427. *Terpene Compounds. Part X.* A Synthesis of (±)-Angustione.*

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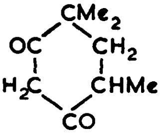
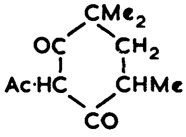
Ethyl ααγ-trimethyladipate is converted into 2 : 3 : 5 : 5-tetramethyl*cyclo*pentanone, which with chromic acid furnishes 2 : 2 : 4-trimethyl-5-oxohexanoic acid, the ethyl ester of which is cyclised to 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione [1] (I), and finally acetylated to give 2-acetyl-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (II), identical with (±)-angustione.[2]

SIMONSEN and his co-workers [1] isolated from the essential oil of *Backhousia angustifolia* two monocyclic triketones, (—)-angustione and (—)-dehydroangustione. On oxidation with potassium hypobromite angustione is quantitatively converted into (—)-ααγ-trimethylglutaric acid, and on hydrolysis with sodium hydroxide into 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (I) and an equivalent of acetic acid. Moreover, (—)-dehydroangustione on hydrogenation over palladium is completely racemised, giving (±)-angustione [2] in a high yield.


(I)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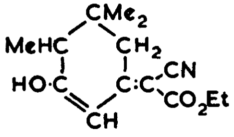
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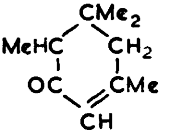
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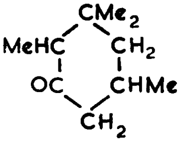

(V)

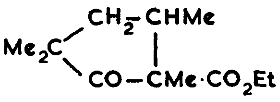
According to Birch [3] angustione is best represented as 2-acetyl-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (II), since its properties and reactions fall into line with those of 2-acetyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione.[4] This structure for angustione has recently been confirmed by Chan and Hassall [5] who synthesised the dione (I) and thence by acetylation a product which gives derivatives identical with those of (±)-angustione, although they did not purify the liquid triketone (II) itself.

$CO_2Et{\cdot}CMe_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH(CN){\cdot}CO_2Et$ (VI)

$CO_2Et{\cdot}CMe_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2Et$ (VII)

The present work was initiated with the same objective, and we record a synthesis of (±)-angustione which we have carried out independently by an alternative route.[6]

5-Chloro-2 : 3 : 3-trimethyl*cyclo*hex-5-enone [7a] was condensed with ethyl sodiocyanoacetate, giving a crystalline product, which owing to its marked acidic properties is formulated [7b] as (III). This on hydrolysis with hydrochloric-acetic acid afforded 2 : 3 : 3 : 5-tetramethyl*cyclo*hex-5-enone (IV), which was hydrogenated over palladium to 2 : 3 : 3 : 5-tetramethyl*cyclo*hexanone (V). The last on oxidation with nitric acid gave a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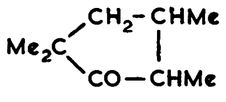
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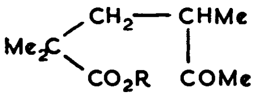
(X)

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* Part IX, *J.*, 1956, 358.

[1] Gibson, Penfold, and Simonsen, *J.*, 1930, 1184.

[2] Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286.

[3] Birch, *J.*, 1951, 3026.

[4] Dieckmann and Stein, *Ber.*, 1904, **37**, 3370; Crossley and Renouf, *J.*, 1912, **101**, 1529.

[5] Chan and Hassall, *J.*, 1955, 2860.

[6] Adhya, Thesis, Calcutta, April, 1955.

[7] (*a*) Crossley and Renouf, *J.*, 1911, **99**, 1106; (*b*) Crossley and Gilling, *J.*, 1910, **97**, 521.

gummy acid, and our expectation to obtain ααγ-trimethyladipic acid [8a] as the sole product was not realised. Ethyl 1-cyano-2 : 4-dimethylpent-1-ene-1 : 4-dicarboxylate [9] was then hydrogenated over palladised charcoal to give ethyl 1-cyano-2 : 4-dimethylpentane-1 : 4-dicarboxylate (VI) in a good yield. The hydrolysis of the latter with hydrochloric acid [8a] did not, however, proceed satisfactorily, probably owing to the remarkable ease with which 1-carboxy- and 1-cyano-adipic acids undergo ketonisation in presence of hot mineral acids.[10] On the other hand, the saturated cyano-ester (VI), on hydrolysis with alcoholic potassium hydroxide followed by decarboxylation of the derived triacid, furnished ααγ-trimethyladipic acid in an excellent over-all yield. The derived diethyl ester (VII) on Dieckmann cyclisation and methylation gave ethyl 1 : 3 : 3 : 5-tetramethyl-2-oxo*cyclo*pentanecarboxylate (VIII). This on hydrolysis with aqueous alkali gave 2 : 2 : 4 : 5-tetramethyl*cyclo*pentanone (IX). Chromic acid converted the latter smoothly into 2 : 2 : 4-trimethyl-5-oxohexanoic acid (X; R = H). The ethyl ester (X; R = Et) was readily cyclised by sodium ethoxide to 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (I), identical with that obtained from angustione.[1] The dione (I) on acetylation by the known method [4] gave 2-acetyl-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (II) indistinguishable in derivatives and in itself from natural (±)-angustione as regards physical constants and ultraviolet and infrared spectra.

EXPERIMENTAL

*Attempts to prepare ααγ-Trimethyladipic Acid from 2 : 3 : 3 : 5-Tetramethyl*cyclo*hexanone* (V).—*Ethyl α-cyano-α-(3-hydroxy-4 : 4 : 5-trimethyl*cyclo*hex-2-enylidene)acetate* (III). 5-Chloro-2 : 3 : 3-trimethyl*cyclo*hex-5-enone [7a] (15 g.) was added with cooling to a suspension of ethyl sodiocyanoacetate prepared from sodium (2 g.), calcium-dried ethanol (28 ml.), and ethyl cyanoacetate (10 ml.). After 12 hr. at the room temperature the mixture was heated on the steam-bath for 6 hr., cooled, diluted with water, acidified with sulphuric acid, and extracted with ether. The ethereal solution was washed, dried, and evaporated. The crystalline residue (13·2 g.), on recrystallisation from aqueous methanol, formed prisms, m. p. 135—136° (Found: C, 67·2; H, 7·6. $C_{14}H_{19}O_3N$ requires C, 67·5; H, 7·6%). The *ester* (III) gives a green colour with ethanolic ferric chloride and is acid in aqueous solution.

2 : 3 : 3 : *5-Tetramethyl*cyclo*hex-5-enone* (IV). The above cyano-ester (25 g.) was refluxed with concentrated hydrochloric acid (25 ml.) and acetic acid (50 ml.) for 35 hr. On cooling, water was added, and the liquid extracted with ether. The *ketone* (IV) was obtained as an oil (8 g.), b. p. 101—102°/20 mm. (Found: C, 78·7; H, 10·5. $C_{10}H_{16}O$ requires C, 79·0; H, 10·4%). The *semicarbazone* separated from aqueous ethanol in prisms, m. p. 188° (Found: C, 62·6; H, 9·0. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·1%).

2 : 3 : 3 : *5-Tetramethyl*cyclo*hexanone* (V). The preceding unsaturated ketone (10 g.) was hydrogenated over colloidal palladium (0·1 g.) in ethanol (10 ml.) until 1770 ml. of hydrogen (at 35°) had been absorbed. The product (9·1 g.) readily yielded a *semicarbazone* which from ethanol formed prisms, m. p. 175° (Found: C, 62·1; H, 9·8. $C_{11}H_{21}ON_3$ requires C, 62·6; H, 9·9%). The regenerated *ketone* (V) had b. p. 90°/11 mm. (Found: C, 77·8; H, 11·6. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). This on oxidation with nitric acid (*d* 1·25), in the usual way, gave a gummy acid which showed no tendency to crystallise and was not further examined.

ααγ-Trimethyladipic Acid.—Ethyl 1-cyano-2 : 4-dimethylpent-1-ene-1 : 4-dicarboxylate [9] (21·5 g.) was hydrogenated over 5% palladised charcoal (1 g.) in ethanol (21 ml.). The catalyst and solvent were removed, and the residue on distillation yielded ethyl 1-cyano-2 : 4-dimethylpentane-1 : 4-dicarboxylate [8b] (VI) (21 g.), b. p. 144—146°/4 mm. (Found: C, 62·1; H, 8·4. Calc. for $C_{14}H_{23}O_4N$: C, 62·4; H, 8·5%). A mixture of this cyano-ester (7 g.), potassium hydroxide (14 g.), water (28 ml.), and ethanol (18 ml.) was refluxed for 40 hr. The excess of ethanol was distilled off, and the solution acidified with hydrochloric acid, and evaporated to dryness on the steam-bath. The solid mass was extracted with ether, the solvent removed, and the residue heated at 180—185° until no more carbon dioxide was evolved, and then esterified, in the usual way. The diethyl ester (VII) (4·8 g.) had b. p. 131°/12 mm. (Found: C, 63·8; H, 9·8. Calc. for $C_{13}H_{24}O_4$: C, 63·9; H, 9·8%). Birch and Johnson [8a] record b. p.

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[8] (*a*) Birch and Johnson, *J.*, 1951, 1495; (*b*) Quadrat-i-Khuda and Ghosh, *J. Indian Chem. Soc.*, 1939, **16**, 287; Quadrat-i-Khuda and Mukherji, *ibid.*, 1946, **23**, 435.

[9] Mukherji and Bardhan, *J.*, 1949, 198; Bardhan and Ganguli, *J.*, 1936, 1853.

[10] Crombie, Hancock, and Linstead, *J.*, 1953, 3496.

123°/9 mm. This on hydrolysis gave ααγ-trimethyladipic acid as prisms, m. p. 101—102° (from water) (lit.,[8a] 100·1—100·5°) (Found : C, 57·3; H, 8·6. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·5%).

Ethyl 1 : 3 : 3 : 5-*Tetramethyl*-2-*oxo*cyclo*pentanecarboxylate* (VIII).—Ethyl ααγ-trimethyladipate (16·2 g.), finely powdered sodium (1·7 g.), and dry benzene (33 ml.) were heated on the water-bath until the sodium dissolved (2 hr.). The product was cooled in ice, treated with methyl iodide (8 ml.), and then heated on the water-bath for 10 hr. The *keto-ester* (VIII) formed a colourless liquid (11 g.), b. p. 115°/7 mm. (Found : C, 67·7; H, 9·5. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%). It did not give a colour with ethanolic ferric chloride.

2 : 2 : 4 : 5-*Tetramethyl*cyclo*pentanone* (IX).—The foregoing keto-ester (18 g.) was hydrolysed by potassium hydroxide (18 g.) in boiling water (225 ml.) for 7 hr. On cooling, the liquid was extracted with ether, and the ethereal solution washed, dried (Na_2SO_4), and distilled. The *ketone* (6·2 g.), b. p. 166—167°/760 mm., had a characteristic smell (Found : C, 77·0; H, 14·4. $C_9H_{16}O$ requires C, 77·1; H, 11·4%). The higher-boiling residue, on hydrolysis as above, gave a further quantity (1·2 g.) of the ketone.

2 : 2 : 4-*Trimethyl*-5-*oxohexanoic Acid* (X; R = H).—To a solution of the preceding ketone (7 g.) in purified acetic acid (10 ml.) cooled in ice was added slowly, with stirring, a solution of chromium trioxide (10 g.) in water (10 ml.) and acetic acid (75 ml.). The liquid was kept overnight and then heated on a water-bath for 1 hr., cooled, and repeatedly extracted with ether. After removal of the solvent from the dried ethereal extract the *acid* (X; R = H) (3·3 g.) distilled as a colourless liquid, b. p. 153—155°/12 mm. (Found : C, 62·6; H, 9·2. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). A semicarbazone could not be prepared under the usual conditions. The *ethyl ester* (X; R = Et), prepared in ethanolic hydrogen chloride, had b. p. 130°/14 mm. (Found : C, 65·9; H, 10·1. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%).

4 : 4 : 6-*Trimethyl*cyclo*hexane*-1 : 3-*dione* (I).—The last keto-ester (4 g.) was heated with a solution of sodium (0·5 g.) in absolute ethanol (30 ml.) for 20 hr. The excess of ethanol was removed, the aqueous solution cooled and acidified with hydrochloric acid, and the crystalline product purified from ethyl acetate–light petroleum (b. p. 60—80°). The dione (I) formed prisms, m. p. 130—131° (lit.,[1] 130—131°) (Found : C, 70·2; H, 9·1. Calc. for $C_9H_{14}O_2$: C, 70·1; H, 9·1%).

2-*Acetyl*-4 : 4 : 6-*trimethyl*cyclo*hexane*-1 : 3-*dione* : (±)-*Angustione* (II).—The preceding dione (3 g.) was refluxed in acetic anhydride (15 ml.) containing fused sodium acetate (0·6 g.) for 7 hr. The product was worked up in the usual way, and purified *via* the copper complex, m. p. 203—204° (from ethanol) (Found * : C, 58·0; H, 6·7. Calc. for $C_{22}H_{30}O_6Cu$: C, 58·2; H, 6·7%). Cahn *et al.*[2] give m. p. 203—204°. The regenerated (±)-angustione had b. p. 126°/14 mm., $d_4^{28 \cdot 5}$ 1·0728, $n_D^{28 \cdot 5}$ 1·5059, $[R_L]_D$ 54·23 (Found * : C, 67·3; H, 8·3. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2%). Cahn *et al.*[2] record b. p. 127°/12 mm., d_{20}^{20} 1·083, n_D^{20} 1·5087, $[R_L]_D$ 54·0. This product gives an orange-red colour with ethanolic ferric chloride. (±)-Aminoangustione which is readily prepared from the synthetic material melted at 139—140° with previous softening, as stated by Cahn *et al.*[2]

The ultraviolet light absorption [$\lambda_{max.}$ 276, 234 mμ (ε 13,720, 10,405)] was determined in ethanol with a Beckman spectrophotometer. Chan and Hassall[5] record $\lambda_{max.}$ 276, 233 mμ (ε 13,500, 13,500) for (−)-angustione. The infrared spectra of synthetic (±)-angustione which were measured (in CS_2) in a Perkin-Elmer double-beam spectrometer show bands at 3·39, 3·44, 3·51, 6·0, 6·29, 7·07, 7·20, 7·32, 7·49, 7·78, 7·81, 8·20, 8·33, 8·51, 8·60, 8·99, 9·24, 9·71, 9·93, 10·7, 11·15, 11·50, 12·2, 12·87, and 13·6 μ, almost identical with those recorded for (−)-angustione.[3]

The micro-analyses marked * and light absorption measurements were made at the Organic-analytical Laboratories of the Swiss Federal Institute of Technology, Zürich, and our best thanks are due to Professor Dr. L. Ruzicka for the facilities which he has kindly placed at the disposal of one of us (J. C. B.).

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