14. *Synthetical Studies of Terpenoids. Part IV.*[1] *Syntheses of Decalin Derivatives.*

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Synthesis of an acetoxytetramethyldecalone and its stereochemistry are reported.[2]

As a step in the synthesis of di- and tri-terpenoids we have synthesised the trimethyldecalone derivatives (I; R = H and OAc) in two forms and have prepared therefrom the tetramethyl derivative (XVII) of known configuration.*

The starting material was 1,10-dimethyl-$\Delta^{1,9}$-2-octalone [3] (II). After a series of experiments, its methylation to the trimethyl ketone (III) in presence of potassium t-pentyloxide [4] was carried out in 92% yield: the previous method [5] had given only a poor yield. The trimethyl ketone (III) was reduced by sodium and ethanol to the alcohol (IV) with a view to obtaining 3-hydroxyl group in the desired equatorial position. The derived acetate (V) with t-butyl chromate [6] or, better, sodium dichromate,[7] afforded the unsaturated ketone (VI) in good yield. In the hope of introducing a chain at position 4 of this ketone and having a functional group which could be used for coupling of two bicyclic units, it was desired to build up a dienone system: the ketone was converted [8] into the bromide (VII) but attempts at dehydrohalogenation failed, the major product, formed by reductive dehalogenation,[9] being the original acetoxy-ketone (VI). Another attempt, by oxidation with selenium dioxide,[10] gave a phenol (pink colour with ferric chloride) and no well-defined ketonic derivative could be obtained. The double bond in the ketone was then hydrogenated in presence of palladium–charcoal in acetic acid to afford a mixture of acetoxy-ketones (IX, XIII) in the ratio 1 : ~4. [The preponderance of the *trans*-form (XIII) arises from steric reasons,[11] but appears to be enhanced [12] in the catalytic reduction

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* All the products were racemic although only form is shown in the formulæ.

[1] Part III, preceding paper.

[2] For a preliminary communication see *Proc. Chem. Soc.*, 1958, 351.

[3] Gunstone and Heggie, *J.*, 1952, 1437; Chakravarty, Dutt, and Dutta, *J.*, 1956, 4978.

[4] Conia, *Bull. Soc. chim. France*, 1959, 690, 943.

[5] Yanagita, Hirakura, and Seki, *J. Org. Chem.*, 1958, **23**, 841.

[6] Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284.

[7] Corey and Urspring, *J. Amer. Chem. Soc.*, 1956, **78**, 183.

[8] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *ibid.*, p. 1422.

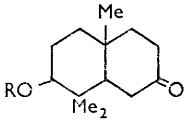
[9] Wendler, Graber, Snoddy, and Bollinger, *ibid.*, 1957, **79**, 4476.

[10] Ringold, Rosenkranz, and Sondheimer, *J. Org. Chem.*, 1956, **21**, 239; Yanagita, Inayama, Hirakura, and Seki, *ibid.*, 1958, **23**, 690.

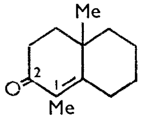
[11] Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1131; Stork and Schulenberg, *J. Amer. Chem. Soc.*, 1956, **78**, 250.

[12] Cf. Halsall, Rodewald, and Willis, *Proc. Chem. Soc.*, 1958, 231.

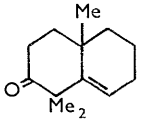
of the hydroxy-ketone (VIII)]. Complete separation of the mixture requires extensive chromatography and indeed the *cis*-form (IX) was only obtained pure by that process. To determine the nature of the ring-junction the ketone (XIII) was subjected to Huang-Minlon reduction and the alcohol (XII) obtained was oxidised with chromic acid in acetone [13] to afford the ketone (XI). This gave an orange 2,4-dinitrophenylhydrazone,



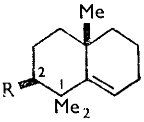
(I)



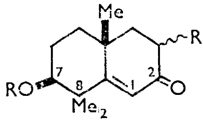
(II)



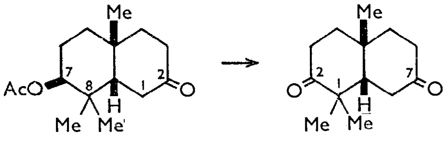
(III)



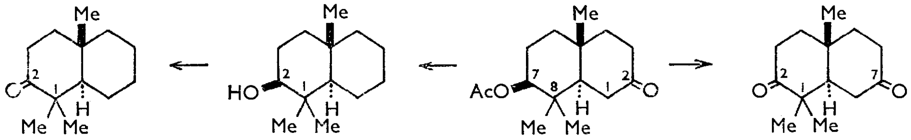
(IV) R = OH
(V) R = OAc



(VI) R = Ac, R′ = H
(VII) R = Ac, R′ = Br
(VIII) R = R′ = H



(IX) (X)



(XI) (XII) (XIII) (XIV)

which showed no depression in melting point with a sample obtained through the courtesy of Dr. Halsall.[14] This establishes the *trans*-junction of the rings in the ketone (XIII). To prove that the isomers (IX) and (XIII) differ only in their ring-junctions, each ketone was hydrolysed to its hydroxy-ketone and oxidised to the diketones (X) and (XIV). Their non-identity being established, the *cis*-junction of the rings in compounds (IX) and (X) is proved. The acetoxy-group in both ketones is probably equatorial, arising as it does through chemical reduction of the carbonyl group followed by acetylation. The ratio of *cis*- and *trans*-isomers on catalytic reduction [12,15] of the unsaturated ketone (VI) supports this statement.

Next we wished to introduce a methyl group in the α-position to the carbonyl group. The ethoxalyl derivative [16] was obtained in an excellent yield; with methyl iodide and potassium carbonate, it afforded a neutral material which on alkaline hydrolysis and acetylation gave the starting material (XIII). Apparently methylation failed; regeneration of the ketone (XIII) can be explained as follows: because of the *trans*-ring-junction, the ethoxalyl derivative enolises preferentially [17] to afford (XV); this structure will also be favoured by the tendency of the cyclohexane ring to accommodate the double bond in the *endo*-position; [18] apparently, the neutral material obtained on methylation has structure (XVI) which regenerates the ketone (XIII) during working up.

The ketone (XIII) was formylated, acetylated, and catalytically reduced [15] without isolation of the intermediates (XIII ⟶ XVII). To ensure the stereochemistry of the newly introduced methyl group, the product was treated with alkali, which led after

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[13] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.

[14] Gaspert, Halsall, and Willis, *J.*, 1958, 624.

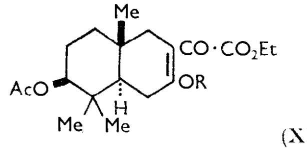
[15] Kalvoda and Loeffel, *Helv. Chim. Acta*, 1957, **40**, 2340.

[16] Cf. Sondheimer and Elad, *J. Amer. Chem. Soc.*, 1957, **79**, 5544.

[17] Taylor, *Chem. and Ind.*, 1954, 250.

[18] Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467; Turner and Garner, *ibid.*, 1958, **80**, 1424.

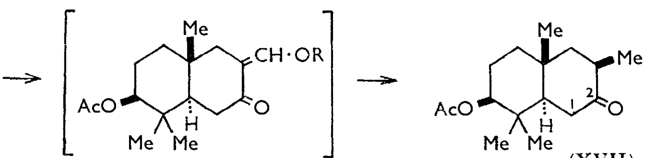
acetylation to the more favourable equatorial form of the tetramethyl compound (XVII). This was crystalline; in one experiment the tetramethyl compound crystallised directly after catalytic reduction and no epimerisation with alkali or subsequent acetylation was necessary.



(XV) R = H

(XVI) R = Me

(XIII) →



(XVII)

Preliminary attempts to introduce a 3,4-double bond into the ketone (XVII) appeared promising; however, 1,4-addition of potassium cyanide to the unsaturated ketone so obtained afforded a crystalline but unidentified acid.

EXPERIMENTAL

Ultraviolet spectra were measured for ethanol solutions.

1 : 1 : 10-*Trimethyl*-Δ^{8}-2-*octalone* (III).—To an ice-cold solution of potassium t-pentyloxide (from potassium 6 g.) in benzene (450 c.c.) was dropwise added 1,10-dimethyl-$\Delta^{1,9}$-2-octalone (II) (20·4 g.) with occasional shaking. The mixture was kept at 50—60° for an hour, then cooled in ice, treated slowly with methyl iodide (28 c.c.), and refluxed for 2 hr. The product was worked up and, on distillation, furnished the ketone (III) (20·4 g., 93%) with a fruity odour, b. p. 105—107°/2 mm. Its yellow 2,4-dinitrophenylhydrazone had m. p. 163° (from ethyl alcohol) (lit., 159—160°) (Found: C, 61·0; H, 6·3; N, 14·5. Calc. for $C_{19}H_{24}O_4N_4$: C, 61·3; H, 6·4; N, 15·0%).

1 : 1 : 10-*Trimethyl*-Δ^{8}-2-*octalol* (IV).—The ketone (III) (20 g.) in warm dry ethanol (240 c.c.) was added quickly to sodium (17·4 g.). After 25 min., the mixture was heated at 140—145° (bath-temperature) till all the sodium dissolved. After cooling to room temperature, the solution was diluted with water (*ca.* 2 l.), saturated with sodium chloride, and extracted with ether. The extract was washed with water and on distillation furnished the alcohol (18·3 g., 90·5%), with a sweet odour, b. p. 112—115°/2 mm., $n_{\mathrm{D}}^{29\cdot5}$ 1·5110 (Found: C, 79·9; H, 11·2. $C_{13}H_{22}O$ requires C, 80·3; H, 11·4%).

To the alcohol (13·58 g.) in cold pyridine (27·65 g.) was slowly added a mixture of acetic anhydride (23·31 g.) and acetyl chloride (10·99 g.). The whole was treated with ether (25 c.c.) and kept overnight at room temperature. The *acetate* (V) (14·7 g., 89%) had b. p. 122—123°/3—4 mm., $n_{\mathrm{D}}^{29\cdot5}$ 1·4997 (Found: C, 76·4; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%).

7-*Acetoxy*-8,8,10-*trimethyl*-$\Delta^{1,9}$-2-*octalone* (VI).—(a) *Oxidation with t-butyl chromate.* To the acetate (V) (14·5 g.) in carbon tetrachloride (150 c.c.) was added, at room temperature, with stirring, a mixture of t-butyl chromate (216 c.c.), acetic acid (67 c.c.), and acetic anhydride (27 c.c.), and the solution was kept overnight. It was next stirred at 80° for 3—4 hr., then cooled to room temperature. Oxalic acid (45 g.) in water (450 c.c.) was added with ice-cooling in 20 min. After 15 min., more solid oxalic acid (31·5 g.) was added and the whole stirred for 2 hr., while attaining room temperature. The pale yellow carbon tetrachloride layer was separated and the aqueous layer extracted with carbon tetrachloride. The combined organic layers were washed with water, 5% sodium hydrogen carbonate solution, and again water, dried (Na_2SO_4), and evaporated. The residue, on distillation, furnished an orange-yellow viscous liquid (9·7 g., 63%), b. p. 150—175°/4 mm. This was kept with potassium hydroxide (15 g.) in methanol (150 c.c.) overnight at room temperature, then refluxed for 1·5 hr., and neutralised with 12N-hydrochloric acid. Distillation furnished the *ketone* (VIII) (6·3 g., 43%), b. p. 165—170°/4 mm., $n_{\mathrm{D}}^{27\cdot5}$ 1·5255 (Found: C, 74·8; H, 9·9. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%). Its 2,4-*dinitrophenylhydrazone* crystallised from ethyl acetate in needles, m. p. 210° (Found: C, 58·4; H, 6·0; N, 14·1. $C_{19}H_{24}O_5N_4$ requires C, 58·7; H, 6·2; N, 14·4%). With pyridine–acetic anhydride, acetyl chloride, and ether, as above, it gave the *acetoxy-ketone* (VI) (77%), b. p. 172—175°/4 mm., $n_{\mathrm{D}}^{27\cdot5}$ 1·5058, $\lambda_{\max}$ 240 mμ (log ε 4·05) (Found: C, 72·1; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%), whose deep-red 2,4-*dinitrophenylhydrazone* crystallised from ethyl acetate in flakes, m. p. 248° (Found: C, 58·8; H, 5·8; N, 12·7. $C_{21}H_{26}O_6N_4$ requires C, 58·6; H, 6·0; N, 13·0%).

(b) *Oxidation with sodium dichromate in acetic acid.* A solution of the acetoxyoctalin (V) (23·6 g.) and sodium dichromate (60 g.) in glacial acetic acid (900 c.c.) was kept overnight at room temperature, then heated at 95—100° for 2 hr. Ethanol (30 c.c.) was added to the hot solution to decompose the excess of dichromate, and the resulting green solution was diluted with hot water (2550 c.c.). The product, on distillation, furnished the acetoxy-ketone (19·5 g., 78%), b. p. 150°/0·1 mm., $\lambda_{max.}$ 240 mμ (log ε 4·05), $n_D^{27.5}$ 1·5058 (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 248°).

7-*Acetoxy*-5,8,10-*trimethyl*-2-*decalone* (IX, XIII).—The ketone (VI) (36·5 g.) was hydrogenated (1 mol. in 24 hr.) in glacial acetic acid (45 c.c.) over palladium–charcoal (1 g., 10%), to a sweet-smelling liquid (32·6 g., 89%), b. p. 150—155°/5 mm. The distillate, on trituration in the cold with light petroleum (b. p. 40—60°) afforded needles (10·4 g., 32%). From the mother-liquor further crystals (2 g.) separated on long storage in the cold. The operation was repeated, the yield of solid in third and the fourth operation being 1·6 and 0·8 g. respectively. The solids collected from first three batches had m. p. 110—111°, which on subsequent crystallisations rose to 113—114° (Found: C, 71·1; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%). This trans-*acetoxy-ketone* (XIII) formed quantitatively a yellow 2,4-*dinitrophenylhydrazone*, m. p. 220—221° [from ethanol–ethyl acetate (3 : 1)] (Found: C, 58·1; H, 6·3. $C_{21}H_{28}O_6N_4$ requires C, 58·3; H, 6·5%).

The fourth batch of crystals (m. p. 92—94°) even on repeated crystallisation showed an anomalous m. p. This (800 mg.) was chromatographed on neutral alumina (30 g.) and eluted with light petroleum (b. p. 40—60°), fractions 1—15 being of 20 c.c. each, and fractions 16—43 of 100 c.c. each. Fractions 12—29 gave prisms (180 mg.), m. p. and mixed m. p. 111—112° [unchanged on crystallisation from light petroleum (b. p. 40—60°)] of the cis-*compound* (IX) (Found: C, 71·4; H, 9·4%). The yellow 2,4-*dinitrophenylhydrazone* (from ethanol) had m. p. 172—173° (Found: C, 58·5; H, 6·5%). The mixed m. p. of the ketones was 88° and of 2,4-dinitrophenylhydrazones was 167—168°.

1,1,10-*Trimethyl*-trans-2-*decalol* (XII).—The acetoxy-ketone (XIII) (756 mg.) in redistilled diethylene glycol (6·3 c.c.) was heated under reflux with 100% hydrazine hydrate (0·45 c.c.) and potassium hydroxide (405 mg.) for 1 hr. and then 185—190° for 1 hr. Dilution with water, acidification, and ether-extraction gave the *decalol* (431 mg.), b. p. 120°/4 mm. (Found: C, 79·5; H, 12·1. $C_{13}H_{24}O$ requires C, 79·6; H, 12·2%).

1,1,10-*Trimethyl*-trans-2-*decalone* (XI).—The decalol (431 mg.) in acetone (10 c.c.) with 8N-chromic acid (1·5 c.c.) gave a liquid ketone (XI) (300 mg.), whose 2,4-dinitrophenylhydrazone separated from ethanol in orange needles, m. p. 185·5—186·5° (186—187° on admixture with an authentic sample).

1,1,10-*Trimethyl*-trans-*decalin*-2,7-*dione* (XIV).—The acetoxy-ketone (XIII) (500 mg.) was refluxed with potassium hydroxide (1 g.) in ethanol (10 c.c.) for 2 hr. Working up gave a liquid (400 mg.) which was treated in acetone (15 c.c.) with 8N-chromic acid (1 c.c.) as above. The usual working up afforded the *dione* (380 mg.), needles [from light petroleum (b. p. 40—60°)], m. p. 121—122° (Found: C, 74·8; H, 9·6. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%).

1,1,10-*Trimethyl*-cis-*decalin*-2,7-*dione* (X).—The acetoxy-ketone (IX) (180 mg.) was hydrolysed and the crude semisolid residue (146 mg.) was oxidised as above. The gummy product afforded a solid (122 mg.) on trituration with light petroleum (b. p. 40—60°) in the cold. Chromatography over neutralised alumina (7 g.) gave traces of an oil [elution with light petroleum (b. p. 40—60°)] and a semisolid mass (90 mg.) (elution with ether). On crystallisation from light petroleum (b. p. 40—60°) the latter afforded the cis-*diketone*, m. p. 87—88° (mixed m. p. with *trans*-dione, 77—79°) (Found: C, 74·8; H, 9·7%).

3-*Bromo*-7-*acetoxy*-8,8,10-*trimethyl*-$\Delta^{1,9}$-2-*octalone* (VII).—The ketone (VI) (2·9 g.) in dry ether (100 c.c.) at 0° with bromine (1·5 g.) in acetic acid (10 c.c.) gave the *bromo-compound*, needles (from methanol) (2·3 g.), m. p. 146—147°, $\lambda_{max.}$ 240 mμ (log ε 4·11) (Found: C, 54·4; H, 6·4; Br, 24·1. $C_{15}H_{21}O_3Br$ requires C, 54·7; H, 6·4; Br, 24·3%).

This product (1·3 g.), when kept in collidine (10 c.c.) at 170° under nitrogen for an hour, regenerated the ketone (VI) (0·7 g.), b. p. 150—155°/0·6 mm. $\lambda_{max.}$ 239 mμ (log ε 4·1) (Found: C, 72·0; H, 8·5%) [2,4-dinitrophenylhydrazone (from ethyl acetate), m. p. 243°, or 246° when mixed with the authentic derivative (m. p. 248°)].

*7-Acetoxy-3,8,8,10-tetramethyl-*trans*-2-decalone* (XVII).—To a stirred suspension of freshly prepared sodium methoxide (2·975 g.; dried in a high vacuum) in dry thiophen-free benzene (85 c.c.), ethyl formate (12·8 c.c.) was added under nitrogen with exclusion of moisture. After *ca.* 30 min., the trimethyl-ketone (XIII) (900 mg.) in benzene (42·5 c.c.) was added dropwise with cooling. The mixture was then stirred for 20 hr. at room temperature and subsequently poured into ice-water. The benzene layer was extracted with ice-cold 5% sodium carbonate solution, and the combined aqueous portions were slowly acidified with cold 17% hydrochloric acid. The acid solution was saturated with sodium chloride and extracted thrice with ether. The viscous brown oil (890 mg.) left after removal of the ether gave a deep violet colour with ethanolic ferric chloride and was treated without purification with acetic anhydride (38·2 c.c.) and pyridine (12·8 c.c.). The solution was left at 20° for 18 hr. A neutral oil (1·08 g.), giving no colour with ferric chloride, was isolated, which crystallised. It was, however, at once hydrogenated in acetic acid (40 c.c.) over 10% palladium–charcoal (750 mg.). In 40 min., 2 mols. of hydrogen were taken up and reaction then ceased. The product (800 mg.) was refluxed with 10% ethanolic potassium hydroxide (10 c.c.) for 2 hr. The crude solid hydroxy-ketone was treated in pyridine (1·7 c.c.) slowly with acetic anhydride (1·5 c.c.) and acetyl chloride (0·7 c.c.) in the cold. The crude acetate (750 mg.) solidified; it was chromatographed in light petroleum (20 c.c.; b. p. 40—60°) on neutral alumina (11 g.), elution with this solvent yielding the *acetoxy-tetramethyl-ketone* (670 mg.), m. p. 87—88°, in 11 fractions (100 c.c. each). After two crystallisations from light petroleum (b. p. 40—60°), needles were obtained melting at 89—90° (Found: C, 72·1; H, 9·6. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8%). The yellow *2,4-dinitrophenylhydrazone* crystallised from ethyl acetate in flakes, m. p. 245—246° (Found: C, 59·2; H, 6·6; N, 12·6. $C_{22}H_{30}O_6N_4$ requires C, 59·2; H, 6·7; N, 12·5%).

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