Studies in Terpenoids. Part XXIII.[1] An Approach to the 1-Aryl-1,2,2-trimethylcyclopentane Skeleton by Intramolecular Ketocarbene Insertion. Synthesis of β-Cuparenone †

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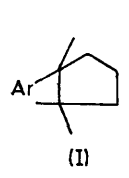
The 1-aryl-1,2,2-trimethylcyclopentane system, which contains the carbon skeleton of many cuparenoids, can be prepared by intramolecular ketocarbene insertion in the benzylic C(5)–H bond of a 5-aryl-1-diazo-4,4-dimethylhexan-2-one. β-Cuparenone (3,4,4-trimethyl-3-*p*-tolylcyclopentanone) has been synthesised in this way.

SEVERAL naturally occurring sesquiterpenoids are based on the 1-aryl-1,2,2-trimethylcyclopentane skeleton. Since the isolation of cuparene[2] (I) (1-*p*-tolyl-1,2,2-trimethylcyclopentane), many related compounds with various oxidation patterns in the aromatic and in the alicylic rings have been identified (*e.g.* cuparenic acid, γ-cuparenol, cuparenal, lagopodin, helicobasidin, cuparenones, and α- and β-cuparenols).[3] The isolation of halogenated and other modified cuparenoids with antifungal and antibiotic properties (laurinterol, aplysin, and various tricothecanes)[3] has attracted further attention to these compounds. We now describe the synthesis of β-cuparenone (II), isolated from the essential oil of Mayur pankhi[4] (*Thuja orientalis* L.).

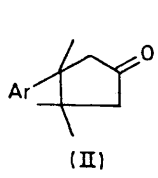
3,3-Dimethyl-4-*p*-tolylvaleric acid (IIId) was prepared by Michael addition of α-*p*-tolylethylmagnesium chloride to ethyl isopropylidene(cyano)acetate.[5] The resulting cyano-ester (IIIa) was hydrolysed by hydrochloric acid–acetic acid to the cyano-acid (IIIb), which was decarboxylated to the nitrile (IIIc). Hydrolysis of (IIIa) with potassium hydroxide in ethyleneglycol also gave the nitrile (IIIc) directly. With more concentrated alkali (30%) and longer time of reflux (30 h) the nitrile underwent further hydrolysis to furnish the valeric acid (IIId). This acid was also obtained, though in much smaller yield, by Michael addition of α-*p*-tolylethylmagnesium chloride to diethyl isopropylidenemalonate.[6] Saponification of the resulting diester (IIIe) gave the dicarboxylic acid (IIIf), which on decarboxylation gave the valeric acid (IIId).

In the above Grignard reaction with ethyl isopropylidene(cyano)acetate a small amount of *meso*-2,3-bis-*p*-tolylbutane (IV) was invariably formed, besides the cyano-ester (IIIa). Use of either α-*p*-tolylethyl bromide in place of the chloride, or copper(I) chloride catalysis for the conjugate addition[7] increased the yield of the hydrocarbon dimer (IV), the configuration of which was inferred to be *meso* on the basis of the chemical shift of the benzylic methyl protons [δ(CS_2) 0·94; *cf.*[8] δ(CS_2) where Ar = Ph, 0·96 for *meso* and 1·22 for (±)].

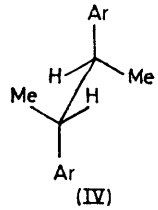
The valeric acid (IIId) was converted into the diazoketone[9] (IIIg), which when refluxed in dilute solution in



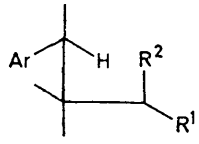
(I)



(II)



(IV)



(III)

a; $R^1 = CO_2Et$, $R^2 = CN$
b; $R^1 = CO_2H$, $R^2 = CN$
c; $R^1 = H$, $R^2 = CN$
d; $R^1 = H$, $R^2 = CO_2H$
e; $R^1 = CO_2Et$, $R^2 = CO_2Et$
f; $R^1 = CO_2H$, $R^2 = CO_2H$
g; $R^1 = H$, $R^2 = CO{\cdot}CHN_2$
h; $R^1 = H$, $R^2 = CO{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(Me)Ar$
Ar = *p*-tolyl

cyclohexane containing anhydrous copper sulphate gave a neutral ketonic substance, whose i.r. spectrum revealed the presence of a substantial amount of cyclopentanone (1743 cm^{-1}), besides other minor ketonic (1720 cm^{-1}) products of carbene insertion [presumably in the aromatic ring and in the solvent], and the carbene dimer (IIIh) (1676 cm^{-1}). Fractional distillation gave the mobile pale yellow liquid cyclopentanone, which exhibited an intense peak at 1743 cm^{-1} and gave a semicarbazone

† This work was presented at the Symposium in Organic Chemistry, University of Madras, January 1973, Abstracts, p. 4.

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[7] V. K. Andersen and J. Munch-Petersen, *Acta Chem. Scand.*, 1963, **17**, 1470.

[8] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 2nd edn., 1969, p. 163.

[9] F. Weygand and H. J. Bestman in 'Newer Methods of Preparative Organic Chemistry,' ed. W. Foerst, vol. III, Academic Press, New York, 1964.

identical (mixed m.p.) with that of naturally occurring β-cuparenone. The ketone regenerated[10] from the synthetic semicarbazone exhibited i.r. and n.m.r. spectra identical with those of naturally occurring material.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord 137 instrument, and n.m.r. spectra on a Varian HA-100D machine. Light petroleum refers to the fraction with b.p. 40—60°. Solvent extracts were appropriately washed and dried (Na_2SO_4) before evaporation.

2-*Cyano*-3,3-*dimethyl*-4-p-*tolylvaleric Acid* (IIIb).—α-*p*-Tolylethyl chloride[11] (34 g) in dry ether (200 ml) was added dropwise to stirred magnesium turnings (17 g) in dry ether (200 ml), and the reaction was initiated by a crystal of iodine. The rate of addition of the halide was controlled (1·5 g) so that the ether gently refluxed. Stirring was continued for 4 h at room temperature, and then ethyl isopropylidene(cyano)acetate[5] (37 g) in ether (100 ml) was added slowly (45 min) at room temperature. The solution was refluxed (2 h) and set aside overnight, and then added to crushed ice (~200 g) and acidified (20% sulphuric acid). The organic layer was separated and the aqueous portion was twice extracted with ether. Removal of solvent from the combined extract gave the crude *cyano-ester* (IIIa), which was hydrolysed by refluxing (15 h) with concentrated hydrochloric acid–acetic acid (1 : 1; 350 ml). The acetic acid was evaporated off and the residue was diluted with water (200 ml) and extracted with ether (3 × 150 ml). The ethereal layer was extracted with aqueous sodium hydroxide (7%; 3 × 100 ml). The neutral organic layer was worked up separately to furnish 2,3-bis-*p*-tolylbutane (see below). The alkaline layer was acidified with dilute hydrochloric acid and the liberated organic acid was extracted with ether. Evaporation gave the *cyano-acid* (IIIb) (24·4 g), m.p. 131—132° (from benzene–light petroleum) (Found: C, 73·2; H, 7·6; N, 5·5. $C_{15}H_{19}O_2$ requires C, 73·4; H, 7·8; N, 5·7%), $\nu_{max.}$ (Nujol) 2290 (C≡N) and 1735 cm^{-1} (CO_2H), δ($CDCl_3$) 1·13 (3H, s, 3-Me), 1·19 (3H, s, 3-Me), 1·35 (3H, d, *J* 7 Hz, 4-Me), 2·35 (3H, s, ArMe), 3·13 (1H, q, 4-H), 3·60 (1H, s, 2-H), 7·13 (4H, s, ArH), and 9·86 (1H, s, CO_2H).

3,3-*Dimethyl*-4-p-*tolylvaleronitrile* (IIIc).—The foregoing cyano-acid (IIIb) (10 g) was refluxed (2 h) with pyridine (50 ml) under nitrogen. Work-up and distillation gave the *nitrile* (IIIc) (7·5 g), b.p. 175—180° at 2 mmHg (Found: C, 85·6; H, 8·4; N, 6·9. $C_{14}H_{19}N$ requires C, 85·3; H, 9·5; N, 7·0%), $\nu_{max.}$ (neat) 2290 cm^{-1} (C≡N), δ(CCl_4) 1·00 (3H, s, 3-Me), 1·12 (3H, s, 3-Me), 1·29 (3H, d, *J* 7 Hz, 4-Me), 2·06 (2H, s, 2-CH_2), 2·30 (3H, s, ArMe), 2·77 (1H, q, 4-H), and 7·02 (4H, s, Ar-H). The nitrile (IIIc) was also obtained when (i) the cyano-acid (IIIb) was heated under vacuum (2 mmHg) at 200°, with (IIIc) distilling off, and (ii) when the cyano-ester (IIIa) was refluxed (4 h) with ethylene glycolic 19% potassium hydroxide.

3,3-*Dimethyl*-4-p-*tolylvaleric acid* (IIId).—(a) *From the nitrile* (IIIc). The nitrile (IIIc) (6·2 g) was refluxed (30 h) with potassium hydroxide (10 g) and ethylene glycol (35 ml). After cooling, the mixture was diluted with water (100 ml) and extracted with ether. The aqueous alkaline layer was acidified with concentrated hydrochloric acid to give an oil which was extracted with ether. Removal of solvent from this extract gave the crude *acid* (IIId), which solidified (5·7 g) after distillation, b.p. 170—175° at 2 mmHg, m.p. 74—75° (from light petroleum) (Found: C, 76·4; H, 9·2. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·2%), δ(CCl_4) 0·98 (3H, s, 3-Me), 1·05 (3H, s, 3-Me), 1·27 (3H, d, *J* 7 Hz, 4-Me), 2·20 (2H, s, 2-CH_2), 2·30 (3H, s, ArMe), 2·83 (1H, q, 4-H), 7·00 (4H, s, ArH), and 11·88 (1H, s, CO_2H).

(b) *From* (1,1-*dimethyl*-2-p-*tolylpropyl*)*malonic acid* (IIIf). Diethyl (1,1-dimethyl-2-*p*-tolylpropyl)malonate (IIIe) was prepared by addition of α-*p*-tolylethylmagnesium chloride [from α-*p*-tolylethyl chloride (4·5 g) and magnesium (1 g)] to diethyl isopropylidenemalonate[6] (5 g) as described for the cyanoester (IIIa). The resulting crude diester (IIIe) was refluxed (6 h) with ethanolic 20% potassium hydroxide (70 ml). Ethanol was removed and the aqueous portion was extracted with ether. Acidification of the aqueous alkaline layer with dilute hydrochloric acid furnished the *dicarboxylic acid* (IIIf) (0·8 g), m.p. 152—154° (from benzene–light petroleum) (Found: C, 68·3; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%), δ($CDCl_3$) 1·04 and 1·21 (each 3H, s, Me_2C), 1·28 (3H, d, *J* 7 Hz, *Me*CH), 2·31 (3H, s, ArMe), 3·19 (1H, q, *J* 7 Hz, MeC*H*), 3·52 [1H, s, C*H*($CO_2H)_2$], 7·09 (4H, s, Ar*H*), and 10·94 [2H, s, ($CO_2H)_2$]. The dicarboxylic acid (IIIf) (0·35 g) was decarboxylated with refluxing pyridine (15 ml) (2 h) as described for the cyano-acid (IIIb) to furnish the valeric acid (IIId) (95%).

2,3-*Bis*-p-*tolylbutane* (IV).—The neutral ether layer, referred to in the preparation of (IIIb), was evaporated, and the residue, which solidified on trituration with light petroleum, was crystallised from the same solvent to give the *dimer* (IV), m.p. 120—121° (10 g) (Found: C, 90·7; H, 9·4. $C_{18}H_{22}$ requires C, 90·7; H, 9·3%), δ(CS_2) 0·94 (6H, d, *J* 7 Hz, HC*Me*), 2·29 (6H, s, Ar*Me*), 2·63 (2H, m, *H*CMe), and 6·96 (8H, s, Ar*H*). The yield of the dimer increased with the addition of copper(I) chloride in the Grignard reaction.

β-*Cuparenone* (3,4,4-*Trimethyl*-3-p-*tolylcyclopentanone*) (II).—3,3-Dimethyl-4-*p*-tolylvaleric acid (IIId) (5 g) was treated with thionyl chloride (8·5 ml) in dry benzene (50 ml) under reflux (3 h). Benzene and thionyl chloride were removed under vacuum to give the crude acid chloride, which was added in dry ether with stirring to a distilled solution of diazomethane in ether [prepared from nitrosomethylurea (15 g), and dried (KOH; 3 h)] at 0°. The solution was left overnight. Removal of ether under vacuum furnished the diazo-ketone (IIIg) as a viscous pale yellow liquid (5·6 g), $\nu_{max.}$ (neat) 2138 (diazo-group) and 1645 cm^{-1} (C=O). The diazo-ketone (IIIg) (5·6 g) in dry cyclohexane (100 ml) was added (8 h) to a stirred suspension of anhydrous copper(II) sulphate (8 g) in dry cyclohexane (300 ml) under reflux, using high dilution apparatus. Refluxing was continued for 2 h more. The mixture was cooled and filtered and the filtrate was successively washed with aqueous sodium hydroxide (5%; 200 ml) and water (200 ml), and was dried. Removal of the solvent gave the crude product (5 g), $\nu_{max.}$ (neat) 1743, 1720, and 1676 cm^{-1}. Distillation gave a pale yellow mobile liquid (2·2 g), b.p., 127—132° at 2 mmHg, $\nu_{max.}$ (neat) 1743s cm^{-1} (cyclopentanone); semicarbazone, m.p. and mixed m.p. 213—215° (from ethyl acetate–light petroleum) (lit.,[4] β-cuparenone semicarbazone, m.p. 213·5—215°). The synthetic semicarbazone (0·1 g) was stirred (6 h) with boiling aqueous oxalic acid (25%; 25 ml) and n-heptane (50 ml) until the solid disappeared,[10] and the regenerated β-*cuparenone* (II)

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was worked up; yield 75 mg, b.p. 115—120° at 1·5 mmHg (Found: C, 83·4; H, 9·5. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%), $\nu_{max.}$ (neat) 1743 cm^{-1} (C=O), $\delta(CCl_4)$ 0·72 (3H, s, 4-Me, *cis* to aromatic ring), 1·22 (3H, s, 4-Me, *trans* to aromatic ring), 1·41 (3H, s, 3-Me), 2·16 (2H, s, 5-CH_2), 2·60 (2H, ABq, J 18 Hz, $\Delta\nu$ 82 Hz, 2-CH_2), 2·32 (3H, s, Ar*Me*), and 7·0—7·2 (4H, m, Ar*H*).

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