Summary

Four new alcohols, thiomorpholine-γ-4-propanol, thiomorpholine-4-ethanol, its oxide and its dioxide have been prepared. A series of esters has been prepared from each of these alcohols and their properties have been studied.

New and more satisfactory preparations of β,β'-dibromodiethyl sulfide, sulfoxide and sulfone have been carried out and their reactions with monoethanolamine studied.

Thiomorpholine derivatives have been shown to be only slightly toxic. The aromatic esters have shown local anesthetic properties similar to those of the corresponding morpholine derivatives.

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Preparation and Properties of β-Monoglycerides

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The β-monoglycerides of fatty acids, together with the analogous unsymmetrical diglycerides, have offered the greatest difficulties in preparation of any of the related glycerol esters. The tendency of an aliphatic acyl group to shift from the beta to the alpha position while preparations are under way was first pointed out by Fischer.[1] Aromatic acyl groups were later fixed in the beta position by Helferich and Sieber,[2,3] who prepared the β-monobenzoate and the β-mono-(*p*-nitrobenzoate) of glycerol, using as an intermediate the α,α'-di-(triphenylmethyl) ether. This method proved unsuitable, however, for the preparation of fatty acid β-glycerides, because of the rapid migration of the acyl group to an alpha position[4] during the removal of the ether groups. The first successful method for the preparation of a fatty acid β-monoglyceride was developed by Bergmann and Carter.[5] They prepared the acetyl, benzoyl, and palmityl esters of 1,3-benzylideneglycerol and succeeded in reducing these to the corresponding β-monoglycerides.

In the present investigation (essentially by the method of Bergmann and Carter) we have prepared the β-glycerol esters of capric, lauric, myristic, palmitic and stearic acids, and have determined their constants for identification.

Since the preparation of mixed unsymmetrical triglycerides by treating α-monoglycerides with acyl chlorides had proved satisfactory,[6,7,8] we investigated the procedure for the preparation of symmetrical mixed triglycerides, using β-monoglycerides as intermediates. A specific study was then made of the factors which influence migration from the beta to the alpha position. In an alcoholic solution of $N/20$ hydrochloric acid at room temperature, β-monopalmitin underwent complete rearrangement to the more stable alpha isomer in twenty-four hours, but in solutions more dilute than $N/200$ there was no significant rearrangement during the same time interval. Higher concentrations (approximately $\times$ 2) of ammonium hydroxide gave similar results.

When the pure β-monopalmitin was held slightly above its melting point for a period of one hour, there was no significant change in structure, but prolonged heating induced a change which did not involve a similar complete transition.

Further evidence of the formation of a cyclic intermediate compound during the change from one isomer to the other has been provided recently by Hibbert and Greig.[9]

Experimental

1,3-Benzylidene glycerol was prepared essentially as described by Hibbert and Carter.[10] It was purified by crystallization first from benzene and heptane (1:1) and then from warm water. A yield of 22% was obtained, m. p. 84°.

Preparation of Esterified Acetals.—The preparation of 2-palmityl-1,3-benzylidene glycerol is given as an example of the method used for the entire series. To a cooled solution of 18 g. of 1,3-benzylidene glycerol in 25 cc. of dry pyridine (cautiously to avoid overheating) 25 g. of palmityl chloride was added. After standing at 20° for twenty-four hours it was washed repeatedly with 200 cc. of ice water until all pyridine was removed. The finely powdered

(1) Fischer, *Ber.*, **53**, 1621 (1920).
(2) Helferich and Sieber, *Z. physiol. Chem.*, **170**, 31 (1927).
(3) Helferich and Sieber, *ibid.*, **175**, 311 (1928).
(4) Jackson and King, THIS JOURNAL, **55**, 678 (1933).
(5) Bergmann and Carter, *Z. physiol. Chem.*, **191**, 211 (1930).
(6) Fischer, Bergmann and Barwind, *Ber.*, **53**, 1589 (1920).
(7) Roche, Averill and King, THIS JOURNAL, **51**, 866 (1929); **54**, 365 (1930).
(8) Robinson, Roche and King, *ibid.*, **54**, 705 (1932).
(9) Hibbert and Greig, *Can. J. Research*, **4**, 254 (1931).
(10) Hibbert and Carter, THIS JOURNAL, **51**, 1601 (1929).

substance was dried in a vacuum desiccator and then dissolved in 200 cc. of warm petroleum ether (35–65°). On standing for twenty-four hours at room temperature, prismatic crystals separated from the solution. The yield was increased by partial evaporation of the solvent. One to two recrystallizations were sufficient to give a constant melting point of 63.5°. The yield was 18 g. Molecular weights were determined as a check on the intermediates.

The 2-substituted 1,3-benzylidene glycerol esters of the following acids were prepared in a similar manner: capric, m. p. 32.5°; lauric, m. p. 46.6°; myristic, m. p. 62°; and stearic, m. p. 69°.

Preparation of β-Monoglycerides.—The β-monoglycerides were prepared by catalytic reduction of the esterified acetals in the presence of palladium black. The preparation of β-monopalmitin will serve as an example. To 10 g. of 2-palmityl-1,3-benzylidene glycerol dissolved in 150 cc. of absolute alcohol, one-half gram of palladium black was added. The flask was then evacuated and hydrogen gas was admitted at a pressure of 30 pounds in a Burgess–Parr hydrogenation apparatus. After two hours the reduction was complete. The catalyst was removed completely by two filtrations, after which the solution was concentrated by warming under reduced pressure until crystallization began. On cooling the solution the β-monopalmitin crystallized in fine white flakes. After two recrystallizations from absolute alcohol, it gave a constant melting point of 68.5°. The yield was 7 g. *Molecular weight* (Menzies–Wright method), determined 323, theoretical 330. Refractive index at 70°, 1.44605.

The melting points and refractive indices at 70° found for the other members of the series were as follows: β-monocaprin, 40.4°, 1.44045; β-monolaurin, 51.1°, 1.44240; β-monomyristin, 61°, 1.44420; β-monostearin, 74.4°, 1.44770. The average dn/dt for the five compounds was 0.000385 over the range of 60 to 80°.

Analyses gave the following results: β-monocaprin; calcd. for $C_{13}H_{26}O_4$: C, 63.36; H, 10.65. Found: C, 63.41; H, 10.75. β-Monolaurin. Calcd. for $C_{15}H_{30}O_4$: C, 65.64; H, 11.03. Found: C, 65.80; H, 10.86. β-Monomyristin. Calcd. for $C_{17}H_{34}O_4$: C, 67.49; H, 11.34. Found: C, 67.31; H, 11.45. β-Monostearin. Calcd. for $C_{21}H_{42}O_4$: C, 70.33; H, 11.81. Found: C, 70.52; H, 11.92.

Preparation of Symmetrical Triglycerides.—The preparation of the symmetrical myristyl distearate will serve as an example. To 3 g. of β-monomyristin dissolved in 25 cc. of chloroform were added 8 g. of stearyl chloride and 3.2 g. of quinoline. After standing for forty-eight hours at 35°, it was taken up in 400 cc. of ether and 120 cc. of half normal sulfuric acid. A second washing with the same amount of half normal sulfuric acid was followed by an equal number of washings with 10% potassium carbonate and finally with distilled water. The solution was dried over anhydrous sodium sulfate and then cooled until crystallization began. After three recrystallizations from ether, the substance gave a constant melting point of 63.5°, in agreement with the finding[8] when 1,3-distearin was condensed with myristyl chloride. The yield was 2 g. Its molecular weight checked with the theoretical value.

Migration of Acyl Groups.—Samples of β-monopalmitin, dissolved in alcoholic solutions of hydrochloric acid, ranging in concentration from $N/10$ to $N/200$, were held at room temperature for twenty-four hours, crystallized by cooling, and dried in a vacuum desiccator. The melting points were determined to provide an index to any significant change in structure. A similar series of tests was carried out in an alcoholic solution of ammonium hydroxide.

The effect of elevated temperatures upon the stability of the β-monoglycerides was investigated by holding melted samples for varying lengths of time at 76–78°, followed by cooling for twenty-four hours and re-melting, to find the exposure necessary to induce a change in melting point.

Summary

The beta esters of 1,3-benzylidene glycerol and the even fatty acids from capric to stearic inclusive were prepared and identified as intermediates for the synthesis of the corresponding β-monoglycerides. After catalytic reduction, using hydrogen gas and palladium black, the β-glycerol esters of capric, lauric, myristic, palmitic and stearic acids were obtained, and their constants for identification established.

The melting point of each member of the homologous series showed a nearly regular increment with chain length of approximately 10° per C_2H_4 group. The refractive indices showed an analogous constant increment of approximately 0.00181 per C_2H_4 unit chain length. The melting points were regularly 7–13° lower than recorded for the isomeric α-monoglycerides.[11]

Two of the new β-monoglycerides were used as intermediates satisfactorily for the preparation of symmetrical mixed triglycerides.

The stability of the β-monoglycerides was found to be affected markedly by the presence of acids and bases. β-Monopalmitin was found not to undergo a significant change in structure when held slightly above its melting point for a period of one hour. On standing for twenty-four hours at room temperature in alcoholic solution with $N/20$ hydrochloric acid, a complete shift to the alpha isomer occurred.

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(11) Rewadiker and Watson, *J. Indian Inst. Science*, Vol. 13A, 128 (1930).