303. *The Total Synthesis of* (±)-*Cuparene.*

By W. Parker, R. Ramage, and R. A. Raphael.

The sesquiterpene cuparene and the related cuparenic acid have been synthesised from 3-methylcyclohex-2-enone. Alternative routes explored are also described.

The sesquiterpene hydrocarbon cuparene was first characterised by Enzell and Erdtman [1] who established its structure as (IV; R = Me). It is widely distributed in the Cupressaceae family together with thujopsene [2] (VIII) and this co-occurrence of the two hydrocarbons [3] may be biogenetically rationalised [4] in terms of the common intermediate (I) derived by protonation of γ-bisabolene. Obvious interactions produce the carbonium ions (II) and (V); deprotonation of the former leads to cuprenene [1] (III; isolated from *Thujopsis dolobrata* [5]) which is the progenitor of both cuparene and cuparenic acid (IV; R = CO_2H). Rearrangement of the spiro-carbonium ion (V) furnishes a bicyclo[5,4,0]-undecane derivative (VI) from which thujopsene (VIII) and the related tertiary alcohol widdrol [3,6] (VII) are readily derivable.

The synthesis of cuparene and the related cuparenic acid presented an interesting problem in view of the steric congestion associated with this degree of vicinal substitution in a cyclopentane ring. The first approach involved alkylation of *p*-methylisobutyrophenone with propargyl bromide to give the ethynyl ketone (IX) which by hydration [7] gave the 1,4-diketone (X). Base-catalysed cyclisation of the latter produced 4,4-dimethyl-3-*p*-tolylcyclopent-2-enone (XI) which, on treatment with methylmagnesium iodide in the presence of cuprous chloride (conditions known to favour conjugate 1,4-addition of Grignard reagents [8]), gave only the cyclopentenol (XII) and none of the desired cuparene progenitor 3,3,4-trimethyl-4-*p*-tolylcyclopentanone.

The next attempt was directed at the synthesis of 3,3-dimethyl-2-*p*-tolylcyclopentanone (XIII) which should be amenable to ready methylation at the benzylic carbon atom α to the carbonyl function. As a route to it *p*-methylisobutyrophenone was cyanoethylated [9] and the product hydrolysed to the keto-acid (XIV). Borohydride reduction of the latter gave the corresponding lactone (XV; R = H) but this proved resistant to fusion with potassium cyanide, a process [10] designed to convert it into the required adipic acid. As expected, cyanohydrin formation from the keto-acid (XIV) proved abortive but treatment with sodium acetylide in dimethylformamide [11] or liquid ammonia gave the corresponding

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[1] Enzell and Erdtman, *Tetrahedron*, 1958, **4**, 361.

[2] Erdtman and Norin, *Chem. and Ind.*, 1960, 622; Ito, Nozoe, Ozeki, Seto, and Takeshita, *Chem. and Pharm. Bull* (*Japan*), 1960, **8**, 936.

[3] Erdtman, Chem. Soc. Symposium on Terpene Chemistry, London, Feb., 1961.

[4] Hendrickson, *Tetrahedron*, 1959, **7**, 82 and refs. cited therein.

[5] Nozoe and Takeshita, *Tetrahedron Letters*, 1960, No. 23, 14.

[6] Nagahama, *Bull. Chem. Soc., Japan*, 1960, **33**, 1467.

[7] Islam and Raphael, *J.*, 1952, 4086.

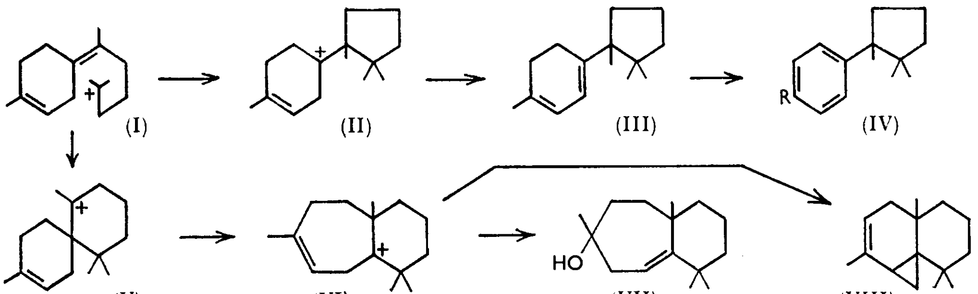
[8] Chiurdoglu and Magnestian, *Bull. Soc. chim. belges*, 1954, **63**, 357.

[9] Heusler, McLamore, Sondheimer, Taub, and Woodward, *J. Amer. Chem. Soc.*, 1952, **74**, 4244.

[10] *Org. Synth.*, 1948, **22**, 30.

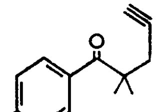
[11] Gorlish and Hildebrandt, *Chem. Ber.*, 1958, **91**, 2388.

ethynyl carbinol, readily convertible into the ethynyl-δ-lactone (XV; $R = C{\vdots}CH$). Low-temperature ozonisation[12] then produced the carboxy-δ-lactone (XV; $R = CO_2H$). Since attempted hydrogenolysis of the benzylic oxygen function in either this acid or its methyl ester proved troublesome, it was decided to construct the cyclopentane ring first. Accordingly methanolysis and esterification of the carboxy-δ-lactone were carried out, giving the hydroxy-diester (XVI). Dieckmann cyclisation of this diester certainly produced a compound with properties fully compatible with those of the expected hydroxy-β-keto-ester (XVII). However, acid hydrolysis and decarboxylation gave, not the expected ketol (XVIII), but a crystalline product possessing the characteristics of an αβ-unsaturated cyclopentenone. Its proton magnetic resonance spectrum unambiguously showed it to be 4,4-dimethyl-5-*p*-tolylcyclopent-2-enone (XIX). This may be plausibly derived from



(I) (II) (III) (IV)

(V) (VI) (VII) (VIII)



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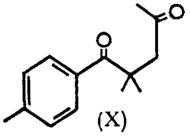

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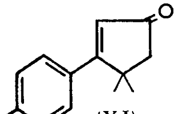

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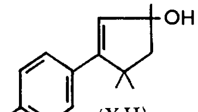

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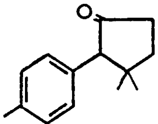

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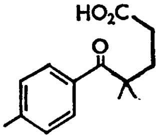

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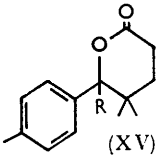
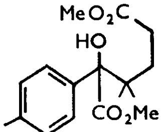
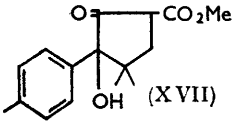


(XV)



(XVI)



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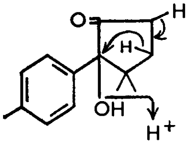

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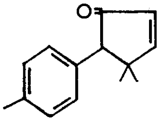

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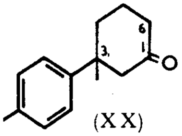

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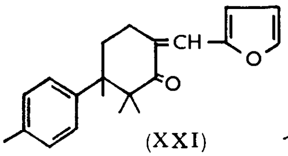
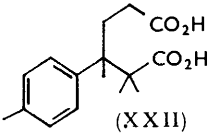
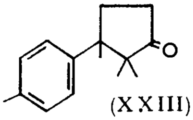


(XXI)



(XXII)



(XXIII)

(XVIII) by a mechanism involving extrusion of the benzylic hydroxyl group by a 1,3-hydride shift[13] as shown. Although this cyclopentenone was obviously convertible into the required cyclopentanone (XIII) the route was discontinued at this point in view of the promise shown by an alternative pathway.

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[12] Hofmann and Ruzicka, *Helv. Chim. Acta*, 1938, **21**, 88; Meystre and Reichstein, *ibid.*, 1939, **22**, 728; Christ and Hurd, *J. Org. Chem.*, 1936, **1**, 141.

[13] Doering and Wolf, XIIth Internat. Congress, Pure Appl. Chem., New York, Sept., 1951, Abs. p. 437.

The successful approach[14] to (±)-cuparene used as starting material 3-methyl-3-*p*-tolylcyclohexanone (XX) which was prepared by interaction of toluene and 3-methylcyclohex-2-enone in the presence of aluminium chloride. Infrared absorption of the ketone (XX) confirmed the *para*-substitution expected on the basis of precedent in a similar reaction.[15] *gem*-Dimethyl groups were introduced at the sterically hindered 2-position by the method devised by Bannister *et al.*[16] Treatment of the ketone (XX) with furfuraldehyde gave exclusively a 6-furfurylidene derivative which was then intensively methylated, to produce the crystalline dimethylated homologue (XXI). Ozonolysis of this compound gave the desired adipic acid (XXII), whose dimethyl ester underwent a smooth Dieckmann cyclisation to give a ferric chloride-positive β-keto-ester, thus confirming the position assigned to the original furfurylidene grouping. Hydrolysis and decarboxylation gave 2,2,3-trimethyl-3-*p*-tolylcyclopentanone (XXIII) which, by Huang-Minlon reduction, gave a hydrocarbon identical in infrared spectrum, mass spectrum, and gas-chromatographic behaviour with (+)-cuparene. Oxidation of the synthetic cuparene gave the crystalline (±)-cuparenic acid, the infrared spectrum of which was superposable on that of natural (+)-cuparenic acid.

EXPERIMENTAL

Ultraviolet spectra were determined for ethanol solutions.

p-*Methylisobutyrophenone*.—*p*-Toluamide (17 g.) was added dropwise to isopropylmagnesium bromide (from magnesium, 15·6 g.) in dry ether (500 ml.). The mixture was heated under reflux in a nitrogen atmosphere for 40 hr., then decomposed at 0° with dilute sulphuric acid, and the whole was extracted with ether. The combined ethereal extracts were washed with dilute sodium hydrogen carbonate solution and water and dried. Removal of the solvent and distillation of the residual oil gave *p*-methylisobutyrophenone (12 g.), b. p. 128—130°/23 mm., n_D^{23} 1·5185.

1,1-*Dimethylbut*-3-*ynyl* p-*Tolyl Ketone* (IX).—A mixture of *p*-methylisobutyrophenone (14 g.) and sodamide (3·9 g.) in toluene (120 ml.) was heated under reflux for 2 hr. Propargyl chloride (7·4 g.) was added dropwise to this stirred mixture at 0°, and the whole heated under reflux for a further 6 hr., then washed with water, dried, and evaporated *in vacuo*. Distillation of the residual oil gave the acetylenic *ketone*, b. p. 84°/0·1 mm., n_D^{22} 1·5296, $\nu_{max.}$ (film) 3280, 1675, 1380—1360 cm.$^{-1}$ (Found: C, 84·1; H, 8·2. $C_{14}H_{16}O$ requires C, 84·0; H, 8·1%). Its 2,4-*dinitrophenylhydrazone* crystallised from ethanol in plates, m. p. 114—115° (Found: C, 63·1; H, 5·4. $C_{20}H_{20}N_4O_4$ requires C, 63·2; H, 5·3%).

2,2-*Dimethyl*-1-p-*tolylpentane*-1,4-*dione* (X).—A mixture of the ketone (IX) (2 g.), mercuric oxide (0·4 g.), trichloroacetic acid (0·01 g.), and boron trifluoride–ether complex (0·2 ml.) in methanol (10 ml.) was shaken at room temperature for 3 hr., then poured into dilute sulphuric acid and extracted with ether. The combined extracts were washed with dilute sodium carbonate solution and water. Drying and removal of the solvent followed by distillation gave the *dione* (1·5 g.), b. p. 92°/0·02 mm., n_D^{26} 1·5163, $\nu_{max.}$ (film) 1705 and 1675 cm.$^{-1}$ (Found: C, 76·7; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). Its *bis*-2,4-*dinitrophenylhydrazone* crystallised from chloroform–methanol in prisms, m. p. 207—208° (Found: C, 53·8; H, 4·0; N, 19·0. $C_{20}H_{22}N_4O_5$ requires C, 53·8; H, 4·5; N, 19·4%).

4,4-*Dimethyl*-3-p-*tolylcyclopent*-2-*enone* (XI).—The dione (X) (1·5 g.) was heated in aqueous-methanolic potassium hydroxide under reflux in nitrogen for 6 hr. The cooled solution was acidified with dilute hydrochloric acid and then extracted with ether. Washing of the organic layer with dilute sodium carbonate solution and water, followed by drying and removal of the solvent, gave the unsaturated ketone (1·2 g.) as an oil, $\nu_{max.}$ (film) 1675 cm.$^{-1}$, whose 2,4-*dinitrophenylhydrazone* crystallised from acetic acid in deep-red prisms, m. p. 223—224°, $\nu_{max.}$ 400 mμ (ε 24,000) (Found: C, 63·15; H, 5·3; N, 14·75. $C_{20}H_{20}N_4O_4$ requires C, 63·2; H, 5·3; N, 14·8%).

Cuprous chloride (0·025 g.) and a solution of this ketone (1 g.) in ether (20 ml.) were added to a stirred solution of methylmagnesium iodide (from magnesium, 0·2 g.) in dry ether (40 ml.).

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[14] Parker, Ramage, and Raphael, *Proc. Chem. Soc.*, 1961, 74; cf. Nozoe and Takeshita, ref. 5.

[15] Barnes and Buckwalter, *J. Amer. Chem. Soc.*, 1951, **73**, 3858; Pines, *ibid.*, 1948, **70**, 2123.

[16] Bannister, Johnson, and Pappo, *J. Amer. Chem. Soc.*, 1956, **78**, 6336.

The mixture was heated for 1 hr., then stirred at room temperature overnight. Saturated ammonium chloride solution was then added. Working up gave, however, a viscous oil (0·9 g.) whose infrared spectrum showed a maxima at 3400 cm.$^{-1}$ but no absorption in the carbonyl region.

*γγ-Dimethyl-δ-oxo-δ-*p*-tolylvaleric acid* (XIV).—A mixture of Triton B (13 g.; 40% w/w), *p*-methylisobutyrophenone (30 g.), and acrylonitrile (42·5 g.) in benzene (700 ml.) and t-butyl alcohol (1400 ml.) was stirred at 50° for 50 hr. under nitrogen. After removal of the solvent, the dark red residual oil was extracted with ether (1 l.). Filtration of the organic extracts through activated charcoal, followed by removal of the solvent *in vacuo*, gave a yellow oil (37 g.) which was heated under reflux for 8 hr. with 20% aqueous potassium hydroxide (200 ml.). The mixture was extracted with ether, then acidified and again extracted with ether. The latter ethereal extract was washed with water, dried, and evaporated. The residue (28 g.) solidified, and it crystallised from light petroleum (b. p. 60—80°)–benzene to give the *keto-acid* in prisms, m. p. 71·5—72·5°, $\nu_{max.}$ (in CCl_4) 1715 and 1675 cm.$^{-1}$ (Found: C, 71·7; H. 7·85. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·75%).

*γγ-Dimethyl-δ-*p*-tolyl-δ-valerolactone* (XV; R = H).—A solution of the acid (XIV) (0·2 g.) and sodium borohydride (0·025 g.) in aqueous dioxan (25 ml.) was left overnight at room temperature. The usual procedure gave the *lactone* (0·1 g.) which crystallised from light petroleum in needles, m. p. 97°, $\nu_{max.}$ (in CCl_4) 1750 cm.$^{-1}$ (Found: C, 76·9; H, 8·0. $C_{14}H_{18}O_2$ requires C, 77·05; H, 8·3%).

Potassium cyanide (0·15 g.) and this lactone (0·15 g.) were heated together at 270° in a sealed tube for 5 hr., cooled, dissolved in water, and extracted with ether. No cyano-carboxylic acid was isolated on acidification of the aqueous layer. The starting lactone was recovered in quantitative yield from the neutral fraction.

*5,5-Dimethyl-6-ethynyltetrahydro-6-*p*-tolylpyran-2-one* (XV; R = ·C⋮CH).—Sodium acetylide was prepared by passing acetylene through a suspension of sodamide (0·9 g.) in dry dimethylformamide (40 ml.) at −20° until the mixture was saturated with acetylene. The acid (XIV) (2 g.) in dimethylformamide (10 ml.) was added to this solution and the mixture stirred at −20° for 1 hr. After being left at room temperature overnight, the mixture was poured on ice–water and acidified with dilute sulphuric acid. The resultant white precipitate was collected, dried, and recrystallised from light petroleum (b. p. 60—80°), to give 4,4-dimethyl-5-hydroxy-5-*p*-tolylhept-6-ynoic acid as prisms, m. p. 126—128°, $\nu_{max.}$ (in Nujol) 3500, 3300, and 1705 cm.$^{-1}$.

This acid was heated under reflux with acetic anhydride (20 ml.) and freshly fused potassium acetate (0·7 g.) for 2 hr., then poured into water and extracted with ether. Removal of the solvent from the extract, after it had been washed with water and dried, gave a gum which was adsorbed on silica (20 g.) from light petroleum (b. p. 60—80°)–benzene (1 : 1). Elution with benzene gave the *lactone* (XV; R = CH⋮CH) (0·68 g.) which crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 97—98°, $\nu_{max.}$ (in CCl_4) 3300 and 1750 cm.$^{-1}$ (Found: C, 79·3; H, 7·7. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

A solution of the keto-acid (XIV; 11·5 g.) in ether (50 ml.) was added dropwise to a solution of sodium acetylide (from sodium, 3·5 g.) in liquid ammonia (250 ml.) and the whole stirred for 6 hr. while acetylene was passed through it. Ammonium chloride (20 g.) was then added and the ammonia allowed to evaporate. The residue was treated as above, to yield eventually the ethynyl-lactone (XV; R = C⋮CH) (8·5 g.).

*3,3-Dimethyltetrahydro-6-oxo-2-*p*-tolylpyran-2-carboxylic acid* (XV; R = CO_2H).—Ozone was passed for 5 hr. through a solution of the ethynyl-lactone (XV; R = C⋮CH) (1·1 g.) in " AnalaR " ethyl acetate (60 ml.) at −70°. The solvent was then removed *in vacuo* and the ozonide decomposed with a mixture of acetic acid (10 ml.), dilute hydrochloric acid (1 ml.), and water (4 ml.). After removal of most of the acetic acid, the residue was extracted with ether, and the ethereal layer then washed with dilute sodium hydrogen carbonate solution, and the aqueous alkaline layer acidified with dilute hydrochloric acid. Ether-extraction gave, after the usual working up, a viscous gum (1·04 g.) which furnished the acid (XV; R = CO_2H) (0·4 g.) on trituration with light petroleum–benzene. The acid crystallised from light petroleum (b. p. 60—80°)–ethyl acetate in prisms, m. p. 170—173°, $\nu_{max.}$ (KCl disc) 1750 and 1710 cm.$^{-1}$.

The *methyl ester*, prepared with diazomethane, crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 101—102°, $\nu_{max.}$ (in CCl_4) 1750 and 1735 cm.$^{-1}$ (Found: C, 69·55; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·3; H, 7·05%).

*Dimethyl α-Hydroxy-ββ-dimethyl-α-*p*-tolyladipate* (XVI).—A solution of the acid (XV;

R = CO_2H) (2·9 g.) in methanol (80 ml.) which had previously been saturated with hydrogen chloride, and kept overnight at room temperature, then diluted with water, and most of the methanol was removed *in vacuo*. The aqueous solution was extracted with ether, and the ethereal layer extracted thoroughly with sodium hydrogen carbonate solution. Acidification of the alkaline layer followed by the usual isolation gave an acid which with diazomethane yielded the *diester* (2·3 g.), b. p. 154°/0·2 mm., n_D^{24} 1·5120, $\nu_{max.}$ (film) 3450 and 1730 cm.$^{-1}$ (Found: C, 66·2; H, 7·6. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

Dieckmann Cyclisation of the Diester (XVI).—The diester (1·8 g.) in t-butyl alcohol (10 ml.) was added to a solution of potassium (1·8 g.) in this alcohol, and the mixture then heated under reflux under nitrogen for 30 hr. Removal of the solvent, followed by dilution of the residue with benzene, acidification with dilute sulphuric acid, and the usual isolation procedure, gave a yellow oil, $\nu_{max.}$ (film) 3500 and 1750—1730 cm.$^{-1}$, which gave a strong positive ferric chloride test.

A solution of this oil in acetic acid (15 ml.), concentrated hydrochloric acid (5 ml.), and water (1 ml.) was heated under reflux in nitrogen for 4 hr., then diluted with water and extracted with ether. The crude product recovered from the ether was adsorbed on alumina (grade III) from light petroleum (b. p. 60—80°). Elution with light petroleum (b. p. 60—80°)–benzene (4 : 1) furnished a solid which sublimed, to give 4,4-*dimethyl*-5-p-*tolylcyclopent*-2-*enone* (XIX) as prisms, m. p. 52°, $\nu_{max.}$ (in CCl_4) 1715 cm.$^{-1}$, $\nu_{max.}$ 219 mμ (ε 20,000) (Found: C, 83·85; H, 8·5. $C_{14}H_{16}O$ requires C, 83·95; H, 8·0%). A molecular-weight determination by the mass-spectrometric method gave a value of 200 (calc. 200). The proton magnetic resonance spectrum of this material exhibited peaks at τ = 9·27 and 8·65 (*gem*-dimethyl), 7·67 (aromatic Me), 6·6 benzylic proton at position-5), 3·87 and 3·78 (vinylic proton at position-2), and 2·52 and 2·44 (vinylic proton at position-3), which are fully consistent with structure (XIX).

3-*Methyl*-3-p-*tolylcyclohexanone* (XX).—3-Methylcyclohex-2-enone (36 g.) was added dropwise to a stirred suspension of aluminium chloride (120 g.) in toluene (150 ml.) at 0° and the stirring then continued for 16 hr. at room temperature. The mixture was poured on ice and extracted with ether. The organic layer was washed with water (6 × 50 ml.), dried, and evaporated *in vacuo*, to give an oil which on fractional distillation afforded 3-methylcyclohex-2-enone (15 g.) and a pale yellow oil (15 g.). Chromatography on silica with benzene gave 3-*methyl*-3-p-*tolylcyclohexanone* (XX) (11·5 g.), b. p. 101°/0·5 mm., n_D^{22} 1·5365, $\nu_{max.}$ (film) 1710, 1600, 1520, and 820 cm.$^{-1}$ (Found: C, 82·7; H, 8·85. $C_{14}H_{18}O$ requires C, 83·1; H, 8·95%).

2-*Furfurylidene*-5-*methyl*-5-p-*tolylcyclohexanone*.—Furfuraldehyde (10 ml.) was added to a solution of 3-methyl-*p*-tolylcyclohexanone (16 g.) in ethanol (100 ml.) and 15% aqueous sodium hydroxide (40 ml.). After 2 hr. at room temperature the mixture was diluted with water and extracted with ether, and the organic extracts were washed with water and dried. Removal of the solvent gave the desired furfurylidene derivative as a yellow oil (22 g.), $\nu_{max.}$ (film) 3100, 1600, and 750 cm.$^{-1}$, $\lambda_{max.}$ 333 mμ.

6-*Furfurylidene*-2,2,3-*trimethyl*-3-p-*tolylcyclohexanone* (XXI).—The furfurylidene derivative (22 g.), prepared as above, in t-butyl alcohol (100 ml.) was added to a stirred solution of potassium t-butoxide (from potassium, 25 g.) in t-butyl alcohol (400 ml.), and the mixture was held at 40° for 4 hr., treated with methyl iodide (150 ml.), and stirred overnight at room temperature under nitrogen. The filtered solution was evaporated to dryness, and the residue taken up in ether, washed with water, dried, and recovered as a gum (22 g.) which on trituration with pentane gave a yellow solid. Recrystallisation from methanol gave the required *ketone* (4·6 g.) as prisms, m. p. 146—148°, $\nu_{max.}$ (in Nujol) 1670, 1600, 1540, 1380, and 1360 cm.$^{-1}$, $\lambda_{max.}$ 323 mμ (ε 10,000) (Found: C, 81·75; H, 7·8. $C_{21}H_{24}O_2$ requires C, 81·8; H, 7·8%). Mass-spectrometric determination gave a molecular weight of 308 (calc. 308).

ααβ-*Trimethyl*-α-p-*tolyladipic Acid* (XXII).—Ozone was passed through a solution of compound (XXI) (1 g.) in ethyl acetate (100 ml.) at −78° until the solution became blue. The solvent was removed *in vacuo* at 40° and a mixture of glacial acetic acid (10 ml.), 30% hydrogen peroxide (2 ml.), and dilute sulphuric acid (6 drops) was added to the residual yellow oil. Next morning the solvent was removed *in vacuo* and saturated sodium hydrogen carbonate solution added. Normal isolation gave the *acid* (XXII) (0·74 g.) as prisms (from aqueous methanol), m. p. 222—224°, $\nu_{max.}$ (in Nujol) 1705 cm.$^{-1}$ and 825 cm.$^{-1}$ (Found: C, 68·8; H, 7·75. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·95%). Mass spectrometry gave a molecular weight of 191 (required, 191).

When the above ozonide was decomposed with acetic acid, 30% hydrogen peroxide, and dilute hydrochloric acid, the product was ααβ-*trimethyl*-β-(3-*chloro*-4-*methylphenyl*)*adipic acid* which crystallised from aqueous methanol in cubes, m. p. 225—229° (Found: C, 62·85; H, 7·25. $C_{16}H_{21}ClO_4$ requires C, 61·45; H, 6·7%). Presumably this adventitious chlorination arose from chlorine or hypochlorous acid generated by oxidation of the hydrochloric acid.

2,2,3-*Trimethyl*-3-p-*tolylcyclopentanone* (XXIII).—The dimethyl ester (1·9 g.) of the acid (XXII), prepared by diazomethane, was treated in benzene (50 ml.) with potassium t-butoxide (from potassium, 7 g.) in benzene (500 ml.). The mixture was refluxed under nitrogen for 6 hr., then stirred at room temperature for 11 hr. After acidification with dilute sulphuric acid, the benzene layer was washed with water (4 × 100 ml.) and dried. Evaporation furnished an oil (1·7 g.), $\nu_{max.}$ (film) 1750 and 1730 cm.$^{-1}$, which gave a purple colour with ferric chloride solution.

This β-keto-ester (1·7 g.) was refluxed in acetic acid, concentrated hydrochloric acid (10 ml.), and water (2 ml.) under nitrogen for 4 hr. The solvent was then removed under reduced pressure and the residue heated at 100° in a mixture of methanol (30 ml.) and 4N-sodium hydroxide (25 ml.). After removal of the solvent, the residue was dissolved in water and extracted with ether. The ethereal solution was then washed with water, dried, and evaporated, giving an oil (1·07 g.) which was adsorbed on alumina (grade III) from light petroleum (b. p. 60—80°). Elution with light petroleum (b. p. 60—80°)–benzene (4 : 1) gave the *ketone* (0·95 g.), $\nu_{max.}$ (film) 1742, 1385, 1380, and 825 cm.$^{-1}$. Molecular-weight determination by mass spectrometry gave a value of 216 (calc. 216). The *semicarbazone* crystallised from aqueous methanol as prisms, m. p. 212—215° (Found: C, 70·25; H, 8·2; N, 15·3. $C_{16}H_{23}N_3O$ requires C, 70·3; H, 8·5; N, 15·35%).

Corresponding treatment of the chloro-adipic acid obtained as above gave 2,2,3-*trimethyl*-3-(3-*chloro*-4-*methylphenyl*)*cyclopentanone* which crystallised from aqueous methanol in prisms, m. p. 66—69°, $\nu_{max.}$ (in CCl_4) 1740, 1380, and 1360 cm.$^{-1}$ (Found: C, 71·55; H, 7·1. $C_{15}H_{19}ClO$ requires C, 71·85; H, 7·6%). Mass spectrometry gave a molecular weight of 250 (required, 250), and all fragments from mass number 250 to 150 contained chlorine (double peaks), confirming the situation of the chlorine atom in the benzene ring.

(±)-*Cuparene*.—100% Hydrazine hydrate (2 ml.) was added to diethylene glycol (40 ml.) and ethylene glycol (10 ml.) containing 2,2,3-trimethyl-3-*p*-tolylcyclopentanone (0·8 g.). The mixture was held at 184° for 90 min., then cooled to 70°, and sodium (1 g.) in diethylene glycol (20 ml.) was added. The mixture was heated under reflux for 4 hr., then poured into ice–water. Extraction with light petroleum (b. p. 40—60°), followed by drying and removal of the solvent, gave an oil (0·79 g.) which was adsorbed on alumina (grade III) from light petroleum (b. p. 40—60°). Elution with the same solvent gave (±)-*cuparene* (0·3 g.) (Found: C, 88·9; H, 10·8. $C_{15}H_{22}$ requires C, 89·05; H, 10·95%). The infrared, ultraviolet, and mass spectra of synthetic and natural (+)-cuparene were identical. The synthetic and the natural terpene showed identical retention times in gas–liquid chromatography on 5% Apiezon–Celite at 166°.

(±)*Cuparenic Acid*.—(±)-Cuparene (150 mg.) was oxidised by Enzell and Erdtman's method [1] to the (±)-*acid* (25 mg.) which crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 151—154° (Found: C, 77·35; H, 8·35. $C_{15}H_{20}O_2$ requires C, 77·55; H, 8·65%). The infrared spectrum (KCl disc) of the synthetic sample was identical with that of (+)-cuparenic acid.

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