Benzyloxyamines as Possible Inhibitors of Histamine Biosynthesis

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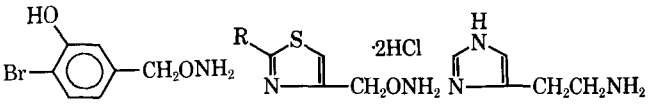
Abstract □ The synthesis of some 26 *O*-substituted hydroxylamine derivatives is described. Potent anti-inflammatory activity in the carrageenin-induced rat paw edema test is shown by *m*-nitrobenzyloxyamine hydrochloride and by *p*-nitrobenzyloxyamine hydrochloride. Moreover, *p*-nitrobenzyloxyamine hydrochloride also possesses potent inhibitory activity when tested *in vitro* against the histamine-forming enzyme, specific histidine decarboxylase, thus lending additional support to the theory linking histamine to the inflammatory process. Further evidence is given for the bioisosterism of the nitrobenzene and pyridine moieties. The necessity of a free aminooxy group for anti-inflammatory activity is demonstrated.

Keyphrases □ Benzyloxyamines—synthesis □ Anti-inflammatory activity—benzyloxyamines □ Anorexigenic activity—benzyloxyamines □ Antimalarial activity—benzyloxyamines □ Histidine decarboxylase inhibition—*p*-nitrobenzyloxyamine HCl □ IR spectrophotometry—identification

Histamine, a naturally occurring amine possessing a wide range of potent pharmacologic effects, has been suggested as playing an important part in the mediation of various physiologic functions (1). Histamine has been implicated in the cause of such human diseases as asthma and other allergic disorders, peptic ulcers, and vascular headaches (2). Histamine also has been proposed as a mediator of the inflammatory process (3–5).

Therefore, a drug that effectively inhibits the biosynthesis of histamine in man should be of interest, both as a tool for physiologic investigations and as a potential therapeutic agent.

Histamine is synthesized in mammalian tissues by enzymatic decarboxylation of the precursor amino acid, histidine. Decarboxylation, being the only enzymic process involved, is rate limiting. In the rat, at least, biosynthesis of histamine is catalyzed by a specific histidine decarboxylase enzyme (6). Therefore, inhibition of histidine decarboxylase activity may result in a depletion of histamine from tissues. Levine and other investigators have reported that the histidine decarboxylase inhibitor, 4-bromo-3-hydroxybenzyloxyamine (I), inhibits histamine synthesis in rats (6) and in man (7). Previous work has shown 4-thiazolylmethoxyamine (II) and 2-amino-4-thiazolylmethoxyamine (III)



I II, R = H III, R = NH_2 IV histamine

to be potent inhibitors, both *in vitro* and *in vivo*, of histidine decarboxylase (8). In addition, these two thiazole compounds possess preliminary anti-inflammatory activity when tested intragastrically against carrageenin-induced rat paw edema (9). Whitehouse and Skidmore

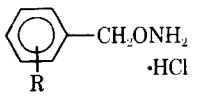


Table I—Benzyloxyamines

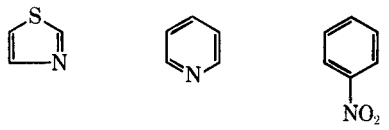
Number	R	Formula	M.p.	Recrystallizing Solvent	Yield, %	Anal., % Calcd.	Found
1	*m*-NO_2	$C_7H_9ClN_2O_3$	164–166°	1-Butanol	80	C, 41.09 H, 4.43 N, 13.49	C, 41.28 H, 4.66 N, 13.08
2	*p*-NO_2	$C_7H_9ClN_2O_3$	209–211°[a]	Methanol	80	C, 41.09 H, 4.43 N, 13.49	C, 41.02 H, 4.55 N, 13.13
3	*m*-Cl	$C_7H_9Cl_2NO$	210–211°	Ethanol	93	C, 43.35 H, 4.68 N, 7.22	C, 43.47 H, 4.64 N, 7.03
4	*p*-Cl	$C_7H_9Cl_2NO$	243–244°[b]	Ethanol	75	—	—
5	*m*-CF_3	$C_8H_9ClF_3NO$	160–170°[c]	Ethyl acetate	50	C, 42.21 H, 3.99 N, 6.15	C, 42.05 H, 4.17 N, 5.98
6	*o*-CH_2ONH_2 ·HCl	$C_8H_{14}Cl_2N_2O_2$	222–224° dec.	Chlorobenzene–methanol	90	C, 39.87 H, 5.81 N, 11.63	C, 40.78 H, 6.14 N, 11.22
7	*m*-CH_2ONH_2 ·HCl	$C_8H_{14}Cl_2N_2O_2$	235–237° dec.	Pyridine	90	C, 39.87 H, 5.81 N, 11.63	C, 40.16 H, 5.91 N, 11.41
8	*p*-CH_2ONH_2 ·HCl	$C_8H_{14}Cl_2N_2O_2$	247–249°[d] dec.	Pyridine	90	C, 39.87 H, 5.81 N, 11.63	C, 41.03 H, 6.09 N, 11.48
9	2-OCH_3, 5-NO_2	$C_8H_{11}ClN_2O_4$	188–190°	Ethanol	77	C, 40.90 H, 4.74 N, 11.95	C, 41.04 H, 4.66 N, 11.69

[a] Reported m.p. 217° dec. (17). [b] Reported m.p. 245° dec. (15). [c] Sublimes. [d] Reported m.p. 263–264° dec. (15).

(10) have shown that a number of anti-inflammatory drugs, such as salicylate, indomethacin, and flufenamic acid, are potent inhibitors of histamine formation through their inhibition of the histidine decarboxylase activity of rat pyloric stomach and fetal rat.

The aims of the present work are the synthesis and structure–activity correlation of various alkoxyamines as histidine decarboxylase inhibitors in relationship to histaminergic mechanisms in inflammation.

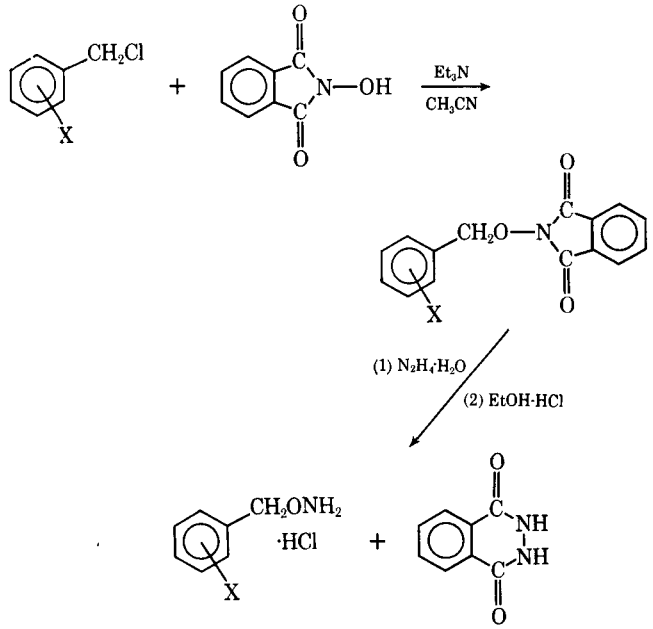
4-Thiazolylmethoxyamine (II) structurally resembles histamine (IV); the methoxyamine side chain is isosteric with the ethylamine group (11) of histamine, while the thiazole ring is isosteric with the imidazole ring. The thiazole ring (V) is also isosteric with the pyridine moiety (VI) as a result of replacement of the sulfur atom, —S—, by the vinylene grouping —CH=CH— (12). However, pyridine, while showing similari-



V VI VII

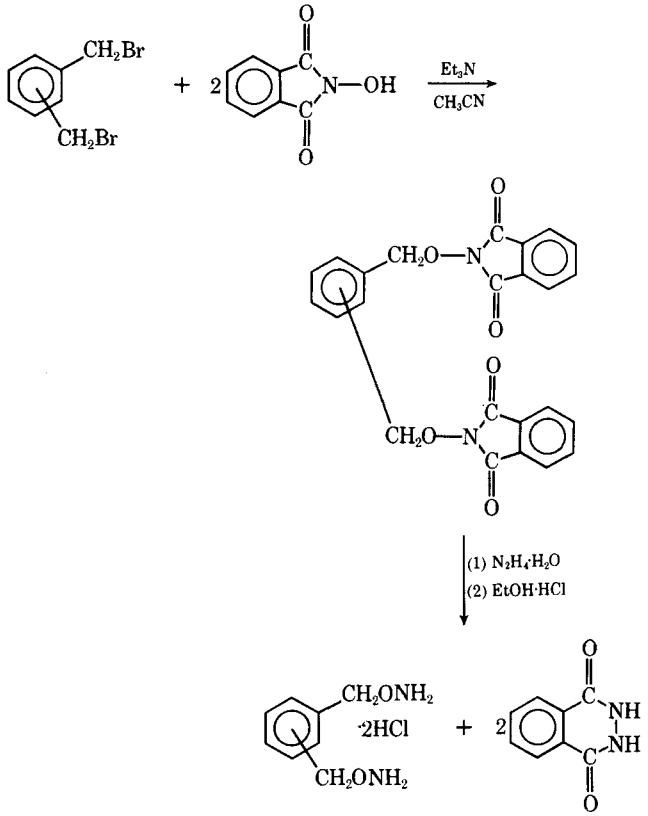
ties to thiazole and benzene (replacement of —CH= by —N=), may also resemble nitrobenzene (VII), but now by virtue of similar polar characteristics (13).

Therefore, the nitrobenzyloxyamines described herein are isosteric with both pyridylmethoxyamines and thiazolylmethoxyamine. This work, as well as reporting the synthesis of the benzyloxyamines containing a nitro substituent, describes the preparation of a number of additional benzene derivatives containing different functional group substituents. These substituted benzyloxyamines may provide data toward a correlation of chemical structure and anti-inflammatory activity, along with any possible relationships to histidine decarboxylase inhibitory potency.



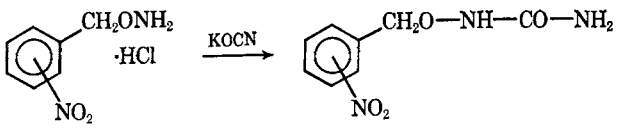
X = Cl, NO_2, CF_3, *etc.*

Scheme I



Scheme II

The nine benzyloxyamines synthesized are listed and their physical properties given in Table I. These benzyloxyamines were prepared by the method of McKay *et al.* (14) and Martin *et al.* (15), as modified by Drain *et al.* (16); it consists of the alkylation of *N*-hydroxyphthalimide, followed by hydrazinolysis as shown in Schemes I and II. The 13 *N*-benzyloxyphthalimide intermediate compounds thus synthesized are listed in Table II. *N*-(3-Pyridylmethoxy)phthalimide and *N*-(2-pyridylmethoxy)phthalimide are shown in Table III. Table IV lists 1-(*m*-nitrobenzyloxy)urea and 1-(*p*-nitrobenzyloxy)urea, synthesized by reacting the appropriate nitrobenzyloxyamine hydrochloride with potassium cyanate (Scheme III) according to the method



Scheme III

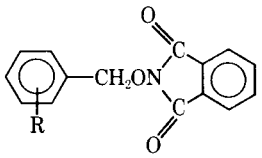
used by Bauer and Dalalian (18) for the preparation of aryloxyureas (19).

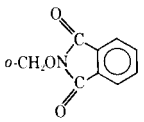
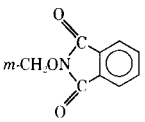
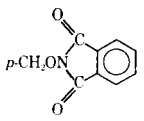
BIOLOGICAL RESULTS

Anti-Inflammatory Screening—Selected compounds have been submitted for pharmacological testing; the preliminary results[1] are shown in Table V. Two of the compounds (Compounds 1 and 2 in Table V) have displayed marked anti-inflammatory activity when

[1] The authors thank Riker Laboratories, Northridge, CA 91324, for performing the pharmacological testing.

Table II—*N*-Benzyloxyphthalimides



Number	R	Formula	M.p.	Recrystallizing Solvent	Yield, %	Anal., % Calcd.	Found
10	*o*-NO_2	$C_{15}H_{10}N_2O_5$	160–161°	Acetone–water	90	C, 60.41 H, 3.38 N, 9.39	C, 60.50 H, 3.50 N, 9.13
11	*m*-NO_2	$C_{15}H_{10}N_2O_5$	186–187°	Acetone–water	75	C, 60.41 H, 3.38 N, 9.39	C, 60.35 H, 3.53 N, 9.67
12	*p*-NO_2	$C_{15}H_{10}N_2O_5$	197–198°	Ethyl acetate	90	C, 60.41 H, 3.38 N, 9.39	C, 60.53 H, 3.47 N, 8.95
13	*m*-Cl	$C_{15}H_{10}ClNO_3$	139–140°	Ethanol	85	C, 62.80 H, 3.53 N, 4.88	C, 62.84 H, 3.69 N, 4.92
14	*p*-Cl	$C_{15}H_{10}ClNO_3$	137–138°[a]	Ethanol	72	—	—
15	*m*-F	$C_{15}H_{10}FNO_3$	130–131°	Ethanol	81	C, 66.50 H, 3.69 N, 5.17	C, 66.58 H, 3.93 N, 5.15
16	*m*-CF_3	$C_{16}H_{10}F_3NO_3$	109–110°	Ethanol	60	C, 59.82 H, 3.14 N, 4.36	C, 59.77 H, 3.26 N, 4.32
17	2-OCH_3, 5-NO_2	$C_{16}H_{12}N_2O_6$	184–185°	Acetone–water	83	C, 58.60 H, 3.99 N, 8.54	C, 58.34 H, 3.79 N, 8.27
18	2-OH, 5-NO_2	$C_{15}H_{10}N_2O_6$	216–218°	1-Butanol	65	C, 57.33 H, 3.21 N, 8.92	C, 58.10 H, 3.57 N, 8.83
19	2-Cl, 4,5-Methylenedioxy	$C_{16}H_{10}ClNO_5$	242–243°	Acetone–water	90	C, 58.10 H, 3.06 N, 4.23	C, 58.03 H, 3.15 N, 4.06
20		$C_{24}H_{16}N_2O_6$	284–285°	Pyridine	80	C, 67.28 H, 3.76 N, 6.54	C, 67.43 H, 3.98 N, 6.38
21		$C_{24}H_{16}N_2O_6$	238–240°	Chlorobenzene	80	C, 67.28 H, 3.76 N, 6.54	C, 67.31 H, 3.94 N, 6.43
22		$C_{24}H_{16}N_2O_6$	306–307° dec.	Pyridine	75	C, 67.28 H, 3.76 N, 6.54	C, 67.19 H, 3.92 N, 6.70

[a] Reported m.p. 137–138° (14).

tested intragastrically against carrageenin-induced rat paw edema (20). The ED_{50} of 230 mg./kg. for *m*-nitrobenzyloxyamine hydrochloride (Compound 1) may be compared with an ED_{50} of approximately 180 for aspirin (9). Furthermore, preliminary testing has shown that *p*-nitrobenzyloxyamine (Compound 2), as well as showing anti-inflammatory activity, possesses potent inhibitor activity of a competitive nature when tested against the histamine-forming enzyme, specific histidine decarboxylase, isolated from fetal rat (21).

The differences in toxicity of the disubstituted aminooxymethyl compounds as related to positions of the two groups on the benzene ring should be noted. The *o*-disubstituted compound (Compound 6) is almost three times as toxic (LD_{50}, mg./kg. i.p. mice) as the *meta*-compound and over four times as toxic as the *p*-di(aminooxymethyl)benzene. The anti-inflammatory activity somewhat parallels the LD_{50}; that is, the *ortho*-compound is the most active, followed by the *meta*- and then the *para*-disubstituted compounds.

Anorexigenic Screening—Several compounds have shown anorexigenic activity in reducing the food intake in rats (Table V) (9). The *o*-di(aminooxymethyl)benzene (Compound 6) is the most active, with an ED_{50} of 64 mg./kg.

Anticancer Screening—The 10 compounds shown in Table V have been submitted to the Cancer Chemotherapy National Service Center (NSC), National Cancer Institute, for screening against the L-1210 lymphoid leukemia test system (22), and they have the following assigned NSC numbers: Compound 1, Table V, NSC 121170; No. 2, NSC 79411; No. 3, NSC 131325; No. 5, NSC 129221; No. No. 6, 123485; No. 7, NSC 123486; No. 8, NSC 123487; No. 9, NSC 132330; No. 11, NSC 130679; and No. 25, NSC 125363. Preliminary results show these compounds lack any significant antitumor activity. However, *m*-nitrobenzyloxyamine hydrochloride (Compound 1) did prolong the life of L-1210-infected mice 124% (compared with controls at 100%). In general, an increase in survival value of 125% is necessary for further experimental work by NSC.

Antimalarial Screening—The 10 compounds shown in Table V have been submitted to Walter Reed Army Institute of Research for testing for antimalarial activity. Preliminary results indicate a lack of potency, with the exception of *m*-nitrobenzyloxyurea (Compound 25) which is active against the parasite (*Plasmodium gallinaceum*) in the mosquito (*Aedes aegypti*), giving 100% abnormal oocysts and 100% complete sporozoite suppression at 0.1% con-

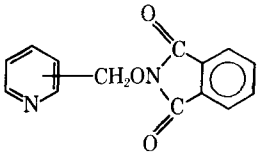


Table III—*N*-Pyridylmethoxyphthalimides

Number	Name	Formula	M.p.	Recrystallizing Solvent	Yield, %	Anal., % Calcd.	Found
23	*N*-(3-Pyridylmethoxy)-phthalimide	$C_{14}H_{10}N_2O_3$	153–154°	Acetone–water	71	C, 66.14 H, 3.96 N, 11.02	C, 66.43 H, 4.19 N, 10.95
24	*N*-(2-Pyridylmethoxy)-phthalimide	$C_{14}H_{10}N_2O_3$	129–130°	Acetone–water	50	C, 66.14 H, 3.96 N, 11.02	C, 65.97 H, 4.06 N, 9.94

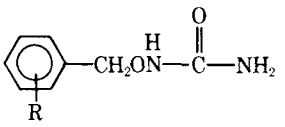


Table IV—Benzyloxyureas

Number	R	Formula	M.p.	Recrystallizing Solvent	Yield, %	Anal., % Calcd.	Found
25	*m*-NO_2	$C_8H_9N_3O_4$	130–131°	Acetone	78	C, 45.50 H, 4.30 N, 19.90	C, 45.59 H, 4.54 N, 20.08
26	*p*-NO_2	$C_8H_9N_3O_4$	209–210°[a]	Acetone–water	89	C, 45.50 H, 4.30 N, 19.90	C, 45.67 H, 4.44 N, 19.56

[a] Reported m.p. 206° (17).

centration (but inactive at 0.01% concentration). However, *m*-nitrobenzyloxyurea was inactive against malaria in chicks (*P. gallinaceum*) and in mice (*P. berghei*).

DISCUSSION

The lack of, or greatly reduced, anti-inflammatory activity of the *m*-chlorobenzyloxyamine hydrochloride (Compound 3) and the other nonnitro-substituted benzyloxyamines gives further evidence for the bioisosterism of the nitrobenzene and pyridine (and thiazole) ring systems. In addition, the lessened activity of *m*-trifluoromethylbenzyloxyamine hydrochloride (Compound 5) as compared to *m*-nitrobenzyloxyamine hydrochloride (Compound 1) is in contrast to reports of the biological equivalence of replacement of NO_2 with CF_3 (23, 24).

The necessity of a free aminooxy group for anti-inflammatory activity may be demonstrated by the essential inactivity of *N*-(*m*-nitrobenzyloxy)phthalimide (Compound 11, Table V). In addition, Schiff base derivatives of *m*-nitrobenzyloxyamine are devoid of anti-inflammatory activity (25). Also, whereas 4-thiazolylmethoxyamine dihydrochloride (II) possesses activity *versus* carrageenin-induced rat paw edema, several nitrogen-substituted Schiff base derivatives are inactive (9). Furthermore, 4-thiazolylmethoxyurea and 1-phenyl-3-(4-thiazolylmethoxy)urea show no *in vitro* inhibition of histidine decarboxylase (8, 19, 26). However, *m*-nitrobenzyloxyurea (Compound 25) and 4-thiazolylmethoxyurea (19) displayed moderate anti-inflammatory activity.

These preliminary results showing histidine decarboxylase inhibitory activity for *p*-nitrobenzyloxyamine hydrochloride (Compound 2) and marked anti-inflammatory activity for *m*-nitrobenzyloxyamine hydrochloride (Compound 1) and for the *para*-isomer lend additional support to the theory linking histamine to the inflammatory process.

Further work will be directed toward synthesis of additional alkoxy amines as possible active site-directed irreversible inhibitors according to the hypothesis of Baker (27, 28). These new inhibitors may be highly specific for the histidine decarboxylase involved in the inflammatory process by virtue of the rigid positioning requirements imposed by: (*a*) the necessity of a reversible fit within the enzyme activity site (formation of an aldimine bond between the aminooxy group and pyridoxal phosphate displacing the lysyl epsilon-amino group of the enzyme); (*b*) fitting an adjacent hydrophobic area; and (*c*) exoalkylation outside the active site.

As additional data are accumulated, it may be possible to apply regression analysis (29) to clarify the exact hydrophobic, steric, and electronic requirements to accommodate the enzyme active site. Successful elucidation of the enzyme active site may enable the design and synthesis of extremely potent, and highly specific, histidine decarboxylase inhibitors which, hopefully, may find application in the treatment of inflammatory diseases.

EXPERIMENTAL

The syntheses of representative compounds reported in Tables I–IV are described here. All melting points were taken on a Fisher-Johns hot-stage and are uncorrected. Elemental microanalyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. The IR spectra of selected compounds were determined on a Perkin-Elmer infracord apparatus in mineral oil mulls and are in agreement with the assigned structures.

***N*-(*m*-Nitrobenzyloxy)phthalimide (Compound 11)**—In a 500-ml. round-bottom flask, fitted with a reflux condenser and heating mantle, were placed 75 ml. of acetonitrile, 10.5 ml. (0.075 mole) of triethylamine, and 12.4 g. (0.075 mole) of *N*-hydroxyphthalimide.[2] After heating to effect solution, 13.0 g. (0.075 mole) of α-chloro-*m*-nitrotoluene[3] was added, and the solution was refluxed for 2 hr. Upon cooling, filtering the resultant solid, adding excess water to the filtrate to obtain a second crop, and recrystallizing the total product from acetone–water, 16.4 g. (75% yield) of a white crystalline solid, m.p. 186–187°, was obtained.

***m*-Nitrobenzyloxyamine Hydrochloride (Compound 1)**[4]—To a solution of 29.8 g. (0.1 mole) *N*-(*m*-nitrobenzyloxy)phthalimide (Compound 11) in 250 ml. warm anhydrous ethanol was added 5 ml. (0.1 mole) hydrazine hydrate (99%), and the solution was refluxed for 2 hr. The reaction mixture was cooled and the precipitated phthalhydrazide removed by filtration. Addition of excess ethanolic HCl to the filtrate, followed by reduction in volume by evaporation,

[2] Aldrich Chemical Co.
[3] Eastman Organic Chemicals.
[4] *Chemical Abstracts* nomenclature; *O*-(*m*-nitrobenzyl)hydroxylamine hydrochloride.

Table V—Pharmacology[a]

Compound No.	LD_{50}, mg./kg. i.p., mice	Carrageenin-Induced Rat Paw Edema, % Reduction, 250 mg./kg.	Anorexigenic, % Inhibition, mg./kg., Rat
1	>800	64	48, 150 mg./kg.
2	>800	50	50, 130 mg./kg.
3	275	(15) increase 176 mg./kg.	22, 75 mg./kg.
5	588	23	9, 100 mg./kg.
6	236	35	50, 64 mg./kg.
7	659	16	24, 100 mg./kg.
8	>800	13	36, 100 mg./kg.
9	—	(4) increase	—
11	>800	13	43, 100 mg./kg.
25	>800	43	34, 100 mg./kg.

[a] The pharmacological testing was performed by Riker Laboratories, Northridge, Calif.

gave 16 g. (80%) white solid, m.p. 160–165°. An analytical sample, m.p. 164–166°, was obtained by three recrystallizations from 1-butanol.

***O,O'*-(*o*-Phenylenedimethylene)bishydroxylamine Dihydrochloride (Compound 6)**—To 74 g. (0.45 mole) of *N*-hydroxyphthalimide, dissolved in 175 ml. acetonitrile and 50 ml. (0.36 mole) triethylamine by warming, was added 40 g. (0.15 mole) α,α'-dibromo-*o*-xylene,[3] followed by 4 hr. of refluxing. The chilled mixture was filtered and the precipitate washed with cold water to give 64 g. (80%) of the bisphthalimido intermediate (Compound 20), m.p. 282–284°. An analytical sample, m.p. 284–285°, was obtained by two recrystallizations from pyridine.

To 42.8 g. (0.1 mole) of Compound 20 in 300 ml. anhydrous ethanol was added 10 ml. (0.2 mole) hydrazine hydrate (99%), and the mixture was refluxed for 3 hr. The precipitated phthalhydrazide was removed by filtration of the cooled reaction mixture. Addition of excess ethanolic HCl to the filtrate gave 21.6 g. (90% yield) of the desired bisaminooxy compound (Compound 6) as a white solid, m.p. 211–214° dec. An analytical sample, m.p. 222–224° dec., was obtained by four recrystallizations from chlorobenzene–methanol.

***m*-Nitrobenzyloxyurea (Compound 25)**—To 20.5 g. (0.1 mole) *m*-nitrobenzyloxyamine hydrochloride (Compound 1) dissolved in 150 ml. H_2O was added 8.1 g. (0.1 mole) potassium cyanate. The desired urea derivative precipitated out almost immediately and was filtered, washed with cold H_2O, and recrystallized from acetone to give 16.5 g. (78%) of analytically pure, white solid, m.p. 130–131°.

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