Nucleophilic Substitution without Neighbouring Acyloxy-group Participation.[1] Reaction of Acylglycerols with the Reagent System Triphenylphosphine–Diethyl Azodicarboxylate–Carboxylic Acid

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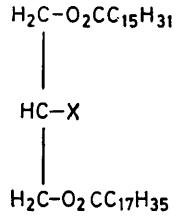
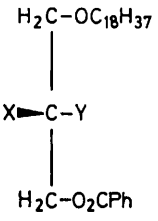
Summary Nucleophilic substitution of HO by RCO_2 at C-2 in acylglycerol derivatives proceeds without acyloxy migration from C-1/C-3 in a ready reaction with the triphenylphosphine-diethyl azodicarboxylate-carboxylic acid reagent system; the reaction is useful for the transformations of partially acylated chiral glycerides into carboxylic esters of the enantiomeric series.

NUCLEOPHILIC substitution reactions at C-2 in C-1/C-3 acylated glycerol derivatives are dominated by neighbouring acyloxy group participation and 1,2- (and/or 3,2-) acyloxy migration.[2-4] Consequently, such reactions have found little application in syntheses. In a search for methods for the control and prevention of such reactivity,





(I) X = OH
(II) X = O_2CPh
(III) X = $O_2CC_{17}H_{33}$
(IX) X = $Ph_3\overset{+}{P}O, \bar{O}_2CPh$

(IV) X = HO, Y = H
(V) X = H, Y = O_2CMe
(VI) X = H, Y = O_2CPh
(VII) X = $MeCO_2$, Y = H
(VIII) X = $PhCO_2$, Y = H
(X) X = $Ph_3\overset{+}{P}O, \bar{O}_2CPh$, Y = H

we reported recently that the reaction of PPh_3–CCl_4 with acylglycerol carrying a hydroxy-group at C-2 gives an enantiomeric 2-chlorodeoxy derivative.[2] We report now that the reaction of related acyl glycerols with the reagent PPh_3–diethyl azodicarboxylate–carboxylic acid causes an S_N2 type substitution of the hydroxy group at C-2 by a new acyloxy residue, without concomitant acyloxy migration from C-1 (and/or C-3).

A solution of 1-palmitoyl-3-stearoyl-*rac*-glycerol (I) and PPh_3 in anhydrous Et_2O, at 20°, was treated successively with diethyl azo dicarboxylate and benzoic acid. The product was 1-palmitoyl-2-benzoyl-3-stearoyl-*rac*-glycerol (II). Use of oleic acid in place of benzoic acid yielded 1-palmitoyl-2-oleoyl-3-stearoyl-*rac*-glycerol (III). Reaction of the chiral substrate 3-benzoyl-1-octadecyl-*sn*-glycerol (IV)† with PPh_3, diethyl azodicarboxylate, and acetic acid, in Et_2O at 0°, gave 2-acetyl-1-benzoyl-3-octadecyl-*sn*-glycerol (V), $C_{30}H_{50}O_5$, m.p. 28°, $[\alpha]_D$ + 0·9°; with benzoic acid, the same substrate (IV) gave 1,2-dibenzoyl-3-octadecyl-*sn*-glycerol (VI), $C_{35}H_{52}O_5$, m.p. 30—32° $[\alpha]_D$ + 9·6°. For comparison, (IV) was treated with acetyl chloride and pyridine, and with benzoyl chloride and pyridine; the respective products, expected to be (VII) and (VIII), had m.p. 25—27°, $[\alpha]_D$ −1·15°, and m.p. 29—31° $[\alpha]_D$ −9·8°. Comparison of (V) with (VII) and (VI) with (VIII), showed that within experimental limits the reaction proceeds with virtually complete inversion of configuration. Fractions obtained by crystallisation were examined using 220 MHz ^1H n.m.r. spectroscopy and by lipolysis, as described earlier for chiral glycerides;[3,4] this showed that all the substitution products were free from structural isomers. The yields (not optimised) ranged from 50 to 70%.

On past experience, the reaction of alcohols with PPh_3–diethyl azodicarboxylate–carboxylic acid is regarded as formally equivalent to the reaction of the corresponding sulphonate esters of the alcohol with carboxylate ions. Clearly, our reactions do not follow the course typified by the toluene-*p*-sulphonate ester of (I) with benzoate ions in MeCN, which produces a mixture of structurally isomeric 1-, 2-, and 3-benzoates.[2] Nevertheless, a tentative mechanism for these substitution reactions follows from an earlier suggestion,[5] that initial interaction between the reagents and an alcohol yields an alkoxy-triphenylphosphonium carboxylate salt as an intermediate. Accordingly, the phosphonium salts (IX) and (X) are expected to be intermediates in the reactions of (I) and (IV) respectively. The structure and the stereochemistry of the final products suggest that triphenylphosphine oxide is displaced by carboxylate in a concerted S_N2 type process.‡

The reaction discussed in this communication provides the only method available so far for conversion of partial acyl-glycerols into esters of the enantiomeric series. Its application is expected to result in a considerable simplification and economy of steps in the syntheses of glycerolipids, especially those belonging to the 1-*sn*-glycerol series.†

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† For details of the stereospecific numbering (*sn*) nomenclature (recommendations of the I.U.P.A.C.–I.U.B. Commission on the nomenclature of lipids) see *Biochim. Biophys. Acta*, 1971, **152**, 1.

‡ For the related reaction of acylglycerols with PPh_3–CCl_4, the intermediary alkoxy-triphenylphosphonium chloride has been questioned on kinetic and other evidence (refs. 2, 6, and R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 1970, **35**, 1627; *ibid.*, 1971, **36**, 403). An alternative requiring fragmentation of a structurally isomeric alkoxychlorotriphenylphosphorane,[2,4,6] to triphenylphosphine oxide and alkyl chloride is even less acceptable because geometrical constraint to the mandatory 4-membered cyclic transition state of the proposed ($\sigma 2_s + \sigma 2_a$) process is severe (R. Aneja, A. P. Davies, and J. A. Knaggs, presented to the Organic Reaction Mechanisms Subject Group Meeting, The Chemical Society, Canterbury, 19—20th July 1973) and further, the fragmentation is equivalent to an endocyclic displacement (L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **53**, 2059).

[1] For previous paper in the series, see R. Aneja and A. P. Davies, *J.C.S. Perkin I*, 1974, 141.
[2] R. Aneja, A. P. Davies, and J. A. Knaggs, *J.C.S. Chem. Comm.*, 1973, 110.
[3] R. Aneja and A. P. Davies, *Tetrahedron Letters*, 1972, 4497 and references therein.
[4] R. Aneja and A. P. Davies, *Chem. Phys. Lipids*, 1974, **12**, 375 and references therein.
[5] O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Japan*, 1967, **40**, 2380; O. Mitsunobu and M. Eguchi, *ibid.*, 1971, **44**, 3427.
[6] R. Aneja, A. P. Davies, and J. A. Knaggs, *Tetrahedron Letters*, 1974, 67.