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Reductive Rearrangement of Flavone Using Sodium Bis(2-methoxyethoxy)aluminum Hydride

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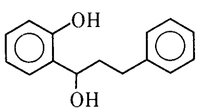
Flavone was reduced with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) to 1-(2-hydroxyphenyl)-3-phenylpropanol (A) and 1-phenylindan-1,3-diol (B). Product yields depended on the molar ratio of SMEAH/flavone. When the molar ratio of SMEAH was from 1 to 2 in relation to flavone, the main product was compound A, but at a ratio of more than 3, the rearranged compound B was predominant.

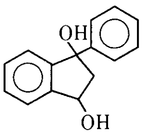
Keywords reduction; rearrangement; flavone; sodium bis(2-methoxyethoxy)aluminum hydride; 1-phenylindan-1,3-diol

Flavonoids have been reduced under various conditions, using $LiAlH_4$,[1,2] B_2H_6,[3] Na–Hg,[4] $CuCrO/H_2$,[5] Raney-Ni/H_2,[6] and PtO_2/H_2,[6] in order to obtain flavanones,[5] 4-OH-flavane,[4,5] flaven-4-ol,[2,5] flav-2-ene,[1,2] 1-phenyl-3-(2′-hydroxy-4-methoxyphenyl)propan-2-ol,[3] 1-(2′-hydroxyphenyl)-3-phenylpropan-1-ol,[6] and dodecahydroflavane.[6] A recent paper reported the reduction of 2,3-dimethyl chromone with sodium bis(2-methoxyethoxy)-aluminum hydride (SMEAH) to 2,3-dimethyl-2*H*-chromene and 2,3-dimethyl-4*H*-chromen-4-ol.[7]

This note describes the reduction of flavone with SMEAH. Two main products were obtained. One was confirmed to be 1-(2-hydroxyphenyl)-3-phenylpropanol (A) by comparison of its melting point, mass spectra (MS), and ^1H-nuclear magnetic resonance (^1H-NMR) spectra with those of the authentic sample obtained as described in the literature.[6] The other compound was assigned a new reductive transformed structure B, 1-phenylindan-1,3-diol, based on its elemental analysis and MS and NMR spectra. Its identity was confirmed by comparing its NMR spectrum with that of the synthetic compound B, prepared as shown in Chart 1. The hydroxyl group of 3-hydroxyindan-1-one, prepared from indan-1,3-dione by a literature method,[8] was protected by conversion to pyranyl ether. Reaction of the pyranyl derivative with phenylmagnesium bromide and decomposition of the reaction product with dilute sulfuric acid gave the desired compound B.



A



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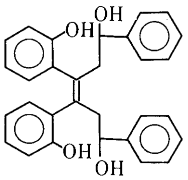

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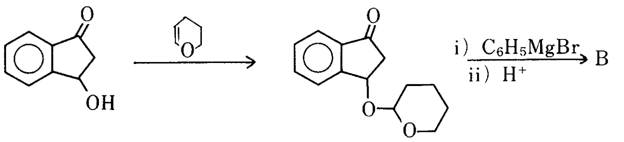

Chart 1

Table I. Relationship between the Yield (%) of Each Product and the Molar Ratio of SMEAH/Flavone at 80 °C

Molar ratio of SMEAH/flavone	Reduction product (%)[a]		Recovered[a] flavone
	A	B	
1.0	23.7	—	50.9
1.5—2.5	32.9	3.2	10.7
3.0—3.5	18.5	20.8	7.8
4.0—	6.3	43.8	4.7

a) Each value is the average of several runs, determined by GC.

In the case of 3-methoxyflavone, the same reductive rearrangement occurred with demethoxylation to give 1-phenylindan-1,3-diol.

The relationships between the yield of each product on a small scale (flavone: *ca.* 50 mg) and the molar ratio of SMEAH to flavone are shown in Table I. When the molar ratio of SMEAH was from 1 to 2 in relation to flavone, the main product was compound A, but at a ratio of more than 3, the new compound B was formed predominantly.

The incorporation of one deuterium each at the C-2 and C-3 positions was found from a comparison of the MS, ^{13}C-NMR and ^1H-NMR data for deuterium-labeled 1-phenylindan-1,3-diol (from reduction of flavone with $LiAlD_2(OCH_2CH_2OCH_3)_2$, prepared from $LiAlD_4$ and dried ethyleneglycol monomethyl ether) with those of the non-labeled compound. Based on the requirement of a large excess of reductant for the reductive rearrangement and the results of the deuteration experiments, the mechanism of the reaction is presumed to be as follows. The free AlH_4^- ion (naked anion) is not an active reducing agent.[9] Similarly, SMEAH is a naked anion, with an Na cation bound to the surrounding side chains,[10] so it is presumed that SMEAH is as mildly reactive as AlH_4^-. From the weak activity and bulkiness of SMEAH, we assume that only one of the active hydrogens in the reagent can be used for the reduction. The reaction may proceed initially in the same manner as in the proposed mechanism of reduction of tetrahydropyran-4-one,[11] and then the final attack of hydride (deuteride) at C-3 causes the rearrangement to give 1-phenylindan-1,3-diol (Chart 2). It is rare that fission of the Ar–O bond occurs during reduction.

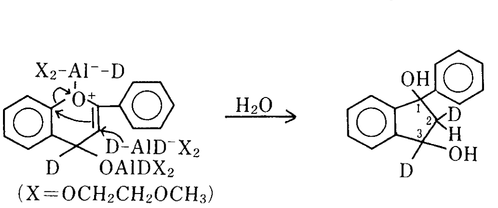

Chart 2

Similar rearrangement of the 3-hydroxy flavone derivative by photoreaction has been reported.[12] In our case, irradiation did not increase the formation of compound B.

Experimental

The structures of the isolated compounds were determined by spectral [infrared (IR), MS and NMR] and elemental analyses. All melting points were measured with a Yanaco MP-S3 apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-420 spectrophotometer and mass spectra with a JEOL JMS-DX 303 spectrometer (electron impact (EI), chemical ionization-negative (CI-negative) and fast atom bombardment (FAB)). ^{1}H-NMR spectra were recorded on a JEOL FX-200 spectrometer, and ^{13}C-NMR (125.0 MHz) spectra were recorded on a JEOL GSX-500 machine with tetramethylsilane as an internal standard in chloroform-*d* or methanol-d_4.

The concentration of commercially available SMEAH in toluene solution was determined by the method of Krynitsky *et al.*[13] $LiAlD_4$ was purchased from Commissariat a l'Energie Atomique (France).

Reduction of Flavone with a Small Excess of SMEAH (Molar Ratio of SMEAH : Flavone = 1.5 : 1) at 80 °C A solution of 70% SMEAH in toluene (6.7 g, SMEAH: 20.3 mmol) diluted with 240 ml of absolute benzene was added dropwise to a solution of flavone (3.0 g, 13.5 mmol) in absolute benzene (120 ml) under stirring at room temperature over 40 min, and then the mixture was refluxed for 30 min. Ethyl acetate (about 50 ml) and then water (about 20 ml) were added to the stirred reaction mixture in an ice bath. The resulting precipitate was removed by suction filtration, then the filtrate was washed with a saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of the solvent from the filtrate under reduced pressure gave an oily yellow residue (3.2 g). The components of the residue were separated by column chromatography on silica gel (containing 10% water), and the oily substance obtained from a fraction of benzene was crystallized from *n*-pentane, giving white crystals, yield 0.65 g, mp 59—61 °C. ^{1}H-NMR ($CDCl_3$): 2.02—2.38 ppm (m, 2H, CH_2), 2.48 (dd, 1H, $J=3.7$, 0.7 Hz, –CH–O$\underline{\text{H}}$), 2.63—2.88 (m, 2H, CH_2), 4.85 (m, 1H, C$\underline{\text{H}}$OH). MS *m/z*: 228 (M^+). *Anal.* Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.76; H, 7.12. The compound was identified as 1-(2′-hydroxyphenyl)-3-phenylpropanol from the results of elemental analysis and by comparison of its ^{1}H-NMR spectrum, MS and melting point with those of an authentic sample, which was obtained by catalytic reduction of 2′-hydroxychalcone.[6]

Reduction of Flavone with a Large Excess of SMEAH (Molar Ratio of SMEAH : Flavone = 5 : 1) at 80 °C The materials were added in the reverse order of that given above. A solution of flavone (3.0 g, 13.5 mmol) in absolute benzene (120 ml) was added gradually to a mixture of 70% solution of SMEAH in toluene (14.6 g, 67.5 mmol) and absolute benzene (240 ml) under stirring at room temperature, and then the mixture was refluxed for 30 min. Next, the mixture was treated as described above. Recrystallization of the reaction product from benzene gave pure 1-phenylindan-1,3-diol, mp 154.5—155 °C, yield 1.15 g (37.9%), which was identified from the results of elemental analysis and by comparison of its ^{1}H-NMR spectrum and MS with those of synthetic 1-phenylindan-1,3-diol. *Anal.* Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.94; H, 6.28.

Higher concentrations of reactants gave dimer derivatives which appeared in the gas chromatogram at 32.2 min and other retention times, under the gas chromatography (GC) conditions described below. One of them (retention time, 32.2 min) was isolated from an ethyl acetate–benzene (1 : 19) fraction in column chromatography on silica gel, and recrystallized from benzene, giving fine colorless needles, mp 195.5—197 °C. The structure C was assigned to this compound based on its ^{1}H-NMR spectrum, MS and elemental analysis. ^{1}H-NMR ($CDCl_3$): 2.30 ppm (d, 2H, $J=2.9$ Hz, CH–O$\underline{\text{H}}$, disappeared on addition of D_2O), 2.64 (dd, 2H, $J=13.6$, 5.0 Hz, CH_2), 3.00 (dd, 2H, $J=13.6$, 9.2 Hz, CH_2), 4.58 (8-plet, 2H, $J=9.2$, 5.0, 2.9 Hz, C$\underline{\text{H}}$–OH; change to dd, $J=9.2$, 5.0 Hz on addition of D_2O), 6.69—7.46 (m, 18H, Ar–H), 7.57 (s, 2H, Ar–OH, disappeared on addition of D_2O). CI-negative-MS *m/z*: 451 $(M-H)^-$, 434 $(M-H_2O)^-$. *Anal.* Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.55; H, 6.25.

1-Phenylindan-1,3-diol (B) 2,3-Dihydro-4*H*-pyran (1.3 g),[14] and concentrated hydrochloric acid (about 2 drops) were added to 3-hydroxyindan-1-one (0.57 g),[8] and the mixture was stirred and left standing overnight at room temperature. Ether (100 ml) was added to the reaction mixture, and the solution was washed with aqueous sodium bicarbonate and water, then dried on magnesium sulfate. Evaporation of the solvent left an oily yellow residue [MS, *m/z* 232: (M^+)]. A solution of the oily 2′-*O*-tetrahydropyranyl ether in anhydrous ether (10 ml) was added dropwise to an ethereal solution of phenylmagnesium bromide, which was prepared from magnesium ribbon (0.4 g) and ethyl bromide (2.6 g) in anhydrous ether (20 ml). The mixture was stirred for 2 h and left standing overnight. The solvent was evaporated, dilute sulfuric acid was added to the residue, and the mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with 10% sulfuric acid and water and then dried on magnesium sulfate. The solvent was removed under reduced pressure, and the oily yellow residue was separated by column chromatography on silica gel; one fraction (benzene : ethyl acetate = 9 : 1) gave 1-phenylindan-1,3-diol (0.15 g). It was recrystallized from benzene as pure fine needles. mp 154—156 °C. MS *m/z*: 226 (M^+), 208 (base peak). ^{1}H-NMR (CD_3OD): 2.34 ppm (dd, 1H, $J=12.9$, 6.7 Hz, CH_2), 2.92 (dd, 1H, $J=12.9$, 6.7 Hz, CH_2), 5.06 (t, 1H, $J=6.7$ Hz, C$\underline{\text{H}}$–OH): 7.15—7.51 (m, 9H, Ar-H). ^{13}C-NMR (CD_3OD): 55.6 ppm (t, C_2), 73.2 (d, C_3), 83.2 (s, C_1), 125.2 (d, Ph), 125.3 (d, Ph), 126.6 (d, 2C, Ph), 127.9 (d, Ph), 129.1 (d, 2C, Ph), 129.6 (d, Ph), 129.7 (d, Ph), 146.1 (s, Ph), 148.4 (s, Ph), 148.6 (s, Ph). *Anal.* Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.79; H, 6.25.

Determination of Reductive Products by GC The relationship between the molar ratio of SMEAH/flavone and the yield of each product was determined. A sample was prepared from flavone (an accurately measured amount, around 50 mg) in dry benzene (2 ml) by addition of a calculated amount of SMEAH in dry benzene (4 ml), followed by treatment as described previously. The resulting oil was dissolved in ethyleneglycol dimethyl ether (2 ml) and trimethylsilanized with 0.4 ml of *N*,*O*-bis(trimethylsilyl)acetamide for 10 min at 80 °C. Programmed-temperature gas liquid chromatography was carried out with an instrument equipped with a hydrogen flame ionization detector (Shimadzu GC-7AG). The columns used were Gas chrom Q (80—100 mesh) coated with a 2% film of OV-101 in a 1.6-m glass tube, 3 mm in diameter. The initial oven temperature was 150 °C, the heating rate was 4 °C/min, the final temperature was 250 °C, and the flow rate of nitrogen was 50 ml/min. Under these conditions, the peak of compound A appeared at 10.3 min and that of compound B at 9.2 min. All quantitative work was performed by comparison of the area responses with those of a known amount of tetracosane as an internal standard. The calculation equations statistically obtained from the area ratio (x) and the weight ratio (y) of the authentic sample per internal standard were $y=0.806x+0.038$ for 1-phenylindan-1,3-diol and $y=0.743x+0.0156$ for 1-(2′-hydroxyphenyl)-3-phenylpropanol in the range of about 1 to 10 μg of each sample.

Reduction of 3-Methoxyflavone with a Large Excess of SMEAH This reaction was carried out under the same conditions as those for flavone. Demethoxylation occurred during reductive rearrangement and 1-phenylindan-1,3-diol, which was spectroscopically identical (^{1}H- and ^{13}C-NMR, MS) with an authentic sample, was obtained (yield 24%).

Reduction of Flavone with the Reaction Mixture of $LiAlD_4$–Ethyleneglycol Monomethyl Ether (1 : 2) A mixture of 0.7 g (16.7 mmol) of pulverized $LiAlD_4$ and 50 ml of dry ether was heated under reflux with stirring for 30 min, and the mixture was cooled in an ice bath. A solution of 2.5 g (32.9 mmol) of anhydrous ethyleneglycol monomethyl ether in 50 ml of dry ether was then added dropwise with vigorous stirring at 0 °C to 5 °C for 30 min. To this reaction mixture, 100 ml of dry benzene was added and the ether was evaporated off *in vacuo*. Next, a solution of 0.07 g (0.31 mmol) of flavone in 50 ml of dry benzene was added dropwise to the above solution at 10 °C, and then the reaction mixture was kept at reflux for 30 min. The excess reductant was decomposed by adding 150 ml of ethyl acetate slowly with stirring. Next came washing with 10% hydrochloric acid, 10% aqueous solution of sodium bicarbonate and then water, and drying over anhydrous magnesium sulfate. The solvent was evaporated off *in vacuo*, and recrystallization of the residue from benzene gave (2,3-$^2H_2$)1-phenylindan-1,3-diol. mp 152—156 °C, yield 24.2%. FAB-MS *m/z*: 229 $(M+H)^+$. ^{1}H-NMR (CD_3OD): 2.89 ppm (s, 1H, CHD), 7.16—7.48 (m, 9H, Ar-H). ^{13}C-NMR (CD_3OD): 55.1 ppm (C_2, split into a triplet by deuterium), 72.8 (C_3, split into a triplet by deuterium), 83.2 (C_1), 125.2 (Ph), 125.3, 126.6 (2C), 127.9, 129.1 (2C), 129.5, 129.7, 146.0, 148.4, 148.6.

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