Reactions of Aliphatic Methanesulfonates. II. Syntheses of Long-Chain Di- and Trialkyl Glyceryl Ethers[1]

WOLFGANG J. BAUMANN AND HELMUT K. MANGOLD

University of Minnesota, The Hormel Institute, Austin, Minnesota

Received June 10, 1965

Saturated and unsaturated long-chain dialkyl glyceryl ethers (2,3-dialkoxy-1-propanols) were synthesized by alkylation of tritylated alkyl glyceryl-(1) ethers (1-alkoxy-3-trityloxy-2-propanols) with methanesulfonates, followed by hydrolytic removal of the trityl groups. Trialkyl glyceryl ethers (1,2,3-trialkoxypropanes) containing three identical, or two or three different, alkyl groups were prepared.

Alkyl glyceryl-(1) ethers[2] and dialkyl glyceryl-(1,2) ethers occur in nature as alkoxyglycerides[3] and phospholipids.[4-7] Marinetti, *et al.*,[5] demonstrated the presence of dialkyl glyceryl-(1,2) ethers in hydrolyzed and hydrogenated extracts of beef heart. Similarly, Sehgal, *et al.*,[6] and other investigators[7] isolated the same type of compounds from *Halobacterium cutirubrum*, and Popović[8] found dialkyl glyceryl-(1,2) ethers in the human heart. The occurrence of trialkyl glyceryl ethers in nature has not been reported.

The only synthesis of dialkyl glyceryl-(1,2) ethers published is limited to the preparation of saturated compounds containing identical alkyl groups. Thus, ditetradecyl,[9] dihexadecyl,[10] and dioctadecyl[10] glyceryl-(1,2) ethers, the only compounds of this type synthesized so far, were prepared by treating α-benzyl glycerol with alkyl bromides and subsequent hydrogenolytic debenzylation. Procedures for the preparation of long-chain trialkyl glyceryl-(1,2,3) ethers have not been published.

The present communication describes a synthesis applicable to the preparation of saturated *and* unsaturated dialkyl glyceryl-(1,2) ethers having identical or different carbon chains. The reaction of an alkyl glyceryl-(1) ether with triphenylchloromethane in pyridine[11] leads preferentially to tritylation of its primary hydroxy group. Small amounts of the 2-trityl and the 2,3-ditrityl derivatives are also formed, as is shown by thin layer chromatography (tlc). These by-products are easily removed by recrystallization. This is verified by tlc and infrared spectroscopy. The tritylated glyceryl ether is treated with a long-chain alkyl methanesulfonate in xylene solution using potassium hydroxide[12] to effect the condensation. The water formed is removed continuously by azeotropic distillation. Eventually, acidic hydrolysis leads to 2,3-dialkoxy-1-propanol. The yields and characterization data of compounds IV–XIV are quoted in Table I. The structure of these dialkyl glyceryl-(1,2) ethers is also assured by comparison of one of the compounds (IX) with one prepared by an alternative route. Alkylation of α-benzylglycerol with octadecyl methanesulfonate, followed by hydrogenolytic removal[10] of the benzyl group, leads to IX. The identity of both preparations is proven by their infrared spectra, melting points, and R_f values.

Long-chain trialkyl glyceryl ethers are synthesized by an alkylating procedure analogous to that described above. The alkylation of glycerol itself does not yield appreciable amounts of trialkyl ether. However, the reaction of alkyl glyceryl-(1) or dialkyl glyceryl-(1,2) ethers with 2 or 1 equiv of methanesulfonates, respectively, utilizing potassium hydroxide in xylene for condensation, yields products which are easily purified by column chromatography[13] on silicic acid. In the case of the chromatographic purification of trioctadecyl glyceryl-(1,2,3) ether (XVI), the significant by-products are isolated. Besides dioctadecyl ether, the two isomeric dioctadecyl glyceryl ethers are obtained and identified. The more polar compound is shown to be 2,3-dioctadecyloxy-1-propanol (IX), the less polar is 1,3-dioctadecyloxy-2-propanol. Both give 1,2,3-trioctadecyloxypropane (XVI) upon further alkylation. The yields and physical data of the pure 1,2,3-trialkoxypropanes XV–XIX, containing the same, or two or three different, alkyl groups, are compiled in Table II. Some of these compounds were shown to be polymorphic, and the melting points recorded do not necessarily refer to the most stable modification.

The infrared spectra of the unsaturated compounds III, XI, XIII, and XIV do not exhibit absorption near 965 cm^{-1} associated with the *trans*-C–H out-of-plane deformation, but they show bands at 2985 cm^{-1} for *cis*-C–H stretching vibrations. 2-*trans*-Octadecenyloxy-3-octadecyloxy-1-propanol (XII) shows the band at 965 cm^{-1}. These spectra indicate that no *cis–trans* isomerization of double bonds occurs during synthesis. In all glyceryl ethers described, the ether groups give a characteristic C–O frequency at 1120 cm^{-1}. The 2,3-dialkoxy-1-propanols IV–XIV show the strong C–O stretching absorption near 1048 cm^{-1} of primary alcohols. The tritylated glyceryl ethers I–III and 1,3-dioctadecyloxy-2-propanol do not exhibit this band.

(1) This investigation was supported by U. S. Public Health Service Research Grant GM 05817.

(2) W. J. Baumann and H. K. Mangold, *J. Org. Chem.*, **29**, 3055 (1964).

(3) E. André and A. Bloch, *Bull. Soc. Chim. France*, [5] **2**, 789 (1935); H. K. Mangold and D. C. Malins, *J. Am. Oil Chemists' Soc.*, **37**, 383 (1960).

(4) H. E. Carter, D. B. Smith, and D. N. Jones, *J. Biol. Chem.*, **232**, 681 (1958); D. J. Hanahan and R. Watts, *ibid.*, **236**, PC 59 (1961).

(5) G. V. Marinetti, J. Erbland, and E. Stotz, *J. Am. Chem. Soc.*, **81**, 861 (1959).

(6) S. N. Sehgal, M. Kates, and N. E. Gibbons, *Can. J. Biochem. Physiol.*, **40**, 69 (1962).

(7) M. Kates, P. S. Sastry, and L. S. Yengoyan, *Biochim. Biophys. Acta*, **70**, 705 (1963); M. Faure, J. Maréchal, and J. Troestler, *Compt. Rend.*, **257**, 2187 (1963); M. Kates, L. S. Yengoyan, and P. S. Sastry, *Biochim. Biophys. Acta*, **98**, 252 (1965).

(8) M. Popović, *Z. Physiol. Chem.*, **340**, 18 (1965).

(9) E. Baer and N. Z. Stanacev, *J. Biol. Chem.*, **240**, 44 (1965).

(10) M. Kates, T. H. Chan, and N. Z. Stanacev, *Biochemistry*, **2**, 394 (1963).

(11) P. E. Verkade and L. J. Stegerhoek, *Koninkl. Ned. Akad. Wetenschap. Proc.*, **B57**, 444 (1954); L. J. Stegerhoek and P. E. Verkade, *Rec. Trav. Chim.*, **75**, 143 (1956).

(12) The use of metallic potassium in benzene for condensation[2] resulted in long reaction times and poor yields of dialkyl glyceryl-(1,2) ether.

(13) J. Hirsch and E. H. Ahrens, Jr., *J. Biol. Chem.*, **233**, 311 (1958).

TABLE I

2,3-Dialkoxy-1-propanols

$$HOCH_2\underset{\displaystyle OR'}{\underset{|}{C}}H_2CH_2OR$$

No.	R	R′	% yield	Mp, °C	Cst, °C[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % O	Found, % C	Found, % H	Found, % O
IV[b]	Hexadecyl	Hexadecyl	60	59.5–60	132	$C_{35}H_{72}O_3$	77.71	13.42	8.87	77.94	13.25	8.85
V	Hexadecyl	Octadecyl	91	61.5–62	139.5	$C_{37}H_{76}O_3$	78.10	13.46	8.44	78.29	13.22	8.54
VI	Octadecyl	Dodecyl	76	41.5–42	123	$C_{33}H_{68}O_3$	77.28	13.36	9.36	76.94	12.99	9.80
VII	Octadecyl	Tetradecyl	78	52–52.5	131.5	$C_{35}H_{72}O_3$	77.71	13.42	8.87	77.46	13.41	9.10
VIII	Octadecyl	Hexadecyl	88	58.5–59	139.5	$C_{37}H_{76}O_3$	78.10	13.46	8.44	78.74	13.56	7.82
IX[b]	Octadecyl	Octadecyl	89	64–65	147	$C_{39}H_{80}O_3$	78.46	13.51	8.04	78.41	13.11	8.56
X	Octadecyl	Eicosyl	87	66.5–67	154	$C_{41}H_{84}O_3$	78.78	13.54	7.68	79.68	13.40	6.96
XI	Octadecyl	*cis*-9-Octadecenyl	69	23–24	136	$C_{39}H_{78}O_3$	78.72	13.21	8.07	78.62	13.11	8.44
XII	Octadecyl	*trans*-9-Octadecenyl	91	48–48.5	138.5	$C_{39}H_{75}O_3$	78.72	13.21	8.07	78.48	12.98	8.58
XIII	*cis*-9-Octadecenyl	Octadecyl	80[c]	20–21	136.5	$C_{39}H_{78}O_3$	78.72	13.21	8.07	78.46	13.09	8.47
XIV	*cis*-9-Octadecenyl	*cis*-9-Octadecenyl	83[c]	...	126	$C_{39}H_{76}O_3$	78.99	12.92	8.09	78.91	13.64	7.47

[a] Critical solution temperatures with nitromethane. [b] See ref 10. [c] Yield of crude material.

TABLE II

1,2,3-Trialkoxypropanes

$$ROCH_2\underset{\displaystyle OR'}{\underset{|}{C}}H_2CH_2OR''$$

No.	R	R′	R″	% Yield	Mp, °C	Cst, °C[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % O	Found, % C	Found, % H	Found, % O
XV	Hexadecyl	Hexadecyl	Hexadecyl	39	47–48	186	$C_{51}H_{104}O_3$	80.03	13.70	6.27	80.16	13.55	6.40
XVI	Octadecyl	Octadecyl	Octadecyl	36	57.5–58	196	$C_{57}H_{116}O_3$	80.59	13.76	5.65	80.44	13.36	6.05
XVII	Dodecyl	Hexadecyl	Hexadecyl	33	36.5–37	178	$C_{47}H_{96}O_3$	79.59	13.64	6.77	80.07	13.18	6.93
XVIII	Dodecyl	Octadecyl	Octadecyl	43	43–44	185.5	$C_{51}H_{104}O_3$	80.03	13.70	6.27	80.08	13.59	6.24
XIX	Octadecyl	Hexadecyl	Dodecyl	46	34–35	182.5	$C_{49}H_{100}O_3$	79.82	13.67	6.51	80.04	13.63	6.40

[a] Critical solution temperatures with nitromethane.

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer spectrophotometer, Model 21, in carbon disulfide solution.

Critical solution temperatures (cst)[14] with nitromethane (Fisher Scientific Co., No. N98) and melting points were determined on a Kofler hot stage[15] and are corrected.

Elemental analyses were by Mikroanalytisches Laboratorium I. Beetz, 8640 Kronach, Germany.

The purity of glyceryl-(1) ethers and methanesulfonates used as starting materials was assured by ascending thin layer adsorption chromatography. These compounds were also shown to be uniform in chain length and degree of unsaturation.[2]

Thin layer adsorption chromatography (tlc) on silica gel G (Merck) was employed for checking the course of reactions and the purity of the final products. All plates were developed with hexane–diethyl ether (90:10 v/v) in tanks lined with filter paper. After chromatography, the plates were sprayed with a solution of 15 g of potassium dichromate and 30 ml of concentrated sulfuric acid in 150 ml of water, and the substances were made visible by charring them at 180°. Tritylated compounds appeared as yellow spots after spraying and heating. Some of the unsaturated intermediates and final products were purified by preparative tlc. Samples of 150–200 mg were conveniently separated from by-products on one 20 × 20 cm plate coated with a 1-mm layer of silica gel G. After developing, as described above, the bands were detectable without the use of a spray reagent and were scraped off. The products were eluted with several portions of dry ether.

Reactions involving unsaturated compounds were carried out in an atmosphere of purified nitrogen. Extractions were done with freshly distilled solvents and oxygen-free water.

1-Alkoxy-3-trityloxy-2-propanols I–III.—Starting with alkyl glyceryl-(1) ethers, tritylation was conducted as described for the preparation of I.

1-Hexadecyloxy-3-trityloxy-2-propanol (I).—Hexadecyl glyceryl-(1) ether[2] (7.9 g, 25 mmoles), 8.4 g (30 mmoles) of triphenylchloromethane (Fluka, No. 58061), and 40 ml of dry pyridine were placed in a round-bottom flask fitted with reflux condenser and calcium chloride tube. The mixture was heated in an oil bath at 100° for 12 hr. After cooling, 300 ml of ether and 150 ml of ice-cold water were added, and the reaction mixture was transferred into a separatory funnel. The separated ether phase was washed consecutively with 50 ml of ice water, 0.5 *N* sulfuric acid (until acidic), 50 ml of water, 1% potassium carbonate solution (until basic), and 50 ml of water, and was dried over anhydrous sodium sulfate. A second extraction of the combined aqueous phases increased the yield slightly.

The solvent was evaporated, the residue was treated with 150 ml of warm petroleum hydrocarbon (Skellysolve F) and the solution was cooled in the refrigerator. After separation of 300–400 mg of hexadecyl glyceryl-(1) ether, the filtrate was evaporated, and the residue was recrystallized from 20 ml of ethyl acetate at −30°, yielding 8.2 g (59%) of I, mp 49°.

Anal. Calcd for $C_{38}H_{54}O_3$: C, 81.67; H, 9.74; O, 8.59. Found: C, 81.63; H, 9.59; O, 8.74.

1-Octadecyloxy-3-trityloxy-2-propanol (II).—A procedure described by Verkade and Stegerhoek[11] was modified according to the preparation of I, yielding 77% of II after recrystallization from ethyl acetate, mp 55.5–56° (lit[11] mp 57–58°).

Anal. Calcd for $C_{40}H_{58}O_3$: C, 81.86; H, 9.96; O, 8.18. Found: C, 81.96; H, 9.76; O, 8.33.

1-*cis*-9-Octadecenyloxy-3-trityloxy-2-propanol (III).—*cis*-9-Octadecenyl glyceryl-(1) ether[2] (10.2 g, 30 mmoles) and 10.0 g (36 mmoles) of triphenylchloromethane were heated in 40 ml of dry pyridine at 100° for 12 hr, using a 250-ml, three-necked flask with inlet and outlet tubes for purified nitrogen. After extraction and evaporation of the solvent (see preparation of I), the slightly yellow residue was dissolved in 100 ml of Skellysolve F, the solution was kept in the freezer at −30°, and the precipitate of unreacted glyceryl-(1) ether was separated on a chilled Büchner funnel at −30°.

Evaporation of the filtrate yielded 15.8 g (91%) of III. This product was difficult to purify by recrystallization, but the crude material was pure enough for further reactions. A sample for elemental analysis was obtained by preparative tlc.

(14) H. H. O. Schmid, H. K. Mangold, and W. O. Lundberg, *Microchem. J.*, **7**, 287 (1963); R. W. Fischer and H. H. O. Schmid, "Standard Methods of Chemical Analysis," Vol. 3, F. J. Welcher, Ed., D. Van Nostrand Co., Inc., Princeton, N. J., in press.

(15) C. Reichert, Optische Werke A. G., Wien 17, Austria.

Anal. Calcd for $C_{40}H_{56}O_3$: C, 82.14; H, 9.65; O, 8.21. Found: C, 81.83; H, 9.97; O, 8.36.

2,3-Dialkoxy-1-propanols IV–XIV.—The synthesis of VIII is described in detail. All other compounds were prepared under the same conditions, working under nitrogen in the case of compounds XI–XIV. The yields and characteristic data of compounds IV–XIV are quoted in Table I.

2-Hexadecyloxy-3-octadecyloxy-1-propanol (VIII).—In a 250-ml, three-necked flask, fitted with water-separation head, reflux condenser, dropping funnel, calcium chloride tubes, magnetic stirrer, and heating mantle, were placed 3.0 g of powdered potassium hydroxide, 80 ml of xylene, and 3.5 g (6 mmoles) of tritylated octadecyl glyceryl-(1) ether II. The mixture was refluxed for 1 hr to remove water by azeotropic distillation. Hexadecyl methanesulfonate[2] (2.1 g, 6.6 mmoles) dissolved in 20 ml of xylene was added dropwise, and refluxing was continued for 6–8 hr. After removing about 50 ml of xylene by distillation, cooling, and addition of 100 ml of water and 150 ml of ether, the water phase was extracted twice with 100 ml of ether. Drying the organic phase over anhydrous potassium carbonate and evaporation yielded 2-hexadecyloxy-3-octadecyloxy-1-trityloxypropane.

This product was dissolved in 100 ml of 95% methanol, a stream of hydrogen chloride was led through the vigorously stirred reaction mixture and refluxing was continued for 5–6 hr. The solvent was removed by distillation, 100 ml of water and 200 ml of ether were added, and the phases were separated in a 1-l funnel. After a second extraction with 100 ml of ether, the combined organic layers were washed consecutively with 50 ml of water, 1% potassium carbonate solution (until basic), and 50 ml of water, and were dried over anhydrous sodium sulfate. The solvent was evaporated. The residue was taken up in 80 ml of Skellysolve F, and the precipitate of triphenylcarbinol formed on storing the solution in the refrigerator was filtered off and was washed with a small amount of ice-cold Skellysolve F. Crystallization from the filtrate at freezer temperature (−30°), separation on a Büchner funnel, and recrystallization first from ethanol, then from Skellysolve F, yielded 3.0 g (88%) of VIII, mp 58.5–59°.

Compound XI was collected at −30° on a chilled Büchner funnel. The unsaturated compounds XIII and XIV were preferably purified by preparative tlc.

1,2,3-Trialkoxypropanes XV–XIX.—Compounds XV–XVIII were prepared from alkyl glyceryl-(1) ethers by alkylation with 2 equiv of alkyl methanesulfonates; XIX was obtained from VIII by alkylation with 1 equiv of methanesulfonate. The procedure used is described for the synthesis of XVIII.

1-Dodecyloxy-2,3-dioctadecyloxypropane (XVIII).—Powdered potassium hydroxide (3.0 g), 80 ml of xylene, and 0.8 g (3.1 mmoles) of dodecyl glyceryl-(1) ether[2] were refluxed in a 250-ml, three-necked flask equipped as described for the preparation of VIII. After 1 hr a xylene solution of 2.4 g (6.8 mmoles) of octadecyl methanesulfonate[2] was added dropwise, and refluxing was continued for 5–6 hr. The extraction was carried out in a similar manner to that with VIII.

The residues of XV–XIX obtained after evaporation of the solvents were purified from contaminating dialkyl ether, dialkyl glyceryl ethers, and other by-products by adsorption chromatography in columns according to Hirsch and Ahrens.[13] Samples of 500 mg were fractionated on 36 g of silicic acid.[16] After checking 20-ml subfractions of fraction 3 by tlc, evaporation of the solvents and recrystallization of the residues from Skellysolve F at −30°, 150–250 mg of pure trialkyl glyceryl-(1,2,3) ethers were obtained. The yields and physical properties of XV–XIX are summarized in Table II.

The by-products formed during the synthesis of the trialkyl glyceryl ethers were isolated and identified. Fractions 1 and 2 contained dioctadecyl ether (mp 61.5°). 2,3-Dioctadecyloxy-1-propanol (IX) was isolated from fraction 5 (mp 64–65°). The characterization data (infrared spectrum, R_f value, melting point) of these compounds were identical with those of reference materials.

1,3-Dioctadecyloxy-2-propanol was obtained from fraction 4 after recrystallization from Skellysolve F: mp 63–63.5°.

Anal. Calcd for $C_{39}H_{80}O_3$: C, 78.46; H, 13.51; O, 8.04. Found: C, 78.34; H, 13.27; O, 8.66.

Alkylation of the products isolated from fractions 4 and 5 with octadecyl methanesulfonate, as described for XVIII, and purification by preparative tlc led to identical compounds (infrared spectrum, R_f 0.7), which were shown to be 1,2,3-trioctadecyloxypropane (XVI).

Acknowledgment.—The authors are indebted to Dr. J. R. Chipault and Mr. W. Deutsch for recording infrared spectra, and to Mr. L. L. Jones for skilled technical assistance.

(16) Bio-Rad Laboratories, Richmond, Calif.

Catalpa Glycosides. III.[1,2] The Structure of Catalposide

J. M. BOBBITT, D. W. SPIGGLE,[3] S. MAHBOOB, H. SCHMID, AND W. VON PHILIPSBORN

Department of Chemistry, University of Connecticut, Storrs, Connecticut, and Organic Chemistry Institute, University of Zürich, Zürich, Switzerland

Received August 26, 1965

Catalposide and its derivatives have been degraded by acidic and basic hydrolysis. Through a study of the chemical properties and the n.m.r. spectra of catalposide, its derivatives, and its degradation products, structure **1** is proposed for the compound.

Catalposide is the major glucoside of the *Catalpa* genus.[4] It has been shown to be a β-D-glucoside and an ester of *p*-hydroxybenzoic acid.[4] Furthermore, it contains one additional hydroxyl group and one easily reduced double bond.[4] Additional structures **1a**[5] and **1b**[6] have been proposed for catalposide (see Chart I). Structure **1** is now proposed for the compound.

Structure **1a** was based primarily on the alleged presence of seven hydroxyl groups in catalposide and its reduction to a derivative,[7] **2**, of aucubin (**11**)[8,9] with lithium and liquid ammonia. After an n.m.r. study, **1b** was suggested.[6] The major differences between **1** and **1a–1b** lie in the number of double bonds and the

(1) Portions of this work have been published in a preliminary communication which is paper II of the series: J. M. Bobbitt, D. W. Spiggle, S. Mahboob, H. Schmid, and W. von Philipsborn, *Tetrahedron Letters*, 321 (1962). Furthermore, the work was discussed at the 1962 I.U.P.A.C. Natural Products Symposium in Brussels, Belgium.

(2) This work was sponsored, in part, by the Cancer Institute of the National Institutes of Health, Public Health Service, Grants CY-4015 and CY-4512, and by the National Science Foundation through a regular postdoctoral fellowship given to J. M. Bobbitt in 1959–1960. The work of H. Schmid and W. von Philipsborn was sponsored by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forchung.

(3) Deceased, 1964.

(4) For a historical summary, see J. M. Bobbitt, H. Schmid, and T. B. Africa, *J. Org. Chem.*, **26**, 3090 (1961).

(5) W. H. Lunn, D. W. Edward, and J. T. Edward, *Chem. Ind.* (London), 1488 (1961).

(6) W. H. Lunn, D. W. Edward, and J. T. Edward, *Can. J. Chem.*, **40**, 104 (1962).

(7) J. Grimshaw and H. R. Juneja, *Chem. Ind.* (London), 656 (1960); A. J. Birch, J. Grimshaw, and H. R. Juneja, *J. Chem. Soc.*, 5194 (1961).

(8) J. Fujise, H. Obara, and H. Uda, *Chem. Ind.* (London), 289 (1960).

(9) M. W. Wendt, W. Haegele, E. Simonitsch, and H. Schmid, *Helv. Chim. Acta*, **43**, 1440 (1960).