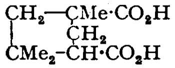
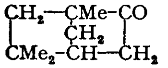
## 46. *Terpene Compounds. Part VI. A Synthesis of* (±)-iso*Fenchone.*

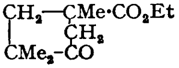
By (Miss) Debi Mukherji and J. C. Bardhan.

Ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate (Bardhan and Ganguli, *J.*, 1936, 1853) condenses with ethyl cyanoacetate to give *ethyl 4-carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylidenecyanoacetate.* This is reduced catalytically to *ethyl 4-carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylcyanoacetate,* which on hydrolysis with hydrochloric acid gave *4-carboxy-2 : 2 : 4-trimethyl*cyclo*pentaneacetic acid.* The last on pyrolysis yielded a ketone identical with (±)-*iso*fenchone. On oxidation with potassium permanganate the synthetic ketone gives an excellent yield of (±)-*cis-iso*fenchocamphoric acid. This synthesis supplies the final proof of the correctness of Semmler's formula for *iso*fenchone.

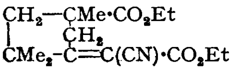
In a previous communication (this vol., p. 192) a synthesis of *cis-* and *trans-*(±)-*iso*fenchocamphoric acid (I) (Wallach, *Annalen*, 1907, **357**, 49; Aschan, *ibid.*, 1912, **387**, 1; Sandelin, *ibid.*, 1913, **396**, 285) was described. The present paper deals with the synthesis of (±)-*iso*fenchone (II) (Bertram and Helle, *J. pr. Chem.*, 1900, **61**, 303; Semmler, " Die Ätherischen Öle ", 1906, III, 549).

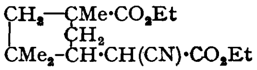

(I.)

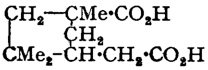

(II.)


(III.)

The condensation of ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate (III) (Bardhan and Ganguli, *J.*, 1936, 1853) with ethyl cyanoacetate proceeds somewhat tardily under the conditions described by Cope, Hofmann, Wyckoff, and Hardenbergh (*J. Amer. Chem. Soc.*, 1941, **63**, 3452), although an appreciable amount of the desired condensation product (IV) could be isolated by a frequent repetition of the process. Reduction of *ethyl 4-carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylidenecyanoacetate* (IV) thus obtained proceeded rapidly in presence of palladised charcoal (Hartung, *J. Amer. Chem. Soc.*, 1928, 3372) in cold alcoholic solution, giving *ethyl 4-carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylcyanoacetate* (V). This on hydrolysis with hydrochloric acid yielded *4-carboxy-2 : 2 : 4-trimethyl*cyclo*pentaneacetic acid* (VI). The latter exhibits a remarkable tendency to ketonise, and when heated with a trace of barium hydroxide at 310—330° gave an excellent yield of (±)-*iso*fenchone (II). This on further purification through the semicarbazone (Wallach, *loc. cit.*) had physical constants which closely corresponded with those recorded before (Bertram and Helle, *loc. cit.*, p. 309; Wallach, *loc. cit.*, p. 556). The identity was also established by comparisons with a number of derivatives of (±)-*iso*fenchone from natural sources. The ketone (II) was also obtained when the lead salt of (VI) was distilled, but the method is inferior to that given above. The Dieckmann ring-closure of the diethyl ester (as VI), on the other hand, did not proceed in the expected manner, although, according to Ruzicka and Kuhn (*Helv. Chim. Acta*, 1920, **3**, 752) ethyl homocamphorate under the same conditions affords a good yield of ethyl camphorcarboxylate. The synthetic (±)-*iso*fenchone, regenerated from the semicarbazone, on oxidation with potassium permanganate, gave, in almost quantitative yield, (±)-*cis*-*iso*fenchocamphoric acid (I) (Aschan, *loc. cit.*), indistinguishable from an authentic specimen. This constitutes an independent synthesis of this acid.


(IV.)


(V.)


(VI.)

The foregoing results appear to us to establish beyond doubt that *iso*fenchone possesses the structure (II) previously assigned to it by Semmler from purely theoretical considerations.

## EXPERIMENTAL.

*Ethyl 4-Carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylidenecyanoacetate* (IV).—Ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate (III) was prepared essentially as described by Bardhan and Ganguli (*loc. cit.*). The condensation of ethyl αα-dimethyl-lævulate with ethyl cyanoacetate was, however, carried out with advantage according to the general method developed by Cope and his co-workers (*loc. cit.*). In a typical experiment the keto-ester (17·2 g.), ethyl cyanoacetate (11·3 c.c.), ammonium acetate (3·8 g.), acetic acid (12 c.c.), and benzene (50 c.c.) were refluxed for 5 hours at 160°. Ethyl 1-cyano-2 : 4-dimethylpent-1-ene-1 : 4-dicarboxylate isolated in the usual way (14·5 g.) had b. p. 165°/5 mm. (Bardhan and Ganguli, *loc. cit.*). Ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate (III) (19·8 g.), ethyl cyanoacetate (11·3 c.c.), ammonium acetate (3·8 g.), acetic acid (12 c.c.), and benzene (50 c.c.) were heated under reflux in an oil-bath at 155—160° for 2—3 hours. After being cooled, the solution was washed with a solution of sodium chloride, dried, and distilled. The desired unsaturated cyano-ester was invariably accompanied by a considerable amount of the unchanged materials which were treated with ammonium acetate and acetic acid as described above. The process was repeated several times until the yield of the condensation product became unprofitably low. *Ethyl 4-carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylidenecyanoacetate* (17·5 g.) formed an almost colourless liquid, b. p. 168°/5 mm. (Found : C, 65·7; H, 7·9. $C_{16}H_{23}O_4N$ requires C, 65·5; H, 7·8%).

*Ethyl 4-Carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylcyanoacetate* (V).—The unsaturated cyano-ester (IV) (17 g.) dissolved in absolute alcohol (22 c.c.) was shaken with palladised charcoal catalyst (Hartung, *loc. cit.*) (1·5 g.) in an atmosphere of hydrogen until the requisite quantity (1492 c.c.) of hydrogen had been absorbed (10—11 hours). The solution was filtered, washed with alcohol, and the excess of solvent removed at the water-pump. The residual oil was shaken with a solution of sodium hydrogen sulphite (35 c.c. of 20%) for 12 hours. The mixture was extracted with ether, and the ethereal solution washed with a little dilute hydrochloric acid, again with water, dried, and distilled, to give *ethyl 4-carbethoxy-2 : 2 : 4-trimethyl*cyclo*pentylcyanoacetate* as a colourless oil, b. p. 158°/4 mm. (Found : C, 65·2; H, 8·5. $C_{16}H_{25}O_4N$ requires C, 65·1; H, 8·4%). Yield, 15·5 g.

*4-Carboxy-2 : 2 : 4-trimethyl*cyclo*pentaneacetic Acid* (*Homo*iso*fenchocamphoric Acid*) (VI).—The foregoing cyano-ester (V) (9·8 g.) was refluxed on a sand-bath with concentrated hydrochloric acid (90 c.c.) for 75 hours. After cooling, the dark crystalline solid (6·1 g.) was collected and purified by repeated crystallisation from aqueous acetone (charcoal). *4-Carboxy-2 : 2 : 4-trimethyl*cyclo*pentaneacetic acid* formed minute, colourless prisms, m. p. 157—158° [Found : C, 61·6; H, 8·4; equiv., 106·5. $C_{11}H_{18}O_4$ (dibasic) requires C, 61·7; H, 8·4%; equiv., 107]. It is sparingly soluble in water and stable to bromine and permanganate. The *ethyl* ester was obtained as a colourless liquid, b. p. 125°/4 mm. (Found : C, 66·6; H, 9·7. $C_{15}H_{26}O_4$ requires C, 66·7; H, 9·6%).

(±)-iso*Fenchone* (II).—A mixture of the above dicarboxylic acid (VI) (3·9 g.) and barium hydroxide (0·4 g.) was heated in a bath of mixed nitrates at 310—330° (internal temperature) in a distilling flask fitted with a thermometer which reached to the bottom. Reaction began at about 310°, and the ketone distilled regularly. When the distillation slackened, the temperature was kept at 330° for 20 minutes. The product was isolated by means of a little ether, and washed with sodium hydrogen carbonate solution and water. After being dried and freed from solvent, the residue (2·6 g.) was gently warmed with semicarbazide hydrochloride (4 g.), sodium acetate (6 g.), and sufficient aqueous alcohol to make a clear solution. The semicarbazone quickly separated, and after recrystallisation from aqueous alcohol had m. p. 222—223°, alone or admixed with an authentic specimen (Found : C, 63·4; H, 9·2. Calc. for $C_{11}H_{19}ON_3$ : C, 63·2; H, 9·1%). Wallach (*loc. cit.*) gives m. p. 223—224°. By distillation of the semicarbazone in steam in an all-glass apparatus with excess of oxalic acid, the ketone was regenerated in almost theoretical yield. (±)-*iso*Fenchone on distillation in a vacuum in an all-glass apparatus had b. p. 82°/12 mm., $d_{4^\circ}^{30^\circ}$ 0·93246, $n_D^{30^\circ}$ 1·457005, $[R_L]_D$ 44·31 (Calc., 43·99) (Found : C, 78·9; H, 10·5. Calc. for $C_{10}H_{16}O$ : C, 78·9; H, 10·5%). Wallach ("Terpene und Campher", 1914, p. 556) gives $d_{4^\circ}^{18\cdot5^\circ}$ 0·948,

$n_D^{18.5°}$ 1·4621, $[R_L]_D$ 44·32. Bertram and Helle (*loc. cit.*) give $d_{4°}^{15°}$ 0·950, $n_D^{15°}$ 1·46189, $[R_L]_D$ 43·97. The substance has a pleasant odour reminiscent of camphor and is saturated to the usual reagents.

The lead salt of the acid (VI) on distillation in a stream of carbon dioxide also furnished the ketone, although in a poorer yield.

(±)-cis-iso*Fenchocamphoric Acid* (I).—A mixture of synthetic (±)-*iso*fenchone (1·1 c.c.) regenerated from the semicarbazone, potassium permanganate (2·5 g.), potassium hydroxide (1·1 g.), and water (100 c.c.) was warmed to 70° and shaken until the colour of the permanganate was completely discharged. (±)-*cis*-*iso*Fenchocamphoric acid (1·0 g.), isolated in the usual way, on recrystallisation from hot water had m. p. 174—175° and did not depress the m. p. of an authentic specimen or of the synthetic acid described previously (Found : C, 60·1 ; H, 8·1. Calc. for $C_{10}H_{16}O_4$ : C, 60·0; H, 8·0%). It also gave the anhydride, m. p. 95—96° (Aschan, *loc. cit.*).

We wish to express our indebtedness to Professor G. Komppa for kindly supplying us with genuine specimens of (±)-*iso*fenchone and various of its derivatives which greatly facilitated this work.

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Calcutta.

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