of solid sodium borohydride (98%) was added. The mixture was allowed to stand at room temperature for 20 hours. Addition of 25 ml. of water and evaporation at reduced pressure left a gelatinous residue which was acidified with 25 ml. of 25% hydrochloric acid. The solution which resulted was extracted with one 50-ml. and three 30-ml. portions of chloroform. The extracts were combined and dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent at 40° under reduced pressure left 1.8 g. of a pale yellow solid which crystallized from absolute methanol to yield 1.71 g. (86.2%) of yellow cubic crystals, m.p. 145.5–147.0°. For analysis this material was crystallized twice more from absolute methanol to produce pale yellow cubes, m.p. 150–151°.

Anal. Calcd. for $C_{12}H_{14}O_5N_2$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.02; H, 5.53; N, 10.67.

***dl*-Vasicine (Ia).**—A mixture of 0.740 g. (3.13 mmoles) of 1-(*o*-nitrobenzyl)-3-hydroxy-2-oxopyrrolidine (IIa) (m.p. 145.0–146.5°) and 1.50 g. of clean iron filings in 18 ml. of 50% aqueous acetic acid was heated on a steam-bath for one hour. After cooling in an ice-bath, the solution was made strongly basic with a 25% solution of sodium hydroxide and extracted for 12 hours with 50 ml. of ether in an apparatus for continuous extraction. During this time a white product separated from the ether. The suspension was cooled and the solid (m.p. 193–198° (dec., vacuum tube)) was collected by filtration. Sublimation in high vacuum at 150° (1 μ) gave 0.535 g. (91%) of *dl*-vasicine as a white solid, m.p. 202–208° (dec., vacuum tube). Crystallization from absolute methanol gave fine white needles, m.p. 209° (dec., vacuum).

For analysis the crude reaction product was sublimed in high vacuum, crystallized from methanol, then from water, sublimed in high vacuum again, and finally crystallized from methanol to give white crystals, m.p. 209–210° (dec., vacuum tube).

Anal. Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.55; H, 6.53; N, 14.92, 14.90.

A hydrochloride was prepared by passing dry hydrogen chloride gas into a solution of 0.1 g. of vasicine in 25 ml. of absolute ethanol. The solvent was distilled to a small volume on a steam-bath and the solution was cooled. Addition of ether precipitated a white solid, which was filtered after the mixture had stood in the refrigerator for several hours. The dry white solid melted at 206–208° dec. The reported[20] melting point for this compound is 205–207° (in vacuum).

(20) E. Späth and F. Kuffner, *Ber.*, **67**, 868 (1934).

***dl*-6-Methoxyvasicine (Ib).**—A mixture of 1-(2-nitro-5-methoxybenzyl)-3-hydroxy-2-oxopyrrolidine (IIb) (4.00 g., 15 mmoles, m.p. 147.5–148.5°) and clean iron filings (8.40 g., 150 mmoles) was treated with 100 ml. of 1:1 aqueous acetic acid. The mixture was stirred and heated on a steam-bath for 90 minutes. After cooling the mixture in an ice-bath, it was made strongly basic with a 25% solution of sodium hydroxide in water. The mixture, which contained a large amount of precipitated ferrous hydroxide, was extracted with two 200-ml. portions of chloroform, the layers being separated by centrifugation. The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated at 40° under reduced pressure. The buff colored residue which remained weighed 2.57 g. (79% yield).

The product was purified by high vacuum sublimation at 155° (1 μ), followed by a crystallization from 95% ethanol. 6-Methoxyvasicine (1.31 g.) crystallized as large thin plates, m.p. 223–224° (dec., vacuum). From the mother liquor of the crystallization was obtained an additional 0.63 g. of crystalline solid, m.p. 219–223° (dec., vacuum). The total yield of purified material was 1.98 g. (59%). This represents an over-all yield of 9.4% for the synthesis, based on 3-methyl-4-nitroanisole consumed. The over-all yield based on 2-nitro-5-methoxybenzylamine was 15%.

The product was prepared for analysis by a high vacuum sublimation, followed by two crystallizations from ethyl acetate, and a third crystallization from 95% ethanol. The melting point of material prepared in this manner was 223–224° (dec., vacuum).[21]

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.53, 65.45; H, 6.35, 6.54; N, 12.91.

The product retained a faint tan color which could be removed only by extensive sublimations and crystallizations. *dl*-6-Methoxyvasicine could be crystallized from water, ethanol, methanol, aqueous alcohol or ethyl acetate, with 95% ethanol giving the best results.

Acknowledgment.—The authors are indebted to Mr. Sheldon E. Cremer for technical assistance.

(21) For measurement of the infrared spectrum, the hydrochloride of *dl*-6-methoxyvasicine, m.p. 219–221°, was prepared by use of a procedure like that used for *dl*-vasicine hydrochloride.

PITTSBURGH 13, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY]

Imidazole Catalysis. III.[1] The Solvolysis of 4-(2′-Acetoxyphenyl)-imidazole

BY GASTON L. SCHMIR[2] AND THOMAS C. BRUICE

RECEIVED SEPTEMBER 9, 1957

The solvolysis of 4-(2′-acetoxyphenyl)-imidazole (I) has been found to occur with participation of the imidazolyl group. The solvolysis of I is compared to that of acetyl salicylate (participation of the carboxylate ion) and of *p*-acetoxybenzoic acid (no participation).

Introduction

The implication of a histidine residue in the catalytic activity of several hydrolytic enzymes[3] has led to studies of the reaction of imidazoles with various compounds susceptible to enzymatic hydrolysis (see ref. 1). The imidazole-catalyzed hydrolysis of phenyl acetates has been particularly well investigated[1,4,5] and provides a basis for further attempts to approximate the mode of action of hydrolytic enzymes through the use of model systems.

If, in the enzymatic hydrolysis of an ester, the decomposition of the enzyme–substrate complex is considered a solvolytic reaction involving participation of acidic and basic groups on the enzyme surface, then the study of the behavior of esters which incorporate an imidazolyl group in position

(1) For preceding paper in this series, see T. C. Bruice and G. L. Schmir, THIS JOURNAL, **80**, 148 (1957).

(2) Public Health Predoctoral Fellow of the National Institutes of Health, 1956–1957.

(3) For pertinent references, see ref. 4 and 5.

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

(5) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

to assist solvolysis is of particular interest. In this paper, we report our studies on the solvolysis of 4-(2'-acetoxyphenyl)-imidazole (I).

Experimental[6]

4-(2'-Acetoxyphenyl)-imidazole Hydrochloride.—To 410 mg. (2.56 mmoles) of 4-(2'-hydroxyphenyl)-imidazole[7] dissolved in 40 ml. of hot chloroform was added 2 ml. (28 mmoles) of acetyl chloride, and the reaction mixture was refluxed with stirring for 12 hours. Concentration of the resulting clear solution to a small volume *in vacuo* yielded a white crystalline product (165 mg., m.p. 92–95°). The filtrate was evaporated to dryness *in vacuo* and to the partially crystalline residue was added 10 ml. of cold chloroform saturated with dry HCl gas. The voluminous white precipitate which appeared was collected and washed with cold chloroform and dry ether (420 mg., m.p. 80–90°). The combined crude products (90% of theory) were recrystallized from ethanol–chloroform by addition of ligroin (b.p. 60–90°) yielding 355 mg. (54%) of the hydrochloride of I, m.p. 108–110°. For analysis, the product was recrystallized several times from the same combination of solvents, and dried in air, melting point unchanged.

Anal. Calcd. for $C_{11}H_{10}N_2O_2 \cdot HCl \cdot H_2O$: C, 51.46; H, 5.10; N, 10.92. Found: C, 51.31; H, 5.08; N, 11.27.

Recrystallization of the product from chloroform–ligroin occasionally yielded a substance melting gradually from 160–170°. Storage of the product (m.p. 108–110°) over calcium chloride in an evacuated desiccator at room temperature led to the formation of a substance possessing a broad melting range extending up to 170°. In both cases, the original product was recovered in high yield by recrystallization from ethanol–chloroform–ligroin (this solvent invariably yielding the low-melting form).

The ultraviolet absorption spectra in 95% ethanol of equal amounts of the two forms of the product were identical in shape, differing only in extinction, with the ratios of the optical densities at each wave length being essentially constant. Neither substance gave a color with aqueous ferric chloride solution, while 4-(2'-hydroxyphenyl)-imidazole (V) produces a blue-violet color with this reagent. The identity of the ultraviolet spectra, as well as the ready interconversion of the two substances suggests that they differ only in degree of hydration. Prior to analysis, the product (m.p. 108–110°) was dried in air only, its facile dehydration preventing the use of conventional drying agents.

Acetylation of V also was accomplished through the use of isopropenyl acetate in the presence of sulfuric acid,[8] this procedure resulting, however, in a crude yield of only 35%.

Apparatus.—The constant temperature water-bath used in the kinetic studies was described previously.[5] Spectrophotometric studies were made with a Beckman model DU spectrophotometer and the *p*H of solutions determined by means of a Beckman model G *p*H meter, standardized against aqueous buffers.

Kinetic Method.—As in previous studies in this series,[1,5] 28.5% (v./v.) aqueous ethanol was employed as solvent, and care was taken to maintain a constant ionic strength of 0.55 *M*, through the addition of the calculated amounts of potassium chloride. The *p*H of reaction mixtures was kept constant by means of acetate or phosphate buffers (for details, see Results).

The buffers were allowed to equilibrate at constant temperature prior to addition of I. In each experiment, the solution of I in aqueous ethanol was prepared immediately before use, added to the equilibrated buffer, and the combined solutions thoroughly mixed. The formation of V was followed spectrophotometrically by withdrawing samples of the reaction mixture at regular time intervals and determining the increase in optical density at 300 mμ. Since I exhibits small but not quite negligible absorption at this wave length, observed optical density readings were corrected for this absorption before calculation of the first order rate constants for appearance of product.

The hydrolysis of *p*-acetoxybenzoic acid[9] was followed by determining the increase in optical density at 260 and 265 mμ. Both substrate and product absorb at these wave lengths, and, depending upon *p*H, each compound may be present as either the ionic or neutral form (or as a mixture of both), each of which possesses a different absorption spectrum. Because of these considerations, the extent of reaction with time at each *p*H was determined by comparison of the observed optical densities to a standard curve, determined at that *p*H, for a series of mixtures of *p*-acetoxybenzoic and *p*-hydroxybenzoic acids, of constant total molarity.

In all experiments, the observed first-order rate constants, k_{obs}, were obtained from the usual plot of ln $(a/(a-x))$ *versus* t, where a was calculated by extrapolation of the appropriate standard curves.

pK_a' Determinations.—The pK_a' values for V and *p*-acetoxybenzoic acid, as well as the second pK_a' of phosphate, were determined by titration of solutions of the compounds (*ca.* 3×10^{-3} *M*) in 28.5% aqueous ethanol, 0.55 *M* in potassium chloride, at 30°, using the apparatus previously described.[1]

While the ready hydrolysis of I prevented the determination of the pK_a' of the imidazolyl group by titration, a solution of I (5×10^{-3} *M*) in 28.5% aqueous ethanol, 0.55 *M* in potassium chloride, was half-neutralized with standard NaOH solution and the *p*H determined immediately. The resulting pK_a' value found was 5.6.

Results

The hydrolysis of I (allowed to proceed to 30–50% completion) was found to be first order with respect to substrate over a tenfold variation in concentration (Table I). That the hydrolysis is not due to the possible catalytic properties of the divalent phosphate ion[10] of the buffer is also indicated in Table I, where an increase in total phosphate concentration, at constant ionic strength, from 0.013 to 0.100 *M* did not alter the rate of hydrolysis. The ultraviolet spectrum of the reaction mixture, taken at approximately 99% completion of reaction (after suitable dilution) was identical to that of V in the same medium. When the progress of the hydrolysis was followed at 279.5 mμ (isosbestic point for I and V), no significant change in optical density was found during 40% of reaction, suggesting that no detectable accumulation of any intermediate occurred during the course of the hydrolysis.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE SOLVOLYSIS OF I[a]

(I) $\times 10^4$, *M*	Phosphate,[b] *M*	$k_{obs} \times 10^4$, min.$^{-1}$	(I) $\times 10^4$, *M*	Phosphate,[b] *M*	$k_{obs} \times 10^4$, min.$^{-1}$
3.0	0.013	15.3	1.0	0.100	14.0
3.0	.027	15.5	2.0	.100	15.1
3.0	.033	15.5	3.0	.100	15.2
3.0	.066	15.4	5.0	.100	15.2
3.0	.100	15.2	10.0	.100	15.1

[a] All experiments performed at *p*H 6.0, 30°. [b] Total concentration of phosphate. Ionic strength maintained at 0.55 *M* with added potassium chloride.

Figure 1 describes the *p*H dependence of the rate of hydrolysis of I in the range 3 to 8. Acetate buffers were used from *p*H 3 to 5, while phosphate buffers were employed in the range 5.5 to 8. When acetate buffer (0.02 *M*) replaced phosphate buffer (0.035 *M*) at *p*H 6.0, the observed first-order constants were not significantly different.

(6) All melting points are corrected. Analysis performed by Elek Micro Analytical Laboratories, Los Angeles, Calif.

(7) R. Weidenhagen and R. Herrmann, *Ber.*, **68**, 1953 (1935).

(8) R. Moffett and D. Weisblat, THIS JOURNAL, **74**, 2183 (1952); J. H. Boyer, *ibid.*, **74**, 6274 (1952).

(9) Prepared by the method of F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931), and recrystallized from chloroform; m.p. found 191–193°, reported 189–190°.

(10) The divalent phosphate ion has been shown to accelerate the rate of hydrolysis of *p*-nitrophenyl acetate (ref. 1).

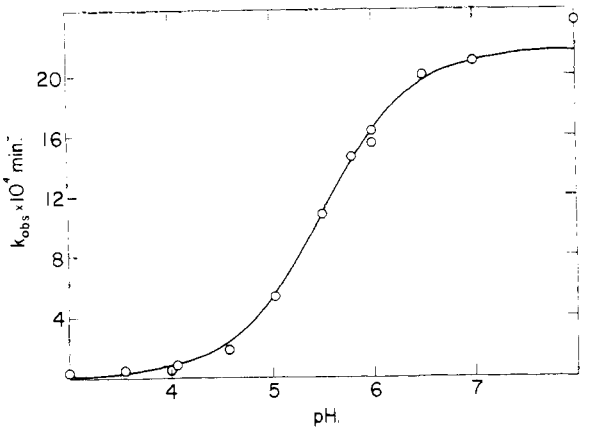


Fig. 1.—The pH dependence of the solvolysis of I at 30°. The solid line represents the theoretical ionization curve for a single group of pK = 5.5. The total concentration of phosphate employed at each pH (from 5.5–8.0) was calculated to provide a constant concentration of 0.003 M in the divalent ion, based on a secondary pK_a' of 7.0 for phosphate in this medium, as determined by titration. Total acetate concentration at each pH (from 3.0 to 5.0) was calculated to provide a constant concentration of about 0.02 M in acetate ion, based on a pK_a' of 4.7. Ionic strength maintained at 0.55 M for all reactions, through addition of KCl.

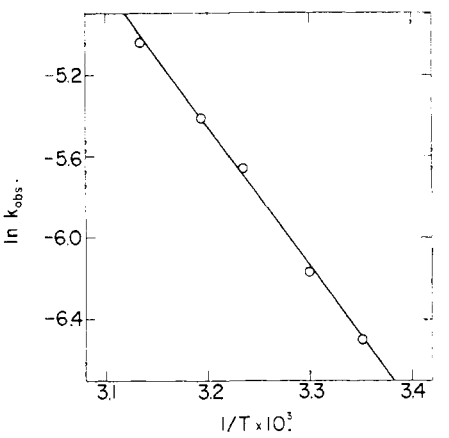


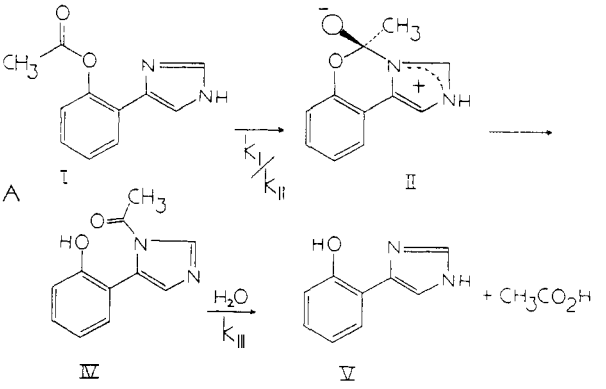
Fig. 2.—The temperature dependence of the solvolysis of I.

The data obtained are best explained on the assumption that the rate of solvolysis of I depends upon the state of ionization of a single group of pK_a' approximately 5.5 (pK_a' of imidazolyl group of I, 5.6). The considerable decrease in rate of hydrolysis of I with fall in pH constitutes additional proof[11] that the acetyl group of I is located on the phenolic oxygen rather than on the imidazolyl group.

The temperature dependence of the hydrolysis of I at pH 7.0 is described in Fig. 2. The data conform well to the Arrhenius equation and the apparent activation energy calculated (least squares) from the slope of the line thus obtained is 13.5 kcal./mole.

Discussion

The experimental results described herein, as well as consideration of the mechanism of the bimolecular reaction of imidazoles with phenyl acetates,[1,4,5] suggest that the solvolysis of I proceeds with assistance of the imidazole base *via* an O → N migration of the acetyl group (equation A). Since the appearance of V is first order with respect to I, it is likely that step k_I/k_{II} is rate limiting. Although attempts to detect the presence of IV spectrophotometrically were without success, the formation of N-acetylimidazole in the bimolecular reaction between p-nitrophenyl acetate and imidazole has been established with reasonable certainty.[4] The known[4,12] instability of N-acylimidazoles in aqueous solution probably explains the failure to observe accumulation of IV and the consequent kinetically first-order appearance of V, with respect to I.



The shape of the pH dependence curve (Fig. 1) is in excellent agreement with the participation of only the non-protonated imidazolyl group in the solvolysis process, a result which is in accord with the previous demonstration of the catalytic role of imidazole in the hydrolysis of p-nitrophenyl acetate, where the imidazolium ion is inactive.[4,5] The small increase in solvolysis observed at pH 8 (Fig. 1) can be attributed to hydroxide ion catalysis, superimposed upon the already maximal hydrolysis

(11) Staab[12c] has shown that the rate of hydrolysis of N-acetylimidazole in very weakly acidic media is increased appreciably over the rate in water, while Wieland[12d] has reported that the hydrolysis of N-acetylimidazole in bicarbonate solution is essentially complete in one minute. Thus, both the relative stability of I at low pH, as well as the behavior of the substance at pH 8, are in marked contrast to the expected properties of an N-acetylimidazolyl compound, and support the assigned structure I. Other data bearing on the structure of I are, in addition to lack of reaction with ferric chloride solution, the following: (a) The ultraviolet spectrum of V in 95% ethanol exhibits 3 major peaks with maxima at 298, 264 and 254 mμ. The spectrum of I possesses one broad peak with a maximum at 251 mμ. The hypsochromic effect of O-acetylation of phenols is well known (see for instance, E. A. Braude, *J. Chem. Soc.*, 1902 (1949); Ramart-Lucas, *Bull. soc. chim.* (*France*), **9**, 867 (1942); Houben-Weyl, "Methoden der organischen Chemie," Vol. III, Part 2, Georg Thieme Verlag, Stuttgart, 1955, pp. 658, 660) while on the contrary, N-acetylation of imidazole produces a pronounced bathochromic shift (see ref. 12b,d). (b) Recrystallization of I involves solution of the substance in boiling ethanol, a treatment which would be expected to cause appreciable or complete decomposition of an N-acetylimidazolyl compound (see ref. 12c,d). (c) I is prepared as the hydrochloride, which would be expected to result in N → O migration of the acylium ion (see, for instance, A. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947); L. Welsh, *ibid.*, **71**, 3500 (1949); G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950); E. E. van Tamelen, *ibid.*, **73**, 5773 (1951)).

(12) (a) M. Bergmann and L. Zervas, *Z. physiol. Chem.*, **175**, 145 (1928); (b) E. R. Stadtmann, "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1954, p. 596; (c) E. R. Stadtmann and F. H. White, THIS JOURNAL, **75**, 2022 (1953); (d) T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953); (e) H. A. Staab, *Ber.*, **89**, 1927 (1956).

caused by the imidazolyl group, which is essentially completely dissociated above *p*H 7.5.

The hydrolysis of acyl esters of salicylic acid has been studied recently in considerable detail,[13] with particular attention to the behavior of these compounds in the *p*H range 3–7. The anomalously high rate of hydrolysis found in the neutral range has been ascribed[13a,14] to the operation of a mechanism involving a cyclic intermediate formed by attack of the *o*-carboxylate anion upon the carbonyl carbon of the ester group. Breakdown of the cyclic intermediate to the products then occurs, possibly through the formation of a salicoyl anhydride, subsequently rapidly hydrolyzed by water. Also, Chanley and co-workers[14a,15] have proposed that the maximal hydrolytic rate observed in the neutral region in the hydrolysis of salicyl phosphate and of *o*-carboxynaphthyl phosphates was due to nucleophilic attack of the carboxylate ion upon the phosphorus atom of the phosphate ester grouping. The *p*H dependence of the hydrolysis of acetyl salicylate[13a] is shown in Fig. 3, and can be seen to

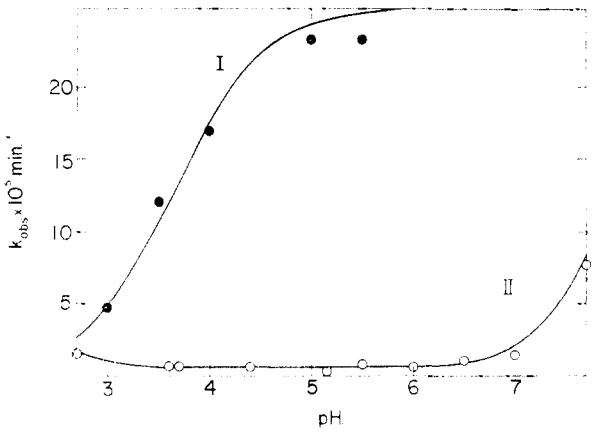


Fig. 3.—The *p*H dependence of the solvolysis of acetyl salicylate and *p*-acetoxybenzoic acid: I, acetyl salicylate, solid line represents theoretical ionization curve for single ionizable group of pK = 3.55, experimental points taken from data of ref. 13a; II, *p*-acetoxybenzoic acid (this investigation), composition of buffers same as for Fig. 1.

be qualitatively similar to the behavior of I. The determined rates for acetyl salicylate hydrolysis in the *p*H region of 2.5–6 fit well the theoretical ionization curve for an ionizable group of pK_a' 3.55, while the pK_a' for acetyl salicylate was found to be 3.6,[13a] implementing the suggestion that the hydrolytic reaction was initiated by nucleophilic attack of the carboxylate anion.

Further support for the participation of the *o*-carboxylate anion is provided by the *p*H dependence of the hydrolysis of *p*-acetoxybenzoic acid (Fig. 3). It can be seen that the dissociation of the *p*-carboxyl group (pK_a' 4.5) causes a threefold decrease in solvolytic rate, while in the case of acetyl salicylate there occurs an eightfold increase in rate upon dissociation of the *o*-carboxyl group. In addition, the solvolysis of *p*-acetoxybenzoic acid is minimal at *p*H 4–6, where "neutral" solvolysis of acetyl salicylate occurs at its maximum rate, which exceeds by 50-fold the rate of solvolysis of the *p*-isomer in the same *p*H range. It is reasonable to conclude that the *p*-isomer of I would exhibit much the same *p*H dependence as *p*-acetoxybenzoic acid.

The data presented in Figs. 1 and 3 allow a comparison of the relative efficiencies of assisted solvolysis of phenyl acetate to the enzymatic hydrolytic process. Thus, the rate constant (*p*H 6.0) for the solvolysis of *p*-acetoxybenzoic acid is 0.05×10^{-4} min.$^{-1}$ as compared to 4.0×10^{-4} min.$^{-1}$ for acetyl salicylate, 15×10^{-4} min.$^{-1}$ for I, and 180 min.$^{-1}$ for the hydrolysis of *p*-nitrophenyl acetate by α-chymotrypsin.[16] Though it is evident that the intramolecular solvolysis of I does not approach the rate of enzymatic action it is, at low concentration, appreciably more efficient than the corresponding bimolecular catalysis of a phenyl acetate hydrolysis by an imidazole of the same pK. Thus, in order to achieve an observed first-order rate constant of 20×10^{-4} min.$^{-1}$ (maximum rate of solvolysis of I at 30°), in the hydrolysis of *p*-nitrophenyl acetate, an imidazolyl compound of pK_a' 5.5 would have to be present at a concentration of about 2×10^{-3} *M*.[17] Furthermore, the resistance of the ester bond in I to nucleophilic displacement is probably appreciably greater than that of *p*-nitrophenyl acetate, as expected from a comparison of the electron-withdrawing properties of the imidazolyl and nitro groups, but unfortunately cannot be evaluated with certainty.[18] Therefore, the concentration of 2×10^{-3} *M* calculated from the data on the hydrolysis of *p*-nitrophenyl acetate represents a minimum value, which perhaps should be greatly increased, in view of the marked sensitivity of the catalytic ability of imidazoles to the strength of the susceptible bond.[5]

The apparent activation energy for the hydrolysis of I was found to be 13.5 kcal./mole, a value lower than the heats of activation reported for the neutral hydrolysis of acetyl[13a] and phosphoryl[14a] esters of salicylic acid (17.6 and 23.5 kcal./mole, respectively). Conclusions drawn from the comparison of the energies and entropies of activation for the above reactions are not meaningful because the magnitude of these terms will be influenced by two factors: (a) the change in basicity with temperature, as reflected in pK_a', will vary for different bases as determined by their heats of dissociation; and (b) the extent to which this change in basicity will influence the variation in rate constant with temperature (and hence the apparent activation energy) is dependent upon the sensitivity

(13) (a) E. R. Garrett, THIS JOURNAL, **79**, 3401 (1957); (b) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950); (c) L. J. Edwards, *ibid.*, **48**, 696 (1952).

(14) For early suggestions of the involvement of cyclic intermediates in reactions of acetyl salicylate, see: (a) J. D. Chanley, E. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952); (b) D. Davidson and L. Auerbach, *ibid.*, **75**, 5984 (1953).

(15) (a) J. D. Chanley and E. M. Gindler, *ibid.*, **75**, 4035 (1953); (b) J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955).

(16) H. Gutfreund and J. M. Sturtevant, *Biochem. J.*, **63**, 656 (1956).

(17) Estimated from data presented in Table II of ref. 1.

(18) The usual method of estimating relative stabilities of substituted phenyl acetates by comparison of the pK_a' of the corresponding phenols fails in this instance: titration of V (see experimental) indicates a pK_a' of 10.6. This value is unusually high, compared to phenol of pK_a' about 10.0, and can be attributed to hydrogen bonding of the hydroxyl group to the basic imidazolyl nitrogen; the similar phenomenon in the case of salicylic acid, pK_2' about 13, is well known.

of the reaction studied to change in basicity of the attacking group, as indicated by the Brönsted catalytic constant α. In the case of imidazole the values of α[1] and the heat of ionization[19] are appreciable and thus useful information concerning the mechanism of imidazole-catalyzed ester hydrolysis may not be obtained from calculated energy terms. However, the heats of ionization for carboxylic acids are quite small and allow mechanistic deductions from activation terms for the hydrolysis of esters of salicylic acid.[13a,14]

Although the present results indicate that the *o*-imidazolyl group is an effective assisting group for the solvolysis of phenyl acetate and exceeds, in efficiency, the *o*-carboxyl anion, the maximum rate of solvolysis of **I** does not approach that of the enzymatic hydrolysis. Clearly factors other than intramolecular reactions play an important role in the mechanism of action of hydrolytic enzymes, and it is possible that the devising of a more efficient model of enzymatic hydrolysis may be more successful if appropriate spatial orientation of "substrate" bond to catalytic site is taken into account.[20]

Acknowledgments.—This work was supported by a grant from the Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

(19) Y. Nozaki, F. Gurd, R. Chen and J. T. Edsall, THIS JOURNAL, **79**, 2123 (1957).

(20) D. E. Koshland, *J. Cell. Comp. Physiol.*, **47** (Suppl. 1), 217 (1956).

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

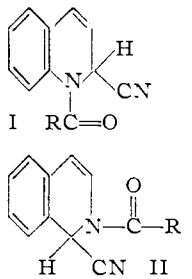
Condensation of Aldehydes and Ketones with Reissert Compounds

BY LEE R. WALTERS, N. THANUKRISHNA IYER[1] AND WILLIAM E. MCEWEN

RECEIVED OCTOBER 11, 1957

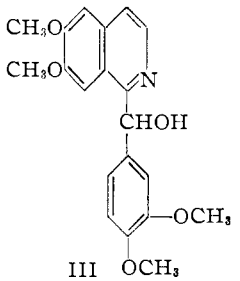
The lithium salts of Reissert compounds undergo reaction with aldehydes to form lithium cyanide and esters of secondary alcohols containing the 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom. There is an analogous reaction with ketones leading to the formation of esters of tertiary alcohols, but this reaction has only limited applicability. Some aspects of the mechanism of the reactions are discussed.

Although Reissert compounds, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II), are mainly noted for their ability to form aldehydes as a result of acid-catalyzed hydrolysis, increased attention in recent years has been directed toward the use of such compounds in the synthesis of diverse quinoline and isoquinoline derivatives.[2] The present communication describes a potentially valuable extension of the latter area of work, one leading to the production, frequently in high yields, of esters of alcohols having the 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom. Subsequent to some of the findings reported in this manuscript, it was possible to devise from appropriate Reissert compounds convenient syntheses of papaverinol (III)[3] and some apparently attractive intermediates for eventual conversion to the ipecac alkaloids.[4]



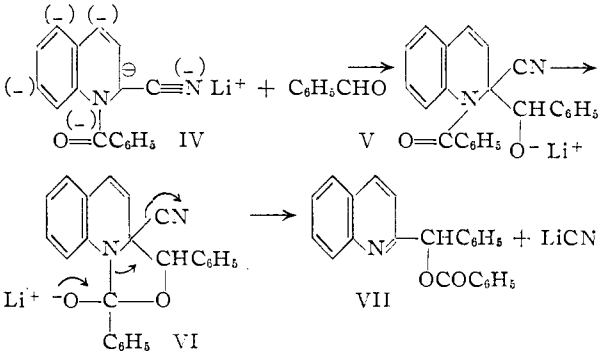
I

II



III

The condensation of the lithium salt IV of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) with benzaldehyde to give phenyl-2-quinolylcarbinyl benzoate (VII) plus lithium cyanide may be taken as the prototype of all of the reactions carried out in this particular study. There can be little doubt that the mechanism of the reaction involves an initial nucleophilic addition of the anion of the Reissert compound to the carbonyl carbon atom of benzaldehyde to form V, which then gives the cyclic derivative VI. Elimination of lithium cyanide (see curved arrows) affords VII, and, in common with other similar reactions of Reissert compounds,[2,5,6] the gain in resonance energy accompanying the elimination–rearrangement step provides an important driving force for the reaction.



IV V VI VII

Inasmuch as the negative charge of the anion of IV is shared by the nitrogen atom of the cyano group and several carbon atoms of the quinoline ring (see the negative charges in parentheses in

(1) Fulbright Scholar 1956-1957; University of Travancore, Trivandrum, India.

(2) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(3) F. D. Popp and W. E. McEwen, THIS JOURNAL, **79**, 3773 (1957).

(4) F. D. Popp and W. E. McEwen, *ibid.*, **80**, 1181 (1958).

(5) V. Boekelheide and J. C. Godfrey, *ibid.*, **75**, 3679 (1953).

(6) A. P. Wolf, W. E. McEwen and R. H. Glazier, *ibid.*, **78**, 861 (1956).