297. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part I. The Composition of the Acylation Products in the Reaction between Acetic Chloroacetic Anhydride and Primary Aromatic Amines.*

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The compositions of the products obtained by interaction of acetic chloroacetic anhydride and two primary aromatic amines in a series of solvent mixtures have been determined. In benzene solution the reaction leads mainly (86%) to a chloroacetyl derivative, but the product contains progressively larger amounts of the acetyl derivative as more polar solvents are employed; in 50% acetone–water 72% of the product is the acetanilide. Possible interpretations of these observations are suggested.

Mixed carboxylic anhydrides have been known for nearly a century. Gerhardt (*Annalen*, 1852, **82**, 132; 1852, **83**, 112) prepared them by a modification of Williamson's mixed ether synthesis (*Annalen*, 1852, **81**, 73) (action of an acyl halide on the anhydrous metal salt of another carboxylic acid) and, in spite of its drawbacks, this remains still the most generally applicable method. At the time of their discovery topical interest in mixed anhydrides was provided by their support for a combination of the " radical " and " type " theories (cf. Chiozza, *Annalen*, 1852, **84**, 102; 1854, **91**, 102). Much later their very existence was doubted by Rousset (*Bull. Soc. chim.*, 1895, **13**, 330) who demonstrated their extremely low thermal stability, but it was nevertheless convincingly established, largely through the work of Autenrieth and his collaborators (*Ber.*, 1887, **20**, 3187; 1901, **34**, 168; 1924, **57**, 423, 1002) and Béhal (*Compt. rend.*, 1899, **128**, 1460; 1899, **129**, 681; *Ann. Chim. Phys.*, 1900, **19**, 274; 1900, **20**, 411).

Several investigators have also studied the nature of the product formed when a mixed anhydride is allowed to react with an amine (or alcohol). There are two conceivable reactions :

$$\mathrm{R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' + R''{\cdot}NH_2 \longrightarrow R''{\cdot}NH{\cdot}CO{\cdot}R + R'{\cdot}CO_2H}$$

or

$$\mathrm{R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' + R''{\cdot}NH_2 \longrightarrow R''{\cdot}NH{\cdot}CO{\cdot}R' + R{\cdot}CO_2H}$$

However, the conclusions of the early workers were contradictory : very often the experimental conditions were inadequately specified; and the purity of the anhydride was often doubtful. The action of heat causes mixed anhydrides to disproportionate into the two symmetrical anhydrides, so that all specimens obtained by distillation at a high temperature must be suspect. The problem is unusually difficult because no *absolute* method of analysis permits an estimate of the amounts of these impurities : an equimolecular mixture of two symmetrical anhydrides is, in all analytical respects, indistinguishable from a mixed anhydride. *Relative* criteria of purity, such as freezing points, cannot be devised without the existence of data for an analytically pure specimen (see also the Experimental section).

Recent work on mixed anhydrides has been stimulated by the discovery of the reaction between a keten and an acid to give a mixed anhydride (Hurd and Dull, *J. Amer. Chem. Soc.*, 1932, **54**, 3427). As keten is easily prepared, this process, together with the application of high-vacuum distillation, has made it comparatively easy to prepare mixed anhydrides of acetic acid in, probably, a fairly pure condition.

The study of the reactivities of some mixed carboxylic anhydrides, reported in the present group of papers, forms part of an investigation of the mechanism of heterolytic reactions of acid anhydrides. This Part describes product analyses from the acylation of aniline and of 2 : 4-dichloroaniline by acetic chloroacetic anhydride in benzene, acetone–benzene, acetone, and acetone–water.

EXPERIMENTAL.

Keten.—The keten lamp and absorption apparatus were all-Pyrex modifications of those described (Williams and Hurd, *J. Org. Chem.*, 1940, **5**, 122; Dunbar and Bolstad, *ibid.*, 1944, **9**, 219; Bolstad and Dunbar, *Ind. Eng. Chem. Anal.*, 1943, **15**, 498). A detachable filament was made by winding 100 cm. of 30-gauge Nichrome No. 1 wire on a $\frac{1}{8}''$ former; it was run at 3·5 amps. Keten was evolved at the rate of approx. 0·1 mole per hour, provided that the filament was renewed after about 6 hours' working.

Acetic Chloroacetic Anhydride.—A slight excess of keten was passed into a saturated solution and suspension of chloroacetic acid in dry benzene. After evaporation under reduced pressure at room temperature the anhydride was distilled (b. p. 27—30°/$\sim$ 0·01 mm.). The distillate is a colourless, lachrymatory liquid, f. p. 4·1—4·7°. The hydrolysable chlorine content was 98—102% of theoretical. The ratio, equivs. of acid produced on hydrolysis with cold water/equivs. of Cl^- produced on complete alkaline hydrolysis, was 1·98—2·03 (theoretical value : 2·00). The ratio, equivs. of acid left after reaction of anhydride with dry aniline in the cold/equivs. of Cl^- produced on complete alkaline hydrolysis, was 1·00—1·08 (theoretical value : 1·00); the excess of the experimental over the theoretical value is a sensitive indication of the amount of free acid in the sample. None of these analytical methods distinguishes between the mixed anhydride and an equimolecular mixture of the two derived symmetrical anhydrides. Nevertheless, the final products used in our experiments were probably fairly pure specimens of acetic chloroacetic anhydride for the following reasons taken collectively : (i) The composition of the acylation product indicates that the preparation must have contained $> 70\%$ of its weight of the mixed anhydride. (ii) The amount of disproportionation was inappreciable when our material was kept at the temperature of the distillation for a comparable time. As the middle portion of the distillate was uniform and the b. p.s of the two symmetrical anhydrides are 80° apart (at 110 mm.), the product collected must have been either the pure mixed anhydride or—less probably—a ternary azeotropic mixture containing equimolecular amounts of the two symmetrical anhydrides. (iii) Repeated fractional freezing failed to yield a product having a higher freezing point or giving different product composition in its reaction with amines. The cooling curves had a long flat arrest at the f. p., showing the specimens to be either pure substances or eutectic mixtures. (iv) The hydrolysis in acetone–water accurately followed a first-order law, the rate being intermediate between the values for acetic anhydride and chloroacetic anhydride, whereas the velocity coefficients for the hydrolysis of a product containing other anhydrides as impurities would have decreased as the reaction proceeded.

The small amount of acid present in the product, which is formed during unavoidable brief exposures to the atmosphere, was always determined (by treatment with dry aniline in the cold and titration of the acid produced) and an appropriate allowance made in the calculations. The anhydride was stored, for short periods only, under rigorous exclusion of moisture at a temperature below the f. p.

Other Materials.—Acetone, benzene, and aniline were purified, dried, and fractionally distilled. 2 : 4-Dichloroaniline was purified by steam-distillation and recrystallisation.

Freezing Points.—That of acetic chloroacetic anhydride was measured in a completely enclosed cryoscope by means of a calibrated thermocouple protected by a thin glass sheath. The enclosed stirrer was actuated magnetically. Fractional freezing was carried out in the cryoscope, and the freezing points re-determined on the purified fraction.

Conditions for Acylation Experiments.—A weighed amount of mixed anhydride was added to the amine solution at the temperature at the bath (thermostat). The reaction was allowed to go to completion, the time required being checked by independent experiments, and the products then worked up for analysis. All reaction mixtures remained homogeneous throughout the reaction.

Analysis of Acylation Products.—The total amount of acid in the product was titrated with standard alkali, thus giving the fractions of the total reaction proceeding as acylation and as hydrolysis. The organic solvent was then completely removed from the accurately neutralised solution by suction at room temperature, since acetone interferes with the subsequent extraction. Benzene was added to the resulting suspension of amine and anilides in water, and the organic materials were separated from the aqueous solution of the sodium salts. The chlorine content of the aqueous layer corresponds to the amount of chloroacetic acid formed during the reaction and is equivalent to the sum of the amounts of reaction leading to acetylation and hydrolysis. It was determined by hydrolysis with boiling 5% sodium hydroxide solution, followed by potentiometric titration with silver nitrate solution. The organic layer was evaporated to dryness on a water-bath, and the amount of the chlorine in it, which is equivalent to the total amount of chloroacetylation, determined in the same way after hydrolysis with boiling as above. The method of analysis, checked against synthetic mixtures, gave consistent results. No correction was applied for the slight systematic error (the aqueous layer dissolving about 3% of the chloroacetanilide formed).

In view of the startling dependence of the product ratio upon the solvent, the qualitative correctness of the result was confirmed by experiments on the preparative scale and identification of the major reaction product.

In all experiments with aniline the anhydride reacted to give anilides only, and no hydrolysis occurred even in the most aqueous solvent. With 2 : 4-dichloroaniline an appreciable amount of hydrolysis always took place concurrently with anilide formation, and an appropriate allowance was made for this in the calculation of the chloroacylation ratios.

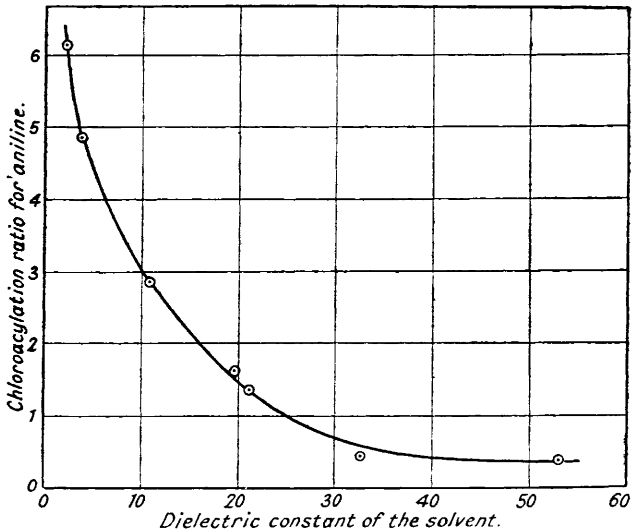
DISCUSSION.

(a) *Experimental Basis.*—The facts which require explanation are given in the Table. They are, briefly : (i) the ratio of chloroacetyl to acetyl derivative (the " chloroacylation ratio ") formed in the acylation of aniline with acetic chloroacetic anhydride is a function of the solvent (figure) ; it decreases from a value > 6 for benzene solution to $\sim 0{\cdot}4$ for 50% aqueous acetone ; (ii) the chloroacylation ratio remains virtually unchanged (it decreases by a factor of less than 2) on passing fron aniline to 2 : 4-dichloroaniline, although the velocity of the reaction is thereby decreased, probably by a factor of several powers of 10 ; and (iii) the chloroacylation ratio with 2 : 4-dichloroaniline in 80% acetone–water is only slightly, if at all, dependent on the amine concentration.

The product composition for the acylation of two primary aromatic amines with acetic chloroacetic anhydride in different solvents. $[Cl{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3]_0 \sim 0{\cdot}06$M.

Expt.	Solvent.	Temperature.	Amine.	$[Amine]_0$.	Chloroacetanilide / Acetanilide (Chloroacylation ratio).
1	Benzene	18°	Aniline	0·6M.	6·1
2	Benzene–acetone (80 : 20 v/v)	,,	,,	,,	4·8
3	Benzene–acetone (50 : 50 v/v)	,,	,,	,,	2·9
4	Acetone	,,	,,	,,	1·6
5	Acetone–water (98 : 2 v/v approx.)	,,	,,	,,	1·3
6	Acetone–water (80 : 20 v/v)	,,	,,	,,	0·44
7	Acetone–water (50 : 50 v/v)	,,	,,	,,	0·39
8	Benzene	25°	2 : 4-Dichloroaniline	0·67	5·5
9	Acetone–water (80 : 20 w/w)	,,	,,	0·148	0·35
10	,, ,, ...	,,	,,	0·67	0·43 ; 0·40
11	,, ,, ...	0°	,,	0·67	0·45

Variation of chloroacylation ratio with dielectric constant of solvent.



It may be remarked that the relative rates of the two acylation reactions are really very similar in all the solvents studied and that the solvent effect only amounts to the reversal of a delicate balance of rates under the influence of a very drastic change of solvent.

(b) *Evidence for Electrophilic Character of the Acylating Agent.*—The acylation of an amine by means of an acid anhydride or acid chloride is known to be a heterolytic reaction in which the amine behaves as the nucleophilic and the acylating species as the electrophilic reagent. These conclusions follow from the parallelism between the ease of electrophilic nuclear substitution in a substituted benzene and the ease of acylation of the corresponding substituted aniline. Available data refer chiefly to acylation by means of acid chlorides (Williams and Hinshelwood, *J.*, 1934, 1079) but this rule for substituents also holds for the acetylation of substituted anilines with acetic anhydride (Bafna and Gold, unpublished). For acylation with substituted benzoyl chlorides (Williams and Hinshelwood, *loc. cit.*) the effect of substituted groups in the nucleus of benzoyl chloride confirms that reactivity runs parallel with depletion of electrons at the carbonyl-carbon atom which forms the new bond.

An acid anhydride also functions as electrophilic reagent in its reaction with an alcohol, as is indicated by the position of bond fission determined by Dedusenko and Brodskii (*Acta Physicochim.*, 1942, **17**, 314) for the reaction between acetic anhydride and ethyl alcohol. By the use of labelled oxygen in ethyl alcohol it was shown that the oxygen of the alcohol was incorporated in the ester molecule, *i.e.*,

$$\mathrm{CH_3{\cdot}CO}\,\vdots\!-\mathrm{O{\cdot}CO{\cdot}CH_3} + \mathrm{H}\,\vdots\!-\mathrm{O^{18}Et} \longrightarrow \mathrm{CH_3{\cdot}CO{\cdot}O^{18}Et} + \mathrm{CH_3{\cdot}CO_2H}$$

(c) *Molecular Condition of Reagents.*—The molecular state of the amine at the moment of reaction is hardly in doubt. Although some of it will, in the presence of acids, be in the form of an anilinium ion, this form will be very much less reactive than the neutral molecule and is unlikely to participate in the reaction to any appreciable extent; but its presence must be taken into consideration in a detailed kinetic analysis as it reduces the amount of the reactive neutral form.

The state of the acylating agent is not so certain and may vary according to circumstances. For acylation by means of an acid anhydride in the absence of strong acid, the acylating species may be the anhydride molecule itself or an acylium cation $\mathrm{R{\cdot}CO^+}$ (Treffers and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1708; Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 159, 171, 243; Gold, *ibid*, p. 506). Such an ionisation is extremely unlikely in benzene solution but must be given serious consideration for the more polar solvents.

(d) *Electronic Considerations regarding the Nature of the Acylation Product.*—If the reactivity of a molecule as an acylating agent is determined by the density of positive charge at the carbon atom of the carbonyl group, then, for the reaction with *molecular* mixed anhydride as reagent, the acylation reaction

$$\mathrm{R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R'} + \mathrm{R''{\cdot}NH_2} \longrightarrow \mathrm{R''{\cdot}NH{\cdot}CO{\cdot}R} + \mathrm{R'{\cdot}CO_2H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(i)}$$

should predominate if R is more strongly electron-attracting than R′ (or, roughly, if $\mathrm{R{\cdot}CO_2H}$ is a stronger acid than $\mathrm{R'{\cdot}CO_2H}$, as will be assumed throughout the discussion), so as to leave the carbonyl group adjacent to R more positively charged than that adjacent to R′ (cf. Hurd and Dull, *loc. cit.*; Hurd and Roe, *J. Amer. Chem. Soc.*, 1939, **61**, 3355, whose oversimplified application of electronic theory leads to the opposite conclusion). The acetic chloroacetic anhydride molecule should therefore, on this theory, be predominantly a chloroacetylating agent.

For the acylation of amines by acetic chloroacetic anhydride in benzene the product composition agrees with the prediction. We therefore conclude that in this case the simplest theory, which regards the acylations as bimolecular substitution reactions involving two neutral molecules and the reaction velocities of the two halves of the anhydride molecule as largely governed by electronic requirements, is adequate. On the other hand, to account for the reversal of the chloroacylation ratio as the polarity of the solvent is increased, we have explored two alternative sets of postulates: (i) occurrence of acylation by acetic chloroacetic anhydride in polar solvents predominantly through acetylium cations; and (ii) the combined operation of solvation and steric factors in the competing reactions of the two halves of the mixed anhydride molecule.

If the reaction proceeds by a primary separation into ions, followed by the attack of the amine by the acylium cation thus formed, we have

$$\left.\begin{array}{l}\mathrm{R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R'} \underset{-1}{\overset{1}{\rightleftharpoons}} \mathrm{R{\cdot}CO^+} + \mathrm{R'{\cdot}CO_2^-} \\ \mathrm{R{\cdot}CO^+} + \mathrm{R''{\cdot}NH_2} \xrightarrow{2} \mathrm{R''{\cdot}NH{\cdot}CO{\cdot}R} + \mathrm{H^+}\end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(ii)}$$

$$\left.\begin{array}{l}\mathrm{R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R'} \underset{-1'}{\overset{1'}{\rightleftharpoons}} \mathrm{R'{\cdot}CO^+} + \mathrm{R{\cdot}CO_2^-} \\ \mathrm{R'{\cdot}CO^+} + \mathrm{R''{\cdot}NH_2} \xrightarrow{2'} \mathrm{R''{\cdot}NH{\cdot}CO{\cdot}R'} + \mathrm{H^+}\end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(ii')}$$

For a full analysis it would be necessary to consider as separate possibilities several relationships among the rate constants in the two schemes. Without at this stage reproducing the mathematical details of this mechanism we may qualitatively predict with some confidence that, if $R \cdot CO_2H$ is a stronger acid than $R' \cdot CO_2H$, the ionisation according to (ii′) will proceed more readily (in both a kinetic and a thermodynamic sense) than that according to (ii), so that it will be more probable to find $CH_3 \cdot CO^+$ ions in solution than $CH_2Cl \cdot CO^+$ ions.* Therefore, if acylation occurs *via* an intermediate acylium cation, we would predict acetylation to occur to a larger extent than chloroacetylation. This hypothesis would, therefore, suffice to explain the reversal of the product ratio with increasing ionising power of the solvent, whereupon the ionic mechanism would gradually assume greater importance. We shall show in Parts II and III that kinetic experiments designed to test the correctness of these assumptions do not, however, offer support for this interpretation.

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