at 108–109° after recrystallization from a mixture of benzene and petroleum ether.

Alkyl and Aryl α-Phthalimido Ketones (See Table II).—The aryl phthalimido ketones were prepared by Friedel-Crafts acylation, excepting β-phenyl-α-phthalimidopropiophenone, not obtainable by Friedel-Crafts acylation, which was prepared by the condensation of β-phenyl-α-phthalimidopropionyl chloride and phenylcadmium according to the procedure (1) described for the synthesis of alkyl β-phthalimidoethyl ketones. The procedure for the alkyl and aryl α-phthalimido ketones is essentially the same as that for the β-phthalimidoethyl ketones, except for the process of purification, as described for 1-phenyl-2-phthalimido-3-nonanone: the organocadmium reagent was prepared from 36.6 Gm. of *n*-hexyl bromide (0.22 mole), 5.3 Gm. magnesium turnings (0.22 mole), and 16 3 Gm. anhydrous cadmium chloride (0.22 mole) in anhydrous ether. After the solvent was replaced with dry benzene, 42 Gm. β-phenyl-α-phthalimidopropionyl chloride (0.134 mole) in benzene was added to the mixture. The reaction was completed and the product isolated in the usual way. The thick oil obtained after the removal of benzene was distilled under reduced pressure, yielding a yellowish oil at 70–240°/0.5 mm. Crystals, 7.6 Gm., were obtained from the alcoholic solution of the oil, corresponding to a yield of 15%. The crystals melted at 86–87° after two recrystallizations from alcohol.

Heterocyclic β-Phthalimidoethyl Ketones (See Table III).—2-Furyl, and 2-thienyl β-phthalimidoethyl ketones were prepared by the procedure described for 2-thienyl β-phthalimidoethyl ketone: a mixture of 22 Gm. β-phthalimidopropionic acid (0.1 mole) and 100 ml. dry benzene was refluxed for 1 hour with constant stirring. The mixture was cooled to room temperature, and 10 Gm. phosphorus pentoxide was added in one portion. The mixture was stirred for 1 hour at room temperature and then refluxed for 5 hours, following which it was filtered, and the filtrate washed successively with 10% sodium carbonate and water, and dried over anhydrous sodium sulfate. A syrupy liquid, obtained when the solvent was removed from the benzene solution, crystallized as a white powder, weighing 6.25 Gm. and corresponding to a yield of 37.5% based upon the quantity of β-phthalimidopropionic acid actually consumed (12.3 Gm.). The white powder crystallized from boiling alcohol as short needles, m.p. 154–155°.

Amino Ketone Hydrochlorides (See Table IV).—Amino ketone hydrochlorides were prepared by the hydrolysis of the phthalimido or the acylamido ketones in a mixture of glacial acetic and concentrated hydrochloric acids under refluxing conditions according to the procedure described in the previous paper (1).

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Solvolysis of Symmetrical and Mixed Aspirin Anhydrides in 75% Dioxane–25% Water

By EDWARD R. GARRETT†

The neutral solvolysis of aspirin anhydride, I, and the mixed anhydrides of aspirin and acetic acid, II, of acetylsalicoylsalicylic and acetic acids, III, have been studied as functions of temperature in 75% dioxane by volume so as to compare them with the literature values on *m*- and *p*-substituted benzoic anhydrides studied in the same solvent. There is very little change in the heats of activation but large increases in the frequency factors of the *ortho*, mixed or symmetrical, over the *meta* and *para*. The mixed anhydrides of an *o*-acylbenzoic acid and acetic acid have higher solvolysis rates by virtue of lower frequency factors than the symmetrical aspirin anhydrides.

RECENT STUDIES (1) have demonstrated the presence of all possible products of acyl transfer in a melt of aspirin anhydride, I. Identification of these products necessitated the synthesis of several mixed anhydrides of aspirin and aspirin derivatives with acetic acid, *viz.*, the mixed anhydride of aspirin and acetic acid, II, and the mixed anhydride of acetylsalicoylsalicylic acid and acetic acid, III.

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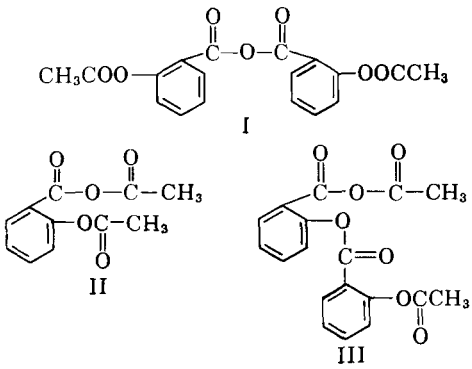

I

II

III

Since a significant amount of data has been obtained on the neutral hydrolysis of *m*- and *p*-substituted benzoic anhydrides in 75% dioxane-25% water solutions (2), studies on the symmetrical *ortho*-substituted benzoic anhydride, aspirin anhydride, and other unsymmetrical anhydrides of this type under the same conditions are of interest.

EXPERIMENTAL

Comparative Solvolysis Rates of Symmetrical and Nonsymmetrical Anhydrides in 75% Dioxane.—The general procedure for the hydrolysis studies in aqueous dioxane was to take a weighed amount of the anhydride up to a given volume with 75% dioxane. Prior to use, the dioxane was refluxed at least 24 hours over sodium to destroy peroxides, distilled, and the first fractions discarded. Both the dioxane and the distilled water used were thoroughly purged with nitrogen. The studies were made on the Cary model 11 recording spectrophotometer in 75% dioxane on aliquots of the solutions maintained in constant temperature baths.

The aspirin anhydride (3), I, aspirin, and salicylic acid were dried under high vacuum for several days before use.

The aspirin anhydride solutions were 2.142×10^{-4} *M*, the mixed anhydride of acetylsalicoylsalicylic acid and acetic acid, III, solutions were 3.827×10^{-4} *M*, and the solutions of the mixed anhydride of aspirin and acetic acid, II, were 6.274×10^{-4} *M*. The preparation of these latter compounds, II and III, has been previously described (1).

The ultraviolet spectra of these compounds are given in Fig. 1 and are plotted as the appropriate multiple of the molar absorptivity against wavelength in mμ since hydrolysis of one-half mole of aspirin anhydride would give one mole of aspirin and subsequently one mole of salicylic acid.

The high spectrophotometric purity of the mixed anhydrides was assured by the fact that the ultraviolet spectra of the hydrolyzing mixed anhydride of acetic acid and aspirin became the ultraviolet spectra of aspirin. The latter, as given in Fig. 1, had been determined from pure aspirin solution in 75% dioxane.

Salicylic acid production did not interfere with the determination of the rates of anhydride hydrolysis. For example, the rate constant for the hydrolysis of aspirin in 75% dioxane at 70.0° is 3.14×10^{-6} sec.$^{-1}$, which is 100 times slower than the hydrolysis of the mixed anhydride of aspirin and

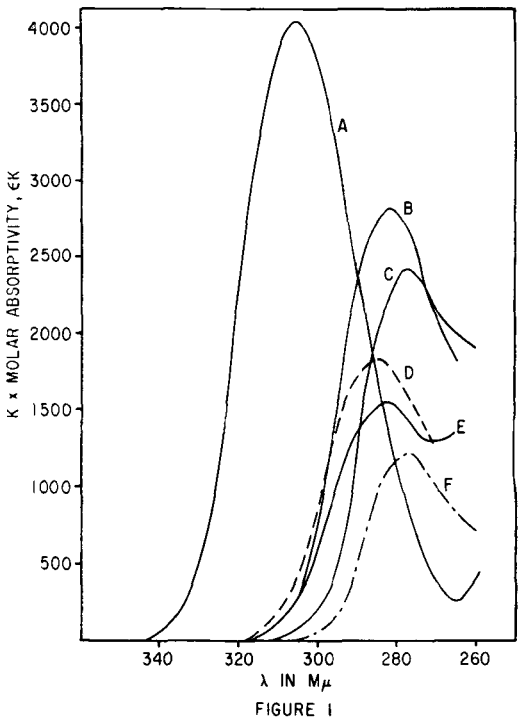

Fig. 1.—Ultraviolet spectra of anhydrides and their hydrolytic derivatives in 75% dioxane-25% water. *A*, Salicylic acid, $K = 1$; *B*, mixed anhydride, acetic and acetylsalicoylsalicylic acids, $K = 1$; *C*, acetylsalicoylsalicylic acid, $K = 1$; *D*, aspirin anhydride, $K = 1/2$; *E*, mixed anhydride, acetic acid, and aspirin, $K = 1$; *F*, aspirin, $K = 1$.

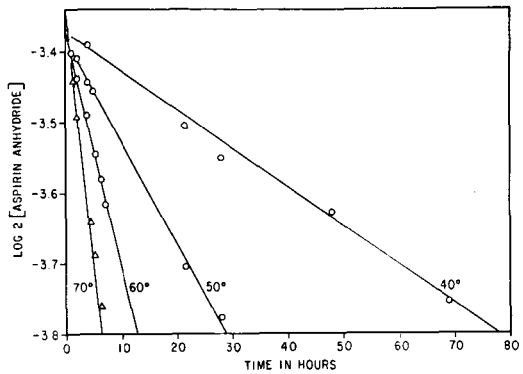

Fig. 2.—First-order plots of the hydrolysis of aspirin anhydride in 75% dioxane-25% water. Initial concentration 2.20×10^{-4} *M*.

acetic acid, II, and more than 12 times slower than the hydrolysis of aspirin anhydride, I, under the same conditions (see Table I).

However, since the spectra of the resultant highly chromophoric salicylic acid might interfere with the calculations for the aspirin anhydride to aspirin hydrolysis rates, the concentration of aspirin anhydride was calculated from the expression

$$[\text{Aspirin Anhydride}] = \frac{A'_{292.5}\,\epsilon^{ASP}_{277.5} - A'_{277.5}\,\epsilon^{ASP}_{292.5}}{\epsilon^{AA}_{292.5}\,\epsilon^{ASP}_{277.5} - \epsilon^{ASP}_{292.5}\,\epsilon^{AA}_{277.5}} \quad \text{(Eq. 1)}$$

TABLE I.—APPARENT FIRST-ORDER RATE CONSTANTS IN SEC.$^{-1}$ AND THERMODYNAMIC QUANTITIES FOR THE HYDROLYSIS OF VARIOUS ANHYDRIDES IN DIOXANE-WATER SOLUTIONS

	Aspirin Anhydride	Mixed Anhydride of Acetylsalicoylsalicylic Acid and Acetic Acid	Mixed Anhydride of Acetylsaliylic Acid and Acetic Acid
10^4 k at 27.0° in 10% dioxane	8.5[b]	62.0	24.0
10^4 k at 70.0° in 75% dioxane	0.474	5.18	5.62
10^4 k at 60.0° in 75% dioxane	0.216	2.08	2.81
10^4 k at 50.0° in 75% dioxane	0.0944	1.08	1.38
10^4 k at 40.0° in 75% dioxane	0.0351	0.52	0.78
S_a[a]	3,890	3,503	3,413
ΔH_a(Kcal./mole)	17.8	16.0	15.6
log P[a]	7.02	6.89	6.70

[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 cal./mole, R is the gas constant in cal./degree, T is the absolute temperature, and S is the slope of the Arrhenius plot. [b] As previously determined (3).

where ϵ is the equivalent absorptivity at the subscripted wavelength in mμ for aspirin anhydride (AA) or for aspirin (ASP) and where A′ is the corrected absorbance at the subscripted wavelength. The true absorbance, A, at the subscripted wavelength was corrected for the interfering absorption of the highly absorbing salicylic acid (SAL) to A′ by

$$A'_{292.5} = A_{292.5} - \epsilon^{SAL}_{292.5}[Sal] \quad \text{(Eq. 2)}$$

$$A'_{277.5} = A_{277.5} - \epsilon^{SAL}_{277.5}[Sal] \quad \text{(Eq. 3)}$$

where the salicylic acid concentration [Sal] was obtained from the absorbance at 320 mμ

$$[Sal] = A_{320}/\epsilon^{SAL}_{320} \quad \text{(Eq. 4)}$$

The logarithmic values of the calculated aspirin anhydride concentrations were plotted against time according to the first-order expression

$$\log [AA] = -kt/2.303 + \text{constant} \quad \text{(Eq. 5)}$$

and the derived first-order rate constants are given in Table I. Such plots are given in Fig. 2.

The other anhydrides studied hydrolyzed at such rates so that the spectral appearances of derived salicylic acids were no problem. The logarithm of the difference between the absorbances at any time, A, and the asymptotic value with time, A_∞, were plotted according to

$$\log [A - A_\infty] = -\frac{kt}{2.303} + \text{constant} \quad \text{(Eq. 6)}$$

and the derived first-order rate constants are also given in Table I. Such plots are given in Figs. 3 and 4.

The Arrhenius plots for the hydrolyses of these anhydrides in 75% dioxane are given in Fig. 5 and the thermodynamic quantities are given in Table I. The relation used is

$$\log k = -(\Delta H_a/2.303\text{R})(1/T) + \log P = -S/T \log P \quad (7)$$

where ΔH_a is the heat of activation in cal./mole, R is the gas constant in cal./degree, T is the absolute temperature, and S is the slope of the Arrhenius plot.

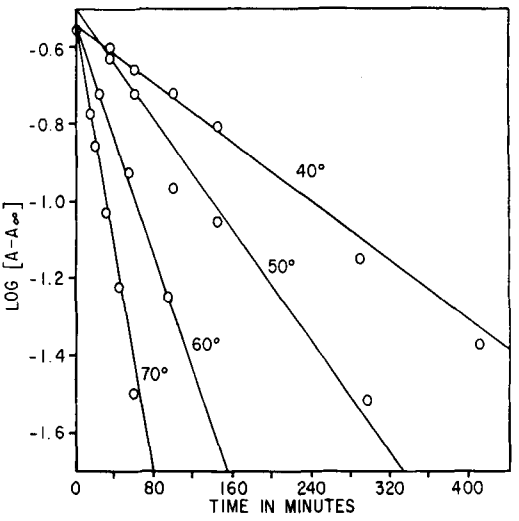

Fig. 3.—Apparent first-order plots of the loss of absorbance at the 283 mμ maximum of the mixed anhydride of aspirin and acetic acid in 75% dioxane-25% water. The A_∞ at 283 mμ (i.e., the absorbance for aspirin) for the 6.27×10^{-4} M solutions was 0.700.

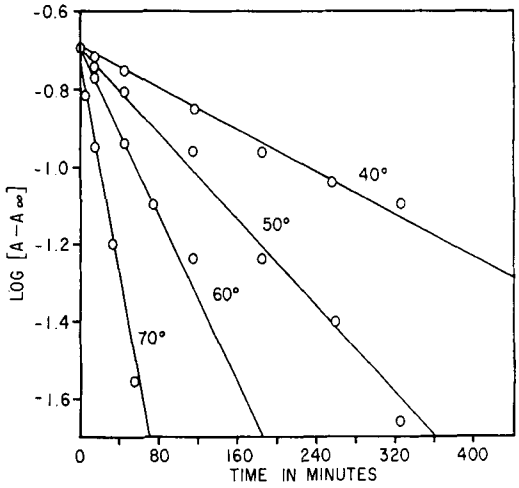

Fig. 4.—Apparent first-order plots of the loss of absorbance at the 282 mμ maximum of the mixed anhydride of acetylsalicoylsalicylic and acetic acids in 75% dioxane-25% water. The A_∞ at 282 mμ for the 3.83×10^{-4} M solutions was 0.870.

DISCUSSION

Comparison of Neutral Solvolyses of Anhydrides of *o*-Acetoxybenzoic Acid with *m*- and *p*-Substituted Benzoic Anhydrides.—In general, the neutral sol-

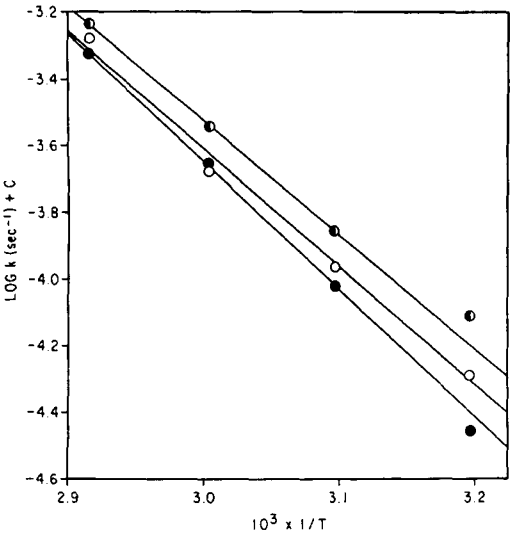

Fig. 5.—Arrhenius' plots for the hydrolysis of anhydrides in 75% dioxane-25% water. ⊙ Mixed anhydride, acetic and acetylsalicoylsalicylic acids, C = 0; ◐ mixed anhydride, acetic acid and aspirin, C = 0; ● aspirin anhydride, C = 1.

volyses of substituted benzoic anhydrides should be favored by electron withdrawing groups since nucleophilic attack is rate determining (2–6).

The acetoxy group in aspirin anhydride should possess less electron withdrawing properties than a methyl substituent (7). The *ortho* position had little effect on the heat of activation for the neutral hydrolysis of aspirin anhydride in 75% dioxane in comparison to the other *m*- and *p*-substituted benzoic anhydrides (2). The ΔH_a of 17.8 Kcal. is the same as that given for the neutral hydrolysis in 75% dioxane of the *m*- and *p*-alkyl benzoic anhydrides (2).

The unsymmetrical mixed anhydride of aspirin and acetic acid, II, and of acetylsalicoylsalicylic and acetic acids, III, may have slightly less heat of activation for their hydrolyses (see Table I).

Although this difference is not of a high order of significance, it may imply that the attack of the water molecule on the carbonyl carbon, which attack requires most of the activation energy, is slightly more facile in the case of the mixed anhydrides.

The most dramatic difference introduced by the *ortho* substituent, as expected by virtue of the proximity effect (8), is in the frequency factor. The log P value for aspirin anhydride hydrolysis is relatively quite high (see Table I) compared to all the *m*- and *p*-substituted benzoic anhydride hydrolyses listed by Berliner and Altschul (2).

The high frequency factor, or the less change in the entropy of activation, may be explained by the restricted rotation in aspirin anhydride due to the bulky *ortho* groups. On activation, the activated state has less degrees of freedom to lose compared to most *m*- and *p*-substituted benzoic anhydrides.

The lower frequency factors in the hydrolysis of the mixed anhydrides account for their higher reactivity over the symmetrical aspirin anhydride (see Table I). This difference from aspirin anhydride may be attributed to the loss in greater degrees of freedom on the preferential attack of the nucleophile on the acetyl carbonyl carbon rather than on the *o*-acetoxyphenylcarbonyl carbon. It may be expected that nucleophilic attack should take place at the acyl group of higher reactivity (4). Thus, since ethyl acetate has a greater alkaline hydrolysis rate under comparable conditions than ethyl benzoate (9), nucleophilic attack on the acetyl carbonyl carbon may be predicted.

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