BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2068—2069 (1969)

Preparation of Epicamphor

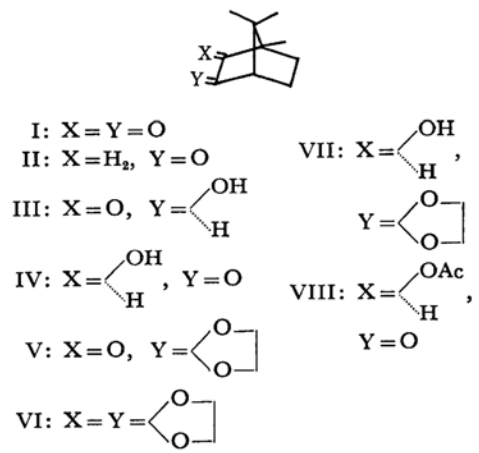
Hitoshi TAKESHITA, Takeo MUROI and Shô ITÔ*1

Department of Chemistry, Tohoku University, Sendai

(Received November 18, 1968)

Although the stepwise reduction of camphorquinone (I) by aluminum and sodium amalgam is reported[1,2] to be the most convenient method for the preparation of epicamphor (II), we have found it to prove inadequate for large scale preparations, affording a mixture of *exo*-3-hydroxycamphor (III) and *exo*-2-hydroxyepicamphor (IV) in varying amounts.[3] In view of the extreme sensitivity of IV toward alkali, as was demonstrated by its conversion to III,[4] IV could not be expected to survive under the conditions used for the reduction even if the reaction first produced IV preferentially. In order to utilize II for other purposes, we have been trying to develop its convenient large-scale synthesis. The preparation and structure elucidation of exo-2-hydroxyepicamphor have recently been described by Fleming and Woodward.[5] Though the first step of our method is essentially the same as theirs, we wish to record in detail our synthesis of epicamphor II.

When I was heated with ethylene glycol and benzene in the presence of *p*-toluenesulfonic acid, monoketal (V) was obtained as the major product



together with a small amount of diketal (VI). These products were separated efficiently by crystallization and alumina column chromatography. V was subsequently reduced stereospecifically with lithium aluminum hydride[5] to yield *exo*-2-hydroxyepicamphor ketal (VII) which was then hydrolysed to IV by 12N sulfuric acid in five minutes with no indication of the presence of the product formed by acyloin rearrangement. Although direct reduction of IV by sodium amalgam afforded a mixture of II and camphor, the same reduction (pH adjusted to 6—8) of the corresponding acetate (VIII), which was obtained quantitatively by mild acetylation of IV, afforded II with a purity of more than 95%. The reaction sequence appears to be the most convenient way of preparing *l*-epicamphor from *d*-camphor.

*1 To whom all correspondence should be addressed.

1) J. Simonsen and L. N. Owen, "The Terpenes," Vol. II, Oxford Univ. Press, London (1957), p. 516.

2) J. Bredt and M. Bredt-Saveisberg, *Ber.*, **62**, 2216 (1929).

3) W. Hückel and O. Fechting, *Ann. Chem.*, **652**, 81 (1962).

4) J. Bredt and J. M. Fischer, *J. Prak. Chem.*, **131**, ii 56 (1931).

5) I. Fleming and R. B. Woodward, *J. Chem. Soc., C*, **1968**, 1289.

Experimental*2

Reaction of Camphorquinone (I) and Ethylene Glycol. I (prepared from *d*-camphor) (17 g), *p*-toluenesulfonic acid (0.5 g) and ethylene glycol (22 g) were dissolved in benzene (200 m*l*) and heated under reflux with azeotropic removal of water. The mixture was poured into water and extracted with benzene. Evaporation of the solvent gave a crystalline solid which was recrystallized from cyclohexane to give pure V (14 g) as colorless needles, mp 88—89.5°C, Found: C, 68.36; H, 8.69%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.68%. IR (KBr): 1752, 1399, 1375, 1041, 1024, 984, 974, 955, 938, 908, 780 cm^{-1}. NMR: 0.85 (3H, singlet), 0.99 (6H, singlet), 3.75—4.35 (4H, multiplet).

Alumina chromatography of the recrystallization mother liquor eluting with benzene - ethyl acetate mixture (3.0 g) gave additional V (4.4 g) and diketal VII (3.0 g) which after recrystallization from cyclohexane formed colorless needles, mp 63—63.5°C. Found: C, 65.97; H, 8.71%. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72%. IR (KBr): 1386, 1364, 1206, 1020, 996, 973, 953, 900, 820 cm^{-1}. NMR: 0.72 (3H, singlet), 0.83 (3H, singlet), 1.27 (3H, singlet), 3.47—4.10 (8H, multiplets).

Lithium Aluminum Hydride Reduction of Camphorquinone Monoketal (V). V (13.7 g) was dissolved in anhydrous ether (50 m*l*) and lithium aluminum hydride (1.5 g) in ether (15 m*l*) were added dropwise at 0°C. After excess of the reagent was decomposed in the usual manner, the reaction mixture was extracted with ether. Removal of the solvent and distillation of the residual oil yielded the hydroxyketal (VII) as a colorless oil, (13.1 g). Found: C, 67.91; H, 9.56%. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%. IR (CCl_4): 3520, 1392, 1372, 1094, 1029, 1009, 990, 982, 950, 918, 811 cm^{-1}. NMR: 0.80 (3H, singlet), 0.84 (3H, singlet), 1.05 (3H, singlet), 2.07 (OH), 3.13 (1H, *sharp* singlet), 3.70—4.10 (4H, multiplet).

***exo*-2-Hydroxyepicamphor (IV).** VII (13.2 g) was shaken with aqueous 12N sulfuric acid for five minutes at room temperature and then extracted with ether. After removal of the solvent, the residue was recrystallized from ligroin to yield IV (8.3 g) as colorless prisms, mp 229—230°C. IR (KBr): 3395, 1745, 1395, 1375, 1096, 980, 809 cm^{-1}. NMR: 0.92 (3H, singlet), 1.00 (6H, singlet), 3.42 (1H, *sharp* singlet).

***exo*-2-Acetoxyepicamphor (VIII).** IV (4.0 g) was heated in acetic anhydride (15 m*l*) at 140°C for 4 hr. After removal of the excess reagent *in vacuo* the residual oil was distilled to give VIII (4.7 g), as a colorless liquid. (Found: C, 67.96; H, 8.53%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.68%. IR (CCl_4): 1758, 1748, 1397, 1376, 1230, 1070 cm^{-1}. NMR: 0.89 (3H, singlet), 0.93 (3H, singlet), 0.99 (3H, singlet), 2.06 (3H, singlet), 4.74 (1H, *sharp* singlet).

Sodium Amalgam Reduction of *exo*-2-Hydroxyepicamphor (IV). *a*) IV (500 mg) in methanol (100 m*l*) was reduced with 1.2% sodium amalgam (5 g) at room temperature. After dilution with water, the reaction mixture was extracted with ether to yield colorless crystals (300 mg), GLC of which showed the presence of more than 95% of epicamphor (II).

b) IV (30 g) in 25% methanol (2 *l*) was reduced with 1.5% sodium amalgam (220 g) at room temperature. The reaction was followed by GLC which indicated the formation of camphor even at an early stage. After completion of the reduction the colorless product isolated was composed of 59% of II and 41% of camphor.

Epicamphor (II). VIII (10 g) in 30% aqueous methanol (300 m*l*) was reduced with sodium amalgam (prepared from 19.2 g of sodium and 1500 g of mercury) the pH of the solution being maintained between 6 and 8 by addition of glacial acetic acid. The reaction was followed by GLC during the reaction period. After the reaction was completed, the reaction mixture was diluted with water and the aqueous layer was extracted with ether. Removal of the solvent yielded colorless crystals, which after sublimation *in vacuo* afforded colorless scales (II), mp 186°C. $[\alpha]_D$ −58.0° (5.1 g) (Found: C, 78.19; H, 10.47%). IR (KBr): 1744, 1415, 1388, 1373, 1200, 1005 cm^{-1}. NMR: 0.94 (6H, singlet), 1.01 (3H, singlet). 2,4-DNP, mp 190.5—191.5°C. (lit[2] mp 189—190°C).

*2 All NMR spectra were measured using a Varian A-60 spectrometer for carbon tetrachloride solutions. Chemical shifts are expressed in ppm from internal tetramethylsilane. Optical rotation was measured for 2.8% methanol solution.

H. T. and S. I. are indebted to the Matsunaga Science Foundation and Takeda Science Foundation, respectively, for their generous grants.