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The Synthesis of Some Esters of Glycerol with Special Attention to the Problem of Acyl Migration

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Abstract

Various triglycerides have been prepared by the acylation of either *cis*-1,3-*O*-benzylideneglycerol or 2,3-*O*-isopropylideneglycerol, followed by removal of the protecting group and acylation of the resultant diol. Alternatively, acylation of dihydroxyacetone, reduction of the intermediate ketone with sodium cyanoborohydride (pH 4) and acylation of the resultant alcohol also provide triglycerides in good yields. In some of these esters of glycerol, ^{13}C n.m.r. spectroscopy (125·7 MHz) was used to monitor potential acyl migration. Finally, 2-halopyridinium salts were investigated as an alternative to the normal dicyclohexylcarbodiimide/dimethylaminopyridine couple for glycerol esterification.

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] Further to our work on the synthesis of some ethers and mixed ether esters of glycerol,[3] we present here our results on the preparation of the glycerol esters required for the above studies.

The first ester required[2] was 2-*O*-octadecanoylglycerol (1) and, to this end, the acylation of *cis*-1,3-*O*-benzylideneglycerol (2) with stearic acid/dicyclohexylcarbodiimide/dimethylaminopyridine gave the ester (3).[4] Hydrogenation of (3) over palladium on charcoal then gave the ester (1),[4] the purity of which was confirmed by ^{13}C n.m.r. spectroscopy (δ 61·4, 2C, CH_2OH; 74·9, CHO). Acylation of 2-*O*-octadecanoylglycerol (1) with oleic acid next gave the triester (4),[5] one of the main compounds necessary for our physiological studies.[1] A

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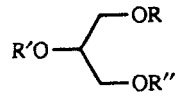
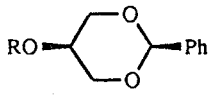


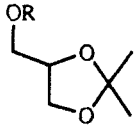
	R	R′	R″
(1)	H	$CH_3(CH_2)_{16}CO$	H
(4)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{16}CO$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$
(5)	$CH_3(CH_2)_{16}CO$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$
(6)	$CH_3(CH_2)_{16}CO$	H	H
(10)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	H	H
(11)	H	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	H
(12)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{12}CO$	$CH_3(CH_2)_{12}CO$
(13)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{14}CO$	$CH_3(CH_2)_{14}CO$
(14)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{16}CO$	$CH_3(CH_2)_{16}CO$
(15)	$CH_3(CH_2)_{12}CO$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{12}CO$
(16)	$CH_3(CH_2)_{14}CO$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{14}CO$
(17)	$CH_3(CH_2)_{16}CO$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	$CH_3(CH_2)_{16}CO$
(19)	$CH_3(CH_2)_{12}CO$	H	$CH_3(CH_2)_{12}CO$
(20)	$CH_3(CH_2)_{12}CO$	$CH_3(CH_2)_{12}CO$	H
(23)	$CH_3(CH_2)_{14}CO$	H	$CH_3(CH_2)_{14}CO$
(24)	$CH_3(CH_2)_{16}CO$	H	$CH_3(CH_2)_{16}CO$
(26)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$	H	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$



R

(2) H

(3) $CH_3(CH_2)_{16}CO$

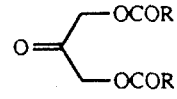


R

(7) H

(8) $CH_3(CH_2)_{16}CO$

(9) $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$



R

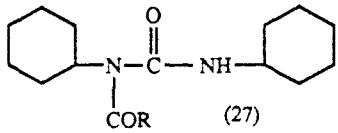
(18) $CH_3(CH_2)_{12}$

(21) $CH_3(CH_2)_{14}$

(22) $CH_3(CH_2)_{16}$

(25) $CH_3(CH_2)_7CH{=}CH(CH_2)_7$

(Z) double bond throughout



(27)

careful inspection of the ^{13}C n.m.r. (125·7 MHz) spectrum of (4) showed it to contain less than 5% of the isomeric triglyceride (5), presumably formed via the sequence (1) → (6) → (5). A sample of pure (5) was available from the acylation of 2,3-*O*-isopropylideneglycerol (7) with stearic acid to give (8),[6] subsequent treatment with concentrated hydrochloric acid in methanol/ether to give 1-*O*-octadecanoylglycerol (6),[7] and acylation with oleic acid.[5]

We next required a series of triglycerides with an oleic acid residue at one terminus of the glycerol moiety and, to this end, the acylation of the alcohol (7) with oleic acid gave (9).[5] Removal of the isopropylidene group by means of the concentrated hydrochloric acid procedure appeared to give the desired diol (10), contaminated by some 10% of the product of acyl migration, the symmetrical diol (11) (^{13}C n.m.r.). A simple low-temperature recrystallization of the mixture then gave the pure diol (10).[8] Acylation of (10) with myristic, palmitic and stearic acids then gave the desired series of triglycerides (12)–(14),[8] with no evidence of acyl migration during the final acylation step (^{13}C n.m.r., carbonyl region). For the related symmetrical triglycerides (15)–(17), acylation of dihydroxyacetone with myristic acid gave the ketone (18), and subsequent reduction with 'neutral' sodium borohydride[9] gave the alcohol (19),[10] apparently contaminated with a small amount of the product of acyl migration, the alcohol (20) (t.l.c., ^{13}C n.m.r.). An alternative reduction of the ketone (18) with sodium cyanoborohydride in tetrahydrofuran at pH 4 gave only the alcohol (19) in almost quantitative yield. Similarly, the ketones (21)[9] and (22)[11] were prepared and converted into the alcohols (23) and (24)[10] by the new reduction procedure, and acylation of the alcohols (19), (23) and (24) with oleic acid gave the desired triglycerides (15)–(17),[12] with no evidence of acyl migration in the final step (^{13}C n.m.r.). The procedure was also used to convert dihydroxyacetone into the previously prepared triglyceride (4), via the ketone (25) and the alcohol (26).[9]

In some of the above acylation reactions the formation of a small amount of the *N*-acylurea (27)[13] both lowered the yield of the required ester and complicated the workup procedure. Therefore, in view of some of Mukaiyama's work with 2-halopyridinium salts,[14] we treated the alcohol (7) with stearic acid in the presence of 2-chloro-1-methylpyridinium iodide and triethylamine, and the ester (8) was formed in moderate yield. Similarly the ester (9) was prepared from the alcohol (7), and the two triglycerides (17) and (4) were obtained from the alcohols (24) and (26), respectively. It is possible that the use of 2-bromo-1-ethylpyridinium tetrafluoroborate may increase the yields of the above acylations.[14]

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Experimental

Experimental details have been given previously.[15] The ^{13}C n.m.r. spectra at 125·7 MHz were recorded on a Varian XR500 spectrometer. Representative experiments for the acylations and reductions are given below.

2,3-O-Isopropylidene-1-O-octadecanoylglycerol (8)

(A) To a stirred solution of 2,3-*O*-isopropylideneglycerol (7) (1·5 g, 11 mmol), stearic acid (3·4 g, 12 mmol) and dimethylaminopyridine (130 mg, 1·1 mmol) in dry carbon tetrachloride (30 ml) under argon was added a solution of dicyclohexylcarbodiimide (2·5 g, 12 mmol) in dry carbon tetrachloride (20 ml). After stirring at room temperature (5 h) the reaction mixture was cooled in ice and filtered (Celite). The filtrate was concentrated to give a white solid (5·1 g). Gradient-elution flash chromatography (petrol to EtOAc/petrol, 1 : 19) gave the ester (8) as a white solid (4·1 g, 90%). Recrystallization of a small portion of the solid gave fine white needles, m.p. 39–40° (EtOH) (lit.[6] 40–41°).

(B) To a stirred suspension of freshly prepared 2-chloro-1-methylpyridinium iodide[14] (610 mg, 2·4 mmol) in dry CH_2Cl_2 (2 ml) was added a solution of 2,3-*O*-isopropylideneglycerol (7) (260 mg, 2·0 mmol), stearic acid (620 mg, 2·2 mmol) and triethylamine (490 mg, 4·8 mmol) in dry CH_2Cl_2 (2 ml) under an argon atmosphere. The mixture was heated at reflux overnight and then poured into water, and extracted with dichloromethane. The combined extracts were washed with 0·1 M HCl, dried, filtered and evaporated to yield an orange solid. Rapid silica chromatography (EtOAc/petrol, 2 : 8) gave a white solid (530 mg). Recrystallization gave the ester (8) as fine white needles (460 mg, 60%), m.p. 41–42°.

Tetradecanoic Acid 2-Oxopropane-1,3-diyl Ester (18)

To a stirred solution of dihydroxyacetone (450 mg, 5·0 mmol), dimethylaminopyridine (1·22 g, 10 mmol) and myristic acid (2·5 g, 11 mmol) in dry CCl_4 (25 ml) and dry CH_2Cl_2 (25 ml) was added dicyclohexylcarbodiimide (2·27 g, 11 mmol) in dry CCl_4 (5 ml). After stirring overnight the reaction mixture was cooled (0°) and filtered (Celite), and the residue washed with CH_2Cl_2. Normal workup and recrystallization gave the *ketone* (18) as white plates (1·8 g, 71%), m.p. 76° (EtOH) (Found: C, 72·7; H, 11·5. $C_{31}H_{58}O_5$ requires C, 72·9; H, 11·4%). ^{13}C n.m.r. (20·1 MHz, $CDCl_3$) δ 14·0, 2C, Me; 67·0, 2C, $\mathbf{C}H_2OCO$; 173·0, 2C, $CH_2O\mathbf{C}O$; 199·0, $CH_2\mathbf{C}OCH_2$.

1,3-Di-O-tetradecanoylglycerol (19)

(A) *Reduction with sodium borohydride.*[9]—The ketone (18) (200 mg, 0·40 mmol) was dissolved in tetrahydrofuran (5 ml) and water (0·5 ml), and the solution cooled (0°). 'Neutral'[9] sodium borohydride (15 mg, 0·40 mmol) was added portionwise to the stirred solution. After 15 min, t.l.c. indicated no starting material to be present, and glacial acetic acid was added dropwise until the mixture was acidic. The reaction mixture was subsequently poured into water, and extracted with dichloromethane. Normal workup (without washing with 0·1 M HCl) and rapid silica chromatography (EtOAc/petrol, 2 : 8) gave a mixture of the alcohols (19) and (20) (180 mg), as assessed by t.l.c. [EtOAc/petrol, 2 : 8; R_F 0·26 for (19) and 0·18 for (20)] and identified by ^{13}C n.m.r. spectroscopy. ^{13}C n.m.r. (75·5 MHz, $CDCl_3$) δ 14·1, 2C, Me; 65·0, 2C, $\mathbf{C}H_2OCO$; 68·4, CHOH; 173·9, 2C, OCO for (19); minor signals due to (20) identified as δ 61·5, 62·0, $\mathbf{C}H_2OCO$, CH_2OH; 72·1, $\mathbf{C}HOCO$. Recrystallization then gave the alcohol (19) (150 mg, 73%), m.p. 63° (MeOH) (lit.[10] 65·5°). ^{13}C n.m.r. (75·5 MHz, $CDCl_3$) δ 14·1, 2C, Me; 65·0, 2C, $\mathbf{C}H_2OCO$; 68·4, CHOH; 173·9, 2C, OCO.

(B) *Reduction with sodium cyanoborohydride.*—To a stirred solution of the ketone (18) (1·0 g, 2·0 mmol) in tetrahydrofuran (40 ml) was added $NaBH_3CN$ (135 mg, 2·2 mmol). Glacial acetic acid was immediately added dropwise until the solution was at pH 4. After 30 min, the reaction mixture was poured into water, and extracted with dichloromethane. Normal workup (without washing with 0·1 M HCl) gave the alcohol (19) as the only product as

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identified by ^{13}C n.m.r. spectroscopy. Recrystallization gave the alcohol (19) as white plates (920 mg, 90%), m.p. 64–65°.

2-O-Octadecanoyl-1,3-di-O-(Z)-octadec-9′-enoylglycerol (4)

^{13}C n.m.r. (125·7 MHz, $CDCl_3$) δ 62·064, 2C, **C**H_2OCO; 68·839, **C**HOCO; 129·682, 129·981, 4C, CH=CH; 172·845, CHO**C**O; 173·226, 2C, CH_2O**C**O.

1-O-Octadecanoyl-2,3-di-O-(Z)-octadec-9′-enoylglycerol (5)

^{13}C n.m.r. (125·7 MHz, $CDCl_3$) δ 62·048, 2C, **C**H_2OCO; 68·852, **C**HOCO; 129·652, 129·677, 129·988, 4C, CH=CH; 172·802, 173·210, 173·240, 3C, CH_2O**C**O, CHO**C**O.

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