413. *Terpene Compounds. Part III. A Synthesis of iso*Fenchocamphononic Acid.

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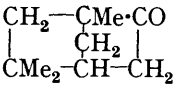
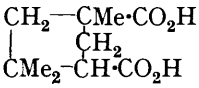
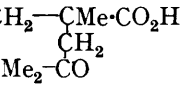
THE hydration of α-fenchene by Bertram and Helle's method (*J. pr. Chem.*, 1900, **61**, 293; also Wallach, *Annalen*, 1907, **357**, 56; 1908, **363**, 3) furnishes a secondary alcohol, from which on oxidation *iso*fenchone, $C_8H_{14}O$, is obtained. From theoretical considerations Semmler ("Die Ätherischen Öle," III, 548) first represented the ketone as (I) and it was subsequently found by Wallach (*Annalen*, 1908, **362**, 196) that on oxidation with alkaline permanganate it formed a dibasic acid, *iso*fenchocamphoric acid, which must therefore be (II). In conformity with these views it was demonstrated by Aschan (*Annalen*, 1912, **387**, 20) that *iso*fenchocamphoric acid on bromination furnished a monobromo-acid, which was converted into the related hydroxy-acid, and the latter on fusion with potassium hydroxide was decomposed into ααα'α'-tetramethylglutaric acid and formic acid. On treatment with lead peroxide, however, the hydroxy-acid yielded a ketonic acid, *iso*fenchononic acid, which was represented by Aschan as (III).



(I.)



(II.)

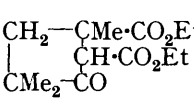


(III.)

Although these experiments of Aschan clearly demonstrated the correctness of the formulæ assigned to *iso*fenchone (I) and *iso*fenchocamphoric acid (II), it seemed to us of interest to confirm the analytical results by synthesis. We directed our attention, in the first instance, to the important ketonic acid (III), since we thought it might be a valuable starting point for the synthesis of (I) and (II). Our first attempt to synthesise this acid failed because we were unable to isolate the desired cyclic imino-compound by the condensation of mesitononitrilecyanohydrin (Lapworth, J., 1904, **85**, 1223) with ethyl sodiocyanoacetate according to Higson and Thorpe's method (J., 1906, **89**, 1466). The following method, however, was successful.

(IV.) $CO_2Et{\cdot}CMe_2{\cdot}CH_2{\cdot}CMe{:}C(CN){\cdot}CO_2Et$

(V.) $CO_2H{\cdot}CMe_2{\cdot}CH_2{\cdot}CMe(CO_2H){\cdot}CH_2{\cdot}CO_2H$



(VI.)

Ethyl αα-dimethyl-lævulate was condensed with ethyl cyanoacetate in presence of piperidine to give the unsaturated *cyano-ester* (IV); this, reacting with potassium cyanide (Lapworth and McRea, J., 1922, **121**, 2752), gave a product the hydrolysis of which with concentrated hydrochloric acid yielded βδ-*dimethylpentane*-αβδ-*tricarboxylic acid* (V), m. p. 200—201°. The *ethyl* ester of (V) on condensation by means of granulated sodium gave *ethyl* 2 : 2 : 4-*trimethyl*cyclo*pentan*-1-*one*-4 : 5-*dicarboxylate* (VI) in 70% yield. The latter was hydrolysed with dilute hydrochloric acid to 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylic acid, m. p. 70—71°, which was further characterised by the formation of a semicarbazone, m. p. 225—226°. Direct comparison is impossible owing to lack of the material, but there can be little doubt that the synthetic acid is identical with the *iso*fenchononic acid (III) isolated by Aschan (*loc. cit.*, p. 80). This synthesis of *iso*fenchononic acid lends support to Semmler's formulation of *iso*fenchone (I), and we are engaged in further experiments with it in order to synthesise *iso*fenchone and *iso*fenchocamphoric acid.

EXPERIMENTAL.

Ethyl αα-Dimethyl-lævulate.—αα-Dimethyl-lævulic acid was prepared from mesityl oxide essentially as described by Lapworth (*loc. cit.*, p. 1219). In working up large quantities of material, however, it was found convenient to remove the alcohol as far as possible under reduced pressure. The residue was then heated for a short time with an excess of concentrated hydrochloric acid, and the whole evaporated to dryness on the steam-bath. The solid acid (semicarbazone, m. p. 195—196°) isolated by repeated extractions with ether was esterified with alcoholic hydrogen chloride, the ethyl ester being obtained in 90% yield, b. p. 97—98°/16 mm.

Ethyl α-Cyano-βδ-dimethyl-Δ$^{\alpha}$-pentene-αδ-dicarboxylate (IV).—A mixture of ethyl αα-dimethyllævulate (172 g.), ethyl cyanoacetate (113 g.), anhydrous sodium sulphate (30 g.), and piperidine (6 c.c.) was heated on the steam-bath for 80 hours, the cooled product poured into water and slightly acidified with dilute hydrochloric acid, and the heavy oil collected in ether. The ethereal solution was washed with sodium bicarbonate solution, dried, and distilled. A considerable portion of a constant-boiling mixture of unchanged materials was first collected and there remained in the distillation flask an appreciable amount of a high-boiling residue. The low-boiling fraction was again treated with piperidine and anhydrous sodium sulphate as before. The process was repeated several times and the combined high-boiling residues were purified by distillation under diminished pressure. *Ethyl α-cyano-βδ-dimethyl-Δ$^{\alpha}$-pentene-αδ-dicarboxylate* formed an almost colourless oil, b. p. 165°/4 mm. (Found: C, 62·7; H, 8·1. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9%).

βδ-*Dimethylpentane-αβδ-tricarboxylic Acid* (V).—The unsaturated cyano-ester (26·7 g.), dissolved in rectified spirit (130 c.c.), was mixed with a solution of 14 g. of 98% potassium cyanide (2 mols.) in water (30 c.c.). The solution, which became warm, on being kept at the ordinary temperature for 7 days was filled with crystals of the potassio-derivative of the condensation product. This after removal of the alcohol was heated with concentrated hydrochloric acid for 6 hours. A solution of the resulting acid (20 g.) in alcohol (50 c.c.) and concentrated sulphuric acid (5 c.c.) was heated at 110° in a current of alcohol vapour for 6 hours and *ethyl* βδ-*dimethylpentane-αβδ-tricarboxylate* (as V), after rectification under diminished pressure, was obtained in excellent yield as a colourless mobile oil, b. p. 161°/4 mm. (Found: C, 60·6; H, 8·9. $C_{16}H_{28}O_6$ requires C, 60·8; H, 8·9%). The ester was quantitatively hydrolysed by boiling concentrated hydrochloric acid; the solution on evaporation yielded the corresponding *acid*, which on recrystallisation from dilute hydrochloric acid formed colourless prisms, m. p. 200—201° [Found: C, 51·8; H, 7·0; equiv., by titration, 77·6. $C_{10}H_{16}O_6$ (tribasic) requires C, 51·7; H, 6·9%; equiv., 77·3]. On one occasion during the distillation of the triethyl ester a high-boiling product was obtained which, on cooling, solidified to a crystalline mass and on purification from light petroleum (b. p. 60—80°) (charcoal) formed colourless plates, m. p. 88—89°, evidently consisting of an *ester-imide* (Found: C, 59·9; H, 8·1; N, 5·9. $C_{12}H_{19}O_4N$ requires C, 59·8; H, 7·9; N, 5·8%). This on hydrolysis with concentrated hydrochloric acid furnished the tricarboxylic acid, m. p. 200—201°, in a state of purity.

Ethyl 2 : 2 : 4-*Trimethyl*cyclo*pentan*-1-*one*-4 : 5-*dicarboxylate* (VI).—Ethyl βδ-dimethylpentane-αβδ-tricarboxylate (31·6 g.) was added to granulated sodium (4·6 g.) covered with benzene (45 c.c.); the whole was heated on the steam-bath for a short time to start the reaction, and again, finally, for 2 hours to complete it. The cooled product was decomposed with ice and dilute hydrochloric acid, and the benzene layer separated, washed with dilute sodium carbonate solution, and water, and distilled. *Ethyl* 2 : 2 : 4-*trimethyl*cyclo*pentan*-1-*one*-4 : 5-*dicarboxylate* was obtained as a colourless oil, having a characteristic sweet smell, b. p. 135°/4 mm. (yield, 70%) (Found: C, 61·5; H, 8·3. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·1%). The ester gave an intense violet colour with ferric chloride.

2 : 2 : 4-*Trimethyl*cyclo*pentan*-1-*one*-4-*carboxylic Acid* (III).—The keto-ester above (20 g.) was hydrolysed by boiling with concentrated hydrochloric acid (35 c.c.) and water (100 c.c.) for 5 hours. The product, which still contained undissolved oil, was cooled, saturated with ammonium sulphate, and repeatedly extracted with ether. After removal of the solvent the residual oil was hydrolysed with 10% methyl-alcoholic potassium hydroxide. The keto-acid was recovered from the alkaline solution as an oil, which quickly solidified on cooling in ice and crystallised from light petroleum (b. p. 60—80°) (charcoal) in clusters of well-formed prisms, m. p. 70—71° (Found: C, 63·4; H, 8·2. Calc.: C, 63·5; H, 8·2%). Aschan (*loc. cit.*, p. 79), who crystallised *iso*fenchononic acid from water, gives m. p. 68—70°.

The semicarbazone, which slowly separated when the keto-acid was heated with semicarbazide acetate for some time, crystallised from aqueous alcohol as a sandy powder, m. p. 225—226° (decomp.) (Found: C, 52·5; H, 7·6; N, 21·3. Calc.: C, 52·4; H, 7·5; N, 21·2%). Aschan (*loc. cit.*) gives m. p. 221°. The *ethyl* ester, prepared by boiling the keto-acid with alcoholic hydrogen chloride, formed a colourless oil, b. p. 96—97°/3 mm. (Found: C, 66·3; H, 9·1. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%); it gave a *semicarbazone*, which on repeated crystallisation from methyl alcohol separated in minute colourless scales, m. p. 180—181° (Found: C, 56·5; H, 8·4. $C_{12}H_{21}O_3N_3$ requires C, 56·5; H, 8·2%).

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