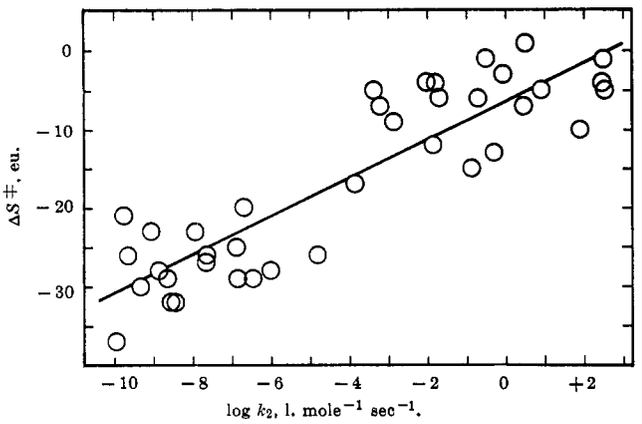

Figure 1.—Variation of the entropy of activation for rate-determining protonation of unsaturated carbon with the logarithm of the second-order rate constant at 25°.

most cases, additional evidence for this mechanism has been presented.

In many cases, activation parameters have been recalculated from rate data given in the references cited. Only those were included for which the acidity dependence of rates had been examined sufficiently to permit extrapolation to $H_0 = 0$ or $[H^+] = 1.0\ M$, whichever was convenient. These standard states certainly differ, but a more exact treatment is not warranted in view of the varied conditions under which reactions were studied. Temperature corrections for H_0[6,7] were applied where possible, a consistent set of H_0 values was used for H_2SO_4,[10,11] and rate constants were extrapolated to the standard state of acidity and 25° for calculation of $\Delta S^{\ddagger}$. It is estimated that most of the $\Delta S^{\ddagger}$ values listed have an uncertainty of several entropy units.

Figure 1 shows a definite trend to increasingly negative entropies of activation for less reactive compounds. The least-squares line, eq 1, fits the data with

$$\Delta S^{\ddagger} = 2.28 \log k_2 - 8.27 \quad (1)$$

a standard deviation in $\Delta S^{\ddagger}$ of 5.00 eu. When the correlation is expressed in terms of the free energy of activation, eq 2, it can be compared with free energy–

$$\Delta S^{\ddagger} = -1.67 \times 10^{-3} \Delta G^{\ddagger} + 20.93 \quad (2)$$

entropy correlations for protonation equilibria of primary aniline[7] and triarylcarbinol[8] bases in sulfuric acid. The slope reported here for entropy–free energy of activation, -1.67×10^{-3}, is in good agreement with the value of -1.5×10^{-3} found for equilibrium protonation of anilines. Both differ from the slope of -6.3×10^{-3} found for triarylcarbinol bases, and from the theoretical slope of -4.63×10^{-3} predicted by simple electrostatic theory for charging a sphere in a continuous dielectric medium.[8]

The complex variations observed in entropies and enthalpies of ionization of weak acids are not well understood.[12] The specific structural and solvation factors involved must also affect entropies of activation of acid-catalyzed reactions. In view of this, even qualitative agreement with the prediction of a simple electrostatic model for charging a spherical ion is somewhat surprising.

Two conclusions may be drawn from the correlation reported here. First, entropies of activation ranging from near zero to strongly negative values are consistent with the A-SE2 mechanism if there is a corresponding difference of several powers of ten in reactivity. Secondly, aniline base protonation is a better model than triarylcarbinol base protonation for this behavior.

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1-Alkyl-2-aryl-5-chloroimidazoles

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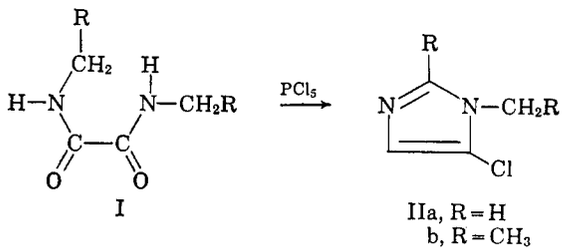
1-Methyl-5-chloroimidazole (IIa) and 1-ethyl-2-methyl-5-chloroimidazole (IIb) represent synthetically useful intermediates, having been employed as starting materials for the preparation of purines[1] and thiapurines.[2]

The method for synthesizing IIa and b, discovered by Wallach[3] and elaborated by Sarasin,[1a] involves the reaction of N,N′-dimethyl- and N,N′-diethyloxamide (Ia and b), *respectively*, with phosphorus pentachloride.



For many years this reaction was believed to be limited in scope to these two cases.[5] Recent publications by Kochergin[4] and by Trout[6,7] have extended the method to include the cyclization of a number of higher, symmetrical N,N′-disubstituted oxamides. Cyclization of the unsymmetrically substituted N-ethyl-N′-butyl-

(1) (a) J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924); (b) F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 3653 (1954); (c) R. N. Prasad and R. K. Robins, *ibid.*, **79**, 6401 (1957).
(2) F. F. Blicke and C.-M. Lee, *J. Org. Chem.*, **26**, 1861 (1961).
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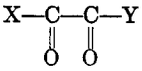
(7) G. E. Trout and P. R. Levy, *ibid.*, **85**, 765 (1966).

TABLE I

OXAMIC ACID ESTERS AND MIXED OXAMIDES

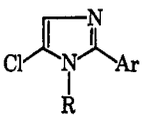


X	Y	Mp, °C (solvent)	Empirical formula	Anal, % N	
				Calcd	Found
$C_6H_5CH_2NH$	OC_2H_5	47–48 (petroleum ether)	$C_{11}H_{13}NO_3$[a]	...	...
p-$ClC_6H_4CH_2NH$	OC_2H_5	77–79 (isopropyl ether)	$C_{11}H_{12}ClNO_3$	5.80	5.64
o-$ClC_6H_4CH_2NH$	OC_2H_5	59–60 (isopropyl ether)	$C_{11}H_{12}ClNO_3$	5.80	5.85
3-Pyridyl-CH_2NH	OC_2H_5	95–96 (alcohol–ether)	$C_{10}H_{12}N_2O_3$	13.46	13.66
$C_6H_5CH_2NH$	$NHCH_3$	184–185 (alcohol)	$C_{10}H_{13}N_2O_2$	14.58	14.67
$C_6H_5CH_2NH$	$NH(CH_2)_3OCH_3$	140–141 (alcohol)	$C_{13}H_{18}N_2O_3$	11.19	11.33
p-$ClC_6H_4CH_2NH$	$NHCH_3$	216–217 (DMF–alcohol)	$C_{10}H_{11}ClN_2O_2$	12.36	11.94
o-$ClC_6H_4CH_2NH$	$NHCH_3$	180–181 (alcohol)	$C_{10}H_{11}ClN_2O_2$	12.36	12.35
3-Pyridyl-CH_2NH	$NHCH_3$	157–158 (water)	$C_9H_{11}N_3O_2$	21.75	22.00

[a] T. Curtius and K. Raschig, *J. Prakt. Chem.*, **125**, 466 (1930).

TABLE II

1-ALKYL-2-ARYL-5-CHLOROIMIDAZOLES

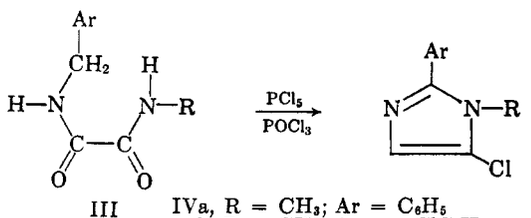


Ar	R	Yield, %	Mp of HCl salt, °C (mp of base, °C)	Ultraviolet spectra in *i*-PrOH, max absorbance, mμ (ϵ_{max})	Empirical formula	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
C_6H_5	CH_3	75	215–216 (106–107)	262 (11.900)	$C_{10}H_9ClN_2 \cdot HCl$[a]	52.42	4.40	12.23	52.53	4.58	12.27
p-ClC_6H_4	CH_3	61	190–192 (88–89)	267 (14.500)	$C_{10}H_8Cl_2N_2 \cdot HCl$[a]	45.56	3.44	10.63	45.35	3.44	10.35
o-ClC_6H_4	CH_3	81	190–194	255 (6.980)	$C_{10}H_8Cl_2N_2 \cdot HCl$[a]	45.56	3.44	10.63	45.39	3.56	10.47
3-Pyridyl	CH_3	...	...								
		39[b]	(116–117)	257 (10.150)	$C_9H_8ClN_3$	55.82	4.10	21.70	55.42	4.12	21.75
C_6H_5	$(CH_2)_3OCH_3$	75	165–166	257 (11.000)	$C_{13}H_{15}ClN_2O \cdot HCl$[a]	53.99	5.58	9.69	54.03	5.71	9.81

[a] The hydrochloride salts, prepared by addition of alcoholic (isopropyl) HCl to alcoholic solutions of the base, were recrystallized from alcohol–ether. [b] The reaction was accompanied by considerable tar formation.

oxamide led, quite expectedly, to the formation of 1-butyl-2-methyl-5-chloroimidazole and 1-ethyl-2-propyl-5-chloroimidazole in approximately equal amounts.[6] It was felt, however, that the use of more dissimilarly substituted N,N′-oxamides would force ring closure to proceed more predominately in one direction.

For this purpose, a series of N-alkyl-N′-arylmethyl-oxamides was prepared by the reaction of a number of benzylic amines with diethyl oxalate in alcohol at 0°. Treatment of the resulting N-substituted oxamic acid esters with a large excess of an aliphatic amine then gave the required compounds IIIa–e. See Table I for descriptive data.

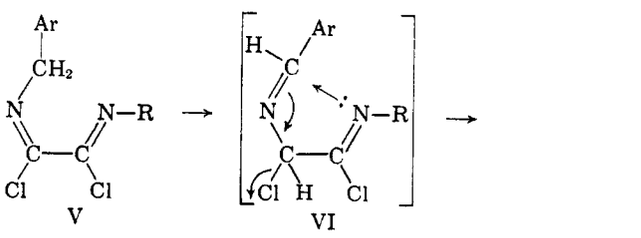


III

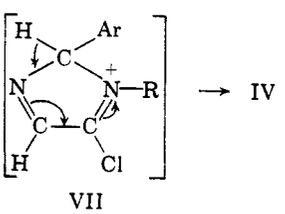
IVa, R = CH_3; Ar = C_6H_5
b, R = CH_3; Ar = o-ClC_6H_4
c, R = CH_3; Ar = p-ClC_6H_4
d, R = CH_3; Ar = 3-pyridyl
e, R = $CH_2CH_2CH_2OCH_3$; Ar = C_6H_5

The reaction of the latter compound with 2 equiv of phosphorus pentachloride was carried out in phosphorus oxychloride and gave exclusively and in good yields 1-alkyl-2-aryl-5-chloroimidazoles IVa–e. The assignment of structures was predicated upon ultraviolet data. Whereas 1-methyl-5-chloroimidazole exhibited no maxima between 220 and 350 mμ and 1-benzylimidazole showed typical isolated phenyl absorption [λ_{max} 251.8 mμ (ϵ 179), 257 (220), 263 (168)], compounds IVa–e all showed ultraviolet maxima and intensities characteristic of aromatic conjugation. The decreased absorption intensity of IVb is presumably attributable to the *ortho* substituent. See Table II for descriptive data.

Conceivably, the reaction of phosphorus pentachloride with III leads, at some stage, to the formation of V. We believe that migration of the double bond occurs at that point, presumably *via* a hydride shift. Imine VI can then cyclize to VII, which, losing a proton



V VI



VII

with concomitant electronic redistribution, then gives IV.

Experimental Section[8]

The preparation of the 1-alkyl-2-aryl-5-chloroimidazoles will be exemplified by the synthesis of IVa.

N-Benzyloxamic Acid Ethyl Ester.—A solution of 107 g (1.0 mole) of benzylamine in 200 ml of alcohol was added dropwise and with stirring to a solution of 157 g (1.20 moles) of diethyl oxalate in 100 ml of alcohol at 0–5°. Upon completion of the addition, the mixture was stirred for another hour, whereupon solvent was removed *in vacuo*. Vacuum distillation of the residue yielded 170 g of product, bp 150–155° (0.2 mm). The distillate solidified upon rubbing with petroleum ether and melted at 47–48°.

N-Benzyl-N′-methyloxamide (IIIa).—A solution of 103.5 g (0.50 mole) of N-benzyloxamic acid ethyl ester in 250 ml of alcohol was added dropwise to 300 ml of 35% aqueous methylamine. The product precipitated out immediately and was isolated by filtration after 3 hr: yield 82 g, 86%; mp 184–185°.

1-Methyl-2-phenyl-5-chloroimidazole (IVa).—To a stirred slurry of 192 g (1.0 mole) of IIIa in 600 ml of phosphorus oxychloride was added over a 10-min period 436 g (2.10 moles) of phosphorus pentachloride. Some cooling was necessary. The mixture was subsequently refluxed for 2 hr. Solvent (600 ml) was then removed at atmospheric pressure, whereupon xylene was alternatively added and distilled off, thereby removing the last traces of phosphorus oxychloride. To the cooled mixture, containing *ca.* 200 ml of xylene, was added 1 l. of water. The aqueous phase was drawn off, and the organic phase was extracted once more with dilute hydrochloric acid. Basification of the combined aqueous phases gave crude, solid product which was filtered off. It was dissolved in the minimum amount of boiling heptane, separated from adhering water, and allowed to crystallize, giving 143 g (75%) of stout needles, mp 106–107°.

Registry No.—N-Benzyloxamic acid ethyl ester, 7142-72-5; IIIa, 7666-51-5; IVa, 7666-52-6; $C_{11}H_{12}ClNO_3$ (*p*), 6951-43-5; $C_{11}H_{12}ClNO_3$ (*o*), 6621-71-2; $C_{10}H_{12}N_2O_3$, 3262-95-1; $C_{13}H_{18}N_2O_3$, 7666-55-9; $C_{10}H_{11}ClN_2O_2$ (*p*), 7666-56-0; $C_{10}H_{11}ClN_2O_2$ (*o*), 7666-57-1; $C_9H_{11}N_3O_2$, 7666-58-2; $C_{10}H_9ClN_2 \cdot HCl$, 7666-59-3; $C_{10}H_8Cl_2N_2 \cdot HCl$, 7631-11-0; $C_{10}H_8Cl_2N_2$, 7666-60-6; $C_{10}H_8Cl_2N_2 \cdot HCl$, 7666-61-7; $C_9H_8ClN_3$, 7631-12-1; $C_{13}H_{15}ClN_2O \cdot HCl$, 7666-62-8.

Acknowledgment.—The authors are indebted to the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support of this program. The reported analyses were performed by Messrs. A. Sels and W. Verkest. Special thanks are due to Mr. J. Loomans for ultraviolet measurements and interpretations.

(8) Melting points were taken on a Fisher-Johns block.

A New Synthesis of 3-Mercapto-2-(mercaptomethyl)propionic Acid by Phosphorothioate Hydrolysis[1]

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Interest in asparagus juice component 3-mercapto-2-(mercaptomethyl)propionic acid[2a] (**3**) earlier prompted its synthesis from 3-iodo-2-(iodomethyl)propionic acid by two groups of investigators. Corse and Jansen obtained **3** by reduction of 3-(benzylthio)-2-[(benzylthio)methyl]propionic acid with sodium in liquid ammonia, basic hydrolysis of the corresponding bis(isothiuronium) derivative having failed.[2b] Schotte and Ström later obtained **3** by reduction of its cyclic disulfide, 1,2-dithiolane-4-carboxylic acid, with zinc powder in aqueous ammonia. Preparation of the cyclic disulfide involved oxidation of a crude preparation of **3** obtained by hydrolysis of the corresponding bis(acetylthio) derivative.[3]

In a search for a reaction sequence that could be easily applied to the preparation of sizable amounts of **3**, we made use of a recently described method in which the acid-labile S-substituted phosphorothioic acid function served as a precursor to the thiol group. In the earlier application, S,S′-1,4-diamino-1,4-cyclohexylenedimethylenebis(phosphorothioic acid) was converted through treatment with phosphoric acid to 1,4-diamino-1,4-cyclohexanedimethanethiol diphosphate, phosphoric acid hydrolysis being used to avoid introduction of a second anion and thereby simplify isolation of the resultant aminothiol salt.[4] Extension of this method to the preparation of **3** involved treatment of the sodium salt of 3-bromo-2-(bromomethyl)-propionic acid[5] (**1**) with 2 molar equiv of trisodium phosphorothioate[6a] in aqueous solution followed by *in situ* hydrochloric acid hydrolysis of the intermediate salt **2**; pure **3** was thus obtained in 50% yield.

$$(BrCH_2)_2CHCOOH \xrightarrow[2.\ 2Na_3SPO_3]{1.\ NaHCO_3} (Na_2O_3PSCH_2)_2CHCOONa \xrightarrow[\text{hydrolysis}]{HCl} (HSCH_2)_2CHCOOH$$

1 — **2** (not isolated) — **3**

Although acid hydrolysis of S-substituted phosphorothioic acids to the corresponding thiols has been used by Åkerfeldt as a precondition for iodometric assay of sulfur in such compounds,[6b] it has not heretofore been developed as a preparative method. The relative efficacy afforded by this method in the examples discussed here, particularly in the synthesis of **3**, suggests that it may be generally useful.

Experimental Section

3-Bromo-2-(bromomethyl)propionic acid (**1**) was prepared by the procedure of Ferris.[5] Recrystallization of the crude product from cyclohexane (instead of water as used by Ferris) afforded pure **1** in excellent recovery.

Trisodium Phosphorothioate.—The hydrolysis (NaOH) of freshly distilled thiophosphoryl chloride was carried out on the same scale and in essentially the same manner as described by Åkerfeldt;[6a] some additional details are noteworthy. The rapidly stirred mixture was carefully maintained at 75–85° until all the $PSCl_3$ had just disappeared (about 40 min required). The solution was immediately chilled until crystals began separating, and the mixture was refrigerated overnight. Following recrystallization and dehydration as described by Åkerfeldt, the product was dried at 100° *in vacuo* for 30 min.

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

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(4) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **9**, 911 (1966).

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(6) (a) S. Åkerfeldt, *Acta Chem. Scand.*, **14**, 1980 (1960); (b) *ibid.*, **16**, 1897 (1962).