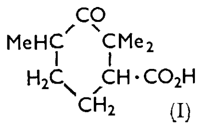
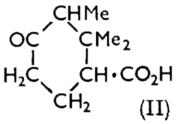
10. *Terpene Compounds. Part XI.* The Synthesis of the Keto-acid* $C_{10}H_{16}O_3$ *Formed with Rearrangement from Camphorquinone.*

By B. B. Datta and J. C. Bardhan.

Ethyl 2,2,3-trimethylcyclohex-3-enecarboxylate has been prepared by conventional methods and converted by unambiguous reactions into 2,2,3-trimethyl-4-oxocyclohexanecarboxylic acid which is identical with a product of the rearrangement of (±)-camphorquinone. A synthesis of the 2,2,4-trimethyl-3-oxo-acid is also reported.

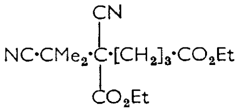
Manasse and Samuel [1] obtained a monocyclic keto-acid, $C_{10}H_{16}O_3$, by dissolving camphorquinone in concentrated sulphuric acid. Since on oxidation with nitric acid it gave an excellent yield of 4-methylpentane-1,3,4-tricarboxylic acid,[2] Gibson and Simonsen [3] concluded that it had structure (I) or (II). Further work [4] favoured structure (II), such a compound being produced by a Wagner-type rearrangement [5] of camphorquinone. Attempts to confirm this formula by direct synthesis have hitherto proved unsuccessful.[6] The present paper deals with the synthesis of both compounds (I) and (II) and proves that Manasse and Samuel's acid was the latter.


(I)

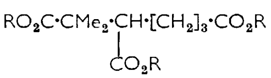

(II)

Ethyl αβ-dicyano-β-methylbutyrate [7] condensed with ethyl γ-chlorobutyrate in presence of alcoholic sodium ethoxide, giving ethyl 4,5-dicyano-5-methylhexane-1,4-dicarboxylate (III) and thence by hydrolysis and elimination of carbon dioxide 5-methylhexane-1,4,5-tricarboxylic acid (IV; R = H). Dieckmann condensation of the derived ester (IV; R = Et) afforded a keto-dicarboxylic ester which might be either (V; R = Et, R′ = H, R″ = CO_2Et) or (VI; R = Et, R′ = CO_2Et, R″ = H). This was hydrolysed with hydrochloric acid to a crystalline keto-acid (semicarbazone, m. p. 210°) (V or VI; R = R′ = R″ = H). The structure (V; R = R′ = R″ = H) was proved by the following unequivocal synthesis of the isomer. Ethyl potassio-2-oxocyclopentanecarboxylate with ethyl α-bromo-α-methylpropionate gave the ester (VI; R = Et, R′ = H, R″ = CO_2Et) in a moderate yield, and this on hydrolysis afforded the acid (VI; R = R′ = R″ = H) as a liquid, b. p. 165—167°/7 mm. (semicarbazone, m. p. 205—206°).

(III)



$$NC{\cdot}CMe_2{\cdot}\underset{CO_2Et}{\overset{CN}{C}}{\cdot}[CH_2]_3{\cdot}CO_2Et$$



$$RO_2C{\cdot}CMe_2{\cdot}\underset{CO_2R}{CH}{\cdot}[CH_2]_3{\cdot}CO_2R$$

(IV)

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* Part X, *J.*, 1956, 2179.

[1] Manasse and Samuel, *Ber.*, 1897, **30**, 3157; 1902, **35**, 3831.

[2] Perkin and Thorpe, *J.*, 1904, **85**, 135; Plattner, Fürst, and Meyer, *Helv. Chim. Acta*, 1954, **37**, 270.

[3] Gibson and Simonsen, *J.*, 1925, **127**, 1295.

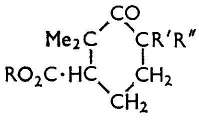
[4] Bhagbat and Simonsen, *J.*, 1927, **129**, 77; Bredt-Savelsberg, Zaunbrecher, and Knieke, *Ber.*, 1927, **60**, 1801.

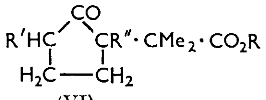
[5] Ingold, *Ann. Reports*, 1927, **24**, 122; cf. P. de Mayo, " Mono- and Sesquiterpenoids," Interscience Publ., Inc., New York, 1959, p. 141.

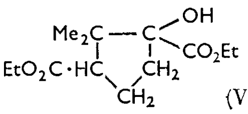
[6] Guha and Dasgupta, *J. Indian Inst. Sci.*, 1939, **22**, *A*, 255; Chakravarti, *J. Indian Chem. Soc.* 1943, **20**, 301; *Experientia*, 1947, **3**, 27; *J.*, 1947, 1565.

[7] Higson and Thorpe, *J.*, 1906, **89**, 1466; Adhya, Ghosh, and Bardhan, *J.*, 1956, **73**, 360.

The ester (V; R = Et; R′ = R″ = H) on successive bromination, hydrolysis with barium hydroxide and re-esterification afforded the hydroxy-ester (VII). Its formation obviously involves ring-contraction, which has been used extensively.[8] Dehydration of the ester (VII) with phosphoryl chloride and pyridine and then hydrolysis furnished 2,2-dimethylcyclopent-3-ene-1,3-dicarboxylic acid (dehydroapocamphoric acid)[9] (VIII).

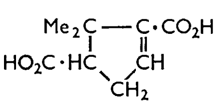

(V)

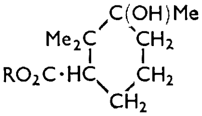

(VI)

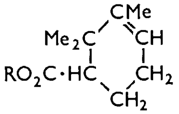

(VII)

Incidentally, the formation of this acid provides further proof of the correctness of structure (V; R = R′ = R″ = H).

The action of methylmagnesium iodide on the ester (V; R = Et; R′ = R″ = H) gave the hydroxy-ester (IX; R = Et) in good yield. Since the corresponding acid (IX; R = H) shows no tendency to form a lactone, the hydroxyl and carboxyl group must be in *trans*-relationship. On dehydration[10] with phosphoryl chloride and pyridine in toluene the hydroxy-ester was smoothly converted, without rearrangement, into the unsaturated ester (X; R = Et) which on hydrogenation over colloidal palladium and hydrolysis furnished 2,2,3-trimethylcyclohexanecarboxylic acid (*p*-phenylphenacyl ester) identical with the product obtained by the Huang-Minlon reduction[11] of Manasse and Samuel's keto-acid (II).


(VIII)


(IX)


(X)

Lastly, epoxidation of the ester (X; R = Et) with peracetic acid[12] and hydrolysis under mild condition gave the 1,2-diol as an oil, which in boiling dilute sulphuric acid afforded, by pinacolic change, 2,2,3-trimethyl-4-oxocyclohexanecarboxylic acid (II) in excellent overall yield. Its formation recalls the conversion[13] of α-campholenic acid by way of dihydrodihydroxy-α-campholenic acid into α-campholonic acid. The synthetic acid showed all the characteristics of the (±)-keto-acid (II), prepared from (±)-camphorquinone by Manasse and Samuel's method.

The triethyl ester (IV; R = Et), on Dieckmann cyclisation, followed by methylation with methyl iodide, readily yielded the ester (V; R = Et, R′ = Me, R″ = CO_2Et) and thence 2,2,4-trimethyl-3-oxocyclohexanecarboxylic acid (I) which differed from the isomer (II).

EXPERIMENTAL

Ethyl 4,5-*Dicyano*-5-*methylhexane*-1,4-*dicarboxylate* (III).—Ethyl γ-chlorobutyrate,[14] b. p. 77—78°/16 mm., was conveniently prepared by the action of alcoholic hydrogen chloride on γ-butyrolactone. To a solution of sodium (9 g.) in absolute alcohol (155 c.c.), cooled in ice,

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[8] Wallach, *Annalen*, 1918, **414**, 296; Swaminatham, Mukherjee, and Bardhan, *J.*, 1949, 193; also ref. 4.

[9] Komppa, *Ber.*, 1901, **34**, 2472; *Annalen*, 1909, **368**, 126.

[10] Inhoffen, Bohlmann, Bartram, Rummert, and Pommer, *Annalen*, 1950, **570**, 54; Inhoffen and Leibner, *ibid.*, 1951, **575**, 105; Ahmad and Weedon, *J.*, 1953, 2126.

[11] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[12] Cf. Swern, " Organic Reactions," John Wiley, New York, 1953, Vol. VII, p. 381; Isler, Lindlar, Montavon, Ruegg, Saney, and Zeller, *Helv. Chim. Acta*, 1956, **39**, 2401.

[13] Komppa and Beckmann, *Ber.*, 1936, **69**, 2783.

[14] Campbell and Campbell, *J. Amer. Chem. Soc.*, 1938, **63**, 1357.

ethyl αβ-dicyano-β-methylbutyrate [7] (70·2 g.), powdered sodium iodide (1 g.), and ethyl γ-chlorobutyrate (59 g.) were added. The mixture was left overnight at room temperature, then refluxed for 12 hr. On cooling, water was added and the oil was extracted with ether. The ethereal solution was washed, dried (Na_2SO_4), and distilled giving a *dicyano-ester* (III) (36 g.), b. p. 181—183°/5 mm., having an unpleasant smell (Found: C, 61·2; H, 7·5. $C_{15}H_{22}N_2O_4$ requires C, 61·2; H, 7·5%).

5-*Methylhexane*-1,4,5-*tricarboxylic Acid* (IV; R = H).—The dicyano-ester (III) (49 g.) was refluxed with potassium hydroxide (25 g.) in water (20 c.c.) and alcohol (80 c.c.) for 1 hr. The excess of alcohol was removed on the water-bath, the brown solution was cooled and acidified with hydrochloric acid, and the oil collected in ether. The solvent was distilled off and the crude residue (45 g.) was cautiously mixed with acetic acid (70 c.c.), sulphuric acid (50 c.c.), and water (70 c.c.) and refluxed (sand-bath) for 50 hr. The excess of acetic acid was removed and, on cooling, the dark liquid was continuously extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated, giving the *tricarboxylic* acid (IV; R = H) (30 g.), which crystallised from water or, better, ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 136—137° [Found: C, 51·4; H, 6·8%; equiv. (by titration), 76·7. $C_{10}H_{16}O_6$ requires C, 51·7; H, 7·0%; equiv. ($3CO_2H$), 77·3]. The *triethyl ester* was prepared by heating the acid (30 g.), absolute alcohol (75 c.c.), and sulphuric acid (7·5 c.c.) at 110—120° and passing the vapour of alcohol (3 l.) through the mixture for 10 hr.; it formed a colourless oil (35 g.), b. p. 162—164°/7 mm. (Found: C, 60·5; H, 8·5. $C_{16}H_{28}O_6$ requires C, 60·7; H, 8·8%).

Self-condensation of the Triethyl Ester (IV; R = Et).—(*a*) The ester (12·6 g.) was refluxed with a suspension of finely divided sodium (1 g.) in benzene (25 c.c.) until a clear solution resulted (3 hr.). On cooling, ice and hydrochloric acid were added and the benzene layer was separated, washed successively with water, sodium carbonate solution, and water, dried (Na_2SO_4), and fractionated. *Diethyl* 2,2-*dimethyl*-3-*oxocyclohexane*-1,4-*dicarboxylate* (V; R = Et, R′ = H, R″ = CO_2Et) (9·5 g.), b. p. 145—146°/7 mm. (Found: C, 62·0; H, 8·0. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·1%), gave a violet colour with alcoholic ferric chloride.

This keto-ester (9 g.), acetic acid (36 c.c.), and concentrated hydrochloric acid (18 c.c.) were refluxed (sand-bath) for 10 hr. The excess of acetic acid was removed and, after cooling, the residue was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue (5 g.), which solidified, on recrystallisation from ethyl acetate, gave 2,2-*dimethyl*-3-*oxocyclohexanecarboxylic acid* (V; R = R′ = R″ = H) as scales, m. p. 90° (Found: C, 63·2; H, 7·9. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%). The *semicarbazone* separated from alcohol in prisms, m. p. 210° (decomp.) (Found: C, 52·6; H, 7·2. $C_{10}H_{17}N_3O_3$ requires C, 52·9; H, 7·5%). The *ethyl ester*, prepared by heating the acid with alcoholic hydrogen chloride, had b. p. 110°/5 mm. (Found: C, 66·3; H, 8·8. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%), and gave a *semicarbazone*, prisms (from alcohol), m. p. 155° (Found: C, 56·2; H, 8·0. $C_{12}H_{21}N_3O_3$ requires C, 56·5; H, 8·2%).

(*b*) The ester (IV; R = Et) (25·2 g.), sodium hydride (3·8 g.), benzene (75 c.c.), and alcohol (0·5 c.c.) were refluxed with stirring on the steam-bath in a slow current of nitrogen for 3 hr. After the mixture had cooled, ice and water were added, and the aqueous solution was separated, cooled, acidified with hydrochloric acid, and extracted with ether. This afforded the preceding dicarboxylate (12·5 g.), b. p. 145—147°/7 mm. (Found: C, 62·1; H, 7·9%), and thence the keto-acid (V; R = R′ = R″ = H), m. p. and mixed m. p. 90° (Found: C, 63·3; H, 8·0%).

α-*Methyl*-α-(2-*oxocyclopentyl*)*propionic Acid* (VI; R = R′ = R″ = H).—Finely divided potassium (5·85 g.) was kept under xylene (100 c.c.), and ethyl 2-oxocyclopentanecarboxylate (23·4 g.) gradually introduced with cooling and occasional swirling. The potassio-salt which separated was mixed with ethyl α-bromo-α-methylpropionate (29·2 g.), and the whole was refluxed (oil-bath) for 15 hr. *Ethyl* α-(1-*ethoxycarbonyl*-1-*methylethyl*)-2-*oxocyclopentanecarboxylate* (VI; R = Et, R′ = H, R″ = CO_2Et), isolated as usual (14·5 g.), had b. p. 152—154°/6 mm. and a characteristic smell (Found: C, 62·1; H, 8·1. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·1%). It gave no colour with alcoholic ferric chloride.

This ester (14 g.) was boiled with concentrated hydrochloric acid (28 c.c.) and acetic acid (56 c.c.) for 10 hr. The *acid* (VI; R = R′ = R″ = H) was a liquid (6 g.), b. p. 165—167°/6 mm. (Found: C, 63·3; H, 8·1; $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%). It readily yielded a *semicarbazone*, needles (from alcohol), m. p. 205—206° (decomp.) (Found: C, 52·6; H, 7·4.

$C_{10}H_{17}N_3O_3$ requires C, 52·9; H, 7·5%). The m. p. was depressed to 175—176° on admixture with the semicarbazone, m. p. 210° of the keto-acid (V; R = R′ = R″ = H). The *ethyl ester*, prepared with alcoholic hydrogen chloride, had b. p. 112—114°/7 mm. (Found: C, 66·3; H, 8·8. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%) and gave a *semicarbazone*, needles (from aqueous alcohol), m. p. 168° (Found: C, 56·2; H, 8·0. $C_{12}H_{21}N_3O_3$ requires C, 56·5; H, 8·2%). The mixed m. p. with the semicarbazone, m. p. 167°, of the keto-ester (V; R = Et, R′ = R″ = H) was 144—145°.

2,2-*Dimethylcyclopent*-3-*ene*-1,3-*dicarboxylic Acid* (*Dehydroapocamphoric Acid*) (VIII).—To a solution of the keto-ester (V; R = Et, R′ = R″ = H) (5 g.) in acetic acid (5 c.c.), cooled in ice, bromine (2·75 c.c.) in an equal volume of acetic acid was added. The resulting pale yellow liquid was poured on ice and the oil collected in ether. The ethereal solution was washed with a dilute solution of sodium carbonate, then with water, dried ($CaCl_2$), and evaporated in a current of dry air at room temperature. The residual brown oil was mixed with a hot solution of barium hydroxide (28 g.) in water (95 c.c.) and gently refluxed for 2 hr. with stirring. The hot solution was filtered and, on cooling, the filtrate was acidified with hydrochloric acid and continuously extracted with ether. The semisolid product (4 g.) obtained on evaporation was esterified in the usual way, giving *ethyl* 1-*hydroxy*-2,2-*dimethylcyclopentane*-1,3-*dicarboxylate* (VII) (2·5 g.), b. p. 140—141°/16 mm. (Found: C, 60·4; H, 8·3. $C_{13}H_{22}O_5$ requires C, 60·5; H, 8·5%). This ester (VII) (1 g.) was heated with phosphorus pentachloride (1 g.) on the water-bath for 30 min., the excess of phosphoryl chloride was removed under reduced pressure, ice was added, and the oily product extracted with ether. The ethereal solution was washed with a little water, dried (Na_2SO_4), and evaporated. The brown residue solidified in a desiccator, and on purification from hot water (charcoal), 2,2-dimethylcyclopent-3-ene-1,3-dicarboxylic acid (VIII) formed needles, m. p. 212° alone or mixed with an authentic specimen (Found: C, 58·6; H, 6·3. Calc. for $C_9H_{12}O_4$: C, 58·7; H, 6·5%).

Ethyl trans-3-*Hydroxy*-2,2,3-*trimethylcyclohexanecarboxylate* (IX).—To ethereal methylmagnesium iodide (magnesium, 0·7 g.; ether, 25 c.c.; methyl iodide, 2·3 c.c.) at 0° the ester (V; R = Et, R′ = R″ = H) (5 g.) in ether (13 c.c.) was added slowly with shaking. The product was worked up as usual and the oily product (5 g.) was hydrolysed (potassium hydroxide, 2 g.; water, 1·5 c.c.; methyl alcohol 20 c.c.). The excess of alcohol was distilled off. The alkaline solution was extracted with ether, acidified, and again extracted with ether. The oily hydroxy-acid (IX; R = H), which contained no lactonic material, was dried ($MgSO_4$) and converted into the *ethyl ester* (IX; R = Et) (2·8 g.), b. p. 120°/9 mm. (Found: C, 67·0; H, 10·1. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%).

Ethyl 2,2,3-*Trimethylcyclohex*-3-*ene*-1-*carboxylate* (X; R = Et).—To the hydroxy-ester (IX; R = Et) (3 g.), toluene (16 c.c.), and pyridine (16 c.c.) at 0° phosphorus oxychloride (5·2 g.) in toluene (16 c.c.) was added gradually with shaking.[10] The mixture was heated at 85—95° for 30 min. and then refluxed (oil-bath) for 2 hr. On cooling, the mixture was diluted with water and acidified with hydrochloric acid (20 c.c.). The aqueous layer was separated and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and distilled. The unsaturated *ester* (X; R = Et) (1·6 g.) had b. p. 105—106°/13 mm. (Found: C, 73·2; H, 10·0. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·2%).

2,2,3-*Trimethylcyclohexanecarboxylic Acid*.—The unsaturated ester (X; R = Et) (2 g.), palladium chloride (0·1 g.), gum arabic (0·1 g.), water (2 c.c.), and alcohol (10 c.c.) were shaken in hydrogen until the calculated amount of hydrogen (256 c.c.) had been absorbed. The catalyst was filtered off and the filtrate refluxed on the water-bath with potassium hydroxide (2 g.) for 1 hr. The excess of alcohol was removed. The alkaline solution, on acidification, afforded 2,2,3-trimethylcyclohexanecarboxylic acid (1·4 g.), b. p. 113°/3 mm. (Found: C, 70·4; H, 10·5. Calc. for $C_{10}H_{18}O_2$: C, 70·6; H, 10·6%). The *p*-phenylphenacyl ester had m. p. 114° alone or mixed with the *p*-phenylphenacyl ester (m. p. 114°; Chakravarti [6]) of the corresponding acid (b. p. 113—114°/3 mm.) obtained by the Huang-Minlon reduction of (±)-keto-acid (II) under standard conditions [11] (Found: C, 78·9; H, 7·8. Calc. for $C_{24}H_{28}O_3$: C, 79·1; H, 7·7%).

2,2,3-*Trimethyl*-4-*oxocyclohexanecarboxylic Acid* (II).—A solution of peracetic acid [12] (2·8 c.c. containing 152 mg. per c.c.) was added slowly to the unsaturated ester (X; R = Et) (1 g.) in acetic acid (0·4 c.c.) with shaking, at 8—12°. The mixture was kept at 20° overnight, then the excess of peracid was decomposed with sodium dithionite (0·2 g.). The mixture was made just alkaline with ice-cold sodium hydroxide solution, shaken at the room temperature for 1 hr., and repeatedly extracted with ether. The solvent was removed from the extracts and the crude diol (1 g.) boiled with 6N-sulphuric acid (6 c.c.) for 3 hr. On cooling, the liquid was extracted with ether, and the ethereal solution washed, dried (Na_2SO_4), and evaporated. The solid residue (0·8 g.) was distilled (b. p. 170°/8 mm.); the distillate recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) as prisms, m. p. 109° (Found: C, 65·0; H, 8·5. Calc. for $C_{10}H_{16}O_3$: C, 65·3; H, 8·6%). The m. p. was not depressed on admixture with (±)-keto-acid (II), m. p. 109°, prepared from (±)-camphorquinone by Manasse and Samuel's method.[1] The semicarbazone of the synthetic keto-acid, on recrystallisation from alcohol, had m. p. 229—230° (Found: C, 54·5; H, 7·7. Calc. for $C_{11}H_{19}N_3O_3$: C, 54·7; H, 7·9%), alone or mixed with the semicarbazone, m. p. 230°, of (±)-keto-acid. The reported [1, 2] m. p.s of the corresponding (+)-keto-acid and its semicarbazone are 97—98° and 217—218°, respectively.

Ethyl 2,2,4-*Trimethyl*-3-*oxocyclohexane*-1,4-*dicarboxylate* (V; R = Et, R′ = Me, R″ = CO_2Et).—The triethyl ester (IV; R = Et) (9·5 g.), finely divided sodium (0·76 g.), and benzene (20 c.c.) were refluxed for 4 hr., then cooled. Methyl iodide (6 c.c.) was added, and the whole refluxed for 20 hr. The resulting *keto-ester* (V; R = Et, R′ = Me, R″ = CO_2Et) (6·5 g.) had b. p. 155—156°/6 mm. (Found: C, 63·3; H, 8·2. $C_{15}H_{24}O_5$ requires C, 63·4; H, 8·4%). It gave no colour with alcoholic ferric chloride.

2,2,4-*Trimethyl*-3-*oxocyclohexanecarboxylic Acid* (I).—The last preceding keto-ester (6 g.), hydrochloric acid (12 c.c.), and acetic acid (18 c.c.) were boiled for 12 hr. The *keto-acid* (I) (isolated in the usual way) recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) as prisms, m. p. 98° (Found: C, 65·1; H, 8·4. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·6%). The *semicarbazone* crystallised from a large volume of alcohol as needles, m. p. 180° (decomp.) (Found: C, 54·6; H, 7·8. $C_{11}H_{19}N_3O_3$ requires C, 54·7; H, 7·9%).

Our thanks are offered to Ciba Pharma Ltd. for repeated grants.

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[*Received, June* 15*th*, 1962.]