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CHEMISTRY OF THE LIPIDS

X. Synthesis of Optically Active α, β-Diglycerides

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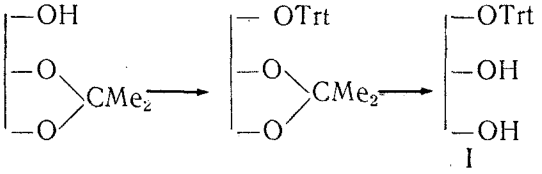
Optically active α, β-diglycerides are the key intermediates in the synthesis of phospholipids [1] and play an important role in their biogenesis [2].

The method of synthesis of optically active α, β-diglycerides proposed by Sowden and Fischer [3] and by N. A. Preobrazhenskii et al. [4], just like the method of acylating a L-α-tetrahydropyranyl ether of glycerol [5], have a number of disadvantages from which the method that we have developed, based on the acylation of L-α-O-tritylglycerol (I) and its D-isomer (3), are free (see preceding communication [6]). We have recently obtained the first of these substances by Scheme 1 in the course of the synthesis of bacterial lipo amino acids.

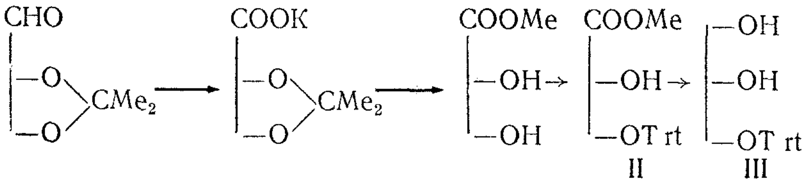
Scheme 1*



Compound (I) has been synthesized similarly from D-(glycerol α, β-carbonate) [5].

We have obtained D-α-O-tritylglycerol (III) by the aluminum hydride reduction of methyl β-O-trityl-D-glycerate (II), the synthesis of which we have reported previously [8] (Scheme 2).

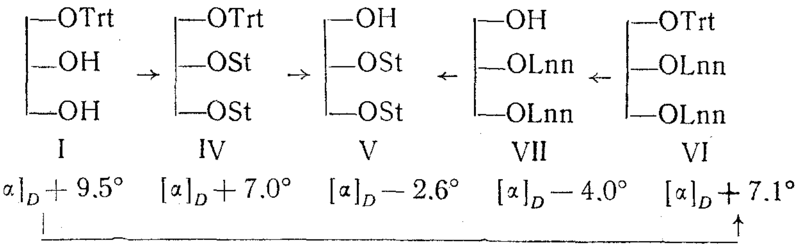
Scheme 2



The suitability of the trityl derivatives I and III for the synthesis of α, β-diglycerides is due not only to their accessibility but also to the fact that after acylation the trityl protective group can be remove under very mild conditions (by chromatography on silica gel) which do not cause the migration of the acyl groups [9, 10].

This paper reports the use of L- and D-α-O-tritylglycerols (I) and (III) for the synthesis of optically active diglycerides (Schemes 3 and 4).

Scheme 3



The acylation of L-α-O-tritylglycerol (I) with stearoyl chloride in pyridine led to D(S)-α-O-trityl-β, γ-distearoylglycerol (IV), which was detritylated on silica gel to form D-α, β-distearin (V). Similarly, D-α, β-dilinolenin

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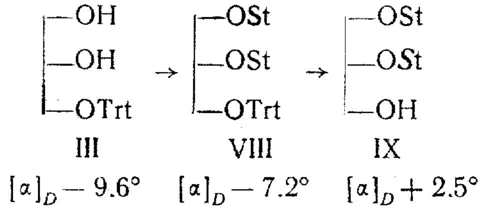
* The following symbols are used in the Schemes: Trt) triphenylmethyl, St) stearoyl, Lnn) linolenoyl.

(VII) was obtained via L(R)-α-O-trityl-β, γ-dilinolenoylglycerol (VI) and was then hydrogenated to give D-α, β-distearin (V). In this case, detritylation was accompanied by partial acyl migration, but on chromatography the α, γ-isomer was satisfactorily separated from the VII.

Scheme 4



In the same way the distearoyl derivative **VIII** was synthesized from D-α-O-tritylglycerol (**III**). Its detritylation on silica gel led to D-α, β-distearin (**IX**). The coincidence of the absolute magnitudes of the angles of rotation of the enantiomeric pairs **I–III**, **IV–VIII**, and **V–IX** shows their optical purity.

Experimental

The melting points were determined on a Kofler block and have been corrected. The angles of rotation were measured in a "Hilger" polarimeter at 17–22° C. The IR spectra were recorded on a UR-10 spectrophotometer (Zeiss, GDR). Thin-layer chromatography (TLC) was carried out on KSK silica gel (<150 mesh) in a fixed layer (with the addition of 7–8% of gypsum) and on alumina in a nonfixed layer. Column chromatography was carried out with KSK silica gel (150–250 mesh) washed free from metal salts with nitric acid and activated at 120° C. The "active" silica gel used for detritylation was prepared as described by Pitra and Sterba [11] and was activated at 140–160° C.

D-α-O-Tritylglycerol (III). With stirring in an atmosphere of nitrogen, a solution of 28 g of unpurified 50% methyl β-O-trityl-D-glycerate (II) [8] in 400 ml of dry ether was added dropwise over 40 min to a solution of 6 g of lithium aluminum hydride in 150 ml of dry ether. The reaction mixture was boiled for 1 hr and cooled, and, with stirring, 100 ml of ethyl acetate was added dropwise. Then 30 ml of a saturated solution of ammonium sulfate and anhydrous sodium sulfate were added until a readily filterable precipitate had formed. The precipitate was filtered off, washed with a 1:1 mixture of dioxane and chloroform (2 × 150 ml) and dissolved in water (300 ml), and the solution was extracted with ether (3 × 150 ml). The filtrates and the ethereal extracts were combined, dried with anhydrous sodium sulfate, and filtered. After the solvent had been distilled off, 25.7 g of an oily mixture was obtained which, according to TLC on alumina, contained D-α-O-tritylglycerol (III), triphenyl carbinol, and traces of the ester II. This mixture was dissolved in 20 ml of chloroform and chromatographed on 500 g of alumina (activity grade IV). Benzene eluted 12.5 g of triphenyl carbinol, and chloroform containg 10% of methanol eluted 11.2 g of D-α-O-tritylglycerol (III) (yield 84.5%) in the form of an oil that crystallized on standing. After recrystallization from chloroform–petroleum ether (2:3), mp 93–94° C, $[\alpha]_D$ −9.6° (c 5.2; dioxane). According to the literature: mp 97–99° C (from cyclohexane), $[\alpha]_D$ −3.3° (c 6; tetrachloroethane) [6].

Found, %: C 78.78; H 6.71. Calculated for $C_{22}H_{22}O_3$, %: C 79.01; H 6.63.

L(R)- and D(S)-α-O-trityl-β, γ-distearoylglycerols (VIII) and (IV). With stirring, a solution of 100 mg of D-α-O-tritylglycerol (III) and 0.5 ml of dry pyridine in 25 ml of dry benzene was added dropwise over 20 min to a solution of 270 mg of stearoyl chloride in 25 ml of dry benzene cooled to 0° C, and the mixture was kept at 40° C for 20 hr and was then diluted with 100 ml of ether, after which the precipitate was filtered off and washed with ether (2 × 30 ml). The combined filtrates were washed with 2 N H_2SO_4 cooled to 0° C, with water, with saturated sodium bicarbonate solution, and with water again and were dried with sodium sulfate. The desiccant was filtered off and washed with ether and the filtrates were evaporated. Crystallization of the residue from dry acetone yielded 230 mg of L(R)-α-O-trityl-β, γ-distearoylglycerol (**VIII**) (yield 47.5%), mp 51–52° C, $[\alpha]_D$ −7.2° C (c 1.1; dioxane).

Found, %: C 80.36; H 10.77. Calculated for $C_{58}H_{90}O_5$, %: C 80.13; H 10.46.

Similarly, L-α-O-tritylglycerol (I) yielded D(S)-α-O-trityl-β, γ-distearoylglycerol (IV), mp 52–52.5° C (from acetone), $[\alpha]_D$ +7.0° (c 6.4; dioxane).

Found, %: C 80.23; H 10.53. Calculated for $C_{58}H_{90}O_5$, %: C 80.13; H 10.46.

L- and D-α, β-Distearins (IX) and (V). L(R)-α-O-Trityl-β, γ-distearoylglycerol (**VIII**) (980 mg) was dissolved in 2 ml of dry benzene and the solution was deposited on a column containing 50 g of active silica gel. On subsequent chromatography, the composition of the fractions was monitored by means of TLC on silica gel in the benzene–ether (3:1) system; the spots were revealed in UV light after the plate had been sprayed with a 0.1% methanolic solution of morin. Benzene and benzene-ether (7:1) eluted 390 ml of triphenyl carbinol containing a small amount of **VIII**, and benzene-ether (3 : 1) eluted 560 mg (62%) of L-α, β-distearin (**IX**), mp 75–76° C, [from chloroform–petroleum ether (2 : 3)], $[\alpha]_D$ +2.5° (c 8.8; chloroform).

Similarly, D(S)-α-O-trityl-β, γ-distearoylglycerol (**IV**) yielded D-α, β-distearin (**V**), mp 71.5–72° C, $[\alpha]_D$ −2.6° (c 8.6; chloroform). Literature data: mp 74.5–75° C, $[\alpha]_D$ −2.7° [4].

D(S)-α-O-Trityl-β, γ-dilinolenoylglycerol (VI). With stirring, a mixture of 390 mg of L-α-O-tritylglycerol (I) and 0.5 ml of dry pyridine in 5 ml of dry benzene was added dropwise to a solution of linolenoyl chloride, prepared from 1.4 g of linolenic acid as described by Kaufmann and Gulinsky [12], in 20 ml of dry toluene which had been cooled to 0° C (all the operations were carried out in an atmosphere of argon). The mixture was stirred at 20° C for 40 min and was left at 40° C for 10 hr. After the usual treatment of the mixture (see the synthesis of **VIII**), 2.17 g of an oily reaction product was obtained. This was dissolved in 15 ml of dry benzene and chromatographed on a column containing 100 g of alumina (activity grade **IV**); the compositions of the fractions were monitored by TLC on silica gel in the benzene–chloroform (4 : 1) system with conc H_2SO_4 as the revealing agent. A mixture of petroleum ether and benzene (2 : 1) eluted 730 mg of D(S)-α-O-trityl-β, γ-dilinolenoylglycerol (**VI**) (yield 92%) in the form of an oil with $[\alpha]_D$ +7.1° (c 1.3; dioxane).

Found, %: C 81.64; H 9.31. Calculated for $C_{58}H_{78}O_5$, %: C 81.45; H 9.19.

D-α, β-Dilinolenin (VII). A solution of 600 mg of D(S)-α-O-trityl-β, γ-dilinolenoylglycerol (**VIII**) in 5 ml of dry benzene was chromatographed on a column containing 10 g of active silica gel. The compositions of the eluates were monitored by TLC (see the synthesis of **IX**). Benzene eluted 250 ml of triphenyl carbinol and a mixture of benzene and ether (3 : 1) eluted 200 mg of a mixture of approximately equal amounts of α, β- and α, γ-dilinolenins and then 125 mg of pure D-α, β-dilinolenin (**VII**) (yield 29%) in the form of a colorless mobile oil with $[\alpha]_D$ −4.0° (c 1.4; chloroform).

Found, %: C 76.44; H 10.62. Calculated for $C_{39}H_{64}O_5$, %: C 76.42; H 10.53.

The D-α, β-Dilinolenin (**VII**) (76.5 mg) was dissolved in 10 ml of n-heptane and hydrogenated over 20 mg of previously-reduced platinum oxide. In 20 min ~100% of the theoretical amount of hydrogen had been absorbed. Chloroform was added to dissolve the precipitate that had deposited, and the catalyst was filtered off and washed with chloroform. The combined filtrates were evaporated, and the residue was crystallized from chloroform–petroleum ether. This gave 70 mg (90%) of D-α, β-distearin with mp 71.5–72° C, $[\alpha]_D$ −2.6° (c 4.6; chloroform).

Conclusions

1. A. new route for the synthesis of optically active α, β-diglycerides has been developed.
2. D- and L-α, β-Distearins and D-α, β-dilinolenin have been synthesized from the readily accessible L- and D-α-O-tritylglycerols.

REFERENCES

1. L. L. M. van Deenen and G. H. de Haas, Advances in Lipid Research, **2**, 168, 1964.
2. G. B. Ansell and J. N. Hawthorne, Phospholipids, Amsterdam, 119, 1964.
3. I. C. Sowden and H. O. L. Fischer, J. Amer. Chem. Soc., **63**, 3244, 1941.
4. V. I. Shvets, L. T. Dorofeeva, I. A. Grum-Grzhimailo, L. V. Volkova, I. S. Shmidt, and N. A. Preobrazhenskii, ZhOKh, **34**, 3303, 1964.
5. J. Gigg and R. Gigg, J. Chem. Soc., C, 431, 1967.
6. Yul. G. Molotkovskii, L. F. Nikulina, and L. D. Bergel'son, Izv. AN SSSR, ser. khim., 927, 1967.
7. Yul. G. Molotkovskii and L. D. Bergel'son, Izv. AN SSSR, ser. khim., 2498, 1967.
8. Yul. G. Molotkovskii and L. D. Bergel'son, Izv. AN SSSR, ser. khim., 2321, 1967.
9. D. Buchnea and E. Baer, J. Lipid Research, **1**, 405, 1960.
10. L. T. Dorofeeva, E. I. Kovshev, L. V. Volkova, and N. A. Preobrazhenskii, ZhOKh, **33**, 2883, 1963.
11. Pitra and I. Sterba, Chem. Listy, **56**, 544, 1962.
12. H. P. Kaufmann and E. Gulinsky, Fette, Seifen und Anstrichmitel, **64**, 592, 1962.

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