The Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with Tetrahydrofuran and Related Cyclic Ethers[1]

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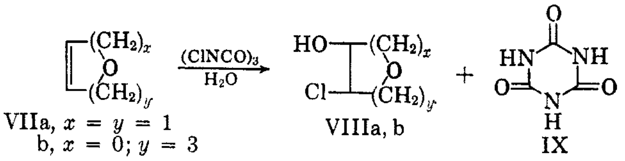
N-Halogen compounds have been extensively used as allylic halogenating agents or oxidizing agents. Well-known examples are N-bromosuccinimide (I), N-bromoacetamide (II), and N-bromohydantoin (III).[3] The structural similarity of these compounds with trichloroisocyanuric acid (IV) is apparent; moreover, it can be seen that IV has three positive halogens available per molecule.

Ziegler has shown that N-bromosuccinimide and trichloroisocyanuric acid react with cyclohexene to give allylic substitution, which suggests free-radical-type reactions.[4] α-Halogenation of saturated cyclic ethers, such as tetrahydrofuran, by common N-halo compounds has not been reported in the literature. Susceptibility to such halogenation would be expected from resonance stabilization of the α free radicals by the alkoxy substitution.[5]

Trichloroisocyanuric acid has served as an oxidizing agent for conversion of secondary alcohols to carbonyls[6] in the presence of water, possibly through the intermediacy of hypochlorous acid. By the same intermediate, hypohalogenation of olefins should be possible. Trichloroisocyanuric acid has been shown to liberate hypochlorous acid in the presence of water.[7] Neither oxidation of cyclic ethers to lactones nor hypohalogenation of unsaturated cyclic ethers by trichloroisocyanuric acid has been reported in the literature. To study halogenation, oxidation, and hypohalogenation reactions utilizing compound IV, we investigated its reaction with tetrahydrofuran, tetrahydropyran, and the related monounsaturated cyclic ethers. Halogenation of tetrahydrofuran[8] and tetrahydropyran[9] has been reported to yield various halogenated cyclic ethers. Air oxidation of tetrahydrofuran[10] has been reported to yield γ-butyrolactone *via* the hydroperoxide. Hypochlorous acid has been reported to give chlorohydrins with 2,5-dihydrofuran[11] and 5,6-dihydro-4H-pyran.[12]

The reaction of trichloroisocyanuric acid (IV) with tetrahydrofuran and tetrahydropyran, at or slightly above room temperature, yielded *trans*-2,3-dichlorotetrahydrofuran and *trans*-2,3-dichlorotetrahydropyran (Va and Vb), respectively, as the major halogenated products. By a simple modification, namely, the addition of water, the reaction may be used for oxidation of an α-methylene group to a carbonyl group. This affords a conversion of cyclic ethers to cyclic esters instead of a conversion of cyclic ketones to cyclic esters as given in the Baeyer–Villiger reaction. This reaction yielded the lactones (VIa and VIb) as well as other products which were not investigated.

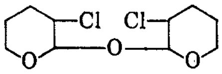
Hypohalogenation can also be effected by the use of trichloroisocyanuric acid in the presence of water. Cyclic ethers which were chosen to illustrate the hypohalogenation reaction were 2,5-dihydrofuran (VIIIa) and 5,6-dihydro-4H-pyran (VIIb). By these reactions *trans*-3-chloro-4-hydroxytetrahydrofuran (VIIIa) and *trans*-2-hydroxy-3-chlorotetrahydropyran (VIIIb) were obtained in about 30% yield. In addition to the latter product 5,6-dihydro-4H-pyran also yielded about 30% (3-chlorotetrahydropyranyl-2) ether (X). Support for structure X was obtained by the preparation of an authentic sample of this compound by hydrolytic treatment of 2,3-dichlorotetrahydropyran with water according to the procedure given by Paul.[13] The 2,3-dichlorotetrahydropyran in this conversion was prepared as described above by chlorination of tetrahydropyran with trichloroisocyanuric acid. The (3-chlorotetrahydropyranyl-2) ethers prepared in these reactions were identical.



VIIa, $x = y = 1$
b, $x = 0; y = 3$

VIIIa, b

IX



X

Experimental Section[14]

This trichloroisocyanuric acid procedure represents a simple, convenient method for chlorination without the use of a cylinder or generation of chlorine gas. Trichloroisocyanuric acid, which is an inexpensive, commercially available compound,[15] was added to an excess of the cyclic ether. Cyanuric acid (IX), which precipitated practically quantitatively, was removed by filtration, and the product was isolated by simple distillation techniques.

Materials.—1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine (trichloroisocyanuric acid) can be prepared by the procedure de-

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[1] Presented at the first regional meeting of the American Chemical Society, Kansas City, Mo., Nov 1965.

[2] Taken in part from the M.S. thesis of P. L. S., Kansas State College of Pittsburgh, 1965.

[3] R. Filler, *Chem. Rev.*, **63**, 21 (1963).

[4] K. Ziegler, *et al.*, *Ann.*, **551**, 80 (1942).

[5] R. E. Lovins, *et al.*, *J. Org. Chem.*, **30**, 1577 (1965).

[6] F. Mukawa, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **78**, 450 (1957); *Chem. Abstr.*, **53**, 5338 (1959).

[7] A. P. Brady, *et al.*, *J. Am. Chem. Soc.*, **85**, 3101 (1963).

[8] (a) L. Crombie and S. H. Harper, *J. Chem. Soc.* 1714 (1950); (b) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Co., New York, N. Y., 1964, pp 367, 370.

[9] L. Crombie, *et al.*, *J. Chem. Soc.*, 136 (1956).

[10] (a) M. Maincon and P. Chassaing (to Usines de Melle), U. S. Patent 2,481,765 (1949); *Chem. Abstr.*, **44**, 1532 (1950); (b) A. Robertson, *Nature*, **162**, 153 (1948); *Angew. Chem.*, **61**, 344 (1949); *Chem. Abstr.*, **42**, 8792 (1948); (c) Usines de Melle, British Patent 614,392 (1948); *Chem. Abstr.*, **44**, 1531 (1948); also French Patent 990,212 (1951); *Chem. Abstr.*, **50**, 7126 (1956).

[11] W. Reppe, *et al.*, *Ann.*, **596**, 97 (1955); *Chem. Abstr.*, **50**, 16777 (1956).

[12] P. A. Hawkins and N. Bennett, British Patent 570,160 (1945); *Chem. Abstr.*, **40**, 5072 (1946).

[13] R. Paul, *Compt. Rend.*, **218**, 122 (1944).

[14] (a) Microanalysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. A Perkin-Elmer Model 137 was used to record infrared spectra and nmr spectra were determined on a Varian A-60 spectrometer. Gas chromatographic separations were made on an A-90-P Aerograph. (b) All yields are based on the amount of trichloroisocyanuric acid with the exception of the hypohalogenation reactions in which trichloroisocyanuric acid was used in excess.

[15] Trichloroisocyanuric acid was received as a research sample from the Monsanto Co.

scribed by Close[16] or by the procedure of Merkel and Claren.[17] The purity of product we obtained in these runs varied somewhat, and the yields were about 90% with melting points ranging from 185 to 230°. Ratios of reaction products obtained varied with the quality of the trichloroisocyanuric acid thus prepared. It was found that trichloroisocyanuric acid was available from the Monsanto Co., and all of the following procedures described employed the same batch of commercial trichloroisocyanuric acid (mp 225–235°, chlorine content 90%). The tetrahydrofuran was dried and purified by refluxing over lithium aluminum hydride for a 2–4-hr period followed by distillation. Alternatively, the ethers were purified by refluxing over sodium for 2–4 hr followed by distillation to give tetrahydrofuran (bp 65–66°) and tetrahydropyran (bp 87–88°). The monounsaturated cyclic ethers were purified by distillation to give 2,5-dihydrofuran (bp 65–67°) and 5,6-dihydro-4H-pyran (bp 84–85°).[18] Acetone containing up to 1% water was used. Sufficient acetone was used to provide enough water to permit the trichloroisocyanuric acid to function as an oxidizing or hypohalogenating agent.

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with Tetrahydrofuran.—To 100 ml (88.80 g, 1.23 moles) of tetrahydrofuran stirred at 0°, 46.48 g (0.20 mole) of trichloroisocyanuric acid was added in small amounts over a 24-hr period. The reaction proceeded smoothly with the appearance of a heavy, white precipitate of cyanuric acid. Since the reaction is quite exothermic, it must be moderated by cooling or by the use of an adequate amount of ether. Inadequate amounts of the ether may lead to a reaction which is violent and boils out the top of the condenser. In one case, in which trichloroisocyanuric acid was wet with the tetrahydrofuran, an explosion occurred. The reaction time above can be cut down by addition of 6–10 g of trichloroisocyanuric acid to 100 ml of tetrahydrofuran. The reaction mixture gets hot, comes to reflux, and quantitatively precipitates cyanuric acid, completing the reaction in about 15 min. The other chlorinations, oxidations, and hypohalogenations described are also exothermic and must be moderated in a similar fashion. After the addition of the trichloroisocyanuric acid was completed, the reaction mixture was allowed to stir overnight. Nitrogen was then passed through the reaction mixture for about 3–4 hr or until only a weak litmus test for acid was observed by holding moist litmus above the condenser. The cyanuric acid (24.3 g) was removed by filtration. The excess ether was removed, and the product was distilled on a spinning-band column to give 11.05 g (26%) of colorless *trans*-2,3-dichlorotetrahydrofuran (Va), bp 59–61° (18 mm), $n^{20}\mathrm{D}$ 1.4845. These physical constants agree with those reported in the literature.[9] A sample of authentic Va prepared by chlorination of tetrahydrofuran, according to the procedure of Crombie and Harper,[8a] gave an infrared spectrum which was identical with that of our product. The chlorinated product also showed a tendency toward decomposition, in agreement with the observation by Crombie and Harper. A reddish color, which was not removed by redistillation, developed after the sample sat at room temperature for about 3 days.

A sample at −10° did not develop any color after being allowed to sit for 3 weeks. Other evidence for decomposition was the coloration of the product on the metallic components of the spinning-band column, if such contact was made, and decomposition of the product during an attempted isolation by gas chromatography.

Anal. Calcd for $C_4H_6Cl_2O$: C, 34.07; H, 4.29. Found: C, 34.76; H, 4.37.

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with Tetrahydropyran.—To 60 ml (51.24 g, 0.59 mole) of tetrahydropyran stirred at 0°, 23.24 g (0.10 mole) of trichloroisocyanuric acid was added in small amounts over a period of 24 hr. A white precipitate of cyanuric acid was observed a short time after adding the first portion of trichloroisocyanuric acid. After the 24-hr addition was completed, the reaction mixture was stirred overnight. The reaction period may be shortened to a few minutes by use of less ether. The cyanuric acid (12.30 g, 95%) was removed by filtration and nitrogen was passed through the filtrate for about 3–4 hr or until a very faint test for acid was obtained by use of moist litmus. The excess ether was removed, and the product was distilled on a spinning-band column to give 6.58 g (28%) of colorless *trans*-2,3-dichlorotetrahydropyran (Vb), bp 89–90° (20 mm), $n^{20}\mathrm{D}$ 1.4950. These physical constants agree with those reported in the literature.[9] An analytical sample of Vb was obtained by gas chromatography. Gas chromatography indicated several other minor products which were not further investigated. The column used was a 5-ft, SS 30%, Q-Fl on 60–80 mesh Chromosorb P. The infrared spectrum of the compound showed the same characteristic peaks as an authentic sample of *trans*-2,3-dichlorotetrahydropyran.

Anal. Calcd for $C_5H_8Cl_2O$: C, 38.74; H, 5.22; Cl, 45.74. Found: C, 38.50; H, 4.98; Cl, 45.84.

Hydrolysis of 2,3-Dichlorotetrahydropyran to Give (3-Chlorotetrahydropyranyl-2) Ether.—Hydrolysis of 2,3-dichlorotetrahydropyran, prepared in the above reaction, was carried out according to the procedure given by Paul.[13] The hydrolysis appeared to be finished after 3 days, resulting in complete conversion of the liquid to crystals of (3-chlorotetrahydropyranyl-2) ether, mp 107–108°.

Anal. Calcd for $C_{10}H_{16}Cl_2O_3$: C, 47.07; H, 6.18. Found: C, 46.89; H, 6.14.

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with Tetrahydrofuran in the Presence of Water.—In order to moderate the reaction, the reaction flask was placed in an ice bath. To 60 ml (53.28 g, 0.74 mole) of tetrahydrofuran, containing 6 ml of water, was added 23.24 g (0.10 mole) of trichloroisocyanuric acid at such a rate as to maintain a gentle reflux. Upon addition of the first amount of trichloroisocyanuric acid, a yellow color appeared and quickly faded. A white precipitate formed immediately. After all of the trichloroisocyanuric acid was added, the reaction mixture was allowed to stir overnight. Cyanuric acid precipitated almost quantitatively and was removed by filtration. A small sample of the reaction mixture at this point when subjected to gas chromatography showed a peak at the characteristic retention time for γ-butyrolactone. The filtrate was combined with 60 ml of ether and extracted three times with 20-ml portions of 5% aqueous sodium bicarbonate. The ether layer was distilled, and found to contain only tetrahydrofuran. The water layer was acidified with aqueous hydrochloric acid, and the water and hydrochloric acid were removed by azeotropic distillation with benzene. The benzene was removed by distillation, leaving 2.55 g (19%) of γ-butyrolactone, bp 88–89° (10 mm), $n^{25}\mathrm{D}$ 1.4332. The infrared and nmr spectra were identical with those of an authentic sample of γ-butyrolactone. An analytical sample was obtained by gas chromatography. The column used was a 5-ft, SS 30%, Q-Fl on 60–80 mesh Chromosorb P.

Anal. Calcd for $C_4H_6O_2$: C, 55.80; H, 7.03. Found: C, 55.86; H, 7.14.

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with Tetrahydrofuran Using Wet Acetone as the Solvent.—To 20 ml (17.60 g, 0.24 mole) of tetrahydrofuran in 250 ml of acetone stirred at 0° was added 23.24 g (0.10 mole) of trichloroisocyanuric acid. The addition was carried out by adding small portions of the acid over a 2–3-hr period. After letting the reaction stir overnight, cyanuric acid had precipitated almost quantitatively and was separated by filtration. Nitrogen was allowed to pass through a 16-cm Vigreux column under reduced pressure. The first fraction, 2.5 g (47%), bp 26–30° (14 mm), $n^{30}\mathrm{D}$ 1.4290, was chloroacetone. Its infrared spectrum was identical with the infrared spectrum of an authentic sample of chloroacetone.

Anal. Calcd for C_3H_5ClO: C, 39.00; H, 5.45. Found: C, 38.70; H, 5.78.

The second fraction, 1.02 g (8%), was shown by comparative gas chromatographic retention time, infrared adsorption, and analysis of a sample collected by gas chromatography to be γ-butyrolactone.

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-3-triazine with Tetrahydropyran in the Presence of Water.—To 100 ml (88.8 g, 1.23 moles) of tetrahydropyran, containing 3 ml of water, was added 23.24 g (0.10 mole) of trichloroisocyanuric acid over a 2–3-hr period at such a rate so as to maintain a gentle reflux. After all of the trichloroisocyanuric acid was added the reaction mixture was allowed to stir for 1 hr. Cyanuric acid precipitated almost quantitatively. Nitrogen was passed through the resulting reaction mixture until only a faint test for acid was obtained by use of moist litmus. An infrared spectrum of the resulting mixture indicated the presence of δ-valerolactone by showing the characteristic lactone band (1738 cm^{-1}). Upon

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(16) W. Close, *J. Am. Chem. Soc.*, **75**, 3619 (1953).

(17) K. Merkel and O. B. Claren, German Patent 1,124,042 (1962); *Chem. Abstr.*, **57**, 16637 (1962).

(18) We wish to express our appreciation for these research samples provided by General Aniline and Film Corp. and the Quaker Oats Co., respectively.

attempted distillation or addition of water to the mixture, the product showed a tendency to polymerize as noted by several other workers.[19]

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with 2,5-Dihydrofuran Using Wet Acetone as the Solvent.—To 11.62 g (0.05 mole) of trichloroisocyanuric acid completely dissolved in 250 ml of acetone containing 3 ml of water and stirred at 0° was added 7.0 g (0.10 mole) of 2,5-dihydrofuran. The reaction mixture was clear and colorless for about 90 min. Then a yellow color appeared for a short period of time and the solution immediately turned white as cyanuric acid precipitated. After allowing the reaction mixture to stir overnight, the cyanuric acid was separated by filtration. The filtrate (150 ml) was distilled through a 16-cm Vigreux column giving 2.26 g (18.5%) of clear *trans*-3-chloro-4-hydroxytetrahydrofuran product, bp 108–110° (19 mm). The physical constants of the product were identical with those reported in the literature for *trans*-3-chloro-4-hydroxytetrahydropyran.[11]

Anal. Calcd for $C_4H_6ClO_2$: C, 39.20; H, 5.76; Cl, 28.93. Found: C, 39.40; H, 5.87; Cl, 29.14.

Reaction of 1,3,5-Trichloro-2,4,6-trioxohexahydro-*s*-triazine with 5,6-Dihydro-4H-pyran Using Wet Acetone as the Solvent.—To 10 ml (9.27 g, 0.11 mole) of 5,6-dihydro-4H-pyran, wet with 3 ml of water and stirred at 25° in 100 ml of acetone, 11.62 g (0.05 mole) of trichloroisocyanuric acid was slowly added over a period of 8 hr. Upon contact of the trichloroisocyanuric acid with the liquid surface of the reaction mixture, a vigorous reaction was observed. After allowing the reaction mixture to stir overnight, the cyanuric acid was removed and nitrogen was then allowed to pass through the filtrate for 3–4 hr. The filtrate was distilled through a 16-cm Vigreux column under reduced pressure. 2-Hydroxy-3-chlorotetrahydropyran, 5.09 g, 34%, bp 95–97° (3 mm), $n^{20}D$ 1.4840, was isolated as the first fraction. It consisted of a light brown viscous liquid which solidified to a white, crystalline mass on setting for about 24 hr, mp 60–62°. These physical constants agree with those reported in the literature.[12]

Anal. Calcd for $C_5H_9ClO_2$: C, 43.97; H, 6.64; Cl, 25.96. Found: C, 44.08; H, 6.68; Cl, 25.98.

(3-Chlorotetrahydropyranyl-2) ether (6.39 g, 45%), bp 100–103° (12 mm), was isolated as the second fraction. On setting at room temperature, the entire liquid turned to a crystalline mass, mp 105–106°. A sample was prepared for analysis by sublimation of a portion of these crystals resulting in colorless crystals, mp 107–108°. This compound was shown to be identical with that prepared above by hydrolysis of *trans*-2,3-dichlorotetrahydropyran as verified by mixture melting point and infrared spectra.

Anal. Calcd for $C_{10}H_{16}Cl_2O_3$: C, 47.07; H, 6.18. Found: C, 46.94; H, 6.07.

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[19] (a) B. Funk, *Ber.*, **26**, 2575 (1893); (b) F. Fichter and A. Beisswenger, *ibid.*, **36**, 1200 (1903); (c) W. H. Carothers, *J. Am. Chem. Soc.*, **51**, 2548 (1929).

5-Hydroxytetrahydropyrimidine and Its 2-Methyl Homolog

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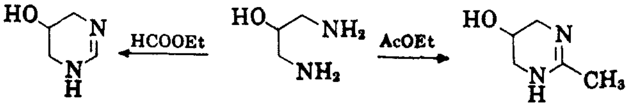
The recent report[1] of unsuccessful attempts to prepare 1,4,5,6-tetrahydro-5-hydroxypyrimidine (I) prompts us to report the synthesis of this compound and of its 2-methyl homolog, as prepared in connection with other studies in these laboratories.

Thus, I was obtained in yields of 10 to 27% by the condensation of 1,3-diaminopropan-2-ol with ethyl formate in ethanol solution. The 2-methyl homolog (II) was prepared in xylene solution, *i.e.*, using conditions similar to those reported for the synthesis of the 2-benzyl analog.[2] Attempts to prepare I in xylene generally resulted in the formation of a brown tar.



I

II

As in the case of the parent 1,4,5,6-tetrahydropyrimidine,[3] both I and II are very strong bases that hydrolyze in water, with a half-life of about 10 min and 2 hr, respectively, at 25°. The hydrolyses were conveniently followed titrimetrically. Here, two inflection points were obtained, the first corresponding to the end point of the strongly basic starting material, the second to that of its less basic amido hydrolysis product. Because of this rapid reaction with water, the pK_a (10.9 at 0.0050 ionic strength) of I was obtained as the pH, measured immediately upon the addition of a calculated 0.5 equiv of hydrochloric acid. The less rapidly hydrolyzed II, however, was dissolved and immediately titrated with little or no detectable hydrolysis, as judged from the plot of its titration curve. Its pK_a value (11.4 at 0.0050 ionic strength) was taken from the half-neutralization point of the initial titration curve.

From the hydrolysis of II, 2-hydroxy-3-acetamidopropylamine was isolated as a crystalline product. The hydrolysis product of I was obtained as an oil, which could not be induced to crystallize.

Because of their hydrolytic instability, both I and II gave rapidly changing nmr spectra in heavy water. At an ambient probe temperature of 42°, for example, I was completely hydrolyzed in 5 min, a rate too fast to be measured by this method. No attempt was made to follow the reaction by nmr at a lower temperature. The slower hydrolysis of II, however, was conveniently followed by nmr at ambient (37°) conditions.

Experimental Section[4]

1,4,5,6-Tetrahydro-5-hydroxypyrimidine (I).—Into a flask equipped with a magnetic stirrer, reflux condenser, and addition funnel was placed 10.0 g (0.11 mole) of redistilled 1,3-diaminopropan-2-ol (Eastman, P 3424), mp 42–45°, dissolved in 40 ml of absolute ethanol. Ethyl formate (8.2 g, 0.11 mole) was added rapidly with stirring, and the temperature rose from 27 to 45° during 5 min. The mixture was refluxed for 15 min, and the ethanol was removed at 110 mm and a pot temperature of 53°. The clear, viscous oil solidified on attempted distillation at 0.4 mm, when the pot reached 100°. A crude yield of 10.8 g was obtained. Two recrystallizations of 6.9 g from acetonitrile gave 2.4 g of I as white flakes: mp 154–155°, ν_{max}^{KBr} 1635 ($\nu_{C=N}$)[3] and 1530 (δ_{NH})[3] cm^{-1}, λ_{max}^{MeOH} 208 mμ (ϵ 6800).

Anal. Calcd for $C_4H_8N_2O$: C, 47.97; H, 8.07; O, 16.00; mol wt, 100.096. Found: C, 47.87; H, 8.22; O, 16.22; mol wt, 100.099 (mass spectrum); neut equiv, 100.[5]

A hydrochloride, mp 168–170°, was prepared using anhydrous hydrogen chloride in isopropyl alcohol and was recrystallized

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[1] R. F. Evans and J. S. Shannon, *J. Chem. Soc.*, 1406 (1965).

[2] C. A. Dornfield, U. S. Patent 2,704,757 (1955); *Chem. Abstr.*, **50**, 5040*g* (1956).

[3] D. J. Brown and R. F. Evans, *J. Chem. Soc.*, 527 (1962).

[4] Melting points are uncorrected. Infrared spectra were run on a Perkin-Elmer 237B grating spectrophotometer. Ultraviolet spectra were obtained by Mr. I. Master with a Cary 14 spectrophotometer, mass spectral data by Mr. L. Daasch with a Consolidated Electrodynamics 21-110 spectrometer, and some of the titration data by Mr. C. Andreasen with a Beckman Zeromatic pH meter.

[5] The hydrolysis reaction does not affect the calculated neutral equivalent, which was obtained from the second inflection point.