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ACYL MIGRATION IN GLYCERIDES. II. REACTION OF SODIUM 1,2-ISOPROPYLIDENEGLYCEROXIDE WITH STEAROYLGLYCERYL-IODIDES AND DISTEAROYLGLYCEROL INVOLVING ION PAIR FORMATION AS AN INTERMEDIATE

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The acyl group migration in partially acylated glycerides are initiated and directed by ion pairs which are formed by the action of acid, base or heat upon glycerides under anhydrous conditions. This ion pair can also be created specifically by reaction of sodium 1,2-isopropylideneglyceroxide with glycerideiodides. The elimination of sodium iodide results in 1,2-isopropylideneglyceryl-glyceride ion pair. In such an ion pair the acyl groups follow both migration mechanisms intermolecular and intramolecular whereas, in a glyceride-glyceride ion pair it seems that only an intermolecular exchange of acyl groups takes place.

The free hydroxyl group and hydroxyl hydrogen atom in carbonium ion (Experiment 3, fig. 3, IIIb) are also subjected to the rearrangement within the ion pair. The rearrangement of hydroxyl group and hydroxyl hydrogen atom has certain connection with the acyl group migration within the same ion pair. The above evidence is based on experiments which are reported.

Introduction

The investigation of acyl migration in partially acylated glycerides catalysed by hydrogen chloride revealed the chlorination of partially acylated glycerides and possible formation of a bimolecular resonant ion complex intermediate. It seems that the regeneration of hydrogen chloride is connected with the conversion of the bimolecular resonant ion complex into ion pairs $[-CH_2-O^- {}^+CH_2]$, $[Cl^- {}^+H]$ and $[HO^- {}^+H]$, which then activate and initiate the acyl groups migration[1]).

In an attempt to prove this hypothesis experimentally, it was decided to replace the action of hydrogen chloride, which is not specific, with sodium and iodine. The sodium was brought into reaction as sodium D-1,2-isopropylideneglyceroxide (I) and iodine as D-1,2-distearoylglyceryl-3-iodide (II), (Williamson synthesis). The reaction was carried out in toluene under

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anhydrous conditions at 20 °C; it proceeds very rapidly; in a few minutes, sodium iodide is almost completely (97%) eliminated from the reaction medium as a precipitate. After removal of the precipitated sodium iodide by centrifugation and concentration of the supernatant liquid under reduced pressure a residue was obtained, consisting, according to the (TLC) analysis of D-1,2-isopropylideneglyceryl-3-stearate (IV) and D-1,2-epoxyglyceryl-3-stearate (V) in ratio 1:1, which were separated by crystallization from petroleum ether (b.p. 35–60 °C). Both compounds on hydrolysis of its isopropylidene group[2]) and epoxy ring[3-7]) afforded exclusively L-3-stearoylglycerol (VI) in an excellent yield (over 90%).

The inversion of compound I and II into L-3-stearoylglycerol (V) is due to the stearoyl groups migration from positions C-1 and C-2 (b) to the positions C-3 (a) and C-3 (b), III, resulting in compounds IV and V. It is evident that the stearoyl groups must have migrated by two different mechanisms, one of these intermolecularly from moiety (b) to moiety (a) C-3 (III) resulting in (IV) and the other by an intramolecular mechanism to the position C-3 (b), III, resulting in (V). This migration is such that no racemization occurs. Therefore the stearoyl groups must have been first activated by the radicals $-CH_2O^-$ (a) and $-H_2C^+$ (b) and then attracted to the positions C-3 (a) and C-3 (b), III. The stearoyl group which is attached to the C-3 compound IV, followed an intermolecular migration mechanism and must have been detached at carbonyl-carbon and ether-oxygen bond ($R-OC\overset{\downarrow}{-}O-CH-$) from the parent moiety (b), III. The stearoyl group which is attached to the C-3 (b), followed and intramolecular migration mechanism and must have been detached at ether-oxygen and glyceryl-carbon bond ($R-OC-O\overset{\downarrow}{-}CH-$) forming an epoxy ring between C-1 and C-2, resulting in compound V, fig. 1.

The following experiment was carried out to resolve which stearoyl group follows the intermolecular migration mechanism and which stearoyl group follows the intramolecular: Sodium D-1, 2-isopropylideneglyceroxide (I) was reacted with L-3-benzyl-2-stearoylglyceryl-1-iodide (II). It was found that the stearoyl group migrated completely from position C-2 (b) to the position C-3 (a) resulting in D-1,2-isopropylideneglyceryl-3-stearate (IV) and L-3-benzyl-2,1-epoxyglyceryl ether (V). These results revealed that this stearoyl group was detached at carbonyl-carbon and ether-oxygen bond ($R-OC\overset{\downarrow}{-}O-CH-$) from the parent moiety (b), fig. 2, following an intermolecular migration mechanism to be attached to the C-3 (a), III, resulting in D-1,2-isopropylideneglyceryl-3-stearate (IV) and the remaining L-3-benzylglyceryl radical rearranged itself to L-3-benzyl-2,1-epoxyglyceryl ether (V).

According to the results of experiment No. 2, it would appear that the stearoyl group from position C-1 (b), III, fig. 1, experiment No. 1, must have followed an intramolecular migration mechanism. Hence sodium D-1,2-

isopropylideneglyceroxide (I) was allowed to react with D-1-stearoylglyceryl-3-iodide (II), experiment No. 3, fig. 3. The reaction of compounds I and II resulted in the formation of the following compounds: D-1,2-Isopropylideneglyceryl-3-stearate (IV), D-1,2-epoxyglycerol (V), D-1,2-epoxyglyceryl-3-stearate (VI) and D-1,2-isopropylideneglycerol (VII). All these four compounds (IV, V, VI, VII) retained their optical activity. On acylation of compounds V and VII with stearoyl chloride compounds IV and VI were obtained, which on hydrolysis of isopropylidene group of compound IV and epoxy ring of compound VI gave exclusively L-3-stearoylglycerol (VIII). These results have proved that in this ion pair (III) not only the stearoyl group changes its position, but also the free hydroxyl group and hydroxyl hydrogen atom are subjected to the rearrangement within this ion pair.

The results of these three experiments (No. 1, 2, 3) proved that there must be a free radical rule which directs the rearrangement of acyl and hydroxyl groups in the ion pair. This was entirely demonstrated by reaction of sodium D-1,2-isopropylideneglyceroxide (I), experiment No. 1, 2, 3, with three other glyceryl derivatives containing iodine as the reaction centre. In these reactions the sodium and iodine were eliminated at once as sodium iodide from the reaction media so that they could not interfere in the rearrangement of acyl groups, (experiments No. 1, 2 and 3).

To prove this postulate, the following experiment was carried out in which the iodine was replaced by a hydroxyl group. The reaction between sodium D-1,2-isopropylideneglyceroxide (I) and D-1,2-distearoylglycerol (II), (experiment No. 4, fig. 4) resulted in a mixture containing D-1,2-isopropylideneglyceryl-3-stearate (IV), approx. 40%, racemic bis (DL-1,2-distearoylglyceryl)-3-ether (V), approx. 39%, 1,3-distearoylglycerol (VI), approx. 5%, and the rest of 15 to 17% of sodium stearate (VII) and the corresponding amount of sodium glyceroxide (VIII). With the exception of the formation of D-1,2-isopropylideneglyceryl-3-stearate (IV), which is obvious, due to the isopropylidene protective group, all other reaction products were racemic and entirely different from the previous three experimental results (experiments No. 1, 2, 3 and figs. 1, 2, 3). The differences in these results are caused by sodium hydroxide which reacts further with radical (b), III, resulting in compounds V, VI, VII and VIII, fig. 4.

Procedures and data

Materials

D-1,2-isopropylideneglycerol and D-1,2-distearoylglyceryl-3-iodide were prepared by the methods of Baer and Fischer[2,8] ,and Baer and Pavanaram [10]. L-3-benzylglycerol was prepared from D-1,2-isopropylideneglycerol by

the method of Sowden and Fischer[11]) introducing a modification by replacing sodium metal with 50% sodium hydroxide, and exclusion of organic solvents (benzene or toluene) as reaction medium. The preparation of L-3-benzyl-2-stearoylglyceryl-1-iodide and D-1-stearoylglyceryl-3-iodide is described in this paper. D-1,2-distearoylglycerol was prepared by the method of Sowden and Fischer[11]). Naphthalene (B.D.H. Micro-Analytical Reagent), was used as provided by manufacturer. 1,2-Dimethoxyethane (Eastman Withe label) was dried before use over sodium wire and distilled. Chloroform for use in infrared and polarimetric work was freed of ethanol by distillation over phosphorus pentoxide. Silica gel H according to Stahl (E. Merck, A. G. Darmstadt, Germany), was used for thin layer chromatography.

EXPERIMENT NO. 1

Reaction of sodium D-1,2-isopropylideneglyceroxide (I) *with D-1,2-distearoylglyceryl-3-iodide* (II). *Reaction scheme fig. 1*

In a dry 250 ml round-bottomed flask equipped with a magnetic stirrer, reflex condenser and calcium chloride tube was prepared 40 ml of a 1/2 molar solution of sodium naphthalene[12,13]). The flask was kept at 20 °C, and a solution of 2.65 g (0.02 M) of freshly prepared D-1,2-isopropylideneglycerol in 20 ml of dry 1,2-dimethoxyethane was added to the vigorously stirred sodium naphthalate, as described by Baer et al.[14]). The stirring was continued until the green colour had disappeared. The 1,2-dimethoxyethane was removed under reduced pressure and the residue sodium D-1,2-isopropylideneglyceroxide was kept in a vacuum of 0.02 mm, at 100 °C to distill off most of the naphthalene. The sodium D-1,2-isopropylideneglyceroxide was then suspended in 100 ml of dry toluene, and to the stirred, translucent suspension of sodium D-1,2-isopropylideneglyceroxide was added 14.7 g (0.02 M) of D-1,2-distearoylglyceryl-3-iodide in 100 ml of dry toluene. The yellow coloured, translucent reaction mixture turned dark brown, and then suddenly became white, sodium iodide precipitating from the reaction mixture. The stirring was continued for 10 hr at 20 °C, and then the reaction mixture was worked up as follows: The solid was removed by centrifugation and washed carefully with small portions of toluene to leave 96 to 98% of sodium iodide, based on the stoichiometry of the reaction (the determination was made as AgI). The combined solutions were concentrated under reduced pressure. The solid residue was dissolved in 100 ml of ether, the ether solution was cleared by centrifugation and the supernatant again concentrated under reduced pressure. The remaining residue which weighed 14.2 g (97%) was examined on thin layer chromatography. The (TLC) was carried out on silica gel H plates using petroleum ether/ether (2:1, v/v) as developing solvent

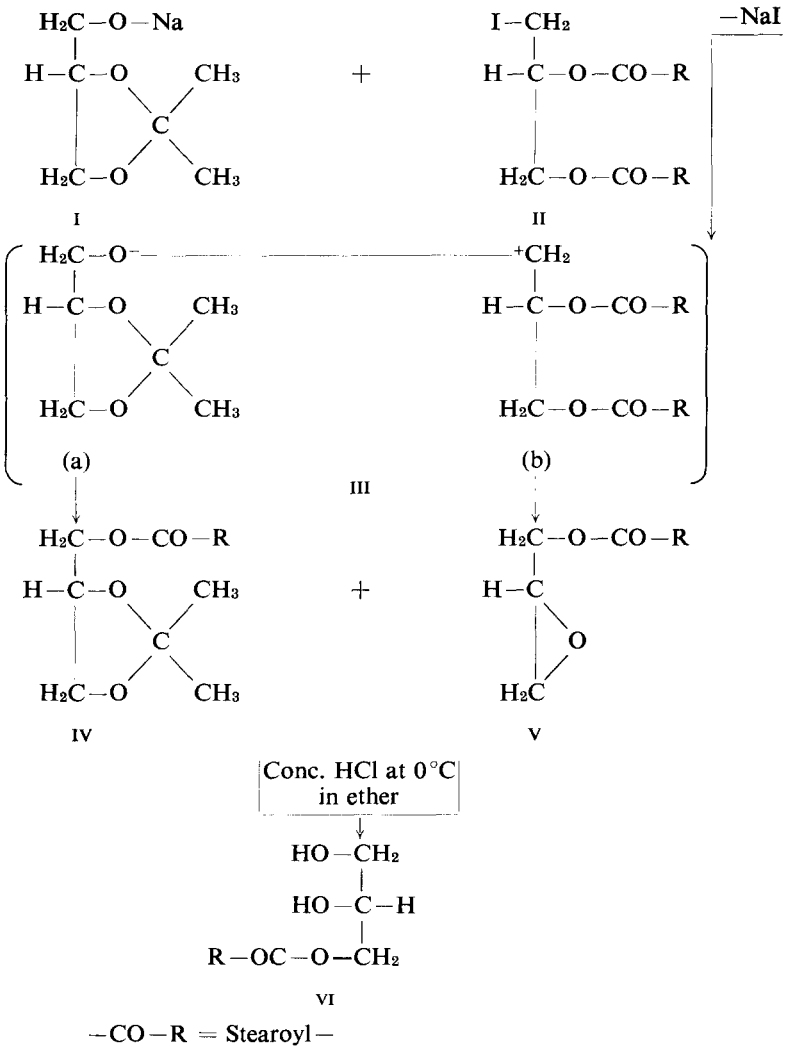

Fig. 1.

and iodine as indicator. The material was found to consist of three compounds; two main spots and a tiny spot near the solvent front. The following substances were identified in the crude reaction product: D-1,2-epoxyglyceryl-3-stearate (v) the first spot from origin ($R_F = 0.53$), D-1,2-isopropylideneglyceryl-3-stearate (iv) the second spot ($R_F = 0.60$) and the third spot, near the solvent front, was naphthalene. The identification was made by using authentic samples as chromatographic markers, which were synthesized by independent and definite routes of synthesis[2-7]).

Isolation of D-1,2-isopropylideneglyceryl-3-stearate (IV)

Fourteen g of the crude reaction product was dissolved in 100 ml of petroleum ether (b.p. 35–60 °C) and cleared by centrifugation. On standing overnight at +7 °C, the solution deposited 6.0 g of D-1,2-epoxyglyceryl-3-stearate (V). The filtrate was concentrated under reduced pressure and the residue was dissolved in 60 ml of 99% ethanol, by warming, and allowing to come to the room temperature. The turbidity was cleared by centrifugation and the clear supernatant was decanted and kept for crystallization at +6 °C. After filtration, the solid was recrystallized once more from 50 ml of ethanol at +6 °C to give 5.4 g (80% of theory) of D-1,2-isopropylideneglyceryl-3-stearate (IV), m.p. 40–41 °C; specific rotation −2.3 °, c, 10 in chloroform. This compound was identical with authentic D-1,2-isopropylideneglyceryl-3-stearate synthesized by Baer and Fischer[2]).

Analysis. Calculated for $C_{24}H_{46}O_4$(396): C, 72.40; H, 11.56
Found (399): C, 72.53; H, 11.60.

Isolation of D-1,2-epoxyglyceryl-3-stearate (V)

Six g of crude D-1,2-epoxyglyceryl-3-stearate on recrystallization from 50 ml of petroleum ether under the same conditions as above gave 5.0 g (77% of theory) of colourless, crystalline product, m.p. 48.5–49.5 °C; specific rotation +8.5 °, c, 10 chloroform. This compound was identical with the authentic D-1,2-epoxyglyceryl-3-stearate obtained by the acylation of the synthetic D-1,2-epoxyglycerol prepared according to the method described by Sowden and Fischer[6]).

Analysis. Calculated for $C_{21}H_{40}O_3$(341): C, 74.10; H, 11.84
Found (342): C, 73.92; H, 11.90.

L-3-stearoylglycerol (VI)

(a) From D-1,2-isopropylideneglyceryl-3-stearate (IV). Three g of D-1,2-isopropylideneglyceryl-3-stearate was dissolved in 20 ml of ether. The solution was cooled in an ice-bath and 20 ml of ice-cold, concentrated hydrochloric acid was added with stirring. The reaction mixture was kept for 20 min in an ice-bath and then diluted with 100 ml of ice-cold water. After the mixture was kept for a further 20 min in an ice-bath, the precipitate was filtered off with suction, washed with ice-cold water, dried over sodium hydroxide and phosphorus pentoxide and identified as L-3-stearoylglycerol (VI) in recovery of 90 to 93% of theory. On recrystallization from warm ether gave 2.3 g (80% yield) of pure L-3-stearoylglycerol. Specific rotation −3.6 °, c, 10 in pyridine; m.p. 76–77 °C, and on titration with periodic acid[16]) assayed for pure 1-isomer (100%). Baer and Fischer[2]) reported for L-3-stear-

oylglycerol the same m.p. 76–77 °C, and a specific rotation of −3.58 °, c, 12.3 in pyridine. A mixed m.p. showed no depression.

(b) L-3-Stearoylglycerol (VI), from D-1,2-epoxyglyceryl-3-stearate (V). Three g of D-1,2-epoxyglyceryl-3-stearate (V) was dissolved in 20 ml of ether cooled to 0 °C and then hydrated with 20 ml of ice-cold, concentrated hydrochloric acid as described above in (a). On recrystallization from warm ether gave 2.5 g (80% yield) of pure L-3-stearoylglycerol (VI), m.p. 76–77 °C; specific rotation −3.6 °, c, 10 in pyridine, and on titration with periodic acid[16]) proved to be 100% 1-isomer. This compound was identical with that obtained from D-1,2-isopropylideneglyceryl-3-stearate (IV).

EXPERIMENT NO. 2

L-3-benzylglyceryl-1-p-toluenesulfonate

L-3-Benzylglycerol 18.2 g (0.1 M) dissolved in 30 ml of anhydrous pyridine was mixed with p-toluenesulfonyl chloride 19.1 g (0.1 M) dissolved in 150 ml of dry benzene. The reaction mixture was kept at 20 °C for 24 hr. At the end of this time, 400 ml of ether was added, and the mixture was washed in succession with three 300 ml portions of ice-cold 2N sulfuric acid, two 300 ml portions of saturated bicarbonate solution, and finally with two 300 ml portions of distilled water. The solution was dried with 30 g of anhydrous sodium sulfate, and the solvents were removed by distillation under reduced pressure. The remaining material was kept at 0.02 mm until its weight was constant (27.7 g). Precipitated from 50 ml ether with 250 ml of low boiling petroleum ether at −20 °C gave 25.0 g (74.4% yield based on L-3-benzylglycerol) of a viscous liquid that had d_4^{20}1.2370; n_D^{20}1.5475, and a specific rotation of +3.6 (in substance).

Analysis. Calculated for $C_{17}H_{20}O_5S$(336): C, 60.70; H, 5.98; S, 9.53
Found : C, 60.21; H, 5.95; S, 9.48.

L-3-benzylglyceryl-1-iodide

To a solution of 23.5 g (0.07 M) of L-3-benzylglyceryl-1-p-toluenesulfonate in 200 ml of dry acetone was added a solution of 30.0 g (0.2 M) of sodium iodide in 300 ml of dry acetone. The reaction mixture was refluxed and stirred in the dark for 10 hr. The sodium p-toluenesulfonate was filtered off and thoroughly washed with acetone. The combined filtrates were brought to dryness at reduced pressure, and the residue was dissolved in 500 ml of ether. The ether solution was washed twice with 300 ml portions of 2% sodium thiosulfate solution, twice with 300 ml portions of distilled water, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The remaining material was submitted to vacuum distillation at

118–120 °C/0.03–0.04 mm which gave 13.0 g (63% of theory) of pure L-3-benzylglyceryl-1-iodide; d_4^{20}1.5200; n_D^{20}1.5685; specific rotation +1.7° (in substance).

Analysis. Calculated for $C_{10}H_{13}O_2I$(292):C,41.11; H,4.50; I,44.44
Found :C,40.98; H,4.64; I,44.00.

L-3-benzyl-2-stearoylglyceryl-1-iodide

To a solution of 11.7 g (0.04 M) of freshly prepared L-3-benzylglyceryl-1-iodide in 50 ml of dry benzene and 10 ml of anhydrous pyridine was added a solution of 12.2 g (0.04 M) of freshly distilled stearoyl chloride[15]) in 50 ml of dry benzene. The reaction mixture was kept under anhydrous conditions at 40 °C for 14 hr then diluted with 400 ml of ether, washed with ice-cold 2 N sulfuric acid, sodium bicarbonate solution and water, dried with anhydrous sodium sulfate and the solvents were removed under reduced pressure. The residue was redissolved in 150 ml of ethanol, cleared by centrifugation and the supernatant liquid kept at −20 °C for crystallization. L-3-benzyl-2-stearoyl-glyceryl-1-iodide, a soft, white substance, was obtained 19.0 g (85% yield); m.p. 25–26 °C; specific rotation of +2.2°, c, 10 (chloroform).

Analysis. Calculated for $C_{28}H_{47}O_3I$(559): C, 60.20; H, 8.50; I, 22.72
Found : C, 60.71; H, 8.62; I, 22.30.

Reaction of sodium D-1,2-isopropylideneglyceroxide (I) *with L-3-benzyl-2-stearoylglyceryl-1-iodide* (II), *reaction scheme, fig. 2*

This experiment was carried out under identical conditions as above. Sodium D-1,2-isopropylideneglyceroxide 4.6 g (0.03 M) was suspended in 100 ml of dry toluene, and to the suspension 16.8 g (0.03 M) of L-3-benzyl-2-stearoylglyceryl-1-iodide dissolved in 100 ml of dry toluene was added. The reaction mixture was stirred for 10 hrs at 20 °C, and then was separated as described in the first experiment. The residue, weighing 15.5 g, was dissolved in 60 ml of ethanol, cleared by centrifugation, and the supernatant solution on standing overnight at −6 °C deposited 10.5 g (87.5% of theory) of white crystalline substance, which was identified as D-1,2-isopropylideneglyceryl-3-stearate (IV), specific rotation −2.2°, c, 10 in chloroform, m.p. 40–41 °C. Authentic D-1, 2-isopropylideneglyceryl-3-stearate[2]) has the same m.p. 40–41 °C, and specific rotation of −2.2°, c, 10 in chloroform.

On hydrolysis of its protective isopropylidene group as described above, it gave L-3-stearoylglycerol (VI), which was identical with the authentic L-3-stearoylglycerol[2]).

Isolation of L-3-benzyl-2,1-epoxyglyceryl ether (V)

The filtrate from crystallization of D-1,2-isopropylideneglyceryl-3-stearate

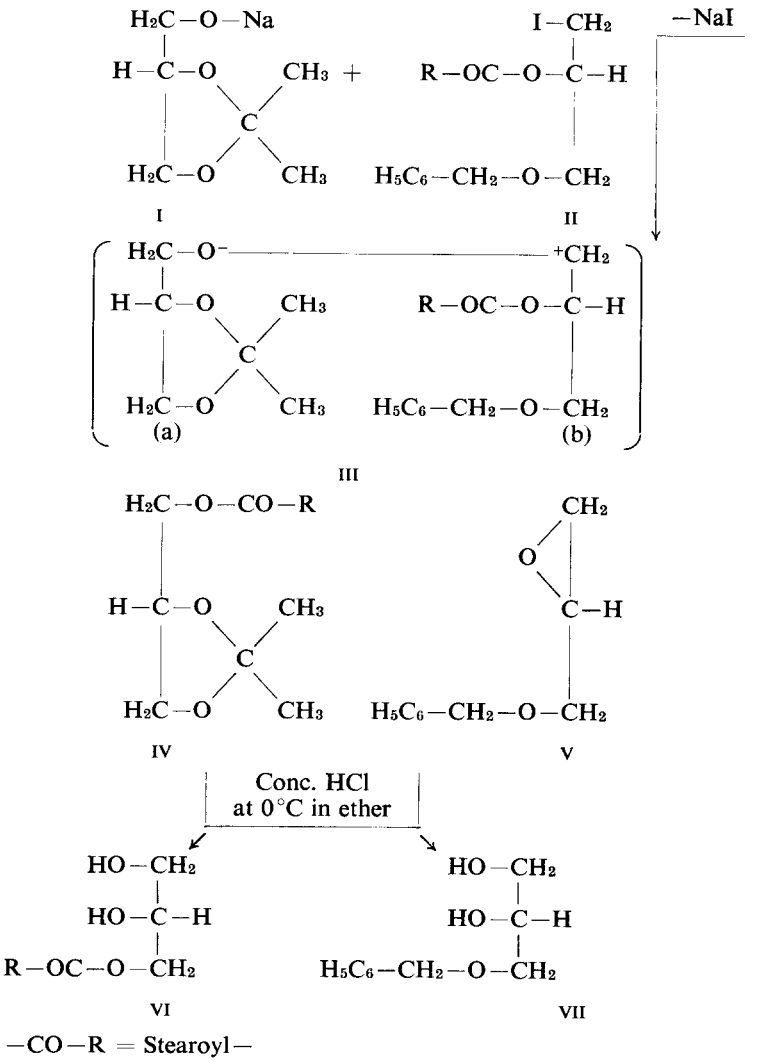

Fig. 2.

(IV) was concentrated under reduced pressure and the residue 5.0 g was submitted to vacuum distillation; at 58–59 °/0.02 mm were collected 4.3 g (82.5% of theory) of a liquid which was identified as L-3-benzyl-2,1-epoxy-glyceryl ether (V), n_D^{20}1.5165, d_4^{20}1.0576.

Analysis. Calculated for $C_{10}H_{12}O_2$(164): C,73.18; H,7.37
Found : C,73,09; H,7.57.

On hydrolysis of epoxy ring the compound V gave almost quantitatively L-3-benzylglycerol ether (VII), with the specific rotation of +2.5 °, c, 10 (in

chloroform). Authentic L-3-benzylglycerol ether[11]) has the same specific rotation of +2.5°, c, 10 in chloroform.

EXPERIMENT NO. 3

D-1-stearoylglyceryl-3-p-toluenesulfonate

To a solution of 71.0 g (0.2 M) of D-1-stearoylglycerol in 130 ml of anhydrous pyridine was added a solution of 38.2 g (0.2 M) of p-toluenesulfonyl chloride in 300 ml of dry benzene. The reaction mixture was shaken at 20 °C for 24 hr. At the end of this time, 1000 ml of ether was added, and the reaction mixture was washed in succession with 600 ml portion of distilled water, two 600 ml portions of ice-cold 2 N sulfuric acid, two 600 ml portions of saturated sodium bicarbonate solution, and finally with two 600 ml portions of distilled water. The solution was dried with 100 g anhydrous sodium sulfate, and the solvents were removed by distillation under reduced pressure. The remaining material (97 g) was recrystallized from 300 ml of ethanol at −6 °C. The D-1-stearoylglyceryl-3-p-toluenesulfonate (77.0 g, 75% yield) was obtained, which has a very small specific rotation in chloroform solution.

Analysis. Calculated for $C_{28}H_{48}O_6S$(513): C,65.60; H,9.43; S,6.25
Found : C,65.56; H,9.52; S,6.30.

D-1-stearoylglyceryl-3-iodide

To a solution of 76.5 g (0.15 M) of D-1-stearoylglyceryl-3-p-toluenesulfonate in 500 ml of dry acetone was added a solution of 45 g (0.3 M) of sodium iodide in 500 ml dry acetone. The reaction mixture was refluxed and stirred in the dark for 14 hr. The sodium p-toluenesulfonate was filtered off and washed with acetone. The combined filtrates were concentrated under reduced pressure, and the residue was dissolved in 1000 ml of ether. The ether solution was washed twice with 600 ml portions of 2% sodium thiosulfate solution, twice with 600 ml of distilled water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The remaining material was recrystallized from ethanol at −6 °C. D-1-Stearoylglyceryl-3-iodide (54.0 g, 77.5% yield) was obtained; m.p. 66–67 °C; specific rotation +2.0°, c, 10 in chloroform.

Analysis. Calculated for $C_{21}H_{41}O_3I$(468): C,53.84; H,8.80; I,27.10
Found : C,53.90; H,8.72; I,27.20.

Reaction of sodium D-1,2-isopropylideneglyceroxide (I) *with D-1-stearoylglyceryl-3-iodide* (II), *reaction scheme, fig. 3*

The reaction was carried out under the identical conditions as previous

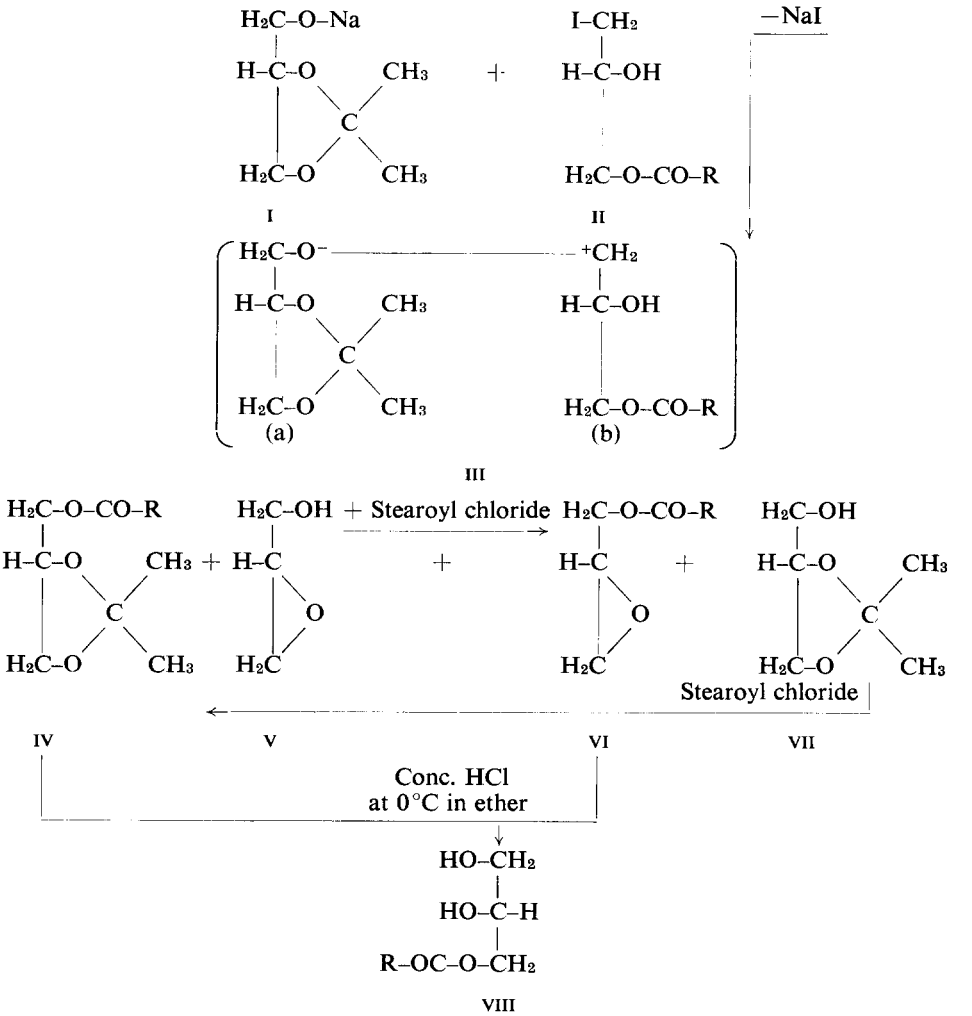

Fig. 3.

experiments. Sodium D-1,2-isopropylideneglyceroxide (I) 17.0 g (0.11 M) was suspended in 200 ml of dry toluene and to this suspension 52.0 g (0.11 M) D-1-stearoylglyceryl-3-iodide (II) dissolved in 200 ml of dry toluene was added. Sodium iodide was formed immediately. The reaction mixture was stirred for 10 hr at 20 °C, and then separated as described above. The residue (weight 51.0 g) was dissolved in 200 ml of ethanol, cleared by centrifugation, and the supernatant was kept overnight at −6 °C. The crystals were filtered in cold and dried over phosphorus pentoxide and sodium hydroxide, 47.0 g of mixture of compound IV and V were obtained. The

mixture was separated by crystallization as described in experiment No. 1, identified as D-1,2-isopropylideneglyceryl-3-stearate (IV) and D-1,2-epoxyglyceryl-3-stearate (VI). Both compounds IV and VI on hydrolysis of isopropylidene group and epoxy ring gave exclusively L-3-stearoylglycerol (VIII).

Isolation of D-1,2-Epoxyglycerol (V) *and D-1,2-Isopropylideneglycerol* (VII)

The mother liquor from crystallization of compounds IV and VI was concentrated under reduced pressure and the residue was distilled at 52–70 °C/9 mm and 4.0 g of a mixture of D-1,2-epoxyglycerol (V) and D-1,2-isopropylideneglycerol (VII) were collected. These two compounds without isolation were acylated with stearoyl chloride[15]) to D-1,2-isopropylideneglyceryl-3-stearate (IV) and D-1,2-epoxyglyceryl-3-stearate (VI), and then isolated as described in experiment No. 1. Both these compounds on hydrolysis of isopropylidene group and epoxy ring gave L-3-stearoylglycerol (VIII).

EXPERIMENT NO. 4

Reaction of sodium D-1,2-isopropylideneglyceroxide (I) *with D-1,2-distearoylglycerol* (II), *reaction scheme, fig.* 4

Sodium D-1,2-isopropylideneglyceroxide (I) was prepared from 5.3 g (0.04 M) of D-1,2-isopropylideneglycerol as described in the first experiment. To the suspension of compound (I) in 150 ml of toluene, 25.0 g (0.04 M) of D-1,2-distearoylglycerol (II) dissolved in 200 ml of toluene was added. The reaction mixture was stirred at 20 °C for 4 hr, and then worked up as follows: Most of the toluene was removed by distillation under reduced pressure, and the residue was extracted with chloroform. The clear chloroform extracts were combined and concentrated by distillation under reduced pressure. The residue (23.0 g) was again extracted twice with 50 ml portions of hot absolute ethanol. From ethanol extract was recovered 9.4 g (40% of theory) of D-1,2-isopropylideneglyceryl-3-stearate (IV), with a specific rotation of −2.2 °, c, 10 (in chloroform); m.p. 40–41 °C.

Analysis. Calculated for $C_{24}H_{46}O_4$(396): C,72.40; H,11.56
Found (401): C,72.91; H,11.57.

Isolation of bis(DL-1,2-glyceryldistearate)-3-ether (V)

The residue (9.2 g) insoluble in ethanol was dissolved in 40 ml of chloroform. The solution was cleared by centrifugation, and on standing overnight at −6 °C deposited 8.8 g of a crystalline material which was identical with the synthetic bis (DL-1,2-glyceryldistearate)-3-ether; m.p. 75–76 °C.

Analysis. Calculated for $C_{78}H_{150}O_9$(1232): C,76.03; H,12.25
Found (1196): C,76.94; H,12.29.

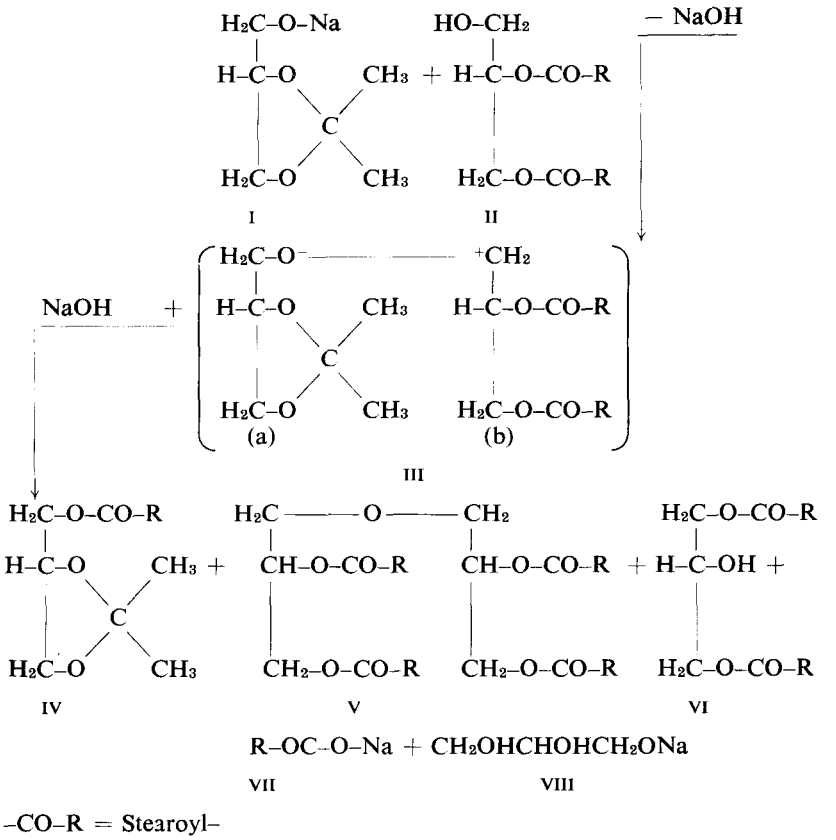

Fig. 4.

Isolation of sodium stearate (VII)

The residue (6.4 g) which was insoluble in chlorioform was dissolved in water. The portion insoluble in water was identified as sodium stearate (VII) which on hydrolysis with hydrochloric acid gave 3.0 g (14% of theory) of stearic acid, m.p. 69.5 °C. The mixed melting point with authentic stearic acid showed no depression.

Isolation of glycerol (VIII)

The water solution was acidified with hydrochloric acid, concentrated by distillation under reduced pressure to dryness and the residue extracted with ethanol. The ethanol solution was concentrated again under reduced pressure and the residue submitted to vacuum distillation recovered 2.0 g of glycerol b.p. 118–120 °C/0.04 mm. The portion insoluble in ethanol (2.1 g) was identified as sodium chloride.

By thin-layer chromatography 1,3-distearin (VI) was also detected, but it was impossible to isolate the small quantity. According to the spot size, the mixture might possibly have contained approx. 5% of 1,3-distearin.

Discussion

According to the experimental results of these investigations it has been demonstrated that sodium 1,2-isopropylideneglyceroxide reacts readily with 1,2-distearoylglyceryl-3-iodide, 1-benzyl-2-stearoylglyceryl-3-iodide and 1-stearoylglyceryl-3-iodide, respectively. The elimination of sodium iodide from these reactions, coincides with the formation of an ion pair which then rearranges its stearoyl groups to form 1,2-isopropylideneglyceryl-3-stearate, 1,2-epoxyglyceryl-3-stearate and 1-benzyl-2,3-epoxyglyceryl ether, respectively. Further, it has also been shown that the hydroxyl group and hydroxyl hydrogen atom are subjected to rearrangement within this ion pair. Furthermore, it has been proved that when the acyl group or acyl groups are attached only to one glyceryl moiety of this ion pair, then they follow migration rules, intermolecular and intramolecular, (experiment No. 1,3). However, when acyl groups are attached to the both glyceryl moieties of the ion pair, then it appears that, in such a case, the acyl groups are subjected to an intermolecular exchange between the two moieties which form this ion pair.

Moreover, the results of the first three experiments have proved definitely that, in these three cases, the acyl migration is stereospecific, and that this stereospecificity in acyl migration is ascribed to the fact that the radicals within ion pair are directing the position to which the acyl groups have to be attached. Winstein *et al.*[17,18]) have used ion pairs in order to rationalize the mechanism and stereochemistry of solvolysis and other organic reactions. Hoge-Esch and Smid[19]) studied the solvent-separated ion pairs of carbanions.

The concept of ion pairs has also been successfully applied by Cram *et al.*[20]) in their extensive investigations of the steric mechanism of electrophilic substitutions at saturated carbon. In the reactions of sodium 1,2-isopropylideneglyceroxide with glyceride iodohydrin or partially acylated glyceride it has been proved that the formation of ion pairs takes place , which catalyses the stereospecific acyl groups migration; therefore, this catalytic effect cannot be ascribed to the sodium 1,2-isopropylideneglyceroxide as it is generally accepted. This fact is also confirmed by the results of the experiment No. 4, which are entirely different from those of the other three previous experiments (No. 1, 2, 3).

Finally, the inversion of the compounds I and II (experiment No. 1, 2, 3) and compound I (experiment No. 4) to L-3-stearoylglycerol (VI and VIII),

fig. 1, 2, 3, is due to the stearoyl group migration. The experimental evidence of these investigations (Part I and II) leads to the conclusion that acyl migration in polyhydroxylic systems involves two step reaction. First, formation of an ion pair, and second, an acyl exchange or rearrangement between these two radicals, which form this ion pair. This is in contrast to the classical conception of an intramolecular rearrangement of acyl group via a cyclic orthoester intermediate[21-29]).

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