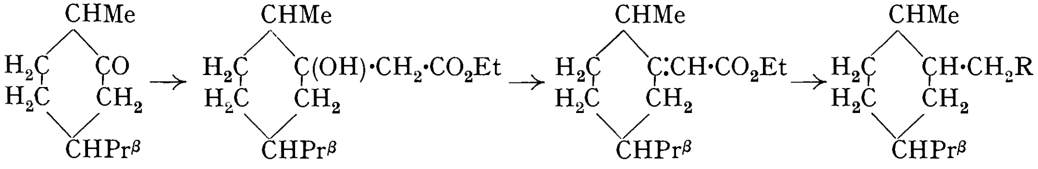
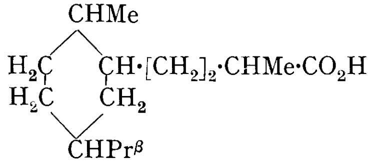
399. *Syntheses in the Sesquiterpene Series. Part I.*

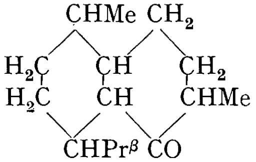
By A. E. BRADFIELD, E. R. JONES, and J. L. SIMONSEN.

THE recent observations on the occurrence in nature of sesquiterpene ketones (Bradfield, Penfold, and Simonsen, J., 1932, 2744; *J. Proc. Roy. Soc. N.S.W.*, 1932, **66**, 420; 1933, **67**, 200; Rupe, Clar, St. Pfau, and Plattner, *Helv. Chim. Acta*, 1934, **17**, 372; Kelkar and Rao, *J. Ind. Inst. Sci.*, 1934, **17**A, 7) have made syntheses of substances of this type desirable. In view of the comparative facility with which α-hydrindone is prepared from β-phenylpropionic acid (Kipping, J., 1894, **65**, 485), and 1 : 1 : 6-trimethyltetralin from 5-*m*-tolyl-2-methylpentan-2-ol (Bogert, Davidson, and Apfelbaum, *J. Amer. Chem. Soc.*, 1934, **56**, 961) it seemed to us probable that the ketone (V) might be obtained by the cyclisation of the acid (IV). This *acid* was prepared comparatively readily from *l*-tetrahydrocarvone (I) through the *bromide* (III; R = CH_2Br) by condensation with ethyl sodiomethylmalonate, with subsequent hydrolysis and elimination of carbon dioxide. The intermediate unsaturated *ester* (II) was assumed to be the menthylidene ester, but the position of the ethylenic linkage was not determined. Evidence was obtained of the formation of a ketone from (IV), but the yield was so poor that further experiments were abandoned.


(I.) (II.) (III.)

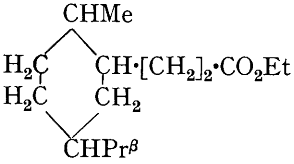
[R = CO_2H, CO_2Et, $CH_2{\cdot}OH$, CH_2Br.]

(IV.)


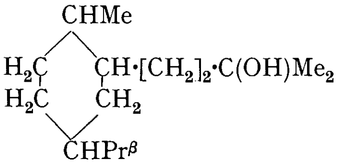

(V.)

The *ester* (VI), prepared from (III; R = CH_2Br) through the *nitrile*, gave on treatment with methylmagnesium iodide the sesquiterpene *alcohol* (VII), from which by dehydration a *hydrocarbon* was obtained. As was to be anticipated, this was a mixture of (VIII) and (IX), since oxidation gave, in addition to formaldehyde and acetone, the menthane acid (III; R = CO_2H) and a ketone (X), characterised by the preparation of its crystalline 2 : 4-*dinitrophenylhydrazone*. The sesquiterpene alcohol and the hydrocarbons are of a type which has not so far been found to occur in nature.

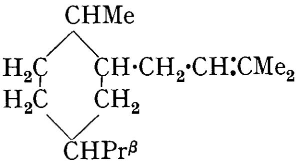
The molecular refractions of the substances described were all normal except those of ethyl menthane-2-acetate (III; R = CO_2Et) and ethyl menthane-2-β-propionate (VI), which showed an exaltation of approximately one unit. A defect in molecular refraction has been recorded for hydrocarbons having a number of alkyl groups in close juxtaposition, but we have been unable to find any reference to an exaltation in saturated substances



(VI.)

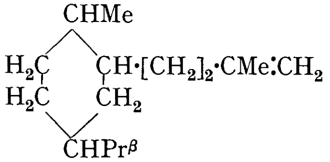


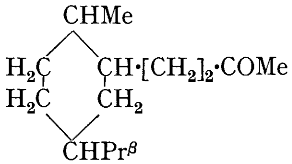
(VII.)



(VIII.)

(IX.)





(X.)

with a normal structure. The occurrence of this anomaly indicates the necessity for caution in the use of this physical constant in the determination of structure.

EXPERIMENTAL.

Ethyl Menthan-2-ol-2-acetate.—To a mixture of *l*-tetrahydrocarvone ($[\alpha]_{5461}$ − 20·3°) (11 g.), benzene (30 c.c.), and zinc (5 g.), ethyl bromoacetate (10 g.) was added. Condensation, after initiation by warming on the water-bath, was vigorous. After refluxing for 3—4 hours, the *hydroxy-ester* was isolated in the usual manner and distilled. It was a pleasant-smelling, somewhat viscid oil, b. p. 144—148°/12 mm., $d_{25^\circ}^{25^\circ}$ 0·9868, $n_D^{25^\circ}$ 1·4759, $[R_L]_D$ 67·6 (calc. 67·8), $[\alpha]_{5461}$ − 18° (Found : C, 69·1; H, 10·6. $C_{14}H_{26}O_3$ requires C, 69·4; H, 10·7%). The *hydroxy-acid*, obtained by hydrolysis of the ester with alcoholic potassium hydroxide, crystallised from ligroin (b. p. 60—80°) in plates, m. p. 77—78° (Found : C, 67·6; H, 10·6. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%).

Ethyl Menthylidene-2-acetate.—Elimination of water occurred smoothly when a mixture of the hydroxy-ester (10 g.) and potassium hydrogen sulphate (10 g.) was heated at 180—200° for 5 hours. The unsaturated *ester*, isolated by addition of water and extraction with ether, was a colourless oil with a characteristic odour, b. p. 133—136°/12 mm., $d_{25^\circ}^{25^\circ}$ 0·9456, $n_D^{25^\circ}$ 1·4795, $[R_L]_D$ 66·07 (calc., 65·83), $[\alpha]_{5461}$ − 59·3° (Found : C, 74·6; H, 10·8. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·7%).

Ethyl Menthane-2-acetate.—The unsaturated ester (25 g.) in ethyl alcohol (100 c.c.) was shaken with hydrogen in the presence of palladium–norit (5 g.; Pd 5%). Absorption was complete in 24 hours. The *ester* was a sweet-smelling mobile oil, b. p. 125—126°/12 mm., $d_{25^\circ}^{25^\circ}$ 0·9253, $n_D^{25^\circ}$ 1·4651, $[R_L]_D$ 67·5 (calc., 66·3), $[\alpha]_{5461}$ + 7·2° (Found : C, 74·4; H, 11·1. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%). The corresponding acid was an oil, b. p. 162—166°/12 mm., the p-*toluidide* of which crystallised from alcohol in small needles, m. p. 133° (Found : C, 79·2; H, 9·9. $C_{19}H_{29}ON$ requires C, 79·4; H, 10·1%).

2-β-*Hydroxyethylmenthane.*—A mixture of ethyl menthane-2-acetate (10 g.) and ethyl alcohol (80 c.c.) was added rapidly to sodium (7·5 g.) covered with xylene, the reaction being completed by heating at 130°. After addition of water 2-β-*hydroxyethylmenthane* (6·6 g.) was isolated, by distillation in steam, as a fragrant oil, b. p. 126—131°/12 mm., $d_{25^\circ}^{25^\circ}$ 0·9068, $n_D^{25^\circ}$ 1·4766, $[R_L]_D$ 57·3 (calc., 57·1), $[\alpha]_{5461}$ + 9·8° (Found : C, 78·0; H, 12·9. $C_{12}H_{24}O$ requires C, 78·2; H, 13·0%). From the alkaline residue, menthane-2-acetic acid (1·4 g.) was recovered.

2-β-*Bromoethylmenthane*, b. p. 126°/12 mm., was obtained when the alcohol (3 g.) was heated with an acetic acid solution of hydrogen bromide (50%; 10 c.c.) at 130° for 16 hours (Found : Br, 32·3. $C_{12}H_{23}Br$ requires Br, 32·4%).

*Ethyl Methyl-*β-2-*menthylethylmalonate.*—To ethyl sodiomethylmalonate, prepared from ethyl methylmalonate (11·4 g.) and sodium (1·5 g.) in ethyl alcohol (80 c.c.), 2-β-bromoethylmenthane (16·2 g.) was added, and the mixture heated in a soda-water bottle at 100° for some hours. After removal of the excess of alcohol, the reaction mixture was diluted with water, and the ester extracted with ether. After removal of the solvent, the *ester* (9·9 g.), purified by two distillations under diminished pressure, had b. p. 193°/12 mm. (Found : C, 70·1; H, 10·9. $C_{10}H_{36}O_4$ requires C, 70·5; H, 10·6%).

Methyl-β-2-*menthylethylacetic Acid.*—The above-mentioned ester (12·6 g.) was hydrolysed with methyl-alcoholic potassium hydroxide (KOH, 9 g.; methyl alcohol, 100 c.c.) (20 hours). After removal of the alcohol, acidification gave the malonic acid, which partly lost carbon dioxide on keeping. It was therefore heated at 165° until evolution of gas ceased and thereafter for some minutes at 200°. The *acetic acid* was a viscid oil, b. p. 160—163°/2 mm., $[\alpha]_{5461}$ + 25° (in chloroform; *c*, 2·55) (Found : C, 75·4; H, 11·9. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%). The p-*toluidide* crystallised from alcohol in needles, m. p. 142° (sint. 139°) (Found : C, 80·5; H, 10·9. $C_{22}H_{35}ON$ requires C, 80·5; H, 10·9%). Evidence was obtained of the formation of a ketone when the acid was heated with phosphoric oxide in either ether or xylene solution and again when the acid chloride (b. p. 154—157°/12 mm.) was treated with aluminium chloride in carbon disulphide, but in all cases the yield was too small to permit of isolation of the ketonic product.

2-β-*Cyanoethylmenthane.*—To a solution of 2-β-bromoethylmenthane (5 g.) in acetone (50 c.c.), sodium iodide (3 g.) was added, and the mixture heated under reflux for 6 hours. After removal of the precipitated sodium bromide the acetone was evaporated and the iodo-derivative, without further purification, was heated with ethyl alcohol (9 c.c.) and potassium cyanide (1·4 g.) for 20 hours. After removal of the alcohol the *nitrile* was isolated by ether and obtained as a colourless oil, b. p. 141—146°/14 mm. (Found : N, 7·1. $C_{13}H_{23}N$ requires N, 7·2%).

Ethyl Menthane-2-β-*propionate.*—The nitrile (12·5 g.) was digested with a mixture of alcohol (34 c.c.) and sulphuric acid (17·6 c.c.); after 12 hours much ammonium sulphate had separated. Ice was added, the oil extracted with ether, the extract washed with sodium carbonate solution to remove a little acid, and the ether dried and evaporated. *Ethyl menthane*-2-β-*propionate* was obtained as a mobile oil, b. p. 145—151°/16 mm., $d_{25^\circ}^{25^\circ}$ 0·9226, $n_D^{25^\circ}$ 1·4659, $[R_L]_D$ 72·1 (calc., 71·0), $[\alpha]_{5461}$ + 17·3° (Found : C, 75·1; H, 11·8. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%).

2-γ-*Hydroxy*iso*amylmenthane.*—To a solution of the ester (6 g.) in ether (ice–salt), the Grignard reagent prepared from magnesium (1·63 g.) and methyl iodide (9·5 g.) was added gradually. After remaining at room temperature for 12 hours, the mixture was heated on the water-bath for 2 hours. Ice and ammonium chloride were added, and the ether separated, washed with dilute sulphuric acid and sodium thiosulphate solution, dried, and evaporated. The *alcohol* (4 g.) was obtained as a pleasant-smelling oil, b. p. 144—147°/17 mm., $d_{25^\circ}^{25^\circ}$ 0·8928, $n_D^{25^\circ}$ 1·4719, $[R_L]_D$ 70·9 (calc., 70·8), $[\alpha]_{5461}$ + 35° (in chloroform, *c*, 3·31) (Found : C, 80·0; H, 13·3. $C_{15}H_{30}O$ requires C, 79·7; H, 13·3%).

δ-2-*Menthyl*-β-*methyl*-Δ^{α}- *and* -Δ^{β}-*butylenes.*—The alcohol (10 g.) and potassium hydrogen sulphate (10 g.) were heated at 180° for 5 hours; the resulting *hydrocarbon*, isolated by distillation in steam and extraction with ether, was a pleasant-smelling oil which after two distillations over sodium had b. p. 127—128°/19 mm., $d_{25^\circ}^{25^\circ}$ 0·8418, $n_D^{25^\circ}$ 1·4702, $[R_L]_D$ 68·9 (calc., 68·8), $[\alpha]_{5461}$ + 60° (Found : C, 86·5; H, 13·7. $C_{15}H_{28}$ requires C, 86·5; H, 13·5%).

Oxidation of δ-2-*Menthyl*-β-*methyl*-Δ^{α}- *and* -Δ^{β}-*butylenes.*—Through a solution of the hydrocarbon (1 g.) in carbon tetrachloride (1 c.c.), ozone was passed until oxidation was complete, the issuing gases being led through water to dissolve the liberated formaldehyde, which was identified by the preparation of its dimedone derivative, m. p. 186—187°. After removal of the carbon tetrachloride the ozonide was decomposed by boiling with water. Acetone was liberated and identified by conversion into its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 120°. The aqueous solution, which contained a viscid oil, was made alkaline, the undissolved oil extracted with ether, the solvent removed, and the residue, after addition of sodium hydroxide solution, distilled in steam. An oil (0·4 g.), b. p. 127—129°/17 mm., was obtained which consisted of somewhat impure methyl 2-β-menthylethyl ketone (Found : C, 78·7; H, 12·5. $C_{14}H_{26}O$ requires C, 80·0; H, 12·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in small yellow prisms, m. p. 113° (Found : N, 14·7. $C_{20}H_{30}O_4N_4$ requires N, 14·4%). The alkaline solution (see above) gave on acidification an oil (0·2 g.), b. p. 168—169°/18 mm., which was identified as menthane-2-acetic acid by the preparation of the *p*-toluidide, m. p. 133° (see p. 1811) (Found : C, 79·2; H, 9·9. Calc. : C, 79·4; H, 10·1%).

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