

Synthesis of glycerol 1,3-dihexadecyl ether

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SUMMARY The synthesis of 1,3-dihexadecyloxy-2-propanol (glycerol 1,3-dihexadecyl ether) is reported. The method is applicable to the preparation of other 1,3-disubstituted glycerols where the substituents are not affected by acid or by catalytic hydrogenolysis conditions.

KEY WORDS glycerol 1,3-dihexadecyl ether · synthesis · benzylidene glycerol

KATES, CHAN, AND STANACEV (1) have described the synthesis of glycerol 1,2-dialkyl ethers. Subsequently, the same laboratory reported (2) the synthesis of dialkenyl and mixed alkyl alkenyl glycerol ethers. Other routes for the preparation of such diethers have been described by Baumann and Mangold (3) and Thomas and Law (4). All of these methods have as their product only the glycerol 1,2-diether. We describe here a method, similar to that of Kates, by which the glycerol 1,3-dialkyl ether has been prepared.

The starting material in the synthesis is 1,3-benzylidene glycerol. A benzyl ether is placed in the 2-position of this acetal to protect this position from acidic and basic reaction conditions. After hydrolytic removal of the benzylidene group and alkylation, the benzyl group is removed by catalytic hydrogenolysis. This preparative method precludes the use of alkenyl groups in the synthesis, but does allow functional changes, such as esterification, at the 2-position of the final product without danger of cleaving or of altering the position of the ether linkages.

The main steps in the synthesis are given in Fig. 1. The 1,3-benzylidene glycerol (I) reacts with benzyl chloride in the presence of dry potassium hydroxide to yield 2-benzyloxy-1,3-benzylidene glycerol (II). This benzyl ether (II) is treated with methanolic hydrochloric acid and gives 2-benzyloxy-1,3-propanediol (III). Compound III is treated with hexadecyl bromide and potassium hydroxide to effect alkylation. After removal of excess hexadecyl bromide by distillation, the blocking benzyl group is cleaved by hydrogenolysis in the presence of freshly prepared palladium metal as a catalyst. The final product of this procedure, 1,3-dihexadecyloxy-2-propanol (V), was shown to be >97% pure by a combination of GLC, TLC, NMR spectroscopy, and elemental analysis.

Abbreviations: GLC, gas-liquid chromatography; NMR, nuclear magnetic resonance; TLC, thin-layer chromatography.

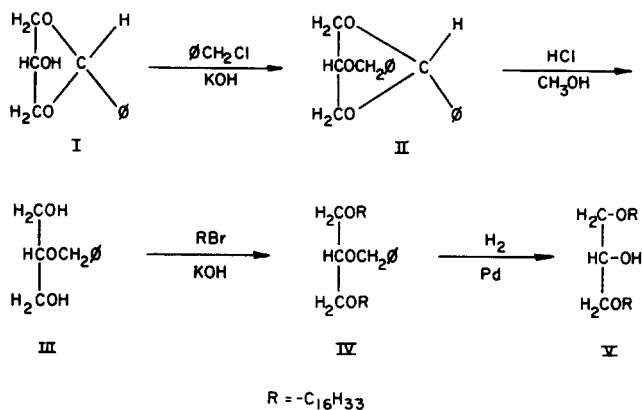


FIG. 1. Reaction scheme.

Experimental Details. Melting points are uncorrected; they were determined on a Mel-Temp melting point apparatus. GLC took place on a 4 ft column of 2% SE-30 (methylpolysiloxo gum, General Electric Co., Silicone Products Department, Waterford, N. Y.) on 60–80 mesh Gas-Chrom P at a programmed temperature of 150–300°C, temperature rise 5.6°C/min. Helium carrier gas was used at a flow rate of 74 ml/min, standard temperature and pressure. The retention time is the time of emergence after the air peak. TLC was on plates of Silica Gel G (Brinkmann Instruments Inc., Westbury, N. Y.) with hexane–diethyl ether–acetic acid 80:20:1 as the developing solvent. The plates were sprayed with sulfuric acid–water 1:3 and the components detected by charring at 180°C.

NMR Spectroscopy. The identities of the intermediates and of the final product were determined mainly by their NMR spectra. The spectra were obtained with the sample dissolved in CCl₄, which contained tetramethylsilane as an internal reference. A 100 mc high-resolution spectrometer (Varian Associates, Palo Alto, Calif.) was used. Chemical shifts are reported in τ units.

2-Benzyloxy-1,3-propanediol (2-Benzyl Glycerol). A mixture of 25 g (0.139 mole) of 1,3-benzylidene glycerol (2-phenyl-*m*-dioxan-5-ol, Distillation Products Industries, Rochester, N. Y.), 35.2 g (0.278 mole) of benzyl chloride, 15.6 g (0.278 mole) of powdered potassium hydroxide, and 100 ml of benzene was stirred and refluxed for 17 hr. The water that formed was continuously collected in a Dean-Stark trap. The reaction mixture was cooled and, after the addition of 100 ml of ether, was washed successively with water, 1 N hydrochloric acid, 2.5% potassium bicarbonate, and water. The ether–benzene solution was dried over anhydrous sodium sulfate and filtered. The solvents were removed on a rotary evaporator. After removal of excess benzyl chloride by distillation, 37.0 g of residue remained. The NMR spectra of this residue showed peaks at τ 2.58

(area 10, phenyl H), 4.62 (area 1, benzylidene C–H), 5.49 (area 2, benzyl CH₂), 5.90 (area 4, glyceryl CH₂), and 6.68 (area 1, glyceryl CH). If the residue was pure 2-benzyloxy-1,3-benzylidene glycerol, the yield was 98%. This material was not purified further.

The benzylidene group was removed by refluxing for 4.5 hr with 120 ml of methanol and 12 ml of concentrated hydrochloric acid. The cooled mixture was added to 100 ml of water and extracted twice with 100-ml portions of chloroform. The water layer was then saturated with potassium carbonate and extracted again with chloroform. All the chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. A pump was used to remove the last traces of benzaldehyde. The remaining liquid was then distilled through a Kontes Bantam-ware still (Kontes Glass Co., Vineland, N. J.) and the fraction of bp 140–147°C/0.08 mm was collected. A total of 9.2 g of 2-benzyloxy-1,3-propanediol was recovered (yield = 35%). No attempt was made to purify this sample further, as its preparation has been reported (5). The NMR spectrum of this compound was found to have peaks at τ 2.59 (area 5, phenyl H), 5.52 (area 2, benzyl CH₂), 6.3–6.7 (area 5, glyceryl CH and CH₂), and 7.18 (area 2, OH).

1,3-Dihexadecyloxy-2-propanol (Glycerol 1,3-Dihexadecyl Ether). A mixture of 9.2 g (0.05 mole) of the 2-benzyloxy-1,3-propanediol, 71.0 g (0.20 mole) of 1-bromohexadecane, 13.2 g (0.20 mole) of powdered potassium hydroxide, and 100 ml of benzene was stirred and refluxed for 16 hr. The water that formed was collected in a Dean-Stark trap. To the cooled reaction mixture, 100 ml of ether was added and the mixture was washed successively with water, 1 N hydrochloric acid, 2.5% potassium bicarbonate, and water. The ether–benzene solution was dried over anhydrous magnesium sulfate and filtered. The solvents were then removed on a rotary evaporator. The excess hexadecyl bromide was removed by distillation and 24.1 g of residue, presumably 2-benzyloxy-1,3-hexadecyloxypropane, was recovered.

This material was distributed among three 500-ml hydrogenation bottles and 60 ml of ethyl acetate was added to each bottle. 1 g of freshly prepared palladium catalyst (6) was added to each bottle and the benzyl ether group was removed by hydrogenolysis on a Parr apparatus (Parr Instrument Co., Moline, Ill.) for 3 hr at a starting pressure of 40 psi of hydrogen. After this time, the mixture was filtered and the catalyst was washed thoroughly with ether. The solvent was removed on a rotary evaporator and 14.7 g of solid was recovered. This material was recrystallized from 150 ml of chloroform–methanol 1:4. After air drying, 11.9 g (yield = 58%) of 1,3-dihexadecyloxy-2-propanol was obtained, mp 57.5–59°C.

Analysis: $C_{35}H_{72}O_8$ (541.6); calculated: C, 77.7; H, 13.4
found: C, 77.5; H, 13.2

The major GLC peak of this material had a retention time of 33 min and constituted 96.8% of the total peak area. TLC showed an intense spot at $R_f = 0.19$ and three minor spots. The NMR spectrum of this product had peaks at τ 6.55–6.80 (area 9, glyceryl CH_2 and CH and $O-CH_2$), 8.65 (area 56, aliphatic CH_2), and 9.10 (area 6, terminal CH_3). The presence of an OH group was detected by its infrared absorption peak at 3610 cm^{-1} (CCl_4 solution).

The analyses given above established that the product was a glycerol diether, but did not delineate the locations of the ether groups. These were established by acylating the diether with oleoyl chloride. The NMR spectrum of this product shows a new band at τ 5.03 (area 1) as well as the expected peaks characteristic of the ether and the oleoyl groups. Acetylated glycerol 1,2-dialkyl ether gives an NMR absorption band at τ 5.95 (area 2) characteristic of the protons on the primary carbon at which the acetyl group is attached (4). The spectrum of our acylated diether did not have a band at τ 5.95. Thus the ether groups must be attached to the 1- and 3-positions of the glycerol. The band at τ 5.03 is attributable to the proton on the secondary carbon at which the oleoyl group is attached. This band has an area of 1, which is in agreement with this structural assignment.

On the basis of these analyses and the route of synthesis, we conclude that the final product is 1,3-dihexadecyloxy-2-propanol and that it has a purity of at least 97%.

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¹ Analyses were performed by the microanalytical laboratory of The Procter & Gamble Company, Miami Valley Laboratories.