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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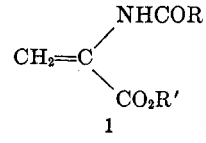
The mode of addition of selected electrophiles to 2-acetamidoacrylic acid and corresponding methyl ester has been investigated. The additions of hydrogen bromide and hydrogen chloride have been shown to yield 2-haloalanine derivatives as kinetically controlled products, while 3-haloalanine derivatives 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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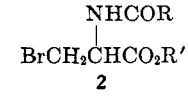

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We report herein results of studies pertaining to electrophilic addition reactions of selected reagents, *i.e.*, hydrogen bromide, hydrogen chloride, thiocyanogen

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

(2) M. W. Farlow, *J. Biol. Chem.*, **176**, 71 (1948).

(3) (a) I. Z. Eiger and J. P. Greenstein, *Arch. Biochem.*, **19**, 467 (1948); (b) H. Behringer and E. Fackler, *Ann*, **564**, 73 (1948); (c) A. Schoberl and A. Wagner, *Chem. Ber.*, **80**, 379 (1947).

(4) O. V. Kil'disheva, L. P. Rasteikene, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 231 (1955); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 260 (1955).

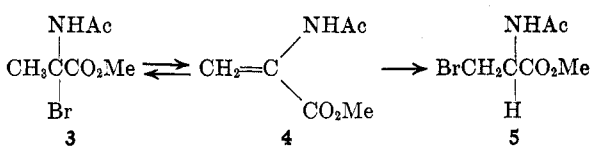
(5) I. L. Knunyants and V. V. Shokina, *J. Gen. Chem. USSR*, **25**, 1175 (1955); *Zh. Obshch. Khim.*, **25**, 1228 (1955).

(6) R. Monzingo and L. A. Patterson, "Organic Syntheses," Collect. Vol., III, Wiley, New York, N. Y., 1955, p 576.

chloride, and sulfur dichloride, to the 2-acetamidoacrylic acid system.

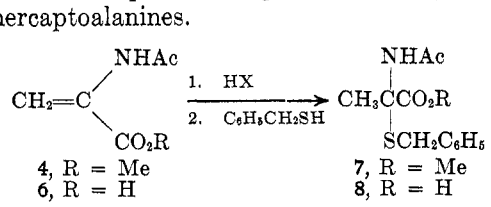
Hydrogen bromide in deuteriochloroform was allowed to react with methyl 2-acetamidoacrylate (**4**), and the course of the addition was followed by recording the nmr spectra of the reaction mixture at various time intervals. The nmr spectrum taken directly following the addition of hydrogen bromide showed the complete disappearance of vinyl proton signals of **4** at δ 6.5 and 5.8, while a singlet at 2.4, assigned to the β protons of the 2-bromo adduct **3**, appeared that was equal in intensity to the methyl ester and acetyl peaks at 3.9 and 2.8, respectively. The observed spectrum is consistent with the rapid, anti-Michael addition of hydrogen bromide to **4** to form methyl *N*-acetyl-2-bromo-DL-alaninate (**3**).

With the passage of time, the peaks at δ 2.8 and 2.4 diminished in intensity, while a singlet at 2.9, an apparent doublet imposed on the methyl ester peak at 3.9, and a quartet at 5.2 appeared. The observed changes in the nmr spectra are attributed to the formation of the 3-bromo adduct **5** and the corresponding decrease in the amount of the 2-bromo compound **3** present in the reaction mixture. After 3 days, the nmr spectrum showed mainly **5** to be present, and methyl *N*-acetyl-3-bromo-DL-alaninate (**5**) was isolated thereupon from the reaction mixture.



It is concluded, therefore, that the 2-bromoalanine **3** is the kinetically controlled addition product, while the product of Michael-type addition, the 3-bromoalanine **5**, is formed under thermodynamically controlled conditions; the latter results are consistent with those reported by Knunyants and Shokina.[5]

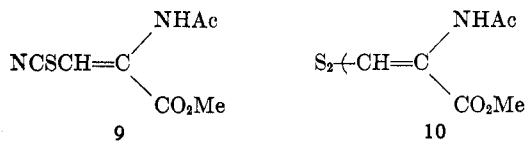
Further evidence for the intermediacy of the 2-bromoalanine **3** was obtained by isolation of the 2-benzylmercapto derivative **7** upon addition of benzyl mercaptan to a solution of **3** in chloroform. The sequence of reactions of **4** with hydrogen chloride and benzyl mercaptan in acetic acid also yielded **7**. In a similar manner, 2-acetamidoacrylic acid (**6**) was converted to the 2-benzylmercaptoalanine **8**. The reaction of alkyl mercaptans with α-haloalanine derivatives has been reported[7] to give the corresponding α-alkylmercaptoalanines.



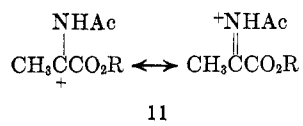
When the addition of hydrogen bromide to **4** in chloroform was allowed to proceed for 4 hr, followed by product isolation, the 3-bromoalanine **5** and methyl pyruvate were isolated. The latter product likely arises from hydrolysis, upon addition of water during work-up of the reaction, of the 2-bromo adduct **3** present. Hydrolysis of 2-bromoalanine derivatives to pyruvic acid derivatives has been reported.[4] If care was not taken to exclude small amounts of water from the reaction, a material thought to be acetamide hydrobromide could also be isolated as a solid that precipitated from the chloroform solution during the course of the reaction.

Methyl acrylate was treated with hydrogen bromide in deuteriochloroform and the reaction followed by nmr to determine if a similar phenomenon as with **4** was occurring. In comparison with **4**, the results were consistent for the initial rapid formation of the reported[6] Michael product, methyl 3-bromopropionate, and no further spectral changes were observed during the course of the reaction.

The addition of thiocyanogen chloride or sulfur dichloride to methyl 2-acetamidoacrylate (**4**) gave the acetamidoacrylic acid derivatives **9** and **10**, respectively. These products apparently result from anti-Michael addition, followed by dehydrochlorination of the 2-chloro compounds thus formed. Facile dehydrohalogenation of α-haloalanines has been observed.[4,8] The orientation in the addition of these sulfur electrophiles, therefore, appears to be the same as for the hydrogen halides discussed above.



These studies establish that the acetamido group in 2-acetamidoacrylic acid derivatives exercises a strong directive effect in the addition of electrophilic reagents to the double bond, as well as lending an enhanced reactivity to the α-halo group thus formed. A reasonable explanation for the orientation effect and reactivity observed is that the acetamido group functions to stabilize any positive charge generated at the α carbon during the course of the reaction, as represented by the resonance-stabilized carbonium ion **11**.



Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-20A spectrophotometer. Nmr data were obtained with a Varian A-60 nmr spectrometer at 60 MHz. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Evaporation *in vacuo* was carried out with a Buchler rotary evaporator.

Addition of Hydrogen Bromide to Methyl 2-Acetamidoacrylate (4).—To 1.0 ml of dry deuteriochloroform was added 0.2 g (1.4 mmol) of methyl 2-acetamidoacrylate[9] (**4**). Hydrogen bromide gas was passed over the solution for 2 min. The solution was then transferred to an nmr sample tube and spectra were recorded at intervals over 3 days. The initial spectrum showed the presence of only the 2-bromoalanine **3**: δ 3.9 (s, 3 H, methyl ester), 2.8 (s, 3 H, acetyl), 2.4 (s, 3 H, β protons). Subsequent spectral changes showed the gradual formation of the 3-bromoalanine **5** and the corresponding decrease in concentration of **3**.

(7) O. V. Kil'disheva, M. G. Lin'kova, V. M. Savosina, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1348 (1958).

(8) (a) O. V. Kil'disheva, L. P. Rasteikene, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 251 (1955); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 282 (1955). (b) R. Pfleger and M. V. Strandtmann, *Chem. Ber.*, **90**, 1455 (1957).

(9) T. Wieland, G. Ohnacker, and W. Ziegler, *ibid.*, **90**, 194 (1957).

The deuteriochloroform solution was added to 10 ml of chloroform, rinsed once with water, dried over magnesium sulfate, and evaporated *in vacuo* to leave 0.16 g of methyl *N*-acetyl-3-bromo-DL-alaninate (**5**, 51%): mp 91–93°; nmr ($CDCl_3$) δ 6.65 (s, 1 H, amide proton), 5.04 (m, 1 H, methine proton), 3.81 (s, 3 H, methyl ester), 3.80 (apparent d, 2 H, methylene protons), 2.07 (s, 3 H, acetyl methyl); *m/e* 225 (3.0), 223 (3.3) (molecular ions typical of mono bromo compounds).[10] When **5** was treated with triethylamine in chloroform, the acetamidoacrylate **4** was obtained in quantitative yield. An analytical sample of **5** was prepared by recrystallization from diethyl ether–ligroin (bp 60–90°), mp 90–91.5°.

Anal. Calcd for $C_6H_{10}BrNO_3$ (224.1): C, 32.2; H, 4.50; N, 6.25. Found: C, 31.8; H, 4.38; N, 5.81.

Methyl *N*-Acetyl-2-benzylmercapto-DL-alaninate (7).—To a solution of the acrylic acid methyl ester **4** (0.30 g, 2.1 mmol) in 8 ml of glacial acetic acid was added 0.52 ml (2.1 mmol) of 4 *N* hydrogen chloride in dioxane. After the mixture was stirred at room temperature for 5 min, benzyl mercaptan (0.28 g, 2.1 mmol) was added to the solution, following which the reaction mixture was stirred for 1 hr. The solvent was removed *in vacuo*, the oil obtained was taken up twice in ethyl acetate, and the solvent was removed *in vacuo* to yield a clear oil that slowly crystallized. Recrystallization from diethyl ether–ligroin (bp 60–90°) gave fine needles: mp 89–90°; nmr (trifluoroacetic acid) δ 1.47 and 1.49 (two s, 6 H, β-methyl and *N*-acetyl), 3.38 and 3.42 (two s, 5 H, methyl ester and benzyl), 6.88 (s, 5 H, phenyl), 7.08 (br s, 1 H, amide proton). This material was indistinguishable (tlc, nmr) from that obtained by the reaction of **4** with hydrogen bromide in chloroform followed by the addition of benzyl mercaptan.

Anal. Calcd for $C_{13}H_{17}NO_3S$ (267.3): C, 58.4; H, 6.40; N, 5.24. Found: C, 58.1; H, 6.26; N, 5.07.

***N*-Acetyl-2-benzylmercapto-DL-alanine (8).**—To a stirred solution of 2-acetamidoacrylic acid[9] (**6**, 0.20 g, 1.5 mmol) in 3 ml of trifluoroacetic acid and 7 ml of acetic acid was added 0.45 ml (1.85 meq) of 4.1 *N* hydrogen chloride in dioxane. The reaction mixture was stirred for 10 min, following which 0.19 g (1.5 mmol) of benzyl mercaptan in 2 ml of acetic acid was added in one portion, and the reaction mixture was stirred at room temperature for an additional 45 min. The solvent was removed *in vacuo* to give a white solid, which, after trituration with ethyl ether, gave 0.32 g (82%) of **8**: mp 150–153°; nmr (trifluoroacetic acid) δ 6.9 (s, 5 H, phenyl), 6.8 (s, 1 H, NH), 3.5 (s, 2 H, benzyl), 1.5 (s, 3 H, acetyl), and 1.4 (s, 3 H, β protons). An analytical sample was prepared by three recrystallizations from ethanol–ethyl acetate, mp 157.0–158.5°.

Anal. Calcd for $C_{12}H_{15}NO_3S$ (253.3): C, 57.0; H, 5.92; N, 5.52. Found: C, 56.9; H, 6.12; N, 5.39.

Identification of Methyl Pyruvate.—Hydrogen bromide was passed through a solution of 4.0 g (28 mmol) of methyl 2-acetamidoacrylate (**4**) in 50 ml of chloroform until the solution ceased to gain weight. After standing at room temperature for 4 hr, the solution was filtered to remove the white solid present and the filtrate was extracted with two 100-ml portions of water. The aqueous extracts were combined and evaporated under an air stream to leave 2.1 g of crude methyl pyruvate. The 3-bromo adduct **5** was isolated from the dried ($MgSO_4$) chloroform extract. The 2,4-dinitrophenylhydrazone of methyl pyruvate was prepared by a modification of an established method.[11] To a solution of 100 ml of water, 100 ml of methanol, and 10 ml of concentrated hydrochloric acid was added 1.0 g of the crude methyl pyruvate (9.8 mmol) and 3.0 g of 2,4-dinitrophenylhydrazine (15.1 mmol). The mixture was heated on a steam bath for 0.5 hr and slowly cooled to room temperature. The yellow 2,4-dinitrophenylhydrazone was removed by filtration and recrystallized twice from dioxane–methanol, mp 185–186° (lit.[11] 186.5–187.5°). The ir spectrum of this material was superimposable with the spectrum of an authentic sample of methyl pyruvate 2,4-dinitrophenylhydrazone.

The white solid obtained above was shown to be identical (ir, nmr) with the compound obtained[12] by treating acetamide with hydrogen bromide in chloroform: ir (KBr) 3230 (NH_2), 1678 cm^{-1} (C=O); *m/e* 82 (16.6, HBr), 80 (16.9, HBr), 59 (37.5, $AcNH_2$), 44 (100, $CONH_2$), 28 (37.5, CO); nmr (trifluoroacetic acid) δ 8.4 (s, 2 H, NH_2), 2.2 (s, 3 H, acetyl methyl protons). An aqueous solution of this material was acidic and treatment with silver nitrate solution immediately produced a precipitate.

Addition of Hydrogen Bromide to Methyl Acrylate.—Hydrogen bromide was passed over a solution of 0.20 g of methyl acrylate in 0.5 ml of deuteriochloroform for a period of 2 min. The sample was placed in an nmr tube and spectra were recorded at intervals over a 2-day period. The spectrum recorded immediately following the addition of hydrogen bromide was consistent for the formation of methyl 3-bromopropionate and no further changes were observed in subsequent spectra: nmr ($CDCl_3$) δ 3.90 (s, 3 H, methyl ester), 3.75 (t, 2 H, β-methylene), 3.00 (t, 2 H, α-methylene).

Methyl 2-Acetamido-3-thiocyanoacrylate (9).—To a solution of thiocyanogen chloride,[13] prepared from 1.5 g (21 mmol) of chlorine and 2.0 g (21 mmol) of potassium thiocyanate in 125 ml of dry acetic acid was added 2.0 g (14 mmol) of **4** and the reaction mixture was stirred at room temperature for 1.5 hr. The solution was concentrated *in vacuo* and solid material was removed by filtration. To the filtrate was added 200 ml of chloroform and the resulting solution was washed with three 300-ml portions of water, dried over magnesium sulfate, and evaporated *in vacuo* to yield 1.6 g (57%) of **9**. Two recrystallizations from chloroform afforded an analytically pure sample: mp 153°; ir (KBr) 3280 (NH), 2120 (SCN), 1677 and 1661 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 8.2 (s, 1 H, vinyl proton), 3.9 (s, 3 H, methyl ester), 2.2 (s, 3 H, acetyl); *m/e* 200 (9.4), 202 (0.57), 142 (81), 110 (100).

Anal. Calcd for $C_7H_8N_2O_3S$ (200.3): C, 42.0; H, 4.20; N, 14.0. Found: C, 42.1; H, 3.93; N, 13.8.

Bis(2-acetamido-2-carbomethoxyvinyl) Sulfide (10).—To a solution of 1.4 g (10 mmol) of **4** in 75 ml of chloroform was added 1.0 g (10 mmol) of sulfur dichloride, whereupon the solution was observed to reflux spontaneously. The solution was cooled in a Dry Ice–acetone bath for 5 hr. An additional 1.4 g (10 mmol) of **4** was added and the solution was stirred at room temperature for 8 hr. The reaction mixture, after being cooled overnight in a refrigerator, was filtered to remove solid material and the filtrate was evaporated *in vacuo* to yield an oil. A solution of the oil in hot ethanol deposited, upon being chilled, 2.0 g (63%) of the sulfide **10**: mp 202.5–204.0°; nmr ($CDCl_3$) δ 7.96 (s, 1 H, amide), 7.59 (s, 1 H, vinyl), 3.48 (s, 3 H, methyl ester), 1.87 (s, 3 H, acetyl protons).

Anal. Calcd for $C_{12}H_{16}N_2O_6S$ (316.3): C, 45.6; H, 5.10; N, 8.86; S, 10.2. Found: C, 45.2; H, 5.28; N, 8.72; S, 10.2.

Registry No.—**4**, 35356-70-8; **5**, 35356-71-9; **7**, 35356-72-0; **8**, 30410-97-0; **9**, 35356-74-2; **10**, 35356-75-3.

Acknowledgment.—This investigation was supported by a grant from the U. S. Public Health Service (National Cancer Institute, CA 10653).

(10) R. M. Silverstein and G. L. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 29.

(11) H. H. Strain, *J. Amer. Chem. Soc.*, **57**, 758 (1935).

(12) The hydrobromide salts of amides have been reported; *e.g.*, see S. J. Kuhn and J. S. McIntyre, *Can. J. Chem.*, **43**, 995 (1965).

(13) R. G. R. Bacon and R. G. Guy, *J. Chem. Soc.*, 318 (1960).