dihydro*-2 - *naphthyl* - α - *propionic acid* (**27**). To a soln of **22** (100 mg), m.p. 78–79° in Ac_2O (3 ml) was added a drop of conc H_2SO_4. The resulting soln was heated on the steam bath for 20 min. Usual processing of the mixture provided the pure *cis*-**20** (32 mg), m.p. 89–90° (ether–light petroleum); ν_{max} 1764 cm^{-1} (lactone C=O); τ 2·54–3·08 (4H, m), 4·46 (1H, d, J 6·5 Hz), 7·12–7·87 (4H, m), 7·96–8·37 (2H, m), 8·68 (3H, d, J 6·98 Hz). (Found: C, 77·22; H, 7·07, $C_{13}H_{14}O_2$ requires: C, 77·20; H, 6·98%).

In another experiment the lactone **22** (120 mg) on treatment with Ac_2O and conc H_2SO_4 as above afforded a neutral (40 mg) and an acidic product (80 mg), m.p. 113–116°. The neutral material failed to provide any crystalline lactone. The above acid on crystallisation gave analytically pure 3,4 - *dihydro* - 2 - *naphthyl* - α - *propionic acid* (**27**), m.p. 118–119° (ether–light petroleum) (reported[14] m.p. 118–119°); ν_{max} 1703 cm^{-1} (acid C=O); λ_{max} 266 nm (ε 14,790). (Found: C, 77·28; H, 6·87. $C_{13}H_{14}O_2$ requires: C, 77·20; H, 6·98%).

Ethyl - α - (3,4 - *dihydro* - 2 - *naphthyl*) *propionate* (**28**). A mixture of the *cis*-**19** and **20** (1·4 g) m.p. 120–140°, purified thionyl chloride (1·5 g) and dry benzene (7 ml) was heated under reflux for 8 h. To the cooled mixture

was then added abs EtOH (7 ml), previously saturated with dry HCl gas. The resulting mixture was further refluxed for 4 h. Most of the solvent was removed under reduced pressure; and the residue was distilled at 120–125° (bath)/0·1 mm to afford a liquid ester which responded the test for chlorine. Further redistillations as above provided the pure unsaturated **28** (1·42 g), b.p. 105–110° (bath)/0·1 mm; λ_{max} 265 nm (ϵ 11,640); ν_{max} 1732 cm^{-1}. (Found: C, 78·10; H, 8·07. $C_{15}H_{18}O_2$ requires: C, 78·23; H, 7·88%).

Hydrolysis of the above **28** (0·5 g) with methanolic KOH gave 3,4 - *dihydro* - 2 - *naphthyl* - *α* - *propionic acid* **27** (360 mg) m.p. 117–119° reported above.

Lactonisation of 3,4 - *dihydro* - 2 - *naphthyl* - *α* - *propionic acid* (**27**)

Formation of a mixture of cis-lactones (**19** *and* **20**). To well stirred conc H_2SO_4 (21 ml) maintained at −10 to −5° was added dropwise during 15 min a soln of **27** (700 mg) in dry $CHCl_3$ (42 ml). After complete addition, the stirring was continued at the same temp for a period of 1 h. The resulting mixture was then poured over crushed ice. Chloroform layer was separated and the aqueous phase was extracted with ether (3 × 100 ml). The combined solvent was successively washed with water, 2% KOH aq and finally with water. Removal of the dry solvent produced a lactonic product (340 mg), m.p. 75–115°; ν_{max} 1764 cm^{-1}. Three recrystallisations of this material provided a mixture of *cis*- **19** and **20**, m.p. 115–135° (ether-light petroleum); two characteristics doublets for C-6 H atoms at τ 4·67 (*J* 5·0 Hz) and 4·47 (*J* 6·00 Hz) indicated the product to be a 5:7 mixture of **19** and **20** respectively. (Found: C, 77·16; H, 7·09%). Several recrystallisations of the above mixture gave a pure sample of the *cis*- **19**, (95 mg), m.p. 140–141°. (Found: C, 77·18; H, 7·16%).

Sodium borohydride reductions of 1 - *keto* - 1,2,3,4 - *tetrahydro* - 2 - *naphthylactic acid* (**18**)

Formation of lactone of cis - 1 - *hydroxy* - 1,2,3,4 - *tetrahydro* - 2 - *naphthylactic acid* (**21**), *and a mixture of cis- and trans-hydroxy-acids* (**31**). The keto-acid **18** (1 g) dissolved in 0·2 N NaOH (70 ml) was reduced with $NaBH_4$ (760 mg) as before. The crude acidic product (870 mg) isolated from the mixture under usual workup appeared to be a mixture of hydroxy-acids and lactone. This product was then separated into a neutral (270 mg) m.p. 92–95°, and an acidic fraction (550 mg) by the usual procedure. The above neutral product on purification afforded the *cis*- **21** (255 mg, 27%) as prisms, m.p. 101–102° (acetone–light petroleum), ν_{max} 1766 ((lactone C=O); τ 2·42–2·92 (4H, m), 4·55 (1H, d, *J* 5·8 Hz), 6·85–8·55 (7H, m). (Found: C, 76·41; H, 6·74. $C_{12}H_{14}O_2$ requires: C, 76·57; H, 6·43%).

The above acid fraction on crystallisation provided a *cis- and trans-mixture of* 1 - *hydroxy* - 1,2,3,4 - *tetrahydro* - 2 - *naphthylacetic acid* **31** (440 mg, 43%), m.p. 133–135° (ether–light petroleum), ν_{max} 1708 cm^{-1}. (Found: C, 70·01; H, 6·59. $C_{12}H_{14}O_3$ requires: C, 69·89; H, 6·84%).

Lactonisation of cis- and trans-mixture of 1 - *hydroxy* - 1,2,3,4 - *tetrahydro* - 2 - *naphthylacetic acid* (**31**)

Formation of cis- (**21**) *and trans-* (**24**) *lactones.* The above hydroxy-acid (440 mg) was sublimed by heating at 130–135° (bath)/0·2 mm to furnish a neutral (315 mg) and an acidic product (110 mg). The crude neutral product on crystallisation afforded a mixture of *cis*- and *trans*- **21** and **24** m.p. 87–115° (ether–light petroleum), ν_{max} 1772 cm^{-1}; two characteristics doublets for C-6 H atoms at τ 4·48 (*J* 5·8 Hz) and 4·96 (*J* 9·7 Hz) indicated 11:9 mixture of **21** and **24** respectively. (Found: C, 76·67; H, 6·27%).

The above crude acidic material (110 mg), m.p. 95–110°, ν_{max} 1710 cm^{-1} on purification gave the unchanged hydroxy-acids (mixture), m.p. 134–135° (ether–light petroleum).

The above mixture of the *cis* and *trans*-lactones (315 mg) was chromatographed over silica gel (18 g). Ether–light petroleum (5:95) eluted the pure *trans*-lactone **24** (100 mg), m.p. 137–138° (ether–light petroleum), ν_{max} 1780 cm^{-1}; τ 2·38–2·88 (4H, m), 4·99 (1H, d, *J* 9·7 Hz), 6·83–8·47 (7H, m). (Found: C, 76·50; H, 6·59%). Elution of the chromatogram with ether–light petroleum (10:95) provided the *cis*- **21** (145 mg), m.p. 102–103°.

The pure *cis*- **21** and the *trans*- **24** was therefore isolated in 42 and 11% yields respectively on the basis of the keto-acid **18** used.

Reduction of **18** according to the procedure of House *et al*[8] provided the *cis*- **21** and the *trans*- **24** lactone in 38 and 14% yields respectively.

3,4 - *dihydro* - 2 - *naphthylacetic acid* (**29**). Treatment of the *cis*- **21** (1 g) with $SOCl_2$ (1·2 g) under benzene (7 ml) and abs alcohol (7 ml) as before afforded an unsaturated ester (1·05 g) λ_{max} 263 nm (ϵ 11,750). Hydrolysis of this ester with methanolic KOH gave **29** (850 mg), m.p. 85–87 (light petroleum) (reported[17] m.p. 89–90°), ν_{max} 1711 cm^{-1}. (Found: C, 76·23; H, 6·72. $C_{12}H_{12}O_2$ requires: 76·57; H, 6·43%).

Action of acetic anhydride and sulphuric acid on the trans-lactone (**24**). Treatment of the *trans*- **24** (110 mg) with Ac_2O and conc H_2SO_4 as described before gave a neutral product (20 mg), m.p. 85–87°; ν_{max} 1772 cm^{-1}; and this is probably a mixture of the *cis*- **21** and the *trans*- **24**. The main product from the above reaction was an acid characterised as 3,4 - *dihydro* - 2 - *naphthylacetic acid* (**29**)[17] (80 mg), m.p. 83–85°; ν_{max} 1711 cm^{-1}.

Acknowledgements—The authors are indebted to E.I.P.W. Ltd., and C.S.I.R., New Delhi, for research fellowships (to D. B. and R. M.), to Drs. M. M. Dhar and R. H. Johnson for NMR spectra and to Mr. B. B. Bhattacharyya for microanalysis. The authors wish to thank Dr. U. R. Ghatak for helpful discussions.

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