Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.54; H, 6.09.

Normal Methyl Ester of *o*-Benzoylbenzoic Acid.[27,28]—Anhydrous *o*-benzoylbenzoic acid was dissolved in a solution of 9.3 g. (0.088 mole) of anhydrous sodium carbonate in 250 ml. of hot water. To this solution was added a hot aqueous solution of silver nitrate (14.9 g., 0.088 mole, in 100 ml. of water). The precipitated silver salt was removed by filtration and the salt was washed first with distilled water and then with ethanol, and finally dried in an oven at 70° for several hours. A slurry of the silver salt in benzene was placed in a round-bottomed flask fitted with a reflux condenser and a calcium chloride tube. Methyl iodide (12.5 g., 0.088 mole) was added, and the contents of the flask were heated for 3 hr. under reflux. The flask was cooled in an ice bath and the benzene solution was filtered. The benzene solution was concentrated, and to the remainder was added a small amount of petroleum ether. This solution was cooled in an ice bath, resulting in the separation of a white solid, which was removed by filtration. Upon recrystallization from petroleum ether (b.p. 60–80°), 6.9 g. (32.6%) of the normal methyl ester was obtained, m.p. 54–55° (lit.[28] m.p. 51.0–51.8°).

Normal Methyl Ester of 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid.—The silver salt was prepared as described above, from 20.0 g. (0.055 mole) of the acid, 2.9 g. (0.028 mole) of anhydrous sodium carbonate, and 9.3 g. (0.055 mole) of silver nitrate, and decomposed with 7.8 g. (0.055 mole) of methyl iodide. Upon recrystallization from methanol, 8.3 g. (39.9%) of the normal methyl ester was obtained, m.p. 90–92° (lit.[16] m.p. 92°).

Normal Methyl Ester of 1-Benzoyl-2-naphthoic Acid.—The silver salt was prepared from 1.0 g. (0.004 mole) of 1-benzoyl-2-naphthoic acid, 0.2 g. (0.002 mole) of anhydrous sodium carbonate, and 0.7 g. (0.004 mole) of silver nitrate. The ester was prepared from 0.6 g. (0.004 mole) of methyl iodide and the silver salt. The oil remaining after concentration of the benzene solution was diluted with pentane, and a white solid separated and was removed by filtration. Upon several recrystallizations from methanol, 0.6 g. (54.5%) of the normal methyl ester was obtained, m.p. 111–114°. That this ester was identical with that obtained in the Fischer esterification of 1-benzoyl-2-naphthoic acid was confirmed by a mixture melting point determination, m.p. 111–115°.

Pseudo Methyl Ester of *o*-Benzoylbenzoic Acid.—The pseudo ester, prepared as previously described,[28] was obtained in crystalline form (13%) only after the oil had been allowed to stand at room temperature for 4 months: m.p. 80–82° (lit.[28] m.p. 81.4–82.4°).

N.m.r. Analysis of Ester Mixtures.—In every case the ether extract from esterification, washed with base and dried, was freed of solvent by means of a rotary evaporator. A sample of the residue was dissolved in spectral grade chloroform and analyzed directly by n.m.r. spectroscopy.

Acknowledgment.—The authors are grateful to the National Science Foundation for financial support to purchase the grating infrared, recording ultraviolet, and n.m.r. spectrophotometers.

(27) A. I. Vogel, "A Text-Book of Practical Organic Chemistry Including Qualitative Organic Analysis," 3rd Ed., Longmans, Green and Co., Ltd., London, 1961, p. 381.

(28) C. V. Wilson, *Org. Reactions*, **9**, 355 (1957).

The Synthesis of (Hydroxylamino)alkyl Mercaptans

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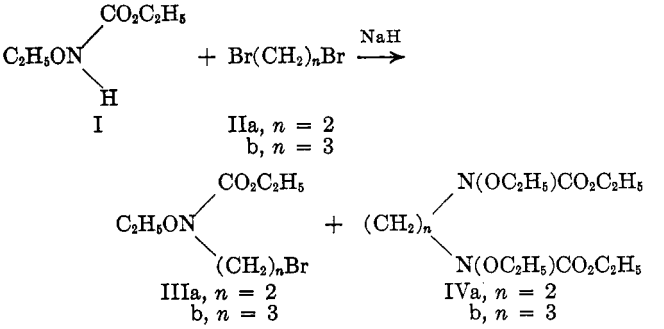
The synthesis of β-(N-ethoxyamino)ethyl and γ-(N-ethoxyamino)propyl mercaptans is reported. This was achieved by converting ethoxyamine first to its urethan which was alkylated by 1,2-dibromoethane and 1,3-dibromopropane to furnish the requisite ω-(N-ethoxy-N-carbethoxyamino)alkyl bromides. The latter were treated with thiourea to yield the corresponding isothiuronium salts, which were hydrolyzed to the mercaptans stated above. A novel migration of a carbethoxy group *from* nitrogen *to* sulfur was observed when β-(N-ethoxy-N-carbethoxyamino)ethyl mercaptan was transformed by hot dilute hydrochloric acid to ethyl S-[β-(N-ethoxyamino)ethyl] thiolcarbonate. In another series of reactions, N-methylhydroxylamine was converted to its urethan, then alkylated by 1,2-dibromoethane and 1,3-dibromopropane to the requisite ω-(N-methyl-N-carbethoxyaminooxy)alkyl bromide. These bromides reacted with sodium thiolacetate to produce the thiolacetate, one of which, *viz.*, S-[β-(N-methyl-N-carbethoxyaminooxy)ethyl] thiolacetate, was hydrolyzed successfully to β-(N-methylaminooxy)ethyl mercaptan. All the products described herein were characterized by their n.m.r. spectra.

In our investigation on the synthesis of hydroxylamine analogs of β-aminoethyl mercaptan as potential antiradiation drugs,[1] we set out to prepare hydroxylamino mercaptans, types $RONH(CH_2)_nSH$ and $R'NHO(CH_2)_nSH$. The synthesis of ω-(alkoxyamino)alkyl mercaptans is presented first and will be illustrated for β-(N-ethoxyamino)ethyl and γ-(N-ethoxyaminopropyl) mercaptans (R = C_2H_5, n = 2 and 3), followed then by that of β-(N-methylaminooxy)ethyl mercaptan (R′ = CH_3, n = 2).

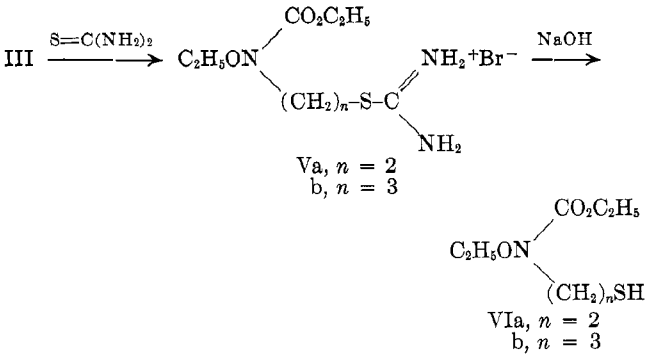
Ethoxyamine, $C_2H_5ONH_2$, was converted first to the urethan I, which was alkylated with 1,2- and 1,3-dibromoalkanes II to give a readily separable mixture of the ω-bromoalkylurethans III, and the bisurethans IV. To substitute a thiol for the bromo group in III, the best results were realized in this series when III



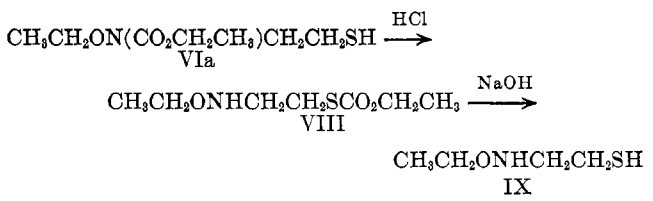
was converted first to the isothiuronium salts V, which were then hydrolyzed. Initially, it was hoped to effect simultaneous hydrolysis of the urethan and isothiuronium groups of V, but it was found experimentally to greater advantage to carry out these hydrolyses to the hydroxylamino thiols stepwise. Relatively short

(1) L. Bauer, K. S. Suresh, and B. K. Ghosh, *J. Org. Chem.*, **30**, 949 (1965).

exposure of V to base hydrolyzed the isothiuronium group preferentially to produce the urethan thiols VI, from which the urethan group was then removed readily by hot dilute hydrochloric acid.



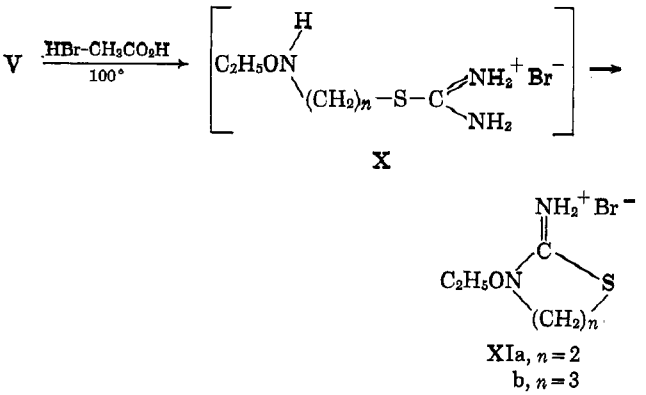
The acid hydrolysis of γ-(N-ethoxy-N-carbethoxyamino)propyl mercaptan (VIb) proceeded without complications to give the required γ-(N-ethoxyamino)-propyl mercaptan, $C_2H_5ONHCH_2CH_2CH_2SH$ (VII), whose spectral characteristics confirmed its structure. However, a similar hydrolysis of VIa proved more eventful. Exposure of VIa to dilute hydrochloric acid induced an interesting acyl migration of the carbethoxy group from nitrogen to sulfur[2] to produce the thiolcarbonate VIII, which in turn was hydrolyzed by base to the thiol IX. The isomeric urethan thiol



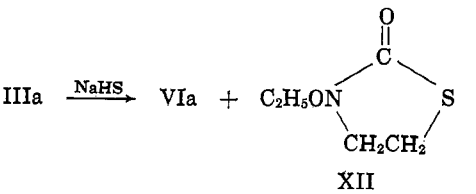
VIa and hydroxylamine thiolcarbonate VIII were distinguished by their markedly different n.m.r. spectra.

The acid hydrolysis of V was also studied in the hope that the urethan would be hydrolyzed to give the (alkoxyamino)alkylisothiuronium salt X, which on subsequent alkaline hydrolysis should yield VII and IX. However, the hydrolysis of V with 34% hydrobromic acid in acetic acid could not be interrupted at the intermediate stage, X, the only isolable product under a variety of conditions being the cyclic isothiuronium salts XI.[3]

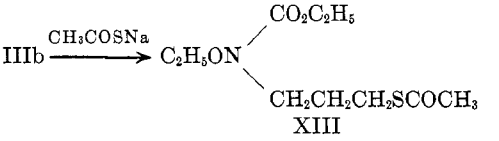
Some alternate approaches to the synthesis of VII and IX were attempted and are described briefly here



The obvious conversion of the bromo group in III to the thiol VI by means of sodium hydrogen sulfide was tried. When the ethane derivative IIIa was treated with sodium hydrogen sulfide, a mixture of the required thiol, VIa, together with the thiazolidinone XII was obtained. Similar treatment of VIb with sodium

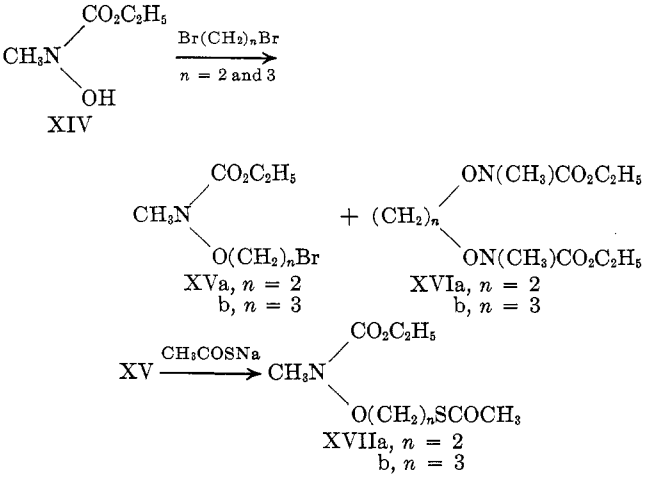


hydrogen sulfide only yielded some VIb accompanied by a number of unidentifiable products. Another attractive path to procure the required products seemed in the transformation of the bromides III to the corresponding urethan thiolacetates whose acid hydrolysis should liberate the hydroxylamine and thiol groups simultaneously. However, the propane analog IIIb reacted successfully with sodium thiolacetate to form



XIII while a similar reaction of IIIa formed an inseparable mixture.

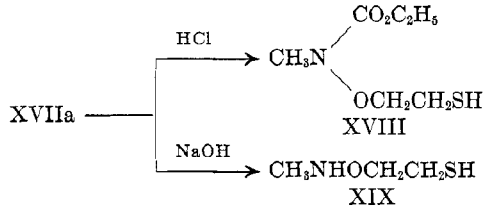
The synthesis of the other series of hydroxylamino thiol commenced with the alkylation of N-hydroxy-N-methylurethan (XIV) by 1,2- and 1,3-dibromoalkanes to give the bromides XV and the bisurethan XVI. In this series, the reaction of the bromides XV with sodium thiolacetate formed the required thiol esters,



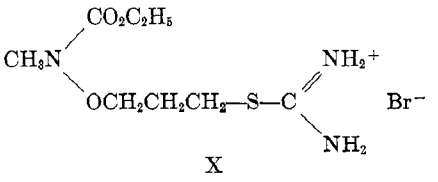
(2) Acyl migration *from* nitrogen *to* sulfur has not been observed very frequently. It has been demonstrated spectrophotometrically that β-acetamidoethyl mercaptan, $CH_3CONHCH_2CH_2SH$, yielded β-acetylmercaptoethylamine, $CH_3COSCH_2CH_2NH_2$ (together with some 2-methylthiazoline) in mineral acid solution [R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959)]. However, the reverse, *i.e.*, sulfur-*to*-nitrogen shifts have been reported frequently on a preparative scale. Invariably, these required basic catalysis. For example, when $CH_3COSCH_2CH_2NH_3^+Cl^-$ is heated with base, $CH_3CONHCH_2CH_2SH$ is formed immediately [S. Wieland and E. Bokelmann, *Ann.*, **576**, 20 (1952)]. In the same vein, when triethylamine is added to $RNHC(=S)SCH_2CH_2NH_3^+Cl^-$, $RNHC(=S)NHCH_2CH_2SH$ is produced [A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 3140 (1963)]. Transfer of an amidinium moiety from sulfur *to* nitrogen has been reported a number of times. For a recent example, note the transformation of $RNH-C(=NHR^+)-S-CH_2CH_2NH_3^+2Br^-$ by ammonia *to* $R-NH-C(=NHR^+)NHCH_2CH_2SH\ Br^-$ [W. O. Foye, *et al.*, *J. Pharm. Sci.*, **54**, 557 (1965)].

(3) A similar phenomenom was reported previously by D. G. Doherty and R. Shapira [*J. Org. Chem.*, **28**, 1339 (1963)] who found that 2-aminobutylisothiourea dihydrobromide was converted to 4-ethyl-2-aminothiazoline at pH 2–5.

XVII. Acid hydrolysis of the urethan thiol ester XVIIa furnished the thiol XVIII, while basic hydrolysis produced the required β-(N-methylaminooxy)-ethyl mercaptan (XIX).



Attempts to apply the isothiuronium route to the conversion of the bromide in XV to the thiols in this series was not particularly successful. The reaction of XVa with thiourea yielded mixtures while XVb formed the isothiuronium salt XX reluctantly, and this approach was abandoned.



X

Experimental Section[4]

N-Ethoxyphthalimide.—A solution of N-hydroxyphthalimide (425 g., 2.6 moles), ethyl bromide (284 g., 2.6 moles), and triethylamine (262 g., 2.6 moles) in N,N-dimethylformamide (1 l.) was allowed to stand at 25° for 24 hr. The reaction mixture was poured into a large excess of water and the solid so obtained was crystallized from ethanol, m.p. 99–101°, lit. m.p. 95–100°,[5] 103°,[6] 97–98°.[7] It weighed 466 g. (92%). Its n.m.r. spectrum ($CDCl_3$) exhibited the ethyl resonances as a triplet at δ 1.43 (CH_3), a quartet at 4.33 (CH_2), and a singlet for the arene protons at 7.83.[8]

Ethoxyammonium Chloride.—A solution of N-ethoxyphthalimide (335 g., 1.76 moles) was boiled in concentrated hydrochloric acid (500 ml.) in acetic acid (1 l.) for 0.5 hr. On cooling, phthalic acid was filtered off, the mother liquor was evaporated *in vacuo*, and the residue was crystallized from ethanol–ether to give an almost quantitative yield of the salt (171 g.), m.p. 133–134°, lit. m.p. 125–126°,[9] 129–131°.[10] Its n.m.r. spectrum (3% in D_2O) showed the CH_3 and CH_2 protons at δ 1.28 and 4.13, respectively. When this solution was neutralized by potassium carbonate (thus forming ethoxyamine), the CH_2 group moved upfield by δ 0.38 to δ 3.75, the methyl group by δ 0.13 to δ 1.15. A similar shift of the alkyl protons was observed when the methyl singlet in methoxyamine hydrochloride moved from δ 3.90 to 3.56 for methoxyamine (3% in D_2O), a shift of δ 0.34 upfield.

N-Ethoxyurethan (I).—To an ice-cold stirred suspension of ethoxyammonium chloride (172 g., 1.76 moles) and potassium carbonate (276 g., 2 moles) in ether (1.5 l.) containing water (20 ml.) was added dropwise ethyl chlorocarbonate (200 g., 1.85 moles). After 8 hr., the mixture was filtered and the ether solution was distilled to give the product (184 g., 79%), b.p. 74–75° (3 mm.). Its infrared spectrum (film) showed a medium band at 3275 (NH) and a strong band at 1720 (C=O) cm.$^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed two sets of ethyl groups, the one furthest downfield being attributed to the ester ethyl (δ CH_2 at 4.13, CH_3 at 1.25, J = 7.0 c.p.s.), while the N-ethoxy ethyl group appeared at δ 3.85 and 1.20 for the CH_2 and CH_3, respectively.

Anal. Calcd. for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.40; H, 7.92; N, 10.03.

β-(N-Ethoxy-N-carbethoxyamino)ethyl Bromide (IIIa) and 1,2-Bis(N-ethoxy-N-carbethoxy)aminoethane (IVa).—N-Ethoxyurethan was converted into its sodio derivative by adding it dropwise (133 g., 1 mole) to an ice-cold stirred suspension of sodium hydride (45 g., 1 mole)[11] in tetrahydrofuran (1 l.). After the evolution of hydrogen had ceased, 1,2-dibromoethane (288 g., 1.53 moles) was added all at once and the mixture was heated at the reflux for 4 hr. Most of the solvents were removed *in vacuo*, the residue was diluted with ice water, and the organic products were extracted into methylene chloride. Distillation yielded the alkyl bromide (168 g., 70%), b.p. 84–85° (0.1 mm.), showing in its infrared spectrum (film) no NH absorption and the C=O stretching band at 1710 cm.$^{-1}$ (strong) with a shoulder at 1740 cm.$^{-1}$. The n.m.r. spectrum (neat) showed the two ethyl groups as two overlapping triplets (δ 1.22 and 1.28) for the CH_3 groups and two overlapping quartets at δ 4.03 and 4.40 for the accompanying CH_2 groups. The two CH_2 groups sandwiched between nitrogen and bromine appeared as an A_2B_2 spectrum, centered at δ 3.78.

Anal. Calcd. for $C_7H_{14}BrNO_3$: C, 35.01; H, 5.88; N, 5.83; mol. wt., 240.1. Found: C, 35.08; H, 6.03; N, 5.87; mol. wt., 239 and 241 (ratio 23:21; mass spectrum).

The second fraction (10 g., 7%) distilled as a colorless liquid, b.p. 116–117° (0.1 mm.), and proved to be the bis compound. Its infrared spectrum (film) showed the C=O stretching frequency at 1695 and 1710 cm.$^{-1}$. Absorption in its n.m.r. spectrum ($CDCl_3$) was observed for the two ethyl groups at δ 1.23 and 4.01, 1.30 and 4.28 and the two CH_2 groups as a singlet at δ 3.78.

Anal. Calcd. for $C_{12}H_{24}N_2O_6$: C, 49.30; H, 8.28; N, 9.58. Found: C, 49.48; H, 8.19; N, 9.40.

S-[β-(N-Ethoxy-N-carbethoxyamino)ethyl]isothiuronium Bromide (Va).—β-(N-Ethoxy-N-carbethoxyamino)ethyl bromide (24 g., 0.1 mole) and thiourea (10 g., 0.13 mole) were heated in ethanol (70 ml.) at the reflux for 4 hr. The solution was cooled and the product was precipitated with dry ether. It was recrystallized from alcohol–ether to give the pure salt (30 g., 95%), m.p. 114–115°. Its infrared spectrum (Nujol) showed, besides the ester C=O band (1700 cm.$^{-1}$), a strong band at 1645 cm.$^{-1}$ attributable to the isothiuronium moiety.[12] Its n.m.r. spectrum (D_2O) showed the two ethyl groups at δ 1.23 and 4.08, 1.32 and 4.25, the CH_2–S as a diffuse triplet at δ 3.53, and the CH_2–N as a triplet at δ 3.98 (partially hidden by one of the ethyl CH_2 groups).

Anal. Calcd. for $C_8H_{18}BrN_3O_3S$: C, 30.39; H, 5.73; N, 13.28. Found: C, 30.30; H, 5.64; N, 13.28.

β-(N-Ethoxy-N-carbethoxyamino)ethyl Mercaptan (VIa).—The isothiuronium salt Va (16 g., 0.05 mole) was treated with 10% sodium hydroxide solution (75 ml.) on a steam bath for 0.25 hr. (nitrogen atmosphere). The mixture was cooled, acidified with acetic acid, and extracted with ether to furnish the product (3.8 g., 40%), b.p. 98–99° (1.3 mm.). Its infrared spectrum (film) showed the SH stretching frequency at 2566 and the C=O stretching mode at 1711, with a shoulder at 1735 cm.$^{-1}$. Its n.m.r. spectrum (neat) showed the ethyl groups belonging to the urethan as a quartet (CH_2 at δ 4.12) and a triplet (CH_3 at δ 1.25, J = 7 c.p.s.), and the one of the N-ethoxy moiety in a similar pattern (CH_2 at 3.92, CH_3 at δ 1.17 J = 7 c.p.s.). The CH_2N protons appeared as a relatively sharp triplet, δ 3.65, and the CH_2S protons as broad multiplet at δ 2.72, being coupled to the SH which showed up as a broad triplet with three distinguishable peaks, δ 1.66 (J = 8 c.p.s.)

Anal. Calcd. for $C_7H_{15}NO_3S$: C, 43.52; H, 7.83; N, 7.25; S, 16.59; mol. wt., 193. Found: C, 43.98; H, 7.84; N, 7.50; S, 16.50; mol. wt., 193 (mass spectrum).

(4) All melting and boiling points are uncorrected. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland, and by MicroTech Laboratories, Inc., Skokie, Ill. Infrared spectra were recorded on the Perkin-Elmer Model 337 recording spectrophotometer. The n.m.r. spectra were obtained by means of the Varian A-60 spectrometer and are recorded in parts per million (δ) downfield from internal standards tetramethylsilane (TMS), for organic solutions, or from sodium 3-(trimethylsilyl)-1-propanesulfonate (TPS), in D_2O solution. Assignment of protons in a certain area is based on correct integral information from the n.m.r. spectrum. Mass spectra were obtained by means of the Hitachi RMU-6D mass spectrometer.

(5) W. R. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

(6) N. I. Putokhin, *J. Russ. Phys. Chem. Soc.*, **62**, 2203 (1930); *Chem. Abstr.*, **25**, 3993 (1931).

(7) R. T. Major and R. J. Hedrick [*J. Org. Chem.*, **30**, 1270 (1965)] reported a 62% yield by a slightly different method.

(8) In our previous paper[1] the arene protons of the phthalimidooxy group were erroneously reported. They should have been listed around δ 7.6.

(9) W. Theilacker and K. Ebke, *Angew. Chem.*, **68**, 303 (1956).

(10) R. T. Major and R. J. Hedrick[7] hydrolyzed using 6 *N* HCl to obtain a 60% yield.

(11) Handled as a 53% suspension in heavy mineral oil as purchased from Metal Hydrides, Inc., Beverly, Mass.

(12) W. Kutzelnigg and R. Mecke [*Spectrochim. Acta*, **17**, 530 (1961)] assign the 1645-cm.$^{-1}$ band in the S-methylisothiuronium cation to a mixture of the C=N stretching and the NH_2 deformation vibrations.

The mercaptan (3.5 g., 0.018 mole) was oxidized in 10% sodium hydroxide (10 ml.) with iodine in potassium iodide solution (until the color persisted). The oil which separated was extracted into ether, washed with sodium thiosulfate, and distilled, b.p. 200–202° (0.1 mm.). The **disulfide** weighed 2.0 g. (58%). The infrared spectrum (film) showed the C=O band at 1720 and 1750 cm.$^{-1}$. Its n.m.r. spectrum ($CDCl_3$) showed, besides the two ethyl groups (δ 1.10 and 4.08, 1.22 and 4.20), two triplets at δ 2.92 (CH_2–S) and 3.80 (CH_2N).

Anal. Calcd. for $C_{14}H_{28}N_2O_6S_2$: N, 7.29. Found: N, 7.45.

Ethyl S-[β-(N-Ethoxyamino)ethyl]thiolcarbonate (VIII).—β-(N-Ethoxy-N-carbethoxyamino)ethyl mercaptan (1.5 g.) was heated in dilute (1:1) hydrochloric acid (7.5 ml.) at 110° for 0.75 hr. The solution was cooled, neutralized with a saturated solution of sodium bicarbonate, and extracted with chloroform. Distillation of the chloroform extract afforded a colorless liquid (1.0 g., 67%), b.p. 95–96° (1 mm.). Its infrared spectrum showed the NH stretching mode at 3260 cm.$^{-1}$ and the C=O band at 1711 cm.$^{-1}$. The n.m.r. spectrum (neat) revealed the ester ethyl groups at δ 4.23 (CH_2) and 1.25 (CH_3), the ethoxy ethyl at δ 3.64 (CH_2) and 1.10 (CH_3), and the NCH_2CH_2S protons as a singlet with a shoulder on each side 1 c.p.s. away and the NH resonance as a broad singlet at δ 5.87.

Anal. Calcd. for $C_7H_{15}NO_3S$: C, 43.52; H, 7.83; N, 7.25; S, 16.59; mol. wt., 193. Found: C, 43.66; H, 7.97; N, 7.41; S, 16.73; mol. wt., 193 (mass spectrum).

β-(N-Ethoxyamino)ethyl Mercaptan (IX).—Ethyl S-[β-(N-ethoxyamino)ethyl]thiol carbonate (VIII, 5.0 g., 0.026 mole) was stirred at room temperature for 2 hr. with sodium hydroxide (5.0 g.) in 50% aqueous ethanol (34 ml.). The mixture was diluted with water (34 ml.), acidified with dilute hydrochloric acid (1:1), and neutralized carefully in the cold with sodium bicarbonate. Extraction with chloroform furnished the product (2 g., 63%), b.p. 35–36° (2 mm.). Its infrared spectrum (film) revealed the SH stretching frequency at 2550 and the NH stretching mode at 3250 cm.$^{-1}$. The n.m.r. spectrum (neat) showed the N-ethoxy ethyl group at δ 3.66 (CH_2) and 1.10 (CH_3), the NH signal at δ 5.92, the SH as a triplet at δ 1.63 (J = 8 c.p.s.), and the NCH_2CH_2S protons as a complex A_2B_2 part of an A_2B_2XY spin system as multiplet between δ 3.2 and 2.4. After several days, it was noticed that the signals owing to the NH and SH protons disappeared, indicative of rapid exchange, and the NCH_2CH_2S absorption now resembled an A_2B_2 system with a chemical shift of the order of δ 0.25 between the A and B protons.

Anal. Calcd. for $C_4H_{11}NOS$: C, 39.64; H, 9.15; N, 11.55; S, 26.45; mol. wt., 121. Found: C, 39.89; H, 9.39; N, 11.50; S, 26.28; mol. wt., 121 (mass spectrum).

β-(N-Ethoxy-N-carbethoxyamino)ethyl Mercaptan (VIa) and 3-Ethoxy-2-thiazolidinone (XII).—To a solution of sodium ethoxide (from 2.3 g. sodium, 0.1 g.-atom) in 100 ml. of ethanol which was saturated with hydrogen sulfide at 30°, was added β-(N-ethoxy-N-carbethoxyamino)ethyl bromide (12 g., 0.05 mole) and the mixture was stirred at 30° for 16 hr. A slow stream of hydrogen sulfide was maintained during that time. The mixture was filtered and solvents were removed *in vacuo*. The residue was diluted with water (200 ml.) and extracted with ether. The ether solution was back extracted with 10% sodium hydroxide solution (20 ml.) and the aqueous layers were combined. Distillation of the ether extract yielded XII (0.9 g., 12%), b.p. 108–110° (2 mm.). As a liquid film, its infrared spectrum showed the C=O band at 1710 cm.$^{-1}$. Its n.m.r. spectrum ($CDCl_3$) showed the ethyl group as two sets of sharp bands (CH_3, δ 1.22; CH_2, δ 3.98), two sets of signals for the NCH_2 at δ 3.68, and those for the SCH_2 at δ 3.23.

Anal. Calcd. for $C_5H_9NO_2S$: C, 40.87; H, 6.15; N, 9.50; S, 21.75. Found: C, 40.86; H, 6.31; N, 9.37; S, 21.67.

The basic aqueous layer was just acidified with acetic acid and re-extracted with ether. Distillation of that extract yielded VIa (5.2 g., 54%), b.p. 87–88° (0.8 mm.), whose infrared and n.m.r. spectrum were identical with that prepared above from the isothiuronium salt Va.

2-Imino-3-ethoxythiazolidine Hydrobromide (XIa).—S-[β-(N-Ethoxy-N-carbethoxyamino)ethyl]isothiuronium bromide (5.0 g., 0.016 mole) was heated with hydrobromic acid (34%, 10 ml.) in acetic acid (10 ml.) at 110° for 4 hr. Removal of the solvents furnished a residue which crystallized from alcohol–ether. It weighed 2.0 g. (55%), m.p. 189–190°. Its infrared spectrum (Nujol) showed two bands at 1650 (strong) and 1595 cm.$^{-1}$ (medium) attributable to the C=N stretching and NH_2 deformation modes. Its n.m.r. spectrum (D_2O) showed the CH_3 as a well-defined triplet (at δ 1.32), a group of signals resembling two very closely overlapping triplets, δ 3.57, assigned to the ring CH_2 attached to S, being coupled to the CH_2N. The resonances of the latter overlapped with those of ethyl CH_2 to give a complex multiplet centered at δ 4.21.

Anal. Calcd. for $C_5H_{11}BrN_2OS$: C, 26.44; H, 4.88; N, 12.34; S, 14.12. Found: C, 26.56; H, 5.03; N, 12.30; S, 13.99.

γ-(N-Ethoxy-N-carbethoxyamino)propyl Bromide (IIIb) and 1,3-Bis(N-ethoxy-N-carbethoxyamino)propane (IVb).—N-Ethoxyurethan (184 g., 1.4 moles) was treated with 1,3-dibromopropane (400 g., ≈2.0 moles) in tetrahydrofuran (1 l.) in the presence of sodium hydride (63 g., 1.4 moles) in a manner similar to the ethyl analogs described above. The alkyl halide (166 g., 47%) boiled at 88–90° (0.2 mm.). The n.m.r. spectrum (neat) showed the two ethyl groups as two overlapping triplets, δ 1.19 and 1.27 (CH_3), two overlapping quartets, δ 3.89 and 4.20 (CH_2), two overlapping triplets, δ 3.53 and 3.65 (CH_2N and CH_2Br), and a quintet, δ 2.18 (C–CH_2–C).

Anal. Calcd. for $C_8H_{16}BrNO_3$: C, 37.80; H, 6.35; N, 5.51. Found: C, 37.73; H, 6.43; N, 5.58.

The bis compound distilled as a colorless oil, b.p. 143–144° (0.2 mm.), and solidified to a colorless solid, m.p. 39–40°. It weighed 65 g. (30%). The n.m.r. spectrum (neat) differed from that of the first product in that it showed the CH_2N as a triplet at δ 3.55 and the C–CH_2–C at δ 1.92.

Anal. Calcd. for $C_{13}H_{26}N_2O_6$: C, 50.97; H, 8.55; N, 9.14. Found: C, 51.04; H, 8.60; N, 9.14.

S-[γ-(N-Ethoxy-N-carbethoxyamino)propyl] Thiolacetate (XIII).—Sodium thiolacetate was prepared from the reaction of sodium hydride (4.8 g., 0.1 mole) with freshly distilled thiolacetic acid (7.6 g., 0.1 mole) in tetrahydrofuran (250 ml.). γ-(N-Ethoxy-N-carbethoxy)aminopropyl bromide (25.4 g., 0.1 mole) was added and the mixture was stirred at 25° for 18 hr. The mixture was filtered and then distilled to give the product (22.0 g., 88%), b.p. 127–130° (0.2 mm.). Besides the customary ethyl resonances, the n.m.r. spectrum ($CDCl_3$) exhibited signals for the CH_2N at δ 3.59, CH_2S at δ 2.96, C–CH_2–C at δ 1.96, and $SCOCH_3$ as a sharp singlet at δ 2.33.

Anal. Calcd. for $C_{10}H_{19}NO_4S$: C, 48.19; H, 7.68; N, 5.62. Found: C, 48.31; H, 7.82; N, 5.63.

S-[γ-(N-Ethoxy-N-carbethoxyamino)propyl]isothiuronium Bromide (Vb).—γ-(N-Ethoxy-N-carbethoxyamino)propyl bromide (5.0 g., 0.019 mole) was allowed to react with thiourea (2.2 g., 0.03 mole) in ethanol (60 ml.) as written up for the ethyl analog (above) to yield the salt (4.6 g., 74%) as colorless solid, m.p. 92–93°. Its infrared spectrum (Nujol) showed the ester C=O at 1695 and the isothiuronium band at 1640 cm.$^{-1}$. Its n.m.r. spectrum (D_2O) showed the ethyl resonances as usual and the CH_2N signals at δ 3.60, the CH_2S at δ 3.33, and the C–CH_2–C at δ 2.10.

Anal. Calcd. for $C_9H_{20}BrN_3O_3S$: C, 32.73; H, 6.10; N, 12.72. Found: C, 33.00; H, 6.04; N, 13.12.

γ-(N-Ethoxy-N-carbethoxyamino)propyl Mercaptan (VIb). Method A.—A solution of S-[γ-(N-ethoxy-N-carbethoxyamino)-propyl] thiolacetate (20.0 g., 0.08 mole) in a mixture of acetic acid (56 ml.) and concentrated hydrochloric acid (28 ml.) was heated at the reflux for 0.3 hr. Distillation furnished a pale yellow liquid (12 g., 72%), b.p. 104–105° (1.5–2.5 mm.), whose infrared spectrum (film) clearly showed the SH stretching mode at 2566 cm.$^{-1}$ and the C=O of the urethan at 1711 cm.$^{-1}$ with a shoulder at 1735 cm.$^{-1}$. Its n.m.r. spectrum ($CDCl_3$) showed peaks due to the ester ethyl group at δ 1.30 (CH_3) and 4.28 (CH_2), the ethyl of the N-ethoxy at δ 1.23 (CH_3) and 3.98, the CH_2N at δ 3.52, the CH_2S at δ 2.57, the C–CH_2–C at 2.00, and the SH (triplet) at 1.53 (the last being subject to the concentration of the solution).

Anal. Calcd. for $C_8H_{17}NO_3S$: C, 46.35; H, 8.26; N, 6.76. Found: C, 46.20; H, 8.32; N, 6.70.

Method B.—S-[γ-(N-Ethoxy-N-carbethoxyamino)propyl]-isothiuronium bromide (17.0 g., 0.05 mole) was heated in 2 *N* sodium hydroxide (50 ml.) at 100° for 0.5 hr. The mixture was cooled and neutralized with acetic acid. Extraction with methylene chloride furnished the mercaptan (6.1 g., 58%), b.p. 92–95° (1.0 mm.), identical with the product of method A.

γ-(N-Ethoxyamino)propyl Mercaptan (VII).—γ-(N-Ethoxy-N-carbethoxyamino)propyl mercaptan (4.0 g., 0.02 mole) was stirred at 100° with dilute (2:1) hydrochloric acid (30 ml.) for 1.5 hr. The mixture was cooled, extracted with methylene

chloride, neutralized with saturated sodium bicarbonate solution, and extracted again with methylene chloride to furnish the product (1.0 g., 38%), b.p. 50–51° (0.6 mm.). The SH and NH stretching frequencies in its infrared spectrum appeared at 2555 and 3250 cm.$^{-1}$ (liquid film), respectively. Its n.m.r. spectrum (in benzene) exhibited signals due to the N-ethoxy group, a triplet at δ 1.07 (CH_3), a quartet at δ 3.57, CH_2N as a triplet at δ 2.76, CH_2S as a set of peaks centered at δ 2.24, and the SH centered at δ 1.16 (J = 7.3 c.p.s.), that signal being subject to exchange with D_2O.

Anal. Calcd. for $C_5H_{13}NOS$: C, 44.43; H, 9.69; N, 10.36; S, 23.71; mol. wt., 135. Found: C, 44.72; H, 9.98; N, 10.14; S, 23.68; mol. wt., 135 (mass spectrum).

2-Imino-3-ethoxytetrahydro-1,3-thiazine Hydrobromide (XIb).—S-[γ-(N-Ethoxy-N-carbethoxyamino)propyl]isothiuronium bromide (12.5 g., 0.038 mole) was treated in acetic acid (50 ml.) containing hydrobromic acid (34%, 25 ml.) at 110° for 6.0 hr. Removal of solvents and crystallization from ethanol yielded the salt (6 g., 66%), m.p. 218–219°. Its infrared spectrum (Nujol) showed the bands due to the C=N and NH_2 deformation modes at 1635 and 1590 cm.$^{-1}$. Its n.m.r. spectrum (D_2O) showed only one ethyl group at δ 4.25 and 1.30, the CH_2N at δ 3.90, the CH_2S at δ 3.25, and C–CH_2–C at δ 2.48.

Anal. Calcd. for $C_6H_{13}BrN_2OS$: C, 29.88; H, 5.43; Br, 33.13; N, 11.62. Found: C, 29.82; H, 5.51; Br, 33.45; N, 11.65.

β-(N-Methyl-N-carbethoxyaminooxy)ethyl Bromide (XVa) and 1,2-Bis(N-methyl-N-carbethoxyaminooxy)ethane (XVIa).—N-Hydroxy-N-methylurethan[13] (6.0 g., 0.05 mole) was added to a stirred suspension of sodium hydride (1.2 g., 0.05 mole) in N,N-dimethylformamide (100 ml.). After salt formation was complete, 1,2-dibromoethane (18.8 g., 0.1 mole) was added and stirring was continued at 25° for 16 hr. The reaction mixture was poured into water (1 l.) and the products were extracted into methylene chloride. Distillation yielded the bromide (2.2 g., 18%), b.p. 76–80° (0.1 mm.). Its infrared spectrum (film) showed the C=O stretching mode at 1720 cm.$^{-1}$. Its n.m.r. spectrum (neat) showed, besides the N-methyl and ester ethyl group, the CH_2O as a triplet buried in the CH_2 of the ethyl ester at δ 4.25 and the CH_2Br at δ 3.65.

Anal. Calcd. for $C_6H_{12}BrNO_3$: C, 31.87; H, 5.35; N, 6.31. Found: C, 31.80; H, 5.54; N, 6.32.

The second fraction boiled at 130–131° (0.2 mm.) and consisted of XVIa (0.2 g., 3%). The C=O stretching mode in its infrared spectrum (film) appeared at 1720 cm.$^{-1}$. Its n.m.r. spectrum ($CDCl_3$) exhibited, besides the N-methyl and ethyl ester group, the CH_2ON as a singlet at δ 4.15.

Anal. Calcd. for $C_{10}H_{20}N_2O_6$: C, 45.43; H, 7.63; N, 10.60. Found: C, 45.62; H, 7.80; N, 10.50.

When the same reaction was carried out in boiling tetrahydrofuran, the yield of the two products tended to be lower.

S-[β-(N-Methyl-N-carbethoxyaminooxy]ethyl Thiolacetate (XVIIa).—Sodium thiolacetate was prepared by the reaction of thiolacetic acid (1.0 g.) and sodium hydride (0.5 g.) in tetrahydrofuran (25 ml.). β-(N-Methyl-N-carbethoxyaminooxy)ethyl bromide (2.3 g., 0.01 mole) was added and the mixture was stirred at 25° for 16 hr. Salts were filtered off and the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. Distillation of the ether solution gave the product as a yellow oil (1.5 g., 68%), b.p. 104–105° (0.2 mm.). The urethan and thiol ester C=O in the infrared spectrum (film) appeared at 1720 and 1685 cm.$^{-1}$, respectively. The n.m.r. spectrum (neat) showed, besides the N-methyl group and ethyl group, the CH_2ON at δ 4.03, the CH_2S at δ 3.17, and the CH_3COS at δ 2.38.

Anal. Calcd. for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.31. Found: C, 43.63; H, 6.89; N, 6.12.

β-(N-Methyl-N-carbethoxyaminooxy)ethyl Mercaptan (XVIII).—The thiol acetate (15 g.) was boiled in acetic acid (40 ml.) containing concentrated hydrochloric acid (20 ml.) for 5 min. Solvents were removed *in vacuo* and the residue was extracted with ether. Distillation of the ether extract yielded the product (4 g.), b.p. 80–81° (0.9 mm.). The infrared spectrum (film) showed the SH stretching mode and the urethan C=O at 2575 and 1725 cm.$^{-1}$, respectively. Its n.m.r. spectrum ($CDCl_3$) showed the ethyl and N-methyl group as indicated,[13] the CH_2ON at δ 4.18, the CH_2SH centered at δ 2.84, and the SH at δ 1.78.

Anal. Calcd. for $C_6H_{13}NO_3S$: C, 40.21; H, 7.31; N, 7.81; S, 17.88. Found: C, 40.55; H, 7.25; N, 7.69; S, 17.71.

β-(N-Methylaminooxy)ethyl Mercaptan (XIX).—A solution of XVIIa (7.5 g.) in alcoholic sodium hydroxide (4 g. in 10 ml. of water and 10 ml. of ethanol) was stirred at room temperature for 2 hr. The solution was diluted with 20 ml. of ice–water and made acid with dilute hydrochloric acid. Extraction with methylene chloride afforded a fraction (1.5 g., b.p. 75–76° at 1 mm.) which was not examined further. The aqueous layer was neutralized with saturated sodium bicarbonate solution and re-extracted with methylene chloride. Distillation furnished the product (1.0 g.), b.p. 30° (1 mm.). Its infrared spectrum (film) showed the NH and SH stretching modes as broad bands at 3260 and 2560 cm.$^{-1}$, respectively. There was no absorption in the carbonyl region above 1500 cm.$^{-1}$. Its n.m.r. spectrum ($CDCl_3$) showed a sharp triplet at δ 3.77 (CH_2ON), the N-methyl at δ 2.83 on top a multiplet for the CH_2S proton at δ 2.72, and the SH as a triplet consisting of broad peaks at δ 1.55.

Anal. Calcd. for C_3H_9NOS: C, 33.61; H, 8.46; N, 13.06; S, 29.90; mol. wt., 107. Found: C, 33.37; H, 8.69; N, 12.83; S, 29.63; mol. wt., 107 (mass spectrum).

γ-(N-Methyl-N-carbethoxyaminooxy)propyl Bromide (XVb) and 1,3-Bis(N-methyl-N-carbethoxyaminooxy)propane (XVIb).—To a vigorously stirred suspension of sodium hydride (8.9 g., 0.37 mole) in tetrahydrofuran (500 ml.) was added N-hydroxy-N-methylurethan (40.0 g., 0.33 mole). After the initial reaction had subsided, 1,3-dibromopropane (101 g., 0.5 mole) was added and the mixture was boiled for 4 hr. Solvents were removed *in vacuo*, the residue was diluted with water and extracted by methylene chloride, and the products were distilled. The bromide (20 g., 25%) distilled at 94–95° (0.2 mm.).

Anal. Calcd. for $C_7H_{14}BrNO_3$: C, 35.02; H, 5.88; N, 5.83. Found: C, 35.78; H, 6.05; N, 5.61.

The higher boiling fraction was the bisurethan (10 g., 22%), b.p. 150–152 (1.2 mm.).

Anal. Calcd. for $C_{11}H_{22}N_2O_6$: C, 47.46; H, 7.97; N, 10.07. Found: C, 47.33; H, 8.06; N, 10.10.

S-[γ-(N-Methyl-N-carbethoxyaminooxy)propyl] Thiolacetate (XVIIb).—γ-(N-Methyl-N-carbethoxyaminooxy)propyl bromide (48.0 g., 0.2 mole) was allowed to react with freshly prepared sodium thiolacetate (0.2 mole) prepared as above for XVIIa) in boiling tetrahydrofuran (400 ml.) for 4 hr. Distillation produced a pale yellow liquid, b.p. 135–136° (0.2 mm., 30 g. (64%). Its n.m.r. spectrum ($CDCl_3$) showed the N–CH_3 (δ 3.18), the usual ester ethyl group (CH_2 at δ 4.25, CH_3 at δ 1.27), CH_2NO (triplet) at δ 3.98, CH_2S at δ 2.95, and the C–CH_2–C at δ 1.96.

Anal. Calcd. for $C_9H_{17}NO_4S$: C, 45.93; H, 7.28; N, 5.95. Found: C, 46.07; H, 7.46; N, 5.70.

S-[γ-(N-Methyl-N-carbethoxyaminooxy)propyl]isothiuronium Bromide (XX).—γ-(N-Methyl-N-carbethoxyaminooxy)propyl bromide (20 g., 0.08 mole) was treated with thiourea (7.6 g., 0.1 mole) in boiling ethanol (100 ml.) for 8 hr. Removal of solvent and addition of dry ether yielded a solid (12.0 g., 46%) m.p. 100–102°. Its infrared spectrum (Nujol) showed the ester C=O at 1705, and the C=N and NH_2^+ deformation frequencies at 1650 with a shoulder at 1620 cm.$^{-1}$. Its n.m.r. spectra (in D_2O) showed the ester CH_3 as a triplet at δ 1.32, the accompanying CH_2 as a quartet at δ 4.26 overlapping the triplet due to the CH_2-ON at δ 4.02, the CH_2S and CH_3 appeared at δ 3.25 and 3.35, and the CCH_2C as a multiplet centered at δ 2.10.

Anal. Calcd. for $C_8H_{18}BrN_3O_3S$: C, 30.39; H, 5.73; N, 13.28. Found: C, 30.21; H, 5.80; N, 13.46.

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(13) Made from N-methylhydroxylamine [E. Beckmann, *Ann.*, **365**, 201 (1909)] by the method of G. Zinner [*Arch. Pharm.*, **292**, 329 (1959)]. A considerable downfield shift of δ 0.31 was observed for the N-methyl signal as N-methylhydroxylamine was converted to its hydrochloride, δ 2.69 to 3.00 (3% in D_2O) compared to only shift of δ 0.09 when methylamine was converted to its hydrochloride, δ 2.50 to 2.59 (3% in D_2O). The attachment of the carbethoxy group shifted the N-methyl resonance in N-hydroxy-N-methylurethan to δ 3.22 ($CDCl_3$). All of the N-methylurethans described following exhibited the N-methyl peak between δ 3.08 to 3.28, the ethyl group of the urethan, CH_3 between δ 4.23 and 4.28, CH_3 between δ 1.27 to 1.32 ($J_{CH_2-CH_3}$ being about 7.0 c.p.s.), being somewhat a function of the medium in which the spectrum was obtained.

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The Reaction of Oxalyl Chloride with Amides. III.[1] The Acylation of Amides

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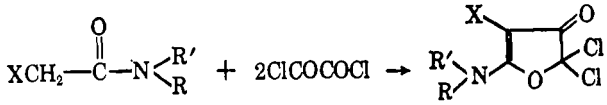
The reaction of N,N-disubstituted acetamides with oxalyl chloride to form furanone amines has been extended to include a variety of α-substituted acetamides. It has been found that α-chloroenamines and N,N-disubstituted thionamides also produce furanone amines on reaction with oxalyl chloride and that α-iodoamides yield 4-chlorofuranone amines. The reaction is discussed in the light of these observations and the mechanism which is proposed led to a new reaction for the formation of acetoacetic amides from treatment of amides with acid chlorides.

Our interest in the synthesis of α-chloroenamines by the treatment of N,N-disubstituted amides I with a variety of chlorinating agents led to an investigation of the reaction of N,N-disubstituted α-chloro- and α-phenylacetamides with oxalyl chloride. This reaction produced 5-(disubstituted amino)-4-chloro- or -phenyl-3(2H)-furanones (II)[2] rather than the chloroenamines and has now been extended to N,N-disubstituted acetamides possessing a variety of α substituents (Table I).



a, X = Cl; R′ = C_6H_5; R = CH_3
b, X = Cl; R′ = R = C_6H_5
c, X = C_6H_5; R = R′ = C_2H_5

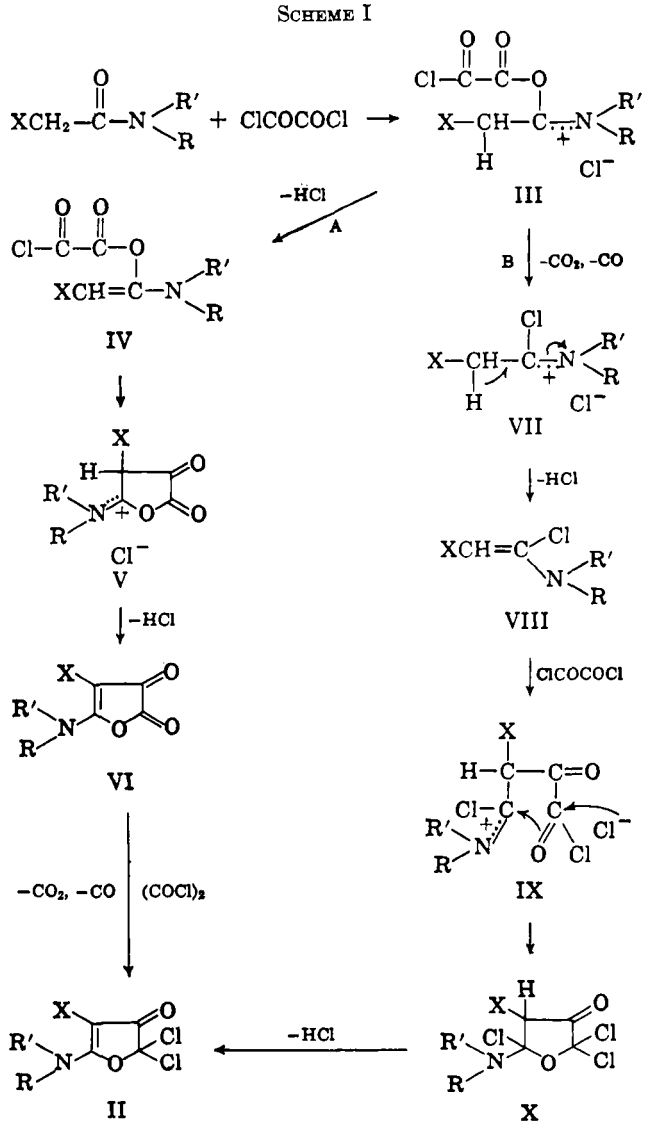
The conversion of an amide to a furanone amine may be visualized to occur principally by two pathways. (Scheme I).

O-Acylation of the amide to produce III is common to both. Pathway A (III → IV → II) would involve the dehydrochlorination of III to the aminovinyl ester IV which would lead to the furandione VI by intramolecular acylation. The chlorination of IV by oxalyl chloride would produce II.

Pathway B (III → VII → II) would proceed *via* the chloroenamine VIII which was initially sought. This enamine would, however, undergo further reaction with oxalyl chloride (acylation) to form IX. Attack of chloride ion on IX, followed by ring closure and loss of hydrogen chloride, would lead to II. In this sequence oxalyl chloride would not act as a chlorinating agent *per se*.

Differentiation between the two mechanisms might be achieved by the preparation of VI and its subsequent reaction with oxalyl chloride. Attempts to prepare the cyclic ketolactone VI by base-catalyzed cyclization of methyl N,N-diethyl-2-phenyloxalacetamate (XI) were not successful. Treatment of XI with refluxing pyridine or potassium *t*-butoxide in refluxing benzene led only to tar formation.

SCHEME I



In view of these results, it was decided to establish the intermediacy of an enamine in pathway B by treating a chloroenamine, rather than an amide, with oxalyl chloride. Reaction of N,N-diphenyl-1,2-dichlorovinylamine[3] (VIII, X = Cl, R = R′ = C_6H_5)

(1) For paper II in this series, see A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963).

(2) A. J. Speziale and L. R. Smith, *ibid.*, **27**, 4361 (1962).

(3) A. J. Speziale and L. R. Smith, *J. Am. Chem. Soc.*, **84**, 1868 (1962).