Synthetic Studies in the Diterpene Series. Part IX.[1] Synthesis of 1,2,3,4-Tetrahydro-1,1,5,7-tetramethyl-6-(3-methylpentyl)naphthalene (Ruzicka's Hydrocarbon)

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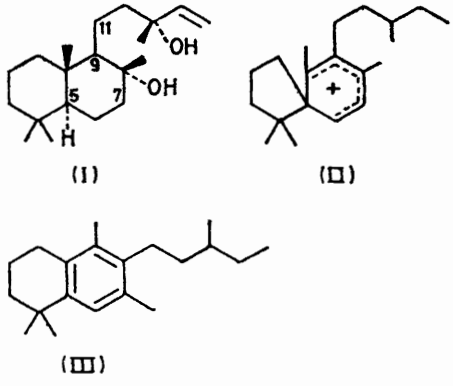
1,2,3,4-Tetrahydro-1,1,5,7-tetramethyl-6-(3-methylpentyl)naphthalene (III) has been synthesised from 1,2,3,4-tetrahydro-1,1,5,7-tetramethylnaphthalene (IV) by Friedel–Crafts acylation with 3-methylpentanoyl chloride followed by reduction, and its identity with Ruzicka's hydrocarbon (acid-catalysed dehydration product of sclareol) has been confirmed by i.r. and n.m.r. spectroscopy. An independent synthesis of the derived α-ketone (VI) from a substituted Hagemann's ester is also reported.

RUZICKA and JANOT[2] obtained a hydrocarbon, $C_{20}H_{32}$, by acid-catalysed dehydration of sclareol (I) to which a bicyclic diterpenoid structure was assigned.[3] Later, Carman and Dennis[4] isolated the same hydrocarbon in higher yield from sclareol and three other closely related diterpenoids, *viz.* manool, biformene, and *cis*-abienol. They discarded Ruzicka's structure on chemical and physical grounds and proposed a new one, that of a hydrophenalene derivative, from mechanistic considerations.[4] However they subsequently withdrew this because some n.m.r. data of the derived ketone did not fit.[5] They finally showed the hydrocarbon to be 1,2,3,4-tetrahydro-1,1,5,7-tetramethyl-6-(3-methylpentyl)naphthalene (III) from n.m.r. and i.r. results.[6] The mechanism suggested for its formation involves dehydration of the diterpenoids followed by double-bond migration to give a 5,7,9(11)-triene, which then passes through a carbonium ion intermediate (II) to give the stable hydrocarbon (III). As precedent, the rearrangement of some steroidal polyenes into anthrasteroids[7] has been cited. In an earlier paper,[8] we reported the synthesis of the above-mentioned isomeric hydrophenalene derivative.[9] We now report a synthesis of the tetralin (III)



(Scheme 1) and an independent synthesis of the tetralone (VI) (Scheme 2), and confirm their identity with materials obtained from the natural products.

Each step in Scheme 1 gave a single product (g.l.c.) in good yield except for the formation of the α-tetralone

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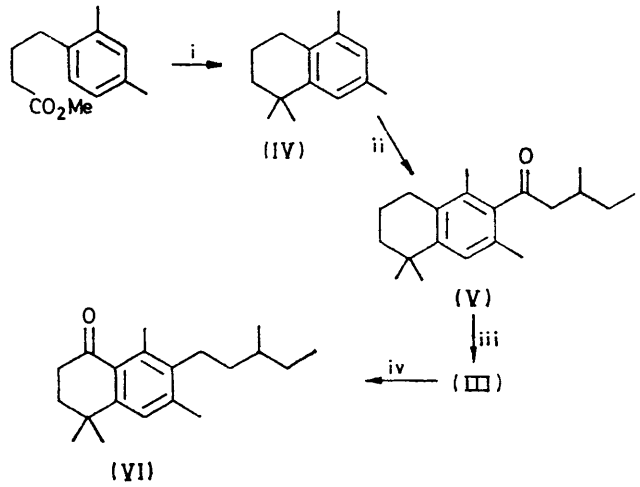
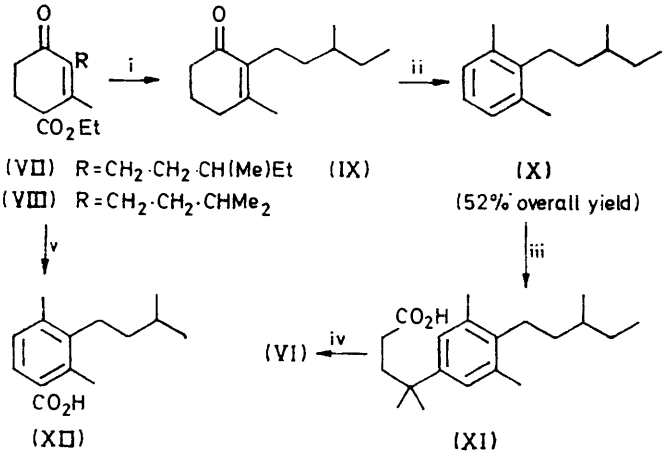
(VI). This was contaminated with the hydrocarbon (III), and was separable by chromatography. The two



SCHEME 1 Reagents and conditions: i, treatment with MeMgI and heating with polyphosphoric acid; ii, Friedel–Crafts reaction with EtCH(Me)CH_2COCl; iii, heating with $LiAlH_4$–$AlCl_3$ in ether; iv, oxidation with chromic acid

aromatic methyl groups in the ketone (V) gave n.m.r. signals 0·1 p.p.m. upfield of the corresponding signals for



SCHEME 2 Reagents and conditions: i, hydrolysis with alkali; ii, treatment with MeMgI and heating with sulphur; iii, Friedel–Crafts reaction ($AlCl_3$) with γγ-dimethylbutyrolactone; iv, cyclisation ($AlCl_3$) of the derived acid chloride; v, reaction with MeMgI, hydrolysis, esterification, and heating with sulphur

the hydrocarbons (III) and (IV) (see Experimental section), proving that they are symmetrically placed with respect to the keto-group. Similar shielding of aromatic methyl groups *ortho* to a crowded carbonyl system has been observed.[10] The alternative possibility of acylation at C-8 was unlikely in view of (i) the more hindered approach and (ii) the position of the benzylic *gem*-dimethyl peak in the n.m.r. spectrum of the ketone (V) remaining unaltered relative to that for the hydrocarbons (III) and (IV).

The substituted cyclohexenone esters (VII) and (VIII) obtained by alkylating Hagemann's ester[11] with appropriate alkyl bromides were each contaminated with 8—15% of C-1 alkylated products (g.l.c. and n.m.r.[12]) in accord with a previous observation.[13] However the derived ketone (IX) was over 95% pure. Conversion of the ester (VIII) into a crystalline acid (XII) was effected, but in view of the poor yield no attempt was made to utilise this route for the synthesis of the hydrocarbon (III). The acid (XI) was obtained in step iii (Scheme 2) as the sole product and its symmetrical structure was confirmed by the appearance of single peaks both for the ring protons and for the ring methyl groups in the n.m.r. spectrum (*cf.* succinoylation of 1,2,3-trimethylbenzene[14]). Steps i and ii may be profitably used for the synthesis of other 1-methyl-2,3-dialkylbenzenes.

EXPERIMENTAL

N.m.r. spectra were measured with a Varian T60 spectrometer for solutions in carbon tetrachloride (unless otherwise stated), with tetramethylsilane as internal standard. G.l.c. was carried out on a column (6 ft × ¼ in) of 10% poly(diethylene glycol succinate) on Gaschrom Z (60—80 mesh) with nitrogen (40 ml min^{-1} at 20 lb in^{-2}) as carrier gas. I.r. spectra were measured for films (unless otherwise stated) and u.v. spectra for solutions in ethanol. Solutions were dried over anhydrous sodium sulphate.

1,2,3,4-*Tetrahydro*-1,1,5,7-*tetramethylnaphthalene* (IV).—Methyl 4-(2,4-dimethylphenyl)butyrate[15] (20·6 g) was treated in ethereal solution with an excess of methylmagnesium iodide. The product was hydrolysed with alcoholic potassium hydroxide to remove any unchanged ester. Distillation of the neutral product afforded 2-*methyl*-5-(2,4-*dimethylphenyl*)*pentan*-2-*ol* as an oil (19·0 g, 90%), b.p. 135° at 0·8 mmHg (Found: C, 81·1; H, 10·6. $C_{14}H_{22}O$ requires C, 81·5; H, 10·7%); τ 3·07br (3H, s, ArH), 7·50 (2H, t, *J* 7 Hz, 5-H_2), 7·63 (1H, s, exchangeable with D_2O, OH), 7·75 (6H, s, 2 × ArMe), 8·50 (4H, m, 2 × CH_2), and 8·87 (6H, s, CMe_2).

The foregoing alcohol (18·5 g) was heated with polyphosphoric acid (300 g) at 160° for 3 h. Work-up and distillation afforded 1,2,3,4-*tetrahydro*-1,1,5,7-*tetramethylnaphthalene* (IV) as a mobile liquid (15·5 g, 90%), b.p. 84° at 0·3 mmHg (Found: C, 89·3; H, 10·8. $C_{14}H_{20}$ requires C, 89·4; H, 10·6%); n_D^{25} 1·5277; $\nu_{max.}$ 1610, 855, 738, and 710 cm^{-1}; τ* 3·10 (1H, s, ArH), 3·30 (1H, s, ArH), 7·47, (2H, t, *J* 6 Hz, 4-H_2), 7·75 (3H, s, 7-Me), 7·87 (3H, s, 5-Me), 8·35 (4H, m, 2 × CH_2), and 8·73 (6H, s, CMe_2). The hydrocarbon showed a single peak on g.l.c.

3-*Methylpentanoic Acid and Derivatives*.—3-Methylpentanoic acid, b.p. 193—195° at 760 mmHg, n_D^{25} 1·4169

* All n.m.r. spectra showed slight broadening of ring proton and ring methyl signals due to long-range coupling.

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was prepared according to ref. 16. The *acid chloride* had b.p. 138—140° at 760 mmHg. The acid was reduced by lithium aluminium hydride in ether to 3-*methylpentan*-1-*ol*, b.p. 51—53° at 8 mmHg; τ($CDCl_3$) 6·34 (2H, t, *J* 7 Hz, 1-H_2), 7·07 (1H, s, OH), 8·57 (5H, m, 2 × CH_2 and CH), and 9·05 (6H, m, 2 × Me). The corresponding *bromide* had b.p. 41—43° at 8 mmHg (Found: C, 43·3; H, 8·1. $C_6H_{13}Br$ requires C, 43·6; H, 7·9%; τ($CDCl_3$) 6·63 (2H, t, *J* 7 Hz, 1-H_2) (otherwise as the alcohol).

1,2,3,4-*Tetrahydro*-1,1,5,7-*tetramethyl*-6-(3-*methylpentanoyl*)*naphthalene* (V).—3-Methylpentanoyl chloride (4·5 g) in methylene chloride (5 ml) was added dropwise to a suspension of anhydrous aluminium chloride (4·5 g) in the same solvent (3 ml) at 5°. Next, the hydrocarbon (IV) (6·2 g) in methylene dichloride (10 ml) was dropped into the mixture with stirring during 25 min. The solution was stirred for 1 h in an ice-bath and then allowed to warm to room temperature. After 15 min, it was decomposed with ice and hydrochloric acid. The usual work-up gave the *ketone* (V) as a viscous liquid (8·0 g, 85%), b.p. 160° at 0·3 mmHg (Found: C, 83·6; H, 10·2. $C_{20}H_{30}O$ requires C, 83·9; H, 10·5%); $\nu_{max.}$ 1698 and 1600 cm^{-1}; τ 3·00 (1H, s, ArH), 7·40—7·60 (4H, m, $ArCH_2$ and $CO{\cdot}CH_2$), 7·84 (3H, s, 7-Me), 7·97 (3H, s, 5-Me), 8·36br (6H, m, 2 × CH_2), 8·73 (6H, s, CMe_2), and 9·03br (6H, d, 2 × Me).* It showed a single spot on t.l.c. and a single peak on g.l.c.

1,2,3,4-*Tetrahydro*-1,1,5,7-*tetramethyl*-6-(3-*methylpentyl*)-*naphthalene* (*Ruzicka's Hydrocarbon*) (III).—The ketone (V) (1·4 g) in ether (6 ml) was slowly added to a cold solution of lithium aluminium hydride (0·52 g) and anhydrous aluminium chloride (3·7 g) in ether (6 ml).[17,18] The mixture was warmed on a steam-bath for 1 h, then cooled, and the excess of reagent was destroyed by cautious addition of ethyl acetate. The product was taken up in ether, washed with water, and dried. The solvent was removed and the residue distilled over sodium to give the *hydrocarbon* (III) (1·2 g), b.p. 145° at 0·3 mmHg (Found: C, 88·0; H, 12·0. $C_{20}H_{32}$ requires C, 88·2; H, 11·8%); n_D^{25} 1·5220; $\lambda_{max.}$ 270, 275, and 280 mm (ε 380, 315, and 330); $\nu_{max.}$ (CCl_4) 1480sh, 1460, 1380, 1361, 1200, 1162, and 878 cm^{-1}; τ 3·12 (1H, s, 8-H), 7·45br (4H, t, *J* 7 Hz, 2 × $ArCH_2$), 7·75 (3H, s, 7-Me), 7·88 (3H, s, 5-Me), 8·43 (8H, m, 4 × CH_2), 8·75 (6H, s, CMe_2), and 9·04br (6H, d, 2 × Me). The u.v., i.r., and n.m.r. spectra were identical with those of the natural compound [6] except for a slight difference in the relative positions of the two aromatic methyl signals in n.m.r. spectra. The ketone (V) was not completely reduced by Martin's procedure [19] of Clemmensen reduction.

The hydrocarbon (III) was oxidised with chromic acid in acetic acid;[6] chromatography over alumina furnished 3,4-*dihydro*-4,4,6,8-*tetramethyl*-7-(3-*methylpentyl*)*naphthalen*-1(2H)-*one* (VI) as a viscous oil (60% yield) (Found: C, 83·5; H, 11·0. $C_{20}H_{30}O$ requires C, 83·9; H, 10·6%); $\lambda_{max.}$ 220, 264, and 303 nm (ε 26,000, 15,000, and 2500); $\nu_{max.}$ 1673, 1590, 1450, 1365, 1250, 1130, 1005, and 872 cm^{-1}; τ 3·03 (1H, s, 5-H), 7·38 (2H, t, *J* 7 Hz, 7-H_2), 7·58 (3H, s, 8-Me), 7·71 (3H, s, 6-Me), 8·10 (2H, t, *J* 7 Hz, 2-H_2), 8·67 (6H, s, 4-Me_2), and 9·10br (6H, d, 2 × Me). The methylene proton signal (6H) formed a broad base around τ 8·60. The u.v., i.r., and n.m.r. spectra were identical with those of the naturally derived ketone.[6] The ketone gave a single peak on g.l.c.

* The position of the side-chain methine signal could not be exactly specified in all these compounds.

3-*Alkylated Hagemann's Esters* (VIII) *and* (VII).—Hagemann's ester was alkylated according to Method B of ref. 13 with isopentyl bromide and with 3-methylpentyl bromide. The 3-isopentyl derivative (VIII) had b.p. 135—140° at 1 mmHg (Found: C, 71·1; H, 9·3. Calc. for $C_{15}H_{24}O_3$: C, 71·1; H, 9·5%); the 3-(3-methylpentyl) compound (VII) had b.p. 150—155° at 1 mmHg (Found: C, 72·0; H, 10·1. Calc. for $C_{16}H_{26}O_3$: C, 72·2; H, 9·8%). The n.m.r. spectra and g.l.c. behaviour of these compounds showed the presence of 8 and 15% of C-1 alkylated product, respectively.

3-*Isopentyl*-2,4-*dimethyl-benzoic Acid* (XII).—To a solution of ethyl 3-isopentyl-2-methyl-4-oxocyclohex-2-enecarboxylate (VIII) (8·0 g) in dry benzene (100 ml) was added methylmagnesium iodide [from magnesium (2·0 g) and ether (50 ml)] during 1 h. The resulting solution was warmed for a few min and then decomposed with cold 5% sulphuric acid. The product after the usual work-up was hydrolysed with refluxing aqueous 10% sodium hydroxide solution for 4 h. After removal of neutral material, the alkaline solution was acidified to afford a gum (3·0 g). This was esterified with diazomethane and the crude ester was heated with sulphur (0·38 g) at 210—250° for 3 h. The dark liquid was hydrolysed and the acidic material crystallised from aqueous methanol in white plates (1·1 g), m.p. 110°, of 3-*isopentyl*-2,4-*dimethylbenzoic acid* (XII) (Found: C, 76·4; H, 9·5%; equiv., 216. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%; equiv., 220); τ (100 HMz; $CDCl_3$) −2·0 (1H, CO_2H), 2·30 (1H, d, *J* 8 Hz, 6-H), 2·98 (1H, d, *J* 8 Hz, 5-H), 7·32 (2H, t, 3-H_2), 7·44 (3H, s, 2-Me), 7·68 (3H, s, 4-Me), 8·30 (1H, m, CH), 8·65 (2H, m, CH_2), and 9·00 and 9·06 (6H, d, CMe_2). Attempts to increase the yield of this acid did not succeed.

3-*Methyl*-2-(3-*methylpentyl*)*cyclohex*-2-*enone* (IX).—The keto-ester (VII) (26·6 g) was hydrolysed with ethanolic 15% potassium hydroxide (70 ml) for 8 h. After removal of ethanol, the solution was acidified with dilute hydrochloric acid and again heated on a steam-bath for 1 h for complete decarboxylation. The ketonic material was taken up in ether and distilled to give 3-*methyl*-2-(3-*methylpentyl*)-*cyclohex*-2-*enone* (IX) as a liquid (12·1 g, 62%), b.p. 92—93° at 0·2 mmHg (Found: C, 80·4; H, 11·5. $C_{13}H_{22}O$ requires C, 80·4; H, 11·3%); n_D^{25} 1·4220; $\nu_{max.}$ 1676 and 1640 cm^{-1}; τ 7·67 (6H, m, 3 × CH_2), 8·03 (3H, s, 3-Me), 8·73br (7H, m, 3 × CH_2 and CH), and 9·10br (6H, d, 2 × Me). G.l.c. showed a minor impurity peak (*ca.* 5%).

1,3-*Dimethyl*-2-(3-*methylpentyl*)*benzene* (X).—The ketone (IX) (9·7 g, 0·05 mol) was treated with methylmagnesium iodide (0·1 mol) in ether (60 ml) (2 h on a steam-bath) and the mixture was decomposed with aqueous ammonium chloride. After conventional work-up and distillation, the product underwent complete dehydration and afforded a cyclohexadiene (9·5 g), b.p. 78—80° at 0·2 mmHg (Found: C, 87·2; H, 12·7. $C_{14}H_{24}$ requires C, 87·5; H, 12·5%); n_D^{25} 1·4850; $\nu_{max.}$ 1628, 1610, 1455, 1375, 872, and 709 cm^{-1}.

The diene (8·8 g) was heated with sulphur (1·6 g) at 220—230° for 5 h and the dark liquid product was distilled in steam. The colourless oil thus obtained was taken up in ether and finally distilled over sodium to give 1,3-*dimethyl*-2-(3-*methylpentyl*)*benzene* (X) (7·3 g, 84%), b.p. 255—258° at 760 mmHg and 100° at 1 mmHg (Found: C, 88·1; H, 11·6. $C_{14}H_{22}$ requires C, 88·4; H, 11·6%); n_D^{25} 1·4940; τ 3·15 (3H, m, ArH), 7·50 (2H, t, $ArCH_2$), 7·74 (6H, s,

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2 × ArMe), 8·43 (4H, m, 2 × CH_2), and 9·0br (6H, d, 2 × Me).

4-[3,5-*Dimethyl*-4-(3-*methylpentyl*)*phenyl*]-4-*methylpentanoic Acid* (XI).—To a mixture of the hydrocarbon (X) (7·0 g) and anhydrous aluminium chloride (2·5 g) cooled to 10°, γγ-dimethylbutyrolactone (2·5 g) was added dropwise with stirring.[20] The temperature of the mixture rose to 60°. After 30 min, the mixture was decomposed with ice–water and the unchanged hydrocarbon (5·0 g) was distilled out in steam. The residue was taken up in ether and extracted with sodium hydrogen carbonate solution. The alkaline solution on acidification afforded the *acid* (XI) (1·5 g, 14%), soluble in petroleum (b.p. 60—80°), from which it crystallised in needles (1·0 g), m.p. 88—90° (Found: C, 78·6; H, 10·7. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·5%); τ($CDCl_3$) −0·53 (1H, CO_2H), 3·17 (2H, s, ArH), 7·50 (2H, t, *J* 7 Hz, $ArCH_2$), 7·72 (6H, s, 2 × ArMe), 8·00br (2H, t, CH_2CO_2H), 8·60br (6H, m, 3 × CH_2), 8·72 (6H, s, CMe_2), and 9·03br (6H, d, 2 × Me). No attempt was made to define optimal conditions for the Friedel–Crafts reaction.

3,4-*Dihydro*-4,4,6,8-*tetramethyl*-7-(3-*methylpentyl*)*naphthalene*-1(2H)-*one* (VI).—The acid (XI) (0·6 g) was converted into the acid chloride by treatment with phosphorus pentachloride (0·45 g). After removal of phosphoryl chloride under vacuum, the acid chloride was dissolved in dry carbon disulphide (4 ml) and treated with anhydrous aluminium chloride (0·3 g). After the usual work-up and removal of acidic material by extraction with aqueous alkali, the ketone (VI) (0·5 g) was obtained. Chromatography of this over alumina furnished a viscous oil (0·45 g) (Found: C, 83·7; H, 10·7%), identical (i.r.) with the sample described before and also with Carman's natural ketone.

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