Kinetics of Hydrolysis of Monothionsuccinimides[1a]

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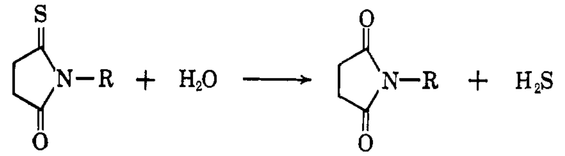
The hydrolysis of monothionsuccinimides (I) to imides (II) was studied at constant temperature (70.0 ± 0.1°) in distilled water to determine the effect of N-substitution on the first-order rate constants. The rates were followed spectrophotometrically, and the data show that N-alkylmonothionsuccinimides hydrolyze more slowly than N-arylmonothionsuccinimides. The results are rationalized in terms of steric and electronic effects when the rate-determining step is represented by nucleophilic attack of water on the partially positive carbon of the C=S group.

Our interest in monothionsuccinimides relative to their ability to protect living systems against ionizing radiation prompted this preliminary investigation of the influence of N-substitution on the stability of the C=S group. Monothionsuccinimides (I) readily undergo hydrolysis to the corresponding imide (II) with evolution of hydrogen sulfide.[2] To date no systematic studies concerned with the effect of substituents in thionimide or thionamide derivatives upon the relative ease of hydrolysis under acidic, basic, or neutral conditions have been reported, although some qualitative predictions can be made on the basis of observations recorded in the literature in the thionamide series.[3] Information gained in this study will be of value in designing sufficiently stable thionimides for biological evaluation.

In this communication we report the first-order rates of hydrolysis of a series of monothionsuccinimides to succinimides. The thionimides were dissolved in 10% ethanol in water (70.0 ± 0.1°) and the rates of hydrolysis were observed by noting the decrease in absorbancy at the high-intensity $\pi \rightarrow \pi^*$ transition[4] at approximately 270 mμ due to the C=S function. Since hydrogen sulfide is an extremely weak acid ($K_1 = 5.7 \times 10^{-8}$) and since the amount generated is extremely small under the conditions of the hydrolysis, its influence upon the reaction rates should be negligible. Hydrolysis studies of several thionimides under the same conditions but in solution saturated with hydrogen sulfide gave no observable change in rate. In addition, no C=S group is detected in the ultraviolet spectrum when the imide is dissolved in water (70.0 ± 0.1°) saturated with hydrogen sulfide. This indicates that the liberated hydrogen sulfide as well as the reverse reaction are of little importance in evaluating the kinetic data. Neutral conditions were employed in these preliminary studies, since alkaline or acidic conditions may severely enhance the rate and, under neutral conditions, opening of the ring does not represent a complicating factor. We, as well as others,[2] have shown that a quantitative yield of the corresponding imide is obtained when an ethanol–water solution of the thionimide is warmed or evaporated to dryness, although higher molecular weight N-alkyl compounds do have increased stability.



I II

Experimental Section

Synthesis.—The thionimides were generally prepared by treating the corresponding imide with phosphorus pentasulfide as described in the literature.[2] N-Phenylmonothionsuccinimide (Ij) and N-(*p*-methoxyphenyl)monothionsuccinimide (Il) were synthesized by treating the respective methyl ester amides with phosphorus pentasulfide in boiling toluene, although this procedure[5] afforded no particular advantage. When N-alkylmonothionsuccinimides were prepared from the corresponding imide, pyridine solvent was preferred since the reaction time was consistently found to require 3 hr. and contamination by unreacted imide was minimal.[6] Liquid monothionsuccinimides were distilled utilizing a 40-cm. Nester–Faust spinning-band column and were isolated as light yellow oils (25 to 30%) which turned dark brown upon prolonged exposure to the atmosphere. The N-arylmonothionsuccinimides were prepared by refluxing with phosphorus pentasulfide for 4–5 hr. in xylene solution.[2] After the usual work-up[2] we observed that the thionimide and the imide crystallized together from ethanol. This cocrystallization was easily detected since carbonyl stretching for the thionimide exhibited a band in the infrared at 5.66–5.70 μ and strong carbonyl stretching for the imide was found at 5.82–5.86 μ. Pure monothionimide shows no band (or shoulder) at the latter wave length. Separation of the thionimide from the imide was readily accomplished by column chromatography on silicic acid with chloroform. The monothionimide was always eluted prior to the imide. Occasionally, traces of dithionimide formed in the reaction and during chromatography were eluted prior to the monothionimide. These purification procedures account for the generally higher melting points which we observed in comparison to those reported in the literature[2] (Table I).

In the aromatic series the *p*-iodo, *p*-bromo, and *p*-nitro derivatives Ii, Ih, and Im represent unreported compounds. Under the above reaction conditions, and after chromatography and recrystallization from 95% ethanol they were obtained in only 10–15% yields. Physical constants and analyses for all monothionsuccinimides investigated are listed in Table I.

Kinetic Studies.—The spectra of each monothionsuccinimide was taken in 10% ethanol in water (1-cm. silica cells) using a Beckman DB spectrophotometer equipped with Sargent recorder. The λ_{max} and log ϵ_{max} are listed in Table II.

The hydrolysis was carried out at 70.0 ± 0.1° and the reaction course was followed by measuring the decrease in absorbancy at the λ_{max} utilizing a Beckman DU spectrophotometer. An accurate weight of the thionimide was dissolved in 10 ml. of 95% ethanol and brought to exactly 100 ml. with distilled water (previously warmed to 70°) to obtain an approximate concen-

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[1] (a) This investigation was initiated with funds from the Research Corporation and is presently supported by funds from the Division of Radiological Health, Bureau of State Services, Public Health Service, Grant No. RH 00324. (b) To whom all correspondence should be addressed.

[2] R. J. Cremlyn, *J. Chem. Soc.*, 5547 (1961).

[3] R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 45 (1961).

[4] J. Sandstrom, *Acta Chem. Scand.*, **17**, 687, 937 (1963).

[5] A. Reissert and A. More, *Ber.*, **39**, 3298 (1906).

[6] When toluene was employed as the solvent as described by Cremlyn,[2] difficulty was experienced in determining the end point of the reaction. If the reaction was run for only 1–2 hr., considerable unreacted imide was obtained which could not be separated from the thionimide by distillation. If the time period for the reaction was longer than 2 hr., poorer yields were obtained and dithionimides could be isolated in some instances.

TABLE I

N-SUBSTITUTED MONOTHIONSUCCINIMIDES

Compd.	N-Substituent	M.p.[a] or b.p. (mm.), °C. Obsd.	Lit.[b]	Formula	Carbon, %[c] Calcd.	Carbon, %[c] Found	Hydrogen, %[c] Calcd.	Hydrogen, %[c] Found	Nitrogen, %[c] Calcd.	Nitrogen, %[c] Found	Sulfur, %[c] Calcd.	Sulfur, %[c] Found
Ia	H	115–116	100–104	C_4H_5NOS	41.7	42.1	4.4	4.1	12.2	12.0	27.8	27.8
Ib	CH_3	56–58	52–54	C_5H_7NOS	46.5	46.2	5.5	5.3	10.9	11.1	24.9	25.2
Ic	C_2H_5	140–141 (0.05)	...	C_6H_9NOS	50.3	50.8	6.4	6.4	9.8	9.9	22.4	21.9
Id	n-C_3H_7	55–56 (0.025)	...	$C_7H_{11}NOS$	53.6	54.0	7.0	7.1	8.9	8.6	20.4	20.0
Ie	n-C_4H_9	68–69 (0.025)	95–100 (0.2)	$C_8H_{13}NOS$	56.1	56.4	7.6	7.3	8.2	7.9	18.7	18.3
If	Cyclohexyl	54–55	54–56	$C_{10}H_{15}NOS$	60.9	61.1	7.6	7.5	7.1	7.0	16.2	15.8
Ig	p-ClC_6H_4	115–117	94–96	$C_{10}H_8ClNOS$	53.2	53.5	3.5	3.8	6.2	6.2	14.2	13.9
Ih	p-BrC_6H_4	144–146	...	$C_{10}H_8BrNOS$	44.4	44.6	3.0	3.3	5.2	5.1	11.9	12.1
Ii	p-IC_6H_4	185–187	...	$C_{10}H_8INOS$	37.8	38.0	2.5	2.5	4.4	4.3	10.0	9.8
Ij	Phenyl	122–123	116–117	$C_{10}H_9NOS$	62.7	62.6	4.7	4.6	7.3	7.5	16.8	17.2
Ik	p-$CH_3C_6H_4$	125–126	98–100	$C_{11}H_{11}NOS$	64.4	64.3	5.4	5.3	6.8	6.8	15.9	16.0
Il	p-$CH_3OC_6H_4$	124–125	110–111	$C_{11}H_{11}NO_2S$	59.7	59.9	5.0	5.0	6.3	6.5	14.5	14.2
Im	p-$NO_2C_6H_4$	171–173	...	$C_{10}H_8N_2O_3S$	50.9	50.8	3.4	3.6	11.9	11.6	13.6	13.6

[a] All melting points are stem corrected and were taken with a Thomas–Hoover melting point apparatus. [b] Reference 2. [c] Analyses were run by Clark Microanalytical Laboratory, Urbana, Ill.

TABLE II

N-SUBSTITUTED MONOTHIONSUCCINIMIDES

Compd.	N-Substituent	λ_{max}, mμ	log ϵ_{max}	10^{-1} k at 70°, hr.$^{-1}$ ± 0.005	$t_{1/2}$, hr.
Ia	H	268	4.42	6.427	1.08
Ib	CH_3	270	4.40	1.181	5.88
Ic	C_2H_5	272	4.34	0.783	8.85
Id	n-C_3H_7	273	4.32	0.618	11.21
Ie	n-C_4H_9	274	4.33	0.556	12.46
If	Cyclohexyl	276	4.35	0.911	7.61
Ig	p-ClC_6H_4	272	4.16	3.450	2.01
Ih	p-BrC_6H_4	272	4.11	3.152	2.20
Ii	p-IC_6H_4	272	4.11	2.880	2.41
Ij	Phenyl	272	4.22	2.680	2.59
Ik	p-$CH_3C_6H_4$	272	4.20	2.288	3.03
Il	p-$CH_3OC_6H_4$	272	4.20	2.250	3.08
Im	p-$NO_2C_6H_4$	266	4.31	7.645	0.91

tration of 5×10^{-5} mole/liter. The hydrolysis was carried out in the 100-ml., glass-stoppered volumetric flask which was immersed in a Tecan thermostated constant-temperature water bath (70.0 ± 0.1°). Aliquots were withdrawn periodically and diluted with water to a definite volume, and the absorbancy was read at the λ_{max}.

Ultraviolet absorption spectra of the corresponding imides (II) showed no absorption at 270 mμ except for N-(p-nitrophenyl)-succinimide which exhibited a λ_{max} at 266 mμ with log ϵ_{max} 3.99. Consequently, in all cases, except for N-(p-nitrophenyl)monothionsuccinimide (Im), first-order rate constants could be observed directly and calculated according to the equation 2.3 log $C_0/C_t = kt$ where C_0 = initial concentration and C_t = concentration at time t. In the case of compound Im the "continuous variation" method[7] was employed to calculate the true concentration of monothionsuccinimide during its conversion to imide.

Results and Discussion

In Table II the rate constants as well as calculated half-lives are listed. These data can readily be explained qualitatively if one assumes that the rate-determining step involves nucleophilic attack of water at the partially positive carbon of the C═S group. Introduction of either alkyl or aryl groups on the imide nitrogen generally slow the rate, a reflection of steric hindrance. However, N-aryl-substituted compounds in this series always hydrolyze faster than N-alkyl-substituted compounds, reflecting the influence of electronic factors.

The instability of the C═S group is readily observed by noting that the unsubstituted monothionsuccinimide Ia undergoes very facile hydrolysis with a half-life of 1.08 hr. Introduction of alkyl substituents on the imide nitrogen increase the stability up to n-butyl (compound Ie) which has a half-life of 12.46 hr. A plot of $t_{1/2}$ *vs.* the number of carbon atoms in the aliphatic chain (Figure 1) indicates that no substantial increase in stability will be realized by extension of the chain length beyond C_4.[8] In addition, an 8.2-fold decrease in rate is observed in going from $n = 0$ to $n = 2$, while only a 1.4-fold decrease in rate is observed in going from $n = 2$ to $n = 4$. These data are in agreement with the general prediction which would be anticipated by Newman's "rule of six,"[9] and can readily be explained in terms of steric effects where the alkyl substituent slows nucleophilic attack by water in the rate-determining step.

Comparison of the rates of hydrolysis of N-alkylmonothionsuccinimides with N-arylmonothionsuccinimides (Figure 2) indicates that all aromatic compounds undergo more rapid hydrolysis than all aliphatic systems. Within the series of monothionimides studied there exists a range of rate acceleration between 1.9-

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(7) P. Job, *Ann. chim.* (Paris), **9**, 113 (1928).

(8) We would expect branching in the N-alkyl group or utilization of t-butyl on N to further increase the stability of the C═S group to hydrolysis because of increased steric hindrance.

(9) M. S. Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950); "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 204–209, and references therein.

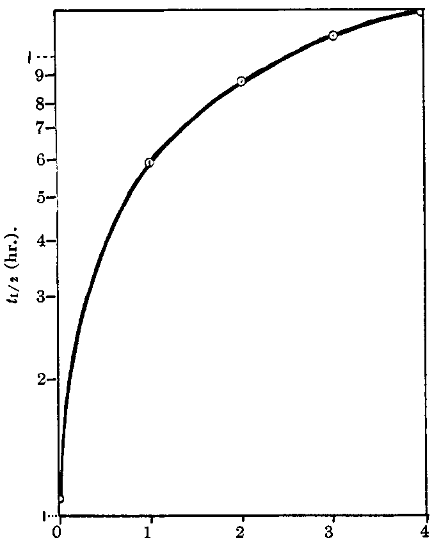

Figure 1.—A plot illustrating the effect of N-alkyl substitution on the stability of the C═S group of thionsuccinimides.

fold[10] and 13.7-fold[11] between N-alkyl and N-aryl derivatives.

This rate difference is not due only to a difference in steric effects between the aromatic and aliphatic systems, since on the basis of *A* values[12] a phenyl ring has been shown to be slightly larger than methyl.[13] While such values can not generally be extrapolated to five-membered ring systems, the assumption that methyl is probably not effectively larger than phenyl in these studies appears reasonable. Further, if phenyl (compound Ij) is replaced by cyclohexyl (compound If) a 2.9-fold decrease in the rate of hydrolysis is observed. Clearly, electronic factors introduced by aromatic substitution on the imide nitrogen are sufficiently important to be reflected in an accelerated rate of hydrolysis. This is supported by the fact that introduction of a *p*-nitro group (compound Im) accelerates the rate of hydrolysis to the extent that the half-life (0.91 hr.) is less than the unsubstituted monothionsuccinimide Ia (1.08 hr.).

Realizing that the rates of hydrolysis of monothionsuccinimides are relatively fast, that the differences between relative rates of the compounds investigated are fairly small, and that a nitrogen atom isolates the reaction center from the aromatic ring, reasonably good correlation with Hammett σ values[14] was still obtained (Figure 3). For the *p*-nitro compound Im the σ^- value (1.27)[14b,15] for aniline and phenol derivatives provided the most reasonable fit with the data. The calculated ρ[16] of +0.348 supports the contention that inductive effects of the substituents are significant and that electron-withdrawing groups will enhance the rate.[14,17]

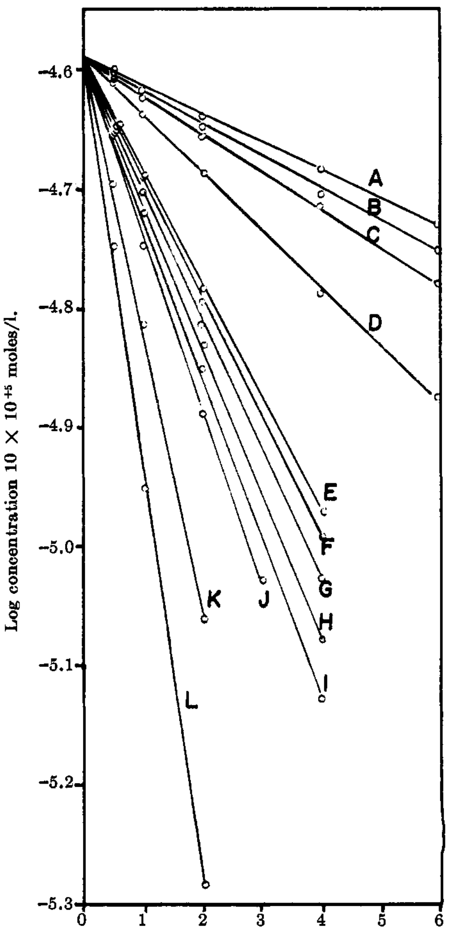

Figure 2.—First-order rates of hydrolysis of monothionsuccinimides: A, N-C_4H_9; B, N-C_3H_7; C, N-C_2H_5; D, N-CH_3; E, N-*p*-$PhOCH_3$; F, N-*p*-$PhCH_3$; G, N-Ph; H, N-*p*-PhI; I, N-*p*-PhBr; J, N-*p*-PhCl; K, N-H; and L, N-*p*-$PhNO_2$.

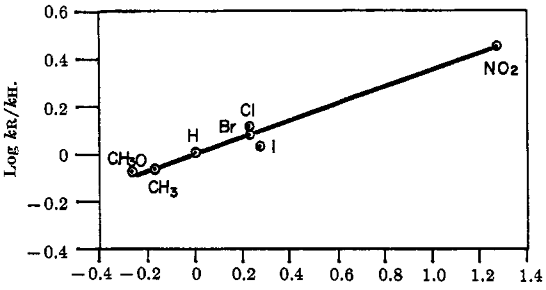

Figure 3.—A Hammett plot for the hydrolysis of C═S in N-arylmonothionsuccinimides. σ^- for *p*-nitro provided the best fit with the data.

It is well known from dipole moment studies that the C═S group is considerably more polar than the C═O group.[18] This increase in contribution of the charge-separated form has been related to the possi-

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[10] Derived from the rates of hydrolysis of the N-methyl (Ib) and the N-*p*-methoxyphenyl (Il) compounds.

[11] Derived from the rates of hydrolysis of the N-*n*-butyl (Ie) and the N-*p*-nitrophenyl (Im) compounds.

[12] S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

[13] E. L. Eliel and M. V. Rerick, *ibid.*, **82**, 1367 (1960); N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenberg, *J. Org. Chem.*, **27**, 4603 (1962).

[14] (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 184–189; (b) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

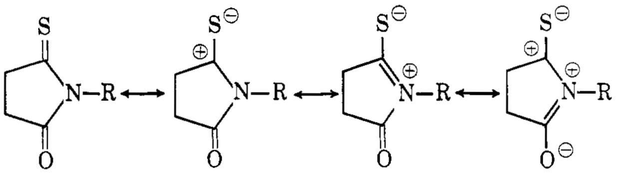
[15] J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 4; R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 1045 (1957); V. S. Hunig, H. Lehmann, and G. Grimmer, *Ann.*, **579**, 87 (1953); A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).

[16] Calculated by the least-squares treatment: A. G. Worthing and J. Geffner, "Treatment of Experimental Data," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 246.

[17] W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

[18] (a) M. H. Krackov, C. M. Lee, and H. G. Mautner, *J. Am. Chem. Soc.*, **87**, 892 (1965); (b) C. M. Lee and W. D. Kumler, *J. Org. Chem.*, **27**, 2052 (1962).

bility of octet expansion in sulfur[18a,19] and probably represents a major reason for the rapid hydrolysis to imide. In thionimides four resonance structures, **1**, **2**, **3**, and **4** contribute to the electronic character of the C=S group. Excluding steric effects introduced by R, the greater the contribution of resonance structure **3**, the slower should be nucleophilic attack by water since the effective positive character on carbon of the C=S group is decreased.[20] The fact that thionimides contain an additional C=O in conjugation with the electron pair on nitrogen (**4**) accounts for the greater instability of C=S in thionimides than in the related thionamides where the polarized form **2** (or **4**) would not exhibit as great an influence on the transition state with respect to the ground state of the molecule. Introduction of phenyl on the imide nitrogen provides another contributing structure **5**, the influence of which is to increase the net positive character at the reaction center. Placement of electron-withdrawing substituents in the *para* position increases the contribution made by resonance form **5** and the rate of hydrolysis is accelerated. A possible rationalization is dependent upon a rate-determining step involving formation of the *solvated*, tetrahedral intermediate III which rapidly collapses to imide II.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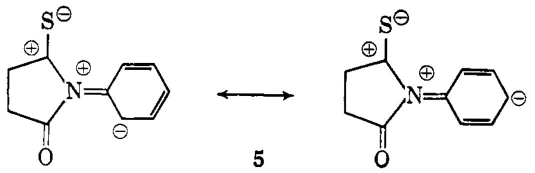
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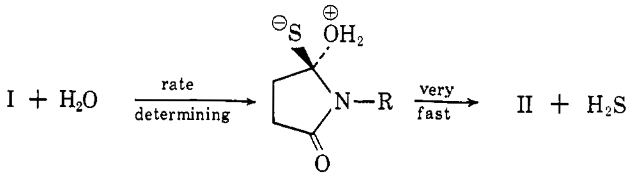

III

More detailed explanations concerning the minor deviations of the observed rates from the rate calculated using $\rho = +0.348$ and the σ constant for p-CH$_3$O and p-halogen derivatives must await more extensive studies involving temperature and pH profiles.[17] However, it does appear that the rates of hydrolysis parallel the electronegativity constant[21] for the p-halogen. This may indicate that polar effects are more important in these systems than would be reflected by the σ constant since +R contributions of *para* substituents are partially blocked by insertion of N between the aromatic ring and the reaction center.

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(19) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946); R. Rothstein, *J. Chem. Soc.*, 1558 (1940).

(20) Alternatively, the greater the resonance contribution by **2** (or **4**) the smaller should be the difference in energy between transition and ground states. This decrease in energy of activation would be reflected in an accelerated rate of hydrolysis.

(21) L. C. Pauling, "The Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1940, pp. 58, 59; E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp. 39–41; H. O. Pritchard and H. A. Skinner, *Chem. Rev.*, **55**, 745 (1955).

Reactions of Perfluoroalkyl Nitriles. V. Synthesis of Perfluoroacyl Imidates[1]

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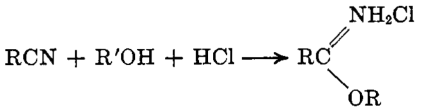
Stable alkyl perfluoroacyl imidates, R$_F$C(=NH)OR, were prepared by the base-catalyzed addition of methyl, isopropyl, and 2,2,2-trifluoroethyl alcohols to perfluoroalkyl nitriles. Tertiary alcohols did not produce imidates under the same conditions, apparently owing to steric hindrance and the tendency of the perfluoroalkyl nitriles toward trimerization. Phenol formed phenyl perfluoroacyl imidate. In a similar reaction the >N–OH group of propanone oxime added to perfluoroalkyl nitriles to produce O-(perfluoroalkylimidoyl)propanone oxime R$_F$C(=NH)ON=C(CH$_3$)$_2$.

The classical synthesis of imidates by Pinner[2] involved the condensation of a nitrile and an alcohol under anhydrous conditions in the presence of hydrogen chloride, and the imidate hydrochloride I was the product obtained. The free imidates were obtained by treating the hydrochlorides with a base.



$$\mathrm{RCN + R'OH + HCl \longrightarrow RC\begin{matrix}\nearrow \mathrm{NH_2Cl} \\ \searrow \mathrm{OR}\end{matrix}}$$

I

Steinkopf and Malinowski[3] studied the effect of negative substituents on nitriles and found that although many α- and β-halogen-substituted nitriles behaved normally in the Pinner synthesis, trichloroacetonitrile, nitroacetonitrile, dichloroacetonitrile, tribromoacetonitrile, and dichloronitroacetonitrile gave amides and no imidates. Dibromoacetonitrile gave both the amide and the imidate. These results were obtained using aliphatic alcohols. Houben[4] found that the Pinner synthesis was successful if aromatic

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(1) (a) This investigation was supported by Public Health Service Research Grant CA-05083 from the National Cancer Institute. (b) For previous paper in this series, see H. C. Brown and P. D. Schuman, *J. Org. Chem.*, **28**, 1122 (1963).

(2) A. Pinner and F. Klein, *Ber.*, **10**, 1889 (1877).

(3) W. Steinkopf and W. Malinowski, *ibid.*, **44**, 2898 (1911).

(4) J. Houben, *ibid.*, **59**, 2878 (1926).