1,3-dichloro-2-butenes also show the same relationship between structure and reactivity, but in this case there is considerable removal of the vinyl chlorine atom during the reaction, thus the reactions may not be strictly analogous.

Acknowledgment.—The authors wish to thank both the Research Corporation, New York, and the Defense Research Laboratory, The University of Texas, for their financial assistance in support of these and related investigations.

Summary

Several allylic chlorides have been hydrolyzed using cuprous chloride as a catalyst to determine the effect of replacing one or more hydrogen atoms on the number one and number two carbon atoms of allyl chloride by a methyl group, a chlorine atom or a bromine atom.

When a hydrogen atom is replaced by a halogen atom in either position, the rate of hydrolysis is less than for allyl chloride.

The rates of hydrolysis of methyl substituted allyl chlorides are greater than for unsubstituted allyl chloride.

It is believed that the catalytic effect of cuprous chloride is due to the formation of some type of coördination complex at the double bond, similar in character to those previously proposed for allyl alcohol.

By analogy to the reactivity of the isomers of 1,3-dichloropropene, the low boiling (alpha) isomer of 1,3-dichloro-2-methylpropene has been assigned the geometrical configuration with the chlorine atom and the chloromethyl group in the *cis* position; the beta isomer has been assigned the structure with the chlorine atom and the chloromethyl group in the *trans* position.

AUSTIN, TEXAS RECEIVED OCTOBER 14, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Study of the Basic Catalysis of the Acylation of α-Acylamino Acids[1,2]

BY SCOTT SEARLES[3] AND GEORGE J. CVEJANOVICH

The base-catalyzed reaction of α-amino acids with acid anhydrides to form α-acylaminoketones,[4] sometimes called the Dakin–West reaction,

$$\mathrm{R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}COOH + (R'CO)_2O \longrightarrow R{-}\underset{\displaystyle NHCOR'}{\underset{|}{CH}}{-}COR' + CO_2}$$

is of value in the synthesis of oxazoles. Recent work by Wiley and Borum[5] and by Cleland and Niemann[6] has extended its useful scope, but several phases of the mechanism remain somewhat obscure.

The report[4] that the reaction seems to be catalyzed by only pyridine and its homologs appeared surprising, but qualitative experiments carried out in this Laboratory indicated that certain tertiary amines also are effective catalysts, whereas certain pyridine homologs are quite ineffective. Since the reaction lends itself readily to quantitative measurements, a kinetic study of the catalysis by different bases has been made.

Acylamino acids were used as starting materials rather than the corresponding amino acids, since the former were completely soluble in the reaction mixture and gave simpler kinetic data. The reaction is followed conveniently by measuring the amount of carbon dioxide evolved, which is formed as a reaction product in equimolar amounts with the α-acetylaminoketone. Except in unfavorable cases, this is the only significant reaction and high yields of the ketone are well-known.[7] We found that the yield of carbon dioxide usually is practically the theoretical for the amount of amino acid used and that side reactions leading to the formation of resinous products do not appear to give rise to carbon dioxide.

Experimental

Materials.—α-Acetamidophenylacetic acid was prepared by slow addition of twice the theoretical amount of acetic anhydride to a solution of α-aminophenylacetic acid in sodium hydroxide at 5° and recrystallized from water; yield, 50%; m. p. 199°. Benzoylalanine was prepared by the method of Carter and Stevens[8]; m. p. 162–163°. Benzoylphenylalanine and α-benzamidophenylacetic acid were prepared also by this method; m. p. 185–186° and 174°, respectively.

Acetic anhydride was purified by fractional distillation over sodium acetate, the 139–140° fraction being used. Benzoic anhydride and 4,4′-dinitrobenzoic anhydride were recrystallized from benzene and petroleum ether and from acetone, respectively; m. p. 42° and 189–190°, respectively. The amines used as catalysts were purified by fractional distillation after drying over barium oxide, except 3- and 4-picoline, which were purified by means of their oxalate salts.[9] Dioxane, which was used as the solvent for much of this work, was purified by the methods of Hess and Frohm.[10]

Procedure.—The reactions were carried out in a 50 ml. flask placed in a steam jacket and equipped with a mercury-sealed stirrer and a water-cooled gas outlet tube. The temperature was 99.5–99.8°, constant to 0.05° in each run. Two standard types of reaction mixtures were used: (1) a solution of 0.01 mole of acylamino acid or azlactone, 20 ml. of pyridine and 10 ml. of acetic anhydride, used for

(1) Much of this material is abstracted from the B.S. thesis of George J. Cvejanovich, University of Illinois, June, 1948.

(2) Presented before the 116th meeting of the American Chemical Society, Atlantic City, N. J., September, 1949.

(3) Department of Chemistry, Northwestern University, Evanston, Illinois.

(4) Dakin and West, *J. Biol. Chem.*, **78**, 91, 745 (1928).

(5) Wiley and Borum, THIS JOURNAL, **70**, 2005 (1948).

(6) Cleland and Niemann, *ibid.*, **71**, 841 (1949).

(7) Wiley, *J. Org. Chem.*, **12**, 43 (1947).

(8) Carter and Stevens, *J. Biol. Chem.*, **138**, 627 (1941).

(9) Lindstrom, *J. Chem. Soc.*, 242 (1940).

(10) Hess and Frohm, *Ber.*, **71**, 2627 (1938).

determining the reaction order; and (2) a solution of 4.00 g. (0.021 mole) of benzoylalanine or α-acetamidophenylacetic acid, 25 ml. of dioxane, 15.0 ml. (0.159 mole) of acetic anhydride and 0.1–2.0 g. of a basic catalyst, used to determine catalyst-dependent zero order rate constants. The standard experimental procedure was to add rapidly the liquid component used in the smallest quantity to the solution of the other components previously heated to 100° in the reaction flask, in order to minimize the time for temperature equilibration. In some rate runs a small piece of solid carbon dioxide was added during the preheating to saturate the solution with carbon dioxide before the reaction commenced. Stirring was employed throughout each run, and the carbon dioxide evolved was measured over mercury in a gas buret at atmospheric pressure. If the solution was not presaturated with carbon dioxide as described above, the first readings were always low, presumably due to the solubility of carbon dioxide in the reaction mixture. When the volumes observed were corrected for this solubility, determined independently to be 6.3 ml. in the case of solution (1) at 100°, good agreement was observed with results obtained after presaturating with carbon dioxide. In either case, the measurements were reliable and reproducible after about 5% of the carbon dioxide had been evolved.

Isolation of Products.—To verify the course of reaction in the above rate studies the ketonic product was isolated in most cases by removal of volatile products and solvent by distillation, neutralization of the residue with sodium bicarbonate solution, followed by extraction with ether and distillation or crystallization from the appropriate solvent. In every case the expected product was obtained, regardless of which catalyst was used and whether dioxane was present or not. From α-acetamidophenylacetic acid and acetic anhydride was obtained 1-phenyl-1-acetamidoacetone, m. p. 97–98°,[7] (72–90% yields). From α-benzamidophenylacetic acid and acetic anhydride was obtained a 65% yield of 1-phenyl-1-benzamidoacetone, m. p. 99–100°[11] and mixed m. p. with the corresponding acetamido ketone 77–89°. Benzoylphenylalanine and acetic anhydride gave a 78% yield of 1-phenyl-2-benzamido-3-butanone, m. p. 113.5–114°. *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41. Found: C, 76.70; H, 6.64. From benzoylalanine and acetic anhydride was obtained 3-benzamido-2-butanone, b. p. 138–142 (1 mm.) in 65–88% yield; the 2,4-dinitrophenylhydrazone forms yellow needles from alcohol, m. p. 198–199°.[12] *Anal.* Calcd. for $C_{17}H_{17}O_5N_5$: C, 54.98; H, 4.62; N, 18.86. Found: C, 54.67; H, 4.67; N, 19.05.

Yield Studies.—With aromatic acid anhydrides the Dakin–West reaction proceeds relatively slowly, and the yields are poorer. For example, we found that with solutions of 0.193 g. (0.001 mole) of benzoylalanine, 0.01 mole of acid anhydride and 10 ml. of pyridine at 100°, the first order rate constants observed with benzoic anhydride and 4,4′-dinitrobenzoic anhydride were 0.0068 and 0.023 min.$^{-1}$, respectively, whereas the rate constant with acetic anhydride under analogous conditions was 0.085 min.$^{-1}$. After three hours reaction time, a 4% yield of α-benzamidopropiophenone, m. p. 103–103.5°, and a 9% yield of *p*-nitro-α-benzamidopropiophenone, m. p. 123–125°, were isolated by the above described procedure. The generally low yields of Dakin–West reactions with benzoic anhydride, even at higher reaction temperatures,[6] suggested testing the practical use of other catalysts here.

A mixture of 2.5 g. of alanine, 26 g. of benzoic anhydride and 10 ml. of 3-picoline was heated with stirring at 135–140° until the carbon dioxide evolution had practically ceased (about two hours). After removal of 3-picoline by distillation under reduced pressure, the residue was treated with sodium bicarbonate solution, and then extracted with ether. The ether extracts were dried and the ether removed by distillation. The tan-colored residue crystallized on standing *in vacuo* for a week; after recrystallization from ligroin 3.2–4.7 g. (47–69% yield) of α-benzamidopropiophenone, m. p. 103–103.5°, was obtained. On standing in our laboratory this changed to a form melting at 71–74°, but both forms gave the oxime, m. p. 156–157°.[6] Using pyridine in place of 3-picoline in the above procedure we obtained a 40% yield of the same product, in agreement with Cleland and Niemann.[6]

The reaction of 2.5 g. of phenylalanine and 22.5 g. of benzoic anhydride in the presence of 0.10 mole of catalyst at 128–132°, until gas evolution had ceased, gave the following yields of α-benzamido-β-phenylpropiophenone, m. p. 144–144.5°, isolated as described above: pyridine as catalyst, 2.0 g. (40%)[6]; 3-picoline, 2.2 g. (44%); 4-picoline, 2.0 g. (40%); 1-methylpiperidine, 2.6 g. (52%). The latter two catalysts were advantageous in that the product crystallized in relatively pure form during the sodium bicarbonate treatment.

Results and Discussion

The reaction of the acylamino acid and the acyl anhydride was found to be first order with respect to both the acylamino acid and the basic catalyst. Because of the dual function of the anhydride in the reaction, no attempt was made to determine its reaction order; in the present work it was present in large excess. Since the concentrations of both the catalyst and the anhydride remained practically constant, the rate constant may be calculated from the integrated form of the first order rate law

$$\log V_\infty/(V_\infty - V) = k_1 t/2.3$$

where V and V_∞ are the volumes of carbon dioxide evolved at time t and at infinite time and the rate constant, k_1, is proportional to the catalyst concentration. The data from four typical runs are plotted in Fig. 1. The first order dependence of the rate constant on the concentration of the

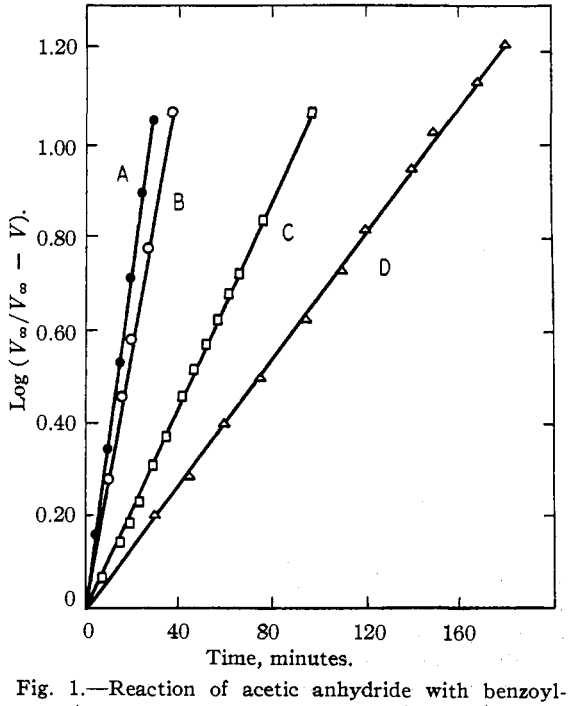

Fig. 1.—Reaction of acetic anhydride with benzoylalanine (A, B, D) and benzoylphenylalanine (C) at 100°, as described in Table I.

(11) Neber and Friedel-Sheim, *Ann.*, **449**, 109 (1926).

(12) Attenburrow, Elliott and Penny, *J. Chem. Soc.*, 310 (1948).

catalyst in pyridine–acetic anhydride mixtures is shown by experiments A and B in Table I. Over

TABLE I

PYRIDINE-CATALYZED REACTION OF ACYLAMINO ACIDS WITH ACETIC ANHYDRIDE AT 100°

Acylamino acid	Experiment	Molarity of pyridine	k_1, min.$^{-1}$
Benzoylalanine	A	8.3[a]	0.034
Benzoylalanine	B	6.2[b]	.022
Benzoylphenylalanine	C	8.3[a]	.011
Benzoylalanine	D	4.5[c]	.0067

[a] Standard reaction mixture type 1, described under "Procedure." [b] Same reaction mixture as A, except that one-half as much pyridine was used. [c] Same reaction mixture as A, except that 25 ml. of dioxane was added.

wider concentration ranges in such solutions the correlation is poorer, presumably due to the resulting changes in the reaction medium, but when dioxane is used as a solvent to minimize medium changes, the rate is very nearly proportional to the catalyst concentration, as shown in Table II. The reaction order is consistent with a mechanism in which the rate-determining step is the reaction of the basic catalyst with the acylamino acid or the azlactone derived from it.

TABLE II

FIRST ORDER RATE DEPENDENCE ON CONCENTRATION OF BASIC CATALYST IN DIOXANE SOLUTION[a] AT 100°

Molarity of pyridine	Initial rate CO_2 evolution, ml./min.	Relative rate
0.066	0.85	1.0
.129	1.67	1.95
.253	2.7	3.2

[a] Composed of 15 ml. of acetic anhydride, 4.00 g. of benzoylalanine, 25 ml. of dioxane, and 0.25–0.98 g. of pyridine.

A comparison of the catalytic activity of the different bases was made by carrying out the reaction with a small amount of base and relatively large amounts of acylamino acid and acetic anhydride in dioxane as solvent, so that the reaction would show practically zero order kinetics for an appreciable time at the start. The rate constant, k_0, calculated by means of the expression

$$k_0 t = M_{CO_2}/M_c$$

where M_{CO_2}/M_c is the ratio of the moles of carbon dioxide evolved in time t per mole of catalyst present in the solution, gives a measure of the activity of the catalyst. Tables III and IV summarize the results.

If the function of the catalyst in the Dakin–West reaction is the removal of a proton from the acylamino acid or its azlactone derivative[4,6] to form the conjugate base of the acylamino acid or azlactone, it might be anticipated that the catalytic activities of a series of bases would parallel their ionization constants, which are generally considered to be a measure of proton-accepting ability. Such seems to be the case in the series pyridine, 3-picoline and 4-picoline,

TABLE III

RATE CONSTANTS FOR THE REACTION OF BENZOYLALANINE WITH ACETIC ANHYDRIDE AT 100°[a] AND IONIZATION CONSTANTS OF BASES

Catalyst	k_0, min.$^{-1}$[a]	Relative rate	k_B[b]
Pyridine	0.024	1.0	2.2×10^{-9}[c]
2-Picoline	.00094	0.04	3×10^{-8}[c]
3-Picoline	.047	1.95	1×10^{-8}[d]
4-Picoline	.089	3.7	1×10^{-8}[d]
2,4-Lutidine	.00093	0.04	
2,6-Lutidine	.00036	0.01	1×10^{-7}[e]
2,4,6-Collidine	.00021	0.01	2×10^{-7}[f]
1-Methylpiperidine	.055	2.3	1×10^{-4}[g]
Triethylamine	.032	1.33	6.5×10^{-4}[h]
Tri-*n*-butylamine	.024	1.0	6.7×10^{-4}[i]
Sodium acetate	.023	0.95	5×10^{-10}[j]

[a] Reaction mixtures used were of type 2 described under "Procedure." [b] Ionization constants in water at room temperature. [c] Barron, *J. Biol. Chem.*, **121**, 313 (1937). [d] Constam and White, *Am. Chem. J.*, **29**, 46 (1903). [e] "I. C. T.," **6**, 281 (1929). [f] Lunden, *J. chim. phys.*, **5**, 574 (1907). [g] Estimated from data of Wynne-Jones and Salomon, *Trans. Faraday Soc.*, **34**, 1321 (1938). [h] Britton and Williams, *J. Chem. Soc.*, 796 (1935). [i] Damsgaard-Sorenson and Unmack, *Z. physik. Chem.*, **A172**, 389 (1935). [j] Hydrolysis constant.

TABLE IV

RATE CONSTANTS FOR REACTION OF α-ACETAMIDOPHENYLACETIC ACID AND ACETIC ANHYDRIDE[a]

Catalyst	k_0, min.$^{-1}$	Relative rate
Pyridine	0.13	1.0
4-Picoline	.19	1.5
1-Methylpiperidine	.072	0.6
Triethylamine	.03	0.2
Sodium acetate	.16	1.2

[a] Reaction mixtures used were of type 2 described under "Procedure."

where the higher rate constants when the latter two are employed as catalysts can be attributed to the greater electron availability about the nitrogen atom.[13]

Comparison of the rate and ionization constants for the other bases studied (see Table III), however, shows that generally there is very little correlation between these factors. The reaction rate constant with 2-picoline as catalyst is very much lower than with pyridine or other picolines although 2-picoline has the highest ionization constant. Furthermore, the presence of a 2-methyl group in other pyridine bases uniformly results in an extremely slow rate, in spite of favorable electronic effects from a 4-methyl group. It would appear that the decrease in rate due to a 2-methyl group in bases of the pyridine series is due to steric hindrance about the nitrogen atom. Steric factors also appear to be of considerable importance in the catalytic activity of aliphatic bases. In the series 1-methylpiperidine, triethylamine and tri-*n*-butylamine the order of increasing catalytic activity is the reverse

(13) Brown and Barbaras, THIS JOURNAL, **69**, 1137 (1947).

of the order of increasing ionization constants but is the same as the order of decreasing bulkiness of the groups attached to the nitrogen atom.

A similar situation has been described by H. C. Brown and his collaborators[14] for the equilibrium of the reaction of aliphatic and pyridine bases with trimethylboron, in which this steric hindrance has been termed "F-Strain." The present case seems to be somewhat different in that here the rate of reaction of a base with a weak acid is found to be subject to steric hindrance, suggesting that in the transition complex it must be necessary for the amine to approach the weak acid very closely to pull off a proton. If such is the case one would expect the steric hindrance in the acid to affect the rate also. This is borne out by the lower rates observed for α-acetamidophenylacetic acid, especially with sterically hindered catalysts, as well as by the results of preliminary studies on other acylamino acids, tabulated in Table V.

TABLE V

EFFECT OF STRUCTURE OF ACYLAMINO ACID ON RATE OF PYRIDINE CATALYZED REACTION WITH ACETIC ANHYDRIDE

Compound	Relative rate
Benzoylalanine	3.7
α-Benzamidophenylacetic acid	1.6
α-Acetamidophenylacetic acid	1.4
Benzoylphenylalanine	1

It is found that the reaction rate decreases as the size of the group on the α-carbon in the acylamino acid increases.

It thus seems plausible that the better yields of acylaminoketone obtained when 2-picoline and 1-methylpiperidine are used as catalysts are due to the more rapid formation of the conjugate base of an azlactone intermediate,[6] thereby decreasing the amount of decomposition of the azlactone in other ways. The use of 4-picoline as a catalyst deserves comment, for in this case the yield was about the same as for the pyridine-catalyzed reaction, although the rate of carbon dioxide evolution was much greater. It is probable that condensation of the ketonic product with the active methyl group of 4-picoline occurs.

A further study of the mechanism of the Dakin–West reaction is in progress.

Summary

1. The reaction rate constants for the Dakin–West reaction of several acylamino acids with several anhydrides have been measured at 100° by measuring the rate of evolution of carbon dioxide. The reaction is first order with respect to both the acylamino acid and the basic catalyst.

2. The reaction is catalyzed by tertiary amines of both the aliphatic and the pyridine series. The catalytic activity of these bases is found to depend more upon steric factors than electronic factors. 3-Picoline and 1-methylpiperidine were found to be somewhat better catalysts for the reaction than pyridine.

URBANA, ILLINOIS RECEIVED DECEMBER 14, 1949

(14) Brown, Schlessinger and Cardon, THIS JOURNAL, **64**, 325 (1942); Brown and Seyishi, *ibid.*, **70**, 2878 (1948).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. IV.[1] Some Thiazolo[5,4-d]pyrimidines

BY ELVIRA A. FALCO AND GEORGE H. HITCHINGS

The observation that antimicrobial action (against *Lactobacillus casei*) is a general property of certain functional derivatives of condensed pyrimidine systems[2,3] indicates the desirability of study of such derivatives whenever they become accessible. During studies on the reaction of pyrimidine derivatives with phosphorus pentasulfide[4,5] the preparation of 5-thiobenzamido-2,4-diaminopyrimidine from the benzamide (I) was attempted. A crystalline product was obtained; however, analysis indicated that although the desired exchange of sulfur for oxygen had taken place, this process had been accompanied by the loss of the elements of ammonia. The product, therefore, appeared to be 5-amino-2-phenylthiazolo[5,4-d]pyrimidine (II). A study of this type of reaction indicates it to be quite generally applicable to the synthesis of 2-substituted-5-amino-, 5,7-diamino- and 5,7-dithiolthiazolo-[5,4-d]pyrimidines, types of functional derivative desired for microbiological study.[2]

Confirmation of the structure of these new substances was sought through the preparation of some members of the series by a known route. The methods employed in Heilbron's laboratory[6,7,8] did not appear to be adaptable to the synthesis of the desired derivatives. However, 2-methyl-5,7-dihydroxythiazolo[5,4-d]pyrimidine (III, R = CH_3) had been prepared by treatment of thiouramil IV with acetic anhydride, followed

(1) Previous papers in this series (unnumbered) deal with pteridines, THIS JOURNAL, **69**, 2553 (1947); **72**, 78 (1950); and *p*-oxazino-(2,3-d)pyrimidines, *ibid.*, **71**, 474 (1949).

(2) Hitchings, Elion, VanderWerff and Falco, *J. Biol. Chem.*, **174**, 765 (1948).

(3) Hitchings, Elion, Falco, Russell, Sherwood and VanderWerff, *ibid.*, **183**, 1 (1950).

(4) Elion and Hitchings, THIS JOURNAL, **69**, 2138 (1947).

(5) Russell, Elion, Falco and Hitchings, *ibid.*, **71**, 2279 (1949).

(6) Cook, Heilbron, Macdonald and Mahadevan, *J. Chem. Soc.*, 1064 (1949).

(7) Cook, Downer and Heilbron, *ibid.*, 1069 (1949).

(8) Cook, Davis, Heilbron and Thomas, *ibid.*, 1071 (1949).