550. *Experiments in the Synthesis of Bicyclic Diterpenes*

By S. Blake and Gurnos Jones

In recent years a great number of synthetic approaches to the A/B rings of diterpenes and triterpenes have been reported.[1] We now report attempts to elaborate decalins of type (I) from 2,2,6-trimethylcyclohexanone through an acetylenic intermediate.[2]

The starting material for this synthetic approach was the ethynylcyclohexanol (II)

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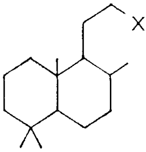
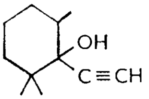
[1] N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.*, 1962, **16**, 117.

[2] F. E. King, T. J. King, and J. G. Topliss, *J.*, 1957, **573**.

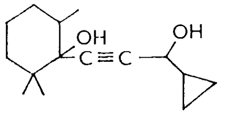
obtained by the action of sodium acetylide on 2,2,6-trimethylcyclohexanone.[3] No attempt was made to dehydrate the alcohol (II), as it has been found that the Grignard reagent which can be prepared from the alcohol reacts with ketones,[4] although our experience shows that a considerable excess of ketone is necessary for high yields. The Grignard reagent in ether reacted with methyl cyclopropyl ketone to give 70% of the acetylenic diol (III). Subsequent to this work, a similar reaction in benzene solution, giving a slightly higher yield of the diol (III), was reported.[5] Of the various procedures, the most consistent results were obtained using a palladium hydroxide on barium carbonate catalyst with hydrogen at atmospheric temperature and pressure. One mole of hydrogen was absorbed before the reduction ceased. Distillation of the reduction product gave an oil which solidified on standing, but which melted at 71—81° and was a mixture of isomers. These isomers were inseparable by chromatography on alumina, but repeated recrystallisation from petroleum gave a pure diol in 13% yield. The petroleum mother-liquors yielded a small quantity of an isomeric diol, whose structure remains undetermined. The infrared spectrum of the major product was in accord with the *cis*-ethylenic diol structure (IV), showing strong intramolecular hydroxylic hydrogen bonding [impossible with the *trans*-structure (V)] and a medium-strength band at 725 cm.$^{-1}$ (*cis*-ethylene out-of-plane deformation). The n.m.r. spectrum confirmed the assignment, showing a four-proton multiplet between δ values of 0·2 and 0·5 p.p.m. (relative to tetramethylsilane) assigned to the cyclopropyl methylene, and a two-proton singlet at 5·56 p.p.m. assigned to the ethylenic protons on the side-chain double bond. All attempts at further reduction of the ethylenic diol (IV) either failed or led to hydrogenolysis of the cyclopropane ring, and so the reaction between the *cis*-ethylenic diol (IV) and hydrobromic acid was examined. When the diol (IV) was vigorously stirred with cold concentrated hydrobromic acid the sole product was a liquid, $C_{16}H_{26}O$, showing no absorption in the 3600—3300 cm.$^{-1}$ region, but strong absorption at 1076 cm.$^{-1}$ assigned to the CO stretching frequency of a dihydrofuran.[6] The absorption at 3067 cm.$^{-1}$ due to the cyclopropyl ring was still present, and the ether showed end-absorption characteristic of a disubstituted double bond; the ether is formulated as (VI).



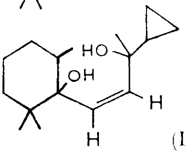
(I)



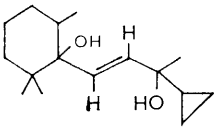
(II)



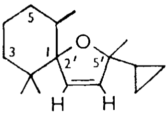
(III)



(IV)



(V)



(VI)

The formula (VI) was confirmed by the n.m.r. spectrum, which showed the presence of three methyl groups as singlets at δ values of 1·18 (5′), 1·05 (2), and 0·85 (2), p.p.m., and a further methyl group as a doublet at 0·92 p.p.m. ($J = 3$ c./sec.). Two ethylenic protons at 5·43 and 5·66 p.p.m. showed as doublets ($J = 6$ c./sec., *cis*-disubstituted double bond). The cyclopropyl methylene protons were present as a multiplet from 0·2 to 0·57 p.p.m. Reduction of the dihydrofuran was difficult, and gave a mixture. Since cleavage of the dihydrofuran (VI) might provide a carbonium ion suitable for cyclisation, the action of hot hydrobromic acid on the diol (IV) was examined. The crude mixture after treatment with hot hydrobromic acid showed more than ten components of which none was present in high proportion, and hence the mixture was not further investigated.

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[3] N. A. Milas, N. S. MacDonald, and D. M. Black, *J. Amer. Chem. Soc.*, 1948, **70**, 1829.

[4] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J.*, 1952, 1049.

[5] M. Julia and C. Descoins, *Bull. Soc. chim. France*, 1962, 1939.

[6] R. Kimura, *J. Pharm. Soc. Japan*, 1955, **75**, 1175.

EXPERIMENTAL

All gas chromatography was performed on a 10 ft. column of 1% SE 30 on Gaschrom " P." M. p.s were determined with a Kofler hot-stage apparatus, and n.m.r. spectra with a Perkin-Elmer 60 Mc. instrument in carbon tetrachloride solution.

3-*Cyclopropyl*-1-(1-*hydroxy*-2,2,6-*trimethylcyclohexyl*)-*but*-1-*yn*-3-*ol* (III). 1-Ethynyl-2,2,6-trimethylcyclohexan-1-ol (44 g.) in ether (100 ml.) was added dropwise to a boiling solution of ethylmagnesium bromide [from magnesium (13·6 g.) and ethyl bromide (58 g.) in ether (600 ml.)]. The mixture was boiled and stirred for 2 hr., cooled to 20°, and a solution of methyl cyclopropyl ketone (44 g.) in ether (100 ml.) added with vigorous stirring which was continued for a further 2 hr., after which the mixture was left overnight. Aqueous ammonium chloride (400 ml.; 20%) was added slowly, the temperature being kept below 20°. The ethereal layer was separated, dried (K_2CO_3), and distilled. After a fore-run fraction, b. p. 60—80°/0·4 mm., consisting largely of the cyclohexanol (II), the acetylenic diol (III) was collected, b. p. 108—110°/0·1 mm. (45 g., 70%), n_D^{25} 1·4978, $\nu_{max.}$ (film) 3450 (hydrogen bonded OH), 3110 cm.$^{-1}$ (cyclopropane CH) (Found: C, 76·45; H, 10·25. Calc. for $C_{16}H_{26}O_2$: C, 76·75; H, 10·45%).

3-*Cyclopropyl*-1-(1-*hydroxy*-2,2,6-*trimethylcyclohexyl*)-cis-*but*-2-*en*-3-*ol* (IV). The acetylenic diol (III) (10 g.) in 95% ethanol (250 ml.) with pre-reduced 5% Pd–$CaCO_3$ (1 g.) was hydrogenated at atmospheric pressure and temperature. Reduction was complete in 25 min. and absorption ceased when 1·1 moles of hydrogen had been absorbed. After removal of the catalyst the solution was evaporated to give a solid residue, m. p. 71—81°, unchanged by distillation at 113—114°/0·1 mm., or by percolation through activated alumina. Four recrystallisations from petroleum (b. p. 40—60°) gave the *ethylenic diol* (IV), m. p. 125·5—126·5°, as needles (1·4 g., 13%) (Found: C, 75·9; H, 11·2. $C_{16}H_{28}O_2$ requires C, 76·1; H, 11·2%), $\nu_{max.}$ (CCl_4) 3605, 3408 (OH stretching, tertiary alcohol un-bonded and intra-molecularly hydrogen bonded), 3079 (cyclopropane), 1120, 1100 cm.$^{-1}$ (C–O stretching, tertiary alcohol), 725 cm.$^{-1}$ (*cis*-disubstituted ethylene). By repeated fractional crystallisation of the mother-liquors, after the diol (IV) had been isolated, an isomeric *diol* was isolated, m. p. 109—111° (Found: C, 76·2; H, 11·0%).

5′-*Cyclopropyl*-2′,5′-*dihydro*-2,2,6,5′-*tetramethylcyclohexanespiro*-2′-*furan* (VI). The diol (IV) (5·1 g.) was vigorously stirred with 50% aqueous hydrogen bromide (20 ml.) for 1 hr. at room temperature. The mixture was extracted with petroleum (b. p. 60—80°) and the extract washed with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), passed through alumina (Peter Spence, Grade O), and eluted with petroleum. One main fraction (4·5 g.) was obtained and this was distilled, giving the *dihydrofuran* (VI), b. p. 149—151°/15 mm. (3·5 g., 74%), n_D^{25} 1·4929, showing a single peak on gas chromatography; $\nu_{max.}$ (CCl_4) 3067 (cyclopropyl CH), 1076 (C–O, dihydrofuran), 748 cm.$^{-1}$ (CH out-of-plane deformation, *cis*-substituted double bond) (Found: C, 82·0; H, 10·8. $C_{16}H_{26}O$ requires C, 82·0; H, 11·2%).

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