The Hydrolysis of Salicylanilide Carbamates

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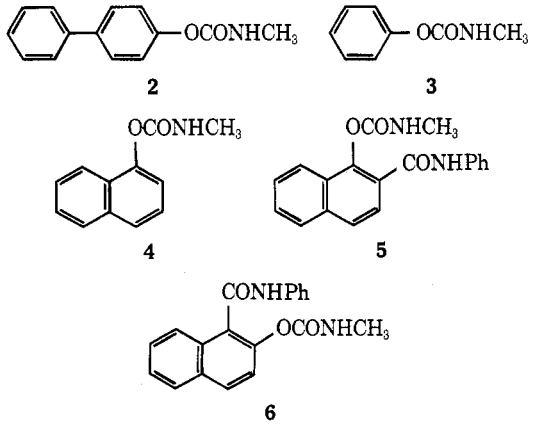
A series of substituted salicylanilide carbamates has been prepared and the rate of hydrolysis of these compounds investigated. The mechanism of the hydroxide ion catalyzed hydrolysis of the carbamates with neighboring-group participation is discussed.

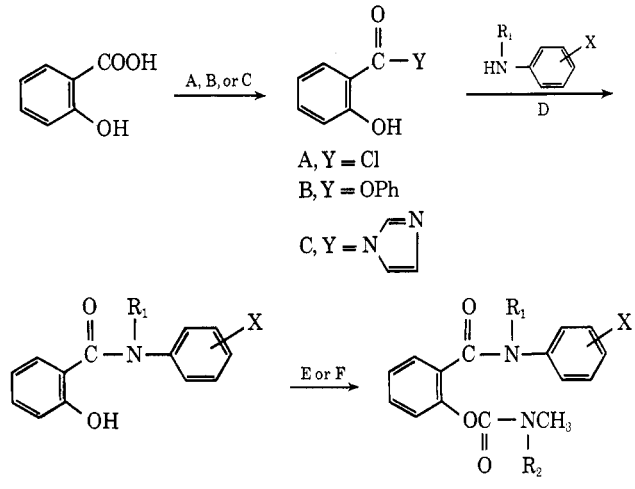
In the course of studying the biological activity of salicylanilide *N*-methylcarbamate (**1e**), we had occasion to determine the stability of this compound at various pH levels, particularly at pH 2 and pH 7.3 such as would be found in the stomach and blood serum. While **1e** is stable in strongly acidic media at 37°, it undergoes rapid hydrolysis at the phenol carbamate bond at or above pH 7.3. In contrast 4-biphenylyl *N*-methylcarbamate (**2**), phenyl *N*-methylcarbamate (**3**), and 1-naphthyl *N*-methylcarbamate (**4**) do not exhibit this susceptibility to alkaline hydrolysis. The facile removal of the carbamate group from **1e** appears to involve participation by the neighboring *o*-carboxanilide function. There are numerous literature examples[1] of participation by neighboring groups in the hydrolysis of esters and amides. This report describes the hydrolysis of a group of aryl carbamates with participation by a neighboring amide function.

Results and Discussion

Syntheses.—The interesting antiinflammatory activity of **1e** led us to search for analogs with greater stability toward hydrolysis and equal or greater biological activity. Compounds **1a–k** (see Table I) and **2–6** were synthesized for stability and activity evaluations as well as for studying the mechanism of this facile hydrolysis. The syntheses were carried out as shown in Scheme I. Salicylic acid was converted to its substituted anilides *via* its acid chloride, phenyl ester, or imidazolide. The anilides were then treated with either MeNCO or Me_2NCOCl to give the desired salicylanilide carbamates (**1**). Compounds **2–6** were



SCHEME I



also obtained in a similar manner by treating the appropriate phenols and naphthols with MeNCO. Table I lists the methods of preparation and melting points of these compounds.

TABLE I

PREPARATION OF ARYL CARBAMATES

Compd[b]	Structure (1) R1	R2	X	Method of prepn	Mp, °C[a]
1a	H	H	4-CN	A, D, E	163.5–164.5
1b	H	H	4-COMe	A, D, E	204–205.5
1c	H	H	4-CO_2Et	A, D, E	168.5–170
1d	H	H	4-Cl	B, D, E	159–161
1e[c]	H	H	H	E	160–161
1f	H	H	4-OMe	B, D, E	158–160
1g	H	H	4-OH	A, D, E[d]	174.5–176
1h	H	H	2,6-Di-Me	A, D, E	164–166
1i	Me	H	H	A, D, E	125–127
1j	Ph	H	H	A, D, E	162.5–164
1k	H	Me	H	F	110–111
5				C, D, E	181–182
6				C, D, E	177–179

[a] Melting points are uncorrected. [b] Satisfactory analytical data (±0.4% for C, N, H) were reported for all new compounds listed in the table: Ed. [c] Prepared by Dr. R. E. Strube. [d] Compound **1g** was obtained as its *o*-benzyl derivative by the indicated route of synthesis. The benzyl ether was then hydrogenolyzed in the presence of 10% Pd/C catalyst to give **1g**.

Hydrolysis Studies.—The hydrolytic reactions were followed by uv spectrophotometry in buffered 50% (v/v) H_2O–EtOH. Analytical wavelengths were selected so that, in each case, increasing absorbance (A_t) was measured at the maximum or prominent shoulder characteristic of the product in the reaction medium (Table II). Although in many cases the

(1) (a) M. S. Newman and S. Hishida, *J. Amer. Chem. Soc.*, **84**, 3582 (1962); (b) M. L. Bender and M. S. Silver, *ibid.*, **84**, 4589 (1962); (c) F. Ramierez, B. Hansen, and N. B. Desai, *ibid.*, **84**, 4588 (1962); (d) J. Zabicky, *Chem. Ind. (London)*, 236 (1964), and references therein; (e) G. L. Schmir and C. Zioudrou, *Biochemistry*, **2**, 1305 (1963); (f) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **83**, 4866 (1961); (g) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (h) M. T. Behme and E. H. Cordes, *ibid.*, **29**, 1255 (1964).

TABLE II

HYDROLYSIS OF ARYL CARBAMATES TO PHENOLS AT 37° IN BUFFERED AQUEOUS ALCOHOL

Compd	Molar concn	Wavelength,[a] nm	Apparent pH of reaction mixtures	k_{OH^-},[b] l. mol^{-1} min^{-1}	Relative stability[c]
1a	6.01×10^{-5}	308	5.4, 6.0, 6.6[d]	3.89×10^{5}	0.51
1b	8.01×10^{-5}	325	5.4, 6.0, 6.6[d]	3.07×10^{5}	0.64
1c	4.75×10^{-5}	308	5.4, 6.0, 6.6[d]	3.07×10^{5}	0.64
1d	6.25×10^{-5}	300	5.4, 6.0, 6.6[d]	2.37×10^{5}	0.84
1e	9.26×10^{-5}	300	5.4, 6.0, 6.6[d]	1.98×10^{5}	1.00
1f	7.10×10^{-5}	310	5.4, 6.0, 6.6[d]	1.52×10^{5}	1.30
1g	3.41×10^{-5}	305	5.4, 6.0, 6.6[d]	1.30×10^{5}	1.52
1h	6.87×10^{-5}	300	5.4, 6.0, 6.6[d]	1.10×10^{5}	1.80
1i	1.92×10^{-4}	285	7.4, 8.1, 8.6[e]	2.71×10^{2}	7.31×10^{2}
1j	1.04×10^{-4}	285	7.4, 8.0, 8.6[e]	2.60×10^{2}	7.62×10^{2}
1k	1.25×10^{-4}	337	10.1, 10.9[f]	5.93×10^{-2}	3.34×10^{6}
2	8.80×10^{-5}	275	10.0, 10.3, 10.6[f]	5.51×10^{1}	3.59×10^{3}
	6.06×10^{-5}		8.0, 8.6[e]	1.05×10^{2}	1.89×10^{3}
3	4.23×10^{-4}	277	9.9, 10.2, 10.6[f]	1.96×10^{1}	1.01×10^{4}
4	1.55×10^{-4}	308	9.8, 10.2, 10.6[f]	4.94×10^{1}	4.01×10^{3}
5	5.17×10^{-5}	346	5.3, 5.85, 6.4[d]	1.57×10^{6}	0.13
6	1.84×10^{-4}	332	7.4, 8.03, 8.55[e]	3.52×10^{3}	5.63×10^{1}

[a] At which reaction was followed. [b] Mean of data for the indicated buffer system. [c] Relative stability = k_{OH^-} of 1e/k_{OH^-} of compound. [d] Acetate buffers. [e] Phosphate buffers. [f] Borate buffers.

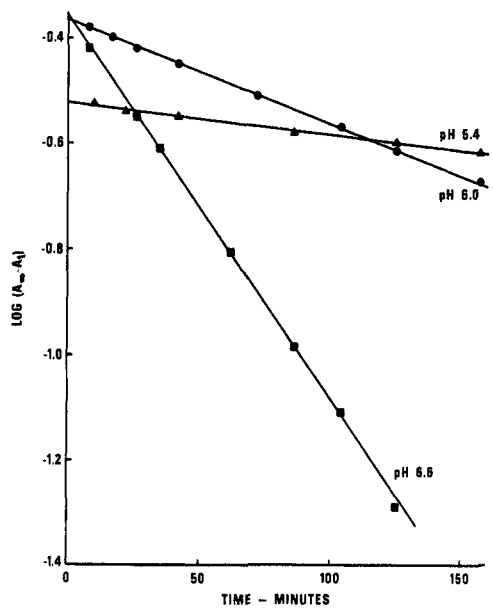


Figure 1.—First-order rate curves for hydrolysis of salicylanilide *N*-methylcarbamate (**1e**) as a function of pH at 37° in 50% EtOH–H_2O.

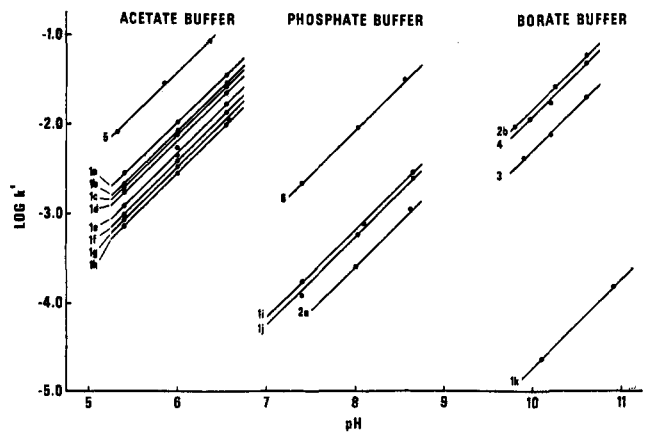


Figure 2.—Plot of log k' *vs.* pH for compounds **1a–k**, **2–6** at 37° in 50% EtOH–H_2O.

parent carbamate also absorbed at this wavelength, the difference in absorptivity for the carbamate and its respective salicylanilide (or phenol) was adequate for accurate determination of the reaction rate. To determine if carbamate hydrolysis was accompanied by significant simultaneous or subsequent hydrolysis of the anilide group, salicylanilide and several of its substituted analogs were examined spectrophotometrically under the reaction conditions. No evidence for anilide hydrolysis was observed. Moreover, in each rate study, hydrolysis of the parent carbamate gave a final uv spectrum which was stable, identical with that of the product anilide (or phenol), but different from that of a mixture of salicylic acid and $PhNH_2$ (or its appropriate analog). Therefore, the specificity of the method chosen for study of the carbamate hydrolysis was established.

Higuchi and Dittert[2] have shown that the hydrolysis of certain carbamates is first order in both hydroxide ion and carbamate. In the present studies a plot of log $(A_\infty - A_t)$ *vs.* time (t) at each pH for each carbamate, such as shown in Figure 1 for salicylanilide *N*-methylcarbamate (**1e**), was linear, confirming the first-order dependence on carbamate. Slopes of these plots provided pseudo-first-order constants, k'. For each carbamate studied, a plot of log k' *vs.* pH was linear with a slope of unity (Figure 2) establishing first-order dependence on hydroxide ion and permitting calculation of the specific reaction rate constants, k_{OH^-}, presented in Table II. Comparative hydrolytic stabilities, based on compound **1e** as a standard, are also shown in Table II.

The extremely low solubilities of the carbamates in H_2O dictated the use of H_2O–EtOH as solvent in these studies. Accordingly, pH values reported must be considered as apparent ones because of the liquid junction potential between the reference electrode and the solvent. The k_{OH^-} for compound **1e** with acetate buffer in H_2O–EtOH (Table II) is in good agreement with the value (1.30×10^5 l. mol^{-1} min^{-1}) reported for its

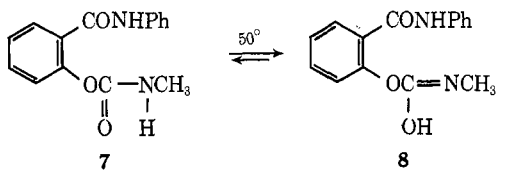
(2) T. Higuchi and L. W. Dittert, *J. Pharm. Sci.*, **52**, 852 (1963).

hydrolysis in a water–diglyme mixture with phosphate buffers, where the nonaqueous component was an inert solvent.[3] Thus, EtOH exerted a relatively minor effect on the hydrolysis rate of **1e**, even in the more basic medium.

In most cases (compounds **1a–h** and **5**), acetate buffers of constant ionic strength were employed. However, the slow rates of hydrolysis exhibited by the more stable compounds required use of more basic buffer systems, *e.g.*, phosphate and borate. The validity of comparing reaction rates obtained in two different buffer systems was examined for compound **2**. Observed k_{OH^-} values in phosphate and borate buffers (Table II and curves 2a and 2b, respectively, Figure 2) differed by less than a factor of two. In contrast, the smallest difference between hydrolysis rates of compounds studied in phosphate and borate buffers compared to those in the acetate system exceeded a factor of 30 (**6** *vs.* **1h**, Table II). Thus, although the use of different buffers affected the hydrolysis rates, these effects were small compared to the wide range of stability of the carbamates investigated. It is therefore felt that comparisons of rate data obtained in different buffer systems, *e.g.*, **1e** *vs.* **1i**, **1j**, **1k**, **2**, **3**, **4**, and **6**, were justified.

Mechanism of Hydrolysis.—The rate studies showed that the hydrolysis of the carbamates listed in Table II was first order with respect to both hydroxide ion and carbamate. Neighboring-group participation in the reaction was clearly demonstrated by the large difference between the hydrolysis rates of **1e** and **3** or **4** and **5**. Indeed all of the bifunctional compounds were hydrolyzed faster than the monofunctional ones by several orders of magnitude. In the three exceptional cases, either the anilide (**1i** and **1j**) or the carbamate (**1k**) nitrogen was disubstituted. Higuchi and Dittert[2] have shown that N,N-disubstituted aryl carbamates are 10^5 to 10^6 times as resistant toward hydrolysis as the corresponding monosubstituted compounds. N,N-Disubstituted amides likewise are known to hydrolyze with greater difficulty than monosubstituted ones. This stabilizing effect of full substitution on nitrogen can be reasonably expected to extend to the anchimerically assisted hydrolysis such as in **1i–k**.

Reasonable mechanisms for the alkaline hydrolysis of **1e** can be written with initial attack by hydroxide ion on either the anilide or the carbamate function. The latter is supported by nmr studies. The spectrum of **1e** in DMF-d_7 with Me_4Si as standard showed singlets at 630 (OH, structure **8**), 600 (anilide NH), and 182 Hz (CH_3, structure **8**), a doublet at 167 and 162 Hz (CH_3, structure **7**), as well as a complex aromatic hydrogen



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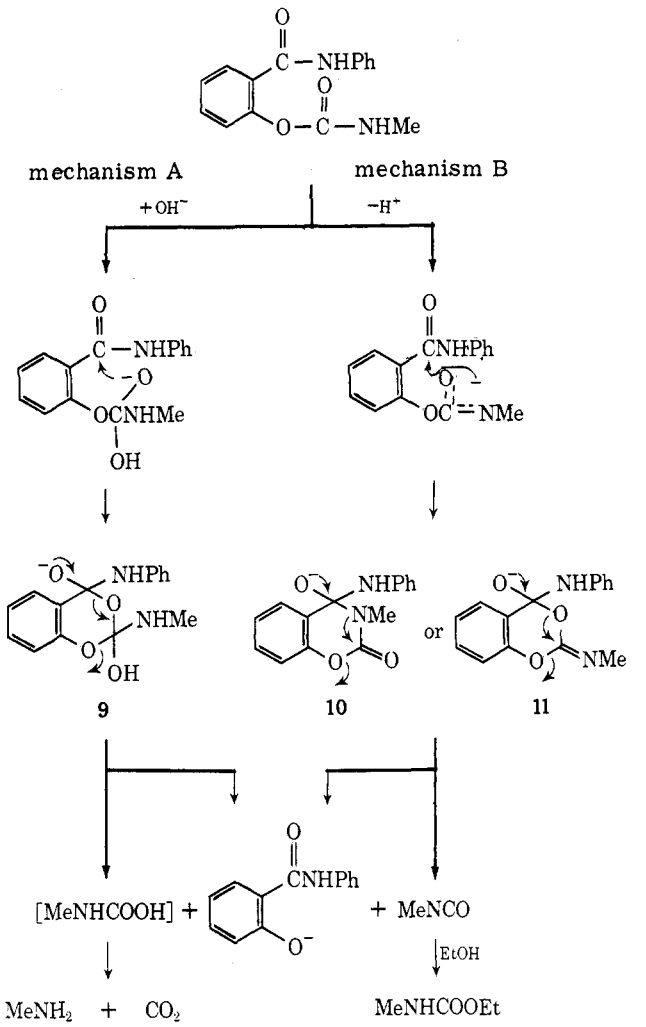
pattern at 480–420 Hz. When the solution was heated to 50°, the 630- and 182-Hz singlets increased in intensity while the doublet diminished. These changes were reversed on cooling the solution. Addition of D_2O erased the 630-Hz singlet and caused the doublet to collapse into a singlet at 165 Hz, while the singlet at 182 Hz remained unchanged. Throughout these studies the aromatic proton signals and the 600-Hz singlet were unaffected by D_2O or temperature changes. These findings clearly showed that the carbamate carbonyl was readily tautomerizable while the anilide carbonyl was not. The greater lability of the carbamate NH strongly suggests that attack by hydroxide ion on the carbamate group would be favored over attack on the anilide group.

The hydroxide ion may attack the carbamate by either addition to the carbonyl carbon (mechanism A, Scheme II) or proton extraction from the nitrogen

SCHEME II

PROPOSED MECHANISM FOR THE HYDROLYSIS OF SALICYLANILIDE *N*-METHYLCARBAMATE



(mechanism B). In either case intramolecular cyclization follows and the resulting intermediates **9** or **10** and/or **11**, on ring opening, would give salicylanilide. Glc analysis of a solution of **1e** in 50% H_2O–EtOH (pH 7.0), which had been kept at room temperature for 40 hr, showed presence of *N*-methylurethane, the expected by-product of mechanism B. No $MeNH_2$, the product of mechanism A, could be detected. Therefore, proton extraction appears to be the mechanism of choice.

The rate data in Table II also show that electron-withdrawing groups in the anilide phenyl ring (**1a–d**) enhance the hydrolysis rate of the carbamate while

(3) L. W. Brown and A. A. Forist, *J. Pharm. Sci.*, **61**, 858 (1972).

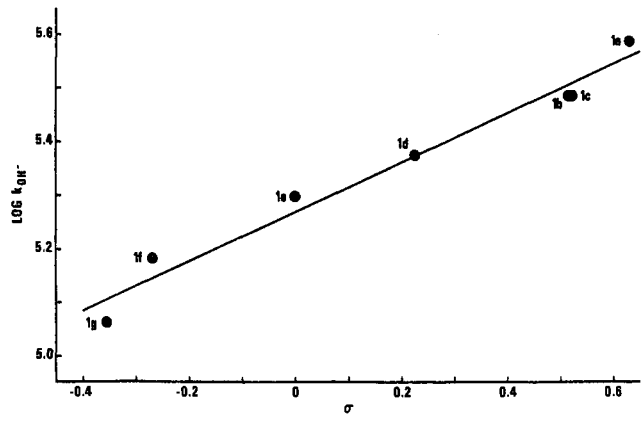
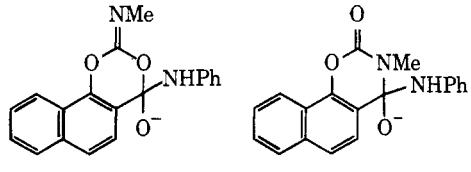


Figure 3.—Plot of log k_{OH^-} *vs.* σ constants for compounds **1a–g** in 50% EtOH–H_2O at 37°.

electron-donating substitutions (**1f–h**) retard the rate. A plot of log k_{OH^-} *vs.* σ[4] for **1a–g** is shown in Figure 3. From the plot, which was fitted by the linear least-squares method, $\rho = 0.4627$ with correlation coefficient of 0.9859. The rate differences attributable to substitutions in the anilide phenyl ring are relatively small. By contrast, the stabilities of the isomeric **5** and **6** differed more than four-hundredfold. This large difference cannot be attributed to the electronic environment of the 1 and 2 positions of the naphthalene ring system as the pK_a's of 1- and 2-naphthols are virtually identical[5a] and the hydrolysis rates of ethyl 1- and 2-naphthoates differ only by a factor of three.[5b] The observed large rate difference between **5** and **6** could, however, be explained as a result of steric interference by the peri hydrogen atom with the formation of the tricyclic intermediates **14** or **15** from **6**. In intermediates **12** or **13** arising from **5**, there is less steric



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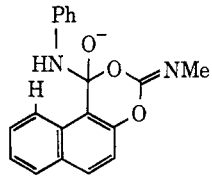

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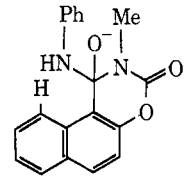

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hindrance, hence its more facile hydrolysis. The ability of these electronic and steric factors surrounding the anilide carbonyl to influence the hydrolysis rate of the carbamate strongly suggests that formation of a cyclic intermediate is the rate-controlling step in the process.

In summary, therefore, the facile anchimerically assisted alkaline hydrolysis of salicylanilide *N*-methylcarbamate appears to proceed with rapid proton extraction by the hydroxide ion from the carbamate nitrogen. A slow intramolecular cyclization follows and, on subsequent ring opening and fragmentation, the cyclic intermediate gives the product salicylanilide.

The great stability of **1k** is not unexpected and does not contradict the proposed mechanism for the hydrolysis of **1e**, because the absence of the carbamate NH in **1k** would force its hydrolysis to occur through some different mechanism. The stability of the N,N-disubstituted carbamate **1k** is 3×10^6 fold (Table II) that of the monosubstituted **1e**. In comparison, phenyl *N*,*N*-dimethylcarbamate has been reported[2] to be 3×10^4 fold as stable as phenyl *N*-methylcarbamate (**3**). Since **3** is 1×10^4 fold (Table II) as stable as **1e**, phenyl *N*,*N*-dimethylcarbamate is calculated to be 3×10^8 times as stable as **1e** or 1×10^2 times as stable as **1k**. The lower stability of **1k** in comparison with phenyl *N*,*N*-dimethylcarbamate suggests that the hydrolysis of **1k** also involves the anchimeric assistance by the neighboring *o*-carboxanilide group, though evidently to a lesser extent than in the case of **1e** in comparison to **3**, where the presence of the *o*-carboxanilide group increases the hydrolysis rate of the carbamate 10^4 fold.

Experimental Section

Salicylanilides from Salicyloyl Chloride. Method AD.—Salicyloyl chloride was prepared in 61–68% yield according to known procedure.[6] A solution of 0.15 mol of salicyloyl chloride in 20 ml of anhydrous THF was added dropwise in 15–30 min to a stirred solution of 0.30 mol of the appropriate aniline in 60 ml of THF. The mixture was stirred for 3–18 hr and evaporated at reduced pressure. The residue was mixed with 300–400 ml of H_2O. The insoluble crude product was recrystallized from benzene or a benzene–Skellysolve B mixture. The yield ranged from 72 to 91%.

Salicylanilides from Phenyl Salicylate. Method BD.—A mixture of phenyl salicylate (0.20 mol), the appropriate aniline (0.25 mol), and 60 ml of 1-methylnaphthalene was gently refluxed under N_2 for 2–3 hr. To the hot mixture was added 3.0 g of activated charcoal (Darco G-60) and 20 ml more of 1-methylnaphthalene. The mixture was heated to reflux with stirring and filtered while hot. The cooled filtrate usually solidified and was triturated with Skellysolve B and filtered. The crude product was recrystallized from EtOH, 86–94% yield.

Hydroxynaphthanilides from Hydroxynaphthoic Acids *via* Their Imidazolides. Method CD.—The appropriate hydroxynaphthoic acid was added in one portion to a stirred suspension of an equimolar amount of *N*,*N*′-carbonyldiimidazole in anhydrous THF (15 ml/g). The mixture was stirred under N_2 for 4 hr or until the evolution of CO_2 became very slow, whereupon an equimolar amount of $PhNH_2$ in anhydrous THF (5 ml/g) was added. The mixture was stirred at room temperature overnight, filtered, and concentrated at reduced pressure. The residual syrup was triturated with 1 *N* HCl and the resulting solids were filtered, washed with saturated $NaHCO_3$ solution, and dissolved in 1 *N* NaOH. Any insoluble material was filtered and the filtrate was acidified with 1 *N* HCl. The precipitates were recrystallized from benzene. In this manner, 1-hydroxy-2-naphthanilide was obtained in 74.4% yield, mp 154–155° (lit.[7] mp 154°), and 2-hydroxy-1-naphthanilide in 55% yield, mp 170–172° (lit.[8] mp 171.6–172.2°).

***N*-Methylcarbamates. Method E.**—To a 20% solution of the appropriate phenol in anhydrous THF was added 20% excess of a 50% solution of MeNCO in PhMe and a few drops of Et_3N. Crystallization of the product usually occurred within a few minutes. After 1–16 hr, the product was filtered, washed with Et_2O, and dried, ~90% yield, often analytically pure without further purification. If necessary the product was recrystallized from EtOH, benzene–Skellysolve B mixtures, or other solvents.

***N*,*N*-Dimethylcarbamates. Method F.**—A mixture of 0.10 mol of the appropriate phenol and 0.11 mol of Me_2NCOCl in 60

(4) σ values were obtained from H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(5) (a) R. T. Arnold and J. Sprung, *J. Amer. Chem. Soc.*, **60**, 1163 (1938); (b) M. Adam-Briers, P. J. C. Fierens, and R. H. Martin, *Helv. Chim. Acta*, **38**, 2021 (1955).

(6) R. Adams and L. H. Ulich, *J. Amer. Chem. Soc.*, **42**, 604 (1920).

(7) E. Schroeder, *Ann.*, **346**, 363 (1906).

(8) G. I. Gershzon, *J. Gen. Chem. USSR*, **13**, 82 (1943); *Chem. Abstr.*, **38**, 1220[9] (1944).

ml of anhydrous THF containing 15.4 ml (0.11 mol) of Et_3N was allowed to stand for 16 hr. The mixture was stirred with 500 ml of H_2O. The crystalline product was washed with Et_2O and recrystallized when necessary, ~70% yield.

Determination of Rate Constants.—The uv spectra of the 16 carbamates studied and their corresponding phenols were obtained on a Cary spectrophotometer. The characteristic shoulder or maximal wavelength for each phenol was used to follow the hydrolysis of the parent carbamate, which was carried out in a Beckman DU equipped with a constant-temperature cell. The wavelengths chosen for the individual compounds are listed in Table II.

A weighed sample of the carbamate was dissolved in 20 ml of 95% EtOH. Aliquots (5 ml) of the solution were diluted to 10 ml with the appropriate buffers. The resulting mixtures were shaken and introduced into previously warmed (37°) spectrometer cells. The absorbance was read at appropriate time intervals at 37° against a 1:1 H_2O–EtOH blank. The data thus obtained were treated as described in the discussion section. The results are summarized in Table II.

The ionic strengths of the acetate, phosphate, and borate buffers were 0.05, 0.08, and 0.07, respectively, before dilution with EtOH. The shifts in the pH values of the buffers upon addition of EtOH were determined with a pH meter and are given in Table III. The buffers were as follows: (1) acetate of pH 4.4, 25 ml of 1 *M* NaOAc plus 45 ml of 1 *M* HOAc diluted to 500 ml with deionized H_2O; (2) acetate of pH 5.0, 25 ml of 1 *M* NaOAc plus 12 ml of 1 *M* HOAc diluted to 500 ml with deionized H_2O; (3) acetate of pH 5.6, 25 ml of 1 *M* NaOAc plus 3.13 ml of 1 *M* HOAc diluted to 500 ml with deionized H_2O; (4) phosphate of pH 6.4, 50 ml of 0.1 *M* KH_2PO_4 plus 11.6 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (5) phosphate of pH 7.0, 50 ml of 0.1 *M* KH_2PO_4 plus 29.1 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (6) phosphate of pH 7.6, 50 ml of 0.1 *M* KH_2PO_4 plus 42.4 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (7) borate of pH 8.4, 50 ml of a mixture 0.1 *M* with respect to both KCl and H_3BO_3 plus 8.6 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (8) borate of pH 8.8, 50 ml of the above mixture (7) plus 15.8 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (9) borate of pH 9.2, 50 ml of the above mixture (7) plus 26.4 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (10) borate of pH 9.7, 50 ml of the above mixture (7) plus 40 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O.

TABLE III

Buffer	pH, H_2O	pH, H_2O–EtOH
Acetate	4.4	5.4
	5.0	6.0
	5.6	6.6
Phosphate	6.4	7.4
	7.0	8.0
	7.6	8.6
Borate	8.4	9.95
	8.8	10.25
	9.2	10.60
	9.7	10.90

Registry No.—**1a**, 16308-12-6; **1b**, 13499-87-1; **1c**, 18066-07-4; **1d**, 35410-11-8; **1e**, 5591-49-1; **1f**, 35410-13-0; **1g**, 35410-14-1; **1h**, 35410-15-2; **1i**, 35410-16-3; **1j**, 35410-17-4; **1k**, 35410-18-5; **2**, 5579-05-5; **3**, 1943-79-9; **4**, 63-25-2; **5**, 35410-20-9; **6**, 35410-21-0.

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Orientation in Electrophilic Addition Reactions to 2-Acetamidoacrylic Acid Derivatives[1]

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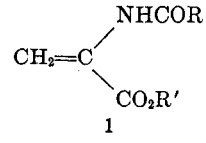
The mode of addition of selected electrophiles to 2-acetamidoacrylic acid and corresponding methyl ester has been investigated. The additions of hydrogen bromide and hydrogen chloride have been shown to yield 2-haloalanine derivatives as kinetically controlled products, while 3-haloalanine derivatives are the products resulting from conditions of thermodynamic control. The addition of thiocyanogen chloride and sulfur dichloride occurred in a similar manner; however, the products isolated were those resulting from subsequent elimination of hydrogen chloride to give the corresponding acetamidoacrylic acid derivatives substituted at the 3 position with a sulfur function.

2-Acylaminoacrylic acid derivatives (**1**) potentially can function as important precursors to a variety of novel α-amino acids. Cysteine derivatives have been prepared from **1** through radical additions.[2] Nucleophilic additions also have been reported[3] to yield substituted amino acids. Electrophilic additions of halogen[3a,4] and hydrogen halide[5] to 2-acylaminoacrylic acid derivatives are known. Knunyants and Shokina have reported[5] that 2-acylaminoacrylic acid derivatives undergo reaction with hydrogen bromide in acetic acid to yield 3-bromoalanine derivatives (**2**), which products likely result from a process of 1,4 addition or, as termed herein, Michael-type addition. Acrylic acid derivatives undergo similar Michael-type addition reactions with hydrogen bromide to give 3-bromopropanoic acid derivatives.[6]



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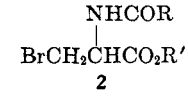

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We report herein results of studies pertaining to electrophilic addition reactions of selected reagents, *i.e.*, hydrogen bromide, hydrogen chloride, thiocyanogen

(1) Presented in part at the 26th Annual Northwest Regional Meeting of the American Chemical Society, Bozeman, Mont., June 1971.

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