684. *Studies in the Synthesis of Terpenes. Part II.* The Preparation of an Intermediate for the Synthesis of Diterpenes.*

By J. D. Cocker and T. G. Halsall.

The conversion of 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione (VI) into 5 : 5 : 9-trimethyl-$\Delta^{4(10)}$-octalin-1-ol (X) and thence by catalytic hydrogenation and oxidation into the corresponding decalone (XII) is described.

Recently we isolated a new bicyclic diterpene, labdanolic acid (I),[1, 2] from gum labdanum. A key step in the structure determination was the degradation of labdanolic acid to the C_{17} acid (II), previously obtained from marrubiin [3] and ambrein.[4] Little has been published on the synthesis of the acid (II) or of any diterpene of the manoöl–agathic acid group to which labdanolic acid belongs. Probably the most closely related compound so far synthesised is *rac*-ambreinolide (III) which has been prepared starting from dihydro-α-ionone.[4]

5 : 5 : 9-Trimethyl-*trans*-decal-1-one (XII) is a possible intermediate for the synthesis of acid (II), and of derivatives of the manoöl-agathic acid group of diterpenes and of deoxyonocerin (IV).[5] In this paper the synthesis of the decalone is described.

The diketone (VI) was the starting material. Previous methods [6–9] for its preparation do not give good yields; *e.g.*, that of Wendler, Slates, and Tishler [7] gives a 7% yield from 2-methyl*cyclo*hexane-1 : 3-dione and methyl vinyl ketone. Repetition of this procedure did not lead to a higher yield, but some 10-hydroxy-9-methyldecalin-1 : 6-dione (V) was also obtained. The diketone (VI) was made in the quantities needed by a method which will be described in the near future by Newman *et at.*[10] and by Robinson and his co-workers.[11]

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* The paper, *J.*, 1956, 2431, is regarded as Part I.

[1] Cocker, Halsall, and Bowers, *J.*, 1956, 4259.

[2] Cocker and Halsall, *J.*, 1956, 4262.

[3] Burn and Rigby, *Chem. and Ind.*, 1955, 386.

[4] Wolff and Lederer, *Bull. Soc. chim. France*, 1955, 1466; cf. Dietrich and Lederer, *Helv. Chim. Acta*, 1952, **35**, 1148.

[5] Barton and Overton, *J.*, 1955, 2639.

[6] Wieland and Miescher, *Helv. Chim. Acta*, 1950, **33**, 2215.

[7] Wendler, Slates, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3816.

[8] Nazarov and Zav'yalov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 300. (Since our work was completed a better method for the preparation of the diketone (VI) has been described by Nazarov, Zav'yalov, Burmistrova, Gurvich, and Shmonina, *J. Gen. Chem. (U.S.S.R.)*, 1956, 465.)

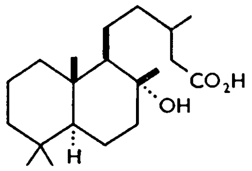
[9] Birch, Quartey, and Smith, *J.*, 1950, 1768.

[10] Newman, Stobaugh, and Swaminathan, forthcoming publication.

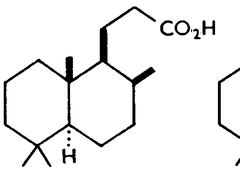
[11] Bannister, Jaeger, Robinson, Smith, and Sneeden, forthcoming publication.

The diketone (VI) was reduced with recrystallised (*iso*propylamine) sodium borohydride; only the saturated keto-group was reduced[cf. 12] giving the oxo-alcohol (VII). The presence of an αβ-unsaturated ketone was shown by the ultraviolet maximum at 2385 Å. Use of non-recrystallised sodium borohydride gave poor results, presumably due to the presence of free alkali causing fission of the very alkali-labile diketone.[cf. 7] The oxo-alcohol had previously been prepared indirectly by Birch, Quartey, and Smith,[9] and also, in an optically active form, by microbiological reduction of the dione (VI).[13] The hydroxyl group is probably *cis* to the angular methyl group (*i.e.*, is equatorial), with attack by the borohydride ion from the side of the diketone opposite to that of the methyl group.[cf. 14]

The next step was the dimethylation of the α-carbon atom of the αβ-unsaturated ketone system. The methylation of such a system has been described by Woodward, Patchett, Barton, Ives, and Kelly.[15] Use of their method with the oxo-alcohol (VII) was not successful, owing to attack by the *tert.*-butoxide ion on the hydroxyl group and fission of the resulting anion (XIII). The tetrahydropyranyl ether (VIII) was, however, satisfactorily methylated; normally directly. It was obtained as prisms with a m. p. range of 6°, which may have been due to the presence of a small amount of a second stereoisomer of the ether involving the $C_{(2)}$-atom of the tetrahydropyran ring. Isolation of the methylation product involved loss of the ether grouping and the hydroxy-ketone (IX) was obtained directly. Infrared and ultraviolet spectra showed the presence of a saturated keto-group, an isolated double bond, and a hydroxyl group, all consistent with structure (IX).



(I)



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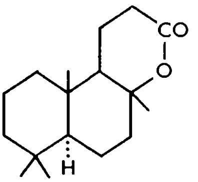

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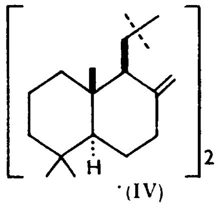
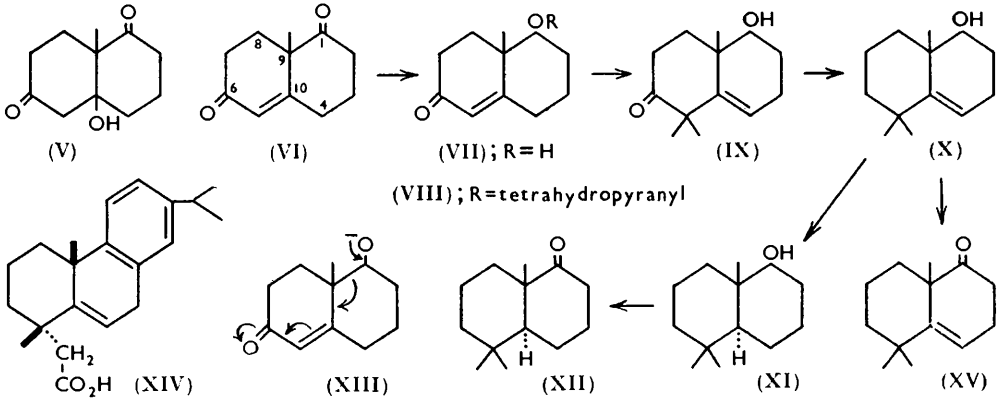


(IV)



(V) (VI) (VII); R=H (VIII); R=tetrahydropyranyl (IX) (X) (XIV) (XIII) (XII) (XI) (XV)

The hydroxy-ketone (IX) was reduced by the Wolff–Kishner method to the unsaturated alcohol (X), which could be hydrogenated in acetic acid, but not in ethanol, with a platinum catalyst. The resulting decalol (XI) showed no bands in the infrared region corresponding to a trisubstituted double bond. The decalol is assumed to be *trans*-fused since similar

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[12] Norymberski and Woods, *Chem. and Ind.*, 1954, 518.
[13] Prelog and Acklin, *Helv. Chim. Acta*, 1956, **39**, 748.
[14] Courtney, Gascoigne, and Szumer, *J.*, 1956, 2119.
[15] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852.

reduction of 4 : 4-dimethylcholest-5-en-3-one followed by oxidation of the resulting dimethylcholestanol, gives 4 : 4-dimethylcholestan-3-one with rings A and B *trans*-fused.[16] Stork and Schulenberg [17] have obtained a similar result on hydrogenating the acid (XIV) with palladium–charcoal in acetic acid, (±)-homodehydroabietic acid being formed. Also, a model of the hydroxy-ketone (IX) indicates that the β-face is much more protected from attack than the α-face.

Oxidation of the decalol (XI) with chromic acid finally afforded the decalone (XII). Its infrared spectrum indicated a *gem*-dimethyl group. A band at 817 cm.$^{-1}$ (in carbon disulphide) was not due to a double bond. The decalone (XII) gave no colour with tetranitromethane whilst the octalone (XV) obtained by the oxidation of the unsaturated alcohol (X) did.

Since our preliminary account [18] Elad and Sondheimer [19] have also briefly described the preparation of the decalone (XII), and King, Ritchie, and Timmons [20] that of the benzoate of the closely related 6-hydroxy-5 : 5 : 9-trimethyldecal-1-one by a different route.

EXPERIMENTAL

M. p.s were determined on a Kofler block and are corrected. Ultraviolet light absorption data refer to ethanol solution. Light petroleum refers to the fraction with b. p. 60—80°.

Preparation of 9-*Methyl*-$\Delta^{5(10)}$-*octalin*-1 : 6-*dione* (VI) *by the Method of Wendler, Slates, and Tishler.*[7]—2-Methyl*cyclo*hexane-1 : 3-dione (10 g.) in methanol (155 c.c.), methyl vinyl ketone (11 c.c.), and triethylamine (1·5 c.c.) were kept at 12° for 17 hr. and shaken periodically. Removal of the solvent (reduced pressure) gave a pale yellow oil. The latter was dissolved in ether and washed with sodium hydrogen carbonate solution (5%), water, and saturated sodium chloride solution. Evaporation of the dried ether solution gave the Michael adduct (5·4 g.) as a yellow oil which was cyclised directly.

The adduct (5·4 g.) in benzene (20 c.c.) and a solution of aluminium *tert.*-butoxide (3·5 g.) in benzene (30 c.c.) were heated under reflux under nitrogen for 20 hr., then treated with ice and water, acidified (Congo red) with hydrochloric acid (3N), and extracted with ether to give a pale yellow oil. Light absorption : Max. 2440 Å; $E^{1\%}_{1\,\text{cm.}}$ 244. This oil was adsorbed from benzene on alumina (180 g.; neutralised and reactivated according to the method of Evans and Shoppee [21]). Elution with ether yielded 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione, prisms (0·20 g.), m. p. 49—50° (from light petroleum). Light absorption : Max. 2440 Å; $\varepsilon = 11{,}900$ (Wendler *et al.*[7] give m. p. 49—50°; light absorption : Max. 2440 Å; ε 12,000). Further elution with methanol afforded a solid, m. p. 176—182°, which crystallised slowly from ethyl acetate to give 10-*hydroxy*-9-*methyldecalin*-1 : 6-*dione* (V) (0·30 g.) as needles, m. p. 184—185° (Found : C, 67·35; H, 8·25. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). Infrared absorption in "Nujol" suspension : bands at 3300 and 1700 cm.$^{-1}$.

The 9-methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione used in the following experiments was prepared [10, 11] from diethylaminobutan-2-one and 2-methyl*cyclo*hexane-1 : 3-dione. The 2-methyl*cyclo*hexane-1 : 3-dione was prepared from resorcinol which was hydrogenated by Thompson's method [22] to *cyclo*hexane-1 : 3-dione; this was then methylated according to Stetter's method.[23] The 4-diethylaminobutan-2-one was prepared as described by Wilds and Shunk.[24]

5-*Hydroxy*-10-*methyl*-$\Delta^{1(9)}$-*octal*-2-*one* (VII).—9-Methyl-$\Delta^{5(10)}$-octalin-1 : 6-dione (50 g.) in ethanol (1 l.) was treated at 8° with sodium borohydride (8·5 g.; recrystallised from *iso*propylamine) in ethanol (1 l.). The mixture was kept for 12 min. at 20° with occasional shaking and then treated with acetic acid (80 c.c.). Evaporation to dryness (reduced pressure), dissolution of the residue in water, and extraction of the solution with chloroform gave a gum, which was

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[16] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.

[17] Stork and Schulenberg, *J. Amer. Chem. Soc.*, 1956, **78**, 250.

[18] Cocker and Halsall, *Chem. and Ind.*, 1956, 1275.

[19] Elad and Sondheimer, *Bull. Res. Council Israel*, 1956, **5**, *A*, 267.

[20] King, Ritchie, and Timmons, *Chem. and Ind.*, 1956, 1230.

[21] Evans and Shoppee, *J.*, 1953, 543.

[22] Thompson, *Org. Synth.*, 1947, **27**, 21.

[23] Stetter, *Chem. Ber.*, 1955, **88**, 77.

[24] Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469.

dissolved in ether (75 c.c.), water (5 c.c.) was added and the solution was kept overnight at −5°. 5-Hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one monohydrate crystallised as prisms (35 g.), m. p. 47—56° (dependent upon the rate of heating) (Found: C, 66·85; H, 9·25. Calc. for $C_{11}H_{16}O_2,H_2O$: C, 66·65; H, 9·15%). Light absorption: Max. 2400 Å; ε 14,700. Infrared absorption in carbon tetrachloride: bands at 3630, 3400, 1670, and 1624 cm.$^{-1}$. Birch *et al.*[9] give m. p. 59—60°; $\lambda_{max.}$ 2400 Å; ε 14,700. When dried in a vacuum the crystals liquefied and the anhydrous substance could not be crystallised. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as prisms, m. p. 176—178° (Found: C, 56·55; H, 5·9; N, 15·5. $C_{17}H_{20}O_5N_4$ requires C, 56·65; H, 5·6; N, 15·55%). The *semicarbazone*, prepared by heating the hydroxy-ketone under reflux for 15 min. with aqueous-ethanolic semicarbazide hydrochloride and sodium acetate, crystallised from ethanol as prisms, m. p. 228—229° (Found: C, 60·9; H, 8·3; N, 17·8. $C_{12}H_{19}O_2N_3$ requires C, 60·75; H, 8·05; N, 17·7%).

10-*Methyl-5-tetrahydropyranyloxy*-$\Delta^{1(9)}$-*octal*-2-*one* (VIII).—5-Hydroxy-10-methyl-$\Delta^{1(9)}$-octal-2-one (1·0 g.), dihydropyran (7 c.c.; redistilled from potassium hydroxide), and ether (2 c.c.) were treated with hydrochloric acid (2 drops). After the mixture had been kept for 2 days at 20° ether was added, and the ethereal solution was washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the ether under reduced pressure gave an oil (2·2 g.) which was adsorbed from light petroleum on neutral alumina (100 g.). Elution with light petroleum–benzene (4 : 1) gave an oil (0·76 g.), whose infrared spectrum did not show a carbonyl band. Further elution with light petroleum–benzene (1 : 1) yielded a fraction (0·7 g.) which gave 10-*methyl-5-tetrahydropyranyloxy*-$\Delta^{1(9)}$-*octal*-2-*one* as prisms (from light petroleum), m. p. 68—74° (Found: C, 72·7; H, 9·2. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·15%). Light absorption: Max.; 2385 Å; ε = 15,800. Infrared absorption in "Nujol" suspension: bands at 1670 and 1614 cm.$^{-1}$.

In later preparations the crude ether was not chromatographed but was methylated directly.

5-*Hydroxy*-1 : 1 : 10-*trimethyl*-Δ^{8}-*octal*-2-*one* (IX).—The tetrahydropyranyl ether (1·98 g.; 0·01 mole) in dry benzene (60 c.c.) was treated with potassium *tert.*-butoxide in *tert.*-butanol (1M) (50 c.c.; 0·05 mole) followed by methyl iodide (15 g.; 0·1 mole). The mixture was kept for 17 hr. at 20° and then water was added and the product was isolated with ether. The pale yellow oil, in methanol (50 c.c.), was treated with hydrochloric acid (3 drops) at 40° for 30 min. Dilution with water and extraction with ether gave a product (2·33 g.) which was adsorbed from benzene on neutral alumina (100 g.). Elution with benzene–ether (5 : 1) yielded a fraction which gave 5-*hydroxy*-1 : 1 : 10-*trimethyl*-Δ^{8}-*octal*-2-*one* (0·70 g.) as prisms, m. p. 92—94° (from light petroleum) (Found: C, 74·7; H, 9·5. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%). Infrared absorption in carbon disulphide: bands at 3580, 1709, 1645, 812, and 793 cm.$^{-1}$.

5 : 5 : 9-*Trimethyl*-$\Delta^{4(10)}$-*octalin*-1-*ol* (X).—5-Hydroxy-1 : 1 : 10-trimethyl-Δ^{8}-octal-2-one (9 g.), in redistilled diethylene glycol (480 c.c.), and hydrazine hydrate (40 c.c.; 100%) were heated at 90—100° for 1 hr. Potassium hydroxide (9 g.) was then added, the temperature raised to 215° (with distillation of water), and heating continued thereat for a further 6 hr. (If the temperature rose above 215°, the mixture became brown and the yield was lowered.) Dilution with water gave a solid (7·5 g.) which was purified by sublimation at 100°/10 mm. or crystallisation (aqueous methanol), giving 5 : 5 : 9-*trimethyl*-$\Delta^{4(10)}$-*octalin*-1-*ol* as needles, m. p. 122—122·5° (Found: C, 80·55; H, 11·45. $C_{13}H_{22}O$ requires C, 80·35; H, 11·4%). Light absorption: ε at 2060 Å = 2500; ε at 2100 Å = 1330; ε at 2140 Å = 520. Infrared absorption in carbon tetrachloride: bands at 3600, 1640, 1381, and 1363 cm.$^{-1}$.

5 : 5 : 9-*Trimethyl*-trans-*decalin*-1-*ol* (XI).—The octalinol (86 mg.) in acetic acid was hydrogenated in presence of Adams's platinum catalyst (100 mg.). Uptake of hydrogen ceased after 15 min. Removal of the catalyst, evaporation of the solvent under reduced pressure, and crystallisation of the solid from light petroleum at 0° gave 5 : 5 : 9-*trimethyl*-trans-*decalin*-1-*ol* as fine needles, m. p. 75—77° (Found: C, 79·65; H, 12·35. $C_{13}H_{24}O$ requires C, 79·55; H, 12·3%). Infrared absorption: band at 3600 cm.$^{-1}$.

5 : 5 : 9-*Trimethyl*-trans-*decal*-1-*one* (XII).—The decalinol (50 mg.) in acetone (5 c.c.) was oxidised with chromic acid (0·1 c.c.; 8N) according to the method of Bowers *et al.*[25] Dilution with water and extraction with ether afforded a solid which gave 5 : 5 : 9-*trimethyl*-trans-*decal*-1-*one* as thick rods (from aqueous methanol), m. p. 41—43° (Found: C, 80·5; H, 11·55. $C_{13}H_{22}O$ requires C, 80·35; H, 11·4%). The 2 : 4-*dinitrophenylhydrazone* formed prisms, m. p.

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[25] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

168·5—170°, from ethanol (Found : C, 61·6; H, 7·3; N, 15·1. $C_{19}H_{26}O_4N_4$ requires C, 60·95; H, 7·0; N, 14·95%).

5 : 5 : 9-*Trimethyl*-$\Delta^{4(10)}$-*octal*-1-*one* (XV).—5 : 5 : 9-Trimethyl-$\Delta^{4(10)}$-octalin-1-ol (0·105 g.) in acetone (5 c.c.) was treated with chromic acid (0·2 c.c.; 8N). Dilution with water and extraction with ether gave a non-crystallisable oil. 5 : 5 : 9-*Trimethyl*-$\Delta^{4(10)}$-*octal*-1-*one* 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as plates, m. p. 118—122° (Found : C, 61·15; H, 6·4. $C_{19}H_{24}O_4N_4$ requires C, 61·25; H, 6·5%).

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