Photochemical Synthesis. Part LVIII.[1] A Photochemical Synthesis of (±)-Cuparene

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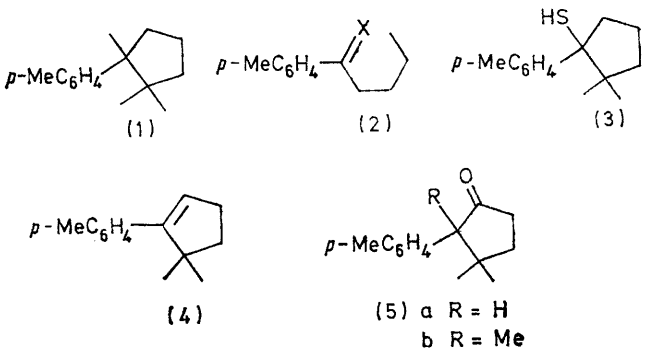
Alkyl aryl thioketones have been recently reported to give cyclopentanethiols on irradiation. With mercury(II) acetate these are converted into the corresponding olefinic hydrocarbons. Based on these reactions a simple synthesis of (±)-cuparene (1,2,2,-trimethyl-1-*p*-tolylcyclopentane) is described.

SINCE the photochemical renaissance in the mid-'fifties, many of the new reactions discovered have been applied to the synthesis of natural products.[2] Most of these applications have involved cycloadditions although there have been some very striking exceptions.[3] Cyclisations in alicyclic systems have, however, been poorly represented. Photochemical methods are available for the generation of various sizes of alicyclic rings, but methods for the preparation of five-membered carbocyclic rings are lacking. Recently we reported that, following excitation to a higher excited state than the low energy $^1(n,\pi^*)$, alkyl aryl thioketones could be cyclised to cyclopentanethiols.[4] The present report describes the application of this new photocyclisation to the synthesis of the sesquiterpenoid cuparane (1).

Cuparene was first isolated by Enzell and Erdtman,[5] and a large number of substances of related structure have been since discovered, some of which have biological activity.[6] A number of syntheses directed towards cuparene itself, or to simply related substances, have been reported using different basic approaches, which include cyclisation,[7,8] ring contraction,[9,10] ring expansion,[11] and modification of other cyclopentane derivatives.[12]



Propylation of 4'-methylisobutyrophenone gave the ketone (2; X = O). This was converted into the corresponding thione (2; X = S) following the method of Paquer and Vialle,[13] but employing a lower reaction temperature. By this means *gem*-dithiol formation was avoided. Irradiation of (2; X = S) in benzene solution,† gave the cyclopentane thiol (3) which, without

† The use of cyclohexane or acetonitrile as solvent gave decreased yields because of reaction with the solvent. Addition products from these reactions have been isolated. Those with the hydrocarbon will be described elsewhere; for that with the acetonitrile see D. S. Blackwell, P. de Mayo, and R. Suau, *Tetrahedron Letters*, 1974, 91.

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purification, was treated with mercury(II) acetate in acetic acid. Under these conditions the thiol was smoothly converted into the cyclopentene (4) in high yield. Even in the presence of an excess of mercury(II) salt no oxidation products were formed.[14] This may well be due to the lack of reactivity of (4) since difficulties in the oxomercuriation of phenylcyclopentene have been reported.[15]

Although (4) could be converted into the ketone (5a) by direct hydroboration–oxidation,[16] a two-stage conversion was more effective. Hydroboration[17] in tetrahydrofuran was efficient and the crude product was then dissolved in ether and subjected to heterogeneous oxidation with chromic acid.[18] The ketone was obtained in 81% yield from (4), and 53% overall yield from (2; X = S). An unsuccessful attempt to prepare (5a) has been reported.[9]

Alkylation at the benzylic position gave the expected ketone (5b) in 80% yield which could be converted into the hydrocarbon (1) by Barton's modification of the Wolff–Kishner reduction.[19] The product was identical in spectra (i.r., n.m.r.) and retention times on chromatography with an authentic specimen of cuparene. The overall yield from (2; X = S) was 28%.

EXPERIMENTAL

M.p.s were obtained on a Kofler hot stage apparatus. Temperatures in bulb-to-bulb distillations are external measurements. Silica gel (Merck) was used for t.l.c. (GF-254) and column chromatography (SG-60, 0·2—0·5 mm). LP refers to light petroleum, b.p. 60—80°. Spectra were obtained on the following spectrometers: Varian T-60 or HA-100 (n.m.r., Me_4Si as internal standard), Cary 14 (u.v.–vis), Beckman IR-20A (i.r.), and Varian M-66 (mass spectra and precise mass determinations).

2,2-*Dimethyl*-1-p-*tolylpentan*-1-*one* (2; X = O). A stirred solution of 4′-methylisobutyrophenone[9] (11 g) and sodium amide (2·9 g) in dry toluene (350 ml) was refluxed for 3 h under N_2. The mixture was cooled to 60° and propyl iodide (17 g) was added. After stirring for 12 h at 90°, the mixture was poured into acidic ice–water (acetic acid) and the organic phase washed with water. Solvent removal and distillation gave the *ketone* (2; X = O) (12·2 g, 88%), b.p. 91—93° at 0·1 mmHg, $\nu_{max.}$ (CCl_4) 1670, 1610, 1570, and 825 cm^{-1}; δ (CCl_4) 7·57 and 7·01 (4H, dd, ArH), 2·28 (3H, s, ArMe), 1·6—1·0 (10H, complex), 1·23 (s, CMe_2), 0·83 (3H, approx. t, *J* 6 Hz, $-CH_2CH_3$); *m/e* 209 (M^+, 5%), 162 (9), and 119 (100) (Found: M^+, 204·1535. $C_{14}H_{20}O$ requires *M*, 204·1513.

2,2-*Dimethyl*-1-*p*-*tolylpentane*-1-*thione* (2; X = S).—Hydrogen sulphide (~5 ml) was condensed over a cooled (−63°; dry ice–chloroform) solution of (2; X = O) (2 g) in absolute ethanol (10 ml). Dry HCl was bubbled through until a purple colour developed and reached its maximum intensity (1·5—2 h). The mixture was cautiously poured into water and extracted with light petroleum. After removing the solvent the crude product was chromatographed on a column of silica gel (LP as eluant). The purple oil obtained was distilled (bulb-to-bulb) (b.p. 85—90° at 0·1 mmHg) giving the *thione* (2; X = S) (0·9 g, 92% based on unrecovered ketone), $\lambda_{max.}$ (C_6H_{12}) 568, 306, and 232 nm (ε 125, 4700, and 8600); δ (CCl_4) 6·93 (4H, approx. s, ArH), 2·29 (3H, s, ArMe), 1·9—1·0 (10H, complex), 1·30 (s, CMe_2), 0·85 (3H, approx. t, *J* 6 Hz, $-CH_2CH_3$); *m/e* 220 (M^+, 8%), 178 (10), and 135 (100) (Found: M^+, 220·1297. $C_{14}H_{20}S$ requires *M*, 220·1285).

3,3-*Dimethyl*-2-p-*tolylcyclopentene* (4).—A solution of (2; X = S) (0·502 g) in benzene (30 ml) contained in a Pyrex tube was degassed by the freeze–pump–thaw method (residual pressure 5×10^{-5} Torr). Irradiation was carried out with a 450 W medium pressure mercury arc to *ca.* 95% conversion (26 h). The solvent-free irradiation product was dissolved in glacial acetic acid (10 ml), treated with mercury(II) acetate (650 mg), and stirred at room temperature for 30 min. The reaction was quenched with chloroform–water and washed with aqueous $NaHCO_3$ (5%). The chloroform solution evaporated and the residue chromatographed on a column of silica gel (LP eluant). The first fraction eluted afforded, after bulb-to-bulb distillation, the *cyclopentene* (4) (0·277 g, 65%), b.p. 50° at 0·1 mmHg, $\nu_{max.}$ (CCl_4) 1610, 865, and 830 cm^{-1}; δ (CCl_4) 7·0 (4H, m, ArH), 5·6 (1H, t, *J* 2·5 Hz, olefinic), 2·50—2·13 (5H, m, ArMe and allylic CH_2), 1·83 (2H, approx. t, *J* 7 Hz, CH_2), and 1·13 (6H, s, CMe_2); *m/e* 186 (M^+, 45%) and 171 (100) (Found: M^+, 186·1416. $C_{14}H_{18}$ requires *M*, 186·1408).

3,3-*Dimethyl*-2-p-*tolylcyclopentanone* (5a).—To a stirred mixture of (4) (190 mg) and sodium borohydride (13 mg) in dry freshly distilled tetrahydrofuran (5 ml), was added boron trifluoride–ether complex (0·07 ml). After 12 h at room temperature, 3N-NaOH (0·4 ml) was added, followed by 30% H_2O_2 (0·37 ml). After 1 h the mixture was saturated with NaCl, the separated organic layer washed twice with saturated brine, and the solvent removed. To the residual oil, dissolved in anhydrous ether (3 ml), chromic acid [2·5 ml; from $Na_2Cr_2O_7,2H_2O$ (5 g) and 96% sulphuric acid (3·75 ml diluted to 25 ml)][13] was added dropwise over 10 min. After stirring for 1 h at 25°, the ethereal layer was separated, the aqueous phase extracted with ether (2 × 5 ml), and the combined extracts were washed with $NaHCO_3$ solution. The residual oil was separated by preparative t.l.c. (silica gel, CH_2Cl_2). The major band (R_F *ca.* 0·5) was extracted, and distilled (bulb-to-bulb) (b.p. 80° at 0·02 mmHg) to afford the *ketone* (5a) (166 mg, 81%), as needles, m.p. 81—82°, $\nu_{max.}$ (CCl_4) 1745 cm^{-1}; δ (CCl_4) 6·85 (4H, q, ArH), 2·98 (1H, s, ArC*H*), 2·54—2·0 (5H, m, ArMe and $CO{\cdot}CH_2$), 1·9 (2H, m, CH_2), 1·10 (3H, s, Me), and 0·66 (3H, s, Me); *m/e* 202 (M^+, 100%), 147 (42), and 132 (50) (Found: M^+, 202·1359. $C_{14}H_{18}O$ requires *M*, 202·1356).

2,3,3-*Trimethyl*-2-p-*tolylcyclopentanone* (5b).—A stirred solution of (5a) (0·822 g) in anhydrous ether (15 ml) was treated with sodamide (0·17 g) under N_2. After 2 h at room temperature, methyl iodide (1 g) was added dropwise, and the mixture was refluxed for 12 h, quenched with water, and thoroughly extracted with ether. The concentrated extracts were chromatographed, as for (5a), to give the *ketone* (5b) as a solid (0·732 g, 80%), m.p. 65—66° (from methanol), $\nu_{max.}$ (CCl_4) 1740 cm^{-1}; δ (CCl_4) 6·91 (4H, s, ArH), 2·7—2·0

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(5H, m, ArMe and $CO{\cdot}CH_2$), 1·70 (2H, m, CH_2), 1·23 (3H, s, ArC*Me*), 1·03 (3H, s, Me), and 0·60 (3H, s, Me); *m/e* 216 (M^+, 100%), 161 (18), and 146 (22) (Found: M^+, 216·1524. $C_{15}H_{20}O$ requires *M*, 216·1513).

Reduction of (5b).—Ethylene glycol (7 ml) and sodium (200 mg) were heated at 180°, and an excess of anhydrous hydrazine (from sodium hydroxide) was distilled in. The mixture was cooled and the ketone (5b) (117 mg) added. After refluxing for 6 h, the mixture was poured into water–LP and extracted. The crude product was purified by t.l.c. (silica gel; LP) to give (±)-cuparene (72 mg, 65%). G.l.c. (10% SE-30) showed a single peak with the same retention time as the natural terpene. I.r. and n.m.r. spectra were identical with those of an authentic sample.*

[4/1485 *Received*, 19*th July*, 1974]

* We thank Professor S. Itô (Tohoku University) for a generous sample of the naturally occurring terpenoid.