THE REACTION BETWEEN ACID HALIDES AND ALDEHYDES.
III.

BY L. H. ULICH WITH ROGER ADAMS.[1]

In 2 previous papers[2] from this laboratory it has been shown that the reaction between aromatic aldehydes and aromatic acid halides to give halogenated esters is a general one. The various reactions of these compounds were studied and described. This investigation had for its purpose a study of the reactions between aliphatic aldehydes and aliphatic acid halides and between aliphatic aldehydes and aromatic acid halides.

The condensation of aliphatic acid halides and aliphatic aldehydes has been studied previously[3] to some extent, but since a comparison of the preparation and properties of the resulting compounds with the aromatic-aliphatic and aromatic-aromatic condensation products was desired, some of the compounds described in the literature, and in addition, several new ones, were made. When the aliphatic acid halides and aliphatic aldehydes were mixed, they reacted with the evolution of heat. To assure completion of the reaction, the mixture was warmed for a few hours. The condensation took place a little more slowly, the higher the molecular weight of the acid halide and aldehyde; thus while the halogen esters formed from such acid halides and aldehydes as acetyl chloride and formaldehyde or acetaldehyde were perfectly stable, the compound from valeryl chloride and heptaldehyde turned dark in the course of a few hours, and gradual decomposition took place. Substituted acid chlorides reacted just as unsubstituted ones, and acid bromides formed condensation products with aldehydes very readily. The brominated esters were much less stable than the corresponding chlorinated compounds.
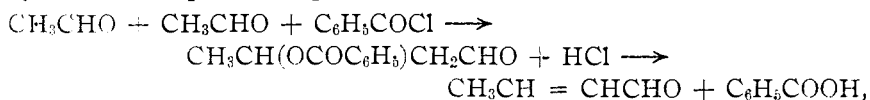
It is reported that benzoyl chloride reacts with paraformaldehyde, but that no condensation will take place between benzoyl chloride and aldehydes of higher molecular weight. In this research it has been shown that benzoyl chloride will condense with aliphatic aldehydes of higher molecular weight to give the expected condensation products. These condensation products form in somewhat poorer yields and with more difficulty than those from aliphatic acid chlorides and aliphatic aldehydes, and refluxing for some time is necessary to get the best results. As by-products, aromatic acids and alkylidene dibenzoate or substituted dibenzoates are always produced. The amount of acid formed is prac-

[2] THIS JOURNAL. 40, 1732 (1918); 43, 651 (1921).
[3] Ibid., 40, 1732 (1918).

tically nil in the case of paraformaldehyde and small when paraldehyde is used. The amount formed as a by-product, however, when butyraldehyde. valerianaldehyde and heptaldehyde are used, is considerable, apparently decreasing slightly with increase in molecular weight of the alde·hyde used. A possible explanation of this acid formation is as follows.

$$CH_3CHO + CH_3CHO + C_6H_5COCl \longrightarrow$$
$$CH_3CH(OCOC_6H_5)CH_2CHO + HCl \longrightarrow$$
$$CH_3CH = CHCHO + C_6H_5COOH,$$

and such an equation would account very well for the fact that the yields of halogenated esters are only 40 to 50% of those calculated. Since an aldol condensation with paraformaldehyde would not take place, the yield of the halogen ester in that case is good and no benzoic acid forms. With paraldehyde, aldol condensation can only form from the acetaldehyde produced by the depolymerization of the paraldehyde in the presence of the acid chloride, consequently the by-product of acid in this reaction is not high. In the condensation of benzoyl chloride with acetaldehyde, butyraldehyde, valerianaldehyde, and heptaldehyde, however, provided the theory of the formation of the acid is correct, the amount of acid produced should be less with the increase in molecular weight of the aldehyde, since the higher aldehydes form aldols less readily than the lower aldehydes. The experimental facts indicated that this is the case. It was impossible to isolate any unsaturated aldehyde, but this would not be expected since such a compound would undoubtedly condense further with benzoyl chloride to give complex products.

The compounds formed from aliphatic acid halides and aliphatic aldehydes are unstable in water, all decomposing in cold water in the course of several hours into the organic acid, aldehyde and halogen acid. The compounds from aromatic acid halides and aliphatic aldehydes, however, are comparatively stable under the same conditions remaining unchanged with water for several days. These latter compounds are even stable to dil. sodium carbonate solution for a considerable time. The stability to water of the compounds from aromatic acid halides and aromatic aldehydes lies between the stability of the other 2 classes.

The halogenated esters just described react immediately in ether solution with ammonia to give acid amide, aldehyde and ammonium chloride. Primary and secondary amines react in a similar manner yielding, respectively, monosubstituted acid amides, alkylidene amines and the halogen acid salt of the amines and disubstituted acid amides, aldehyde and the halogen acid salt of the amines. Aniline causes an analogous decomposition to the primary aliphatic amines.

Aromatic aldehydes and aliphatic acid halides react together vigorously, but under ordinary conditions only tarry products result. By

varying the conditions of reaction, it is hoped that the expected condensation products may be isolated.

Experimental.

For the preparation of the aliphatic-aliphatic addition compounds equimolecular amounts of the aliphatic aldehyde and aliphatic acid halide are mixed in a round-bottomed flask holding a ground stopper fitted with a reflux water condenser. A minute quantity of anhydrous zinc chloride is then added. Upon mixing the aliphatic aldehyde and acid halide, there is considerable heat evolved, in many cases causing the reaction mixture to boil gently. However, the reaction soon subsides and further heating on the water-bath at about 90° for 3 to 4 hours is advisable. At the end of this time the reaction mixture is distilled with a good fractionating column preferably under diminished pressure. The distillate is then redistilled either under atmospheric or diminished pressure. In this manner, from 50 to 70% yields of the halogenated ester boiling over a 2° to 3° range, are obtained.

The aliphatic halogenated esters[1] from paraformaldehyde or paraldehyde are colorless, stable liquids, while those from higher aldehydes are liquids which gradually darken and decompose on standing.

The general method of preparation for the aromatic acid halide-aliphatic aldehyde condensation products, except when paraformaldehyde is used, follows. The aromatic acid halide is heated in a flask, the neck of which holds a ground glass stopper connected to a reflux condenser, and then an equimolecular amount of the aliphatic aldehyde is added slowly from a dropping funnel. The mixture is refluxed gently from $1/2$ to 1 hour. After cooling, it is treated with ether, then shaken with sodium carbonate solution to remove the aromatic acid formed as a side reaction. The ether layer is separated, dried with calcium chloride and distilled, the ether under ordinary pressure and the residual oil carefully with a fractionating column under diminished pressure. The yields of the addition products in this series are from 40 to 60%. The halogenated esters prepared were in every instance heavy oils.

If these aldehydes and acid halides were mixed together all at once much heat was evolved and fumes of hydrochloric acid were given off. After cooling, the mixture solidified. Practically no ester was obtained in this way, the reaction going completely to give benzoic acid.

Chloromethyl Benzoate, $C_6H_5COOCH_2Cl$.—One hundred and forty g. of benzoyl chloride, and a minute quantity of fused zinc chloride were heated on the water-bath with 30 g. of dry paraformaldehyde, until the latter disappeared (2 hours). After the reaction was complete, the odor of benzoyl chloride was not perceptible. The oil was then distilled *in vacuo*, 102 g. (60% yield) of chloromethyl benzoate, b. p. 114–115° at 8 mm. being obtained. As a by-product 35 g. of a solid remained in the dis-

[1] *Ann. chim.*, [7] **29**, 488 (1903).

| | Boiling point. | | | | Analyses. | | | |
| | This research. | | In the literature. | | | | Halogen. | |
Name.	°C.	Pressure. Mm.	°C.	Mm.	Subs. G.	Ag halide. G.	Calc. %.	Found. %.
Chloromethyl acetate.....	113–5	748	115	758[a]	....	....	..	..
Chloromethyl propionate.	128–30	740	128–30	740[a]	....	....	..	..
Chloromethyl n-butyrate..	148–9	738	150	745[a]	....	....	..	..
Chloromethyl n-valerate..	163–6	750	....	...	0.1744	0.1550	23.6	23.9
α-Chloro-ethyl acetate....	113–6	740	121.5	746[b]	....	....	..	..
α-Chloro-ethyl propionate	133–5	740	134–6	...[c]	....	....	..	..
α-Chloro-ethyl n-butyrate	150–3	740	149–51	...[c]	....	....	..	..
α-Chloro-ethyl n-valerate.	163–5	750	162–4	...[c]	....	....	..	..
α-Chloro-iso-butyl acetate	78–81	50	....	...	0.2254	0.2070	23.6	23.5
α-Chloro-iso-butyl propionate.................	67-70	18	....	...	0.1740	0.1535	21.5	21.8
α-Chloro-iso-butyl n-butyrate..................	74–6	10	....	...	0.2481	0.3100	19.9	19.8
α-Chloro-iso-butyl n-valerate..................	80–3	8	....	...	0.1984	0.1491	18.4	18.6
α-Chloro-iso valeryl acetate..................	89–92	60	....	...	0.2300	0.1980	21.6	21.3
α-Chloro n-heptyl acetate.	104–5	15	....	...	0.2680	0.2026	18.4	18.7
α-Chloro n-heptyl n-butyrate..................	120–2	15	....	...	0.1660	0.1100	16.1	16.3
Chloromethyl monochloroacetate.................	130–2	745	....	...	0.1477	0.2892	48.8	48.5
Bromomethyl acetate.....	130–3	750	130	746[d]	....	....	..	..
α-Bromo-ethyl acetate....	122–5	738	....	...	0.2344	0.2644	47.8	48.1
α-Bromo-iso-butyl acetate	73–5	30	....	...	0.2030	0.1946	41.0	40.8
α-Bromo-iso-valeryl acetate..................	85–8	25	....	...	0.2400	0.2134	38.2	37.9
α-Bromo n-heptyl acetate	113–6	15	....	...	0.2812	0.2220	33.7	33.5
α-Bromo-ethyl mono-bromo-acetate.........	95–7	8	....	...	0.2060	0.3175	65.0	65.3
Chloromethyl benzoate....	114–5	8	116	10[a]	....	....	..	..
α-Chloro-ethyl benzoate..	120	8	....	...	0.1750	0.1370	19.2	19.3
α-Chloro n-butyl benzoate	135–8	18	....	...	0.2562	0.1700	16.7	16.4
α-Chloro-iso-valeryl benzoate..................	145–7	18	....	...	0.2114	0.1325	15.6	15.5
α-Chloro n-heptyl benzoate	180–3	18	....	...	0.2282	0.1265	13.9	13.6
Chloromethyl p-chlorobenzoate.................	163–5	20	....	...	0.2340	0.3260	34.6	34.5
Bromomethyl benzoate....	135–7	19	....	...	0.1920	0.1680	37.2	37.2

[a] *Ann. chim.*, [7] **29**, 488 (1903).
[b] *Rec. trav. chim.*, **1**, 243 (1882).
[c] *Ann.*, **225**, 274 (1884).
[d] *Compt. rend.*, **133**, 97 (1903).

tilling flask, which after recrystallization from alcohol melted at 100° and proved to be methylene dibenzoate, $(C_6H_5COO)_2CH_2$.

This halogenated ester has already been described in the literature.[1] It was

[1] *Ann. chim.*, [7] **29**, 488 (1903).

made by heating paraformaldehyde and benzoyl chloride for several hours in a sealed tube at 120° and was reported to have the b. p. 116° at 10 mm.

Chloromethyl-*p*-chlorobenzoate, *p*-ClC$_6$H$_4$COOCH$_2$Cl.—Thirty g. of *p*-chlorobenzoyl chloride and 5 g. of dry paraformaldehyde were heated on the water-bath until the latter had disappeared (6 hours). On fractional vacuum distillation, 5 g. of unreacted acid chloride and 16 g. (50% yield) of chloromethyl-*p*-chlorobenzoate, b. p. 163–165° at 20 mm., were obtained.

Bromomethyl Benzoate, C$_6$H$_5$COOCH$_2$Br.—Fifty g. of benzoyl bromide and 8.2 g. of dry paraformaldehyde were heated on the water-bath until the paraformaldehyde had disappeared (3 hours). The reaction mixture was then fractionated under diminished pressure and 30 g. (50% yield) of bromomethyl benzoate, b. p. 135–137° at 18 mm., was obtained. As by-products 12 g. of unreacted benzoyl bromide and 14 g. of methylene dibenzoate resulted.

α-Chloro-ethyl Benzoate, C$_6$H$_5$COOCHClCH$_3$.—One hundred and seventy-six g. of benzoyl chloride and 75 g. of paraldehyde were heated on the water-bath for 1 hour. At the end of this time, the dark reaction mixture was cooled and treated with ether and 10% sodium carbonate solution. In this way 10 g. of benzoic acid was recovered. The ether layer was dried with calcium chloride and fractionally distilled, the ether under ordinary pressure and the residual oil under diminished pressure. There was obtained 148 g. (60% yield) of the halogenated ester, b. p. 120° at 8 mm.

When 140 g. of benzoyl chloride and 40 g. of acetaldehyde were heated gently on the water-bath for 1 hour, no halogenated ester resulted and practically all the acid chloride was recovered as benzoic acid.

α-Chloro *n*-Butyl Benzoate, C$_6$H$_5$COOCHClCH$_2$CH$_2$CH$_3$.—Seventy g. of benzoyl chloride and 36 g. of *n*-butyraldehyde were refluxed gently over a free flame for $^1/_2$ hour. At the end of this time, the reaction mixture was treated with ether and sodium carbonate solution, then dried with calcium chloride and distilled, the ether under ordinary pressure and the oil with fractionation under diminished pressure. In this way, 25 g. of benzoic acid was recovered and 40 g. (45% yield) of the halogenated ester was obtained, b. p. 135–138° at 18 mm.

α-Chloro-*iso*-valeryl Benzoate, C$_6$H$_5$COOCHClCH$_2$CH(CH$_3$)$_2$.—Forty g. of benzoyl chloride and 43 g. of *iso*-valeraldehyde were refluxed gently for $^3/_4$ hour. The reaction mixture was cooled and treated with ether and 10% sodium carbonate solution. The ether layer was separated, dried with calcium chloride and fractionally distilled. In this way 45 g. of the halogenated ester, b. p. 145–147° at 18 mm. (50% yield), was obtained.

α-Chloro *n*-Heptyl Benzoate, C$_6$H$_5$COOCHCl(CH$_2$)$_5$CH$_3$.—Seventy g. of benzoyl chloride and 57 g. of heptaldehyde were allowed to react, and the products worked up in a manner similar to that for reaction products between benzoyl chloride and *n*-butyraldehyde or *iso*-valeraldehydes. In this experiment 45 g. (40% yield) of the halogenated ester, b. p. 180–183° at 18 mm., was obtained.

Lees[1] reports the preparation of the vinyl ester, C$_6$H$_5$COOCH = CH(CH$_2$)$_4$CH$_3$, by refluxing benzoyl chloride and heptaldehyde for 4 to 6 hours. It is noticeable that refluxing for only a short time produces the halogenated ester. By following Lees' directions or by boiling the halogenated ester for several hours the unsaturated ester, b. p. 185–187° at 45 mm., was obtained. It is significant that the corresponding unsaturated esters from benzoyl chloride and *n*-butyraldehyde or *iso*-valeraldehyde could not be prepared. This may possibly be explained by the fact that the temperature attained at the respective boiling points of the 2 halogenated esters was not sufficiently high to cause decomposition.

[1] Lees, *J. Chem. Soc.*, **83**, 145 (1903).

Reactions of the Addition Compounds.

In addition to the reactions already known[1] for the aliphatic acid-halide aliphatic aldehyde addition products, the following were studied.

Chloromethyl Acetate with Ammonia and Aliphatic Amines.—When ammonia gas was passed into an anhydrous ether solution of chloromethyl acetate there were produced as the chief products of the reaction, acetamide, ammonium chloride and formaldehyde.

Under the same conditions, primary and secondary aliphatic amines gave the substituted acid amides, the amine hydrochloride and formaldehyde.

Chloromethyl Acetate and Aniline.—When 20 g. of chloromethyl acetate was treated with 25 g. of aniline in dry ether, there was obtained 20 g. of acetanilide, m. p. 114–115°, and 15 g. of a yellow solid. m. p. 140–141°, insoluble in ether, identified as anhydroformaldehyde aniline. It was undoubtedly produced by the action of formaldehyde (liberated from chloromethyl acetate) upon the excess of aniline.

Chloromethyl Benzoate and Ammonia.—Twenty g. of chloromethyl benzoate was dissolved in 100 cc. of dry ether and dry ammonia was passed into the solution at room temperature until no further precipitate was produced. The solid was filtered off by suction and treated with hot benzene. On cooling, 5 g. of benzamide, m. p. 128°, separated. The portion of the solid remaining after extraction with hot benzene was identified as ammonium chloride. There was also 8 g. of benzamide in the ether solution. Formaldehyde was liberated during the reaction.

Chloromethyl Benzoate and Diethyl Amine.—Fifteen g. of chloromethyl benzoate was dissolved in 100 cc. of dry ether and 12.8 g. of diethyl amine added. A white solid separated at once. The reaction mixture was set aside for 24 hours and then the solid filtered off. It was diethylamine hydrochloride, m. p. 200–205°. There was 5 g. of the hydrochloride. On evaporating the ether 8 g. of an oil was obtained, b. p. 173–175° at 35 mm., which proved to be diethyl benzamide.

Chloromethyl Benzoate and Aniline.—Fifteen g. of chloromethyl benzoate, dissolved in 75 cc. of dry ether was treated with 16.4 g. of aniline and allowed to stand for 24 hours. A yellow precipitate separated immediately. The solid was filtered off by suction. It was a mixture of aniline hydrochloride and anhydroformaldehyde aniline. The ether was distilled and 10 g. of benzanilide was obtained, m. p. 159–160° after crystallization from alcohol.

When chloromethyl acetate and benzoate were mixed with equimolecular portions of diethyl aniline and allowed to stand for 2 weeks no reaction took place as all the starting materials were recovered by distillation.

Chloromethyl Benzoate and Pyridine.—When chloromethyl benzoate

[1] *Ann. chim.*, [7] **29**, 488 (1903).

was treated with a mol of pyridine, heat was evolved, and a stable addi-tion compound formed. This was readily soluble in absolute alcohol and came down as pure white crystals, m. p. 177–178°, when precipitated with absolute ether.

Subs., 0.4796: 18.75 cc. of 0.1022 N AgNO$_3$.
Calc. for C$_{18}$H$_{12}$O$_2$NCl: Cl, 14.2. Found: 14.2.

Chloromethyl acetate also formed a pyridine addition compound, but this was less stable than the benzoate. α-Chloro n-heptyl acetate, α-chloro-ethyl benzoate, α-chloro-iso-valeryl benzoate and α-chloro n-heptyl benzoate were treated with pyridine, but no reaction product was ob-tained. The mixtures, after standing several days, were treated with ether and dil. hydrochloric acid. The esters were recovered unchanged from the ether solution.

Chloromethyl Acetate and Quinoline.—Chloromethyl acetate with one mol of quinoline formed a product which was readily soluble in abso-lute alcohol, and easily precipitated with dry ether. It melted with decomposition at 214–216°.

Subs., 0.5200: 21.49 cc. of 0.1022 N AgNO$_3$.
Calc. for C$_{12}$H$_{12}$O$_2$NCl: Cl, 14.9 Found: 15.2.

Chloromethyl and α-Chloro-ethyl Acetates and Benzoates with Water.—Five cc. of chloromethyl acetate and α-chloro-ethyl acetate, respec-tively, were treated with 5 cc. of water. The halogenated esters de-composed gradually during 24 hours into acetic acid, hydrochloric acid and the corresponding aldehyde.

In a similar manner, 5 cc. of chloromethyl and α-chloro-ethyl benzoates were treated with 5 cc. of water and allowed to stand. These esters in contrast to the aliphatic esters were stable and showed no signs of de-composition after 2 weeks.

Halogenated Esters and Potassium Hydroxide.—A number of the esters were treated with powdered potassium hydroxide. In every case, the potassium salt of the organic acid, potassium chloride and the alde-hyde were produced.

Summary.

1. The reactions between aliphatic acid halides and aliphatic alde-hydes, and between aliphatic aldehydes and aromatic acid halide to give halogenated esters are general, just as is the case with aromatic aldehydes and aromatic acid halides previously prepared.

2. Addition compounds between formaldehyde, acetaldehyde, n-butyl-iso-butyl-, iso-valeryl- and heptaldehydes with simple and substituted aliphatic acid halides were prepared.

3. The halogenated ester addition products between formaldehyde, acetaldehyde, n-butyraldehyde, iso-valeraldehyde and heptaldehyde, with aromatic acid chlorides were prepared.

4. The stability to water of the various types of halogenated esters varies as follows: the aromatic acid chloride-aliphatic aldehyde addition compounds are the most stable; the aromatic acid halide-aromatic aldehyde next; and the aliphatic acid halide-aliphatic aldehyde compounds the least stable.

5. The aliphatic acid halide-aliphatic aldehydes form condensation products in 50 to 70% yields, the aromatic acid halide-aliphatic aldehydes form products in 40 to 60% yields.

6. The action of ammonia, certain amines, pyridine, quinoline, potassium hydroxide and water, on chloromethyl acetate and benzoate was studied. The reactions of the halogenated esters from aliphatic acid halide-aliphatic aldehydes and aromatic acid halide-aliphatic aldehydes resemble those of the aromatic acid halide-aromatic aldehyde compounds described in a previous paper.

URBANA, ILLINOIS.

A METHOD OF PURIFYING CERTAIN KINDS OF PROTEINS.[1]
(Preliminary Paper.)

BY ADA M. FIELD.

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The importance of the iso-electric point in connection with the behavior of proteins has been emphasized by a number of investigators since it was first recognized and defined by Michaelis.[2] Jacques Loeb[2] recently reported a series of experiments on gelatin showing that on one side of the iso-electric point gelatin behaves as an acid, combining with positive ions only, while on the other side it behaves as a base and combines with negative ions only. A compound such as calcium gelatinate must therefore give up its calcium ions when brought into equilibrium with acid of greater hydrogen-ion concentration than the iso-electric point of gelatin, and gelatin chloride likewise give up its chloride ions if the hydrogen-ion concentration of the solution falls below that of its iso-electric point. These considerations suggested a simple method for purifying proteins having iso-electric points differing considerably from the reaction of pure water. Any protein with iso-electric point at a hydrogen-ion concentration greater than that of water will lose any combined basic elements when dialyzed for a sufficient length of time against dilute acid, and the resulting acid-protein compound can then be completely hydrolyzed and the acid removed by dialysis against pure water. Likewise a protein with iso-electric point at a concentration of hydrogen ion below that of

[1] Michaelis, *Biochem. Z.*, 24, 79–91 (1910).

[2] Loeb, *J. Gen. Physiol.*, I, (1918–1919).