out in 250-ml. volumetric flasks agitated on an Eberbach shaking machine. Reactions at 20 ± 1° were carried out in air conditioned room; reactions at 30 ± 0.2° were immersed in a constant temperature water-bath. In each flask there was placed 30 millimoles of the butyl halide or tosylate dissolved in 10 ml. of dry tetrahydrofuran. At zero time there was added 10 ml. of a tetrahydrofuran solution containing sodium diethyl phosphonate (prepared from 10 millimoles of diethyl phosphonate). After shaking for the appropriate time period, the reaction was stopped by the addition of 150 ml. of water and 60 ml. of pentane. After thorough mixing, the pentane layer was removed; the aqueous layer was diluted to volume and aliquot portions were analyzed for halide ion by the Volhard titration and for tosylate ion by comparison of the ultraviolet absorption at 261 mμ with that of a standard solution of sodium tosylate.

Diethyl γ-Chloropropylphosphonate (IIIa) from Trimethylene Chlorohydrin Tosylate (I).—A solution of I (14.9 g., 0.06 mole) and sodium diethyl phosphonate, prepared by the action of excess sodium on diethyl phosphonate (8.57 g., 0.06 mole), in tetrahydrofuran (50 ml.) was stirred at room temperature for 72 hr. Then dry pentane (70 ml.) was added and the mixture filtered. The solid residue (9.41 g.) contained chlorine (6.0%), sulfur (13.1%) and phosphorus (2.6%). The filtrate was concentrated under reduced pressure and the residue (14.2 g.) distilled. The fraction (4.3 g.) boiling at 59–78° (0.04 mm.) was redistilled to yield diethyl γ-chloropropylphosphonate (IIIa), 2.1 g., 16%, b.p. 68–70° (0.05 mm.), $n^{25}D$ 1.4423.

Anal. Calcd. for $C_7H_{16}O_3PCl$: C, 39.16; H, 7.51; P, 14.44. Found: C, 38.53; H, 7.80; P, 14.10.

The higher boiling fraction (6.7 g.) appeared to be a mixture from which no pure substances could be isolated.

Repetition of the above reaction on a 0.4 molar scale yielded similar results with diethyl γ-chloropropylphosphonate isolated in 22% yield.

From Trimethylene Chlorobromide (II).—To a stirred solution of sodium diethyl phosphonate, prepared by the action of excess sodium on diethyl phosphonate (27.6 g., 0.20 mole) in tetrahydrofuran (400 ml.), trimethylene chlorobromide (63.0 g., 0.40 mole) was added. After 15 minutes a white solid began to separate. After stirring at room temperature for 4 hr. the reaction mixture was filtered, the filtrate concentrated under reduced pressure and the residue distilled. After recovery of the excess chlorobromide, a fraction boiling at 85–100° (0.32 mm.) was collected and redistilled to yield diethyl γ-chloropropylphosphonate (IIIa), 23.2 g., 54%, b.p. 97–99° (0.25 mm.), $n^{25}D$ 1.4429.

γ-Chloropropylphosphonic Acid (IIIb).—A mixture of IIIa (3.0 g.) and concentrated hydrochloric acid (30 ml.) was heated under reflux overnight. Then the hydrochloric acid was removed under reduced pressure, and benzene (10 ml.) was added and distilled away to remove the last traces of acid. The crystalline residue (2.0 g., m.p. 95–102°) was recrystallized from chloroform to give γ-chloropropylphosphonic acid, 1.7 g., 76%, m.p. 101–104°. Further recrystallization from chloroform furnished the analytical sample, m.p. 104–105°.

Anal. Calcd. for $C_3H_8O_3PCl$: C, 22.72; H, 5.08; P, 19.55; Cl, 22.37; neut. equiv., 158.6. Found: C, 23.12; H, 5.12; P, 19.60; Cl, 22.14; neut. equiv., 158.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, CHEMICAL WARFARE LABORATORIES AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Synthesis of a Series of Vicinally Substituted Hydroxamic Acids[1]

BY MARVIN A. STOLBERG,[2] WILLIAM A. MOSHER AND THEODOR WAGNER-JAUREGG

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A series of hydroxamic acids were prepared by standard procedures from the corresponding esters with the exception of *o*-methoxybenzohydroxamic acid which was obtained from the acid chloride. Compounds which have not been previously reported in the literature are: *o*-nitrobenzohydroxamic, *o*-methoxybenzohydroxamic, *o*-dimethylaminobenzohydroxamic, *cis*-hexahydrophthalohydroxamic and *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acids. *cis*-N-Hydroxyhexahydrophthalamide and *endo-cis*-N-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide were obtained from the reaction of the corresponding anhydrides with hydroxylamine. Their infrared spectra were compared to that of N-hydroxyphthalimide and N-hydroxyisophthalimide.

Hydroxamic acids may be prepared by treating esters, acid chlorides or acid anhydrides with hydroxylamine.[3] Other methods, although useful in certain specific cases, generally have limited application. The hydroxamic acids described in this paper were prepared from the corresponding esters with the exception of *o*-methoxybenzohydroxamic acid which was obtained from the acid chloride. Since difficulties were encountered in the isolation and purification of the hydroxamic acids and prime attention was paid to the purity of the products, the yields reported do not necessarily reflect efforts to reach a maximum. A good general method for the separation of certain hydroxamic acids from the corresponding carboxylic acids which are frequent impurities is by treatment of an alkaline aqueous solution with carbon dioxide, which results in precipitation of the hydroxamic acid. This method is applicable to water-insoluble hydroxamic acids that have a pK_a above 9.0.

Compounds prepared for this investigation which have not been previously reported in the literature are: *o*-nitrobenzohydroxamic,[4] *o*-methoxybenzohydroxamic,[4] *o*-dimethylaminobenzohydroxamic, *cis*-hexahydrophthalohydroxamic and *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acids. The latter compound proved to be a powerful vesicant and contact with the skin should be avoided. This compound has a basic structure similar to cantharidine, which is a well known vesicant.

An attempt was made to prepare *o*-hydroxymethylbenzohydroxamic acid from phthalide and hydroxylamine. A small portion of the crude sodium salt of the product obtained produced a deep wine color when treated with ferric chloride in 0.1 *N* HCl which is typical of hydroxamic acids. However, treatment of an aqueous solution of the salt with carbon dioxide or hydrochloric acid

(1) Abstracted from the dissertation submitted by M. A. Stolberg to the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956.

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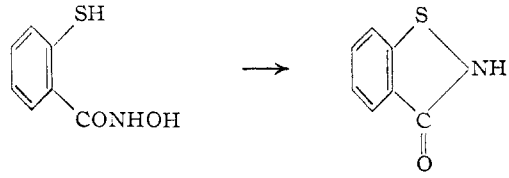
(3) H. L. Yale, *Chem. Revs.*, **33**, 209 (1943); F. Mathis, *Bull. soc. chim., France*, **5**, D9 (1953).

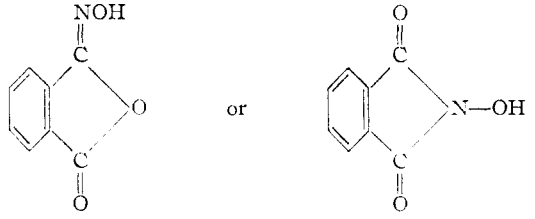
(4) These compounds were reported as the barium salts by R. D. Bright and C. W. Hauser, THIS JOURNAL, **61**, 618 (1939).

yielded phthalide instead of the hydroxamic acid. Similarly, phthalide was obtained from a methanolic solution of the salt when treated with a carboxylic acid resin (IRC-50). The reaction of methyl *o*-mercaptobenzoate and hydroxylamine produced benzisothiazol-3-one (I) instead of the desired *o*-mercaptobenzohydroxamic acid. The formation of I from the ester and hydroxylamine could occur by the elimination of water from *o*-mercaptobenzohydroxamic acid formed as an intermediate.



I does not produce a color with ferric chloride in anhydrous alcohol, in contrast to hydroxamic acids, but when a drop of water was added to the light orange solution, a deep wine color was produced. This indicated that compound I may hydrolyze in water to form the desired hydroxamic acid. However, all attempts to isolate the hydroxamic acid from aqueous solution were unsuccessful.

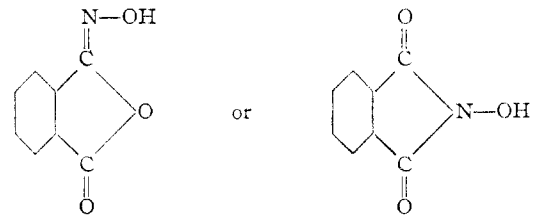
The disodium salt of phthalohydroxamic acid when acidified yields "phthaloxime" (II) instead of the hydroxamic acid.[5]



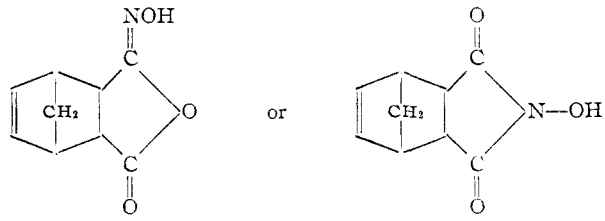
Phthalic anhydride mono-oxime (IIa) N-hydroxyphthalimide (IIb)

Since *cis*-hexahydrophthalohydroxamic acid is stable, an attempt was made to prepare the corresponding half-hydroxamic acids from the reactions of *cis*-hexahydrophthalic anhydride and *endo-cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride with hydroxylamine. The products isolated, III and IV, respectively, had analyses which corresponded to the "phthaloxime" structure instead of the desired half-hydroxamic acids. The titration of these compounds with alkali gave no indication of the formation of the corresponding half-hydroxamic acids.

Brady and associates[6] formulated the structure of "phthaloxime" (II) as phthalic anhydride mono-oxime (IIa). Ames and Grey[7] reported the preparation of N-hydroxyphthalimide (IIb) by the reaction of phthalic anhydride with O-benzylhydroxylamine followed by hydrogenolysis, and this product was found to be identical with "phthaloxime." Ames and Grey believe that the correct structure is N-hydroxyphthalimide (IIb) based upon the following observations: 1. N-benzyloxy- and N-hydroxy-phthalimide show infrared



III



IV

imide absorption bands (1700–1800 cm.$^{-1}$) similar to those of N-ethylphthalimide. 2. The ultraviolet absorption spectra are also similar to those of phthalimide. 3. The pK_a value (7.0) is well outside the normal range of oximes (pK_a *ca.* 10–12).

The infrared spectra of IIb, III and IV indicated that they are structurally similar. The carbonyl absorption bands around 1700 cm.$^{-1}$ (see Table I) are clearly different from those of N-hydroxyisophthalimide (phthalic anhydride monoöxime, IIa) obtained by Carpino[8] which has the characteristic doublet at 1810 and 1825 cm.$^{-1}$. Carpino also noted that the iso derivatives lack the very broad carbonyl bands of normal phthalimides which are present in II, III and IV. III and IV have therefore been assigned the structures *cis*-N-hydroxyhexahydrophthalimide and *endo-cis*-N-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide.

TABLE I

INFRARED CARBONYL ABSORPTIONS AND pK_a VALUES

	Carbonyl absorptions[a]			
	a	b	c	pK_a
IIa	..	1825, 1810 s	..	..
	..	1690m 1610w	..	..
IIb	1708, 1745 s	1705, 1745 s	1745	7.0
	1795s	1787s	1795	..
III	1690, 1710 s 1790s	..	..	6.0
IV	1695, 1710 s 1770s	..	..	5.9

[a] a, present investigation; b, Carpino[8]; c, Ames and Grey.[7]

Experimental

***o*-Methoxybenzohydroxamic Acid.**—A chloroform solution of 8.5 g. (0.5 mole) of *o*-methoxybenzoyl chloride was added dropwise, with stirring, to 100 ml. of a chloroform solution containing 3.8 g. (0.055 mole) of hydroxylamine hydrochloride and 10.6 g. (0.105 mole) of triethylamine. The solution was stirred for an hour to ensure complete reaction after which the solvent was vacuum distilled. The solid residue was dissolved in water and hydrochloric acid

(5) C. D. Hurd, C. M. Buess and L. Bauer, *J. Org. Chem.*, **19**, 1140 (1954).

(6) O. L. Brady, L. C. Baker, R. F. Goldstein and S. Harris, *J. Chem. Soc.*, 529 (1938).

(7) D. E. Ames and T. F. Grey, *ibid.*, 3518 (1955).

(8) Private communication from Dr. L. A. Carpino.

was added with cooling to *p*H *ca.* 2, yielding a precipitate which was filtered, washed with cold water and dissolved in dilute alkali. Small pieces of Dry Ice were added to the alkaline solution and a precipitate was obtained which was recrystallized from acetone–ether, m.p. 129–131°, yield 6.4 g. (77%).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.5; H, 5.5; N, 8.4. Found: C, 58.2; H, 5.8; N, 8.2.

o-Aminobenzohydroxamic Acid.—The procedure used for the preparation of the other hydroxamic acids was very similar, differing only in the quantities employed and methods of isolation. The general procedure was as follows, using *o*-aminobenzohydroxamic acid as an example. To a solution of 5.0 g. (0.03 mole) of sodium in 150 ml. of absolute methanol there was added a solution of 7.0 g. (0.1 mole) of hydroxylamine hydrochloride in 100 ml. of absolute methanol. The sodium chloride which precipitated was removed by filtration, and 15.1 g. (0.1 mole) of methyl anthranilate was added to the filtrate. The resulting solution was heated on a steam-bath for 30 minutes. Upon cooling, the sodium *o*-aminobenzohydroxamate which precipitated was filtered, dissolved in a minimum quantity of water and the solution acidified to *p*H 4 with acetic acid. The resultant precipitate was recrystallized twice from water to yield a colorless product, m.p. 142–143°, yield 3.2 g. (71%). The melting point reported in the literature is 149°.[9]

Anal. Calcd. for $C_7H_8O_2N_2$: C, 55.5; H, 5.3; N, 18.6. Found: C, 55.3; H, 5.3; N, 18.4.

o-Nitrobenzohydroxamic Acid.—When 20.0 g. (0.11 mole) of methyl *o*-nitrobenzoate was added to the alcoholic hydroxylamine solution, an orange color developed. Only a small quantity of the sodium salt precipitated using conditions described above. The solvent was removed under reduced pressure and the resulting crude solid was dissolved in water. Upon acidification a yellow precipitate was obtained which was recrystallized from hot water. The yellow needles melted at 131–133°, yield 10.0 g. (50%).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.2; H, 3.3; N, 15.4. Found: C, 46.3; H, 3.6; N, 15.2.

o-Dimethylaminobenzohydroxamic Acid.—Only a small quantity of hydroxamic acid formed during the first hour based upon the test with ferric chloride. Heating the solution yielded products which were difficult to separate and isolate. The best procedure was to stir the ester and hydroxylamine at room temperature for 24 hr. The solvent was vacuum evaporated and the solid residue stirred with ether to remove any unreacted ester. The precipitate was filtered, dissolved in a small quantity of water and carbon dioxide bubbled into the aqueous solution. The hydroxamic acid precipitated and was recrystallized from ether, m.p. 129–131°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.1; H, 6.7; N, 15.6. Found: C, 59.5; H, 6.7; N, 15.3.

(9) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).

***cis*-Hexahydrophthalohydroxamic Acid.**—This hydroxamic acid obtained from 10.0 g. (0.05 mole) of methyl *cis*-hexahydrophthalate was prepared and isolated exactly as above, m.p. 191–193°, yield 6.0 g. (60%).

Anal. Calcd. for $C_8H_{14}O_4N_2$: C, 47.5; H, 7.0; N, 13.9. Found: C, 47.9; H, 7.1; N, 13.3.

***exo-cis*-3,6-Endoxohexahydrophthalohydroxamic Acid.**—Treatment of the aqueous solution of the disodium salt of *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acid (obtained as above) with carbon dioxide or hydrochloric acid did not produce a precipitate. The aqueous solution, after treatment with hydrochloric acid, was evaporated to dryness. The mixture was extracted with acetone in a Soxhlet extractor 4 hr., and a white crystalline product was obtained on evaporation of the acetone, m.p. 186° dec. *Care* should be exercised when handling this compound because it is a vesicant.

Anal. Calcd. for $C_8H_{12}O_5N_2$: C, 44.5; H, 5.7; N, 13.0. Found: C, 44.8; H, 5.8; N, 12.8.

N-Hydroxyhexahydrophthalimide.—A solution of 7.7 g. (0.05 mole) of *cis*-hexahydrophthalic anhydride[10] in 50 ml. of methyl alcohol was added to a solution containing 1.82 g. (0.05 mole) of hydroxylamine in 10 ml. of methyl alcohol. A red color was obtained with ferric chloride immediately. The reaction mixture was stirred for several hours at room temperature after which the solvent was vacuum removed. A colorless viscous oil was obtained which crystallized by scratching with a glass rod. The water-soluble, white crystalline product was recrystallized from chloroform–ligroin (60–90), m.p. 110–112°, yield 7.0 g. (83%).

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.7; H, 6.6; N, 8.3. Found: C, 56.7; H, 6.6; N, 8.4.

N-Hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide.—To a solution of 9.85 g. (0.06 mole) of *endo-cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride[10] in 50 ml. of methyl alcohol there was added an equimolar mixture of hydroxylamine and sodium methoxide in methanol. A small quantity of precipitate was observed after 24 hr. at room temperature. The solvent was removed under reduced pressure after which the salt was dissolved in a minimum quantity of water and precipitated with acid. The white crystalline product was recrystallized from chloroform–ligroin (60–90) and produced a red color with ferric chloride, m.p. 165–166°, yield 8.6 g. (80%).

Anal. Calcd. for $C_9H_9O_3N$: C, 60.3; H, 5.1; N, 7.8. Found: C, 60.1; H, 5.0; N, 7.6.

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(10) Samples were kindly supplied by the National Aniline Division of the Allied Chemical and Dye Corporation, 40 Rector Street, New York 6, N. Y.