106. *Terpene Compounds. Part I. Preliminary Synthetical Investigations in the Cadinene Group.*

By J. C. BARDHAN and S. K. BANERJI.

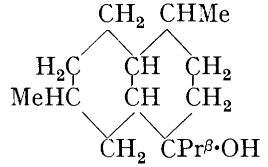
THE structure of the dicyclic sesquiterpenes of the cadinene group has been definitely established by Ruzicka and his collaborators (*Helv. Chim. Acta*, 1921, **4**, 505; 1922, **5**, 357, 369; 1923, **6**, 86) by conversion into the fundamental naphthalene hydrocarbon cadalene and by analytical methods. Apart from the work of Ruzicka and Capato (*ibid.*, 1925, **8**, 289), no attempt appears to have been made hitherto to confirm the structural details respecting the orientation of the double bonds by rational synthesis.

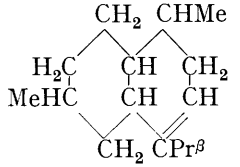
Preliminary experiments which we have carried out in this direction, with the object of synthesising dihydrocadinol (I) and dihydrocadinene (II) (compare, however, Ruzicka and Stoll, *ibid.*, 1923, **6**, 94), are now described.

The starting point was ethyl Δ^3-tetrahydro-*p*-toluate, the preparation of large quantities of which from 4-methyl*cyclo*hexanone presented little difficulty. This was condensed with ethyl sodiocyanoacetate, and the resulting sodio-derivative allowed to react with ethyl β-chloropropionate, a good yield of *ethyl* 1-*carbethoxy*-4-*methyl*cyclo*hexane*-2-α-

(*α-cyanoglutarate*) (III) being obtained. This on hydrolysis with sulphuric acid gave the expected tricarboxylic acid (as IV). The corresponding *ester* (IV) was cyclised with granu-

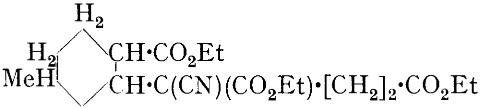
(I.)



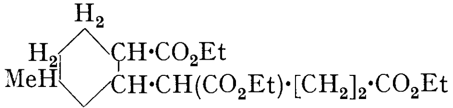


(II.)

lated sodium in dry benzene, and the product on hydrolysis gave a crystalline substance (V) which showed all the properties of a ketonic acid.



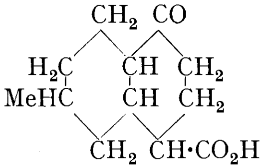
(III.)

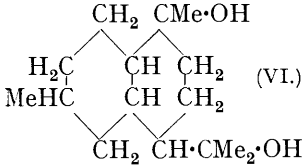


(IV.)

The *keto-ester* (as V), treated with methylmagnesium iodide, gave a neutral product; this was probably derived from (VI), since on dehydrogenation with selenium it furnished a good yield of cadalene, identified by its boiling point and by its picrate, m. p. 115°.

(V.)

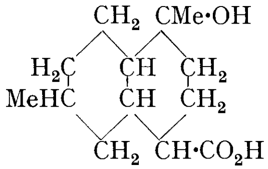




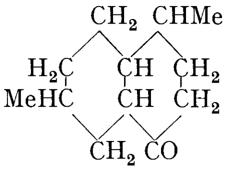
(VI.)

The yield of the acid fraction in the above condensation was very small. We are trying to improve the yield of the product (VII), from which by a simple series of transformations we hope to prepare the ketone (VIII).

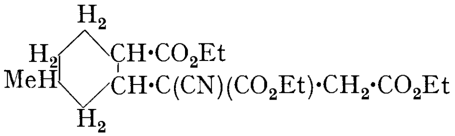
At the outset of this research we made some preliminary experiments on the formation of *bicyclo*nonane derivatives from ethyl Δ^3-tetrahydro-*p*-toluate. The product of the interaction of ethyl sodiocyanoacetate and ethyl Δ^3-tetrahydro-*p*-toluate readily reacted with ethyl bromoacetate to give (IX), which on hydrolysis gave a gummy acid. It is somewhat remarkable that tricarboxylic acids of this series show no tendency to solidify, especially in view of the fact that the corresponding tricarboxylic acid from ethyl Δ^1-*cyclo*pentenecarboxylate can be readily obtained in the solid state (compare Bardhan and Banerji, preceding paper). The *ester* (X) on condensation with granulated sodium gave the dicyclic *keto-ester* (XI), which on hydrolysis furnished a keto-acid (XII), characterised by its *semicarbazone*.



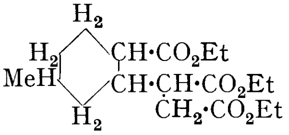
(VII.)



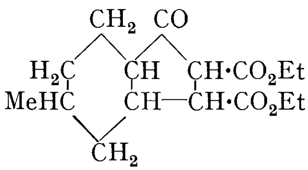
(VIII.)



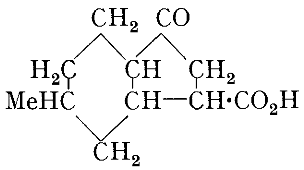
(IX.)



(X.)



(XI.)



(XII.)

EXPERIMENTAL.

Δ^3-Tetrahydro-*p*-toluic acid was first prepared by Perkin and Pickles (J., 1905, **87**, 645) from *p*-toluic acid (they named it Δ^1-tetrahydro-*p*-toluic acid). For the preparation of the large quantities required for the present research the following method gave excellent results. 4-Methyl*cyclo*hexanone (100 g.) was shaken with a solution of sodium bisulphite (200 g.) in water (250 c.c.), and the mixture was then cooled in ice and gradually treated with a solution of potassium cyanide (75 g.) in water (150 c.c.). After some time the cyanohydrin was collected in ether, washed with water, and dried (anhydrous sodium sulphate), and the solvent removed with the addition of 2—3 drops of concentrated sulphuric acid. The crude cyanohydrin was refluxed with 5—6 vols. of concentrated hydrochloric acid (*d* 1·19) for 5 hours on the steam-bath, and the hydroxy-acid extracted with ether (yield, 100 g.; m. p. 130°). The hydroxy-acid (50 g.) was cautiously mixed with phosphorus pentachloride (135 g.) and heated on the steam-bath until the latter had gone into solution (10—12 hours). The product was well cooled, poured into ice-cold absolute alcohol (200 c.c.), and left over-night. Dilution in much water precipitated a heavy oil, which was separated and hydrolysed with an excess of 20% potassium hydroxide solution. The last traces of alcohol were removed on the water-bath, the brown solution cooled, filtered, and acidified with hydrochloric acid, and the solid product collected (yield, 33 g.; m. p. 132°).

Ethyl Δ^3-tetrahydro-*p*-toluate was prepared by refluxing a mixture of the acid (126 g.), absolute alcohol (350 c.c.), and concentrated sulphuric acid (50 c.c.) for 8 hours (yield, 125 g.; b. p. 95°/5 mm.) (compare Perkin and Pickles, *loc. cit.*).

Ethyl 1-*Carbethoxy*-4-*methyl*cyclo*hexane*-2-α-(α-*cyanoglutarate*) (III).—A solution of sodium (11·5 g.) in absolute alcohol (188 c.c.) was cooled in ice and gradually mixed with ethyl cyanoacetate (57 g.). After ½ hour ethyl Δ^3-tetrahydro-*p*-toluate (84 g.) was added, and the mixture refluxed on the steam-bath for 24 hours. The brownish crystalline mass, consisting of the sodio-derivative of the condensation product, was cooled in ice and treated with ethyl β-chloropropionate (69 g.), the mixture being finally heated for 6 hours. After cooling, the product was poured into water, and the oil extracted with ether, washed, dried, and fractionated under diminished pressure. *Ethyl* 1-*carbethoxy*-4-*methyl*cyclo*hexane*-2-α-(α-*cyanoglutarate*) had b. p. 198°/2 mm., $d_{4^\circ}^{30\cdot2^\circ}$ 1·08347, $n_{\mathrm{D}}^{30\cdot2^\circ}$ 1·46340, $[R_L]_{\mathrm{D}}$ 97·01 (calc., 97·14) (Found: C, 62·4; H, 8·3. $C_{20}H_{31}O_6N$ requires C, 62·7; H, 8·1%). Yield, 118 g.

Ethyl 1-*Carbethoxy*-4-*methyl*cyclo*hexane*-2-α-*glutarate* (IV).—A solution of the above cyano-ester (118 g.) in concentrated sulphuric acid (120 c.c.) was diluted with water (120 c.c.) and refluxed for 40 hours, the condenser being removed from time to time to allow the alcohol produced to escape. After cooling, the mixture was diluted with water, and the semi-solid mass extracted with ether. The gummy acid (80 g.) obtained was converted by the alcohol vapour method [in a typical experiment: acid, 115 g.; absolute alcohol, 230 c.c.; concentrated sulphuric acid, 23 c.c.; 6 l. of alcohol vaporised; (7 hours)] into *ethyl* 1-*carbethoxy*-4-*methyl*cyclo*hexane*-2-α-*glutarate*, a colourless limpid oil, b. p. 168°/2 mm., $d_{4^\circ}^{30\cdot6^\circ}$ 1·0326, $n_{\mathrm{D}}^{30\cdot6^\circ}$ 1·45542, $[R_L]_{\mathrm{D}}$ 93·61 (calc., 92·7) (Found: C, 64·6; H, 9·0. $C_{19}H_{32}O_6$ requires C, 64·0; H, 9·0%) (yield from the above quantities, 112 g.).

1-*Keto*-6-*methyldecalin*-4-*carboxylic Acid* (V).—A mixture of the foregoing ester (26·7 g.) and granulated sodium (3·45 g.) in dry benzene (54 c.c.) was refluxed for 1 hour to start the reaction. The heating was discontinued until the vigour of the reaction abated and was then continued for 3—4 hours. After cooling, the product was treated with cold dilute sulphuric acid, and the benzene layer was washed with aqueous sodium carbonate and with water, dried, and evaporated. The residue gave a violet coloration with ferric chloride, but could not be distilled without decomposition. The crude product (13 g.) was refluxed with excess of dilute sulphuric acid (20%) for 8 hours, the cooled solution saturated with ammonium sulphate and repeatedly extracted with ether, and the extract washed with water, dried, and distilled; as the residue of acid contained an appreciable amount of the ester, it was further hydrolysed with 10% alcoholic potash, and the product isolated in the usual way. The keto-acid was thus obtained as a semi-solid crystalline mass, which was spread on a porous plate and purified by several crystallisations from aqueous alcohol (charcoal). 1-*Keto*-6-*methyldecalin*-4-*carboxylic acid* formed colourless prisms, m. p. 191° (previous softening), sparingly soluble in ether (Found: C, 67·9; H, 8·5. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%). The *semicarbazone* separated from methyl alcohol in colourless needles, m. p. 216° (Found: C, 58·7; H, 7·9. $C_{13}H_{21}O_3N_3$ requires C, 58·4; H, 7·9%), and when warmed with dilute hydrochloric acid regenerated the keto-acid, m. p. 191°.

The *ethyl* ester, prepared by refluxing a solution of the keto-acid (105 g.) in absolute alcohol (350 c.c.), with the addition of absolute alcohol (35 c.c.) saturated at 0° with hydrogen chloride, formed a colourless, somewhat viscous oil (65 g.), b. p. 142°/3 mm., $d_{4^\circ}^{22^\circ}$ 1·04887, $n_{\mathrm{D}}^{22^\circ}$ 1·47985, $[R_L]_{\mathrm{D}}$ 64·4 (calc., 64·1) (Found: C, 70·7; H, 9·3. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·2%); its *semicarbazone*, crystallised from ethyl alcohol, had m. p. 192° (Found : C, 61·7; H, 8·9. $C_{15}H_{25}O_3N_3$ requires C, 61·0; H, 8·5%), and the *oxime* separated from dilute alcohol in colourless silky needles, m. p. 160° (Found : C, 66·7; H, 9·3. $C_{14}H_{23}O_3N$ requires C, 66·4; H, 9·1%).

Action of Methylmagnesium Iodide on Ethyl 1-Keto-6-methyldecalin-4-carboxylate.—The ester (10 g.), diluted with dry ether (10 c.c.), was slowly added to a solution of methylmagnesium iodide (prepared from magnesium, 3·6 g., dry ether, 100 c.c., and methyl iodide, 11 c.c.) cooled in ice-water. After standing for 12 hours at the ordinary temperature, the product was decomposed with ice and dilute hydrochloric acid. The solution was extracted ten times with ether and the extract was washed with water, dried, and evaporated. The brown residue was boiled with a solution of potassium hydroxide (10 g.) in water (10 c.c.) and alcohol (90 c.c.) for 1 hour, the alcohol removed as completely as possible, and the residue diluted with water and repeatedly extracted with ether (extract A) (yield, 4 g.). The alkaline solution was acidified with hydrochloric acid and again extracted with ether (extract B). Extract A on removal of the solvent gave a neutral oil having a terpene-like odour. No product of definite composition could be obtained from it, but when it was heated with selenium it gave a good yield of cadalene, b. p. 130—159°/10 mm. (picrate, m. p. and mixed m. p. 115°). The regenerated cadalene was a colourless oil, b. p. 149°/10 mm. (Found : C, 91·2; H, 9·2. Calc. : C, 90·9; H, 9·1%).

Extract (B) consisted of acidic products, the investigation of which is not yet complete.

*Ethyl 1-Carbethoxy-4-methyl*cyclo*hexane-2-α-cyanosuccinate* (IX) [with R. G. Chatterjee and N. N. Chatterjee].—The condensation of ethyl tetrahydro-*p*-toluate with ethyl sodiocyanoacetate was carried out as described above, and the resulting sodio-derivative heated with ethyl bromoacetate for 6 hours. The *ester* (IX) is a colourless viscous liquid, b. p. 215°/7 mm., $d_{4°}^{30·1°}$ 1·095225, $n_{D}^{30·1°}$ 1·467172, $[R_L]_D$ 92·75 (calc., 92·52) (Found: C, 61·5; H, 8·1. $C_{19}H_{29}O_6N$ requires C, 62·1; H, 7·9%). Yield, 50 g.

*Ethyl 1-Carbethoxy-4-methyl*cyclo*hexane-2-succinate* (X).—Hydrolysis of the above cyano-ester with 8% sulphuric acid yielded a gummy acid which, esterified by the alcohol vapour method, gave the *triethyl* ester (X), b. p. 165—167°/2 mm. (Found : C, 63·1; H, 9·0. $C_{18}H_{30}O_6$ requires C, 63·15; H, 8·8%).

Ethyl 7-Methyl-[0 : 3 : 4-bicyclo]*nonan-2-one-3 : 4-dicarboxylate* (XI).—The above ester (10 g.) was heated with granulated sodium (1·4 g.) and benzene (25 c.c.) until the whole of the sodium disappeared (2 hours). The *ester* (XI) was obtained as a colourless oil (5 g.), b. p. 186°/7 mm. (Found : C, 64·9; H, 8·1. $C_{16}H_{24}O_5$ requires C, 64·8; H, 8·1%). Its alcoholic solution gave a violet coloration with ferric chloride. Hydrolysis of the ester furnished a keto-acid (XII), which would not solidify but readily gave a *semicarbazone*, minute prisms, m. p. 221—222° (decomp.), after recrystallisation from alcohol (Found : N, 16·4. $C_{12}H_{19}O_3N_3$ requires N, 16·6%). The regenerated keto-acid was a gum which partly solidified and probably consisted of a mixture of stereoisomerides.

Ethyl 3 : 7-Dimethyl-[0 : 3 : 4-bicyclo]*nonan-2-one-3 : 4-dicarboxylate.*—The ester (X) (9 g.) was cyclised with sodium (1·4 g.) in benzene, the product cooled in ice and gradually treated with an excess of methyl iodide (10 c.c.), and the whole warmed until neutral. The mixture was treated with cold water and the benzene layer was separated, dried, and distilled, *ethyl 3 : 7-dimethyl-*[0 : 3 : 4-bicyclo]*nonan-2-one-3 : 4-dicarboxylate* being obtained as a colourless oil (4 g.), b. p. 175°/8 mm. (Found : C, 66·1; H, 8·3. $C_{17}H_{26}O_5$ requires C, 65·9; H, 8·3%). It did not give a coloration with alcoholic ferric chloride.

*Ethyl 1-Carbethoxy-4-methyl*cyclo*hexane-2-(α-cyano-α′-methylsuccinate).*—This *ester*, obtained in good yield by treating the product of the condensation of ethyl Δ³-tetrahydro-*p*-toluate and ethyl sodiocyanoacetate with ethyl α-bromopropionate, was an almost colourless oil, b. p. 208°/8 mm. (Found : C, 62·9; H, 7·9. $C_{20}H_{31}O_6N$ requires C, 62·9; H, 8·1%).

*Ethyl 1-Carbethoxy-4-methyl*cyclo*hexane-2-α′-methylsuccinate.*—The foregoing cyano-ester on hydrolysis with sulphuric acid gave the expected tricarboxylic acid as a gum. The corresponding *ester* was readily obtained as a colourless oil, b. p. 175°/7 mm. (Found : C, 64·3; H, 8·8. $C_{19}H_{32}O_6$ requires C, 64·0; H, 8·8%).

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