Analogs of natural lipids. I. Synthesis and properties of tris-*homo*acyl derivatives of cyclopentane-1,2,3-triols

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Abstract A new series of analogs of triglycerides has been synthesized, in which the glycerol moiety is replaced by each of the three isomeric cyclopentanetriols. For each of the isomeric cyclopentane-1,2,3-triols (1,2,3/0; DL-1,2/3; and 1,3/2), the tris-*homo*acyl derivatives of octanoic, decanoic, lauric, myristic, palmitic, stearic, and dihydrosterculic acids were prepared by treatment of the respective triols with the appropriate acyl chloride in pyridine. The dihydrosterculates were prepared by fusing the triols with a mixture of the acyl anhydride and the corresponding potassium salt. It is proposed that because of restricted rotation of the carbon–carbon bonds the cyclopentanoid compounds are analogs of specific rotamers of triglycerides. Infrared spectra (KBr discs) obtained at room temperature show differences in crystal structure from series to series. A band near 720 cm^{-1} (CH_2 rock) is doubled in the 1,2,3/0 and 1,2/3 series and is single in the 1,3/2 series and the triglycerides. In each spectrum with a doublet at 720 cm^{-1}, a band near 1470 cm^{-1} (CH_2 bend) is doubled also. A strong band at 890 cm^{-1} present in the triglyceride spectra is weak or missing from the spectra of the analogs. A band at 1418 cm^{-1} (bending of CH_2 adjacent to C=O) present in the triglyceride spectra is demonstrable only in the 1,2/3 and 1,3/2 series. Thin-layer chromatography on silica gel shows marked differences in apparent polarity of all the 1,2,3/0 derivatives in comparison with the other three series. In all series the dihydrosterculates show a decrease in apparent polarity, relative to the stearates, significantly greater than expected from the introduction of an additional carbon atom. The potential utility of the analogs as probes of the effects of conformation on the physical properties and enzymatic susceptibility of glycerides is discussed.

Supplementary key words cyclitols · infrared spectroscopy · thin-layer chromatography · conformation of glycerides · cyclopropane fatty acids · dihydrosterculic acid · polarity of lipids

Extensive studies involving systematic alterations at specific sites in lipid molecules have already contributed to knowledge of the relationship of structure to function in these compounds and hence to the significance of their ubiquitous presence in biomembranes. For example, the structural basis for substrate specificity (or inhibition) of lipolytic enzymes has been examined by varying acyl chain length (2) and degree (2, 3) and position (3, 4) of chain unsaturation of synthetic lipids. Other enzyme studies involved the behavior of chemically modified lecithin analogs (5, 6) differing in stereochemical configuration, in the phosphate moiety, in the glycerol backbone, and in having abnormal alkyl chains. However, the design of these lipid analogs does not necessarily reflect the *molecular conformation* of the compounds in a rigorous sense. Substantial advances in the understanding of substrate specificity of lipids, and of the properties of membranes of which they are a part, may be provided by a study of lipid molecular conformation. Because of free rotation about C—C single bonds, the glycerol backbone of natural lipids can adopt, in theory, a large number of rotameric forms. Although a few of these rotamers will be energetically favored, the actual molecular conformation during any physiological involvement can only be a subject of speculation. On the other hand, cyclane triols and particularly each of the three isomeric cyclopentane-1,2,3-triols are plausible analogs of glycerol, and analogs of natural lipids based on cyclopentanetriols may per-

Abbreviations: 2,2-DMP, 2,2-dimethoxypropane; GLC, gas–liquid chromatography; TLC, thin-layer chromatography; Ip, isopropylidene $(CH_3)_2C=$; MEK, 2-butanone; TFA, trifluoroacetic acid.

Cyclic compounds described in this paper are named according to the Tentative Rules for Nomenclature of Cyclitols (1). The names are derived from those of the parent cyclanes of which they are formal derivatives; the location and disposition of the hydroxyl groups are indicated by a configurational fraction in which all the substituents on one side of the plane of the cyclane ring are assembled in the numerator, and those on the other side are assembled in the denominator. The lowest possible numbers are used in each case and no absolute configuration is implied by this fraction. When absolute configuration must be specified, a separate convention relates the lowest-numbered asymmetric center to D- or L-glyceraldehyde. For example, the enantiomer of compound **2** depicted in Fig. 1 would be designated as 1-D -(1,2/3)-cyclopentane-1,2,3-triol. We emphasize that in the present work only *meso*- or racemic substances are involved.

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mit the assessment of the rotameric state of glycerol-containing lipids to a good approximation (see Results and Discussion). We have undertaken the synthesis of such analogs of several natural series of glycerol-containing lipids, and in this paper we report the synthesis of three homologous series of analogs of the natural triglycerides (see **Fig. 1**). The backbone of each of these series of pseudotriglycerides is one of the three cyclopentane-1,2,3-triols **1a, 2a,** and **3a.** Most of the synthetic routes for these compounds have been described (7–11). The conformational aspects of cyclopentanoid cyclitols have also been studied extensively (9–11); the cyclopentanoid compounds are considerably more flexible than their cyclohexanoid analogs, and axial disposition of bulky or polar groups is often favored over equatorial disposition (see Results and Discussion).

This communication is the first in a series dealing with a systematic approach to the synthesis and the physicochemical and biochemical study of the cyclopentanoid analogs of natural lipids that is being undertaken in this laboratory. The present report deals with the synthesis of the even-numbered tris-*homo*acyl compounds C_8–C_{18} and the tris-dihydrosterculate compounds derived from the three isomeric cyclopentanetriols **1a, 2a,** and **3a.** The synthesis of the three tris-dihydrosterculates (as well as the corresponding triglyceride) was undertaken because the cyclopropyl group prevents the alkyl chain from assuming the regular zigzag conformation of an idealized hydrocarbon chain. The resulting kink in the hydrocarbon chain may be geometrically compared to that caused by a single *cis* double bond (12, 13). We can therefore simulate the effect of chain unsaturation in these compounds without concern for the lability towards peroxidizing agents characteristic of unsaturated lipids. Some of the physical and spectroscopic properties of the analogs are presented, and future directions of the work are indicated.

MATERIALS AND METHODS

Acyl chlorides, triglycerides, and methyl oleate were purchased from Nuchek Prep, Elysian, Minn. Silica gel for column chromatography was purchased from Clarkson Chemical Co., Williamsport, Pa. (Unisil, 200–325 mesh), and was used without prior activation.

Physical measurements

Infrared spectra were measured on KBr dispersions (1–1.5%) or in CS_2 (1%) with a Perkin-Elmer 237B or 621 double-beam spectrophotometer. The C—H deformation frequencies were determined at a slow scan rate on the 621 spectrophotometer using a fivefold-expanded frequency scale. The spectra were calibrated at 10-cm^{-1} intervals against the 621 digital readout, and the instrument was

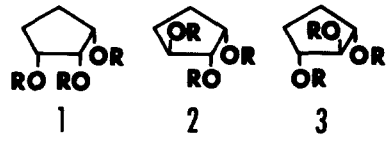


Fig. 1. Compounds described in this publication. All are based on the three diastereoisomeric cyclopentanetriols, **1a, 2a,** and **3a** (R = H). The other compounds, series b–h, are the tris-*homo*acyl derivatives of **1a, 2a,** and **3a.** In series: **b,** R = *n*-octanoyl; **c,** R = *n*-decanoyl; **d,** R = *n*-dodecanoyl (lauroyl); **e,** R = *n*-tetradecanoyl (myristoyl); **f,** R = *n*-hexadecanoyl (palmitoyl); **g,** R = *n*-octadecanoyl (stearoyl); **h,** R = $CH_3(CH_2)_7[CH(CH_2)CH](CH_2)_7CO$- (dihydrosterculoyl).

then calibrated against appropriate polystyrene absorption bands.

Melting points were determined on a Kofler micro hot stage (Arthur H. Thomas Co.) and are uncorrected. Refractive index was measured with an Abbé refractometer.

Chromatography

Gas–liquid chromatographic analysis was done with a Victoreen gas chromatograph (4000 series) using 6-ft columns of 6% SE-30 on Chromosorb W. Analytical thin-layer chromatography was carried out on silica gel layers (0.25 mm thickness) spread on 20 × 20 cm glass plates (EM Reagents, Brinkmann). For routine analysis of reaction products, these plates were cut into pieces measuring 7.5 × 2.5 cm. Epoxides were detected on plates by spraying with the reagent of Buchanan and Schwarz (14) and heating the plate to ca. 200°C. Other compounds were detected by spraying with 40% H_2SO_4 in 50% aqueous ethanol followed by charring.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

EXPERIMENTAL PROCEDURES

Synthesis of cyclopentane-1,2,3-triols

DL-(1,2/3)-Cyclopentane-1,2,3-triol **2a,** prepared by hydrolysis of the *cis*-anhydrotriol **8** (10) was shown by GLC analysis to contain 10% of the diastereoisomeric (1,3/2)-cyclopentane-1,2,3-triol **3a** (see **Chart I**). Purification was achieved by forming the isopropylidene derivative **9** (see General Methods) and partitioning the mixture between hexane and aqueous methanol (CH_3OH–H_2O 9:1). Free triol **3a** remained in the methanol and could be recovered easily. The isopropylidene compound was purified by sublimation, recrystallized from acetone (mp 49–50°C, lit. 50–52°C [10]), and hydrolyzed in 0.1 N H_2SO_4 to give the desired triol (see General Methods).

(1,3/2)-Cyclopentane-1,2,3-triol **3a** was prepared routinely by hydrolysis (10) of *trans*-anhydrotriol **7,** the latter compound being prepared by a simpler method[2] than that

[2] Powell, K. A. Unpublished experiments.

Chart I

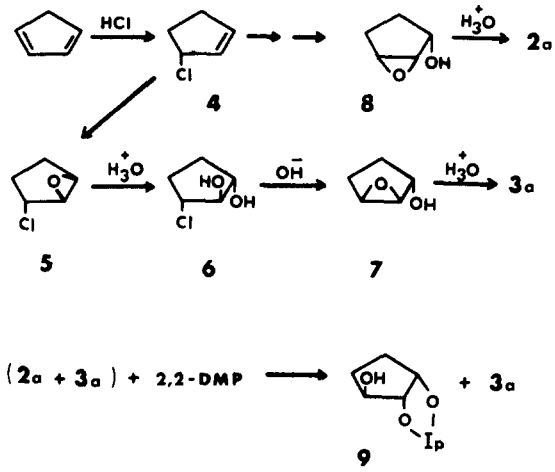
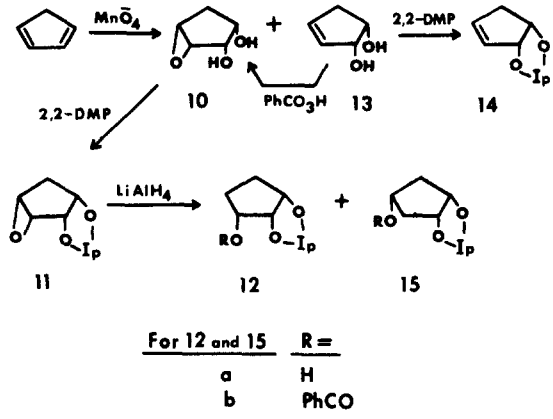


Chart II



formerly used. For the synthesis of **7**, 3-chlorocyclopentene **4** was prepared (15) and was used immediately after preparation because it decomposed rapidly on storage. A solution of 22 g of 85–87% *m*-chloroperoxybenzoic acid (108–111 mmoles) in 450 ml of chloroform was chilled and stirred at 3–5°C in a 2-l wide-mouthed brown bottle, and a solution of 10 g (98 mmoles) of **4** in 20 ml of $CHCl_3$ was added dropwise over 30 min, with magnetic stirring. Stirring was continued for 1 hr, and much *m*-chlorobenzoic acid precipitated during this time. Usually, four such preparations were carried out simultaneously. The mixtures were stored overnight at 4°C then filtered, and the filtrate was washed with 5% Na_2CO_3 (4 × 250 ml) and water (1 × 250 ml) and dried over Na_2SO_4. Chloroform was removed in a rotary evaporator, and the chlorocyclopentene oxide **5** was purified by vacuum distillation (bp 50–52°C/17 Torr); $n_D^{25} = 1.4775$; yield 7.1–7.7 g (60–65%). 10 g of 3-chlorocyclopentene-1,2-oxide **5** (85 mmoles) was hydrolyzed by heating to reflux in 500 ml of 0.2 N H_2SO_4 for 2.5 hr. The cooled solution was neutralized with 5 N KOH and cooled again to ca. 5°C; 29 g of solid KOH was added (to give a solution 1 N with respect to KOH), and the solution was stirred overnight at room temperature. The solution was cooled to ca. 5°C and carefully neutralized with 6 N H_2SO_4 (ca. 86 ml required). The neutral solution was continuously extracted with diethyl ether for 36 hr; the extract was dried with anhydrous Na_2SO_4 and evaporated to give 6.9 g of an oil (81% based on chlorocyclopentene oxide) with R_f 0.60 in chloroform–methanol–water 90:10:1. The oil was purified by vacuum distillation (bp 60–62°C/0.5 Torr).

(1,2,3/0)-Cyclopentane-1,2,3-triol **1a** was prepared[3] by reductive ring opening of the isopropylidene derivative **11** with $LiAlH_4$ (see **Chart II**). The epoxydiol **10** [DL-(1,2,3,4/0)-1,2-anhydrocyclopentane-1,2,3,4-tetrol] was generally prepared from cyclopentadiene by oxidation with $Zn(MnO_4)_2$ by the method of Sable et al. (16), with the following modifications: 33 g of cyclopentadiene (0.5 mole) dissolved in 1 l of acetone in a 3-l flask was chilled to −30°C in a dry ice–ethanol bath; a solution of 1.33 moles of $Zn(MnO_4)_2 \cdot 6\ H_2O$ (nominally 137.1 g[4]) in 500 ml of water, freshly prepared and filtered through glass wool, was added during 3 hr with vigorous mechanical stirring, and the mixture was worked up as described (16). The CH_2Cl_2 extract was concentrated in vacuo to leave a brown oil (10–14 g, 17–24%) that showed two spots on TLC in MEK–2% boric acid–glacial acetic acid 9:1:1 (16). The R_f of the major epoxide-positive (14) spot was 0.60–0.64; the value for the minor epoxide-negative spot was 0.85–0.90. GLC analysis (16) showed that epoxydiol **10** comprised 90–95% of the product, and the minor product was the diol **13**. After conversion to the corresponding acetonides **11** and **14**, the mixture was fractionated by vacuum distillation (bp **11**, 63–65°C/0.8 Torr).

Reductive opening of anhydrotetrol acetonide 11

15 g of $LiAlH_4$ (394 mmoles) was mechanically stirred with 1 l of anhydrous diethyl ether at 0–5°C, and a solution of 15 g of acetonide **11** (96 mmoles) in 20 ml of anhydrous ether was added during 15 min. The mixture was allowed to reach room temperature, and stirring was continued during 3 hr; the mixture was then cooled to ca. 5°C and diluted with 100 ml of water-saturated ether. Saturated Na_2SO_4 solution[5] (ca. 100 ml) was then cautiously

[3] Korsch, B. H. Unpublished experiments.

[4] The zinc permanganate contained varying amounts of free MnO_2. Each batch was assayed by titration against oxalate (17), and the weight was adjusted accordingly. Various batches assayed from 50 to 90% active MnO_4^-.

[5] We thank Dr. A. A. Gallo for this procedure by which one avoids producing a gelatinous suspension that is troublesome to filter.

added until the suspension became white and granular and could be filtered easily through Celite. After drying, the filtrate was concentrated under reduced pressure, leaving a nearly colorless oil (11–15 g, 74–100%) that gave two peaks on GLC. The major peak (80–82%) cochromatographed with authentic DL-1,2-*O*-isopropylidene-(1,2,3/0)-cyclopentane-1,2,3-triol (**12a**), and the minor peak (18–20%) corresponded to authentic 1,2-*O*-isopropylidene-(1,2,4/0)-cyclopentane-1,2,4-triol (**15a**). Separation was achieved by conversion to the benzoates[2,3] (10) **12b** and **15b** and fractional crystallization of the latter from ethanol; the GLC-pure 1,2,3/0 isomer **12b** melted at 109–111°C (lit. [10] 109.5–111°C) and showed no depression of melting point on admixture with authentic **12b.** Saponification of **12b** gave **12a** in nearly quantitative yield: 15 g of **12b** was heated at reflux in 200 ml of 0.1 N KOH in methanol–water 40:1 for 3 hr and neutralized with acetic acid, and the product **12a** was extracted into chloroform. Distillation (bp 58–60°C/0.8 Torr) gave **12a** as a colorless oil, n_D^{24} 1.4540 (lit. [10] n_D^{25} 1.4544).

TABLE 1. Purification of tris-*homo*acyl cyclopentanetriols and glycerides by column chromatography[a]

Compound		Solvent	
Isomer	Chain Length	I	II
1,2,3/0	C_8–C_{18}; C_{19}[b]	Hexane–benzene 1:3	Benzene 100%
1,2/3 } 1,3/2 }	C_8–C_{18}; C_{19}	Hexane–benzene 3:1	Hexane–benzene 1:1
Glyceride	C_{19}	Hexane–benzene 1:1	Hexane–benzene 1:3

[a] The acylation mixture was freed of excess acyl chloride, fatty acid, and fatty acid anhydride as described in the text. Solid products were recrystallized once before column chromatography, but oily products were applied directly to the column. 2.0 g (2–4 mmoles) of product was dissolved in the minimum amount of solvent I and applied to 75 g of silica gel in a 1.8-cm (ID) column; column height was 55 cm. The column was eluted with solvent I, and 50-ml fractions were analyzed by TLC. Usually, ca. 300 ml of solvent I was required to remove fast-moving components of the reaction mixture. The desired products were then eluted with solvent II.
[b] C_{19} denotes dihydrosterculoyl derivatives.

GENERAL METHODS

Formation of *O*-isopropylidene derivatives (acetonides)

Anhydrous compounds possessing a *cis* vicinal diol group were dissolved in acetone, and the solution was diluted with 2,2-dimethoxypropane (molar ratio 2,2-DMP: diol = 4:1) and stirred at room temperature with a catalytic amount of TFA (large scale preparations, containing 0.3–0.5 mole of diol, required 1 ml of TFA). The reaction was monitored by GLC and usually required 2–5 hr for completion. The solution was neutralized with $BaCO_3$, filtered over Celite, and evaporated to dryness. Because of the relatively high volatility of the acetonides (especially **14**), the water bath temperature had to be at or near room temperature. The acetonides were then distilled under reduced pressure, and their identity and purity were checked by GLC.

Acylation of triols

Straight-chain saturated tris-*homo*acyl derivatives of the triol isomers were prepared by direct acylation using pure acyl chloride[6] as follows. A solution of fatty acyl chloride (17.5 mmoles) in anhydrous diethyl ether (30 ml) was added slowly to a stirred solution of triol (5.0 mmoles) in anhydrous pyridine (10 ml) at 0–3°C. The ice bath was then allowed to reach room temperature as the mixture was stirred for 12–18 hr; ca. 15 g of ice was added to decompose excess acyl chloride (30 min), and the mixture was extracted thoroughly with chloroform. The $CHCl_3$ phase was washed with 1 N H_2SO_4 (4 × 100 ml), 5% $NaHCO_3$ solution (3 × 100 ml), and water and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave a product that on TLC showed a major spot due to pseudotriglyceride, R_f 0.2–0.5, and minor spots nearer the origin (see **Table 1**). The products of acyl chain lengths C_{12}–C_{18} (except **1d**) crystallized as the solvent was removed, while the lower homologs (C_8 and C_{10}) remained liquid, even in vacuo. Purification of the tris-*homo*acyl compounds was achieved by a combination of crystallization and column chromatography. (The chromatographic procedure for each homolog is given in Table 1.) The higher homologs (C_{12}–C_{18}) were recrystallized before and after chromatography by dissolving them in warm hexane, adding methanol to the point of incipient immiscibility, and cooling the solution to 5°C. The lower members (C_8 and C_{10}) were chromatographed as oils, and the eluted products were then crystallized from methanol at −20°C. The (1,2,3/0)-C_8 homolog could not, however, be induced to crystallize even at −20°C.

In addition to the analogs containing straight-chain fatty acids, the corresponding derivatives of the cyclopropyl fatty acid, dihydrosterculic acid (**1h, 2h, 3h**), were prepared as well as tris-dihydrosterculoyl glycerol. These substances were obtained by the fusion method of Cubero Robles and Vanden Berg (18); the purification procedure was modified as follows. The melt was cooled and triturated with cold methanol to remove most of the free fatty acid and acid anhydride. The lower oily layer containing essentially all the tris-acylated product was freed of solvent and repeatedly

[6] A sample of each acyl chloride was methanolyzed and the methyl ester was analyzed by GLC (SE-30 at 140°C). All samples were found to be >99.4% pure with respect to other homologs.

TABLE 2. Analytical data and yields[a] for synthetic tris-*homo*acyl analogs of triglycerides and for glyceryl tris-dihydrosterculate

Homolog	Theory C	Theory H	1,2,3/0 Found C	1,2,3/0 Found H	1,2,3/0 Yield	1,2/3 Found C	1,2/3 Found H	1,2/3 Yield	1,3/2 Found C	1,3/2 Found H	1,3/2 Yield
	%				%			%			%
C_8 [$C_{29}H_{52}O_6$ (496.71)]	70.12	10.55	70.62	10.58	83	70.39	10.43	83	69.87	10.59	88
C_{10} [$C_{35}H_{64}O_6$ (580.86)]	72.37	11.11	72.27	11.01	81	72.72	11.14	83	72.77	11.37	66
C_{12} [$C_{41}H_{76}O_6$ (665.02)]	74.04	11.52	74.30	11.58	76	73.75	11.43	83	74.07	11.44	68
C_{14} [$C_{47}H_{88}O_6$ (749.17)]	75.35	11.84	75.50	11.52	80	75.20	11.53	91	75.60	11.73	75
C_{16} [$C_{53}H_{100}O_6$ (833.33)]	76.38	12.10	76.39	12.08	72	76.00	12.11	85	76.68	11.92	88
C_{18} [$C_{59}H_{112}O_6$ (917.49)]	77.23	12.30	77.41	12.32	82	77.33	12.23	74	77.32	12.34	81
C_{19}[b] [$C_{62}H_{112}O_6$ (953.52)]	78.09	11.84	77.83	12.10	46	78.11	12.08	52	78.36	11.70	58
C_{19} [$C_{60}H_{110}O_6$ (927.48)][c] (glyceride)	77.69	11.95	77.57	11.96	66						

Numbers in parentheses are molecular weights.

[a] Based on triol starting material and chromatographically homogeneous product recovered after column chromatography.

[b] C_{19} denotes dihydrosterculoyl derivative.

[c] Value for glyceryl tris-dihydrosterculate.

chromatographed on silica until pure. The dihydrosterculic acid was prepared according to Kornberg and McConnell (12) and was converted to its anhydride as described by these authors.

RESULTS AND DISCUSSION

The tris-*homo* saturated acyl derivatives of each of the diastereoisomeric cyclopentane-1,2,3-triols were obtained in good yields as stable, analytically pure substances by direct acylation of the triol with acyl chloride in pyridine. The yields of purified lipid and the elemental analyses are presented in **Table 2.** The products are very soluble in solvents of low polarity (hexanes, benzene, chloroform, ether) but much less soluble in acetone and alcohols. The compounds are purified easily by column chromatography and show no sign of lability even after protracted periods in contact with silica.

Each homologous series of pseudotriglycerides resembles the triglyceride series in having an approximately linear dependence of melting point on acyl chain length (see **Table 3**). For a given carbon number (n_C) the pseudotriglyceride invariably has a lower melting point than the corresponding triglyceride. The mean differences, Δt, between the pseudotriglyceride and true triglyceride melting temperatures within the 1,3/2, 1,2,3/0, and 1,2/3 homologous series are, respectively, 8.9°C, 6.0°C, and 3.9°C. This implies, to a first approximation, that the 1,2/3 series (mean Δt = 3.9°C) has the most stable crystal lattice. This series may represent the closest approach to the triglyceride structure with respect to packing of the hydrocarbon chains. On this basis, the least favored crystal packing appears, unexpectedly, to be that of the 1,3/2 series (all-*trans* disposition of chains). If the crystal structure is based on parallel extended chains, it is to be expected that differences in chain packing would be revealed by the thermodynamics of crystal melting. It has been observed (19) that subtle changes in the chains do affect these parameters. For example, $\Delta H°$ and $\Delta S°$ for the melting of crystalline hydrocarbons (n_C 13–20, inclusive) vary with even and odd values of n_C. However, before firm conclusions are drawn from our melting data, it must be observed that triglycerides characteristically exhibit a series of polymorphic (20–22) forms whose behavior (melting point, latent heat of fusion, etc.) differ. Consequently, comparisons made within a series must take into account the thermodynamic stability of the polymorph under study. We have not yet studied the possible polymorphism in the pseudotriglycerides beyond noting that these compounds behave "normally" during conventional melting point determinations. We do not rule out the possibility that our simple examination may have been insufficiently sensitive to detect subtle thermal phenomena. We therefore plan to undertake a detailed investi-

TABLE 3. Melting points[a] of triglycerides and of cyclopentanoid analogs of triglycerides

Homolog	Isomeric Series 1,2,3/0	1,2/3	1,3/2	Triglyceride
C_8	liq	liq	liq	liq
C_{10}	liq	28–29	liq	
C_{12}	36–37	44–45	37–38	47–48 (46.4)[b]
C_{14}	50–51	53–55	48–49	57–58
C_{16}	61–62	61–63	60–61	67–68 (65.7)
C_{18}	69–70	69–71	64–66	74–75 (72.5)
C_{19}[c]	liq	liq	liq	liq

[a] °C, uncorrected.

[b] Literature values (21) are given in parentheses.

[c] C_{19} denotes dihydrosterculoyl derivative.

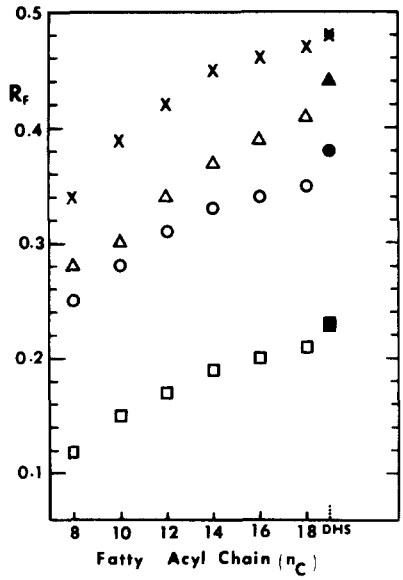


Fig. 2. Thin-layer chromatography of tris-*homo*acyl compounds. TLC was carried out on 20 × 20 cm glass plates coated with silica gel G, 0.25 mm thick, and developed at ambient temperature with CCl_4–ethyl acetate 25:1. ×, 1,3/2-cyclopentanetriol series; △, 1,2/3-cyclopentanetriol series; ○, triglycerides; □, 1,2,3/0 cyclopentanetriol series. The altered symbols corresponding to the point on the abcissa marked *DHS* indicate the tris-dihydrosterculoyl derivatives of each series.

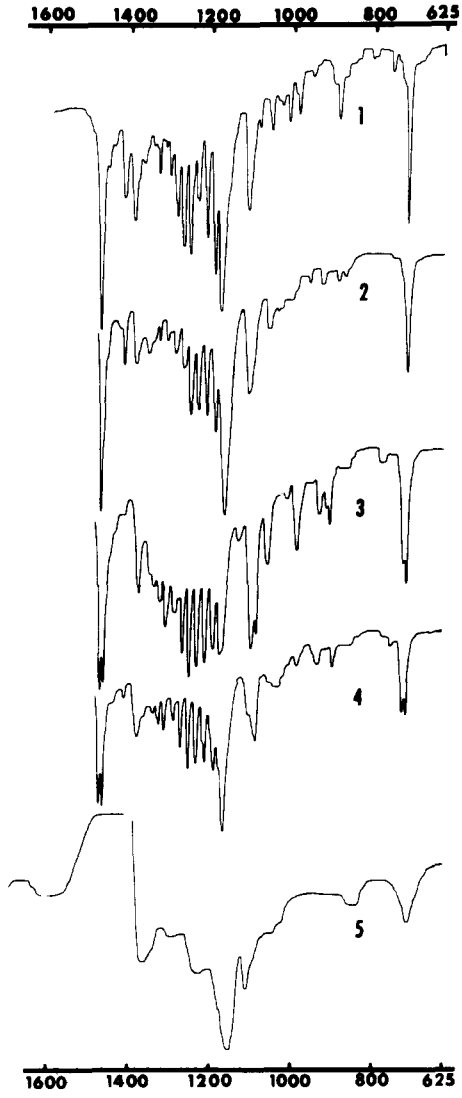


Fig. 3. Infrared spectra of tristearoyl derivatives. The abscissa represents frequency in cm^{-1}. Spectra 1, 2, 3, and 4 were recorded for dispersions in KBr (discs), 1.5% lipid. *1*, glyceryl tristearate; *2*, tristearate of 1,3/2 cyclopentanetriol **3g**; *3*, tristearate of 1,2,3/0 cyclopentanetriol **1g**; *4*, tristearate of DL-1,2/3 cyclopentanetriol **2g**. Spectrum *5* is that of a solution of tristearate **2g** in CS_2. Only the spectral region between 625 and 1600 cm^{-1} is shown.

gation of the thermal properties of these homologous series by differential thermal analysis in order to detect, and then compare, any polymorphism and phase transitions across the three series.

Thin-layer chromatographic analysis of the four series of tris-acyl compounds is represented graphically in **Fig. 2.** Within each series the effect of the variation of chain length on apparent polarity is clearly evident: with increasing length of the fatty acyl chain the mobility of the compound in the nonpolar solvent system increases. Successive increments in chain length, however, exert a progressively smaller influence on the mobility. The mobility is not governed by chain length alone, as is shown by the points representing the dihydrosterculate derivatives. These compounds invariably move farther in this solvent system than do any of the other derivatives within a series. Evidently, the constraints imposed upon the conformations of the fatty acyl chains (12, 13) by the cyclopropyl group exert a profound influence on the apparent polarity of the compounds. A smooth curve drawn through the points for the C_{12}–C_{18} members of each of the series shows that the effect of the chain alteration is significantly greater than might be expected merely from the addition of one carbon atom. The differences in mobility not only between the triglycerides and the three series of analogs but also among the three series themselves exemplify the type of variation in physical properties we had hoped to observe when we undertook this program of synthesis. The difference in apparent polarity between the all-*trans*-(1,3/2) and the all-*cis*-(1,2,3/0) series that this analysis reveals is remarkable, and it encourages us to extend the studies to include other physical means for assessing the properties and interactions of the analogs.

The infrared spectra of the pseudotriglycerides in general resemble those of the triglycerides (**Fig. 3**). Solutions of both series of compounds give spectra in which the bands are broad and poorly resolved, whereas KBr dispersions give well-resolved spectra with fine structure particularly evident in the 1500–700 cm^{-1} region. However, in the spectra of the pseudotriglycerides, this region (including C—H bending, wagging, and rocking absorption modes

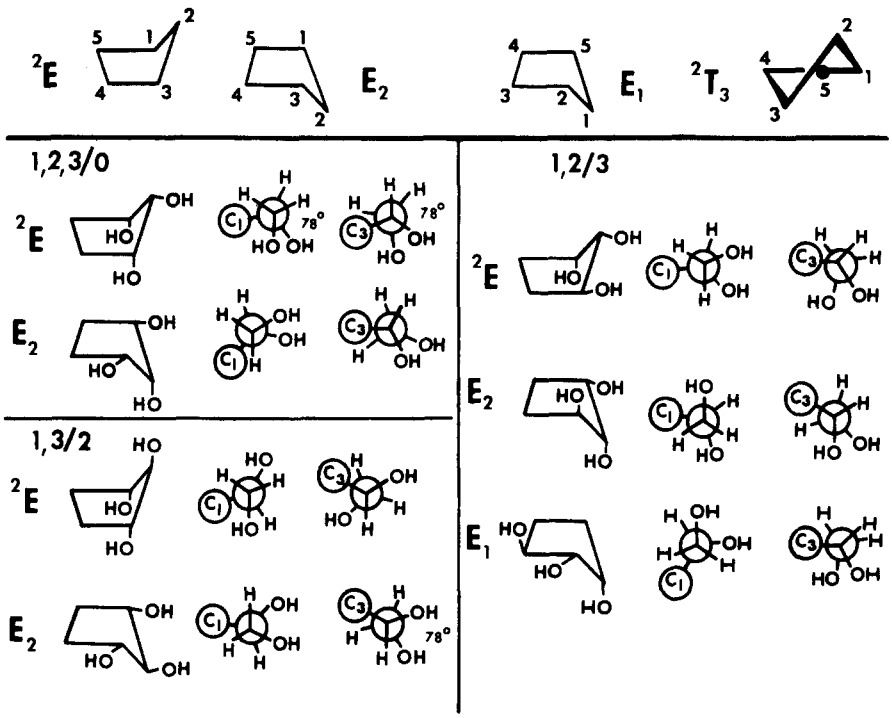


Fig. 4. Conformers of the three cyclopentanetriols. Only envelope conformers, designated *E*, are shown. In such conformers, four of the ring atoms occupy a plane, and the atom displaced above or below the plane is designated by a preceding superscript or a following subscript, e.g., ^2E and E_1 in some of the examples in the figure. At the right of each conformer are two Newman projections defining the rotameric form of glycerol that is analogous to the cyclopentanoid conformer. The torsional angles indicated correspond to the puckering in the cyclopentanoid system (11). In each case, one Newman projection shows C_3 in front eclipsing C_2 and the other shows C_2 in front eclipsing C_1.

[23]) differs significantly from that of the triglycerides as follows. An absorption band at 1418 cm^{-1} has been assigned (23) to a C—H bending mode of CH_2 groups adjacent to a carboxyl group and is present in the spectra of all crystalline triglycerides we have examined; this band is present in the spectra of all the 1,3/2 analogs and present at lower intensity in the 1,2/3 series, but it is either absent or very weak in the spectra of 1,2,3/0 analogs. The strong absorption band at 890 cm^{-1} (22) in the triglyceride spectra is very weak, or absent, in the spectra of the 1,3/2 series and is present only in the C_{12} member of the 1,2/3 series. The band at 890 cm^{-1} is not seen in the spectra of the 1,2,3/0 series, but the same mode may be represented by a weak absorption band closer to 910 cm^{-1}. Chapman (24) observed that the absorption at or near 720 cm^{-1} (CH_2 rocking mode) in Nujol mulls of triglycerides occurred as a singlet or doublet depending on the manner in which the compound was crystallized. We observe a sharp singlet in spectra of KBr dispersions of both the triglyceride and the 1,3/2-pseudotriglyceride series (718 cm^{-1}). However, the spectrum of each member of the 1,2,3/0 and 1,2/3 series of triglycerides contains a well-resolved doublet (719 ± 2, 728 ± 2 cm^{-1}). An absorption at 1465–1470 cm^{-1} is also assigned to a C—H bending mode of CH_2 groups (23). Those spectra that have a doublet in the 720 cm^{-1} region invariably have a doublet centered at or near 1467 cm^{-1}, whereas spectra of analogs that have a singlet at 718 cm^{-1} invariably have a singlet at 1471 cm^{-1}. Stein and Sutherland (25) have reported a doubling phenomenon in the CH_2 bending mode region; they find 1460 cm^{-1} absorptions to be double below the transition point of solid paraffins but single above this temperature and in the liquid state.

The rationale for the undertaking of this research was the expectation that the analogs may provide the basis for better understanding of some of the physical and biological properties of natural, glycerol-containing lipids. Because of the restriction of rotation imposed by the ring, only alicyclic triols may be used as analogs of rotameric states of glycerol. Cyclopropanoid and cyclobutanoid systems are too immobile. Cyclohexanoid systems can exist (26) in boat, skew, and chair forms, but generally only the two chairs have much probability of contributing to the conformational equilibrium, and both chairs are relatively rigid. In the cyclopentanoid system, however, the conformational equilibrium is rarely restricted to one or even two forms, and the conformers are much less rigid, allowing a certain amount of deformation of the ring from the preferred form (9, 11, 27, 28) (pseudolibration). It has been possible to evaluate the various contributions to conformational stabil-

ity in such systems (9, 11). Fig. 4 shows some important conformers of the three triols. Opposite each of these are the two Newman projections (29) that define the rotameric form of glycerol to which the conformer is analogous. For convenience, only envelope conformations (30), designated E, are shown. The rotamers of glycerol are not necessarily low-energy forms. In fact, the rotamers of glycerol shown as corresponding to the ^2E and E_2 conformers of the 1,2,3/0 triol would be subject to serious repulsion between the vicinal carbon—oxygen bonds and would, therefore, be relatively unstable.

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