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SYNTHESIS OF MONO- AND SESQUITERPENOIDS—IV*

RACEMIC SABINA KETONE

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Abstract—Racemic sabina ketone (I) was synthesized by the application of the intramolecular α-ketocarbene—olefin addition reaction.

RECENTLY a total synthesis of racemic sabinene (II) and *cis*- and *trans*-sabinene hydrates (IIIa,b) *via* sabina ketone (I) has been accomplished employing the Simmons-Smith reaction for the construction of the bicyclo [3·1·0] hexane ring system.[1, 2] Herein is described an alternate synthesis of racemic sabina ketone (I) by the intramolecular α-ketocarbene—olefin addition.[3]

The key intermediate XII was prepared as follows. Ethyl isopropylcyanoacetate (IV)[4] was reduced with sodium borohydride to give a cyano alcohol (V) in 83% yield. This was treated with sodium hydroxide in aqueous ethanol to afford an unsaturated acid (VIa, 51%). The corresponding methyl ester (VIb) was obtained in 85% yield by esterification with an equimolar amount of diazomethane. Reduction of the ester (VIb) with aluminum hydride (LAH-$AlCl_3$ 3:1)[5] gave an allyl alcohol (VII, 67%).‡ This was converted into a vinyl ether (VIII) by transetherification with ethyl vinyl ether in the presence of mercuric acetate in 99% yield.[6] Its thermal rearrangement at 195–200° in a sealed tube afforded an aldehyde (IX, 77%). This was characterized as a crystalline 2,4-dinitrophenylhydrazone, m.p. 108–109°. Silver oxide oxidation of the aldehyde (IX) gave an acid (X) in 84% yield. Its sodium salt was treated with oxalyl chloride to give the corresponding acyl chloride (XI) which was converted into the key intermediate (XII) by treatment with diazomethane.

A cyclohexane solution of the diazoketone (XII) was heated under reflux in the presence of powdered Cu and $CuSO_4$ to give crude racemic sabina ketone (I) in 38% yield from the acid (X). After GLC purification, the synthetic product showed entirely identical IR[1, 7] and NMR[1, 8] spectra with those of sabina ketone recorded in the literature.[1, 7, 8] It gave a crystalline 2,4-dinitrophenylhydrazone, m.p. 175–176·5°. In view of the reported conversion of dl-sabina ketone (I), into dl-sabinene (II) and dl-*cis*- and *trans*-sabinene hydrates (IIIa,b),[1] this work constitutes the synthesis of these monoterpenes.

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* Part III, Mori, M. Ohki, A. Kobayashi and M. Matsui, *Tetrahedron* **26**, 2815 (1970).

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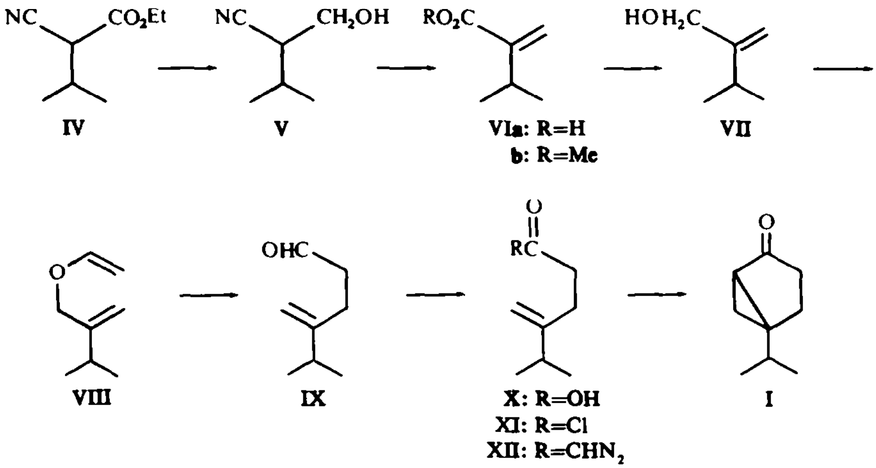
‡ Reduction with LAH alone afforded the alcohol (VII) in poor yield (31%).

I

II

IIIa: R=Me; R′=OH
b: R=OH; R′=Me



EXPERIMENTAL

All m.ps and b.ps. were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for liquids. NMR spectra were recorded at 100 MHz in CCl_4 with TMS as an internal standard unless otherwise stated.

2-Cyano-3-methylbutan-1-ol (V). $NaBH_4$ (24 g) was added portionwise to a stirred soln of IV (60 g) in MeOH (400 ml) at 0–5° during 1 h. After the addition, the mixture was stirred for 3 h at 5–10°, concentrated *in vacuo*, diluted with water and extracted with ether. The ether extract was washed with NaCl aq. dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 36·5 g (83%) of V, b.p. 93–97°/6 mm, n_D^{20} 1·4345; ν_{max} 3280, 2220, 1610, 1455, 1383, 1365, 1070, 1025 cm^{-1}; δ 1·09 (6H, d, $J=6$ Hz), 1·85–2·20 (1H, m), 2·54–2·77 (1H, m), 3·15–3·60 (1H, br), 3·77 (2H, d, $J=7$ Hz)ppm. (Found: C, 63·21; H, 9·59; N, 12·26. $C_6H_{11}ON$ requires: C, 63·68; H, 9·80; N, 12·39%).

α-Isopropylacrylic acid (VIa). A soln of V (130g) in 95% EtOH (750 ml) was mixed with NaOH aq (120 g in 200 ml). The mixture was heated under reflux for 2 days, concentrated *in vacuo*, acidified with conc. HCl under ice-cooling and extracted with ether. The extract was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 66·8 g (51%) of crude (VIa) b.p. 88–98°/5mm. An analytical sample boiled at 82–84°/4 mm, n_D^{20} 1·4380; ν_{max} ~3400—~3100, ~2650, 1680, 1620, 1435, 1300, 1205, 1155, 1120, 970 cm^{-1}; δ 1·13 (6H, d, $J=6$ Hz), 2·60–3·00 (1H, m), 5·66 (1H, s), 6·33 (1H, s), 11·41 (1H, br.) ppm. (Found: C, 63·49; H, 8·89. $C_6H_{10}O_2$ requires: C, 63·13; H, 8·83%).

Methyl α-isopropylacrylate (VIb). Ethereal CH_2N_2 was added to soln of VIa (66·0 g) in ether at 0–5° with shaking. After concentration, the residue was distilled to give 61·0 g (85%) of VIb, b.p. 70–78°/70–75 mm. An analytical sample boiled at 50–53°/28 mm, n_D^{27} 1·4198; ν_{max} 1715, 1630, 1475, 1450, 1380, 1290, 1210, 1150, 1125, 965, 880, 840 cm^{-1}; δ 1·10 (6H, d, $J=7$ Hz), 2·75 (1H, m), 3·70

(3H, s), 5·47 (1H, s), 6·05 (1H, s) ppm. (Found: C, 64·99; H, 9·37. $C_7H_{12}O_2$ requires: C, 65·59; H, 9·44%).

2-*Isopropylallyl alcohol* (VII). A soln of AlH_3 was prepared by adding $AlCl_3$ (17·8 g) in dry ether (200 ml) to LAH (10·4 g) in dry THF (150 ml) at 0–5°. To this soln was added a soln of VIb (45·7 g) in dry ether (200 ml) at 0–5°. The mixture was kept at this temp for 2 h with stirring. Then the excess of AlH_3 was destroyed by adding wet ether (200 ml) and water. The mixture was filtered through Celite and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated. The residue was distilled to give 24·6 g (67%) of VII, b.p. 80–88°/50 mm. An analytical sample boiled at 81–83°/50 mm, n_D^{21} 1·4335; ν_{max} 3280, 1640, 1460, 1110, 1055, 920 cm^{-1}; δ 1·10 (6H, d, $J = 7$ Hz), 2·27 (1H, m), 4·01 (2H, s), 4· 2 (1H, s), 4·95 (1H, s) ppm. (Found: C, 71·32; H, 11·92. $C_6H_{12}O$ requires: C, 71·95; H, 12·08%).

2-*Isopropylallyl vinyl ether* (VIII). A soln of VII (27·9 g) and $Hg(OAc)_2$ (12·0 g) in purified ethyl vinyl ether (500 g) was heated under reflux for 5 h. After being left to stand overnight at room temp, the soln was mixed with ice–cooled 10% K_2CO_3 aq (300 ml) and stirred for 30 min at 0–5°. The organic layer was separated, dried (K_2CO_3) and concentrated. The residue was distilled *in vacuo* to give 34·9 g (99%) of VIII, b.p. 66–70°/78 mm, n_D^{21} 1·4305; ν_{max} 3120, 1635, 1610, 1470, 1325, 1200, 1065, 905, 820 cm^{-1}; δ 1·10 (6H, d, $J = 7$ Hz), 2·35 (1H, m) 3·85–4·23 (2H, m) ppm. This was contaminated with unidentified Hg-containing impurities. Therefore correct analytical data could not be obtained (Found: C, 71·14; H, 10·86. $C_8H_{14}O$ requires: C, 76·14; H, 11·18%).

4-*Methylene-5-methylhexanal* (IX). Neat VIII (15 g) in a sealed tube was heated at 195–200° for 15 min and distilled *in vacuo* to give 11·5 g(77%) of IX, n_D^{23} 1.4350; ν_{max} 3120, 2770, 1730, 1640, 1470, 1380, 1100, 1050, 880 cm^{-1}; δ 1·09 (6H, d, $J = 7$ Hz), 2·05–2·70 (5H, m), 4·17 (1H, s), 4·33 (1H, s), 9·86 (1H, s) ppm. (Found: C, 75·07; H, 11·16. $C_8H_{14}O$ requires: C, 76·14; H, 11·18%). In one occasion the sealed tube exploded violently. 2,4-*dinitrophenylhydrazone*: yellow plates from EtOH, m.p. 108–109°. (Found: C, 54·31; H, 5·88; N, 18·36. $C_{14}H_{18}O_4N_4$ requires: C, 54·89; H, 5·92; N, 18·29%).

4-*Methylene-5-methylhexanoic acid* (X). Neat IX (9·46 g) was added during 10 min to a stirred and ice-cooled aqueous suspension of Ag_2O prepared from $AgNO_3$ aq (22 g in 50 ml) and NaOH aq (15 g in 50 ml). After the addition, the mixture was stirred for 20 min at room temp and filtered. The solid was washed with water. The combined filtrate and washings were acidified with 10% HCl and extracted with ether. The extract was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled *in vacuo* to give 8·14 g (84%) of X, b.p. 108–110·5°/7mm, n_D^{21} 1·4442; ν_{max} ~3400–~3100, ~2700, 1710, 1640, 1420, 1290, 880 cm^{-1}; δ 1·08 (6H, d, $J = 7$ Hz), 2·10–2·65 (5H, complex m.), 4·70 (1H, s), 4·82 (1H, s), 11·18 (1H, s) ppm. (Found: C, 67·18; H, 9·77. $C_8H_{14}O_2$ requires: C, 67·57; H, 9·93%).

4-*Methylene-5-methylhexanoyl chloride* (XI). A soln of X (2·6 g) in MeOH (10 ml) was neutralized with NaOMe (0·65 g) and concentrated *in vacuo*. The Na salt was suspended in dry benzene (10 ml) and the benzene was removed *in vacuo*. This was repeated three times to give the dry Na salt of X which was then suspended in dry benzene (20 ml). Oxalyl chloride (6·5 g) was added to the suspension with shaking at 0–5°. The mixture was stirred for 1 h at 0–5°, filtered through Celite and concentrated *in vacuo* to give oily XI. This was employed for the next step without further purification.

1-*Diazo-5-methylene-6-methylheptan-2-one* (XII). A soln of the above described XI in benzene (10 ml) was added to CH_2N_2 (approx 2 g) in ether (200 ml) at 0–5°. The mixture was stirred at 0–5° for 1 h and concentrated to give crude XII, ν_{max} 2150, 1645 cm^{-1}. This was employed for the next step without further purification.

Racemic sabina ketone (I). A soln of the above described XII in cyclohexane (10 ml) was added dropwise to a stirred and refluxing suspension of powdered Cu (0·5 g) and $CuSO_4$ (0·1 g) in cyclohexane (100 ml) during 15 min. After the addition, the mixture was stirred and heated under reflux for 1 h, then cooled, filtered and concentrated *in vacuo*. The residue was distilled under N_2 to give 1·05 g (38% from X) of crude I, b.p. 75–78°/6 mm. This was purified by GLC separation—Column; Carbowax–6000 (30% on Diasolid), 2 m × 0·3 mm i.d.; Column temp: 150°; Carrier gas: He, 1·8 kg/cm^2; R_t: 15·8 min. The purified I showed the following properties: n_D^{23} 1.4678; ν_{max} 3120, 1728, 1470, 1300, 1182, 1020, 910, 770 cm^{-1}; δ 0·98 (3H, d, $J = 8$ Hz), 1·02 (3H, d, $J = 7$ Hz), 1·05–1·30 (2H, complex m), 1·45–1·75 (2H, m), 1·80–2·25 (4H, m) ppm. These values are in good accord with the published values.[1,7,8] (Found: C, 77·74; H, 10·31. Calc for $C_9H_{14}O$: C, 78·21; H, 10·21%). 2,4-*Dinitrophenylhydrazone*: orange–red needles from $CHCl_3$—MeOH, m.p. 175–176·5°. (Found: C, 56·65; H, 5·62; N, 17·25. $C_{15}H_{18}O_4N_4$ requires: C, 56·59; H, 5·70; N, 17·60%).

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