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NUCLEOPHILIC SUBSTITUTION IN GLYCEROL DERIVATIVES, PART II:[1] UNSYMMETRICAL DIOXOLENIUM IONS AS INTERMEDIATES IN THE REACTIONS OF DIACYLGLYCEROSULPHONATES WITH CARBOXYLATE IONS

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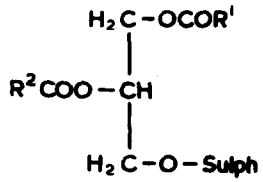
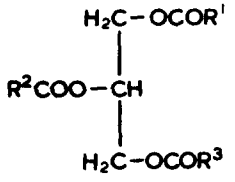
The recent[3,4,5] revival of interest in the use of halo-deoxy and related derivatives of partial glycerides as intermediates in the syntheses[6-9] of mixed acid triglycerides, prompts us to present the results of our studies on nucleophilic substitution in diacyl-glycero-sulphonates by carboxylate ions.

Diacylglycero-3-sulphonates I and II and the glycero-2-sulphonates III and IV were used as the substrates, with benzoate or fatty alkyl carboxylate ions as the nucleophiles. In a typical experiment, a solution of 1,2-di stearoyl-sn-glycero-3-methanesulphonate (I) and tetrabutylammonium oleate in dry acetonitrile was heated under reflux for 2 hr. Work-up gave a triglyceride fraction (76% yield). Analysis by the usual lipolysis procedure[10] showed that the triglyceride was a mixture of 1,2-distearoyl-sn-glycero-3-oleate[11] (V), 92%, and 1,3-distearoyl-rac-glycero-2 oleate (VI), 8%. Similarly, using sodium benzoate in place of tetrabutylammonium oleate, a mixture (43% yield) of 1,2-distearoyl-sn-glycero-3-benzoate, m.p. 60.1°, $[\alpha]_D^{21}$ + 2.3°, (VII), 95%, and 1,3-distearoyl-rac-glycero-2-benzoate (VIII), 5%, was obtained[12]. Almost identical results were obtained when the p-toluene-sulphonate II, m.p. 75.4°, $[\alpha]_D^{21}$ + 3.9°, was used as the substrate or when benzene was used as the reaction solvent. Similarly, reaction of 1-palmitoyl-3-stearoyl-rac-glycero-2-methanesulphonate (III), m.p. 64.6°, or the p-toluene-sulphonate, (IV), m.p. 54.0° with sodium benzoate, in solution in acetonitrile under reflux, produced a mixture (50% yield) of 1-palmitoyl-2-benzoyl-rac-glycero-3-stearate (IX), 5%, and the isomeric 1- & 3-benzoates



I $R^1=R^2=C_{17}H_{35}$, Sulph=$MeSO_2$

II $R^1=R^2=C_{17}H_{35}$, Sulph=p-$MeC_6H_4SO_2$

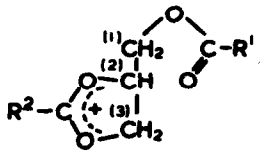


V $R^1=R^2=C_{17}H_{35}$, $R^3=C_{17}H_{33}$

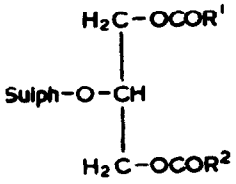
VII $R^1=R^2=C_{17}H_{35}$, $R^3=C_6H_5$

X $R^1=C_{15}H_{31}$, $R^2=C_{17}H_{35}$, $R^3=C_6H_5$

XI $R^1=C_6H_5$, $R^2=C_{15}H_{31}$, $R^3=C_{17}H_{35}$

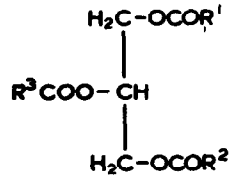


XII



III $R^1=C_{15}H_{31}$, $R^2=C_{17}H_{35}$, Sulph=$MeSO_2$

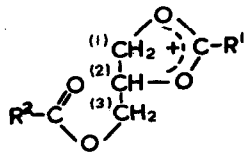
IV $R^1=C_{15}H_{31}$, $R^2=C_{17}H_{35}$, Sulph=p-$MeC_6H_4SO_2$



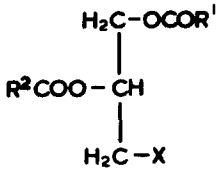
VI $R^1=R^2=C_{17}H_{35}$, $R^3=C_{17}H_{33}$

VIII $R^1=R^2=C_{17}H_{35}$, $R^3=C_6H_5$

IX $R^1=C_{15}H_{31}$, $R^2=C_{17}H_{35}$, $R^3=C_6H_5$

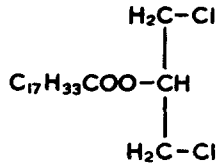


XIII



XIV X = Br

XV X = Cl



XVI

(95%), i.e. an equimolar mixture of 1-palmitoyl-2-stearoyl-rac-glycero-3-benzoate (X) and 1-benzoyl-2-palmitoyl-rac-glycero-3-stearate (XI). The reaction with 2-sulphonates was slower than with 3-sulphonates. In all cases, diglycerides (mixtures of 1,3- and 1,2-isomers) were by-products.

The results show that the 3-sulphonates (I, II), as well as the 2-sulphonates (III, IV) yield the same proportion of the corresponding 3-benzoates and the 2-benzoates in the products; with optically active I and II, the products V and VII retain their configuration. Obviously, substitution is accompanied by acyloxy migration but the extent of migration is very different for structurally isomeric substrates. It is reasonable to infer that the displacement of the sulphonate group in I - IV occurs with participation by the neighbouring carboxylate ester and proceeds via the Winstein[13] type dioxolenium ion XII as the reaction intermediate. In contrast with the symmetrical dioxolenium ion obtainable from 2-acetoxycyclohexyl tosylate[13], the intermediate XII is unsymmetrically substituted and attack on it by the incoming nucleophile is highly regioselective towards the terminal carbon atom; the inductive effect of the carboxylate group on C-1 and the inevitable (from models) better alignment of the incoming nucleophile for reaction at C-3 than at C-2, together appear to ensure this[14]. Presumably, in the case of the intermediate from I and II, this attack occurs (largely) on the same terminal carbon atom (C-3) as was previously occupied by the sulphonate group, although experimental evidence for, or against isomerisation[15] of XII into XIII and subsequent attack on the other terminal carbon atom (C-1) is not available.

Two recent publications[3,4] respectively describe (i) the reactions of 1,2-diacyl-3-bromodeoxy-rac-glycerols (XIV) with potassium salts of fatty acids in boiling chloroform solution in the presence of trimethylbenzylammonium chloride, and (ii) the reactions of 1,2-diacyl-3-chlorodeoxy-rac-glycerols (XV) with sodium salts of fatty acids in hot dimethylformamide. In contrast with our findings that 5-8% of the triglyceride product from the 3-sulphonates I and II is formed by substitution with acyloxy migration from C-2 to C-3, such migration was not noted for the halodeoxy glycerides XIV and XV[3,4]. In common with some earlier reports[6-9], it is implied that these reactions proceed by direct substitution at C-3.

However, in view of the well known general similarity between sulphonate and bromide as leaving groups, and the demonstrated[13] identical behaviour of 2-acetoxy-cyclohexylsulphonates and 2-acetoxy-cyclohexyl bromide towards nucleophiles, it is plausible that the reactions of XIV and XV proceed via the dioxolenium ion XII and that substitution is accompanied by some acyloxy migration. Additional support for this view is provided by our observation[16] that for the closely related reaction of 1,3-dichlorodideoxy-glycero-2-oleate XVI with sodium stearate in dimethylformamide, the product is not[17] pure 1,3-distearoyl-rac-glycero-2-oleate (VI) but contains 5-10% of 1,2-distearoyl-rac-glycero-3-oleate (V) as well.

In general, the separation of isomeric triglycerides from mixtures is difficult. Therefore, substitution reactions of the type discussed above can be used for the synthesis of high purity mixed acid triglycerides only when reliable easy means for purification are available.

Micro analyses and spectral data for all new compounds were in accord with the structures shown.

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11. The configuration was assigned by analogy with the corresponding 3-benzoate (VII).
12. The ratio of 3-benzoate to 2-benzoate in the product was determined as follows: crystallisation from acetone gave crystals of pure 3-benzoate and m. liquors containing a mixture of 2- and 3-benzoates; the yield of the m.liq together with the relative intensities of signals at τ 4.58 ($\underline{H}COCOC_{17}H_{35}$) and 4.50 ($\underline{H}COCOC_6H_5$) in its 220 MHz ^{1}H NMR were used to compute the ratio 3-benzoate : 2-benzoate in the product.
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