THE STRUCTURE AND PROPERTIES OF DL-1,2-O-CYCLOHEXYLIDENEGLYCEROL[1]

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ABSTRACT

DL-1,2-*O*-Cyclohexylideneglycerol was prepared by reacting cyclohexanone and glycerol in the presence of sulphuric acid. It is miscible with all common organic solvents and is slightly soluble in water. It is not affected by hydrogenolysis at 25°C. over palladous oxide at 50 p.s.i. for 24 hr. The DL-1,2-*O*-cyclohexylidene-3-*O*-*p*-nitrobenzoylglycerol is readily cleaved by mineral acids to yield 3-*O*-*p*-nitrobenzoylglycerol. Proof of the 1,2 ketal structure was obtained by (*a*) preparation of the monomethyl derivative, acid hydrolysis, and periodic acid oxidation of the resultant 1-monomethyl ether of glycerol and (*b*) treatment of the tosyl derivative with sodium iodide which gave a 93% yield of sodium *p*-toluenesulphonate.

O-Cyclohexylideneglycerol was first prepared by Kühn (3) in 1940 but the structure was not established. The compound was most likely a 1,2 ketal similar to DL-1,2-*O*-isopropylideneglycerol. Since *O*-cyclohexylideneglycerol can be prepared readily in large quantities it seemed desirable to investigate the structure and the chemical properties to evaluate the compound as a possible starting material for the synthesis of glycerides.

O-Cyclohexylideneglycerol was prepared in 58% yield by reacting glycerol with cyclohexanone in the presence of sulphuric acid. It is miscible with all common organic solvents, slightly soluble in water, and is not affected by catalytic hydrogenolysis at 25°C. over palladous oxide at 50 p.s.i. for 24 hr. It is readily cleaved by mineral acids.

Evidence of the 1,2 cycloketal structure was obtained by preparation of the monomethyl derivative and subsequent acid hydrolysis. Periodic acid oxidation of the resultant monomethylglycerol showed consumption of 1 mole of oxidant. The DL-1,2-*O*-cyclohexylidene-3-*O*-*p*-toluenesulphonylglycerol was prepared and reacted with sodium iodide in acetic anhydride at 100°C. Sodium *p*-toluenesulphonate was obtained in 93% yield and constituted proof that the tosyl group was at a terminal position in the glycerol. DL-1,2-*O*-Cyclohexylidene-3-*O*-*p*-nitrobenzoylglycerol was prepared and the ketal was cleaved with dilute sulphuric and dilute hydrochloric acids to give 1-*O*-*p*-nitrobenzoylglycerol in yields of 70 and 73% respectively.

The DL-1,2-*O*-cyclohexylideneglycerol appears to be similar to DL-1,2-*O*-isopropylideneglycerol and could be used in glyceride synthesis. It offers an advantage in the ease of preparation.

EXPERIMENTAL

(1) DL-*1,2-O-Cyclohexylideneglycerol*

A mixture of 665 gm. (700 ml.) of anhydrous cyclohexanone, 330 gm. (262 ml.) of anhydrous glycerol, and 46 ml. of concentrated sulphuric acid

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was shaken at room temperature for 20 min. Anhydrous $CuSO_4$ (160 gm.) was added and shaking was continued for 30 min., whereupon the mixture was filtered by suction. The filtrate was dissolved in 400 ml. of ethyl ether and was stirred vigorously with a solution of 200 gm. K_2CO_3 in 3000 ml. of water for 30 min. The ethereal layer was separated, washed once with water, and dried over anhydrous K_2CO_3. After evaporation of the ether the product was distilled in a Podbielniak Heligrid distillation column to yield 360 gm. (58% of the theoretical amount) of analytically pure ketal, b.p. 137° at 17 mm., 252° at 714 mm., $n_D^{25} = 1.47645$, reported b.p. 133–135° at 15 mm. (3).

The DL-1,2-*O*-cyclohexylideneglycerol is miscible with all common organic solvents. It is soluble in water at 26°C. to the extent of 6.5% and the solubility of water in the cyclohexylideneglycerol at 26°C. is 30%.

The ketal is stable to hydrogenolysis by catalytic hydrogenation at 25°C. over palladous oxide at 50 p.s.i. for 24 hr. with methanol as a solvent.

(2) DL-*1,2-O-Cyclohexylidene-3-O-p-nitrobenzoylglycerol*

p-Nitrobenzoyl chloride, 43.2 gm., was added to a solution of 40 gm. of DL-1,2-*O*-cyclohexylideneglycerol in 200 ml. of anhydrous pyridine. The mixture was shaken at room temperature for 18 hr., poured into 1000 ml. of ice water, and stirred. The crystals were filtered off, dried in a desiccator, and recrystallized once from *n*-butanol. Yield, 50 gm. (67% of the theoretical amount). Further recrystallizations from ethanol, Skellysolve "B", and methanol gave the pure compound, m.p. 49.5–50.0°C. (stout prisms with a slightly yellow color). Analysis for $C_{16}H_{19}O_6N$: C, 59.92%; H, 5.99%; N, 4.35%. Calc. for C, 59.80%; H, 5.96%; and N, 4.36%.

The compound is very soluble in acetone and chloroform, soluble in methanol, benzene, ethanol, and carbon tetrachloride, slightly soluble in ethyl ether, and nearly insoluble in water.

(3) DL-*1,2-O-Cyclohexylidene-3-O-methylglycerol*

Acetone, 1500 ml., and DL-1,2-*O*-cyclohexylideneglycerol, 200 gm., were placed in a 3 liter flask equipped with a stirrer, reflux condenser, and two dropping funnels. The solution was heated to 50°C., 370 gm. (278 ml.) of dimethyl sulphate and a 50% aqueous solution of NaOH (272 gm.) in the dropping funnels were added simultaneously at a rate sufficient to maintain reflux and an alkaline medium. After the addition of the alkylating agents was completed, the bulk of the acetone was distilled off with continuous stirring. The remaining liquid was stirred with 400 ml. of 30% NaOH solution at 100°C. for three hours. The nonaqueous layer was separated and distilled on the Podbielniak distillation column. Yield, 184 gm. (85% of the theoretical amount), b.p. 106° at 12 mm., 226° at 714 mm., n_D^{25} 1.4539. Analysis for $C_{10}H_{18}O_3$: C, 64.03%; H, 9.70%. Calc. for C, 64.48%; H, 9.74%.

The compound is miscible with common organic solvents, and is insoluble in water and glycerol.

(4) *Hydrolysis of* DL-*1,2-O-Cyclohexylidene-3-O-methylglycerol*

Sixty milliliters of DL-1,2-*O*-cyclohexylidene-3-*O*-methylglycerol and 60 ml. of 10% sulphuric acid were refluxed for four hours. The aqueous layer was neutralized with sodium carbonate solution, separated from the cyclohexanone and distilled. A second distillation of the product yielded 30 gm. of 1-*O*-methylglycerol, b.p. 135° at 40 mm. (reported b.p. 135.5–136°C. at 40 mm.) (2). The product was oxidized with periodic acid in aqueous solution at room temperature. Periodic acid, 0.99 moles, was consumed after one hour and no change was observed after an additional 20 hr.

(5) DL-*1,2-O-Cyclohexylidene-3-O-p-toluenesulphonylglycerol*

p-Toluenesulphonyl chloride, 4.5 gm., was added to a solution of 4 gm. of DL-1,2-*O*-cyclohexylideneglycerol in 20 ml. of anhydrous pyridine cooled in an ice-water mixture. The mixture was allowed to stand at room temperature for 48 hr. and was then poured into 110 ml. of ice water and stirred. The DL-1,2-*O*-cyclohexylidene-3-*O*-*p*-toluenesulphonylglycerol, which crystallized, was filtered and dried. Yield of crude material, 6.5 gm. (86% of the theoretical amount), m.p. 49°. Several recrystallizations from Skellysolve "B" – amyl alcohol (1:1) gave the analytically pure compound in the form of prisms, m.p. 48.5–49.0°C. Analysis for $C_{16}H_{22}O_5S$: C, 59.05%; H, 6.76%; S, 9.88%. Calc. for C, 58.87%; H, 6.79%; and S, 9.82%.

The compound is very soluble in acetone, chloroform, benzene, ethyl acetate, and ethyl ether, soluble in methanol, ethanol, and carbon tetrachloride, slightly soluble in Skellysolve "F", and almost insoluble in water.

(6) *Reaction of* DL-*1,2-O-Cyclohexylidene-3-O-p-toluenesulphonylglycerol with Sodium Iodide*

One gram of the tosyl derivative and 1.2 gm. of anhydrous sodium iodide were dissolved in 15 ml. of acetic anhydride and the solution was heated at 100°C. on a steam bath. Precipitation of sodium *p*-toluenesulphonate began after 15 min. and heating was continued for five hours. The precipitate was collected, dried, and weighed. Yield, 0.55 gm. (93% of the theoretical amount).

(7) *Acid Hydrolysis of* DL-*1,2-O-Cyclohexylidene-3-O-p-nitrobenzoylglycerol with Mineral Acids*

(*a*) *Sulphuric Acid*

Two grams of the compound was added to a solution of 38 ml. of acetone and 5 ml. of 1.0 *N* H_2SO_4 and the mixture was refluxed for four hours. The solution was diluted with an equal volume of water, neutralized by passing through a column of Amberlite IR-4B, and evaporated to a volume of 25 ml. The oil which separated was taken up in 60 ml. of hot chloroform; the chloroform layer was separated and evaporated to a volume of 15 ml. The 1-*O*-*p*-nitrobenzoylglycerol was crystallized from this solution. Yield, 1.05 gm. (70% of the theoretical amount), m.p. 107° (reported m.p. 107°) (1).

(*b*) *Hydrochloric Acid*

Acid hydrolysis was carried out in the same manner with 1.0 *N* hydrochloric acid. Silver oxide was used to neutralize the acid after hydrolysis. Yield, 1.1 gm. (73% of the theoretical amount), m.p. 107°.

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