to 25.5°. At zero time a sealed ampoule of methyl iodide containing a known quantity of methyl iodide was broken under the surface of the solution. Samples were withdrawn at various time intervals with an automatic pipet carrying a filter tip and delivered to a definite excess of standard thiocyanate solution. The excess thiocyanate was determined by a Volhard titration with a standard silver nitrate solution. No transience of the ferric thiocyanate color was observed when methyl iodide was added to a solution from which the silver had been precipitated with excess thiocyanate.

Ethyl Iodide Rates.—The procedure in the more concentrated solutions was similar to that described above for runs with methyl iodide. In dilute solutions the Volhard titration was not sufficiently accurate and was replaced by direct potentiometric titration of the residual silver ion with aqueous sodium chloride using platinum and calomel electrodes.

Isopropyl Iodide Rates.—The procedure for both silver nitrate and perchlorate with isopropyl iodide is the same. It was found that the rate could not be followed by the indirect Volhard titration as in the methyl iodide runs. When excess sodium thiocyanate was added to quench the reaction and ferric alum indicator added, the indicator color faded upon standing. The excess thiocyanate apparently reacts with something, probably excess isopropyl iodide, other than silver since thiocyanate was in excess.

The proper volumes of the reactants were mixed at zero time in a glass-stoppered erlenmeyer flask. Samples were withdrawn with an automatic pipet and delivered into a separatory funnel containing 15 ml. each of cold water and carbon tetrachloride. The contents were shaken and the two phases separated. The water layer was washed with two additional 10-ml. portions of carbon tetrachloride. The layers were then separated again and the water phase was titrated with standard thiocyanate solution using ferric alum indicator.

Neopentyl Iodide Rates.—The proper volumes of the iodide and silver solutions were mixed at zero time in several 25-ml. stoppered erlenmeyer flasks. At various intervals the flasks were removed and 10 ml. of 1 N HNO_3 was added. The unreacted silver was titrated with standard thiocyanate solution. Again the data were analyzed by use of the proper integrated rate expressions.

Solubility Measurements.—A large test-tube carrying a standard taper Trubore stirrer was charged with excess powdered silver nitrate and the acetone solution of lithium perchlorate was added. The mixtures were stirred for 10 hours while thermostated at 25.5 ± 0.05°. The contents of the tube were then centrifuged, and an aliquot was removed from the surface of the solution and titrated for silver by the Volhard method with a standard sodium thiocyanate solution. Control experiments showed that equilibrium was attained in two hours. Table X summarizes the results.

TABLE X

SOLUBILITY OF SILVER PERCHLORATE IN ACETONE AT 25.5°

Concentrations, mole/l. × 10^2	
Lithium perchlorate added	Silver at equilibrium
None	1.03
10.3	2.50
15.6	3.06
46.7	5.85
77.9	8.15

Products.—Products were not studied in the nitrate reactions, but published examples[21] show that methyl, ethyl and isopropyl iodides must give high yields of alkyl nitrates in acetonitrile. Titration of a solution after complete precipitation of silver iodide in a reaction with isopropyl iodide showed that no acid was produced in the reaction.

A solution remaining after completion of a kinetic run with isopropyl iodide and silver perchlorate in acetonitrile was examined in some detail. Titration with standard 0.1 N sodium hydroxide showed that acid equivalent to the original charge of silver nitrate was produced. A sample was diluted with water and tested for chlorate with brucine[38] with negative results. Addition of 2,4-dinitrophenylhydrazine and acid gave no precipitate although it was shown by a control that the 2,4-dinitrophenylhydrazone was easily obtained from acetonitrile solutions containing acetone equivalent to the original silver perchlorate. An infrared spectrum of the solution, run in a double beam instrument against acetonitrile, showed only one maximum, at 6.1 μ in the 4–6 μ region. The ultraviolet spectrum showed a maximum at 257 mμ. Addition of cupric acetate to the solution, in an attempt to isolate a copper chelate of the absorbing species, gave no precipitate. The solution decolorized 2% aqueous permanganate as did a solution of perchloric acid in acetonitrile.

The reaction of silver perchlorate with methyl iodide in acetone produced dark brown solutions. These solutions neutralized an indeterminate amount of 0.1 N aqueous sodium hydroxide.

Acknowledgment.—The authors gratefully acknowledge the support of this work by the Redstone Arsenal Research Division of the Rohm and Haas Co. and the Ordnance Corps of the United States Army.

(38) F. Feigl, "Spot Tests," third ed., Elsevier Publishing Co., New York, N. Y., 1946, p. 245.

AMES, IOWA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Solvolysis of Aspirin Anhydride

BY EDWARD R. GARRETT

RECEIVED MAY 20, 1959

Aspirin anhydride hydrolyzes to aspirin with no evidence of prior or concomitant hydrolysis of the acetyl linkages and with no evidence of hydrogen ion accelerated hydrolysis. These facts do not support a cyclization mechanism. Aspirin anhydride is hydrolyzed by water, acetate and hydroxyl ions; undissociated acetic acid inhibits hydrolysis. Dielectric constant and temperature effects on the kinetics have been studied.

The enhancement of hydrolysis of the *ortho* ester in salicyl phosphates,[1-3] aspirin,[1,4,5] 4-(2′-acetoxyphenyl)-imidazole,[6] methyl pyrrolidylacetylsalicylate hydrochloride[7] and diethyl aminoethylacetylsalicylate hydrochloride[8] by an *o*-phenyl substitutent has been considered in the light of possible cyclic intermediates or intramolecular condensations involving interaction of the adjacent

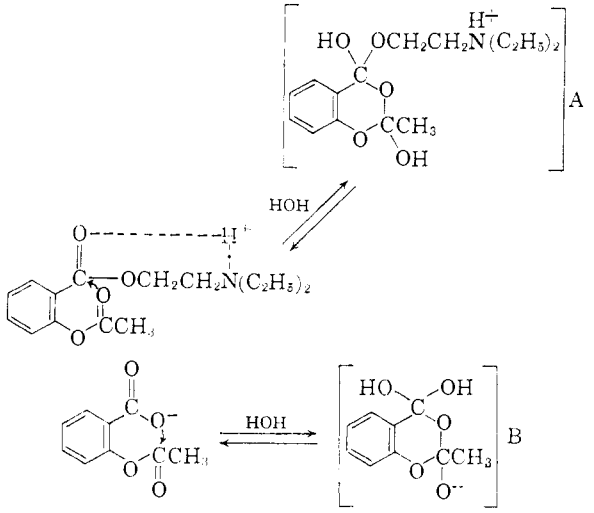
(1) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).
(2) J. D. Chanley and E. M. Gindler, *ibid.*, **75**, 4035 (1953).
(3) J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955).
(4) D. Davidson and L. Auerbach, *ibid.*, **75**, 5984 (1953).
(5) E. R. Garrett, *ibid.*, **79**, 3401 (1957).
(6) G. L. Schmir and T. C. Bruice, *ibid.*, **80**, 1173 (1958).
(7) E. R. Garrett, *ibid.*, **79**, 5206 (1957).
(8) E. R. Garrett, *ibid.*, **80**, 4049 (1958).

nucleophile or charged group. Significant and original contributions on this theme have been presented by Morawetz, *et al.*,[9-12] and Bender, *et al.*[13-15]

In the case of aspirin, interaction of the carboxylate anion and the *ortho* acetylated phenolic group provides a rational explanation for the so-called "spontaneous," non-*p*H dependent, hydrolysis in the neutral *p*H region.[5,16] However, whether the cyclization or the reaction of the cyclic intermediate is rate determining is still open to question.[1,5,14]

Although both non-cyclic and cyclic mechanisms for ester hydrolysis can be written in the cases of methyl pyrrolidylacetylsalicylate hydrochloride and diethylaminoethylacetylsalicylate hydrochloride, the non-cyclic mechanism is preferred for the former where nucleophilic attack is directly on the pyrrolidylacetyl ester[7,8] and the cyclic mechanism is preferred for the latter whereby the positively charged diethylaminoethyl group potentiates cyclization and subsequent solvolysis of the *ortho* acetylated phenolic group.[8]

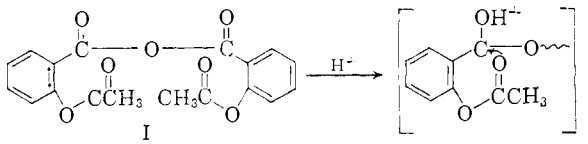
This proposed cyclization is analogous to, but, from charge considerations, different from the proposed cyclization prior to the solvolysis of the aspirin anion as



Schmir and Bruice[6] have proposed an intramolecular nucleophilic attack similar to reaction B to explain the "spontaneous" hydrolysis of 4-(2′-acetoxyphenyl)-imidazole. This is the uncharged analog of the aspirin anion. An uncharged analog in reaction A would be a compound such as methyl acetylsalicylate. However, alkyl benzoates are less susceptible to alkaline hydrolysis[17] and nucleophile-catalyzed solvolysis[18] than acylphenates. This was also shown in the maintenance of the methyl carboxylate linkage in the nucleophile-catalyzed solvolysis of methyl pyrrolidylacetylsalicylate hydrochloride,[7] one of the facts which permit doubt of any cyclization intermediates.[8]

Thus, the one fact of prior solvolysis of the acyl phenate linkage over the alkyl benzoate linkage in an alkyl acylsalicylate would not be evidence in favor of an intramolecular condensation abetting the solvolysis of the acyl phenate linkage. Contradiction of the order of expected hydrolysis could provide such evidence.

A possible model is aspirin anhydride (I) where hydrolysis of the acetylphenate prior to that of the anhydride linkage would indicate a cyclic intermediate analogous to that of reaction B since the reverse solvolytic priority would be expected.[19] An intermolecular analog of the proton activation of reaction B would be by strong acid as



I

Anhydride hydrolysis shows little change with hydrogen ion concentration[19] below 1.0 molar although a low order of hydrogen ion-catalyzed solvolysis has been claimed in relatively concentrated acidic[20-23] solutions.

Thus a more definitive dependence of anhydride hydrolysis on (or a possible greater yield of acetic acid with) acid concentration may also be predicted if cyclization occurs to abet aspirin anhydride linkage (or acetylphenate group) solvolysis.

This paper reports on the products of aspirin anhydride hydrolysis and the effects of solvent, acids and the nucleophiles water and acetate ions on the solvolytic kinetics.

Experimental

Spectrophotometric Studies.—The aspirin anhydride[24] was dried under high vacuum for several days before use. The general procedure for the studies in aqueous dioxane was to make up a weighed amount to a given volume with dioxane and take aliquots up to the appropriate volume with the appropriate aqueous buffer to achieve the desired concentrations at zero time.

The dioxane used was refluxed at least 24 hours prior to use over sodium to destroy peroxides, distilled, and the first fractions discarded.

Preliminary studies were made on the Cary model 11 recording spectrophotometer of 2.000×10^{-4} M aspirin anhydride in 0.200 M and 0.025 M HCl and in 10% dioxane-water. Typical ultraviolet spectra are given in Fig. 1 for various times after preparation. Very little change in spectra occurred after 40 minutes as is shown by the coincident spectra at 50 and 70 minutes. These spectra are the same as that given by aspirin at the same equivalent concen-

(9) H. Morawetz and P. E. Zimmering, *J. Phys. Chem.*, **58**, 753 (1954).

(10) H. Morawetz and E. Westhead, Jr., *J. Polymer Sci.*, **16**, 273 (1955).

(11) P. E. Zimmering, E. W. Westhead, Jr., and H. Morawetz, *Biochim. et Biophys. Acta*, **25**, 376 (1957).

(12) E. W. Westhead, Jr., and H. Morawetz, THIS JOURNAL, **80**, 237 (1958).

(13) M. L. Bender, Y. Chow and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(14) M. L. Bender, F. Chloupek and M. C. Neveu, *ibid.*, **80**, 5384 (1958).

(15) M. L. Bender and M. C. Neveu, *ibid.*, **80**, 5388 (1958).

(16) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).

(17) Compare values in Tables No. 212.442 and 212.443 of, and see references in, "Tables of Chemical Kinetics: Homogeneous Reactions," National Bureau of Standards Circular 510, U. S. Department of Commerce, Washington, D. C., 1951.

(18) M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1652, 1656 (1957).

(19) E. Berliner and L. H. Altschul, *ibid.*, **74**, 4110 (1952), and references therein.

(20) M. Kilpatrick, *ibid.*, **50**, 2891 (1928).

(21) M. Kilpatrick, *ibid.*, **52**, 1410 (1930).

(22) V. Gold and J. Hilton, *J. Chem. Soc.*, 838 (1955).

(23) V. Gold and J. Hilton, *ibid.*, 843 (1955).

(24) Prepared by Mr. R. D. Birkenmeyer of the Chemistry Department of the Upjohn Co. according to German Patent 201,325.

TABLE I

OBSERVED AND CALCULATED RATE CONSTANTS FOR THE SPECTROPHOTOMETRICALLY (λ 253 mμ) DETERMINED HYDROLYSIS OF ASPIRIN ANHYDRIDE IN 10% DIOXANE AT 25.1°. THE INITIAL CONCENTRATION OF ASPIRIN ANHYDRIDE IS 2.000×10^{-4} M[a]

Run	pH	[HCl]	[KCl]	[$HC_2H_3O_2$]	[$C_2H_3O_2^-$]	[NaCl]	10^4 k, sec.$^{-1}$ Obsd.[b]	10^4 k, sec.$^{-1}$ Calcd.[c]
1	0.46	0.400					8.1	
2	1.08	.100					7.6	
3	1.96	.010					7.2	
4	1.86	.0167	0.050				7.3	7.6
5							7.4	
6[a]							7.6	
7[a]							7.6	
8	2.59			0.57	(Assume		6.0	5.8
9	3.10			.057	0.001)		7.3	7.2
10	3.74			.116	.012		9.6	9.0
11	4.18			.060	.015	0.085	10.7	10.7
12	4.21			.120	.030	.070	14.0	13.9
13	4.23			.200	.050	.050	18.1	18.1
14	4.17	4.20[d]		.200	.050	.050	18.0	18.1
15	4.20			.260	.065	.035	20.8	20.6
16	4.18			.320	.080	.020	24.3	24.3
17	4 19			.400	.100	.000	27.7	28.5
18	4.68			.080	.060	...	21.5	22.1
19	4.83			.015	.015	.085	11.3	11.3
20	4.82			.030	.030	.070	15.1	14.9
21	4.83			.050	.050	.050	19.5	19.8
22	4.86	4.80[d]		.065	.065	.035	23.6	23.5
23	4.79			.080	.080	.020	27.0	27.1
24	4.78			.100	.100	.000	31.2	32.0
25	5.24			.033	.084	...	28.5	28.9
26	5.36			.010	.040	.160	19.5	17.8
27	5.36			.020	.080	.120	28.6	28.0
28	5.36	5.36[e]		.030	.120	.080	40.0	38.2
29	5.40			.040	.160	.040	49.1	48.4
30	5.39			.050	.200	.000	61.1	58.6
31	5.81			.009	.095	..	31.5	32.1
32	6.16			.004	098	...	32.9	32.9
33	5.99			.027	.4865	...	130	133

[a] Except for runs 6 and 7 where the initial aspirin anhydride concentrations are, respectively, 1.333×10^{-4} and 0.667×10^{-4} M. [b] Based on first-order plots similar to Fig. 2 of $\log (A_t - A_\infty)$ *vs.* time where A is the absorbance at any time, t, and A_∞ is the asymptotic absorbance at infinite time and $\log (A_t - A_\infty) = -kt/2.303 + \text{constant}$. [c] Based on the derived expressions: $k = k'_{Ac}[C_2H_3O_2^-] + k_0 = \{k_{Ac} - k'_{HAc}[H^+]\}[C_2H_3O_2^-] + k_0$, where $k_{Ac} = 0.0250$, $k'_{HAc} = 80$, $k_0 = 7.6 \times 10^{-4}$ and $[H^+] = 10^{-pH}$. [d] Constant ionic strength, μ 0.100. [e] Constant ionic strength, μ 0.200.

tration in the same media. After 18 hours a new band appears in the 300 mμ region which is characteristic of salicylic acid. It is thus concluded that aspirin anhydride hydrolyzes to aspirin at a much faster rate than the latter goes to salicylic acid. There is no indication of salicylic acid anhydride which was expected to have the spectra of methyl salicylate or acidified salicylic acid. Figure 1 indicates large differences in the absorbances of aspirin anhydride and aspirin, the initial product of anhydride hydrolysis, in the 250–260 mμ region.

The kinetic studies were carried out with the Beckman spectrophotometer, model DU, equipped with constant temperature control. The control was maintained by the circulation of water from a constant temperature bath through thermal spacers in contact with the cell containing the solution under spectrophotometric study. The absorbance readings were made at 253, 256 and 260 mμ and the apparent first-order rate constants k (in sec.$^{-1}$) were determined by application of the standard equation 1 to the slopes of the plot of $\log (A_t - A_\infty)$ against time

$$\log (A_t - A_\infty) = -kt/2.303 + \text{constant} \quad (1)$$

where A_t is the absorbance at any time and A_∞ is the final or asymptotic absorbance. Typical plots of the experimental data are given in Fig. 2.

The determined k-values were the same at all three of the studied wave lengths for a given run. Temperature control was obtained by maintaining all solutions prior to the mixing at the temperature of the kinetic run and by immediately filling the thermostated cell in the spectrophotometer with the final solution. In general, the cell temperature was lower than the setting of the circulating bath, but the heat differential was constant. The equilibrated cell temperatures were taken as the temperatures of the reactions.

The composition of a series of solutions of aspirin anhydride with the observed first-order rate constants at 25.1° in 10% dioxane by volume is given in Table I. Variation in the initial aspirin anhydride molarity from 0.667×10^{-4} to 2.000×10^{-4} M (runs 5,6,7 in Table I) showed no difference in the apparent first-order rate constants for hydrolysis to aspirin. The buffers used were various concentrations of hydrochloric acid and sodium acetate–acetic acid. Acetate ion concentration was varied at constant pH in three cases and constant ionic strength was maintained for this variation.

The effect of per cent. dioxane on the apparent first-order rate constants for the hydrolysis of 2.000×10^{-4} M aspirin anhydride to aspirin was studied. The dioxane concentrations were varied from 2 to 10% by volume at 2% intervals. These studies were conducted in 0.1000 M HCl and 0.1000 M acetic acid–0.1000 M sodium acetate. The experimental data are given in Table II.

The same buffer systems were used to study the effect of temperature on the apparent first-order rate constants in 10% dioxane by volume. The experimental data are given in Table III.

Preliminary studies of aspirin anhydride in 75% dioxane showed very little hydrolysis within several hours. No sig-

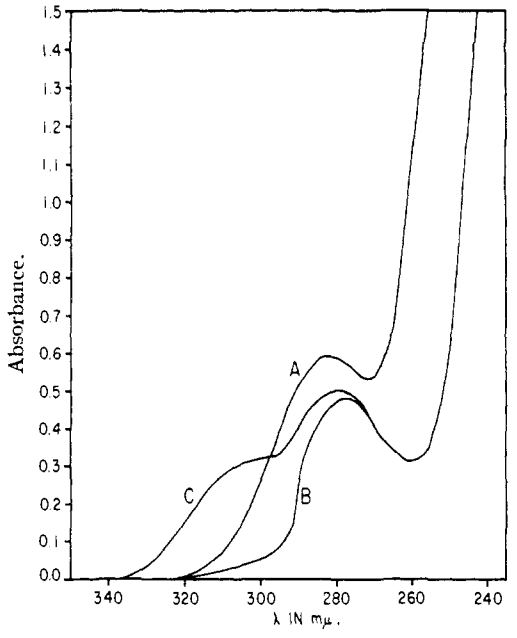


Fig. 1.—Change of ultraviolet spectral curves of acidified aspirin anhydride (2×10^{-4} *M*) in 0.2 *M* HCl with time. The solvent was 10% dioxane at 25°: curve A is at 5 min. after preparation; curve B is at 50 and 70 min. after preparation and is also the spectra of 4×10^{-4} *M* aspirin in 0.2 *M* HCl; curve C is at 18 hr. after preparation where the 303 mμ maximum is that of salicylic acid.

nificant spectral change was observed for aspirin anhydride in 100% dioxane.

Constant *p*H Titration Studies.—It was expected that alkaline hydrolysis of aspirin anhydride would proceed at too fast a rate for spectrophotometric study unless a buffer system of moderate alkalinity were to be used. Then other general base catalytic constants would have had to be evaluated before determining the kinetic effect of hydroxyl ion alone.

TABLE II

VARIATION OF PSEUDO FIRST-ORDER RATE CONSTANTS (k IN SEC.$^{-1}$) OF ASPIRIN ANHYDRIDE HYDROLYSIS WITH % DIOXANE AT 25.1°

Initial concentration of aspirin anhydride was 2.000×10^{-4} *M*

Run	Addend	Dioxane by vol.,[a] %	*p*H	$10^4 k$, sec.$^{-1}$	Dielectric constant, (D)[b]
34	0.1000 *M* HCl	2	1.15	16.5	76.8
35		4	1.06	13.5	75.2
36		6	1.15	11.0	73.5
37		8	1.16	8.87	71.8
2		10	1.08	7.62	70.1
38	0.1000 *M* $HC_2H_3O_2$ + 0.1000 *M* $NaC_2H_3O_2$	2	4.72	62.9	76.8
39		4	4.72	52.3	75.2
40		6	4.79	44.5	73.5
41		8	4.85	37.6	71.8
24		10	4.78	31.2	70.1

[a] % Dioxane by weight may be calculated from H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1950, p. 545. A relation that may be used between 0–10% dioxane by volume is: (% dioxane by wt.) = 1.014 × (% dioxane by vol.) + 0.05. [b] Interpolated from F. E. Critchfield, J. A. Gibson and J. L. Hall, THIS JOURNAL, **75**, 1991 (1953). The dielectric constant of water is 78.5.

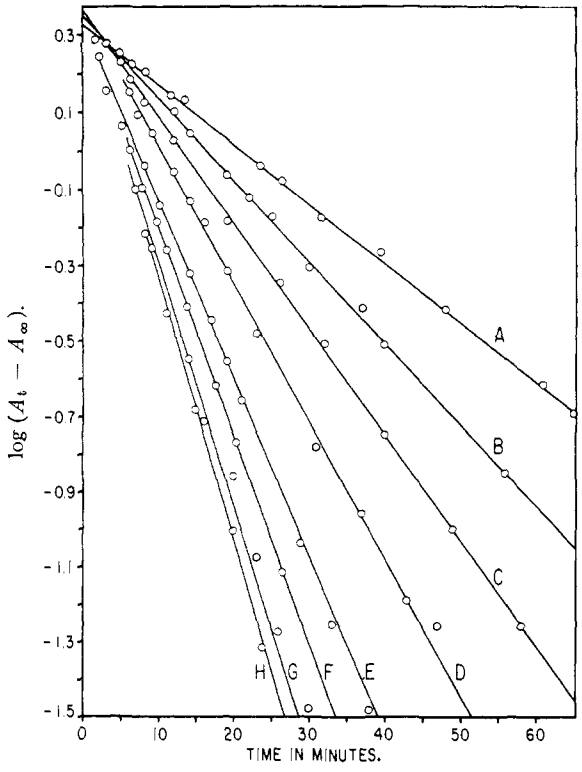


Fig. 2.—Typical first-order rate plots for the hydrolysis of 2.000×10^{-4} *M* aspirin anhydride in buffered 10% dioxane at 25.1° as measured by absorbance (A) changes at 253 mμ; A_∞ is the asymptotic absorbance. The respective curves, apparent *p*H values and Table I runs are: A, 2.59, 8; B, 0.46, 1; C, 4.18, 11; *D*, 4.21, 12; E, 4.23, 13; F, 4.20, 15; G, 4.18, 16; H, 4.19; 17.

Thus, the hydrolysis of aspirin anhydride in the regions where hydroxyl ion concentration is significant was studied by following the consumption of standard alkali by the aspirin product at constant *p*H. The machine used was the Cannon automatic di-functional recording titrator,[25] In-

TABLE III

VARIATION OF PSEUDO FIRST-ORDER RATE CONSTANTS (k IN SEC.$^{-1}$) FOR ASPIRIN ANHYDRIDE HYDROLYSIS WITH TEMPERATURE

Solvent is 10% dioxane; the initial anhydride concentration is 2.000×10^{-4} *M*; the rates were determined spectrometrically at 253 mμ.

Run	Addend	*T*, °C.	*p*H	$10^4 k$, sec.$^{-1}$	$10^3 k'_{Ac}$[a]
2	0.1000 *M* HCl	25.1	1.08	7.62	23.6
42		30.0		9.71	32.9
43		39 6	1.19	15.6	47.6
44		49.2	1.17	23.3	60.7
45		56.6	1.17	38.8	75.2
46		65.8	1.15	52.6	135
24	0.1000 *M* $HC_2H_3O_2$ + 0.1000 *M* $NaC_2H_3O_2$	25.1	4.78	31.2	
47		30.0	4.89	42.6	
48		39 6	4.93	63.2	
49		49.2	4.91	84.0	
50		56.6	4.93	114	
51		65.8	4.94	188	

[a] Calculated from $k'_{Ac} = (k_{(0.1\ M\ C_2H_3O_2^-)} - k_{(0.1\ M\ HCl)})/[C_2H_3O_2^-]$ where the $k_{(0.1\ M\ C_2H_3O_2^-)}$ and $k_{(0.1\ M\ HCl)} = k_0$ were determined in the buffer system 0.1000 *M* acetic acid–0.1000 *M* sodium acetate and in 0.1000 *M* HCl, respectively.

(25) J. B. Neilands and M. D. Cannon, *Anal. Chem.*, **27**, 29 (1955).

ternational Instrument Co., Canyon, Calif. This machine automatically plots the volume of alkali needed to maintain a constant *p*H as a function of time. The titration cell is jacketed and thermostated by water circulated from a constant temperature bath. The electrode system was glass-saturated calomel.

Aspirin anhydride was dissolved in dioxane up to a given volume and maintained in the constant temperature bath. An aliquot of this was brought up to the appropriate volume with thermostated nitrogen-purged water at zero time. The resultant aspirin anhydride solution was 8.34×10^{-4} *M* in 10% dioxane by volume. Fifteen ml. was immediately pipetted into the thermally equilibrated titration cell and the *p*H control activated. Hydrolysis studies were made as close as possible to the *p*H values of 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0 at 25.8°. The degree of oscillation about the chosen *p*H control point was a function of the normality of the alkali, the speed of the reaction, the *p*H separation from neutrality, and the buffering capacity at the control *p*H of the product to be neutralized.

Equation 1 was applied to the data to estimate the pseudo first-order rate constants except that the log $(\lambda_\infty - \lambda_t)$ was plotted against time where λ_∞ is the final volume of titer and λ_t is the volume of titer added at any time. The conditions and estimated rate constants are given in Table IV. Typical plots of the experimental data are given in Fig. 3.

TABLE IV

RATE CONSTANTS FOR THE WATER AND ALKALINE HYDROLYSIS OF ASPIRIN ANHYDRIDE IN 10% DIOXANE AT 25.8°

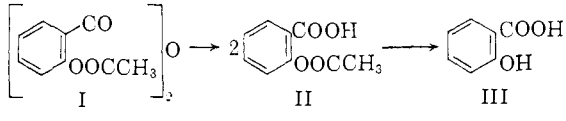
The first order rates were determined from the rate of standard alkali[a] addition at constant *p*H to 15 ml. of $8.34 \cdot 10^{-4}$ *M* aspirin anhydride

Run	*p*H range	Estd. mean *p*H[b]	$10^4 k$, sec.$^{-1}$	$10^4 k_{OH^-}[OH]$[c]
52	4.00–4.10	4.0	7.8	
53	4.96–5.02	5.0	8.3	
54	5.98–6.20	6.0	6.3	Avg., *i.e.*, $k_0 = 8.0$
55	6.90–7.20	7.0	6.4	
56	6.88–7.35	7.2	10.8	
57	7.85–8.15	8.1	13.6	5.6
58	7.90–8.35	8.2	17.5	9.5
59	8.96–9.10	9.0	38	30
60	8.85–9.10	9.0	47	39
61	9.1–9.4	9.3	80	72

[a] 0.2500 *M* NaOH except runs 56, 58 and 60 where 0.5000 *M* and run 61 where 2.0 *M* were used. [b] Since the pK_w in 10% dioxane at 25.8° is 14.26, *p*OH may be estimated from *p*OH = 14.3 − *p*H. The pK_w is estimated from the literature.[29] [c] As calculated from $k_{OH^-} = k - k_0$.

Calculations and Results

It was concluded from the spectrophotometric studies that the hydrolysis of aspirin anhydride(I) to aspirin(II) in homogeneous solution is a fast reaction and can be studied spectrophotometrically and titrimetrically without any significant appearance of the relatively slowly appearing salicylic acid(III).



I II III

Catalytic Species in Neutral and Acidic Hydrolysis.—Water, hydroxyl ions and other nucleophiles (such as carboxylate anions, amines, etc.) affect the hydrolysis rate of anhydrides.[20,26]

The hydrolysis of aspirin anhydride in strong acid where the conjugate base is non-nucleophilic, such as hydrochloric acid in concentrations from 0.0 through 0.4 *M*, was not a discernible direct function of strong acid or hydrogen ion concentration in agreement with the report for other anhydrides[19] (see runs 1 through 7 in Table I). The first-order rate constants of hydrolysis were not functions of the initial concentration of aspirin anhydride (see runs 5, 6 and 7 in Table I).

(26) V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948).

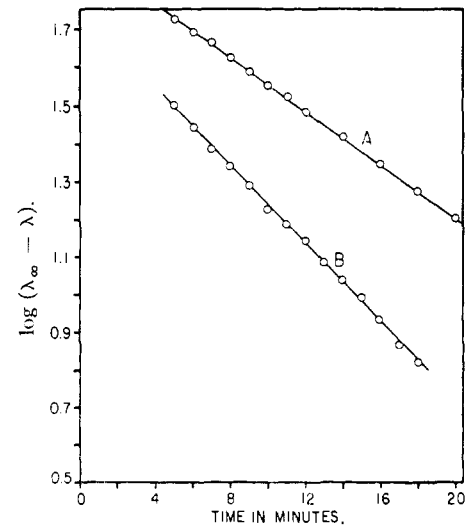


Fig. 3.—Typical first-order rate plots for the hydrolysis of aspirin anhydride (15 ml. 8.34×10^{-4} *M* in 10% dioxane) at constant *p*H 8.0 by measurement of standard alkali consumption in λ volumes where λ_∞ is the asymptotic volume of titer: curve A, 25.8°; B, 29.7° where 0.25 *M* NaOH was used with curve A and 0.50 *M* NaOH with curve B.

The most probable mechanisms for aspirin anhydride hydrolysis to aspirin are by "spontaneous" hydration or water attack and by catalysis due to nucleophiles or bases. In the acetic acid–acetate system, acetate ion should be a catalytic species.

Figure 4 plots some of the observed rate constants of Table I against acetate ion concentration for three different *p*H values. Ionic strength was maintained constant for a given *p*H. The linearity of the plots confirmed the expectation that the observed first-order rate constant, *k* in sec.$^{-1}$, depends on acetate ion concentration, $[C_2H_3O_2^-]$, where

$$k = k'_{Ac}[C_2H_3O_2^-] + k_0 \qquad (2)$$

where the slopes, k'_{Ac} and intercepts, k_0, of such plots are given in Table V. These results indicate very little change in rate as a direct function of *p*H below *p*H 5.0 and that $k_0 = 7.6 \times 10^{-4}$ sec.$^{-1}$ can be attributed to "spontaneous" hydration by water in agreement with the constancy of hydrolyses rate in water and in varying HCl concentrations (runs 1 though 7, Table I).

The k'_{Ac} values of Table V indicate an apparent variation of the catalytic rate constant for acetate ion with *p*H. This is not a function of ionic strength, μ, since k'_{Ac} differs more at a constant $\mu = 0.100$ for the studies at the two *p*H values 4.20 and 4.80 than it does at double the ionic strength for the studies at different *p*H values. Compare the values at *p*H 4.80 and 5.36. Since ionic strength and hydrogen ion concentration *per se*

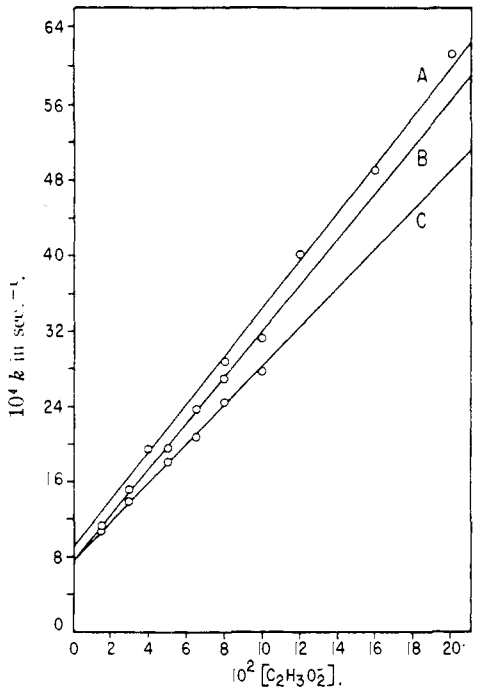


Fig. 4.—Effect of varying acetate ion concentration at constant ionic strength, μ, at several pH values on the first-order rate constants (k in sec.$^{-1}$) of hydrolyses of 2.000×10^{-4} M aspirin anhydride at 25.1° in 10% dioxane. The respective curves, pH values and ionic strengths are: A, 5.36, 0.200; B, 4.80, 0.100; and C, 4.20, 0.100.

are not directly responsible, the only other variable to consider is the concentration of undissociated acetic acid, $[HC_2H_3O_2]$, which only indirectly is a function of hydrogen and acetate ions, as

$$[HC_2H_3O_2] = K'_a[H^+][C_2H_3O_2^-] \quad (3)$$

where K'_a is the apparent dissociation constant of acetic acid. Kilpatrick[21] has shown that the hydrolysis of anhydrides is linearly retarded by the presence of undissociated acid so that the following relations may be formulated

$$\begin{aligned} k &= k_{Ac}[C_2H_3O_2^-] - k_{HAc}[HC_2H_3O_2] + k_0 \\ &= k_{Ac}[C_2H_3O_2^-] - k_{HAc}K'_a[H^+][C_2H_3O_2^-] + k_0 \\ &= \{k_{Ac} - k'_{HAc}[H^+]\}[C_2H_3O_2^-] + k_0 \end{aligned} \quad (4)$$

Thus

$$k'_{Ac} = k_{Ac} - k'_{HAc}[H^+] \quad (5)$$

and the plot of the observed acetate ion catalytic constant, k'_{Ac}, against the hydrogen ion concentration, $[H^+] = 10^{-pH}$, permits the evaluation of slope, $-k'_{HAc}$, and intercept, k_{Ac}. Thus, the observed rate constant, k in sec.$^{-1}$, at 25.1° in 10% dioxane before hydroxyl ion concentration has any significance may be estimated by the expression

$$k = \{0.0259 - 80[H^+]\}[C_2H_3O_2^-] + 7.6\ 10^{-4} \quad (6)$$

The observed rate constants from additional studies at various pH values and various buffer concentrations are also given in Table I. The rate constants calculated from equation 6 and listed in this table agree with the observed to confirm the proposed rate dependencies.

TABLE V

DEPENDENCE OF PSEUDO FIRST-ORDER RATE CONSTANTS (k IN SEC.$^{-1}$) OF ASPIRIN ANHYDRIDE HYDROLYSIS ON ACETATE ION. $[C_2H_3O_2^-]$, *i.e.*, $k = k'_{Ac}[C_2H_3O_2^-] + k_0$

pH	Ionic strength	Based on items in Table I	$10^2k'_{Ac}$	10^4k_0
4.20	0.100	11–17	2.08	7.6
4.80	.100	19–24	2.44	7.6
5.36	.200	26–30	2.55	9.1

Effects of Percentage Dioxane on Acetate-catalyzed and "Spontaneous" Rate.—The data of Table II show the effect of various dioxane concentrations from 2 to 10% by volume on the rate constants at 25.1° in 0.1000 M HCl (where $k = k_0$) and in a buffer system, 0.1000 M acetic acid and 0.1000 M sodium acetate (where $k'_{Ac} = (k - k_0)/[C_2H_3O_2^-]$).

The relation of the observed rate constant, k (sec.$^{-1}$), to some function of the dielectric constant, D, *i.e.*, $f(D)$, is of the form

$$\log k = m_i f_i(D) + b_i \quad (7)$$

Within the small range of dioxane concentrations studied and at the high dielectric constants, the expression 7 is linear for practically any $f_i(D)$, *i.e.*, $f_1(D) = \%$ dioxane, $f_2(D) = D$, $f_3(D) = 1/D$ or $f_4(D) = (D - 1)/(2D + 1)$ and the parameters[27,28] of these relations are listed in Table VI.

Effect of Temperature on Acetate-catalyzed and "Spontaneous" Rate.—The studies of the effect of temperature on the rate constant (Table III) in 10% dioxane in 0.1000 M HCl (where $k = k_0$) and in a buffer system, 0.1000 M acetic acid and 0.1000 M sodium acetate (where $k'_{Ac} = (k - k_0)/[C_2H_3O_2^-]$) were plotted according to the Arrhenius relation

$$\log k = -\Delta H_a/2.303RT + \log P \quad (8)$$

The heats of activation, ΔH_a, and log P values are given in Table VII.

Alkaline Hydrolysis as a Function of pH.—Kinetic studies of the hydrolysis of aspirin anhydride at constant pH in 10% dioxane at 25.8° without any added buffers (Table IV) showed that no significant enhancement of rate can be attributed to hydroxyl ion below a pH of 7.0. The rates are constant within the experimental error of this technique and can be attributed solely to "spontaneous" hydration.

The observed rate constant, k in sec.$^{-1}$, should depend on hydrolysis by water, k_0, and hydroxyl ion concentration in the alkaline region as

$$k = k_0 + k_{OH^-}[OH^-] \quad (9)$$

where

$$[OH^-] = 10^{-pOH} = 10^{-(pK_w - pH)} \quad (10)$$

where the pH is experimental and the pK_w may be estimated from the literature[29] as 14.26 at 25.8°.

(27) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1st Ed., 1941, p. 419 *et seq.*

(28) E. S. Amis, "Kinetics of Chemical Change," The Macmillan Co., New York, N. Y., 1949, Chapter IX.

(29) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1950, pp. 545, 581.

TABLE VI

DEPENDENCE OF RATE CONSTANT (k IN SEC.$^{-1}$) FOR ASPIRIN ANHYDRIDE HYDROLYSIS OF SOME FUNCTION [f(D)] OF THE DIELECTRIC CONSTANT (D) IN 0-10% DIOXANE–WATER SOLUTIONS AT 25.1° BY THE EXPRESSION LOG $k = m_i \times F_i(D) + b_i$

	$f_1(D)$ = % dioxane[d]			$f_2(D) = D$			$f_3(D) = 1/D$			$f_4(D) = \frac{D-1}{2D+1}$		
Rate constant	m_1	b_1	10^4k in H_2O[e]	m_2	b_2	10^4k in H_2O[e]	m_3[g]	b_3	10^4k in H_2O[e]	m_4[g]	b_4	10^4k in H_2O[e]
k_{H_2O}[a]	−0.0436	−2.696	20.3	0.0540	−6.929	20.2	−272.2	0.755	19.4	394.2	−196.083	19.6
$k_{(0.1\ M\ C_2H_3O_2^-)}$[b]	− .0377	−2.124	75.2	.0447	−5.639	74.3	−238.9	0.904	72.1	311.0	−154.702	70.0
k_{Ac}[c]	− .0364	−2.257	555	.0418	−4.548	537	−230.0	1.658	537	312.9	−154.755	531
k_{Ac}[f]			549[f]			541[f]			527[f]			504[f]

[a] Runs 34 through 37 and 2 of Table III. [b] Runs 38 through 41 and 24 of Table III. [c] $k'_{Ac} = k_{(0.1\ M\ C_2H_3O_2^-)} - k_{H_2O})/[C_2H_3O_2^-]$. [d] This is by volume. It may be converted by (% dioxane by wt.) = 1.014 × (% dioxane by vol.) + 0.05. [e] Calculated at 0% dioxane and at $D = 78.5$ for the given slope (m) and intercept (b). [f] Calculated from the values above it in the column by the relation of footnote c. [g] From A. H. Fainberg and S. Winstein, THIS JOURNAL, **78**, 2770 (1956), at high values of D, $m_3 = -(3/4)m_4$; these values are consistent with this relation.

TABLE VII

THERMODYNAMIC QUANTITIES[a] FOR THE HYDROLYSIS OF ASPIRIN ANHYDRIDE IN 10% DIOXANE

	S	ΔH_a	log P
k (sec.$^{-1}$) in 0.1000 M HCl = k_0	1960	9.0	3.46
k (sec.$^{-1}$) in 0.1000 M $HC_2H_3O_2$ and 0.1000 M $C_2H_3O_2^-$ = $k'_{Ac}[C_2H_3O_2^-] + k_0$	1712	7.8	3.26
k'_{Ac} (l./mole/sec.)	1674	7.7	4.01

[a] The quantities are derived from the logarithmic form of the Arrhenius relation: $\log k = (\Delta H_a/2.303R)(1/T) + \log P = S/T + \log P$, where ΔH_a is the heat of activation in kcal./mole, R is the gas constant in cal./degree, T is the absolute temperature and S is the slope of the Arrhenius plot.

Equation 9 may be expressed as

$$-\log (k - k_0) = -\log k_{OH^-}[OH^-] = -\log k_{OH^-} + p\mathrm{OH} \quad (11)$$

The data of Table IV have been plotted in Fig. 5 according to equation 11 using $k_0 = 8.0 \times 10^{-4}$ sec.$^{-1}$ at 25.8° and a line with the theoretical slope of unity drawn through the points. The intercept $-\log k_{OH^-} = 2.92$ so that $k_{OH} \sim 10^3$ l./mole/sec. in 10% dioxane.

Discussion

The observed general base-catalyzed hydrolysis of anhydrides as by acetate ion has been explained by mixed anhydride formation on nucleophilic attack.[20,21,30] This concept is strengthened by the fact that the catalytic effects of anions on anhydride hydrolysis fail to follow the order of base strengths.

The studies and concepts of Gold and Jefferson,[31] and Denney and Greenbaum,[32] may also be used to postulate the following schemes to explain the possible mechanism for aspirin anhydride hydrolysis by water, acetate and hydroxyl ions. The symbol R– represents the O-acetoxyphenyl group.

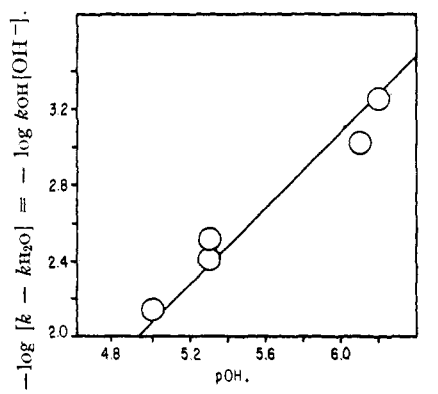


Fig. 5.——log k_{OH} [OH^-] *vs.* pOH from constant pH titration at 25.8° to determine hydrolysis dependence on [OH^-]. The theoretical slope is unity.

The equilibrium A with a non-reactive species may explain the inhibitory effect of acetic acid concentration on the hydrolysis rate.

The route B to the mixed anhydride by direct nucleophilic attack of the acetate ion conforms to Kilpatrick.[20,21,30] The adherence of the data of the spectrophotometric studies to first-order kinetics, Fig. 2, indicates that either the mixed anhydride is not an intermediate or its hydrolysis is extremely fast relative to that of the symmetrical aspirin anhydride. The presence of large *o*-acetoxy groups may raise some doubt that steric considerations are favorable for such a route in this case.

Gold and Jefferson[31] imply that the catalytic mechanism by uncharged amine differs from that by anion since the so-called catalytic constants widely differ for similar basicity. The routes C, F, G and C, D, H are possible other alternatives through the hydrated equilibrium form of the anhydride.[33]

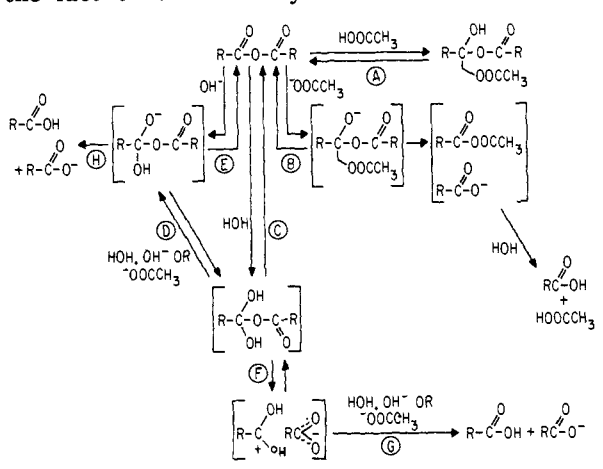


CHART I.

(30) M. Kilpatrick, THIS JOURNAL, **52**, 1418 (1930).

(31) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409 (1953).

(32) D. B. Denney and M. A. Greenbaum, THIS JOURNAL, **79**, 3701 (1957).

(33) C. Bunton, T. Lewis and D. Llewellyn, *Chemistry & Industry*, 1154 (1954).

These routes involve charge transfer by the classically accepted schemes of general acid–base catalysis. The route, C, F, G implies rate determination in G, the bimolecular reaction, after the formation of the ion pair. The route C, D, H implies rate determination in D or H, but since hydrogen ion concentration *per se* has little effect on the rate it is difficult to conceive of step H as rate determining. If this were so, increase in hydrogen ions would shift the equilibrium D to the right and lower the rate of product formation which is not in agreement with experiment.

Gold and Jefferson[33] also prefer a different mechanism of attack by hydroxyl ion than by carboxylate anion. A glance at the schemata shows a short cut, E, that results in the same fast-acting intermediate as through C and D. Direct nucleophilic attack by hydroxyl ion should have low energy and low entropy requirements.

The low heat of activation (9 kcal./mole) of aspirin anhydride is in accord with the effect of groups such as acetoxy, that will favor nucleophilic attack.[19,34] Its *o*-position should even increase its action in lowering the activation energy. The lower frequency factor is also consistent with Berliner and Altschul's premise[19] that groups favoring attack energetically withdraw electrons and lower the probability of the formation of the activated complex.

The lack of evidence for any acetylphenate ester hydrolysis concomitant with (or prior to) anhydride linkage hydrolysis in aspirin anhydride does not support an intramolecular condensation or cyclization with the *o*-groups in aspirin anhydride. The lack of significant acceleration of the anhydride linkage solvolysis by hydrogen ion does not support such mechanisms or intermediates in the anhydride hydrolysis.

The reaction rate of aspirin anhydride hydrolysis is fantastically enhanced by a relatively small decrease in dioxane concentration (from 10% dioxane), concomitantly with a very small increase in dielectric constant. A possible explanation consistent with the proposed hydrolysis mechanisms is that the activated complex has a high dipole moment. Reactions with such complexes should have rates accelerated by solvents of higher dielectric constant.[27,28]

Acknowledgment.—The author is greatly indebted to Mrs. Lillian G. Snyder for excellent technical assistance.

KALAMAZOO, MICH.

(34) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL TECHNOLOGY, UNIVERSITY OF BOMBAY]

Reaction of Lithium Aluminum Hydride with Arylaminomethylenemalonate Esters and Related Compounds[1]

BY R. L. SHIVALKAR AND S. V. SUNTHANKAR[2]

RECEIVED MAY 19, 1959

A series of ethyl arylaminomethylenemalonates, ethyl arylaminomethylenecyanoacetates and arylaminomethylenemalononitriles has been prepared, and their reaction with lithium aluminum hydride has been studied. In the reduction of ethyl arylaminomethylenemalonates partial hydrogenolysis took place and the products obtained were 3-arylaminoallyl alcohols. In the case of ethyl arylaminomethylenecyanoacetate and arylaminomethylenemalononitrile cleavage took place, and the starting primary aromatic amines were obtained. The mechanism of the partial hydrogenolytic reduction is discussed.

In connection with some other studies, 2-(β-naphthylaminomethylene)-1,3-propanediol, was required. The most convenient method for the synthesis of this compound was thought to be the reduction of ethyl β-naphthylaminomethylenemalonate,[3] which was readily obtained in high yield by the condensation of diethyl ethoxymethylenemalonate and β-naphthylamine. However, the reduction, even under mild conditions, gave 3-(2-naphthylamino)-allyl alcohol (II) as the result of partial hydrogenolysis. Such a smooth hydrogenolytic reduction was of interest and, therefore, we studied this reaction more carefully. When ethyl β-naphthylaminomethylenemalonate was treated with excess of lithium aluminum hydride (4 moles) in ether for three and a half hours, allyl alcohol (II) was obtained in 90% yield. In order to see whether the excess of lithium aluminum hydride was responsible for hydrogenolysis, the reduction was carried out with one molar proportion of the reagent. However, the products obtained were the allyl alcohol and the unconverted ester, which during isolation by distillation under vacuum gave a benzoquinoline derivative[4] (III). Similarly ethyl anilinomethylenemalonate[5] gave the corresponding 3-anilinoallyl alcohol in 90% yield. Next ethyl N-ethylanilinomethylenemalonate was treated with excess of lithium aluminum hydride under similar conditions. However, cleavage took place and N-ethylaniline was recovered in 80% yield.

In order to verify that the partial hydrogenolysis is not due to the α,β-unsaturated character of the compounds but due to the β-amino group, ethyl benzalmalonate[6] was reduced under similar conditions. The product isolated in this case was the

(1) A preliminary report of this work has appeared: K. S. Sardesai, R. L. Shivalkar and S. V. Sunthankar, *J. Sci. Industr. Res.*, **17**, 282 (1958).

(2) To whom correspondence concerning this article should be addressed.

(3) Robert E. Foster, *et al.*, THIS JOURNAL, **68**, 1327 (1946).

(4) K. S. Sardesai and S. V. Sunthankar, *Cur. Sic.*, **26**, 250 (1957).

(5) Byron Riegel, *et al.*, THIS JOURNAL, **68**, 1264 (1946).

(6) *Org. Syntheses*, **25**, 42 (1945).