73. *Terpene Compounds. Part IX.* A Method of Formation of Homoapocamphoric Acid.*

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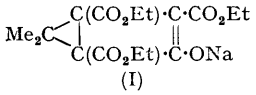
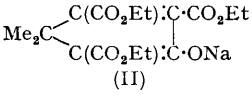
The product of the action of ethyl bromoacetate on Perkin and Thorpe's yellow sodium compound from ethyl αα′-dibromo-ββ-dimethylglutarate and ethyl sodiomalonate [1] on successive hydrogenation, hydrolysis, and Wolff–Kishner reduction affords homo*apo*camphoric acid, the formation of which is consistent only with the monocyclic structure (II) for the yellow compound. An authentic specimen of homo*apo*camphoric acid has been prepared by the condensation of ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate [2] with ethyl cyanoacetate followed by catalytic reduction and hydrolysis. A new preparation of *cis-apo*camphoric acid *via* the cyanohydrin of ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate is also described.

The yellow sodium compound, $C_{16}H_{21}O_7Na$, first prepared by Perkin and Thorpe [1] from ethyl αα′-dibromo-ββ-dimethylglutarate, ethyl sodiomalonate, and sodium ethoxide has formed the subject of much controversy. As a result of many investigations Perkin, Thorpe, and their co-workers [3] were led to represent it as (I). According to Toivonen,[4]


(I)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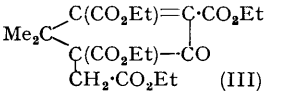
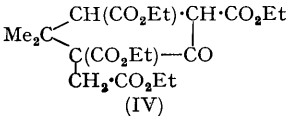

(III)

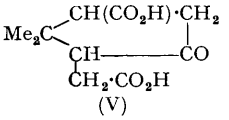
on the other hand, the sodio-derivative consists largely, at any rate, of the unsaturated monocyclic structure (II). The present communication records certain observations which support the latter view. Thus it is found that the compound readily condenses with

* Part VIII, *J.*, 1956, 260.

[1] Perkin and Thorpe, *J.*, 1901, **79**, 729.
[2] *Idem*, *J.*, 1904, **85**, 18.
[3] Cf. Farmer and Ingold, *J.*, 1920, **117**, 1362; Farmer, Ingold, and Thorpe, *J.*, 1922, **121**, 128; and later papers.
[4] Toivonen, *Ann. Acad. Sci. Fennicæ*, 1927, **19**, 20; *Annalen*, 1919, **419**, 176; *Acta Sci. Fennicæ*, *Phys.-math.*, *Cl.* I, 1922, **26**, 1.

ethyl bromoacetate, giving ethyl 1 : 2 : 4-triethoxycarbonyl-2 : 2-dimethyl-5-oxo*cyclo*pent-3-enylacetate (III), which is hydrogenated over Adams's catalyst at room temperature to the saturated ester (IV); the bridged-ring analogue would not be expected to react under such mild conditions.[5] On hydrolysis with hydrochloric acid the latter afforded 3-carboxy-2 : 2-dimethyl-5-oxo*cyclo*pentylacetic acid (V), yielding on Wolff–Kishner reduction 3-carboxy-2 : 2-dimethyl*cyclo*pentylacetic acid (homo*apo*camphoric acid [6]) (VI), the identity of which was established by comparison with a specimen prepared as follows.


(IV)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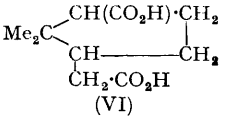
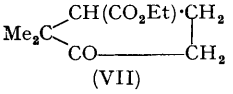
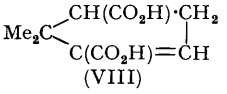
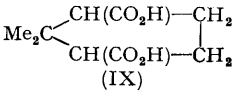

(VI)

Ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate [7] (VII), prepared by an improved method, was allowed to react with hydrogen cyanide; the product on dehydration with phosphorus oxychloride and pyridine followed by hydrolysis with hydrochloric acid gave a good yield of 2 : 2-dimethyl*cyclo*pent-3-ene-1 : 3-dicarboxylic acid (VIII), which on

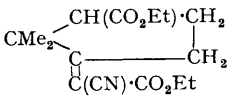

(VII)

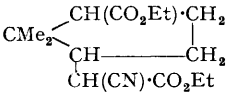

(VIII)


(IX)

hydrogenation in acetic acid in presence of Adams's catalyst gave *cis-apo*camphoric acid [8] (IX). The corresponding anhydride, however, could not be converted satisfactorily into homo*apo*camphoric acid by Komppa's method.[6]

The keto-ester (VII) readily condensed with ethyl cyanoacetate under the conditions

(X) 


(XI)

prescribed by Cope *et al.*,[9] giving the cyano-ester (X), which on hydrogenation in alcohol in presence of palladised charcoal [10] afforded the saturated ester (XI). This was hydrolysed by hydrochloric acid to homo*apo*camphoric acid (VI), identical with the product obtained from Perkin and Thorpe's compound. The bicyclic structure (I) for the latter is thus untenable.[11]

Experimental

The crude sodium compound prepared according to Perkin and Thorpe's directions [1] was recrystallised once from boiling absolute ethanol.

Ethyl 1 : 3 : 4-*Triethoxycarbonyl*-2 : 2-*dimethyl*-5-*oxo*cyclo*pent*-3-*enylacetate* (III).—The preceding sodium compound (15 g.) was suspended in dry benzene (50 ml.), ethyl bromoacetate (6 ml.) was added, and the mixture refluxed until the original deep yellow colour had almost disappeared (40—45 hr.). The mixture was diluted with water, the benzene layer isolated, and the aqueous solution extracted with benzene. The benzene extract was washed with dilute sodium carbonate solution and water, dried, and distilled. The *product* (14·5 g.) had b. p. 195—196°/4 mm., $d_4^{21\cdot5}$ 1·1530, $n_D^{21\cdot5}$ 1·4804, $[R_L]_D$ 101·6 (Calc., 98·52) (Found: C, 57·6; H, 6·7. $C_{20}H_{28}O_9$ requires C, 58·2; H, 6·7%). It gives no colour with ethanolic ferric chloride.

Ethyl 1 : 3 : 4-*Triethoxycarbonyl*-2 : 2-*dimethyl*-5-*oxo*cyclo*pentylacetate* (IV).—The preceding ester (39 g.) in ethanol (30 ml.) was shaken with Adams's catalyst (0·3 g.) in hydrogen at 30°

[5] Cf. Shriner and Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 2733.
[6] Cf. Komppa, *Ber.*, 1911, **44**, 1541.
[7] (*a*) Perkin and Thorpe, *J.*, 1904, **85**, 18; (*b*) Gibson, Hariharan, and Simonsen, *J.*, 1927, 3009.
[8] (*a*) Marsh and Gardner, *J.*, 1896, **69**, 64; (*b*) Wallach, *Annalen*, 1898, **300**, 317; 1901, **315**, 291; (*c*) Gardner and Cockburn, *J.*, 1898, **73**, 278.
[9] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.
[10] Hartung, *ibid.*, 1928, **50**, 3372.
[11] Cf. Acheson and Robinson, *J.*, 1952, 1130.

(absorption, 2436 ml. in 3·5 hr.; calc., 2441 ml.). The solution was filtered, excess of ethanol evaporated off, and the residue distilled, giving the saturated *ester* (36·6 g.), b. p. 190—191°/4 mm., which crystallised and recrystallised from light petroleum (b. p. 40—60°) as needles (18 g.), m. p. 75—76° (Found: C, 57·8; H, 7·2. $C_{20}H_{30}O_9$ requires C, 57·9; H, 7·2%). It gives a violet colour with ferric chloride. The mother-liquor was evaporated and the residue on distillation gave an oil, b. p. 185—188°/3 mm. This partly solidified and also showed a positive ferric reaction.

3-*Carboxy*-2 : 2-*dimethyl*-5-*oxo*cyclo*pentylacetic Acid* (V).—The foregoing keto-ester (9 g.) was refluxed with concentrated hydrochloric acid (50 ml.) until a clear solution resulted (20 hr.). The solution was evaporated to dryness on the steam-bath and the crystalline product (4·2 g.) purified by recrystallisation from water. The *diacid* formed prisms, m. p. 183—184° (Found: C, 56·0; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The *semicarbazone* separated from water in prisms, m. p. 228° (decomp.) (Found: C, 48·3; H, 6·2. $C_{11}H_{17}O_5N_3$ requires C, 48·7; H, 6·3%). The *ethyl ester*, prepared with ethanolic hydrogen chloride, had b. p. 155°/4 mm. (Found: C, 62·0; H, 8·1. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%).

3-*Carboxy*-2 : 2-*dimethyl*cyclo*pentylacetic* (*Homo*apo*camphoric*) *Acid* (VI).—(*a*) The semicarbazone (1 g.) described above was heated with a solution from sodium (1·2 g.) in absolute ethanol (6 ml.) at 180—190° for 26 hr. On cooling, water was added, the excess of ethanol removed on the water-bath, the solution acidified with hydrochloric acid, and the solid collected. Recrystallisation from water (charcoal) gave prisms, m. p. 202—203° (Komppa [6] gives m. p. 203—204°) (Found: C, 59·8; H, 8·0. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). This showed no m. p. depression with homo*apo*camphoric acid described below.

(*b*) The keto-ester (V) (4·5 g.), amalgamated zinc (50 g.), and concentrated hydrochloric acid (50 ml.) were refluxed for 30 hr., during which concentrated hydrochloric acid (5 × 10 ml.) was added. The solution was evaporated to a small bulk, saturated with ammonium sulphate, and extracted repeatedly with ether. The ethereal solution was washed with a little water, dried, and evaporated. The residue on recrystallisation from water gave homo*apo*camphoric acid, m. p. 201—202°.

2 : 2-*Dimethyl*cyclo*pent*-3-*ene*-1 : 3-*dicarboxylic Acid* (VIII).—Ethyl 2 : 2-dimethyl-3-oxo-*cyclo*pentanecarboxylate (VII), b. p. 95°/3 mm., was prepared essentially as described by Perkin and Thorpe and by Gibson *et al.*,[7] but the following modification was more satisfactory for the preparation of large quantities of 4-methylpentane-1 : 3 : 4-tricarboxylic acid. Ethyl αβ-dicyano-β-methylbutyrate,[12] b. p. 129—131°/6 mm., was prepared by the addition of hydrogen cyanide to ethyl 2-cyano-3-methylbut-2-enoate [13] as described by Hope and Sheldon [14] in an analogous case. A stirred solution of ethyl αβ-dicyano-β-methylbutyrate (18 g.) in *tert.*-butyl alcohol (40 ml.), heated to 40°, was mixed with methanolic 30% potassium hydroxide (1 ml.), then treated dropwise with acrylonitrile (6 g.) in *tert.*-butyl alcohol (20 ml.) during 30 min. The mixture was heated at 40—45° for a further 2 hr., diluted with water (100 ml.), and acidified with 10% hydrochloric acid (40 ml.), and the oil was collected in benzene. The benzene solution was washed with water, dried, and distilled. The resulting *ethyl* 2 : 3 : 5-*tricyano*-2-*methylpentane*-3-*carboxylate* (18 g.) had b. p. 185—190°/8 mm. (Found: C, 61·6; H, 6·6. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·4%). This on hydrolysis with sulphuric acid [7b] readily yielded 4-methylpentane-1 : 3 : 4-tricarboxylic acid, m. p. 155°.

Hydrogen cyanide (from potassium cyanide, 10 g.), cooled in a freezing mixture, was treated with a few drops of potassium cyanide solution and then dropwise with ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate (5 g.). The mixture was kept in ice over-night, then treated with two drops of concentrated sulphuric acid, the excess of hydrogen cyanide was removed, and the product heated at 140—150° with pyridine (85 ml.) and phosphorus oxychloride (23 ml.) for 1 hr. On cooling, ice-water was added and the solution acidified with concentrated hydrochloric acid (40 ml.) and extracted with ether. The ethereal solution was washed, dried, and evaporated, and the residual oil refluxed with concentrated hydrochloric acid (70 ml.) for 20 hr. 2 : 2-*Dimethyl*cyclo*pent*-3-*ene*-1 : 3-*dicarboxylic acid* (4·3 g.) which separated on cooling recrystallised from water in needles, m. p. 212° (Found: C, 58·8; H, 6·7. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%).

cis-apo*Camphoric Acid* (IX).—The foregoing unsaturated acid (2 g.), dissolved in purified acetic acid (30 ml.), was shaken with Adams's catalyst (0·1 g.) in hydrogen at 23°; the calculated

[12] Higson and Thorpe, *J.*, 1906, **89**, 1465.
[13] Vogel, *J.*, 1928, 2019.
[14] Hope and Sheldon, *J.*, 1922, **121**, 2223.

quantity of hydrogen was absorbed in 15 min. The solution was filtered and evaporated, and the solid residue recrystallised from water, giving needles, m. p. 205—206° (Found : C, 58·2; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·1; H, 7·5%). Marsh and Gardner [8a] record m. p. 203—204°; Wallach [8b] gives m. p. 205—206°; and Komppa [15] gives m. p. 203·5—204·5°. The anhydride prepared by the action of acetyl chloride crystallised from chloroform–light petroleum (b. p. 40—60°) as needles, m. p. 177° (Komppa [15] gives m. p. 174·5—175·5°; Wallach [8b] gives m. p. 176—177°) (Found : C, 64·0; H, 6·9. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·1%).

*Ethyl α-Cyano-α-(3-ethoxycarbonyl-2 : 2-dimethyl*cyclo*pentylidene)acetate* (X).—Ethyl 2 : 2-dimethyl-3-oxo*cyclo*pentanecarboxylate (VII) (11·4 g.), ethyl cyanoacetate (7 ml.), acetic acid (10 ml.), ammonium acetate (3·8 g.), and benzene (50 ml.) were heated at 150—160° for 3 hr. The benzene layer was isolated, washed with a little water, dried, and distilled, giving the cyclo*pentylideneacetate* (11·3 g.), b. p. 200—202°/12 mm. (Found : C, 64·2; H, 7·5. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·5%).

*Ethyl α-Cyano-α-(3-ethoxycarbonyl-2 : 2-dimethyl*cyclo*pentyl)acetate* (XI).—A solution of the unsaturated ester (X) (10·2 g.) in ethanol (10 ml.) was shaken with palladised charcoal (1 g.) in hydrogen at 24° until 943 ml. of hydrogen (943 ml.) had been absorbed. The solution was filtered, the solvent removed, and the residue distilled, giving the cyclo*pentylacetate* (9·3 g.), b. p. 195—197°/12 mm. (Found : C, 63·9; H, 8·2. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·2%).

*Homo*apo*camphoric Acid.*—The foregoing ester (10·3 g.) was heated with concentrated hydrochloric acid (100 ml.) for 6 hr. The acid (3 g.) which separated on cooling was collected and on repeated crystallisation from water formed prisms, m. p. 202—203° alone or on admixture with the acid described above (Found : C, 59·9; H, 8·0. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%).

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[15] Komppa, *Ber.*, 1901, **34**, 2474; *Annalen*, 1909, **368**, 126.