Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; mol wt, 190. Found: C, 75.56; H, 7.49; mol wt, 190 (mass spectroscopy), 189 (titration).

Photolysis of 4,6-Dimethylbenzocyclobutenone *p*-Tosylhydrazone Sodium Salt.—The salt prepared from 3.14 g (0.01 mol) of 4,6-dimethylbenzocyclobutenone *p*-tosylhydrazone and 0.5 g (0.011 mol) of 54% sodium hydride dispersion in mineral oil was suspended in 250 ml of dry dioxane and irradiated for 30 min at 25° using a Hanovia 550-W mercury vapor insertion lamp. The reaction mixture was poured into 400 ml of water and extracted with three 75-ml portions of pentane and then three 75-ml portions of benzene. The combined organic extracts were dried over calcium chloride. Removal of solvent left 1.6 g of a brown gummy oil which was chromatographed on 80 g of acid-washed alumina. Elution with 8% ether–pentane gave a total of 108 mg of a white solid which melted at 188–189° after two recrystallizations from heptane. The infrared spectrum of this compound exhibited a weak peak at 1705, medium peaks at 1600, 1470, 1320, 1265, and 1040, and two strong peaks at 850 (very strong) and 725 cm^{-1}. The nmr spectrum showed three singlets at τ 3.23, 6.27, and 7.68, with a ratio of 0.98:1.00:3.09, respectively. Mass spectral analysis gave a molecular weight of 260. The material was assigned the structure of 1,1′-bi(4,6-dimethylbenzocyclobutylidene) on the basis of its elemental analysis and spectra.

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74; mol wt, 260. Found: C, 91.96; H, 8.08; mol wt, 260 (mass spectroscopy).

Elution with 25% ether gave 0.2 g of a yellow oil which could not be induced to crystallize. The infrared spectrum showed peaks at 3020, 2900, 1610, 1500, 1130, and 890 cm^{-1}, indicating that both aromatic and ether groups were present. This material was not characterized further. With 50–75% ether, a total of 0.4 g (14%) of 4,6-dimethylbenzocyclobutenyl *p*-tolyl sulfone, mp 102–104°, was isolated. The infrared spectrum of this material was identical with that of the product obtained by pyrolysis; a mixture melting point of the two samples was not depressed.

Registry No.—4,6-Dimethylbenzocyclobutenone, 6670-28-6; 4,6-dimethylbenzocyclobutenone (azine derivative), 20643-22-5; **1a**, 20643-23-6; **2**, 20678-94-8; **3**, 20643-24-7; **4**, 20643-25-8; **6**, 20643-26-9.

The Sulfation of Hydroxamic Acids

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The reaction of hydroxamic acids with sulfur trioxide–tertiary amine complexes proceeds by O sulfation to give crystalline water-soluble *t*-ammonium N-acylhydroxylamine-O-sulfonates. The reaction of a solution of any of these salts with a base generates an isocyanate function *in situ*. If the base employed is a primary or secondary amine, urea derivatives are obtained in good yield. Carbamates are formed by the decomposition of the salts with phenoxide ion. Aliphatic isocyanates are prepared in good yield by treatment of the salts with tertiary amine in the presence of an inert solvent.

The Lossen rearrangement is a useful method for the preparation of organic isocyanates.[1] This conversion is accomplished by treating a hydroxamic acid with a dehydrating agent such as acetic anhydride, phosphorus pentoxide, or a carbodiimide,[2] forming an isocyanate. The reaction proceeds through an O-ester intermediate which is converted either thermally or by base treatment to an isocyanate and the acid corresponding to the O ester or its conjugate base. The ease of the rearrangement has been shown to be directly related to the acidity of the departing acid.[3]

The preparation of sulfate esters of hydroxamic acids has been examined. These products have been found to undergo a facile Lossen rearrangement to form isocyanates.

Discussion

Sulfation Reactions.—Treatment of benzohydroxamic acid with trimethylamine–sulfur trioxide gave a crystalline, water-soluble product in moderate yield.

$$C_6H_5CONHOH + R_3N{:}SO_3 \longrightarrow C_6H_5CONHOSO_3HNR_3$$

I, $R_3 = (CH_3)_3$
II, $R_3 = C_5H_5$

Elemental analysis and the nmr spectrum of this material indicated a 1:1 adduct. The latter in deuterium oxide contained a nine-proton singlet at 2.68 ppm [$DN(CH_3)_3^+$] and a five-proton multiplet (C_6H_5) centered at 7.45 ppm. The infrared spectrum contained bands at 3225 cm^{-1} (NH), 1663 cm^{-1} (C=O), and 1200 and 1256 cm^{-1} (O=S=O).[4] Dissolution of the adduct in 5% ammonium hydroxide solution at room temperature gave an 82% yield of phenylurea, while treatment with hot 1.5 *N* potassium hydroxide solution gave a 68% yield of *sym*-diphenylurea. These data are consistent with the O-sulfation product (I).

A similar reaction was performed with the more reactive sulfating agent pyridine–sulfur trioxide.[5] The adduct (II) was obtained in 80% yield, employing conditions which were far milder than those required with the trimethylamine reagent. Owing to the high reactivity of this complex, further studies of the scope of the sulfation reaction were conducted with this material.

A number of other mono- and dihydroxamic acids have been treated with pyridine–sulfur trioxide to form the pyridinium N-acylhydroxylamine-O-sulfonates in yields of 70 to 89%. The data are summarized in Table I. With the exception of the stearic acid derivative, all of the salts are water soluble and quite stable in aqueous solution.[6] Another characteristic of these salts is the presence in their infrared spectra of two strong bands between 1200 and 1300 cm^{-1}. Generally, they occur at 1250 and 1300 ± 10 cm^{-1}. These are attributed to the symmetric and asymmetric stretching vibrations of the sulfonic acid function.[4]

(1) R. G. Arnold, J. A. Nelson, and J. J. Verbane, *Chem. Rev.*, **57**, 47 (1957); H. L. Yale, *ibid.*, **33**, 209 (1943).

(2) D. G. Hoare, A. Olson, and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **90**, 1638 (1968).

(3) R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1959.

(5) E. E. Gilbert, "Sulfonation, Related Reactions," Interscience Publishers, Inc., New York, N. Y., 1965, p 12.

(6) A 10% aqueous solution of II underwent less than 5% decomposition during 10 days at room temperature.

TABLE I

SULFATION OF HYDROXAMIC ACIDS

$$RCONHOH + C_5H_5N{:}SO_3 \longrightarrow RCONHOSO_3HNC_5H_5$$

R	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	75	140–141	48.64	4.08	9.45	48.23	4.32	9.26
p-Cl-C_6H_4[a]	88	172–174	43.57	3.35	8.47	43.81	3.47	8.40
$CH_2{=}C(CH_3)$[b]	70	109–110	41.53	4.64	10.76	41.28	4.60	10.33
n-C_7H_{15}[c]	76	109–110	49.03	6.96	8.79	48.96	6.82	8.46
n-$C_{11}H_{23}$[c]	85	119–121	54.55	8.02	7.50	54.44	8.08	7.44
n-$C_{17}H_{35}$[c]	71	116–117	60.22	9.23	6.10	60.16	9.32	6.01
$CH_2{=}CH(CH_2)_8$[d]	75	111–112	53.60	7.25	7.82	53.75	7.49	7.79
$(CH_2)_4$[e]	75	156–157	38.86	4.44	11.33	38.77	4.39	11.24
$(CH_2)_6$[e]	95	160–161	41.37	5.01	10.72	40.99	5.17	10.84

[a] Reference 8. [b] H. Smith, British Patent 852,176 (Oct 26, 1960). [c] Y. Inone and H. Yukawa, *Bull. Chem. Soc. Jap.*, **16**, 510 (1940); *Chem. Abstr.*, **35**, 731[2] (1941). [d] G. Kurono, T. Sakai, and Y. Kagotam, *Yakugaku Zasshi*, **84**, 463 (1964); *Chem. Abstr.*, **61**, 4968 (1964). [e] C. D. Hurd and D. G. Batteron, *J. Org. Chem.*, **11**, 207 (1946).

The preference for O sulfation of hydroxamic acids can be anticipated from a consideration of the reactivity of these substrates with acylating and sulfonating agents.[7]

Preparation of Ureas and Carbamates.—The behavior of I with potassium and ammonium hydroxide indicated that phenyl isocyanate was being formed in solution. Upon generation of the anion (III), isocyanate should form rapidly by loss of sulfate.[8]

$$\underset{\text{III}}{C_6H_5CONOSO_3^-} \longrightarrow C_6H_5NCO + SO_4^{2-}$$

When a salt was added to an aqueous solution containing 2 to 3 equiv of primary or secondary amine, the isocyanate formed was intercepted by the amine, yielding a urea derivative. Representative amines used in

$$RCONHOSO_3HNR'_3 + R''R'''NH \longrightarrow RNHCONR''R'''$$

this reaction include methyl, *n*-butyl, dimethyl, and diethyl. With multifunctional amines such as ethanolamine and D-glucamine, urea derivatives were formed to the virtual exclusion of urethans. With ethylenediamine, a diurea was formed. In some instances, such as ethylenediamine and D-glucamine, it was not desirable to use an excess of amine. In these cases, a tertiary amine such as triethyl- or trimethylamine was added to assist isocyanate formation. A total of 20 examples of urea formation using this procedure have been recorded. The yields range from 60 to 93% with the majority being 80% or greater (see Experimental Section).

The addition of these salts to an aqueous solution of phenoxide ion gave the corresponding phenyl carbamates.

$$RCONHOSO_3HNR_3' + C_6H_5OK \longrightarrow RNHCOOC_6H_5$$

The behavior of the methacrylic acid derivative (IV) in basic media was examined. When this material was added to potassium hydroxide solution, an 82% yield of acetone, isolated as its 2,4-dinitrophenylhydrazone derivative, was obtained. The rearrangement generated a vinyl isocyanate derivative which then underwent hydrolysis to form acetone.

(7) F. M. Hershenson, L. Bauer, and K. F. King, *J. Org. Chem.*, **33**, 2543 (1968), and references cited therein.

(8) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **77**, 3651 (1955).

The decomposition of IV with diethylamine gave a 61% yield of urea derivative (V). The nmr spectrum

$$\underset{\text{IV}}{CH_2{=}C(CH_3)CONHOSO_3HC_5H_5N} + R_2NH \longrightarrow (CH_3)_2C{=}NCONR_2$$

V, R = C_2H_5
VI, R = $CH_2CH{=}CH_2$

$$(CH_3)_2C{=}NCONR_2 \rightleftarrows CH_2{=}C(CH_3)NHCONR_2$$

of this material indicated that it existed exclusively in the form of the C=N tautomer. The spectrum (neat) contained a pair of overlapping triplets at 1.03 and 1.13 ppm (J = 7.0 Hz) and a pair of overlapping quartets at 3.19 and 3.38 ppm (J = 7.0 Hz). These are assigned to the methyl and methylene groups, respectively, of the N-ethyl groups. Their magnetic nonequivalence is due to restricted rotation about the nitrogen–carbonyl bond.[9] A pair of singlets at 1.97 and 2.03 ppm are also present in the spectrum. These are assigned to the methyl groups of the isopropylidene function. This nonequivalence results from *syn* and *anti* isomerism about the imine double bond.

The position of the equilibrium between the tautomers was found to be solvent independent when examined by nmr. The spectra were recorded in carbon tetrachloride, deuterated acetone, and deuterated dimethyl sulfoxide. No change was noted in the spectra except that the methyl groups of the isopropylidene coalesced to a singlet at 2.00 ppm. Contributions from the vinylurea tautometer were not found in any of the spectra.

The urea derivative (VI) from diallylamine was formed in 63% yield. The equilibrium position of this product was the same as that of the diethyl derivative on the basis of nmr data.

The thermal isomerization of vinylureas to their ketimine derivatives has been demonstrated by Sato.[10] Since the infrared spectra of crude products before distillation are essentially identical with that of the pure product, the isomerization is probably also base catalyzed owing to the presence of pyridine and excess amine in the reaction mixture. Attempts to prepare a similar derivative using ethylenimine were unsuccessful. The crude product was quite unstable, and it decomposed to a dark brown resinous solid.

Preparation of Isocyanates.—The *in situ* formation of an isocyanate by treatment of a sulfated hydroxamic

(9) R. H. Bible, "Interpretation of NMR Spectra: An Empirical Approach," Plenum Press, New York, N. Y., 1965, p 66.

(10) M. Sato, *J. Org. Chem.*, **26**, 770 (1961).

acid with a tertiary amine was employed in the preparation of certain carbamate and urea derivatives. A similar technique was employed for the isolation of the isocyanates. The sulfated hydroxamic acid was treated with a tertiary amine in aqueous solution in the presence of an inert solvent such as petroleum ether or carbon tetrachloride. As the isocyanate was formed it was extracted into the organic layer. Work-up of the reaction gave the crude isocyanate, which was purified by distillation.

$$RCONHOSO_3HC_5H_5N + R'_3N \longrightarrow RNCO + C_5H_5N(NR'_3)H_2SO_4$$

This procedure is quite satisfactory for the preparation of aliphatic isocyanates. Yields ranging from 63 to 75% were obtained. The fatty acid derivatives often produced emulsions, which made it difficult to separate the organic phase. In most cases, this problem was overcome by addition of a small amount of acetonitrile to the reaction mixture. With the stearic acid derivative, however, the problem was too severe, and prevented isolation of heptadecyl isocyanate. The infrared spectrum of the crude mixture showed bands assignable to isocyanate and urea.

The preparation of phenyl isocyanate by this procedure gave only a 20% yield of product. In addition, a 45% yield of *sym*-diphenylurea was also formed. These data reflect the greater reactivity of aromatic *vs.* aliphatic isocyanates.

A number of unsuccessful attempts were made to prepare aliphatic diisocyanates by this method. In all cases, polymeric materials were obtained.

Experimental Section

Nuclear magnetic resonance spectra were run on a Varian A-60 spectrometer in the appropriate solvent, with tetramethylsilane as an internal or external standard. Infrared spectra were recorded on a Beckman Model IR-12 or a Perkin-Elmer 137 infrared spectrophotometer. Melting points were obtained using a Thomas–Hoover melting point apparatus and are uncorrected.

Preparation of Starting Materials.—The hydroxamic acids were prepared according to literature procedures. The pyridine sulfur trioxide was prepared according to the method of Baumgarten.[11] The trimethylamine sulfur trioxide was obtained from the American Cyanamid Co., New York 20, N. Y.

Sulfation of Benzohydroxamic Acid with Trimethylamine–Sulfur Trioxide.—A mixture of 40.0 g (0.29 mol) of benzohydroxamic acid and 40.0 g (0.29 mol) of trimethylamine–sulfur trioxide was slurried in 300 ml of acetone at ambient temperature for 5 days. The mixture was filtered and evaporated to dryness. The residue was dissolved in 200 ml of hot ethanol and cooled to give 33 g (0.12 mol, 41%) of trimethylammonium N-benzoylhydroxylamine-O-sulfonate (I), mp 150–154°. An analytical sample was prepared by recrystallization from ethanol: mp 155–156°.

Anal. Calcd for $C_{10}H_{16}N_2O_5S$: C, 43.46; H, 5.83; N, 10.13. Found: C, 43.38; H, 5.95; N, 10.13.

General Procedure for the Sulfation of Hydroxamic Acids with Pyridine–Sulfur Trioxide.—A solution of 0.1 mol of hydroxamic acid (or 0.22 mol for dihydroxamic acids) and 0.11 mol of pyridine–sulfur trioxide in 150 ml of acetonitrile was refluxed with stirring for 0.5 to 4.0 hr. The solvent was evaporated at aspirator pressure and the residue was purified by recrystallization from ethanol or acetonitrile. Similar yields may be obtained by keeping the reaction mixture at room temperature for about 18 to 24 hr. With the 10-undecylenic acid derivative, this latter procedure was preferred.

Preparation of Ureas.—The sulfated hydroxamic acid was added portionwise or as a 30–50% aqueous solution to a stirred solution of 2 to 3 equiv of ammonia, or primary or secondary amine in water. (The amine concentration in the aqueous solution was about 5–10% by weight.) The reaction temperature was maintained at 20–30° by external cooling. After addition was complete, the mixture was stirred at ambient temperature for 0.5 hr and filtered. The residue was washed with water and air dried. Using this procedure, the following ureas were prepared: $C_6H_5NHCONH_2$, mp 146–148°, 82%; $C_6H_5NHCON(C_2H_5)_2$, mp 84–85°, 75% (trimethylammonium salt), 89% (pyridinium salt); $C_6H_5NHCONHC_4H_9$-*n*, mp 126–127°, 83% (trimethylammonium salt), 94% (pyridinium salt); $C_6H_5NHCON(CH_3)_2$, mp 127–128°, 87% (trimethylammonium salt); $C_6H_5NHCONHCH_2CH_2OH$, mp 122–123°, 72% (pyridinium salt); *n*-C_7H_{15}NHCONHC$_4$H$_9$-*n*, mp 56–57°, 78%; *p*-Cl-$C_6H_4NHCONHC_4H_9$-*n*, mp 172–174°, 86%; *p*-Cl-$C_6H_4NHCON(C_2H_5)_2$, mp 114–116°, 88%; *n*-$C_{11}H_{23}NHCONHCH_3$, mp 66–67°, 81%; *n*-$C_{17}H_{35}NHCONHCH_3$, mp 99–100°, 89%; CH_2=CH—$(CH_2)_8$NHCONHCH$_2$, mp 69–70°, 82%; $[(CH_2)_2NHCONHCH_3]_2$, mp >280°, 79%; $[(CH_2)_3NHCONHCH_3]_2$, mp 201–203°, 91%; $[(CH_2)_3NHCONHC_4H_9$-$n]_2$, mp 192–194°, 88%.

Preparation of 1,1-Diethyl-3-phenylurea Using Trimethylamine as Catalyst.—Pyridinium N-benzoylhydroxylamine-O-sulfonate (3.0 g) was added portionwise to a stirred solution of 4.8 g of 25% trimethylamine in methanol and 1.0 g of diethylamine in 18 ml of water maintained at 20–25° by a cooling bath. After addition was complete, the mixture was stirred at room temperature for 0.5 hr and filtered. The residue was washed with water and air dried to give 1.4 g of product (75%), mp 84–86°. Using the same type of procedure $[C_6H_5NHCONHCH_2]_2$, mp 276–277°, and D-gluco-$C_6H_5NHCONHCH_2(CHOH)_4CH_2OH$, mp 173–174°, were obtained in yields of 61 and 71%, respectively.

Preparation of Phenyl Carbanilate.—Trimethylammonium N-benzoylhydroxylamine-O-sulfonate (3.0 g) was added portionwise at room temperature to a stirred solution of 5.8 g of potassium phenoxide in 25 ml of water. After addition was complete, the mixture was stirred at room temperature for 0.5 hr, filtered, and air dried to give 1.85 g (79%) of product mp 122–123°. Using this procedure, *n*-$C_7H_{15}NHCOOC_6H_5$, mp 36–37°, was prepared in 71% yield.

Reaction of Pyridinium N-Methacryloylhydroxylamine-O-sulfonate with Potassium Hydroxide.—Compound IV, 2.6 g (0.01 mol), was added portionwise with cooling and stirring to 10 ml of 3 *N* potassium hydroxide solution. After addition was complete, this solution was added slowly with cooling and stirring to a solution of 3.0 g of 2,4-dinitrophenylhydrazine in 15 ml of concentrated sulfuric acid, 25 ml of water, and 50 ml of absolute ethanol. The solution was then chilled and filtered to give 1.95 g (82%) of acetone 2,4-dinitrophenylhydrazone, mp 122–124°. A mixture melting point with an authentic sample was undepressed.

Preparation of 1,1-Dialkyl-3-isopropylideneureas.—A 30% aqueous solution of IV was added dropwise to a vigorously stirred solution of 3 equiv of secondary amine in 200 ml of chloroform cooled in an ice water bath. After addition was complete, the chloroform layer was separated and the aqueous layer was extracted with chloroform. The chloroform extracts were combined, dried, and evaporated to give the crude product, which was purified by vacuum distillation. The following ureas were prepared.

(a) 1,1-Diethyl-3-isopropylideneurea[12] (61%): bp 122° (19 mm); n^{26}D 1.4562.

Anal. Calcd for $C_8H_{16}N_2O$: N, 17.93. Found: N, 17.87.

(b) 1,1-Diallyl-3-isopropylideneurea (63%): bp 65° (0.05 mm); n^{26}D 1.4790; nmr (neat) 2.00 [s, 6 H, $(CH_3)_2C$=], 3.83 and 4.05 (d, 4 H, J = 5.0 Hz, CH_2N), and 4.90–6.30 ppm (complex m, 6 H).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.62; H, 8.95; N, 15.54. Found: C, 66.25; H, 8.87; N, 15.88.

General Procedure for the Preparation of Isocyanates.—A 25% aqueous solution containing 0.25 mol of trimethylamine was added dropwise to a vigorously stirred mixture of a solution of 0.1 mol of N-acylhydroxylamine-O-sulfonic acid *t*-ammonium salt in 150 ml of water and 250 ml of carbon tetrachloride or petroleum ether cooled in an ice bath. After addition was complete, the mixture was stirred at ice-bath temperature for 0.25 hr and then diluted with water. A 100- to 150-ml portion of acetonitrile was added (this was not necessary in the preparation of *n*-heptyl isocyanate or phenyl isocyanate) and the organic layer was separated. The aqueous phase was reextracted with the organic

(11) P. Baumgarten, *Ber.*, **59**, 1166 (1926).

(12) J. B. Dickey, U. S. Patent 2,592,254 (April 8, 1952).

solvent, and the extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to yield the crude isocyanate, which was purified by distillation. The following isocyanates were prepared by this procedure: (a) *n*-heptyl[13] (63%), bp 83–84° (23 mm), $n^{26}D$ 1.4326; (b) *n*-undecyl[13] (54% from petroleum ether, 75% from carbon tetrachloride), bp 144° (18 mm), $n^{26}D$ 1.4358; (c) 9-decenyl[13] (70%), bp 127–128° (17 mm), $n^{26}D$ 1.4446; (d) phenyl (20%), identified by gpc and infrared spectroscopy.

Registry No.—I, 20633-41-4; $C_6H_5NHCONH_2$, 64-10-8; $C_6H_5NHCON(C_2H_5)_2$, 1014-72-8; $C_6H_5NHCONH$-C_4H_9-*n*, 3083-88-3; $C_6H_5NHCON(CH_3)_2$, 101-42-8; $C_6H_5NHCONHCH_2CH_2OH$, 3747-47-5; *n*-$C_7H_{15}NHCONHC_4H_9$-*n*, 20633-46-9; *p*-$ClC_6H_4NHCONHC_4H_7$-*n*, 6333-41-1; *p*-$ClC_6H_4NHCON(C_2H_5)_2$, 15737-37-8; *n*-$C_{11}H_{23}NHCONHCH_3$, 20633-56-1; *n*-$C_{17}H_{35}NHCONHCH_3$, 20633-49-2; $CH_2{=}CH{=}(CH_2)_8NHCONHCH_3$, 20633-50-5; $[(CH_2)_2NHCONHCH_3]_2$, 20633-51-6; $[(CH_2)_3NHCONHCH_3]_2$, 20633-52-7; $[(CH_2)_3NHCONHC_4H_9$-$n]_2$, 20633-53-8; II, 20633-55-0; $[C_6H_5NHCONHCH_2]_2$, 849-97-8; D-gluco-$C_6H_5NHCONHCH_2(CHOH)_4CH_2OH$, 20642-67-5; phenyl carbanilate, 4930-03-4; *n*-$C_7H_{15}NHCOOC_6H_5$, 2594-41-4; 1,1-diallyl-3-isopropylideneurea, 20642-56-2.

(13) V. E. Shoshoua, W. Sweeney, and R. F. Trietz, *J. Amer. Chem. Soc.*, **82**, 866 (1960).

The Effect of the Imidazole Group on the Hydrolysis of N-[2-(4-Imidazolyl)ethyl]phthalimide[1a]

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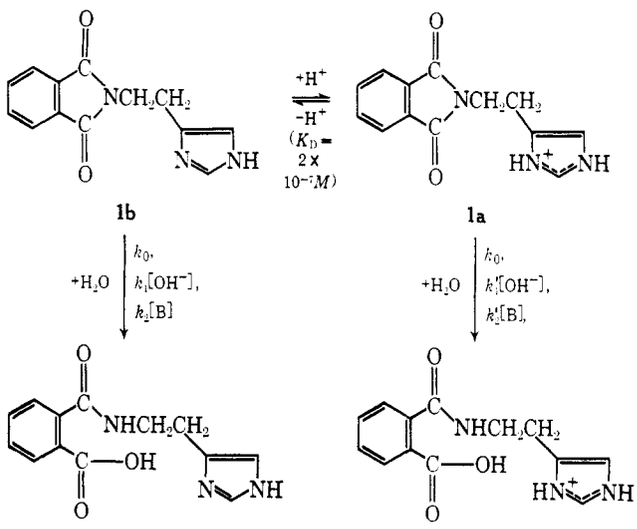
The pH dependencies (at 25°) of the pseudo-first-order rate constants for the hydrolysis (to phthalamic acids) of N-[2-(4-imidazolyl)ethyl]phthalimide (**1**), N-(2-trimethylaminoethyl)phthalimido bromide (**2**), N-(3-trimethylaminopropyl)phthalimido bromide (**3**), and N-methylphthalimide (**4**) were determined. The cationic imides **2** and **3** are most susceptible to hydroxide ion catalyzed hydrolysis. Below pH 7, however, **1** hydrolyzes most rapidly. This effect was ascribed to the neighboring imidazole residue functioning as a general base in catalyzing attack by water. A deuterium oxide solvent isotope effect of 2.1 is associated with this process. The possibility that this effect reflects the susceptibility of the protonated form of **1** to attack by hydroxide ion was deemed unlikely, since the second-order rate constant for this reaction would be 333 $sec^{-1}\,M^{-1}$, while the second-order rate constants for the hydroxide ion catalyzed hydrolysis of cationic imides **2** and **3** with their positive charges closer to the carbonyl carbon atom are 91 and 41 $sec^{-1}\,M^{-1}$, respectively. Also, cationic imides **2** and **3** are susceptible to direct attack by water, whereas the protonated form of **1** is much less susceptible to attack by water. It is unlikely that a neighboring imidazole residue functions as a general acid in catalyzing attack by hydroxide ion, since the calculated rate constant for this process is not significantly lowered by deuterium oxide. The first-order rate constants for intramolecular catalysis of the hydrolysis of **1** by the neighboring imidazole group (2.9×10^{-5} sec^{-1}) was found to be similar in magnitude to the second-order rate constant for the imidazole-catalyzed hydrolysis of **4** (2.0×10^{-5} $sec^{-1}\,M^{-1}$).

Neighboring amide groups are potent nucleophiles, and under physiological conditions amide groups can enhance the rate of hydrolysis of adjacent ester and amide residues by several orders of magnitude.[2] Often, the rate-limiting step in these reactions is the hydrolysis of the imide intermediate. Because of the possible importance of the amide group in enzymically catalyzed hydrolytic reactions, we have investigated the effect of the imidazole group on the hydrolysis of N-[2-(4-imidazolyl)ethyl]phthalimide (**1**) (Scheme I).

SCHEME I



Experimental Section

Materials.—N-Methylphthalimide was obtained from Eastman Organic Chemicals and recrystallized twice from 95% ethanol: mp 134–135° cor (lit.[3] mp 133–134°).

N-(2-Trimethylaminoethyl)phthalimido bromide was prepared by mixing 5.08 g (20 mmol) of N-(2-bromoethyl)phthalimide (from Eastman Organic Chemicals) dissolved in 75 ml of dioxane with 5.4 g (91 mmol) of trimethylamine (from Eastman Organic Chemicals) dissolved in 150 ml of dioxane. After the mixture stood overnight at room temperature, the precipitate was collected and recrystallized three times from 95% ethanol: dec pt 290–291° cor. *Anal.* Calcd for $C_{13}H_{17}N_2O_2Br$: C, 49.85; H, 5.47; N, 8.95; Br, 25.52. Found: C, 49.59; H, 5.46; N, 8.75; Br, 25.20.

N-(3-Bromopropyl)phthalimide was prepared from potassium phthalimide (from Eastman Organic Chemicals) and 1,3-dibromopropane (from CalBiochem) according to the method of Gabriel:[4] mp 71–73° cor (lit.[4] mp 72–73°).

N-(3-Trimethylaminopropyl)phthalimido bromide was prepared by mixing 2.68 g (10 mmol) of N-(3-bromopropyl)phthal-

(1) (a) This study was supported by a grant (AM-09276) from the National Institutes of Health, U. S. Public Health Service. (b) To whom inquiries regarding this work should be made.

(2) S. C. K. Su and J. A. Shafer, *J. Org. Chem.*, in press, and references therein.

(3) M. Freund and H. Beck, *Ber.*, **37**, 1942 (1904).

(4) S. Gabriel and J. Weiner, *ibid.*, **21**, 2669 (1888).