oxide to an isocyanate[4] which leads to complex mixtures which were difficult to separate and purify. At lower temperature and longer reaction time, however, a small amount of isoxazoline was isolated and identified.

The introduction of the second nitro group stabilizes the nitrile oxide. The addition reaction with 1-MVT occurred immediately and the yield of XI was nearly quantitative. The lower yield of the 3-(2,4-dinitrophenyl)-5 (2-methyltetrazoyl)isoxazoline (XII) can be explained by lower reactivity of the 2-MVT. The failure of the addition reaction with 1-MCT and 2-MCT might be attributed to the steric effect as well as lower reactivity of MCT.

The infrared spectra of isoxazolines (N—O band at 1300–1380 cm^{-1}, C=N band at 1600–1635 cm^{-1}) and oxadiazoles (C—O band at 1030–1035 cm^{-1}) are consistent with infrared data reported in the literature.[7]

The CH_2 and CH bands could not be rigorously assigned. However, further support for the assigned structure of these compounds was obtained from nmr spectra.

The chemical shifts of the resonance lines in the range δ 3.97 to 4.17 and 6.02 to 6.17 are assigned, respectively, to the methylene and methine protons of the isoxazoline ring. The area of the methylene resonance to that of the methine resonance is in the ratio 2:1. These protons seem to approximate an ABX pattern from which the following coupling constants and chemical shift were estimated: $|J_{AB}| \sim 17.0$, $|J_{AX}| \sim 5.4$, $|J_{BX}| \sim 11.6$ cps; $\nu_0\delta_{AB} \sim 26.3$ ppm.

The chemical shift of the 1-methyl and 2-methyl resonances of the tetrazole ring occurred at δ 4.24–4.26 and 4.35–4.41, respectively. These values are in agreement with reported chemical shifts for methyl substituted tetrazoles.[8]

(7) M. Milone and E. Borello, *Gazz. Chim. Ital.*, **81**, 677 (1951); *cf. Chem. Abstr.*, **46**, 2402 (1952).

(8) (a) F. J. Pisacane and M. J. Cziesla, 151st National Meeting of the American Chemical Society, Abstracts, Organic Division, Pittsburgh, Pa., 1966, Abstracts, p K 95; (b) J. H. Markgraf, W. T. Bachmann, and D. P. Hollis, *J. Org. Chem.*, **30**, 3472 (1965).

Experimental Section[9]

General Procedure for I, II, and III.—A solution of nitrobenzhydroxyamoyl chloride (0.01 mole) in 120 ml of ether was extracted with a cold 5% aqueous sodium carbonate solution (13 ml, 0.01 mole) in a separatory funnel and the ether layer containing nitrobenzonitrile oxide was then removed, washed with a small quantity of water, dried over anhydrous calcium chloride for about 2 min, and treated with 1-MVT (0.009 mole).[10] A reaction developed almost immediately at the end of which the reaction mixture was set aside for about 2 hr at room temperature. Removal of the solvent under diminished pressure afforded an oily product which was treated with a small quantity of methanol and left in the refrigerator overnight. The solid that separated was filtered, washed with a little ice-cold methanol, and recrystallized from methanol or benzene.

General Procedure for IV and V.—The procedure was similar to that above, except that benzene was used instead of ether and 2-MVT was used instead of 1-MVT. The mixture was refluxed for 4–6 hr then allowed to stand at room temperature for 24 hr. Removal of the solvent under diminished pressure afforded an oily product which was treated similarly as above.

In the case of *o*-nitrobenzonitrile oxide the reaction mixture was stored at room temperature for 1 week, then worked up as above.

General Procedure for Oxadiazole.—A solution of nitrobenzhydroxamoyl chloride (0.01 mole) in 150 ml of ether was extracted with a cold 5% aqueous sodium carbonate solution (13 ml, 0.01 mole) in a separatory funnel and the ether layer containing nitrobenzonitrile oxide was then removed, washed with a small quantity of water, dried over anhydrous calcium chloride for about 2 min, and treated with 1- or 2-MCT.[11] The reaction mixture was allowed to stand at room temperature with occasional shaking for 2–5 days. Removal of the solvent under diminished pressure afforded an oily product which was treated with a small quantity of ethanol. The solid that separated was filtered, washed with ethanol, and repeatedly recrystallized from ethanol.

In the case of the *o*-nitrobenzonitrile oxide or 2,4-dinitrobenzonitrile oxide, the reaction conditions were varied but only oily, reddish tarlike materials were obtained.

Registry No.—I, 10221-26-8; II, 10221-27-9; III, 10221-28-0; IV, 10221-29-1; V, 10221-30-4; VI, 10221-31-5; VII, 10239-66-4; VIII, 10221-32-6; IX, 10221-33-7; X, 10221-34-8; XI, 10221-35-9; XII, 10221-36-0.

(9) All melting points are uncorrected.

(10) W. G. Finnegan, R. A. Henry, and S. Skolink, U. S. Patent 3004959 (1961); *cf. Chem. Abstr.*, **56**, 15518c (1962).

(11) E. Oliveri-Mandala and T. Passalacqua, *Gazz. Chim. Ital.*, **43**, 468 (1913).

Preparation of Unsymmetrical Dithiooxamides[1a]

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A series of unsymmetrical aryl-substituted dithiooxamides were synthesized by thionation of the corresponding oxygen analogs with phosphorus pentasulfide. The ultraviolet absorption spectra of several monothiooxamides isolated have been reported and structural assignments made on the basis of these spectra. A number of alkyl-substituted dithiooxamides were synthesized by means of a new one-step reaction between the sodium salt of dithiooxamide and an aliphatic amine.

A widespread interest has recently been shown in the chemistry of dithiooxamide (rubeanic acid) and its derivatives. Hurd[2] has reviewed the literature of dithiooxamide and its derivatives; applications as metal deactivators in petroleum products, vulcanization accelerators, bacteriostatic agents, plant growth regulators, spirit duplication, photoconductolithography, and analytical reagents have been reported. More recently, publications have appeared on the possible application of these compounds in thermography[3] and as semiconductors.[4]

The majority of the dithiooxamide derivatives previously reported are N,N′ symmetrically substituted compounds, although a small number of unsymmetrical

(1) (a) A portion of this work was carried out at Wheeling College, Wheeling, W. Va. (b) To whom communications should be addressed.

(2) R. N. Hurd, "Review of Scientific and Patent Literature on Dithiooxamide: Its Substituted Derivatives and Their Metal Complexes," Mallinckrodt Chemical Works, St. Louis, Mo., 1963.

(3) Xerox Corp., British Patent 1,029,997 (May 18, 1966).

(4) M. J. S. Dewar and A. M. Talati, *J. Am. Chem. Soc.*, **86**, 1592 (1964).

TABLE I

$C_6H_5NHC(=S)C(=S)NHR$

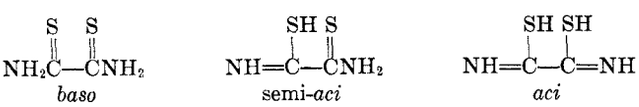
No.	R	Formula	% yield	Mp, °C	Calcd, % S	Calcd, % N	Found, % S	Found, % N
I	*n*-C_3H_7	$C_{11}H_{14}N_2S_2$	21.2	−3 to −4[a]	26.90	11.75	26.40	11.50
II	*i*-C_3H_7	$C_{11}H_{14}N_2S_2$	66.9	46.4–48.0[b]	26.90	11.75	26.58	11.86
III	$C_6H_5CH_2$	$C_{15}H_{14}N_2S_2$	46.7	54.4–55.0	22.39	9.78	21.87	9.72
IV	4-$CH_3C_6H_4$	$C_{15}H_{14}N_2S_2$	62.5	136.6–138.6	22.39	9.78	22.27	9.60
V	4-$CH_3OC_6H_4$	$C_{15}H_{14}N_2OS_2$	12.4	119.6–120.8	21.20	9.27	21.01	9.19
VI	4-FC_6H_4	$C_{14}H_{11}FN_2S_2$	70.8	152.4–155.4	22.07	9.65	21.89	9.84
VII	4-ClC_6H_4	$C_{14}H_{11}ClN_2S_2$	39.9	138.6–139.2	20.90	9.13	20.75	9.01
VIII	4-BrC_6H_4	$C_{14}H_{11}BrN_2S_2$	24.8	129.2–130.6	18.25	7.98	18.77	8.20
IX	4-HOC_6H_4	$C_{14}H_{12}N_2OS_2$	5.5	153.6–154.8	22.24	9.71	22.08	9.92
X	4-$NO_2C_6H_4$	$C_{14}H_{11}N_3O_2S_2$	19.1	182.8–183.8	20.21	13.24	19.96	13.86
XI	2-(5-ClC_5H_3N)	$C_{13}H_{10}ClN_3S_2$	0.35	146.8–147.8	20.83		20.54	[c]
XII	4,4′-Difluorodithiooxanilide	$C_{14}H_{10}F_2N_2S_2$	2.8	202–202.5	20.80	9.09	20.88	9.24

[a] Bp 150–153° (0.15 mm). [b] Bp 160–168° (0.5 mm). [c] Insufficient material available.

TABLE II

No.	Structure	Formula	Mp, °C	Calcd, % S	Calcd, % N	Found, % S	Found, % N
XIII	4-$FC_6H_4NHC(S)C(O)NHC_6H_5$	$C_{14}H_{11}FN_2OS$	157–159	11.70	10.21	11.72	9.91
XIV	4-$NO_2C_6H_4NHC(O)C(S)NHC_6H_5$	$C_{14}H_{11}N_3O_3S$	186–187	10.64	13.94	10.46	13.87
XV	2-(5-ClC_5H_3N)$NHC(O)C(S)NHC_6H_5$	$C_{13}H_{10}ClN_3OS$	163–164	10.99	14.40	10.83	14.47
XVI	4,4′-Difluorothiooxanilide	$C_{14}H_{10}F_2N_2OS$	180–182	10.97	9.58	10.85	9.62

derivatives have been prepared.[5] In this investigation, a series of unsymmetrical aryl- and alkyl-substituted derivatives have been synthesized in an attempt to determine the effect of varied electronic substituents on the structure and reactivity of this class of compounds. Although the dithiooxamide system can exist in the *baso*, semi-*aci*, or *aci* forms, existing data support the *baso* form as the predominant structure.[5h,6]



Aryl Dithio- and Thiooxamides

A series of arylalkyl- and diaryl-substituted dithiooxamides (Table I) were prepared by the thionation of the corresponding oxamides with phosphorus pentasulfide in boiling xylene. Several preparations were carried out by the fusion of phosphorus pentasulfide and the oxamide but this method offered no advantage in yield over the solvent reaction. Isolation and purification of the reaction products were affected by chromatographic separation on an alumina column. Incomplete thionation in several of the above reactions resulted in the formation of monothiooxamide derivatives (Table II). Structural assignments for these compounds (XIII–XVI) were made on the basis of ultraviolet spectra.[7]

Sandstrom has studied thioamide spectra extensively and he reports[5h] bathochromic shifts of $\pi \rightarrow \pi^*$ transitions on extended conjugation of the thioamide system. Monothiooxamides (RNHCSCONHR) undergo a $\pi \rightarrow \pi^*$ transition at longer wavelengths than do corresponding thioamides (RCSNHR). We found that a study of the ultraviolet absorption spectrum of monothiooxanilide ($C_6H_5NHCSCONHC_6H_5$) [λ_{max} 314 mμ (ϵ 15,400) and 227.5 mμ (ϵ 20,900)][8] in relation to the spectra of the component systems thioacetanilide ($CH_3CSNHC_6H_5$) [λ_{max} 297.5 mμ (ϵ 11,720)] and acetanilide ($CH_3CONHC_6H_5$) [λ_{max} 242 mμ (ϵ 14,400)][9] and a similar study of the substituted derivatives XIII, XIV, and XV (Table II) provides a means for structural assignments. When the conjugation of thioacetanilide is extended by coupling with an acetanilide fragment (C_6H_5NHCO), as in monothiooxanilide, the $\pi \rightarrow \pi^*$ transition of thioacetanilide (297.5 mμ) shifts approximately 16 mμ to longer wavelengths (314 mμ). At the same time the monothiooxanilide spectrum shows additional strong absorption (227.5 mμ) which is approximately 14 mμ to shorter wavelengths than the absorption maximum of acetanilide (242 mμ). It is assumed, therefore, that monothiooxanilides will show two ultraviolet absorption maxima, one at longer wavelengths than the position of absorption of the independent thioamide component, and one at shorter wavelengths to the absorption maximum of the independent amide component.

Consideration of the spectra of the N-2-(5-chloropyridyl) derivative XV and its component systems suggests a N^O-2-(5-chloropyridyl)-N^S-phenylthiooxamide[10] structure [2-(5-ClC_5H_3N)$NHCOCSNHC_6H_5$]. By an analogy to the unsubstituted monothiooxanilide system the spectrum of XV, with maxima at 302.5 mμ (ϵ 18,000) and 230 mμ (ϵ 17,300), represents a bathochromic shift from the position of thioacetanilide absorption (λ_{max} 297.5 mμ) and a hypsochromic shift from the position of absorption of 2-acetamido-5-chloropyridine

(5) (a) O. Wallach, *Ann.*, **262**, 354 (1891); (b) A. Reissert, *Ber.*, **37**, 3708 (1904); (c) H. L. Klöpping and G. J. M. VanDerKerk, *Rec. Trav. Chim.*, **70**, 917 (1951); (d) J. Metzger and H. Plank, *Bull. Soc. Chim. France*, 684 (1956); (e) G. Bahr, *Angew. Chem.*, **73**, 628 (1961); (f) B. Kumelj and M. Tisler, *Vestn. Slov. Kem. Drustva*, **5**, 69 (1958); (g) A. D. Grabenko and P. S. Pelkis, *Zh. Obshch. Khim.*, **30**, 1222 (1960); A. D. Grabenko and P. S. Pelkis, *ibid.*, **31**, 2739 (1961); (h) B. Persson and J. Sandstrom, *Acta Chem. Scand.*, **18** (1964), 1059, and preceding papers.

(6) P. J. Wheatley, *J. Chem. Soc.*, 396 (1965).

(7) Ultraviolet, infrared, and proton magnetic resonance spectra of the compounds contained in this paper will be discussed in a forthcoming publication.

(8) All spectra were taken in ethanol.

(9) H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 5133 (1954).

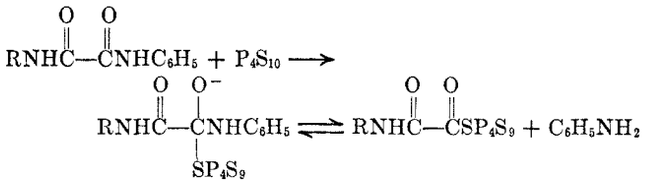
(10) This is a nomenclature designation adopted by B. Milligan and J. W. Swan [*J. Chem. Soc.*, 2969 (1959)] to indicate amide or thioamide nitrogen.

[λ_{max} 244 mμ (ϵ 17,100)]. The alternate structure for XV in which the position of sulfur and oxygen are exchanged [2-(5-ClC_5H_3N)$NHCSCOC_6H_5$] is discounted on the basis that N-2-(5-chloropyridyl) thioacetamide has a maximum at 310 mμ (ϵ 19,800) and a hypsochromic shift to the 302.5-mμ maximum observed for XV is inconsistant with the above observations of long wavelength shifts on increased conjugation.

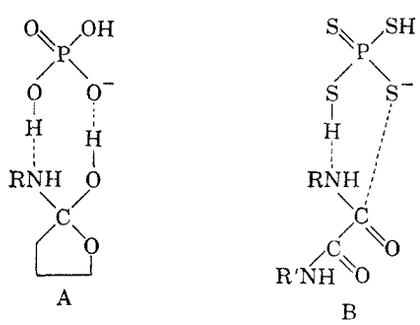
In the case of the 4-nitromonothiooxanilide derivative XIV only one band is observed in the 220–360-mμ region at 322.5 mμ (ϵ 25,900). This spectrum represents a bathochromic shift of the thioacetanilide band at 297.5 mμ on conjugation with a 4-nitroacetanilide function and is consistent with the structural assignment N^O-(4-nitrophenyl)-N^S-phenylthiooxamide (4-$NO_2C_6H_4NHCOCSNHC_6H_5$). The anticipated maximum at shorter wavelengths than the position of 4-nitroacetanilide absorption [λ_{max} 316 mμ (ϵ 11,400)][9] fails to appear in the spectrum of XIV apparently because this absorption falls within the region of the 322.5-mμ maximum and in fact must contribute to the intensity of this band. The alternate structure for XIV containing a N-phenylamide moiety (C_6H_5-NHCO) and a N-(4-nitrophenyl)thioamide moiety (4-$NO_2C_6H_4NHCS$) is eliminated for several reasons; a bathochromic shift of the 4-nitrothioacetanilide absorption [λ_{max} 343 mμ (ϵ 13,890)] should clearly provide absorption at longer wavelengths than the maximum observed at 322.5 mμ and hypsochromic shift of the position of acetanilide absorption at 242 mμ should result in a maximum in the 230-mμ region. Neither is observed.

A structural assignment for the 4-fluoromonothiooxanilide derivative XIII is difficult because of the similarity of absorption of the unsubstituted and fluoro-substituted analogs. The spectra of acetanilide [λ_{max} 242 mμ (ϵ 14,400)] and 4-fluoroacetanilide [λ_{max} 240 mμ (ϵ 13,100)][9] and thioacetanilide [λ_{max} 297.5 mμ (ϵ 11,720)] and 4-fluorothioacetanilide [λ_{max} 291 mμ (ϵ 10,700)] permit either possible structural assignment for XIII [λ_{max} 312.5 mμ (ϵ 13,020) and 227.5 mμ (ϵ 16,340)]. An unequivocal proof of structure of this and the above monothiooxanilide derivatives can best be established by independent synthesis. An appropriate synthetic approach to monothiooxanilides has previously been reported by Milligan and Swan.[11]

In the thionation reactions of N-phenyl-N′-(4-hydroxyphenyl)oxamide, N-phenyl-N′-(4-nitrophenyl)oxamide, and N-phenyl-N′-2-(5-chloropyridyl)oxamide, dithiooxanilide was isolated from the reaction mixture along with the normal substituted dithiooxamide products. Sufficient data is not available to indicate the manner in which this dithiooxanilide is formed; however, the possibility exists that the symmetrical product results from partial hydrolysis and/or amine exchange. Hurd, *et al.*,[12] report amine exchange when they refluxed excess butylamine with N,N′-dimethyldithiooxamide. In order for dithiooxanilide to be formed, however, it is necessary for aniline to be present to exchange with the 4-hydroxyaniline, 4-nitroaniline, and 5-chloro-2-aminopyridine fragments. This could conceivably occur as a result of cleavage of an oxamide–phosphorus pentasulfide complex formed as an intermediate in the thionation reaction as is shown below.



The subsequent exchange of aniline for 4-hydroxyaniline, 4-nitroaniline, and 5-chloro-2-aminopyridine would then be favored by the stronger nucleophilic character of aniline as compared to these weaker bases. It is also possible that aniline could arise from a hydrolysis reaction catalyzed by a phosphorus oxygen or phosphorus sulfur species. Small amounts of water which could be present under reaction conditions can result in the formation of phosphate or thiophosphate species which might catalyze amide cleavage. Cunningham and Schmir[13] have reported phosphate-catalyzed hydrolysis of imino lactones in which phosphate concentration is as low as 0.0005 *M*. The phosphate–imino lactone intermediate (A) which they propose could have analogy in a thiophosphate intermediate (B) in the



thionation reaction. This intermediate (B) alternatively could proceed to thiooxamide product or hydrolysis products. A more complete study of this reaction will be necessary before a complete mechanistic picture is available.

Alkyldithiooxamides

N,N′-Dialkyldithiooxamides are readily prepared in good yield by means of the Wallach reaction between primary aliphatic amines and dithiooxamide in ethanolic solution. Monosubstituted aliphatic dithiooxamides are more difficult to prepare by a one-step synthesis and to date only one such preparation has been reported.[5h] A series of alkyldithiooxamides has been synthesized (Table III) by a new one-step method which makes use of the acidic nature of the thiooxamide proton. It was found that one of the thioamide functions of the dithiooxamide system could be blocked effectively by formation of the dithiooxamide salt, thereby enabling ready formation of the monosubstituted product. The yields in this reaction, however, are low owing to hydrolytic decomposition of the dithiooxamide system under the alkaline experimental conditions employed. Hydrolysis of dithiooxamide in varying concentrations of boiling alkali[14] and cold 10% NaOH[5b] have been reported to give sulfide, cyanide, thiocyanate, oxalate, and ammonia. In the course of

(11) B. Milligan and J. M. Swan, *J. Chem. Soc.*, 1194 (1961).
(12) R. N. Hurd, G. DeLaMater, G. C. McElheny, and L. V. Peiffer, *J. Am. Chem. Soc.*, **82**, 4454 (1960).
(13) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).
(14) C. Völckel, *Ann.*, **38**, 314 (1841).

TABLE III

$NH_2C(=S)CNHR$

No.	R	Formula	% yield	Mp, °C	Calcd, % S	Calcd, % N	Found, % S	Found, % N
XVII	C_2H_5	$C_4H_8N_2S_2$	8.1	81.6–82.8	43.25	18.90	42.91	18.98
XVIII	*n*-C_3H_7	$C_5H_{10}N_2S_2$	6.9	42.0–42.7	39.51	17.27	39.73	17.14
XIX	*n*-C_4H_9	$C_6H_{12}N_2S_2$	5.7	35.2–36.0	36.37	15.89	36.42	15.71
XX	$HOCH_2CH_2$	$C_4H_8N_2S_2O$	15.3	100.8–102.6	39.04	17.06	38.84	16.89
XXI	$HOCH_2CH_2CH_2$	$C_5H_{10}N_2S_2O$	6.75	67.2–69.0	35.97	15.71	36.18	15.54
XXII	$(CH_3)_2NCH_2CH_2CH_2$	$C_7H_{15}N_3S_2$	13.2	128–130	31.25	20.46	31.22	20.37

TABLE IV

$C_6H_5NHC(=O)CNHR$

No.	R	Formula	% yield	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
XXIII	4-$CH_3OC_6H_4$	$C_{15}H_{14}N_2O_3$	29	218–220	66.60	5.22	66.43	5.27
XXIV	4-FC_6H_4	$C_{14}H_{11}FN_2O_2$	50	244–245	65.10	4.29	64.82	4.28
XXV	4-ClC_6H_4	$C_{14}H_{11}ClN_2O_2$	52	230–233	61.21	4.04	60.99	3.98
XXVI	4-BrC_6H_4	$C_{14}H_{11}BrN_2O_2$	30	243	52.67	3.48	52.77	3.59
XXVII	4-HOC_6H_4	$C_{14}H_{12}N_2O_3$	47	275–278	65.61	4.72	65.77	4.67
XXVIII	2-(5-ClC_5H_3N)	$C_{13}H_{10}ClN_3O_2$	59	210.5–212.5	56.63	3.66	56.78	3.84
XXIX	4,4′-Difluorooxanilide	$C_{14}H_{10}F_2N_2O_2$	49	252.2–253.2	60.87	3.65	61.02	3.67

this study we have isolated sulfur and detected H_2S on the acidification of the reaction mixture but we have not attempted to isolate the other degradation products expected. Attempts to minimize hydrolysis by shorter reaction times resulted in increased recovery of starting material.

Biological Testing[15]

All of the dithiooxamide derivatives reported in Tables I and III, with the exception of XII, were tested with Gram-positive (*Staphlococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria for antibacterial action. Tetracycline and chloramphenicol were used as standards for II, III, IV, V, VII, and VIII while Roccal was used as a standard for all other compounds tested. In addition, II, III, IV, V, VII, and VIII were tested for antifugal activity using 1-(3-isoquinolyl)-2-nitropropene as standard and for Metrazol antagonism activity at oral doses of 200 mg/kg. These tests all failed to show any significant activity and the compounds were classified as inactive. Toxicity tests at single oral doses of 500 mg/kg to groups of five mice with IV, V, VII, and VIII gave 0/5 deaths at 3 days. Compound III gave 2/5 deaths within 24 hr and 3/3 (remainder) deaths at 2 days. Compound II gave 5/5 deaths within 3 hr.

Experimental Section[16]

General Procedure for Preparation of N-Aryl-Substituted Dithiooxamides.—Aryl dithiooxamides were prepared by thionation of the corresponding oxamide[17] with excess phosphorus pentasulfide in dry xylene. The xylene reaction mixture was filtered hot and the filtrate steam distilled to remove the xylene. The product mixture was dissolved in benzene and chromatographed on an alumina column.

N-Phenyl-N′-(*n*-propyl)dithiooxamide (I).—N-Phenyl-N′-(*n*-propyl)oxamide[18] (45 g, 268 mmoles) and phosphorus pentasulfide (97 g, 436 mmoles) in dry xylene (1000 ml), heated to reflux for 2 hr, yielded 11.0 g (21.2%) of I, bp 150–153° (0.15 mm), mp −3 to −4°, sulfur (2.17 g, 0.068 g-atom), mp 105–118°, and 2.5 g (12 mmoles) of starting material.

N-Phenyl-N′-(isopropyl)dithiooxamide (II).—N-Phenyl-N′-(isopropyl)oxamide[18] (27.7 g, 134 mmoles) and phosphorus pentasulfide (32.4 g, 146 mmoles) in dry xylene (800 ml), heated to reflux for 4 hr, yielded 21.36 g (66.9%) of II, bp 160–168° (0.5 mm). Recrystallization from ligroin yielded 6.1 g (19.1%) of pure II, mp 46.4–48.0°.

N-Phenyl-N′-benzyldithiooxamide (III).—N-Phenyl-N′-benzyloxamide[18] (50.8 g, 200 mmoles) and phosphorus pentasulfide (88.8 g, 400 mmoles) in dry xylene (800 ml), heated to reflux for 3.25 hr, yielded 7.28 g (12.7%) of crude III, mp 46–55°, and 26.73 g (46.7%) of III, mp 52–54°, which was recrystallized from ligroin to give pure III, mp 54.4–55.0°. In addition sulfur (1.49 g, 0.047 g-atom), mp 112–118°, was isolated.

N-Phenyl-N′-(4-tolyl)dithiooxamide (IV).—N-Phenyl-N′-(4-tolyl)oxamide[19] (78.0 g, 307 mmoles) and phosphorus pentasulfide (54.0 g, 240 mmoles) in dry xylene (700 ml), heated to reflux for 2.75 hr, yielded 58.3 g (62.5%) of crude IV, mp 125–137°, and sulfur (2.4 g, 0.075 g-atom), mp 119.5–121°. Recrystallization from ethanol yielded pure IV, mp 136.6–138.6°.

N-Phenyl-N′-(4-methoxyphenyl)dithiooxamide (V).—N-Phenyl-N′-(4-methoxyphenyl)oxamide (XXIII) (34.0 g, 126 mmoles) and phosphorus pentasulfide (56 g, 250 mmoles) in dry xylene (800 ml), heated to reflux for 3.5 hr, yielded 4.71 g (12.4%) of crude V, mp 105–118°. Recrystallization from ethanol yielded pure V, mp 119.6–120.8°.

N-Phenyl-N′-(4-fluorophenyl)dithiooxamide (VI).—N-Phenyl-N′-(4-fluorophenyl)oxamide (XXIV) (3.0 g, 11.6 mmoles) and phosphorus pentasulfide (2.05 g, 9.2 mmoles) fused at 240° in a sand bath and extracted with acetone yielded 2.39 g (70.8%) of crude VI, mp 135–145°, on evaporation of the acetone and chromatographic purification of the residue. Recrystallization from ethanol yielded pure VI, mp 152.4–155.4°. In addition N^O-phenyl-N^S-(4-fluorophenyl)thiooxamide (XIII) (0.23 g, 0.8 mmole) was isolated. Recrystallization from ethanol gave pure XIII, mp 157–159°.

N-Phenyl-N′-(4-chlorophenyl)dithiooxamide (VII).—N-Phenyl-N′-(4-chlorophenyl)oxamide (XXV) (35.0 g, 127 mmoles) and phosphorus pentasulfide (56.0 g, 250 mmoles) in dry xylene (1000 ml), heated at reflux for 4.5 hr, yielded 15.6 g (39.9%) of

(15) The authors are grateful to Smith, Kline and French Laboratories, Philadelphia, Pa., and Dr. K. E. Yaw and Mr. B. O. Benton, Washington College, for biological testing reported herein.

(16) Melting points and boiling points are uncorrected. Ultraviolet spectra were determined on a Beckman DU spectrophotometer. Dithiooxamide was generously supplied by Mallinckrodt Chemical Works, St. Louis, Mo. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Dr. Alfred Bernhardt, Mülheim, Germany.

(17) Oxamides previously unreported (Table IV) were prepared from the reaction of equimolar quantities of ethyl-N-phenyloxamate and the appropriate amine. The oxamide products were purified by recrystallization from xylene.

(18) A. G. Richardson, J. S. Pierce, and E. E. Reid, *J. Am. Chem. Soc.*, **74**, 4011 (1952).

(19) G. Heller, *Ann.*, **332**, 267 (1904).

VII, mp 134–138°. Recrystallization from ethanol yielded pure VII, mp 138.6–139.2°.

N-Phenyl-N′-(4-bromophenyl)dithiooxamide (VIII).—N-Phenyl-N′-(4-bromophenyl)oxamide (XXVI) (31.9 g, 100 mmoles) and phosphorus pentasulfide (44.4 g, 200 mmoles) in dry xylene (700 ml), heated to reflux for 4 hr, yielded 8.7 g (24.8%) of VIII, mp 126–130°. Recrystallization from ethanol yielded pure VIII, mp 129.2–130.6°.

N-Phenyl-N′-(4-hydroxyphenyl)dithiooxamide (IX).—N-Phenyl-N′-(4-hydroxyphenyl)oxamide (XXVII) (5.0 g, 19.5 mmoles) and phosphorus pentasulfide (2.87 g, 12.9 mmoles) in dry xylene (113 ml), heated to reflux for 9 hr, yielded 0.31 g (5.5%) of IX, recrystallized from ethanol, mp 153.6–154.8°. In addition dithiooxanilide (0.56 g, 2.1 mmoles), mp 136–137°, was isolated and identified by mixture melting point and infrared spectral comparison with an authentic sample.[20]

N-Phenyl-N′-(4-nitrophenyl)dithiooxamide (X).—N-Phenyl-N′-(4-nitrophenyl)oxamide[21] (10.0 g, 35 mmoles) and phosphorus pentasulfide (5.22 g, 23.5 mmoles) in dry xylene (170 ml), heated to reflux for 6.5 hr, yielded 2.12 g (19.1%) of crude X. Recrystallization from ethanol gave pure X, mp 182.8–183.8°. In addition, crude N^S-phenyl-N^O-(4-nitrophenyl)thiooxamide (XIV) (3.11 g, 10.3 mmoles) was isolated and recrystallized from ethanol to give pure XIV, mp 186–187°. Finally, crude dithiooxanilide (0.10 g, 0.38 mmole), mp 127–129°, was isolated and recrystallized from ethanol to give dithiooxanilide (0.01 g, 0.038 mmole), mp 134–135°. Mixture melting point with an authentic sample showed no depression.

N-Phenyl-N′-2-(5-chloropyridyl)dithiooxamide (XI).—N-Phenyl-N′-2-(5-chloropyridyl)oxamide (XXVIII) (12.8 g, 46.6 mmoles) and phosphorus pentasulfide (6.7 g, 30.1 mmoles) in dry xylene (283 ml), heated to reflux for 4 hr, yielded 0.05 g (0.35%) of XI which was recrystallized from ethanol to mp 146.8–147.8°. In addition N^S-phenyl-N^O-2-(5-chloropyridyl)-thiooxamide (XV) (0.28 g, 0.96 mmole), mp 163–164° (from ethanol), and dithiooxanilide (0.32 g, 1.2 mmoles), mp 136.5–137.5° (from ethanol), were isolated.

4,4′-Difluorodithiooxanilide (XII).—4,4′-Difluorooxanilide (XXIX) (5.16 g, 18.7 mmoles) and phosphorus pentasulfide (3.0 g, 13.5 mmoles) in dry xylene (106 ml), heated to reflux for 5.5 hr, yielded 0.16 g (2.8%) of XII, mp 202–202.5°, 0.10 g (0.34 mmole) of 4,4′-difluorothiooxanilide (XVI), mp 180–182°, and 1.18 g of a mixture of the two products, mp 165–187°.

N-2-(5-Chloropyridyl)thioacetamide.—2-Acetamido-5-chloropyridine (3.7 g, 22 mmoles) (mp 168–171°) (lit.[22] 171°) and phosphorus pentasulfide (2.0 g, 9.0 mmoles) in dry toluene (20 ml), heated to reflux for 1 hr, filtered hot, yielded 0.8 g (19.5%) of crude product on cooling the filtrate. Recrystallization from ethanol and water yielded pure product, mp 148–150°. *Anal.* Calcd for $C_7H_7ClN_2S$: S, 17.18; N, 15.01. Found: S, 17.12; N, 15.20.). In addition 0.8 g (4.75 mmoles) of starting material, mp 168–171° (no mixture melting point depression), was recovered.

General Procedure for the Preparation of N-Alkyldithiooxamides.—Alkyl dithiooxamides were generally prepared by dissolving dithiooxamide in aqueous sodium hydroxide, followed by the addition of an equimolar amount of aliphatic amine. The mixture was stirred at room temperature until reaction was complete, as evidenced by a darkening of the solution. Work-up was accomplished by acidification with dilute acetic acid followed by extraction with ether. The residue from evaporation of the ether extracts was chromatographed on an alumina column, eluting with petroleum ether (bp 30–60°), benzene and ether to separate the desired alkyldithiooxamide.

N-Ethyldithiooxamide (XVII).—Ethyl amine (7.5 g, 167 mmoles) was added to dithiooxamide (20.0 g, 167 mmoles) in aqueous NaOH (10 g/400 ml), precooled in an ice bath. The reaction mixture was warmed to room temperature, stirred for 1 hr, and filtered to yield N,N′-diethyldithiooxamide (1.7 g, 10 mmoles), mp 51–55.[23] Acidification and chromatographic work-up of the filtrate yielded 2.0 g (8.1%) of crude XVII, mp 74–80°. Recrystallization from ethanol yielded pure XVII, mp 81.6–82.8°. In addition dithiooxamide (2.3 g, 19 mmoles) was recovered.

N-*n*-Propyldithiooxamide (XVIII).—*n*-Propylamine (4.9 g, 83 mmoles) was added to dithiooxamide (10 g, 83 mmoles) in aqueous NaOH (6 g/200 ml) and stirred for 1.5 hr to yield 0.9 g (6.7%) of XVIII. Recrystallization from ethanol gave pure XVIII, mp 46.5–47.5°.

N-*n*-Butyldithiooxamide (XIX).—*n*-Butylamine (6.1 g, 83 mmoles) was added to dithiooxamide (10 g, 83 mmoles) in aqueous NaOH (6 g/200 ml) and stirred for 1.5 hr to yield 1.0 g (5.7%) of XIX. Recrystallization from petroleum ether gave pure XIX, mp 35.2–36°. In addition, N,N′-di-*n*-butyldithiooxamide (1.0 g, 4 mmoles), mp 34–35° (lit.[24] 37–38°), identified by mixture melting point with an authentic sample, and sulfur (0.4 g, 0.013 g-atom), mp 114–116°, were isolated. A mixture melting point of XIX and N,N′-di-*n*-butyldithiooxamide was depressed below room temperature.

N-(2-Hydroxyethyl)dithiooxamide (XX).—Ethanolamine (10.2 g, 167 mmoles) was added to dithiooxamide (20 g, 167 mmoles) in aqueous NaOH (10 g/300 ml) and stirred for 0.67 hr to yield 4.2 g (15.3%) of crude XX, mp 97–101°. Recrystallization from benzene gave pure XX, mp 100.8–102.6°. In addition dithiooxamide (3.0 g, 25 mmoles) was recovered.

N-(3-Hydroxypropyl)dithiooxamide (XXI).—3-Aminopropanol (6.25 g, 83 mmoles) was added to dithiooxamide (10.0 g, 83 mmoles) in aqueous NaOH (6 g/200 ml) and stirred for 1.5 hr to yield 1.1 g (6.75%) of XXI. Recrystallization from benzene gave pure XXI, mp 67.2–69°. In addition N,N′-bis(3-hydroxypropyl)dithiooxamide (0.2 g, 0.8 mmole), mp 68–69.5°, was isolated. *Anal.* Calcd for $C_8H_{16}N_2O_2S_2$: N, 11.85. Found: N, 12.18. Mixture melting point of the mono- and disubstituted product was 52–65°.

N-[3-(Dimethylamino)propyl]dithiooxamide (XXII).—N,N-Dimethyl-1,3-propanediamine (8.5 g, 83 mmoles) was added to dithiooxamide (10 g, 83 mmoles) in aqueous NaOH (6 g/200 ml) and stirred for 1.25 hr to yield 2.1 g (13.2%) of crude XXII, mp 126–128°. Recrystallization from benzene–petroleum ether gave pure XXII, mp 128–130°, which decomposed on standing in air.

Registry No.—I, 10197-23-6; II, 10197-24-7; III, 10197-25-8; IV, 10197-26-9; V, 10197-27-0; VI, 10197-28-1; VII, 10197-29-2; VIII, 10197-30-5; IX, 10197-31-6; X, 10197-32-7; XI, 10197-33-8; XII, 10197-34-9; XIII, 10197-35-0; XIV, 10197-36-1; XV, 10197-37-2; XVI, 10197-38-3; XVII, 10197-39-4; XVIII, 10197-40-7; XIX, 10197-41-8; XX, 10197-42-9; XXI, 10197-43-0; XXII, 10197-44-1; XXIII, 10197-45-2; XXIV, 10197-46-3; XXV, 10197-47-4; XXVI, 10197-48-5; XXVII, 10197-49-6; XXVIII, 10197-50-9; XXIX, 10197-51-0.

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