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SUGAR ESTERS—IV

THE PREPARATION OF CHLOROESTERS UNDER ESSENTIALLY-NEUTRAL CONDITIONS

J. B. Lee and I. M. Downie
Department of Chemistry, Loughborough University of Technology, Leicestershire

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Abstract—A method is described for the conversion of hydroxy-esters to chloroesters using very mild conditions. The reaction proceeds with inversion of configuration at the reacting centre. Neighbouring optical centres are not affected.

The variety of routes available for the preparation of haloesters from hydroxy- or unsubstituted esters, either employ fairly vigorous reaction conditions, e.g. the direct action of halogens or halogenating agents upon esters,[1] or involve several stages, e.g. conversion of hydroxy-esters to their sulphonyl derivatives,[2] followed by Finkelstein reaction with a metal halide.[3]

Some difficulty in preparing halo esters we required was due to the sensitivity of our compounds to acidic or basic reagents. Since we found the Rydon method of conversion of hydroxyl groups to halides[4] unsatisfactory, we sought an alternative mild method for the preparation of the desired compounds. We report here a method for preparing chloro or bromo esters which proceeds under neutral conditions with very short reaction times at about 80°.

When a hydroxy-ester is mixed with a tertiary phosphine in carbon tetrachloride and the mixture warmed to about 80°C, a rapid reaction ensues with production of phosphine oxide, chloroester and chloroform. Even with α-hydroxy esters, which are possibly the most hindered sterically of the straight chain esters, reaction proceeds smoothly. Use of carbon tetrabromide gives rise to the corresponding bromo ester. Providing water is excluded from the mixture (HCl is formed otherwise) the reaction conditions are neutral throughout, and the separation of product is uncomplicated. Thus when ethyl lactate and triphenyl phosphine were mixed in equimolar amounts in carbon tetrachloride as solvent, and the mixture heated under reflux for a short time, rapid formation of triphenyl phosphine oxide, ethyl 2-chloropropionate, and chloroform occurred. The identities of the chloro ester and the triphenyl phosphine

[1] E.g. H. T. Clarke and E. R. Taylor, *Org. Syn. Coll.* Vol. 1, 115; C. F. Ward, *J. Chem. Soc.* **121**, 1161 (1922); H. R. Le Seur, *Ibid.* **87**, 1895 (1905); R. H. Horn, *Ibid.* 2900 (1950); H. H. Guest, *J. Amer. Chem. Soc.* **66**, 2074 (1944); **69**, 300 (1947).

[2] Direct chlorination may occur in attempting to prepare the sulphonate ester, particularly if temps are not controlled. Thus, for example, we have observed formation of dimethyl D-(+)-chlorosuccinate in good yield in tosylations of diethyl L-(−)-malate cf. C. L. Butler, A. C. Renfrew, L. H. Cretcher, and B. L. Souther, *J. Amer. Chem. Soc.* **59**, 227 (1937); K. Hess and W. Eveking, *Ber. Dtsch. Chem. Ges.* **67**, 1908 (1934).

[3] E.g. M. F. Clarke and L. N. Owen, *J. Chem. Soc.* 315, 326 (1949); G. Eglington and M. C. Whiting, *Ibid.* 3650 (1950).

[4] H. N. Rydon and S. R. Landauer, *J. Chem. Soc.* 2224 (1953).

oxide were confirmed by comparison of PMR and IR spectra with authentic materials, together with other physical constants, the formation of chloroform was confirmed by GLC and PMR examination.

Under similar conditions ethyl glycollate was converted to ethyl chloroacetate, triphenyl phosphine oxide and chloroform again being the other products. Likewise ethyl mandelate, ethyl 2-hydroxybutyrate, ethyl 4-hydroxybutyrate, ethyl 2-hydroxy valerate, ethyl hydracrylate, and ethyl 7-hydroxyheptoate gave, respectively, ethyl phenylchloroacetate, ethyl 2-chlorobutyrate, ethyl 4-chlorobutyrate, ethyl 2-chlorovalerate, ethyl 3-chloro propionate, and ethyl 7-chloroheptoate. In each case triphenyl phosphine oxide and chloroform were also produced.

Since we were interested in applying this reaction to sugars and terpenes, it was important to know the stereochemical results of the conversion. We therefore examined the action of the reagent upon some optically active esters.

When diethyl L(−)-malate reacted with triphenylphosphine in carbon tetrachloride we were able to isolate a chloroester in good yield from the reaction mixture.

Examination of PMR and IR spectra, and of behaviour on GLC, in comparison with authentic diethyl 2-chlorosuccinate[5] confirmed its identity. The optical rotation and refractive index corresponded to those reported for diethyl D(+)-2-chlorosuccinate confirming that inversion had occurred in its formation, with no noticeable racemization.

Whilst it is unusual for an optical centre adjacent to the reacting centre to be affected in the course of reaction, cases are known where this occurs. For completeness we also examined an ester in which the hydroxyl group was adjacent to the optical centre. The compound, methyl 4-methyl-5-hydroxy-L-pentanoate (I) on treatment with triphenyl phosphine in carbon tetrachloride reacted smoothly to give a chloro ester, (II) analysing correctly for, and having the correct PMR and IR spectra for, the expected product. However, since we were unable to find any authentic data for this product, it was necessary to confirm its optical purity by further reaction. Treatment with potassium acetate[6] converted the halo-ester II to the acetoxy compound III, which with sodium in methanol[7] gave an hydroxyester identical in all respects with the original ester, thus confirming that no racemization of the adjacent optical centre occurred.

The method outlined should prove useful in both sugar and terpene series since 2-hydroxy esters for example are readily available, from nitriles,[8] prepared by the cyanohydrin method,[9] in these series, and esters having free hydroxyl groups in other positions are also reasonably accesible. Preliminary studies carried out here[10] confirm the usefulness of the method, and these will be reported in detail later.

It seems likely that the initial stage in the reaction is the formation of a quasi-phosphonium ion IV by reaction of triphenyl phosphine with carbon tetrachloride. Reaction of the ion IV with the hydroxy compound could then give chloroform and

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[5] I am indebted to D. Brett, Esq., for the gift of a sample of this material.

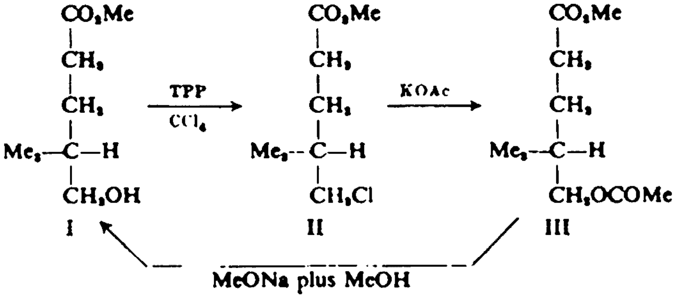
[6] Modified method of B. K. Mereschkowsky, *Liebigs. Ann.* **431**, 231 (1923).

[7] G. Zemplen and A. Kunz, *Ber. Dtsch. Chem. Ges.* **56**, 1705 (1923). G. Zemplen, *Ibid.* **59**, 1254 (1926).

[8] E.g. N. W. Cronyn, *J. Org. Chem.* **14**, 1013 (1949); J. Colonge, *Bull. Soc. chim. Fr.* 245 (1947).

[9] C. S. Hudson, O. Hartley and C. B. Purves, *J. Amer. Chem. Soc.* **56**, 1248 (1934); W. Militzer, *Arch. Biochem.* **21**, 143 (1949).

[10] D. Brett, Thesis Loughborough University (1966).



a second ionic intermediate V of the type usually postulated in the Arbusov reaction;[11] this then would decompose by the usual Arbusov route[11] to give the halide, and the phosphine oxide

$$\varnothing_3P + CCl_4 \rightarrow \varnothing_3\overset{+}{P}CCl_3\overset{-}{Cl}$$

IV

$$(IV) + ROH \rightarrow \varnothing_3\overset{+}{P}OR\overset{-}{Cl} + HCCl_3$$

V

$$\overset{-}{Cl})R{-}\overset{\frown}{O}{-}\overset{+}{P}\varnothing_3 \rightarrow RCl + \varnothing_3PO$$

A somewhat similar scheme was suggested[12] to explain an observation that triethyl phosphite, carbon tetrachloride, and ethanol react together to produce ethyl chloride, triethyl phosphate, and chloroform. In this case reaction probably proceeds[12] *via* the trichloromethyl triethyl phosphonium ion VI and the tetraethyl phosphonium ion VII:

$$(EtO)_3\overset{+}{P}CCl_3\overset{-}{Cl} \qquad (EtO)_4\overset{+}{P}\overset{-}{Cl}$$

VI VII

In the case of ion VII, competition between the four alkyl groups can occur, whereas with ion V only one form of breakdown is possible. Although no other cases were examined, it is likely that the reaction should be general for trialkyl phosphites and alcohols, and we have indeed found it to work with a number of other phosphite esters and alcohols. Reaction is, however, generally much slower, and, as the final stage involves competition for the halide ion between the four substituent groups, the use of these compounds in halide synthesis is limited. By the choice of a suitable alkyl phosphite and alcohol the method may be adapted to give convenient syntheses of phosphate esters, and we have synthesized and examined a number of sugar and terpene phosphate esters by this route.[13]

EXPERIMENTAL

IR spectra: Unicam SP 200, or SP 100, or Perkin–Elmer 237 instruments; PMR spectra. Perkin–Elmer 40 M/C or 60 M/C instruments; GLC: Perkin–Elmer 461 Wilkens Autoprep, or Griffen and George G.D. 4 instruments with a variety of columns.

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[11] B. A. Arbusov, *Zh. Russ. Fiz. Khim. Obshch.* 38, 687 (1906).

[12] P. C. Crofts and I. M. Downie, *J. Chem. Soc.* 2559 (1963).

[13] J. B. Lee, unpublished results cf. J. Furniss, Thesis, Loughborough University (1963).

CCl_4 was dried over $CaCl_2$ followed by distillation, rejecting the first and last quarter of distillate. Triphenylphosphine was dried by dissolution in Na-dried benzene followed by removal of solvent under vacuum, and was stored over P_2O_5.

Commercial samples of hydroxy esters were dried by keeping over Na_2SO_4 followed by distillation *in vacuo*.

Failure to obtain good yields was in most cases traced to inadequate drying of materials and apparatus.

Ethyl 2-chloropropionate. To a mixture of 11·0 ml of ethyl lactate and 25 g triphenylphosphine was added 200 ml anhyd CCl_4, and the soln was heated on a steam bath under reflux, with protection from atmospheric moisture. After approximately 15 min the mixture was distilled under a partial vacuum. (In one preparation propylbenzene was added as a "chaser" to ensure complete recovery of chloroester, but an only slightly better yield was obtained). The distillate was fractionated to give a colourless liquid, (b.p. 140–144°), n_D^{20} 1·4176, which showed a strong band in the IR at 1743 cm^{-1} but no band in the 3100–3500 cm^{-1} region. The PMR spectrum showed bands at approximately T 8·5, 5·5, 5·9 and 8·7.

Authentic ethyl 2-chloropropionate was identical in IR spectrum and behaviour on GLC with this material.

The residue from the reaction mixture was recrystallized from petrol-ether giving a white crystalline powder m.p. 148–149° not depressed on admixture with authentic triphenylphosphine oxide,[14] and identical in IR and PMR spectra with authentic material. The TLC comparison of materials further confirmed their identity.

Examination of the first fractions of the distillate from the reaction mixture by GLC upon carbowax, apiezon and poly-ethyleneglycoladipate columns showed it to be a mixture of chf and CCl_4. The PMR spectrum showed only a singlet T 2·7, confirming the presence of chf.

Ethyl chloroacetate. A soln of 5·0 ml ethyl glycollate in 100 ml CCl_4 was distilled until approximately 25 ml distillate had collected. To the soln was added 11·5 g anhyd triphenylphosphine, and heating was continued under reflux for several min. The mixture was then distilled under slightly red. press. The residue was recrystallized to give triphenylphosphine oxide (identical with authentic material).

The distillate was fractionated, the presence of chf in the first fractions was confirmed, and the fraction b.p. 139–141° was examined by IR (absence of OH, presence of a single ester band) and PMR (peaks at 5·7 T (quartet), 5·95 T (singlet), 8·75 triplet) methods, confirming it as ethyl chloroacetate, n_D^{21} 1·4236.

Ethyl phenylchloroacetate. Equimolar quantities of ethyl mandelate and triphenylphosphine were treated under similar conditions with hot CCl_4. From the mixture ethyl phenylchloroacetate was isolated (b.p. 137–138°/12 min) identical with authentic material in spectral properties.

Ethyl 2-chlorobutyrate. Treatment of ethyl 2-hydroxybutyrate under similar conditions gave ethyl 2-chlorobutyrate, b.p. 160–165°, identical in spectral characteristics with authentic material.

Ethyl 4-chlorobutyrate. Butyrolactone was converted to ethyl 4-hydroxybutyrate,[15] which on treatment under similar conditions gave ethyl 4-chlorobutyrate b.p. 63–68/15 min, n_D^{17} 1·4333, showing peaks in the PMR spectrum at T 6·4, 8·3, 5·85, 8·65 and 7·8.

Ethyl 2-chlorovalerate. Under similar conditions ethyl 2-hydroxyvalerate was converted to ethyl 2-chlorovalerate, b.p. 180–181° identical in spectra to authentic material.

Ethyl 7-chloroheptoate. Ethyl 7-hydroxyheptoate[16] was likewise converted to ethyl 7-chloroheptoate b.p. 101–107°/5 mm.

Ethyl 3-chloropropionate. Ethyl hydracrylate gave ethyl 3-chloropropionate b.p. 159–162°, $n_D^{16·6}$ 1·4284.

Effect on water on reactions. Addition of one molar proportion of water to the mixture of the hydroxy ester, CCl_4 and triphenylphosphine followed by heating briefly upon the steam bath led to production of HCl fumes. From the mixture triphenylphosphine oxide and chf were obtained, but the hydroxy ester has largely recovered unchanged. Traces of hydroxy acid were found.

Diethyl-D-(+)-*2-chlorosuccinate*. Attempted preparation of diethyl L-(−)-malate from L(−)-malic acid by the literature methods gave poor yields largely contaminated with unsaturated esters.

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[14] H. Goetz, F. Nerdel and K. H. Wiechel, *Liebigs Ann.* **665**, 1 (1963).

[15] A. Kailan, *S. Phys. Chem.* **94**, 111 (1919).

[16] R. Robinson and L. H. Smith, *J. Chem. Soc.* 371 (1937).

The following method has generally given almost quantitative yields of diester,[10] which proved particularly useful in some experiments involving the rather expensive D-acid.

A soln of 10·2 g L(−)-malic acid in 280 ml abs EtOH and 150 ml dry benzene was heated under reflux in a flask fitted with a Dean and Stark separator surmounted by a condensor. Approximately 30 ml distillate was removed from the separator. Acetyl chloride was added in five 1 ml/portions *via* the condensor. From time to time fractions were removed from the side arm and equiv volumes of benzene added. Reflux was continued for 4 hr and the mixture set aside overnight. After addition of 100 ml CCl_4, the soln was distilled to half volume and a further 100 ml CCl_4 added. The soln was again distilled to half volume, and 250 ml CCl_4 added. Solvent was again removed at atm. press. until a steady boiling point of 76° was reached.

Solvent was then removed under red. press. and the residue distilled under vacuum to give diethyl L(−)-malate (13·8 g) b.p. 80–82°/0·7 mm, n_D^{21} 1·4362, $[\alpha]_D^{20}$ −9·980 (Lit. values, b.p. 128°/10 mm, n_D^{20} 1·4362 $[\alpha]_D^{20}$ −10·18).

Reaction of diethyl L(−)-*malate with triphenylphosphine*. A mixture of 2·75 g diethyl L(−)-malate and 78 g CCl_4 was distilled to remove approximately 20 ml solvent. To the mixture was added 3·8 g triphenylphosphine and the soln was refluxed on the water bath. After some time a further 5·3 g triphenylphosphine was added. Heating was continued sometime longer. The reaction mixture was fractionated to give diethyl D-(+)-chlorosuccinate, b.p. 48–50°/0·11 mm, n_D^{22} 1·4368, $[\alpha]_D^{20}$ +31°. This showed peaks in the PMR spectrum at T 8·68, 8·72 (two triplets) 5·7, 5·75 (two quartets) 6·9 (doublets) and 5·35 (triplet).