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The Preparation of *α*-Halogeno-*sec.*-alkyl Esters of Aliphatic Acids

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α,β-Dichloro-*sec.*-propyl acetate (b.p. 27—28°C/1.4 torr), *α,β*-dichloro-*sec.*-propyl *n*-butyrate (b.p. 48—50°C/1.3 torr), and *α,β,β'*-trichloro-*sec.*-propyl acetate (b.p. 55—56°C/2.5 torr) have been prepared by allowing acetyl or *n*-butyryl chloride to react with chloroacetone or *sym.*-dichloroacetone in the presence of anhydrous zinc chloride. The reaction is a new one for ketones. *α*-Chloro-*sec.*-propyl acetate was not found among the products of the reaction between acetone and acetyl chloride. *α,β,β'*-Trichloro-*sec.*-propyl acetate was probably also produced when 3-chloropropen-(1)-yl-(2) acetate (b.p. 150—152°C/754 torr) was chlorinated. Other attempts to synthesize the above or other *α*-halogeno-*sec.*-alkyl esters by treating saturated or unsaturated esters with halogens or hydrogen halides did not lead to the expected compounds, the products being always an acid halide and a ketone.

It might be expected that *α*-halogeno-*sec.*-alkyl esters RCOOCXR'R'' (R' and R'' $\neq$ H) could be prepared by the following methods which are similar to those by which primary *α*-halogenoalkyl esters have been synthesized (for references, see Euranto [1-3]): (1) the reaction between a ketone and an acid halide in the presence of anhydrous zinc chloride, (2) the halogenation of *sec.*-alkyl esters, (3) the addition of halogen to the double bonds of *α,β*-unsaturated *sec.*-alkyl esters, and (4) the addition of hydrogen halide to *α,β*-unsaturated *sec.*-alkyl esters. Three reports on the preparation of *α*-halogeno-*sec.*-alkyl esters have been published. Bruylants, Tits, Dieu, and Gauthier [4] have claimed having prepared *α*-chloro-*sec.*-propyl acetate by chlorinating *sec.*-propyl acetate in the gaseous state. On the basis of experimental data presented below, however, it seems probable that the compound evidently produced in the first stage of the reaction reacted further in the described reaction conditions to chloroacetone and acetyl chloride *. On the other hand, Utermohlen [5], has reported on the synthesis of *α,β*-dihalogeno-*sec.*-alkyl and arylalkyl esters of the type $RCOOCXR'CH_2X$ (X = Cl or Br, R and R' are aryl, alkyl, or aryl-

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* Bruylants *et al.* report the boiling point of the ester to be 64—68°C/100 torr. This boiling point seems too low to be that of the ester, but would better represent that of chloroacetone. These authors state that the compound is unstable and lachrymatory; the latter property is typical of chloroacetone. See the experimental part of the present paper.

alkyl groups) by halogenation of the corresponding unsaturated esters. Physical constants for the 1,2-dichloro- and 1,2-dibromo-*sec.*-propyl acetates were given. On the basis of the reported values of the constants, it is obvious that the compound first formed decomposed into the acid halide and the halogenoacetone during the treatment.* One α-halogeno-*sec.*-alkyl ester has evidently been prepared, for Gayler and Waddle [9] obtained a compound which they reported to be α-chloro-*sec.*-propyl trichloroacetate in 25 % yield by the action of chlorine on *sec.*-propyl trichloroacetate at 120°C under exposure to light.

The cases mentioned above refer to reactions (2) and (3). In the case of *sec.*-propenyl acetate, reaction (4) leads to the formation of acetone and acetyl chloride [10]. Also here the initially formed α-halogeno-*sec.*-alkyl ester decomposes into an acid halide and a ketone by a reaction that is the reverse of reaction (1). On the other hand, it has been found that α,β-unsaturated *sec.*-alkyl esters are formed when acetoacetic ester and acetyl or benzoyl chloride react in the presence of pyridine [11] and when aliphatic ketones with a relatively long chain are boiled with benzoyl or valeryl chloride [12]. The intermediate compounds have been assumed to be α-chloro-*sec.*-alkyl esters, which lose hydrogen halide by a reaction which is the reverse of reaction (3). The reaction between acetone and acetyl chloride has been reported to yield the compounds

$$(CH_3)_2CCl-CH_2-CO-CH_3 \quad \text{and} \quad (CH_3)_2CCl-CH_2-CO-CH_2-CCl(CH_3)_2,$$

which react further to mesityl oxide and phorone [13].

In the following the results of experiments are described which were carried out to prepare α-halogeno-*sec.*-alkyl esters for kinetic studies.

EXPERIMENTAL

Analytical

The indices of refraction of the isolated compounds were determined with an Abbe refractometer and the densities with a Sprengel-Ostwald pyknometer. The molar refractions calculated from these values were compared with the theoretical molar refractions derived from refraction equivalents [14]. For analysis, the esters were hydrolysed in water or in an excess of sodium hydroxide solution. The total amount of acids liberated on hydrolysis was determined by acid-base titration and the amount of halide ion formed by titration with silver nitrate. The titrations were performed with a Radiometer titrator TTT 1 employing glass and calomel or silver and mercury/mercury(I) sulphate electrodes.

The progress of the reaction in the syntheses was followed by a kinetic method. Samples withdrawn from the reaction mixture were added to a water-acetone mixture (containing 50 or 75 % acetone by weight). After a period of time sufficient for the remaining acid halide to hydrolyse completely, the hydrolysis reaction was followed by conductometry or by titrating the halide ion produced (*cf.* Refs.[1-3]). In this way it was found whether α-halogenoalkyl esters had been formed and in what amounts. In some cases the acid halides were identified kinetically by determining conductometrically the rate of hydrolysis in water-acetone mixtures containing about 5 % water.

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* The boiling point reported for the former compound was 45—46°C/41 torr and that reported for the latter compound 62—63.5°C/40 torr. The following boiling points have been reported for chloro- and bromoacetone: CH_3COCH_2Cl, 35°C/29 torr [6]; CH_3COCH_2Br, 63.5—64°C/50 torr [7]. The boiling point obtained in the present study for 1,2-dichloro-*sec*-propyl acetate is much higher (see the experimental part). The reaction products were used to prepare 2-amino-4-alkylthiazoles by allowing them to react with thiourea and treating the products with potassium hydroxide. It has long been known that 2-amino-4-methylthiazole can be prepared by the same procedure from chloroacetone and thiourea [8].

Syntheses by method 1

*α,β,β′-Trichloro-*sec.*-propyl acetate.* 9 g (0.11 mole) of freshly distilled acetyl chloride and 14.5 g (0.11 mole) of *sym.*-dichloroacetone, which was obtained as a by-product in an attempt to prepare α,β-dichloro-*sec.*-propyl acetate and which was recrystallized several times, were mixed and a small amount of anhydrous zinc chloride added to the mixture. Heat was evolved and the mixture slowly became dark brown in colour. After the reaction mixture had stood at room temperature about 24 h, it was heated at 50—60°C for one hour. The mixture was then washed with ice water, dried with calcium chloride and distilled twice under reduced pressure. The yield of α,β,β′-trichloro-*sec.*-propyl acetate (b.p. 55—56°C/2.5 torr) was 6 g (26 % of theory). A small amount of unreacted *sym.*-dichloroacetcne was also recovered. Physical data for the ester: n_D^{20} 1.4705, d_4^{20} 1.3905, $[R]_D$ 41.27 (calc. 41.27). Analytical data: On hydrolysis in water 0.738 mmole of the ester yielded 1.328 mmoles of acid and 0.680 mmole of chloride ion. On hydrolysis in sodium hydroxide solution, 0.607 mmole of the ester yielded 2.812 mmoles of acid and 1.780 mmoles of chloride ion. A possible explanation for the analytical results obtained is the following. On hydrolysis in water one equivalent each of hydrogen chloride, acetic acid, and *sym.*-dichloroacetone is formed whereas on hydrolysis by sodium hydroxide the last-mentioned compound decomposes further giving two equivalents of chloride ion and, in addition, some organic acid.

*α,β-Dichloro-*sec.*-propyl acetate.* 44 g (0.56 mole) of acetyl chloride and 38.5 g (0.42 mole) of chloroacetone (b.p. 119.0—119.5°C/748 torr), the latter prepared by chlorinating acetone in the presence of marble chips and purified by washing with water and distilling [15], were mixed. The mixture was cooled in ice before anhydrous zinc chloride was added to it. The reaction mixture first turned green and gradually dark brown. After the mixture had stood several hours at room temperature, it was analysed kinetically and found to contain about 40 % α-chloroalkyl ester. Heating of the reaction mixture to 30—40°C decreased the yield of ester. The reaction mixture was stored about 24 h at room temperature and about 5 days at —6°C. After this treatment, the mixture was washed with a small quantity of ice water, dried with calcium chloride, and distilled under reduced pressure. In addition to unreacted chloroacetone, acetic acid, *etc.*, 45 g (62 % of theory) of pure, colourless α,β-dichloro-*sec.*-propyl acetate (b.p. 27—28°C/1.4 torr) was obtained. Physical data for the ester: n_D^{25} 1.4442, d_4^{25} 1.2474, $[R]_D$ 36.43 (calc. 36.43). Analytical data: On hydrolysis in water 0.637 mmole of the ester gave 1.250 mmoles of acid and 0.623 mmole of chloride ion. On hydrolysis in sodium hydroxide solution 0.596 mmole of ester gave 1.950 mmoles of acid and 1.180 mmoles of chloride ion (*cf.* preceding paragraph).

*α,β-Dichloro-*sec.*-propyl* n*-butyrate.* 65 g (0.61 mole) of *n*-butyryl chloride and 45.5 g (0.49 mole) of chloroacetone (see above) were mixed and cooled in ice water and a small quantity of anhydrous zinc chloride was added to the mixture. The mixture became first yellow and later dark brown. The mixture was kept at room temperature for 16 h, washed with ice water, dried with calcium chloride and distilled under reduced pressure. In addition to *n*-butyryl chloride, chloroacetone, and *n*-butyric acid, 24 g (25 % of theory) of pure, colourless α,β-dichloro-*sec.*-propyl *n*-butyrate (b.p. 48—50°C/1.3 torr) was isolated. Physical data: n_D^{25} 1.4432, d_4^{25} 1.1523, $[R]_D$ 45.82 (calc. 45.74). Analytical results: On hydrolysis in water, 1.017 mmoles of the ester gave 2.009 mmoles of acid and 0.986 mmole of chloride ion. An attempt that was made to distill the crude reaction mixture without washing it with water to remove the zinc chloride led to the complete decomposition of the ester, evidently into the original reactants.

The reaction between acetone and acetyl chloride. A small quantity of anhydrous zinc chloride was added to a mixture of 44 g of acetyl chloride and 32.5 g of acetone. The temperature of the mixture rose and the mixture became first green and later dark brown. Kinetic experiments revealed that possibly a small amount (at most 5 % of theory) of the α-chloroalkyl ester had formed. The amount of ester did not increase when the reaction mixture was allowed to stand at room temperature and at about —6°C. α-Chloro-*sec.*-propyl acetate was not isolated from the mixture, the distillation products containing, besides other compounds, mesityl oxide and phorone.

Syntheses by method 2

The chlorination of sec.*-propyl acetate. sec.*-Propyl acetate was prepared from acetic acid and *sec.*-propanol employing sulphuric acid as catalyst [16]. The ester boiled at 88.2—88.8°C/761.0 torr. The chlorination of the ester was carried out in three different ways: (a) equimolar amounts of *sec.*-propyl acetate and sulphuryl chloride were dissolved in a small volume of carbon tetrachloride and 0.2 mole-% of benzoyl peroxide was added to the mixture (*cf.* Brown and Ash [17]); (b) chlorine gas was led into cold *sec.*-propyl acetate under exposure to ultraviolet light [4] (mercury vapour lamp Philips No. 93 110); (c) chlorine was led into a reaction vessel which contained the gaseous ester and which was irradiated with ultraviolet light [18]. The reaction mixture was in each case distilled in a fractionation assembly. The distillation yielded, in addition to unreacted ester, β-chloro-*sec.*-propyl acetate (b.p. 69—70°C/40 torr) and a fraction boiling in the range 40—60°C/40 torr from which a substance was isolated which according to its boiling point [6] (118—120°C/751 torr), odour [19], and dye reaction [20] was evidently chloroacetone. A kinetic study of the low-boiling part of the fraction in 95 % acetone-water at 15°C gave a rate coefficient of hydrolysis equal to about 1.5×10^{-2} s^{-1}. The rate coefficient of the hydrolysis of acetyl chloride under the same conditions was found to be 2.5×10^{-3} s^{-1}. These experimental data show that the fraction in question probably contained chloroacetyl chloride (b.p. 104.8—104.9°C/743 torr) and dichloroacetyl chloride (b.p. 107.9—108.1°C/766 torr) which solvolyse at a somewhat higher rate than acetyl chloride [21].

Syntheses by method 3

The chlorination of sec.*-propenyl acetate. sec.*-Propenyl acetate was obtained by passing ketene into warm acetone to which sulphuric acid had been added [22]. The compound was chlorinated in the dark either by leading chlorine gas into the ice-cold ester or by adding the ester at about —60°C dropwise to liquid chlorine. The reaction products were distilled under reduced pressure. The distillates were found to contain primarily acetyl chloride and chloroacetone and a small amount of *sym.*-dichloroacetone. Some of the fractions were found kinetically to contain small amounts of some α-chloroalkyl ester, but this compound could not be isolated. The reaction products resulting from the chlorination at —60°C were not found kinetically even before warming and distillation to contain any other compound than acetyl chloride that underwent solvolysis.

The bromination of sec.*-propenyl acetate.* An equimolar amount of bromine was slowly added dropwise to ice-cold *sec.*-propenyl acetate with which it reacted readily. Only bromoacetone and acetyl bromide were isolated from the reaction products.

The chlorination of 3-chloropropen-(1)-yl-(2) acetate. 3-Chloropropen-(1)-yl-(2) acetate was prepared by leading ketene [23] into chloroacetone (see preceding paragraph) which contained 3 mole-% sulphuric acid. The reaction mixture was stirred with a magnetic stirrer and its temperature held at 80—90°C. The mixture was then cooled, the sulphuric acid neutralised with sodium bicarbonate, and the product distilled under ordinary pressure. The fraction boiling in the range 136—160°C was washed with water, dried with calcium chloride and redistilled. A small amount (about 8 ml from 100 g of chloroacetone) of pure, colourless 3-chloropropen-(1)-yl-(2) acetate (b.p. 150—152°C/754 torr, n_D^{20} 1.4378, d_4^{20} 1.1333, $[R]_D$ 31.16 (calc. 31.16)) was isolated. On hydrolysis in sodium hydroxide solution, 0.867 mmole of the ester gave 1.680 mmoles of acids and 0.817 mmole of chloride ion.

The ester was chlorinated in the dark as described above. On distilling the reaction mixture, there was obtained in addition to highly chlorinated matter and substances that had been produced by other reactions (see Discussion) a small amount of matter that probably contained trichloro-*sec.*-propyl acetate identical with that obtained from *sym.*-dichloroacetone and acetyl chloride, which shows that the initial product was actually 3-chloropropen-(1)-yl-(2) acetate. A kinetic study of the product of the chlorination yielded values of the rate coefficient that decreased during the hydrolysis from an initial value that was about 60 % of the value of the rate coefficient obtained for α,β,β'-trichloro-*sec.*-propyl acetate. This result must evidently be ascribed to the presence of some slowly reacting ester whose presence was also indicated by the poorer solubility of the reaction product in 40 % acetone-water (see below).

Syntheses by method 4

The addition of hydrogen chloride to sec.*-propenyl acetate.* Hydrogen chloride gas was directed into *sec.*-propenyl acetate that had been cooled with a mixture of ice and salt. A reaction was observed but no α-chloro-*sec.*-propyl acetate was isolated by distilling the reaction mixture under reduced pressure, probably because the ester had decomposed during the reaction or during the distillation into acetone and acetyl chloride which could not be condensed at the pressure employed.

DISCUSSION

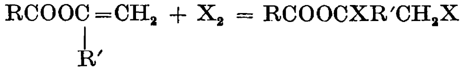
Of the attempted syntheses of α-halogeno-*sec.*-alkyl esters RCOOCXR′R″, only those of α,β-dichloro-*sec.*-propyl acetate, α,β-dichloro-*sec.*-propyl *n*-butyrate and α,β,β′-trichloro-*sec.*-propyl acetate were successful. At least one of the groups R′ and R″ in these compounds contains an electronegative chlorine atom. Of these, the dichloro-substituted compounds where R″ is a methyl group are relatively unstable because heating of the reaction mixture to about 30°C lowered the yield of the ester and distillation of the reaction mixture with zinc chloride led to a complete decomposition of the ester already at pressures so low that the distillation temperature did not exceed 30—40°C. In addition to the α-halogeno-*sec.*-alkyl esters prepared in this study, only α-chloro-*sec.*-propyl trichloroacetate, which has the highly electronegative trichloromethyl group as the acyl group R, has been prepared previously [9], using a temperature as high as 120°C. Aldehydes (R″ = H) react with halogen halides almost quantitatively to α-halogenoalkyl esters at room temperature, but already at about 80°C α-chloroethyl acetate and butyrate and α,β-dichloroethyl acetate and at about 110°C α-chloroethyl chloroacetate decompose into acid chloride and aldehyde in the presence of zinc chloride [24]. The anhydrous zinc chloride obviously only catalyses the reactions, and hence the success of the above distillations in the absence of zinc chloride is due to the fact that the equilibrium did not have time enough to shift during the distillation.

It is hence obvious that the equilibrium

$$\mathrm{RCOX + R'R''CO \rightleftharpoons RCOOCXR'R''}$$

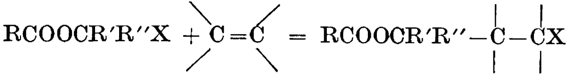
is farther on the left the higher the temperature (the reaction to the right is exothermic) and the more electropositive the groups R, R′ and R″. The polarities of these groups do not, however, alone determine the equilibrium state, since, *e.g.*, α-chloroethyl acetate (R′ = CH_3, R″ = H) is more stable than α,β-dichloro-*sec.*-propyl acetate (R′ = CH_3, R″ = CH_2Cl) although the electronegativity of the chloromethyl group is greater than that of the hydrogen atom (Taft's polar substituent constants σ* are 1.050 for chloromethyl and 0.490 for the hydrogen atom ($\sigma^*_{CH_3} = 0$)) [25].

α-Halogeno-*sec.*-alkyl esters could be more easily prepared from ketones and carboxylic acid halides than by chlorinating α,β-unsaturated *sec.*-alkyl esters, although the reaction products revealed that the following reaction evidently does take place in the latter case:



$$\mathrm{RCOO\underset{\displaystyle R'}{\underset{|}{C}}{=}CH_2 + X_2 = RCOOCXR'CH_2X}$$

It may be noted that *a,β*-dichloro-*sec.*-propyl acetate ($R' = CH_3$, $X = Cl$) was not found in the reaction mixture even when *sec.*-propenyl acetate was chlorinated at −60°C. The reason may be that the chlorination reaction is so exothermic that the ester $RCOOCXR'CH_2X$ first formed decomposes immediately to RCOX and CH_2XCOR', *i.e.* before the energy has dissipated from the reacting molecule. It seems furthermore possible on the basis of the observations made that at least in the chlorination of 3-chloropropen-(1)-yl-(2) acetate a reaction of the type [26]



$$\mathrm{RCOOCR'R''X} + {>}C{=}C{<} = \mathrm{RCOOCR'R''}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}X$$

which leads to high-molecular halogenoalkyl compounds, takes place between the *a*-halogenoalkyl ester already formed and the unsaturated ester that has not reacted.

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