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The Synthesis of Some Ethers and Mixed Ether Esters of Glycerol

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Abstract

The syntheses of various monoethers of glycerol, the derived diesters and two triethers are reported. As well, one of the chiral ether diesters of glycerol has been prepared in both optically active forms.

We have recently reported the effect of added mono- and tri-acylglycerols on the removal from plasma of chylomicron-like emulsions injected intravenously in rats.[1,2] To expand the scope of this work we required a range of monoethers of glycerol, the derived diesters, and some triethers of glycerol, and it is the synthesis of some of these molecules that is presented here.

Our first target was the simple 2-*O*-octadecylglycerol (1), obviously available from 1,3-*O*-benzylideneglycerol (2). Thus, glycerol was converted into a mixture of benzylideneglycerols by treatment with benzaldehyde/sulfuric acid in benzene at reflux,[3,4] and *cis*-1,3-*O*-benzylideneglycerol (3) was isolated in 42% yield—the key to success here was the use of pure reagents and solvents. Alkylation of (3) with octadecyl bromide under basic conditions to form (4) was never satisfactory, with the product of elimination, namely octadec-1-ene, always being present in varying amounts. The formation of this alkene, however, could be essentially avoided by using octadecyl methanesulfonate as the alkylating agent.[5] Treatment of (4) with methanol containing a few drops of concentrated hydrochloric acid then gave the desired diol (1).[6]

In a similar sequence, the 2-*O*-octadecenylglycerol (5) was prepared by alkylation of (3) with (*Z*)-octadec-9-enyl methanesulfonate and sodium

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[1] Mortimer, B.-C., Simmonds, W. J., Joll, C. A., Stick, R. V., and Redgrave, T. G., *J. Lipid Res.*, 1988, **29**, 713.

[2] Mortimer, B.-C., Simmonds, W. J., Joll, C. A., Stick, R. V., and Redgrave, T. G., *Biochim. Biophys. Acta*, 1989, **1002**, 359.

[3] Baggett, N., Brimacombe, J. S., Foster, A. B., Stacey, M., and Whiffen, D. H., *J. Chem. Soc.*, 1960, 2574.

[4] Serdarevich, B., *J. Am. Oil Chem. Soc.*, 1967, **44**, 381.

[5] Baumann, W. J., and Mangold, H. K., *J. Org. Chem.*, 1966, **31**, 498.

[6] Davies, W. H., Heilbron, I. M., and Jones, W. E., *J. Chem. Soc.*, 1934, 1232.

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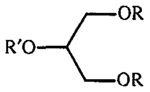
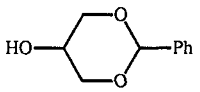
hydride/dimethylformamide (76%), or utilizing potassium hydroxide/benzene (89%), to give (6), followed by removal of the benzylidene protecting group (methanol/conc. HCl, 79%; or sodium in liquid ammonia, 63%). The material so obtained was essentially pure by t.l.c. and ^1H and ^{13}C n.m.r. spectroscopy, but a satisfactory elemental analysis was never obtained.

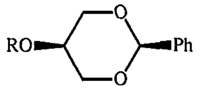
For the synthesis of triethers of glycerol such as (7), the direct alkylation of glycerol was unsuccessful. However, a successful preparation of (7) was achieved by treatment of the diol (1) with octadecyl methanesulfonate in benzene in the presence of potassium hydroxide. Similarly, the diol (5) was converted into the triether (8) by treatment with (*Z*)-octadec-9-enyl methanesulfonate/potassium hydroxide/benzene.



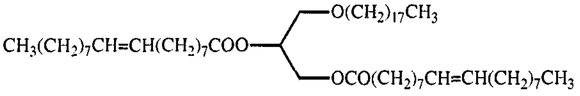
	R'	R
(1)	$(CH_2)_{17}CH_3$	H
(5)	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	H
(7)	$(CH_2)_{17}CH_3$	$(CH_2)_{17}CH_3$
(8)	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$
(9)	$(CH_2)_{17}CH_3$	$CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$
(10)	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	$CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$



(2)

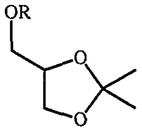


(3) R = H
(4) R = $(CH_2)_{17}CH_3$
(6) R = $(CH_2)_8CH{=}CH(CH_2)_7CH_3$

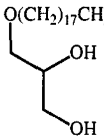


(11)

(*Z*) double bond throughout



(12) R = H
(13) R = $(CH_2)_{17}CH_3$



(14)

For the synthesis of mixed ether esters of glycerol, the diols (1) and (5) were treated with (*Z*)-octadec-9-enoic acid (oleic acid) in carbon tetrachloride in the presence of *N,N'*-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine[7] to yield (9) and (10), respectively, in good yields. Also required was the regioisomer of (9), namely (11), and this was prepared in good yield from the alcohol (12) by alkylation to (13), hydrolysis to (14) and acylation. As (11) is a chiral molecule it was of interest for further physiological studies to prepare both enantiomers, and this was easily done from (+)- and (−)-(12).

Experimental

Experimental details have been given previously.[8]

cis-1,3-O-Benzylidene-2-O-(Z)-octadec-9'-enylglycerol (6)

(A) To a stirred suspension of petrol-washed sodium hydride (120 mg of 80%, 4 mmol) in dry dimethylformamide (3 ml) under argon was added *cis*-1,3-*O*-benzylideneglycerol (3)

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[7] Neises, B., and Steglich, W., *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.

[8] Rodriguez, E. B., and Stick, R. V., *Aust. J. Chem.*, 1990, **43**, 665.

(360 mg, 2 mmol) in dry dimethylformamide (3 ml). After stirring at room temperature (20 min) the mixture was heated at 60° (bath temperature; 20 min). The reaction mixture was then cooled to room temperature and (*Z*)-octadec-9-enyl methanesulfonate (690 mg, 2 mmol) added. After heating at 60° (17 h) the reaction mixture was cooled and methanol (1 ml) added. Normal workup with ethyl acetate gave a yellow oil (890 mg). Flash chromatography (EtOAc/petrol, 2:8) then gave the *unsaturated ether* (6) as a colourless oil (650 mg, 76%) (Found: C, 77·9; H, 10·5. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%). ^{1}H n.m.r. (60 MHz, CCl_4) δ 0·7–2·2, m, CH_2, Me; 3·0–3·2, m, OCH; 3·2–3·6, m, $CH_2\mathbf{CH_2}OCH$; 3·6–4·3, m, 4H, CH_2O; 5·1–5·4, m, CH=CH; 5·30, s, Ph**CH**; 7·0–7·4, m, Ph.

(B) A stirred suspension of *cis*-1,3-*O*-benzylideneglycerol (3) (460 mg, 2·55 mmol) and finely powdered potassium hydroxide (2 g) in dry benzene (40 ml) at reflux under argon was treated with (*Z*)-octadec-9-enyl methanesulfonate (910 mg, 2·6 mmol) to give, after workup, a yellow oil (1·14 g). This was subjected to flash chromatography (EtOAc/petrol, 1:9) twice to give the unsaturated ether (6) as a colourless oil (980 mg, 89%).

2-O-(Z)-*Octadec-9′-enylglycerol (5)*

(A) Compound (6) (650 mg) in methanol (10 ml) containing concentrated hydrochloric acid (3 ml) was heated under reflux (20 h) under argon and then cooled. The solvent was removed under reduced pressure and residual hydrochloric acid was removed as an azeotrope with toluene to give a yellow oil (580 mg). Flash chromatography (EtOAc/petrol, 7:3) gave the diol (5) as a colourless oil (410 mg, 79%).[9] ^{1}H n.m.r.[10] (80 MHz) δ 0·52–2·19, m, CH_2, Me; 3·31–3·91, m, 9H, CH_2OH, CH_2OCH; 5·25–5·50, m, CH=CH. ^{13}C n.m.r. (20·1 MHz) δ 14·1, Me; 22·7, $\mathbf{C}H_2Me$; 26·2–32·0, CH_2; 63·1, CH_2OH; 70·3, $\mathbf{C}H_2OCH$; 79·8, OCH; 130·0, 130·1, CH=CH.

(B) A solution of compound (6) (800 mg, 1·9 mmol) in diethyl ether (4 ml) was dispersed in liquid ammonia (40 ml) with vigorous stirring. Sodium (200 mg, 9 mmol) was added in small pieces, the solution being allowed to decolorize before each successive piece was added, until a persistent blue colour (30 min) indicated completion of the reaction. Ammonium chloride was added and the solvent left to evaporate. The solid residue was extracted with dichloromethane; the extract was filtered and evaporated to give a yellow oil (640 mg). Flash chromatography (EtOAc/petrol, 1:1) gave the diol (5) as a colourless oil (400 mg, 63%). The ^{1}H n.m.r. spectrum was identical to that reported in (A).

Tri-O-(Z)-*octadec-9′-enylglycerol (8)*

A stirred suspension of compound (5) (420 mg, 1·2 mmol) and finely powdered potassium hydroxide (1 g) in dry benzene (30 ml) under argon was treated with (*Z*)-octadec-9-enyl methanesulfonate (1·3 g, 3·8 mmol) to give a yellow oil (1·35 g). Radial chromatography (EtOAc/petrol, 1:49, 1:19, 1:9) then gave the *unsaturated triether* (8) as a colourless oil (970 mg, 96%) (t.l.c., EtOAc/petrol, 2:8, R_F 0·7) (Found: C, 80·9; H, 13·2. $C_{57}H_{110}O_3$ requires C, 81·2; H, 13·1%). ^{1}H n.m.r. (60 MHz, CCl_4) δ 5·1–5·4, m, CH=CH. ^{13}C n.m.r. (20·1 MHz) δ 14·1, Me; 22·7, $\mathbf{C}H_2Me$; 26·1–31·9, CH_2; 70·6, 70·8, 71·6, $\mathbf{C}H_2OCH$, $CH_2CH_2O\mathbf{C}H_2$; 77·9, OCH; 129·8, 129·9, CH=CH.

1,3-Di-O-(Z)-*octadec-9′-enoyl-2*-O-*octadecylglycerol (9)*

To a stirred solution of 2-*O*-octadecylglycerol (1) (1·20 g, 3·5 mmol), oleic acid (2·24 g, 8·0 mmol) and 4-(dimethylamino)pyridine (85 mg, 0·7 mmol) in dry carbon tetrachloride (18 ml) under argon was added a solution of *N,N′*-dicyclohexylcarbodiimide (1·63 g, 8·0 mmol) in dry CCl_4 (7 ml). After stirring for 20 h, the reaction mixture was cooled (0°), water added (2 ml), and the precipitate of *N,N′*-dicyclohexylurea removed by filtration. The filtrate was washed with dilute hydrochloric acid, saturated sodium bicarbonate, brine and dried ($MgSO_4$). Evaporation then yielded a colourless oil (3·0 g), and flash chromatography (EtOAc/petrol,

[9] Gupta, S. C., and Kummerow, F. A., *J. Org. Chem.*, 1959, **24**, 409.
[10] Wood, R., and Snyder, F., *Lipids*, 1967, **2**, 161.

1:9) followed by radial chromatography (EtOAc/petrol, 1:19) gave the *ether diester* (9) as a colourless oil (2·11 g, 69%) (Found: C, 78·5; H, 12·5. $C_{57}H_{108}O_5$ requires C, 78·4; H, 12·5%). ^{1}H n.m.r. (80 MHz) δ 0·72–2·19, m, CH_2, Me; 2·19–2·46, m, 4H, $CH_2\mathbf{CH_2}COO$; 3·44–3·82, m, CH_2OCH; 4·03–4·25, m, 4H, CH_2OCO; 5·12–5·44, m, 4H, CH=CH. ^{13}C n.m.r. δ 14·1, Me; 22·8–32·0, CH_2; 34·3, $CH_2\mathbf{C}H_2COOCH_2$; 63·2, $\mathbf{C}H_2OCO$; 70·8, $\mathbf{C}H_2OCH$; 75·4, OCH; 129·9, 130·2, CH=CH; 173·7, C=O.

1,3-Di-O-(Z)-*octadec-9′-enoyl-2*-O-(Z)-*octadec-9″-enylglycerol (10)*

The above acylation procedure was followed on 2-*O*-(*Z*)-octadec-9-enylglycerol (5) (400 mg) except that the reaction mixture was heated (45°). Workup yielded the crude product as a yellow oil (1·06 g). Flash chromatography (EtOAc/petrol, 2:8) gave the *ether diester* (10) as a colourless oil (840 mg, 83%) (Found: C, 78·4; H, 12·5. $C_{57}H_{106}O_5$ requires C, 78·6; H, 12·3%). ^{1}H n.m.r. (80 MHz) δ 0·75–2·48, m, CH_2; 3·44–3·88, m, CH_2OCH; 4·06–4·25, m, 4H, CH_2OCO; 5·12–5·50, m, 6H, CH=CH. ^{13}C n.m.r. (20·1 MHz) δ 14·2, Me; 22·8–34·2, CH_2; 63·2, $\mathbf{C}H_2OCO$; 70·8, $\mathbf{C}H_2OCH$; 75·4, OCH; 129·9, 130·2, CH=CH; 173·6, C=O.

(S)-*1,2-Di*-O-(Z)-*octadec-9′-enoyl-3*-O-*octadecylglycerol*

(*R*)-1-*O*-Octadecylglycerol[11] (1·40 g) was treated with oleic acid, *N,N′*-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine in CCl_4 as before to yield a colourless oil (4·18 g). Gradient elution flash chromatography (EtOAc/petrol, 1:99, 1:49, 1:19, 1:9) gave (S)-*1,2-di*-O-(Z)-*octadec-9′-enoyl-3*-O-*octadecylglycerol* as a colourless oil (2·22 g, 63%), $[\alpha]_D$ +4·6° (Found: C, 78·5; H, 12·5. $C_{57}H_{108}O_5$ requires C, 78·4; H, 12·5%). ^{1}H n.m.r. (60 MHz, CCl_4) δ 0·7–2·4, m, CH_2; 3·1–3·6, m, CH_2OCH_2; 3·7–4·5, m, CH_2OCO, CHOCO; 4·8–5·3, m, 4H, CH=CH. ^{13}C n.m.r. (20·1 MHz) δ 14·1, Me; 22·8–32·0, CH_2; 34·4, $\mathbf{C}H_2COOCH$, $CH_2\mathbf{C}H_2COOCH_2$; 62·9, $CH_2\mathbf{C}H_2OCH_2$; 69·1, CH_2O; 70·3, OCH; 71·9, $\mathbf{C}H_2OCO$; 129·9, 130·2, CH=CH; 173·2, 173·6, C=O.

(R)-*1,2-Di*-O-(Z)-*octadec-9′-enoyl-3*-O-*octadecylglycerol*

(*S*)-1-*O*-Octadecylglycerol[11] (1·0 g) was esterified as above with oleic acid to give a pale yellow oil (3·36 g). Flash chromatography (EtOAc/petrol, 1:49) gave (R)-*1,2-di*-O-(Z)-*octadec-9′-enoyl-3*-O-*octadecylglycerol* as a colourless oil (2·50 g, 99%), $[\alpha]_D$ −4·6° (Found: C, 78·2; H, 12·5%).

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[11] Baer, E., and Fischer, H. O. L., *J. Biol. Chem.*, 1941, **140**, 397.