A reaction time of 1 hr. at 25° (1:1 molar ratio of reactants) decreased the yield of thioformanilide to 49%; reaction for 1 hr. at 90° (1:1 molar ratio of reactants) gave only aniline (6%), *N*-methylaniline (74%), and a solid melting above 200° which was probably tris(*N*-methylanilino)borine (9%) but was not further investigated.

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S-[ω-(Aminoöxy)alkyl]isothiuronium Salts, ω,ω′-Bis(aminoöxy)alkanes and Related Compounds[1]

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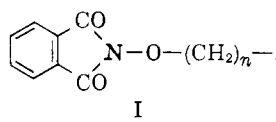
The reaction of N-hydroxyphthalimide with ω,ω′-dibromoalkanes yields ω-(phthalimidoöxy)alkyl bromides, Ia, and ω,ω′-bis(phthalimidoöxy)alkanes, Ib. Reaction of Ia with thiourea, followed by hydrolysis, leads to a facile synthesis of S-[ω-(aminoöxy)alkyl]isothiuronium salts, IIc. Hydrolysis of Ib makes available ω,ω′-bis(aminooxy)alkanes which were characterized by their salts, amide and sulfonamide derivatives.

To continue our studies[2] on the synthesis of potential prophylactic agents capable of protecting animals from otherwise lethal doses of ionizing radiation, we turned our attention to the synthesis of S-[ω-(aminoöxy)alkyl]-isothiuronium salts, IIc. Such molecules are analogs and homologs of the active 2-aminoethanethiol and the corresponding isothiuronium salt, $H_3\overset{+}{N}-(CH_2)_2-S-C(-NH_2)=NH_2^+\ 2X^-$. Structure IIc meets the criteria seemingly essential for protective activity: a basic group, in this instance the aminoöxy moiety, in close vicinity of a thiol or potential thiol group, *viz.*, the isothiuronium group.

In designing these molecules, the aminoöxy function was to be liberated last by the acid hydrolysis of the corresponding phthalimidoöxy derivative.[3] The key intermediates in the synthesis of IIc were the ω-(phthalimidoöxy)alkyl bromides, Ia, which became readily available from the reaction of N-hydroxyphthalimide and ω,ω′-dibromoalkanes.



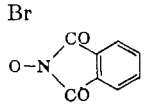
I

$H_3N^+-O-(CH_2)_n-Z\ \ Br^-$

II

where the substituent Z is, in

(a) Br

(b) 

(c) $S-C(-NH_2)=NH_2^+\ Br^-$

(d) $S-SO_3^-\ Na^+$

(e) $O-NH_3^+\ Br^-$

(f) SH

Displacement of the bromo group in Ia with thiourea furnished the S-[ω-(phthalimidoöxy)alkyl]isothiuronium bromide, Ic, which was hydrolyzed readily by hydrobromic acid to the aminoöxy isothiuronium salt, IIc. This sequence of reactions was used to prepare five homologs of IIc (n = 2 to 6).

The formation of the ω-(phthalimidoöxy)alkyl bromide Ia, was invariably accompanied by some ω,ω′-bis(phthalimidoöxy)alkane, Ib The mixture was separated either by fractional crystallization or column chromatography. Hydrolysis with hydrobromic acid of Ib afforded the corresponding ω,ω′-bis(aminoöxy)-alkane dihydrobromides, IIe. The free bases were characterized by solid amide or sulfonamide derivatives.

These series of reactions are described somewhat in detail for one member of the series, *viz.*, when n = 2. N-Hydroxyphthalimide was treated with 1,2-dibromoethane in the presence of triethylamine at room temperature and gave a mixture of Ia and Ib (n = 2). The reaction of Ia with thiourea afforded the crystalline salt, Ic from which the phthaloyl moiety was readily cleaved off with hydrobromic acid to produce IIc (n = 2). A similar reaction of Ia with N-methylthiourea furnished the crystalline N-methyl analog of Ic (n = 2) but hydrolysis led to an oily salt, $H_3\overset{+}{N}-O-(CH_2)_2-S-C(-NH_2)=NHCH_3{}^+2Br^-$, which was characterized as a crystalline dipicrate. When Ib (n = 2) was hydrolyzed with hydrobromic acid, 1,2-bis(aminoöxy)-ethane was isolated as the crystalline dihydrobromide. The free base was characterized as its benzamide ($C_6H_5CONHOCH-)_2$, its *p*-toluenesulfonamide, (p-$CH_3-C_6H_4SO_2NHOCH^{2-})_2$, and its *p*-acetamidobenzenesulfonamide. The last one of these was hydrolyzed further to the sulfanilamide analog, (p-$H_2N-C_6H_4SO_2-NHOCH_2-)_2$.

It was also possible to remove the protective phthaloyl group from Ia (n = 2) with hydrobromic acid to give β-(aminoöxy)ethyl bromide hydrobromide (IIa. n = 2).

Benzoylation of this compound produced the crystalline derivative $C_6H_5CONHO(CH_2)_2Br$ which reacted further with thiourea to give the isothiuronium salt, $C_6H_5CONHO(CH_2)_2SC(-NH_2)=NH_2{}^+Br^-$. An attempt to prepare 2-(aminoöxy)ethanethiol, IIf (n = 2), from Ia (n = 2) by the following approach was un-

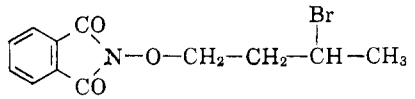
(1) This project was sponsored by the office of the Surgeon General U. S. Army Medical Research and Development Command, whose generous support through a research contract (DA-49-193-MD-2047) is gratefully acknowledged.

(2) Our previous paper, L. Bauer and T. L. Welsh, *J. Org. Chem.*, **27**,4382 (1962), summarizes the background in this field.

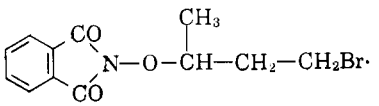
(3) The introduction of the aminoöxy group into a molecule *via* the phthalimidoöxy derivative was first described by A. F. McKay, *et al.*, *Can. J. Chem.*, **38**, 343 (1960), and presents certain advantages. The alkylation of N-hydroxyphthalimide is rapid and usually affords a crystalline derivative which is hydrolyzed with great ease by hydrobromic acid (3–5 min.). Other methods are available for the preparation of aminoöxyalkyl compounds *via* suitable derivatives of hydroxylamine. Recently, E. L. Schulmann, *et al.*, *J. Med. Pharm. Chem.*, **5**, 464 (1962), used acetoxime and benzohydroxamic acid to prepare a series of aminoöxy acids; R. M. Khomutov, *J. Gen. Chem., USSR* (Eng. Transl.), **31**, 1863 (1961), used ethyl N-hydroxyacetimidate, $CH_3-C(=NOH)OC_2H_5$, for the initial alkylation. The three references quoted here summarize this field.

successful. The reaction of Ia (n = 2) with sodium thiosulfate yielded the crystalline Bunte salt Id (n = 2) which on hydrolysis[4] with hydrobromic acid gave phthalic acid and no other identifiable product.

Other members of these series of compounds behaved similarly and important variations are mentioned in the Experimental section. An interesting reaction was encountered when N-hydroxyphthalimide was treated with the unsymmetrical 1,3-dibromobutane. There was isolated a bromo compound to which either structure III or IV could be assigned and a small quantity of 1,3-bis (phthalimidoöxy)butane. Structures III and IV arise if displacement had occurred either at the primary



III



IV

or secondary carbon atom, respectively. To establish the structure of this phthalimidoöxyalkyl bromide, the rates of reaction of 1- and 2-bromobutane with N-hydroxyphthalimide were compared. Under identical conditions, 1-bromobutane reacted with N-hydroxyphthalimide for 48 hours to give N-butoxyphthalimide in 64% yield while the 2-isomer gave N-(1-methylpropoxy)phthalimide in 23% yield. As expected these experiments indicated that the same reagent displaced the primary bromo group faster than the secondary one.

To establish structure of our product, III or IV, it was hydrolyzed to give a salt for which either structure $H_3\overset{+}{N}O-(CH_2)_2CH(Br)CH_3\ Br^-$ or $H_3\overset{+}{N}OCH(CH_3)-(CH_2)_2Br\ Br^-$ is plausible. Reduction of this aminoöxyalkyl bromide hydrobromide with lithium aluminum hydride[5] produced only 1-butanol, thus confirming the structure of the phthalimidoöxyalkyl bromide in question to be III. Thiourea was able to displace the bromo group of III to give the corresponding isothiuronium salt. An attempt to desulfurize this salt with Raney nickel to the corresponding aminoöxybutane was unsuccessful.

Experimental[6]

ω-(Phthalimidoöxy)alkyl Bromides, Ia, and ω,ω′-bis(phthalimidoöxy)alkanes, Ib.—A typical reaction is described, that for the preparation of Ia and Ib when n = 2. A solution of N-hydroxyphthalimide[7] (16.3 g.; 0.1 mole) in N,N-dimethylformamide (120 ml.), ethylene bromide (37 g.; 0.2 mole), and triethylamine (20 g.; 0.2 mole) were allowed to stand at 25° until the red reaction mixture had turned colorless (17 hr.). The precipitate which had formed was filtered off and washed with water to free it from triethylammonium bromide. This product (5.0 g.; 28% based on N-hydroxyphthalimide) consisted mainly of 1,2-bis(phthalimidoöxy)ethane, m.p. 250°. Recrystallization from N,N-dimethylformamide afforded colorless needles, m.p. 254°. Analytical data of it and its homologs are presented in Table II.

The preceding filtrate was diluted with water (800 ml.) and the solid which precipitated was filtered off. It weighed 13.6 g. (50% based on N-hydroxyphthalimide), m.p. 80–89°. This product, as well as those listed in Table I were crystallized from dilute ethanol. Analytical data of it and its homologs are also reported in Table I.

TABLE I

ω-(PHTHALIMIDOÖXY)ALKYL BROMIDES, Ia

n in Ia	Yield, %	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	50	94–96	$C_{10}H_8NO_3Br$	Calcd.	44.46	2.98	5.18
			(270.1)	Found	44.56	3.08	5.15
3	35	60–65	$C_{11}H_{10}NO_3Br$	Calcd.	46.50	3.54	4.92
			(284.1)	Found	46.70	3.65	4.90
4	37	70–72	$C_{12}H_{12}NO_3Br$	Calcd.	48.34	4.05	4.69
			(298.1)	Found	48.28	4.24	4.74
5	49	71–73	$C_{13}H_{14}NO_3Br$	Calcd.	50.02	4.52	4.48
			(312.2)	Found	50.17	4.61	4.54
6	36	66–69	$C_{14}H_{16}NO_3Br$	Calcd.	51.55	4.94	4.29
			(326.2)	Found	51.71	5.06	4.24
R[a]	45	86–89	$C_{12}H_{12}NO_3Br$	Calcd.	48.34	4.05	4.69
				Found	48.43	4.14	4.66

[a] R represents the $-CH_2CH_2CH(CH_3)-$ group, structure III.

When only 1 mole of ethylene bromide was used the yield of β-(phthalimidoöxy)ethyl bromide was 33% and that of 1,2-bis-(phthalimidoöxy)ethane was 39%.

In the reaction of the homologs both products remained in the N,N-dimethylformamide solution and were precipitated by water as a mixture. Other methods of separations were resorted to. The crude reaction product was washed with petroleum ether (b.p. 30–60°) to remove excess dibromoalkane and separation effected in the following way.

The products from the reaction starting with 1,3-dibromopropane and 1,4-dibromobutane were boiled with aqueous methanol and 2-propanol, respectively, in which the bis(phthalimidoöxy)-alkanes were insoluble; the (phthalimidoöxy)alkyl bromides crystallized on cooling the aqueous alcohol solutions.

The reactions which involved 1,3-dibromobutane, 1,5-dibromopentane and 1,6-dibromohexane yielded a mixture of two products which were separated by chromatography on alumina in the following manner. A benzene solution containing 1.5 g. of the mixture was placed on a column of acid-washed alumina (30 g.; Merck Reagent). Elution with benzene (in 20-ml. fractions) gave the phthalimidoöxy alkyl bromide and the bis(phthalimidoöxy) alkanes were eluted by methylene chloride.

S-[ω-(Phthalimidoöxy)alkyl]isothiuronium Bromides, Ic.—This general method is illustrated by preparation of S-[β-(phthalimidoöxy)ethyl]isothiuronium bromide, (Ic. n = 2). A solution of β-phthalimidoöxy)ethyl bromide (2.7 g.; 0.01 mole) and thiourea (1.1 g.; 0.014 mole) in ethanol (30 ml.) was heated under reflux for 4.5 hr. The reaction mixture was cooled and upon addition of ether, the salt crystallized. Purification procedures, yields, constants, and analytical data are given for it and the homologs in Table III. In other cases equimolar quantities of (phthalimidoöxy)alkyl bromide and thiourea were used and the time of reflux was varied from 3.5 to 4.5 hr.

N-Methyl-S-[β-(phthalimidoöxy)ethyl]isothiuronium bromide was obtained when Ia (n = 2) (5.4 g.; 0.02 mole) reacted with N-methylthiourea (1.8 g.; 0.02 mole) in ethanol (50 ml.) for 5 hr. as described before. The reaction mixture was cooled and ether added when a white crystalline product separated. It was dissolved in cold water, filtered, and the solvent removed *in vacuo*. The residue was dissolved in methanol and precipitated with ether, m.p. 183–185° (4.0 g.; 55%).

Anal. Calcd. for $C_{12}H_{14}N_3O_3SBr$ (360.2): C, 40.01; H, 3.91; N, 11.67. Found: C, 40.16; H, 4.09; N, 11.46.

A reaction between 1-(phthalimidoöxy)-3-bromobutane, III, (2.9 g.; 0.01 mole) and thiourea (0.76 g.; 0.01 mole) in tetrahydrofuran (50 ml.) at reflux for 48 hr. did not afford a crystalline hydrobromide. The solvent was evaporated *in vacuo* to yield a

(4) For references of the hydrolysis of Bunte salts by mineral acid see, E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., Inc., New York, 1958, pp. 32, 328.

(5) Aliphatic halo groups are frequently reduced to alkanes by lithium aluminum hydride. B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 358 (1962), have shown that lithium aluminum hydride in boiling ether reduced 2-(carbethoxyaminoöxy)ethanol, $C_2H_5O_2CNHO(CH_2)_2OH$, to ethylene glycol.

(6) All melting points are uncorrected. The microanalyses reported were performed by Micro-Tech Laboratories, Skokie, Ill., and Dr. Kurt Eder, Geneva, Switzerland.

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

TABLE II

ω,ω'-BIS(PHTHALIMIDOÖXY)ALKANES, Ib

n in Ib	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	28	$HCON(CH_3)_2$	254	$C_{18}H_{12}N_2O_6$ (352.3)	Calcd.	61.36	3.43	7.96
					Found	61.57	3.46	8.08
3	3	C_2H_5OH	179–181	$C_{19}H_{14}N_2O_6$ (366.3)	Calcd.	62.29	3.85	7.64
					Found	62.33	4.05	7.67
4	18	$HCON(CH_3)_2$	260–265	$C_{20}H_{16}N_2O_6$ (380.3)	Calcd.	63.16	4.22	7.36
					Found	63.34	4.37	7.46
5	11	CH_3OH–$CHCl_3$	172–174	$C_{21}H_{18}N_2O_6$ (394.4)	Calcd.	63.96	4.60	7.10
					Found	63.89	4.66	7.20
6	10	CH_3OH–$CHCl_3$	175–176	$C_{22}H_{20}N_2O_6$ (408.4)	Calcd.	64.69	4.93	6.86
					Found	64.63	5.07	6.92
R[a]	3	CH_3OH–$CHCl_3$	190–192	$C_{20}H_{16}N_2O_6$ (380.3)	Calcd.	63.16	4.22	7.36
					Found	63.19	4.41	7.16

[a] R stands for —$CH_2CH_2CH(CH_3)$- grouping.

TABLE III

S-[ω-(PHTHALIMIDOÖXY)ALKYL]ISOTHIURONIUM BROMIDES, Ic

n in Ic	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	61	C_6H_6–CH_3OH	188–189	$C_{11}H_{12}N_3O_3SBr$ (346.2)	Calcd.	38.16	3.46	12.14
					Found	38.44	3.77	12.06
3	58	C_6H_6–CH_3OH	182–183	$C_{12}H_{14}N_3O_3SBr$ (360.2)	Calcd.	40.01	3.91	11.66
					Found	40.09	4.09	11.76
4	74	C_6H_6–CH_3OH	161–164	$C_{13}H_{16}N_3O_3SBr$ (374.3)	Calcd.	41.72	4.30	11.23
					Found	41.64	4.54	11.13
5	75	H_2O	194–196	$C_{14}H_{18}N_3O_3SBr$ (388.30)	Calcd.	43.30	4.67	10.82
					Found	43.20	4.60	10.64
6	63	CH_3OH–$(C_2H_5)_2O$	128–130	$C_{15}H_{20}N_3O_3SBr$ (402.3)	Calcd.	44.77	5.01	10.44
					Found	44.82	5.03	10.47

TABLE IV

S-[ω-(AMINOÖXY)ALKYL]ISOTHIOUREA DIHYDROBROMIDES, IIc

n in IIc	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)		Analysis, % C	H	N
2	77	C_2H_5OH–$(C_2H_5)_2O$	135–137 (dec.)	$C_3H_{11}N_3OSBr_2$ (297.0)	Calcd.	12.13	3.73	14.15
					Found	12.22	3.80	14.10
3	85	CH_3OH–$CHCl_3$	159–161 (dec.)	$C_4H_{13}N_3OSBr_2$ (311.0)	Calcd.	15.44	4.21	13.51
					Found	15.73	4.31	13.22
4	67	CH_3OH–$CHCl_3$	158–159 (dec.)	$C_5H_{15}N_3OSBr_2$ (325.0)	Calcd.	18.47	4.65	12.92
					Found	18.71	4.76	12.85
5	72	CH_3OH–$(C_2H_5)_2O$	137–139 (dec.)	$C_6H_{17}N_3OSBr_2$ (339.1)	Calcd.	21.25	5.05	12.39
					Found	21.35	5.10	12.59
6	91	CH_3OH–$(C_2H_5)_2O$	141–144 (dec.)	$C_7H_{19}N_3OSBr_2$ (353.1)	Calcd.	23.81	5.43	11.90
					Found	23.89	5.61	12.08

water-soluble gummy residue which did not crystallize. It formed a picrate (m.p. 230–232°) which crystallized from acetone; m.p. 233–235°.

Anal. Calcd. for $C_{19}H_{18}N_6O_{10}S$ (522.4): C, 43.67; H, 3.47; N, 16.09. Found: C, 43.95; H, 3.57; N, 16.28.

S-[ω-(Aminoöxy)alkyl]isothiourea Dihydrobromide (IIc from Ic).—The hydrolysis of Ic to give IIc is described for one member of the series, *viz.*, $n = 2$: A suspension of S-[β-(phthalimidoöxy)-ethyl]isothiuronium bromide (3.8 g.; 0.012 mole) in glacial acetic acid (10 ml.) and 48% hydrobromic acid (15 ml.) was boiled for 3–5 min. until solution was effected. On cooling, phthalic acid (1.8 g.; 99%; m.p. 206°, m.m.p. 206°) separated and was filtered off. Solvents were removed *in vacuo*, ether added to the residue, and the solid was filtered. Recrystallization solvent, yields, melting points, and analyses are listed for all members of the series in Table IV.

Hydrolysis of N-methyl-S-[β-(phthalimidoöxy)ethyl]isothiuronium bromide did not yield a crystalline product. The residue obtained after evaporating the solvents *in vacuo*, therefore was dissolved in water and treated with aqueous picric acid when N-methyl-S-[β-(aminoöxy)ethyl] isothiourea dipicrate separated. It was crystallized from ethanol; m.p. 204°.

Anal. Calcd. for $C_{16}H_{17}N_9O_{15}S$ (607.4): C, 31.63; H, 2.82; N, 20.75. Found: C, 31.80; H, 2.93; N, 20.65.

ω,ω'-Bis(aminoöxy)alkane Dihydrobromides, IIe.—The hydrolysis of ω,ω'-bis(phthalimidoöxy)alkanes was carried out as has been described for that of S-[ω-(phthalimidoöxy)alkyl]-isothiuronium bromides. Phthalic acid was obtained in 70–90% yield. The residue after evaporating off the solvents were washed with chloroform, filtered, and crystallized from methanol–chloroform unless indicated otherwise in Table V.

ω,ω'-Bis(benzamidoöxy)alkanes.—The dibenzoyl derivatives were prepared from IIe as shown for a typical example ($n = 2$): To an aqueous solution of 1,2-bis(aminoöxy)ethane dihydrobromide (1.0 g. in 15 ml.) was added sodium acetate trihydrate (2.5 g.) and benzoyl chloride (1.0 ml.) and the mixture shaken for 0.5 hr., then poured onto ice. The solid so obtained was purified and its yield, melting point, and analyses for it and similar derivatives are assembled in Table V.

1,3-Bis(benzamidoöxy)propane and 1,5-bis(benzamidoöxy)-pentane could not be obtained in crystalline form and hence their di-*p*-toluenesulfonyl derivatives were prepared.

ω,ω'-Bis(arenesulfonamidoöxy)alkanes.—The general method is given for the preparation of 1,2-bis(*p*-toluenesulfonamidoöxy)-ethane. *p*-Toluenesulfonyl chloride (3.2 g.) was added slowly to an ice-cold solution of IIe ($n = 2$) in pyridine (2.0 g. in 10 ml.). After the addition, the mixture was warmed for 10 min. at 100°, then poured onto ice, and the product purified (see Table V).

TABLE V

DIHYDROBROMIDES AND DERIVATIVES OF ω,ω′-BIS(AMINOÖXY)ALKANES, IIe

n in IIe	Yield, %	M.p., °C.	Mol. formula (mol. wt.)	Analysis, % C	Analysis, % H	Analysis, % N	Derivatives	Yield, %	Solvent of crystallization	M.p., °C.	Mol. formula (mol. wt.)	Analyses, % C	Analyses, % H	Analyses, % N
2	77	209 (dec.)	$C_2H_{10}N_2O_2Br_2$[b]	Calcd. 9.45	3.96	11.03	Dibenzoyl	68	C_2H_5OH-H_2O	148–150	$C_{16}H_{16}N_2O_4$ (300.3)	Calcd. 63.99	5.37	9.32
			(253.9)	Found 9.61	3.86	10.82						Found 64.11	5.39	9.27
							Di-*p*-toluenesulfonyl	95	C_6H_6 *or* CH_3OH	141–142	$C_{16}H_{20}N_2O_6S_2$ (400.1)	Calcd. 47.99	5.03	6.99
												Found 47.91	4.88	7.15
							Di-*p*-(acetamidobenzene)sulfonyl	85	C_6H_5-$CH_3CO_2C_2H_5$	201–202	$C_{18}H_{22}N_4O_8S_2$ (486.5)	Calcd. 44.44	4.55	11.52
												Found 44.63	4.50	11.34
3	73	171–173[a] (dec.)	$C_3H_{12}N_2O_2Br_2$ (267.9)	Calcd. 13.45	4.51	10.46	Di-*p*-(aminobenzene)sulfonyl	88	C_2H_5OH	193–195	$C_{14}H_{18}N_4O_6S_2$ (402.5)	Calcd. 41.78	4.58	13.92
				Found 13.49	4.55	10.55						Found 41.96	4.42	14.02
							Di-*p*-toluenesulfonyl	94	C_6H_6	120–122	$C_{17}H_{22}N_2O_6S_2$ (414.5)	Calcd. 49.26	5.35	6.75
												Found 49.13	5.52	6.72
4	54	206–206.5 (dec.)	$C_4H_{14}N_2O_2Br_2$ (282.0)	Calcd. 17.04	4.96	9.93	Dibenzoyl	68	C_6H_5-CH_3OH	142–143.5	$C_{18}H_{20}N_2O_4$ (328.3)	Calcd. 65.84	6.13	8.53
				Found 17.16	5.16	10.09						Found 65.89	6.24	8.63
5	82	158 (dec.)	$C_6H_{16}N_2O_2Br_2$[c] (296.0)	Calcd. 20.29	5.44	9.46	Di-*p*-toluenesulfonyl	66	C_2H_5OH-H_2O	97–99	$C_{19}H_{26}N_2O_6S_2$ (442.5)	Calcd. 51.57	5.92	6.33
				Found 20.38	5.47	9.55						Found 51.78	6.00	6.46
6	91	194–195 (dec.)	$C_6H_{18}N_2O_2Br_2$[d] (310.0)	Calcd. 23.24	5.85	9.02	Dibenzoyl	71	C_6H_6	120–120.5	$C_{20}H_{24}N_2O_4$ (356.4)	Calcd. 67.40	6.78	7.86
				Found 23.31	5.95	9.16						Found 67.51	6.89	7.98

[a] Recrystallized from methanol–ether. [b] Reported by C. M. Luxmoore, *J. Chem. Soc.*, **67**, 1018 (1895), not to melt up to 250°. [c] The free base has been described by G. Palazzo, E. F. Rogers, and G. B. M. Bettolo, *Gazz. chim. ital.*, **84**, 915 (1954). [d] The dihydrochloride has been reported by A. T. Fuller and H. King, *J. Chem. Soc.*, 963, (1947).

Analytical data for the diverse sulfonamides are tabulated in Table V.

In similar fashion, from the reaction of IIe (n = 2) and *p*-acetamidobenzenesulfonyl chloride there was prepared 1,2-bis(*p*-acetamidobenzenesulfonamidoöxy)ethane (see Table V). Hydrolysis of the latter (8.2 g.) with 10% sodium hydroxide solution (50 ml.) at 100° for 1 hr., followed by acidification with acetic acid to pH 6.5 gave 1,2-bis(*p*-aminobenzenesulfonamidoöxy)ethane also listed in Table V.

1-Aminoöxy-2-bromoethane Hydrobromide.—Hydrolysis of Ia (n = 2) with hydrobromic acid as described above for S-[ω-(phthalimidoöxy)alkyl]isothiuronium salts, Ic, formed the **salt**, (71% yield) m.p. 185–187° (from methanol–chloroform).

Anal. Calcd. for $C_2H_7NOBr_2$ (220.9): C, 10.87; H, 3.19; N, 6.34. Found: C, 11.02; H, 3.33; N, 6.46.

Benzoylation as reported in the procedure for ω,ω′-bis(benzamidoöxy)alkanes gave 2-benzamidooxy-1-bromoethane (97%), m.p. 85–87° (from benzene).

Anal. Calcd. for $C_9H_{10}NO_2Br$ (244.1): C, 44.28; H, 4.12; N, 5.73. Found: C, 44.24; H, 4.01; N, 5.59.

S-[2-(Benzamidoöxy)ethyl]Isothiuronium Bromide.—A solution of 2-(benzamidoöxy)-1-bromoethane (2.44 g., 0.01 mole) and thiourea (0.76 g., 0.01 mole) in tetrahydrofuran was heated under reflux for 3 hr. The solvent was evaporated *in vacuo*, and the gummy residue triturated with anhydrous ether. The solid so obtained was purified by several recrystallizations from methanol–ether; m.p. 127–129°.

Anal. Calcd. for $C_{10}H_{14}N_3O_2SBr$ (320.2): C, 37.51; H, 4.40; N, 13.13. Found: C, 37.61; H, 4.54; N, 13.05.

1-(Aminoöxy)-3-bromobutane Hydrobromide.—This salt was prepared in 40% yield by the hydrolysis of 1-(phthalimidoöxy)-3-bromobutane, III, as described for the conversion of Ic to IIc. The salt was crystallized from methanol and ether; m.p. 121–124°.

Anal. Calcd. for $C_4H_{11}NOBr_2$ (248.9): C, 19.30; H, 4.45; N, 5.63. Found: C, 19.38; H, 4.59; N, 5.74.

Reduction of 1-(aminoöxy)-3-bromobutane Hydrobromide with Lithium Aluminum Hydride.—The salt (5 g.) was added gradually to a stirring suspension of lithium aluminum hydride (1.4 g.) in anhydrous ether (300 ml.) along with a trace of aluminum chloride. The reaction mixture was cooled during addition and then heated under reflux for 3 hr. Methanol (8 ml.) in ether (8 ml.) was added after the reaction, followed by water (40 ml.) and 6 *N* sulfuric acid (40 ml.). The ether layer was separated, dried over anhydrous sodium sulfate, and distilled. The fraction boiling between 70–90° at 50 mm. was collected.

The infrared spectrum was identical with that of 1-butanol.

The identity was further established by heating the liquid (100 mg.) under reflux with 48% hydrobromic acid (5 ml.) and thiourea (0.5 g.) for 1.25 hr. The solvent was evaporated *in vacuo* and the residue treated with aqueous picric acid. The crystals so obtained were purified from ethanol, undepressed on admixture with one authentic specimen; m.p. 178–179°.

The Reaction of 1- and 2-Bromobutane with N-Hydroxyphthalimide.—1-Bromobutane (6.8 g., 0.05 mole) reacted with N-hydroxyphthalimide (8.15 g., 0.05 mole) at 25° for 48 hr. as described for the preparation of Ia to yield N-butoxyphthalimide (7.0 g.; 64%), b.p. 145–151° at 0.3 mm.

Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.2): C, 65.74; H, 5.97; N, 6.38. Found: C, 65.77; H, 5.93; N, 6.65.

Under identical conditions, 2-bromobutane reacted to give a mixture of unchanged N-hydroxyphthalimide (2.1 g.) and N-(1-methylpropoxy)phthalimide (2.5 g., 23%); m.p. 50–53° (from aqueous ethanol).

Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.2): C, 65.74; H, 5.97; N, 6.38. Found: C, 65.95; H, 6.17; N, 6.50.

The yield of the product increased to 40% when the reaction mixture stood for 3 weeks.

1-(Aminoöxy)butane Hydrobromide.—This was obtained in 64% yield by hydrolyzing 1-(phthalimidoöxy)butane as has been described for the transformation of Ic to IIc. The salt crystallized from 48% hydrobromic acid; m.p. 158°.

Anal. Calcd. for $C_4H_{12}NOBr$ (170.0): N, 8.23. Found: N, 8.51.

The hydrochloride (m.p. 152°, lit. m.p. 155–156°[8b], 152–153°[8a]) was prepared in a similar way except that the heating time was 20 min.

(8) (a) L. Neuffer and A. L. Hoffman, *J. Am. Chem. Soc.*, **47**, 1686 (1925); (b) P. Mamalis, J. Green, and D. Mehale, *J. Chem., Soc.*, 229 (1960).

N-(1-Methylpropoxy)phthalimide (4.4 g.) on hydrolysis with hydrobromic acid gave 0.7 g. of a salt (31%), m.p. 128–130° with analysis for hydroxylammonium bromide.

Anal. Calcd. for NH_4OBr: N, 12.15; H, 3.53; Br, 70.13. Found: N, 12.11; H, 3.80; Br, 70.60.

Sodium S-[2-(Phthalimidoöxy)ethyl]thiosulfate.—A mixture of β-(phthalimidoöxy)ethyl bromide Ia (n = 2); (25 g., 0.092 mole) and sodium thiosulfate pentahydrate (24 g., 0.096 mole) was refluxed in 50% ethanol (300 ml.) for 3.5 hr. The reaction mixture was evaporated to dryness and the residue extracted twice with boiling absolute ethanol. On cooling the salt (15 g., 50%) was obtained; m.p. 144°. Recrystallization from methanol raised the m.p. to 153–156°.

Anal. Calcd. for $C_{10}H_8NO_6S_2Na$ (325.3): C, 36.92; H, 2.47; N, 4.30; S, 19.71; Na, 7.06. Found: C, 36.72; H, 3.02; N, 4.26; S, 19.68; Na, 6.94.

Some Chemical Reactions of 3,9-Dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide

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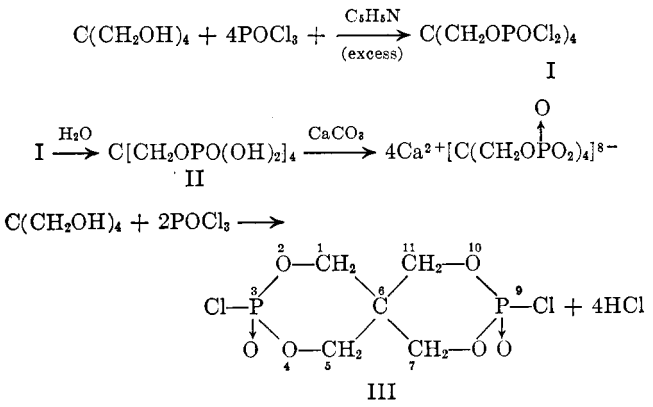
The preparation of pure 3,9-dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-dioxide and its chemical reactivity are described.

Condensation products of pentaerythritol with phosphoryl chloride have been described.[1,2] With an excess of phosphoryl chloride in the presence of pyridine as an acid acceptor, the open-chain structures I and II were obtained,[1] the latter in the form of its neutral calcium salt. Condensation of pentaerythritol with an excess of more than two moles of phosphoryl chloride in the absence of an acid acceptor apparently led to the difunctional cyclic spiro structure III in contaminated crude form. The analytical data reported for III are incomplete, however, and no reference is made to attempted purification.[2]



III

In the present study, we have found that, for the preparation of pure III, a large excess of phosphoryl chloride has to be employed. The crude reaction product finally obtained must be subjected to treatment with several solvents, followed by recrystallization from glacial acetic acid. The compound so obtained, 3,9-dichloro - 2,4,8,10 - tetraoxa - 3,9 - diphosphaspiro[5.5]-undecane 3,9-dioxide, melted at 233–235°, contrary to a previous report.[2]

Anhydrous dimethylformamide dissolves the phosphospirane in all proportions at room temperature with the formation of clear and colorless solutions. On prolonged standing the solutions remain clear, but become deep yellow after a few hours. Upon careful evaporation at reduced pressure, a yellow-brown glassy material is obtained which possesses the properties of a salt. Structure IV is assigned to this product, which resembles the structure of the so-called Vilsmeier-Haak adducts, since it is soluble in water and contains ionic chlorine.

Such adducts with dimethylformamide are known for highly reactive phosphorus halides, such as phosphoryl chloride[3] and dialkyl phosphorochloridates.[4] The structural formula IV is also supported by the presence of a strong absorption band at approximately 6.0 μ, in its infrared spectrum, indicative of the presence of C=N groups, and the presence of a group of absorptions characteristic of the phosphospirane structure appearing at 10.85–14.60 μ (*cf.* tables of infrared spectra).

A surprising result was obtained when the yellowish solutions of III in dimethylformamide were refluxed in the presence of equimolar amounts of aliphatic compounds containing hydroxyl groups, such as ethylene glycol, 1,4-butanediol, 1,4-hydroxymethylcyclohexane, and 1-octanol. A quantitative amount of the well crystallized acidic dimethylammonium salt (V) separated from the solution after a short heating period. It is apparent that the dimethylammonium cation must have been formed by cleavage of the amide. The relationship of this salt to the hitherto unknown free acid, 3,9-dihydroxy - 2,4,8,10 - tetraoxa - 3,9 - diphosphaspiro-[5.5]undecane 3,9-dioxide (VI), was demonstrated convincingly by titration of an authentic sample, obtained by direct hydrolysis of III in water at 90°, with one mole of dimethylamine. This titration resulted in a crystalline material, m.p. 263°, identical in all respects with V.

The unexpected reaction of solutions of III in dimethylformamide with aliphatic alcohols will be discussed in detail for the case of 1,4-butanediol. In the absence of solvent, III was converted by the diol into VI. Considerable amounts of tetrahydrofuran, 1,4-dichlorobutane, and 4-chlorobutanol were detected in this reaction. Scheme 1 describes in detail the fate of the phosphorus-containing component in the course of this reaction.

Identification of the diacid VI obtained by the three different routes indicated was made by titration, analysis, and infrared spectrum. The titration curve of VI

(1) V. Bellavita and O. Tiberi, *Ricerca sci.*, **1952**, 69.

(2) R. Charonnat, J. V. Harispe, M. Harispe, O. Efimovsky, and M. L. Chevillard, *Ann. pharm. franc.*, **10**, 666 (1951).

(3) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Ber.*, **92**, 837 (1959).

(4) F. Cramer and M. Winter, *ibid.*, 989 (1961).