101. *Synthetical Studies of Terpenoids. Part VII.*[1] *Synthesis of* (±)-10-*Methyltricyclo*[7,2,1,$0^{1,6}$]*dodecan*-11-*one with the Natural Configuration of Rings.*

By Nitya Gopal Kundu and Phanindra Chandra Dutta.

The ketone (XII) named in the title has been prepared and the stereochemistry of the ring-junctions established.

In view of a recent synthesis of phyllocladene [2] and of a model compound [3] we record the synthesis of the ketone (XII) incorporating rings B, C, and D of phyllocladene and related compounds. The stereochemistry of the ring-junction in the synthetic ketone has been established as that in the natural products.

Conjugate addition [4] of hydrocyanic acid to the octalone (II) in aqueous alcohol afforded a product which on hydrolysis and subsequent esterification showed an infrared band for a hydroxyl group (2·8 μ) and a γ-lactone (5·6 μ), the latter slightly shifted,[5] together with strong absorption at 5·8 and a shoulder at 4·25 μ. A detailed examination of this reaction will be reported later. The desired addition of hydrogen cyanide was effected in an acid medium,[6] leading to a mixture of *trans*- and *cis*-cyano-ketones (II). Inhomogeneity is possibly due to the reversibility of the addition, leading to 9-substituted decalones where the energy difference between *cis*- and *trans*-forms is insignificant. The nitrile (II) was converted into the keto-esters (III) and thence into the decalindicarboxylic acids (IV, V).[7] Separation was effected by partial hydrolysis, the *cis*-isomer (IV), which has an equatorial ester group, being preferentially hydrolysed; the *trans*-isomer (V) was isolated by more drastic alkaline hydrolysis. The individual constituents were thus found to be present in approximately equal amounts in the mixture.

The stereochemically inhomogeneous keto-ester (III) was allowed to undergo a Reformatsky reaction with ethyl bromoacetate. Dehydration of the crude product afforded a mixture from which the lactone (VI) crystallised in a poor yield. The keto-nitrile (II) was then allowed to react with ethyl bromoacetate; and the saturated ester (VIII)

---

[1] Part VI, Ramachandran and Dutta, *J.*, 1960, 4766.

[2] Turner and Gänshirt, *Tetrahedron Letters*, 1961, No. 7, 231.

[3] Masamune, *J. Amer. Chem. Soc.*, 1961, **83**, 1009.

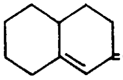
[4] Jilek and Protiva, *Coll. Czech. Chem. Comm.*, 1958, **23**, 692; Ayres and Raphael, *J.*, 1958, 1779.

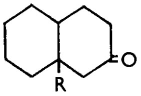
[5] Singh, *J. Amer. Chem. Soc.*, 1956, **78**, 6109.

[6] Chakravarty and Banerjee, *J. Indian Chem. Soc.*, 1946, **23**, 377.

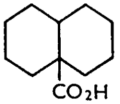
[7] Dauben, *J. Amer. Chem. Soc.*, 1955, **77**, 48; 1957, **79**, 5002; Haworth and Turner, *J.*, 1958, 1240.

obtained on catalytic hydrogenation of the unsaturated ester (VII) was subjected to ring-closure with potassium t-butoxide in boiling benzene; the resulting product finally afforded the ketone (IX), m. p. 59°, having a camphoraceous odour. This ketone was found to be homogeneous on chromatography and fractional crystallisation of the 2,4-dinitrophenylhydrazone. To establish its stereochemistry, it was condensed with ethyl formate, the resulting formyl derivative being oxidised[8] by alkaline hydrogen peroxide to the dicarboxylic acid (X). Esterification with diazomethane and partial hydrolysis gave an acid ester that was subjected to Borodin–Hunsdiecker degradation.[9] The resulting bromo-ester, on treatment with zinc dust and acetic acid and later hydrolysis, afforded *trans*-decalin-9-carboxylic acid (V), proving thereby the stereochemistry of the ketone (IX).

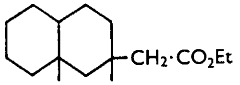

(I)

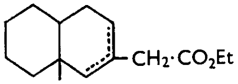

(II) R = CN

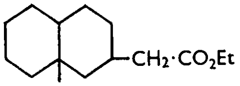
(III) R = CO_2Me

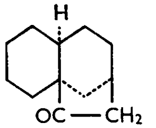

(IV) *cis*

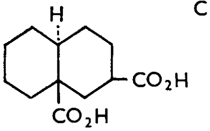
(V) *trans*

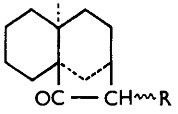

(VI)


(VII)


(VIII)


(IX)


(X)


(XI) R = $CH_2\cdot OAc$

(XII) R = Me

In order to introduce a methyl group, the ketone (IX) was again condensed with ethyl formate. The crude formyl derivative, on treatment with acetic anhydride, gave an enol acetate, which on catalytic reduction[10] afforded a mixture of compounds (XI) and (XII). The former, on treatment with sodium methoxide and subsequent catalytic reduction, afforded a further quantity of the desired ketone (XII). This could not be characterised by any solid derivative, evidently for steric reasons, and the stereochemistry of the methyl group has not been established.[11]

EXPERIMENTAL

9-Cyano-2-decalone (II).—To $\Delta^{1,9}$-2-octalone (15 g.) in alcohol (100 c.c.) at <0° and acetic acid (6 c.c.) was added potassium cyanide (13 g.) in water (40 c.c.) with stirring. The solution gradually became yellow and, overnight in the refrigerator, deep red; needles separated. The mixture was diluted with water and saturated with sodium chloride. An oil that separated was extracted with ether (thrice). The extract (200 c.c.) was washed with water, dried, and evaporated. The residue afforded a low-boiling fraction (2 g.), b. p. 115—160°/9 mm., along with the desired *cyano-ketone* (12 g.), b. p. 165—171°/9 mm., n_D^{29} 1·4960 (Found: C, 74·6; H, 8·4. $C_{11}H_{15}NO$ requires C, 74·5; H, 8·5%). It afforded a yellow *2,4-dinitrophenylhydrazone* as needles (from methanol–ethyl acetate), m. p. 193—194° (Found: C, 57·3; H, 5·4; N, 19·4. $C_{17}H_{19}N_5O_4$ requires C, 57·1; H, 5·4; N, 19·6%).

Methyl 2-Oxodecalin-9-carboxylate (III).—(*a*) A solution of 9-cyano-2-decalinone (5 g.) and potassium hydroxide (5 g.) in water (10 c.c.) and ethylene glycol (40 c.c.) was refluxed under nitrogen for 24 hr., then diluted with water (200 c.c.), filtered, and extracted with ether. Acidification of the aqueous layer with hydrochloric acid in the cold and extraction with ether afforded an acid which was esterified in methanol with excess of ethereal diazomethane, to

---

[8] Aebi, Barton, Burgstahler, and Lindsey, *J.*, 1954, 4659.

[9] Cf. Johnson and Ingham, *Chem. Rev.*, 1956, **56**, 219.

[10] Kalvoda and Loeffel, *Helv. Chim. Acta*, 1957, **40**, 2340.

[11] Cf. Vorbrüggen and Djerassi, *Tetrahedron Letters*, 1961, No. 3, 119.

afford a colourless *ester* (2·2 g.), b. p. 135—140°/6 mm., n_D^{23} 1·4939 (Found: C, 68·3; H, 8·7. $C_{12}H_{18}O_3$ requires C, 68·5; H, 8·6%). It afforded an orange 2,4-*dinitrophenylhydrazone*, plates (from methanol–ethyl acetate), m. p. 183—184° (Found: C, 55·5; H, 5·7; N, 14·4. $C_{18}H_{22}N_4O_6$ requires C, 55·4; H, 5·7; N, 14·4%).

(*b*) 9-Cyano-2-decalone (15 g.), sulphuric acid (60 c.c.; *d* 1·84), water (60 c.c.), and acetic acid (120 c.c.) were refluxed for 20 hr. The acid obtained on working up in the usual way was esterified with diazomethane, affording a colourless liquid (5·3 g.), b. p. 150—155°/10 mm., n_D^{23} 1·4919 (Found: C, 68·2; H, 8·5%), the 2,4-dinitrophenylhydrazone from which had m. p. and mixed m. p. 183—184° (Found: N, 14·4%).

Methyl Decalin-9-*carboxylate* (III).—Amalgamated zinc (30 g.), water (15 c.c.), concentrated hydrochloric acid (35 c.c.), benzene (25 c.c.), and methyl 2-oxodecalin-9-carboxylate (6 g.) were refluxed for 60 hr. Additional hydrochloric acid (10 c.c.) was added at intervals of 10 hr. The benzene layer was separated and the aqueous layer extracted with benzene. The organic solvent was removed and the residue treated with diazomethane, whereupon a sweet smelling *ester* (4·8 g.) was obtained, having b. p. 105—110°/8 mm., n_D^{27} 1·4796 (Found: C, 73·5; H, 10·3. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%).

Decalin-9-*carboxylic Acid*.—Methyl decalin-9-carboxylate (2·5 g.) and potassium hydroxide (2·2 g.) in water (2—3 c.c.) and ethylene glycol (20 c.c.) were refluxed for 45 hr. under nitrogen. The filtrate was extracted with ether and acidified, whereupon a solid separated. This *cis*-acid (IV) was filtered off; it crystallised from aqueous ethanol as needles, m. p. 122—123° (lit., 122—122·5°) (Found: C, 72·6; H, 9·7. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·9%).

The unhydrolysed material from the ethereal extract was refluxed with potassium hydroxide (2 g.) in water (2 c.c.) and diethylene glycol (20 c.c.) under nitrogen for 25 hr. After dilution with water, the mixture was extracted with ether, and the alkaline layer acidified with hydrochloric acid. The *trans*-acid (V) obtained crystallised from aqueous ethanol, having m. p. 135° (lit., m. p. 133—134°) (Found: C, 72·3; H, 10·0%). The mixed m. p. of the two acids was 90—110°.

γ-*Lactone* (VI) *of Ethyl* 2-*Hydroxy*-9-*carboxy*-2-*decalylacetate*.—To methyl 2-oxodecalin-9-carboxylate (6 g.) and ethyl bromoacetate (8 c.c.) in ether (50 c.c.) and benzene (50 c.c.), zinc wool (9 g.) was added, and the whole was refluxed for 4 hr. after addition of a small amount of iodine. Zinc wool (3 g., total 9 g.) and ethyl bromoacetate (4 c.c., total 8 c.c.) were added at hourly intervals. Yellow solid separated. The mixture was cooled and decomposed with aqueous acetic acid. The ether–benzene layer was separated and the aqueous layer extracted with benzene thrice. The combined extracts were washed repeatedly with 1% ammonia solution and with water. After removal of the solvent and drying, the residue was dissolved in pyridine (40 c.c.), cooled in ice, and treated dropwise with phosphorus oxychloride (7·5 c.c.). The whole was left overnight and then heated on a boiling-water bath for 3 hr., then decomposed with ice and hydrochloric acid and extracted with ether. The extract was washed with dilute hydrochloric acid, water, and 5% sodium carbonate solution, and evaporated. The residue, on distillation, afforded a colourless *lactone* (5·4 g.), b. p. 168—175°/0·5 mm., n_D^{27} 1·4999, $\lambda_{max.}$ (in EtOH) 226 mμ (log ε 3·36, αβ-unsaturated ester) (Found: C, 67·8; H, 8·4. $C_{15}H_{22}O_4$ requires C, 67·6; H, 8·3%), $\nu_{max.}$ (in $CHCl_3$) 1760 (γ-lactone), 1720 cm.$^{-1}$ (αβ-unsaturated ester). A part of the liquid solidified; from light petroleum (b. .p. 40—60°) it formed star-shaped crystals, m. p. 64—65° (Found: C, 67·4; H, 8·0%).

Ethyl 9-*Cyano*-2-*octalylacetate* (VII).—9-Cyano-2-decalone (10 g.) and ethyl bromoacetate (10 c.c.) in ether (50 c.c.) and benzene (50 c.c.) were refluxed with zinc wool (11 g.) as described above. Extra zinc wool (4 g., total 12 g.) and ethyl bromoacetate (5 c.c., total 10 c.c.) were added periodically. The product was dehydrated with phosphorous oxychloride (12 c.c.) in pyridine (55 c.c.) and worked up. On distillation it afforded fractions (i), b. p. 165—178°/6 mm. (2·1 g.), and (ii) b. p. 178—184°,6 mm. (8·4 g.). The second was the expected *product*, n_D^{27} 1·4931 (Found: C, 72·7; H, 8·6. $C_{15}H_{21}NO_2$ requires C, 72·8; H, 8·6%).

Ethyl 9-*Cyano*-2-*decalylacetate* (VIII).—The preceding unsaturated ester (6·8 g.) was reduced in ethanol in the presence of 10% palladium–charcoal (200 mg.). The uptake of hydrogen was very slow. A colourless *ester* (6·3 g.) was obtained, having b. p. 156—160°/0·4 mm. (Found: C, 72·4; H, 9·2. $C_{15}H_{23}NO_2$ requires C, 72·2; H, 9·3%).

Tricyclo[7,2,1,$0^{1\cdot 6}$]*dodecan*-11-*one* (IX).—Potassium t-butoxide [from potassium (5·6 g.)] was heated at 100° in a vacuum and, when dry, added to benzene (200 c.c.). To the boiling solution was added dropwise ethyl 9-cyano-2-decalylacetate (3·5 g.) in benzene (130 c.c.)

during 2·5 hr., benzene (*ca.* 100 c.c.) being simultaneously distilled off. The mixture was heated further with dropwise addition of benzene (300 c.c.) and simultaneous removal of it during 3·5 hr. The brown mixture was then cooled under nitrogen and decomposed with 17% hydrochloric acid (35 c.c.). The yellowish benzene layer was separated and the aqueous layer was extracted thrice with benzene after saturation with sodium chloride. On removal of the solvent, the residue was hydrolysed by a refluxing mixture of acetic acid (25 c.c.), water (19 c.c.), and concentrated hydrochloric acid (12 c.c.) for 12 hr., then extracted with ether. This afforded a colourless *ketone* (1·4 g.), b. p. 117—124°/7 mm., with a camphoraceous odour; it solidified and from light petroleum (b. p. 40—60°) formed plates, m. p. 58—59° (Found: C, 81·0; H, 10·2. $C_{12}H_{18}O$ requires C, 80·9; H, 10·2%). It readily afforded a yellow 2,4-*dinitrophenylhydrazone*, m. p. 191—192° (Found: N, 15·4. $C_{18}H_{22}N_4O_4$ requires N, 15·6%).

trans-*Decalin*-cis-2,9-*dicarboxylic Acid* (X).—To cooled sodium ethoxide [from sodium dust (1·3 g.) and ethanol 3·4 c.c.)] under ether was added dropwise a mixture of the ketone (IX) (1 g.) and ethyl formate (4·15 g.). The whole was left in the cold for 1 hr., then refluxed for 45 min., left overnight under nitrogen, and poured into ice-water. The ethereal layer was separated and the aqueous layer extracted with ether. This was combined with the previous ethereal layer and the whole again washed with 10% sodium hydroxide solution. The combined alkaline solutions were cooled, acidified with hydrochloric acid, and extracted repeatedly with ether. These ethereal extracts were washed with water, dried, and evaporated. A crystalline residue (*ca.* 1 g.), m. p. 113—118°, remained that gave a bluish-violet colour with alcoholic ferric chloride. The crude formyl derivative was dissolved in alcohol (30 c.c.), and 10% sodium hydroxide solution (20 c.c.) was added in the cold. To this mixture was added, with stirring, 30% hydrogen peroxide (10 c.c.) at 30° and the whole was left overnight. More hydrogen peroxide (10 c.c.) was then added and the solution stirred for 2 hr. and finally heated in the boiling-water bath for 1·5 hr. This oxidation was repeated thrice. The solution was extracted with ether to remove neutral material. The alkaline layer was acidified in the cold, saturated with sodium chloride, and extracted repeatedly with a large volume of ether. Removal of the ether gave a solid *acid* which separated from aqueous ethanol in colourless plates, m. p. 210°, sparingly soluble in ether (Found: C, 63·6; H, 8·1. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

trans-*Decalin*-9-*carboxylic Acid* (V). The decalin-2,9-dicarboxylic acid (0·7 g.) was esterified with diazomethane (from nitrosomethylurea, 5 g.), to afford the crystalline dimethyl ester (0·7 g.), m. p. *ca.* 70°. Potassium hydroxide (0·23 g.), in a minimum quantity of water, was added to the crude diester in ethanol (10 c.c.). The solution was left at 30° for 1·5 hr., then refluxed for 3 hr. and next cooled. The neutral fraction was removed with ether. The alkaline portion was acidified and extracted with ether. On evaporation of the second ether extract a gummy liquid (0·6 g.) was obtained that was dissolved in methanol (25 c.c.) and neutralised (phenolphthalein) by N-sodium hydroxide. Silver nitrate (1 g.) in distilled water (25 c.c.) was added dropwise and the precipitated silver salt was filtered off and washed with distilled water until free from silver nitrate and finally with methanol. This salt (7·5 g.) was thoroughly dried in a vacuum at 90°, then stirred in boiling carbon tetrachloride (100 c.c.) while bromine (2 c.c.) in carbon tetrachloride (40 c.c.) was added during 30 min. Refluxing was continued for 2 hr. more with stirring. The mixture was then cooled and filtered from silver bromide which was washed with ether. The combined ether–carbon tetrachloride layer was washed with 10% sodium hydroxide solution and with water and dried. On removal of the solvents, a neutral fraction (3·5 g.) was obtained. From the alkaline extract a crude acidic material (2·5 g.) was recovered on acidification. The neutral fraction (3·5 g.) was dissolved in glacial acetic acid (70 c.c.) and to this was added zinc dust (20 g.) portionwise during an hour, and the mixture was left overnight. It was then refluxed for 25 hr. with the addition of more zinc (10 g.). Acetic acid was removed (oil-bath; 115—120°) at 14 mm. and the residue was extracted with ether, extraction being facilitated by dissolving the zinc in dilute hydrochloric acid. The ethereal extract was then washed successively with dilute hydrochloric acid, water, 10% sodium hydroxide solution, and water. The residue after removal of the solvent was distilled, affording a sweet-smelling colourless liquid (0·5 g.), b. p. 95—105°/5 mm. with a considerable amount of a high-boiling residue. The low-boiling fraction (0·5 g.) was hydrolysed by refluxing it with potassium hydroxide (1 g.) in water (1 c.c.) and diethylene glycol (9 c.c.) for 25 hr. This mixture was diluted with water and extracted with ether to remove the unhydrolysed material. The alkaline layer was next acidified and extracted with ether. This ether extract gave a solid which on crystallisation from aqueous ethanol afforded needles, m. p. 134°, alone or mixed with *trans*-decalin-9-carboxylic acid. It melted at 85—100° when mixed with the corresponding *cis*-acid.

10-*Acetoxymethyl*-6-*tricyclo*[7,2,1,0 ^{1,6}]*dodecan*-11-*one* (XI).—An ice-cold solution of the formyl derivative (900 mg.) of the ketone (IX) in pyridine (13 c.c.) was treated dropwise with acetic anhydride (40 c.c.) and left for 20 hr., then poured into ice-water; a solid separated; the whole was extracted with ether after saturation with salt. The ethereal layer was washed successively with 5% sodium hydrogen carbonate solution (until alkaline), water, dilute hydrochloric acid, and water, dried, and evaporated. The residue (*ca.* 1·1 g.), m. p. 75°, did not give a colour with alcoholic ferric chloride. This crude enol acetate (*ca.* 1·1 g.) was treated with charcoal and then reduced in glacial acetic acid in the presence of 10% palladium–charcoal (200 mg.). After the required amount of hydrogen had been absorbed, the catalyst was filtered off. The product was taken up in ether, washed with 5% sodium hydrogen carbonate solution until alkaline, and with water, and then dried. On distillation it afforded a fraction (0·8 g.), b. p. 140—160°/6 mm. A part of this *ketone* solidified and recrystallised from light petroleum (b. p. 40—60°) as plates, m. p. 54° (Found: C, 71·9; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

10-*Methyltricyclo*[7,2,1,0 ^{1,6}]*dodecan*-11-*one* (XII).—The liquid fraction (0·5 g.) obtained in the last experiment was refluxed with sodium methoxide [from sodium (0·2 g.)] in methanol (10 c.c.) under nitrogen for 4 hr.; the whole was then cooled, acidified with dilute hydrochloric acid, and extracted with ether. The residue obtained on removal of the ether was hydrogenated in glacial acetic acid in the presence of palladium–charcoal (200 mg.). After usual working-up, a liquid *ketone* (XII), b. p. 118—122°/8 mm., was obtained (Found: C, 81·0; H, 10·3. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%).

The authors thank Mrs. Chhabi Dutta for microanalyses, and the Chemical Society for a financial grant. One of them (N. G. K.) thanks the C.S.I.R. for a Junior Research Fellowship.

INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE, CALCUTTA-32, INDIA.
[Present address (N. G. K.): DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES 7, CALIF., U.S.A.]

[*Received, September 14th,* 1961.]