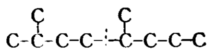
97. *Syntheses of Structural Isomers of the Terpenes. Part I.*

By G. R. Clemo and B. K. Davison.

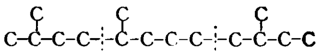
Syntheses of 2 : 5-dimethylocta-1 : 5-dien-8-ol and 3 : 8 : 11-trimethyldodeca-2 : 7 : 11-trien-1-ol, isomeric with geraniol and farnesol respectively, are described.

The structures of nearly all the terpenes can be represented by the head-to-tail union of isoprene units. It is of interest therefore to examine similar systems condensed in a non-head-to-tail manner. In furtherance of this, syntheses of one representative each of types (I) and (II) have been effected, for comparison with the well-known C_{10} terpenes and C_{15} sesquiterpenes.

(I.)



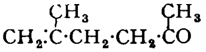
$\mathrm{C{-}\overset{C}{C}{-}C{-}C{-}\vdots{-}\overset{C}{C}{-}C{-}C{-}C}$



$\mathrm{C{-}\overset{C}{C}{-}C{-}C{-}\vdots{-}\overset{C}{C}{-}C{-}C{-}C{-}\vdots{-}C{-}\overset{C}{C}{-}C{-}C}$

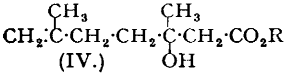
(II.)

The method attempted was similar to the well-known syntheses of citral and geraniol. 2-Methylallyl chloride was condensed with ethyl acetoacetate, and the product obtained hydrolysed smoothly to 5-methylhexa-5-en-2-one (III). This ketone was then converted into the hydroxy-ester (IV) by a Reformatsky reaction and was expected to yield unsaturated ester (V; R = Et) by dehydration. Unfortunately, all the usual methods failed to eliminate water from (IV) or the corresponding acid : either a cyclic oxide (VI or VII; R = Et or H) isomeric with (IV) was obtained, or no change or decomposition took place. Analogous examples of this type of ring closure are to be found in the literature : *e.g.*, Kilby and Kipping (*J.*, 1939, 435) obtained a cyclic oxide from ethyl 3-hydroxy-3 : 6 : 7-trimethyloct-6-enoate * on attempted dehydration, and Rupe and Lang (*Helv. Chim. Acta*, 1929, **12**, 1133) found that dehydrolinaloöl did not rearrange to give citral but yielded a six-membered tetrahydropyran derivative whose structure was confirmed by oxidation to the known α-cinenic acid. We have no evidence which would enable us to decide between a five- or six-membered ring structure and, as the substances obtained were useless for our main purpose, they were not investigated further.



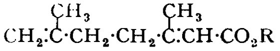
$\mathrm{CH_2{:}\overset{CH_3}{C}{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{CH_3}{CO}}$

(III.)



$\mathrm{CH_2{:}\overset{CH_3}{C}{\cdot}CH_2{\cdot}CH_2{\cdot}\underset{OH}{\overset{CH_3}{C}}{\cdot}CH_2{\cdot}CO_2R}$

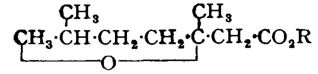
(IV.)



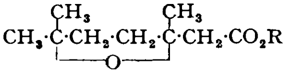
$\mathrm{CH_2{:}\overset{CH_3}{C}{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{CH_3}{C}{:}CH{\cdot}CO_2R}$

(V.)

(VI.)



$\mathrm{\overset{CH_3}{C}H_3{\cdot}CH{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{CH_3}{C}{\cdot}CH_2{\cdot}CO_2R}$ (–O– bridge)



$\mathrm{CH_3{\cdot}\overset{CH_3}{C}{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{CH_3}{C}{\cdot}CH_2{\cdot}CO_2R}$ (–O– bridge)

(VII.)

An alternative to the Reformatsky reaction for the synthesis of αβ-unsaturated acids from ketones was provided by Heilbron, Jones, *et al.* (*J.*, 1949, 1823) in the condensation with ethoxyacetylene and subsequent rearrangement with 10% sulphuric acid. From 5-methylhex-5-en-2-one this method provided ethyl 3 : 6-dimethylhepta-2 : 6-dienoate (V; R = Et) in good yield. The derived acid was then converted into ethyl 2 : 5-dimethylocta-1 : 5-dienoate (VIII) by the Arndt–Eistert process, although in only 14% overall yield. The only other record of

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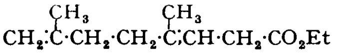
* Geneva numbering (CO_2H = 1) is used throughout this paper.

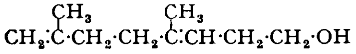
the Arndt–Eistert process being applied to an αβ-unsaturated acid is that of Barnard and Bateman (*J.*, 1950, 926) who converted geranic acid into homogeranic acid, obtaining a yield of 7% from the diazo-ketone and consequently a much lower overall yield. The ester (VIII) was then reduced with lithium aluminium hydride to the corresponding alcohol (IX) which is isomeric with geraniol.

The bromide obtained from (IX) by means of phosphorus tribromide in benzene, was condensed with ethyl acetoacetate and the product hydrolysed to 2 : 5-dimethylundeca-1 : 5-dien-10-one (X), which with ethoxyacetylene gave ethyl 3 : 8 : 11-trimethyldodeca-2 : 7 : 11-trienoate (XI) and thence by reduction with lithium aluminium hydride 3 : 8 : 11-trimethyldodeca-2 : 7 : 11-trien-1-ol (XII), isomeric with farnesol.

(VIII.)



$CH_2{:}\overset{CH_3}{C}\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CH_2\cdot CO_2Et$



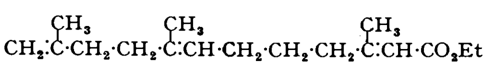
$CH_2{:}\overset{CH_3}{C}\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CH_2\cdot CH_2\cdot OH$

(IX.)

$CH_2{:}\overset{CH_3}{C}\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CH_2\cdot CH_2\cdot CH_2\cdot CO\cdot CH_3$

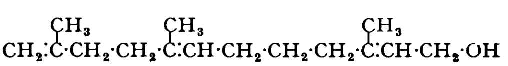
(X.)

The C_{10} compound (IX) showed a greater likeness in odour to its naturally occurring isomer geraniol than did the C_{15} alcohol (XII) to farnesol and, like geraniol, the alcohol (IX) becomes less fragrant when kept, but it does not become discoloured. Although the position of one of the methyl groups and one of the double bonds has been altered as compared with the natural terpenes, boiling points are similar, and the refractive indices are not appreciably different.



$CH_2{:}\overset{CH_3}{C}\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CH_2\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CO_2Et$

(XI.)



$CH_2{:}\overset{CH_3}{C}\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CH_2\cdot CH_2\cdot CH_2\cdot\overset{CH_3}{C}{:}CH\cdot CH_2\cdot OH$

(XII.)

The work is being continued.

EXPERIMENTAL.

(M. p.s are uncorrected.)

Ethyl 2-*Methylallylacetoacetate* (2-*Acetyl*-4-*methylpent*-4-*enoate*).—Ethyl acetoacetate (112 g.) was added to a boiling solution of sodium (18·4 g.) in absolute alcohol (80 ml.) in benzene (100 ml.), followed by 2-methylallyl chloride (80 ml.), and the whole refluxed for 10 hours. Excess of benzene and alcohol was partly removed, water added, and the oil taken up in ether. The aqueous layer was extracted, and the extracts were combined, washed with water, dried (Na_2SO_4), and distilled, giving an oil (123 g.), b. p. 85—86°/4—6 mm.

5-*Methylhex*-5-*en*-2-*one*.—The above ester (20 g.) was refluxed for 2 hours with sodium hydroxide (160 ml.; 10%), and the whole cooled, acidified (hydrochloric acid), and refluxed for a further hour, cooled again, and extracted with ether. The extract was dried (Na_2SO_4), the ether removed, and the residue distilled, giving the ketone (12 g.), b. p. 34°/4—6 mm • 150°/760 mm. The 2 : 4-*dinitrophenylhydrazone*, crystallised from light petroleum (b. p. 40—60°), had m. p. 104° (Found : C, 53·3; H, 5·6. $C_{13}H_{16}O_4N_4$ requires C, 53·4; H, 5·5%). The semicarbazone, crystallised from aqueous alcohol, had m. p. 135—136° (Found : C, 56·6; H, 8·7. Calc. for $C_8H_{15}ON_3$: C, 56·8; H, 8·9%).

Ethyl 3-*Hydroxy*-3 : 6-*dimethylhept*-6-*enoate*.—Methylhexenone (22·5 g.), zinc wool (16 g.), dry benzene (300 ml.), and ethyl bromoacetate (30 g.) were heated under reflux until the vigorous reaction commenced. When this subsided the whole was refluxed for 3 hours, then cooled, and excess of dilute sulphuric acid added. The benzene layer was separated and dried (Na_2SO_4), the benzene removed, and the *product* distilled, giving an oil (22 g.), b. p. 97—100°/3—4 mm. (Found : C, 66·2; H, 10·4. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%). Microhydrogenation, using Adams's catalyst in absolute alcohol, showed that the product had one double bond.

The ethyl ester (1 g.) was refluxed with sodium hydroxide (5 ml.; 10%) for 2 hours. The *acid* was liberated with dilute hydrochloric acid and distilled in a vacuum as a very viscous liquid (0·3 g.), b. p. 132—135°/3—4 mm. (Found : C, 62·5; H, 9·0%; equiv., 175, 175. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%; equiv., 172).

Attempted Dehydration of Ethyl 3-*Hydroxy*-3 : 6-*dimethylhept*-6-*enoate*.—The ester (IV; $R = Et$) (3·35 g.) was heated with potassium hydrogen sulphate (2·25 g.) in an oil-bath at 160—180° for 3 hours. The mixture was then allowed to cool, water (10 ml.) added, and the oil extracted with ether. The ethereal extract was dried ($MgSO_4$), the solvent removed, and the residue distilled, giving an oil (1·9 g.), b. p. 69—70°/2—3 mm. (Found : C, 66·5; H, 10·0%). Microhydrogenation, using Adams's catalyst in absolute alcohol, showed the absence of a double bond.

Ethyl 3 : 6-*Dimethylhepta*-2 : 6-*dienoate*.—To well-stirred ethylmagnesium bromide [from magnesium (2·3 g.), ethyl bromide (10·9 g.), and ether (100 ml.)], ethoxyacetylene (7·4 g.) in ether (50 ml.) was added during 30 minutes and the mixture heated under reflux for 2·5 hours, an oil separating. The mixture was then cooled in a freezing mixture, and 5-methylhex-5-en-2-one (7 g.) in ether (50 ml.) added during 30 minutes with vigorous stirring, a brownish complex separating. The whole was refluxed for 1·5 hours, then cooled in a freezing mixture, the complex decomposed with ammonium chloride (20 g.) in water (100 ml.), and the ethereal layer separated. The whole was extracted with ether and the combined ethereal liquids were shaken for 10 minutes with sulphuric acid (100 ml.; 10% w/v). The ethereal layer was separated, washed with water, dried (Na_2SO_4) and distilled, giving fractions (i) (1·7 g.), b. p. 30—42°/1—2 mm., and (ii) (7·25 g.), b. p. 64—68°/1—2 mm., and a black residue. Fraction (ii), the required *product*, decolorised bromine in water or carbon tetrachloride, gave a positive test with tetranitromethane, and was found by microhydrogenation to possess two double bonds (Found: C, 72·3; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%).

This ester (13 g.) was refluxed with potassium hydroxide (6·5 g.) in methanol (80 ml.) for 5 hours, allowed to cool, and poured into water (120 ml.). Unhydrolysed material was extracted with ether, the residue acidified with sulphuric acid (10% w/v), and extracted with ether, and the extract dried (Na_2SO_4). After removal of the ether, the oil was distilled, giving 3 : 6-*dimethylhepta*-2 : 6-*dienoic acid* (V; R = H) (8·5 g.), b. p. 138—142°/18—19 mm. (Found: C, 69·5; H, 8·75. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). Microhydrogenation showed that it possessed two double bonds.

The p-*bromobenzylthiuronium* salt, crystallised from alcohol, had m. p. 144—145° (Found: C, 51·2, 51·15; H, 5·8, 5·8. $C_{17}H_{23}O_2N_2SBr$ requires C, 51·2; H, 5·8%).

3 : 6-*Dimethylhepta*-2 : 6-*dienoyl Chloride*.—The foregoing acid (2 g.) in ether (2 ml.), thionyl chloride (2·3 ml.) in ether (5 ml.), and one drop of pyridine were mixed and kept at room temperature overnight. Then the excess of thionyl chloride and ether was removed, benzene was added and distilled off, and the *chloride* distilled (1·1 g.), having b. p. 93—97°/16 mm. (Found: Cl, 20·4. $C_9H_{13}OCl$ requires Cl, 20·6%).

Ethyl 3 : 6-*Dimethylocta*-2 : 6-*dienoate* (VIII).—The above acid chloride (6·3 g.) in ether (15 ml.) was added slowly, with shaking, to diazomethane (5 g.) in ether (400 ml.), cooled in a freezing mixture, and kept at room temperature overnight. The ether and excess of diazomethane were removed in a vacuum, leaving the diazo-ketone as a viscous yellow liquid. Freshly purified absolute alcohol (50 ml.) was added, the whole heated to 50—60°, and a slurry of freshly prepared silver oxide (from 40 ml. of 10% silver nitrate solution) and absolute alcohol were added gradually until the evolution of nitrogen ceased (10 hours). The whole was then refluxed for 2½ hours, charcoal added, and the mixture refluxed a further few minutes and filtered hot. The alcohol was removed from the filtrate in a vacuum and the residue distilled, giving fractions (i) (2 g.), b. p. 114—118°/18 mm. and (ii) (0·8 g.), b. p. 120—130°/18 mm., and a large tarry residue. Fraction (i) was a colourless liquid *ester*, shown by microhydrogenation to possess two double bonds (Found: C, 73·9; H, 10·5. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%).

3 : 6-*Dimethylocta*-2 : 6-*dien*-1-*ol* (IX).—Ethyl dimethyloctadienoate (VIII) (2 g.), in ether (5 ml.), was added dropwise to lithium aluminium hydride in ether (10 ml.; excess) and kept overnight. The excess of lithium aluminium hydride was decomposed with water, and the complex decomposed with sulphuric acid (10% w/v). The ethereal layer was separated, the residue was extracted with ether, and the extracts were combined, washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, giving fractions (i) (0·15 g.), b. p. 66—80°/18 mm., (ii) (1·3 g.), b. p. 110—116°/18 mm., and (iii) (0·1 g.), b. p. 116—120°/18 mm. Fraction (ii) was the colourless liquid *alcohol*, n_D^{18} 1·4698, having a characteristic odour, and was shown by microhydrogenation to possess two double bonds (Found: C, 77·5; H, 11·5. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%) (cf. geraniol, n_D^{20} 1·4766).

The *diphenylurethane* recrystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 80° (Found: C, 78·8; H, 7·9. $C_{23}H_{27}O_2N$ requires C, 79·1; H, 7·75%).

8-*Bromo*-2 : 5-*dimethylocta*-1 : 5-*diene*.—Phosphorus tribromide (1·4 ml.) in benzene (20 ml.) was added slowly at room temperature to the above alcohol (4 g.) in benzene (30 ml.), the mixture was kept overnight, then poured on ice, and the benzene layer separated, washed with sodium carbonate solution, and distilled, giving a colourless *bromide* (1·8 g.), b. p. 90—96°/18 mm., which quickly became brown in the air (Found: C, 55·9; H, 8·1; Br, 36·1. $C_{10}H_{17}Br$ requires C, 55·4; H, 7·85; Br, 36·9%). The derived *thiuronium picrate*, recrystallised from alcohol, had m. p. 138° (Found: C, 45·7; H, 5·4. $C_{17}H_{23}O_7N_5S$ requires C, 46·1; H, 5·2%).

Ethyl 2-*Acetyl*-6 : 9-*dimethyldeca*-5 : 9-*dienoate*.—Ethyl acetoacetate (2·7 g.) was run into sodium ethoxide [from sodium (0·3 g.) and ethanol (3 ml.)] in benzene (5 ml.) and refluxed for 0·5 hour. Then the above bromide (2·4 g.) in benzene (5 ml.) was added, the whole refluxed for 36 hours and then allowed to cool, water (20 ml.) added, and the benzene layer separated. Solvent and excess of ethyl acetoacetate were removed in a vacuum and the product distilled, giving a small fore-run and the *keto-ester* as an oil (1·4 g.), b. p. 160—180°/18 mm., which was unsaturated (tetranitromethane) (Found: C, 71·95, 72·4; H, 9·9, 9·7. $C_{16}H_{26}O_3$ requires C, 72·25; H, 9·8%).

7 : 10-*Dimethylundeca*-6 : 10-*dien*-2-*one* (X).—The above ester (1·4 g.) was refluxed for 4 hours with methanolic potassium hydroxide (1·4 g. in 14 ml.), most of the methanol removed, water added, and the whole acidified (hydrochloric acid), refluxed for a further 2 hours, cooled, and extracted with ether. The extract was dried ($MgSO_4$), the solvent removed, and the product distilled, giving fractions (i) (1·0 g.), b. p. 70—78°/1 mm. (bath-temp., 100°), and (ii) (0·2 g.), b. p. 100—120°/1 mm. (bath-temp., 140—160°). Fraction (i), the colourless *ketone*, was unsaturated (Found: C, 80·7; H, 11·2. $C_{13}H_{22}O$ requires C, 80·4; H, 11·3%), and microhydrogenation showed that it possessed two double bonds. Fraction (ii) was a different *substance* (Found: C, 72·55; H, 10·25. $C_{16}H_{26}O_3$ requires C, 72·25; H, 9·8%). An attempted preparation of the 2 : 4-dinitrophenylhydrazone, using 2 : 4-dinitrophenylhydrazine sulphate in ethanol, gave only a dark red oil.

Ethyl 3 : 8 : 11-*Trimethyldodeca*-2 : 7 : 11-*trienoate* (XI).—The above ketone (0·9 g.) in ether (5 ml.) was added dropwise to a stirred suspension of ethoxyethynylmagnesium bromide [from magnesium (0·18 g.) and ethoxyacetylene (0·53 g.)] in ether (5 ml.), the whole refluxed for 4½ hours, then cooled, and the complex decomposed with ammonium chloride (5 g.) in water (15 ml.). The ethereal layer was separated and the residue extracted with ether. From the combined extracts, the solvent was removed, the product taken up in methanol (7 ml.) containing 10 drops of sulphuric acid (10% w/v), set aside at room temperature for 30 minutes, poured into water (20 ml.), and extracted with ether. The extract was dried, the solvent removed, and the product distilled, giving an *ester* (0·4 g.), b. p. 70—80°/1 mm. (bath-temp., 140—160°), which decolourised bromine in water or carbon tetrachloride (Found : C, 77·6 ; H, 10·6. $C_{17}H_{28}O_2$ requires C, 77·3 ; H, 10·6%).

3 : 8 : 11-*Trimethyldodeca*-2 : 7 : 11-*trien*-1-*ol* (XII).—The ester (XI) (0·3 g.) in ether (4 ml.) was added to lithium aluminium hydride in ether (2 ml. ; 90 vols.) and left overnight. Excess of lithium aluminium hydride was decomposed with water, and the complex with sulphuric acid (10% w/v). The ethereal layer was separated, the residue was extracted, and the combined extracts and ethereal layer were washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, giving a colourless *alcohol* (0·2 g.), b. p. 60—70°/1 mm. (bath-temp., 120—140°), n_D^{18} 1·4845 (Found : C, 81·5 ; H, 12·1. $C_{15}H_{26}O$ requires C, 81·1 ; H, 11·7%). The product was unsaturated and microhydrogenation showed it to possess three double bonds. The *diphenylurethane* crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 110° (Found : C, 80·1 ; H, 8·2. $C_{28}H_{35}O_2N$ requires C, 80·6 ; H, 8·4%).

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