Experimental

All the melting points are corrected. The methyl pyrazinoate was prepared from pyrazinoic acid using the procedure described by Hall and Spoerri.[10] Pyrazinoic acid was obtained by selenium dioxide oxidation[11] of 2-methylpyrazine.[12]

Yield determinations of aldehydes were made *via* the 2,4-dinitrophenylhydrazones according to the method of Iddles, *et al.*[13]

Pyrazinealdehyde I.—Methyl pyrazinoate (25.0 g., 0.181 mole) in 500 ml. of dry tetrahydrofuran was cooled to −70° under nitrogen. While maintaining the temperature at −68° to −73°, 268 ml. of 0.34 *M* lithium aluminum hydride in tetrahydrofuran[14] (0.091 mole) was added with stirring over a period of 30 min. After stirring for an additional 15 min. at −75°, the reaction was stopped by slow addition of 25 ml. of glacial acetic acid. The light brown reaction mixture containing 0.142 mole of I was evaporated *in vacuo*. The residue was dissolved in 170 ml. of 2.5 *N* hydrochloric acid and 100 ml. of chloroform. The aqueous layer was extracted eight times with 50-ml. portions of chloroform. The combined extracts were stirred with 50 ml. of water and 25 g. of sodium bicarbonate until neutral. After filtration, the chloroform layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. Fractional vacuum distillation with tetraethyleneglycol dimethyl ether (Ansul ether 181) as chaser yielded 9.04 g. (46%) of pyrazinealdehyde, b.p. 57–58° at 6 mm., as a light yellow liquid. Redistillation afforded 5.26 g. of pure I, b.p. 57.0–57.8° at 6 mm., m.p. 31–33°, b.p. (Emich) 174°. The infrared spectrum of I (as a film) revealed a prominent band at 5.90 μ (C=O). I, octahydroxanthene, had m.p. (benzene–hexane) 176–177°.

Anal. Calcd. for $C_{21}H_{24}N_2O_8$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.31; H, 7.08; N, 7.64.

I, 2,4-dinitrophenylhydrazone, had m.p. 239–240° (lit.[2] m.p. 239–240°).

I, nicotinoylhydrazone, had m.p. (ethyl acetate) 195–195.5° (lit.[4] m.p. 195°).

I, isonicotinoylhydrazone, had m.p. (ethyl acetate) 197–198° (lit.[4] m.p. 200°).

α-Pyrazyl-α-hydroxymethanesulfonic Acid (II).—Sulfur dioxide was bubbled into a cooled mixture of 0.35 g. of I in 17 ml. of chloroform and 5 ml. of water. Addition of 100 ml. of acetone and subsequent refrigeration yielded 0.46 g. (75%) of II as light yellow crystals. Recrystallized from water–acetone, II melts at 159–159.5° (partial dec., sealed capillary); neut. equiv., 192.2 (theory, 190.1).

Pyrazoin(1,2-dipyrazyl-1,2-ethenediol) (III).—Potassium cyanide (0.2 g.) was added to 0.27 g. of I in 19 ml. of water. The solution darkens quickly with formation of yellow-brown crystals. The crystal slurry was stirred at room temperature for 1 hr., acidified with 0.2 ml. of glacial acetic acid, and filtered. Yield: 0.23 g. of III (85%), bronze colored crystals, m.p. (ethyl acetate) 218–219° dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.75; H, 3.86; N, 25.78.

Pyrazoin gives a positive Fehling test and decolorizes Tillmann's reagent. The infrared spectrum of III (in potassium bromide) shows no significant absorption bands between 5.5 and 6.2 μ.

Pyrazylmethanol (IV).—Pyrazinealdehyde (2.0 g.) and 3 ml. of 40% aqueous sodium hydroxide were mixed in a test tube cooled in ice–water. The resultant white paste was stirred for 10 min., then diluted with 12 ml. of water. Carbon dioxide was bubbled into the clear solution until the pH was 8–9. Evaporation to dryness *in vacuo*, extraction of the residue with chloroform, and distillation yielded 0.60 g. (59%) of pyrazylmethanol as a colorless, hydroscopic oil; b.p. 59–62° at 0.1 mm., m.p. 35–36°. Infrared spectrum (film): 3.0 μ (–OH), 9.40 μ (–C–OH). Ultraviolet spectrum (in 95% ethanol): maxima at 266 mμ, ϵ 6700; 309 mμ, ϵ 800. For analysis, the α-naphthylcarbamate of IV was prepared; m.p. (benzene–hexane) 110–110.5°.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.04. Found: C, 68.65; H, 4.81; N, 14.99.

The residue from the chloroform extraction was dissolved in water and acidified with hydrochloric acid to liberate the pyrazinoic acid. Yield: 1.02 g. (89%) white crystals, m.p. 224.5° dec., m.m.p. 224.5 dec.

Pyrazylmethyl Pyrazinoate.—This ester was formed in the reduction of pyrazinoyl chloride with lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran by the method of Brown and Subba Rao.[9] With slow addition of the reductant over a 2-hr. period, a yield of 55% of pyrazylmethyl pyrazinoate was obtained as colorless needles, m.p. (benzene–hexane) 115–115.5°.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.64; H, 3.82; N, 25.83.

Saponification of the ester with 0.1 *N* sodium hydroxide at room temperature for 1 and 2 days gave a saponification equivalent of 211 and 214, respectively (theory 216.2). The distillation residue yielded pyrazinoic acid, m.p. 224.5° dec., undepressed on admixture with authentic pyrazinoic acid.

Lithium Aluminum Hydride Reduction Procedure on Esters Other than Methyl Pyrazinoate.—All reductions were conducted on a 1-mmole scale. The compound dissolved in 4 ml. of tetrahydrofuran was stirred magnetically while cooling to −70° to −75° in a methanol–Dry Ice bath. The lithium aluminum hydride solution (0.43 *M*) was added from a 10-ml. buret (protected from the atmosphere by a nitrogen-filled balloon) over a period of 5–7 min. After an additional 15 min. at −70°, the reaction was stopped by adding 0.25 ml. of glacial acetic acid. On warming to room temperature the reaction mixture was poured into 55 ml. (1.1 mmoles) of saturated 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid and allowed to stand for 48 hr. The 2,4-dinitrophenylhydrazone derivatives were filtered, washed with 5% hydrochloric acid, then water, and dried at 120° for 1 hr. before weighing. As a control, the yield of pyrazinealdehyde 2,4-dinitrophenylhydrazone from methyl pyrazinoate was reproducible within 0.5% in four reductions performed on three different days.

(10) S. A. Hall and P. E. Spoerri, *J. Am. Chem. Soc.* **62**, 664 (1940).

(11) H. Gainer, *J. Org. Chem.*, **24**, 691 (1959).

(12) The 2-methylpyrazine used in this study was generously supplied by Wyandotte Chemicals Corp.

(13) H. A. Iddles, A. W. Low, B. D. Rosen, and R. T. Hart, *Anal. Chem.*, **11**, 102 (1939).

(14) The concentration of LAH was determined by gravimetric analysis of the aluminum with oxine.

Participation of a Neighboring Amide Group in the Decomposition of Esters and Amides of Substituted Phthalamic Acids[1]

J. A. SHAFER AND H. MORAWETZ

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 1, New York

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The labilization of amide groups by a second neighboring amide function has been described recently for succinamide[2] and for phthalamide.[3] A similar labilization of benzyl esters has been reported also.[4] Because of the predominance of amide groups in proteins, the possibility arises that these groups may also, in some cases, be involved in the mode of action of hydrolytic enzymes. This possibility seemed to justify a further study of activation by neighboring amide groups.

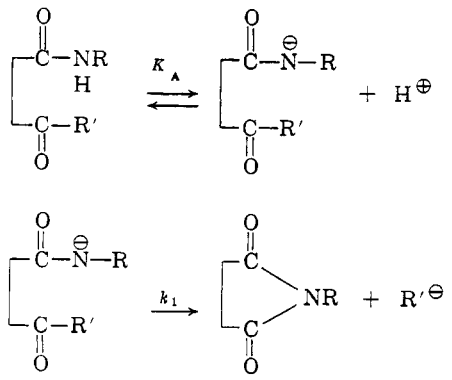
The attack of neighboring amide on amide or ester groups to form an imide intermediate proceeds at a rate inversely proportional to hydrogen ion concentration, suggesting the following mechanism.

(1) Financial support of this research by the National Institute of Health is gratefully acknowledged.

(2) B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. soc. chim. Belges*, **69**, 616 (1960).

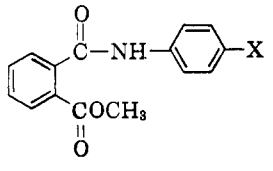
(3) P. Crooy, doctoral dissertation, Catholic University, Louvain, 1961.

(4) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962).



This is assuming that $K_A/(H^+) \ll 1$.

It would be expected that an increase in the acidity of the neighboring amide function would increase the concentration of the amidate nucleophile but at the same time reduce its reactivity. Kinetic investigation of a series of compounds in which each R is a *para* substituted phenyl group would then offer a convenient method for assessing the relative importance of these two factors[5] and such a study was carried out on compounds of type I with X = H, CN, NO_2, and CH_3.

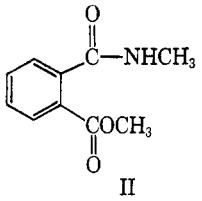


I

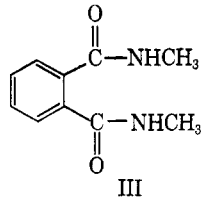
Applying the classical Hammett treatment to the effect of X on the reaction rate we obtain

$$\log (k/k^\circ) = (\rho_A + \rho_1)\sigma^* \qquad (1$$

where ρ_A and ρ_1 describe the sensitivity of K_A and k_1 to substituent effects. Applying equation 1 to data for compounds with electron-withdrawing substituents in Table I and using σ^* values recommended by Jaffe,[6] we obtain for $\rho_A + \rho_1$ a small negative value between -0.1 and -0.2. (With this small substituent sensitivity, the effect of *p*-methyl substitution would be expected to be negligible and the slight deactivation observed is not considered significant.) It may, therefore, be concluded that the increased concentration of the amidate ions resulting from increasingly electronegative substituents is insufficient to compensate for their reduced nucleophilic reactivity. The fact that methyl N-methylphthalamate (II) is four times more reactive than methyl phthalamate is qualitatively in the direction to be expected from the results discussed earlier, although the magnitude of the effect is surprising since unsubstituted amides and N-methylamides would be expected to differ in acidity less than anilides and *p*-nitroanilides. The observation that there is a smaller



II



III

(5) We are indebted to C. H. W. Hirs for suggesting this approach.

(6) H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

TABLE I

RATES OF IMIDE FORMATION FROM *para* SUBSTITUTED METHYL N-(PHENYL)PHTHALAMATES[a]

X	$10^4 k_1$ sec.$^{-1}$
H	3.9
CH_3	3.8
NO_2	2.8
CN	2.5

[a] Temp. = 25.3°, 40/60 v./v. dioxane-water, μ = 0.12, apparent pH = 7.8. Initial ester concentration 1.7×10^{-2} to 2.7×10^{-2} mg./ml.

TABLE II

RATES OF IMIDE FORMATION FOR SOME PHTHALAMIC ACID DERIVATIVES[a]

	k_2 (l. mole^{-1} sec.$^{-1}$)
Methyl N-methylphthalamate[b]	12,400
Methyl phthalamate[c]	3,100
N,N'-Dimethylphthalamide[d]	7.6
Phthalamide[e]	4.9

[a] In aqueous solution, temp. = 25.9°, μ = 0.1. [b] 6×10^{-3} mg./ml. [c] 6×10^{-3} mg./ml. [d] 5.9×10^{-2} mg./ml. [e] 3.2×10^{-1} mg./ml.

difference between the reactivities of N-N'-dimethyl phthalamide (III) and phthalamide is not surprising, since the nucleophilicity of the attacking and leaving groups is being changed by similar factors.

It may be pointed out that methanol is eliminated from the methyl esters of phthalamic acid and N-methylphthalamic acid more rapidly than from methyl *o*-formylbenzoate, which has been described recently[7] as the most reactive known methyl ester. This comparison is of interest since the release of methanol is the primary process reflecting the efficiency of neighboring group attack on the ester function. On the other hand, since the imide intermediate formed from II is relatively stable (200–300 times less reactive than the parent ester), methyl *o*-formylbenzoate is converted faster to the corresponding acid. The stability of the imide intermediate has to be taken into account also in considering the possibility that an amide group might form part of the active site of an esteratic enzyme. This difficulty does not arise when the neighboring amide serves to activate another amide; the reactivity of the imide intermediate is then comparable to that of the parent amide.

Experimental

Materials.—Substituted N-phenylphthalamic acids were prepared according to a method previously described.[8] The corresponding silver salts were made by neutralizing the acid with 1 *N* ammonia and mixing the resulting solution with an equivalent of concentrated silver nitrate solution.

Methyl esters of substituted N-phenylphthalamic acids were prepared by treating overnight with vigorous stirring the dry silver salt with excess methyl iodide in dry benzene or acetone at room temperature. These methods are reported elsewhere.[9,10] The benzene or acetone was evaporated and the residue was taken up in chloroform. The resulting products were then precipitated with hexane. The esters were crystallized three times

(7) M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962).

(8) M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *ibid.*, **50**, 474 (1928).

(9) M. M. S. Hoogewerff and W. A. Van Dorp, *Rec. trav. chem.*, **18**, 358 (1899).

(10) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, London, 1959, pp. 388–389.

TABLE III
ANALYSES OF ESTERS STUDIED

Compound		Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Dec., °C.	Rep. dec., °C.
Methylphthalamate	$C_9H_9NO_3$	60.33	5.06	7.82	60.20	5.12	7.90	98-102	98-102[a]
Methyl N-methylphthalamate	$C_{10}H_{11}NO_3$	62.17	5.74	7.25	62.17	5.90	7.50	112-114	
Methyl N-phenylphthalamate	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.81	5.28	5.67	111-112	
Methyl N-(*p*-methylphenyl)-phthalamate	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.09	5.63	5.22	145-146	
Methyl N-(*p*-nitrophenyl)-phthalamate	$C_{15}H_{12}N_2O_5$	60.00	4.03	9.33	60.06	4.14	9.24	158-159	
Methyl N-(*p*-cyanophenyl)-phthalamate	$C_{16}H_{12}N_2O_3$	68.56	4.32	10.00	68.81	4.48	9.87	157-158	

[a] See ref. 9.

from chloroform–hexane at room temperature, and gave acceptable elemental analyses (Table III).

Substituted N-phenylphthalimides were prepared by heating the corresponding substituted anilines in refluxing glacial acetic acid for half an hour with phthalic anhydride.[11] These imides have been reported previously and their melting points checked with those reported in the literature.

Ammonium phthalamate and ammonium N-methylphthalamate were prepared by adding phthalic anhydride to concentrated ammonia or 25% aqueous methylamine according to a method described by Chapman and Stephen.[12] The corresponding silver salts were prepared by dissolving the ammonium salts in water and adding an equivalent of concentrated silver nitrate solution.

Methyl N-methylphthalamate and methylphthalamate were prepared from their silver salts by methods described earlier.

All materials whose origin is not specified were obtained commercially in the highest purity available and purified when necessary, until their melting points corresponded to those previously reported.

Solutions.—Dioxane–water buffer was 40/60 v./v. The solution formally contained 0.0112 *M* Na_2HPO_4, 0.0128 *M* NaH_2PO_4, and enough sodium chloride to make the ionic strength 0.12. The apparent pH was 7.8. In all other buffers water was the only solvent and the ionic strength was 0.10 with the concentration of ionized acid less than 0.02 *M*.

Measurements of pH were made with a Cambridge Research Model pH meter.

Kinetics.—The rate of disappearance of reactant or the appearance of product was followed with a Beckman DU spectrophotometer by observing the change in optical density (D) with time in a thermostated cell. The following wave lengths were employed to study the various decompositions: phthalimide, N-methylphthalimide, N,N′-dimethylphthalamide, phthalamide, methyl phthalamate, and methyl N-methylphthalamate, 299 mμ; methyl N-phenylphthalamate, 275 mμ; methyl N-(*p*-methylphenyl) phthalamate, 281 mμ; methyl N-(*p*-nitrophenyl)phthalamate, 320 mμ; methyl N-(*p*-cyanophenyl)phthalamate, 294 mμ. For the esters plots of $-\ln (D - D_\infty)$ or $-\ln (D_\infty - D)$ were linear in time, and their slopes gave the pseudo first-order rate constants. In the case of the decomposition of phthalamide and N,N′-dimethylphthalamide, consecutive first-order reaction theory was used to obtain the rate of imide formation and decomposition. The formation of the imide intermediates was verified by the similarity between the rate constants assigned to the hydrolysis of the imides from the decomposition of the amides and to the rate constants observed from the separate hydrolyses of the imides.

Where the products were stable, they were identified by the similarity between their ultraviolet spectra and those of the expected products.

In the case of the methyl esters of the substituted phthalamic acids, the fact that the ultraviolet spectra of the esters approached that of the corresponding imide was taken as verification of the postulated reaction path. However, here the true infinity reading had to be calculated from the extinction coefficients of the imide and the concentration of the reactant, since in a time corresponding to ten half-lives of imide formation, the imide hydrolysis could not be neglected. Imide hydrolysis could be neglected during the first half-life of imide formation.

(11) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, London, 1959, p. 423.

(12) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1791 (1925).

Derivatives of Sulfenic Acids. XLII. 3-Chloroformylpropanesulfenyl Chloride and 1,2-Thiazan-3-one[1]

NORMAN KHARASCH AND ROBERT B. LANGFORD

Department of Chemistry, University of Southern California, Los Angeles 7, California

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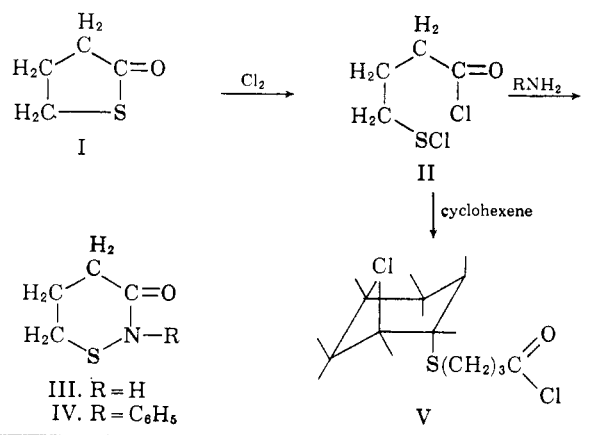
While aromatic sulfenyl chlorides have been studied in considerable detail,[2] less attention has been given to aliphatic examples, although the works of Douglass and co-workers, and of Brintzinger and others are notable.[3] Aliphatic polyfunctional sulfenyl chlorides have been mentioned in only a few cases, and even those recorded are very little known.[4]

We now report the synthesis of 3-chloroformylpropanesulfenyl chloride (II), by chlorinolysis of γ-thiobutyrolactone (I), and describe the properties of the former compound. For laboratory scale, the preparation of I is carried out conveniently by pyrolysis of γ-mercaptobutyric acid,[5] which is obtained, in turn, from γ-butyrolactone *via* the isothiuronium bromide.[6] Treatment of I with chlorine, or with sulfuryl chloride, in anhydrous chlorinated solvents at −20° leads



(1) This study was supported by a grant from the Stauffer Chemical Co., and contract DA-04-495-Ord 901 with the Army Research Office (Durham).

(2) Earlier papers in this series; *cf.* also N. Kharasch, Chap. 32, "Organic Sulfur Compounds," Vol. 1, Pergamon Press, 1961, pp. 375–396.

(3) I. B. Douglass, *ibid.*, pp. 350–360.

(4) H. Brintzinger, M. Langheck, and H. Ellwanger, *Ber.*, **87**, 320 (1954); H. Brintzinger, H. Schmahl, and H. Witte, *ibid.*, **85**, 338 (1952); *cf.* also ref. 3.

(5) B. Holmberg and E. Schjanberg, *Arkiv Kemi, Mineral. Geol.*, **14A**, No. 7 (1940); *Chem. Abstr.*, **35**, 2113 (1941).

(6) L. Schotte, *Arkiv Kemi*, **8**, 457 (1955).