Nitrones. 3.[1] α-(5-Nitro-2-furyl)-*N*-hydroxyalkylnitrones and Their Derivatives

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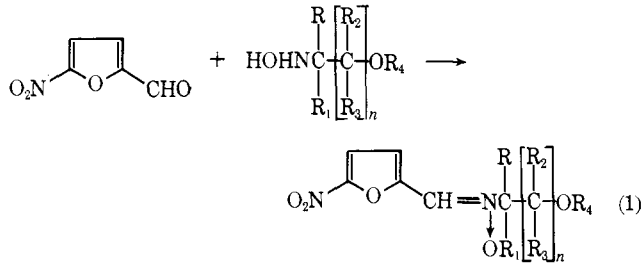
A series of α-(5-nitro-2-furyl)-*N*-hydroxyalkylnitrones and their derivatives were synthesized and evaluated as antibacterial, antifungal, and antiprotozoal agents. *N*-(2-Hydroxyethyl)nitrone (**4**) was found to be 2.4 times as active as the *N*-methylnitrone (**1**), formerly the most active compound of the series. Derivatives of *N*-(2-hydroxyethyl)nitrone (**4**) were generally less active. Structure–activity relationships are discussed.

We recently reported that the antibacterial activity of α-(5-nitro-2-furyl)-*N*-alkylnitrones[1] decreased with increasing chain length or substitution. On the assumption that hydroxylation of an essential alkyl group in the drug molecule plays an important role in enhancing biological activity,[3] we undertook such derivation of the alkyl nitrones. This publication presents our findings on the biological activity of a series of these hydroxyalkylnitrones.

Compounds **4–21** were obtained in 14–89% yield by the reaction of 5-nitrofurfural with N-substituted hydroxylamine salts in the presence of base according to eq 1. Compounds **4**, **5**, **8**, and **11** were reported[4] subsequent to our work.



(1)

R, R_1 R_2, R_3, R_4, and *n* (see Table I)

The esters **21–26** were obtained in 72–93% yield by treatment of the corresponding hydroxyalkylnitrones with the appropriate carboxylic acid anhydride in the presence of pyridine in the usual manner. Compound **21**, obtained by this method, was identical with a sample prepared by the former method (eq 1) as shown by ir and mmp. The ir spectrum of **21** was devoid of OH absorption and showed C=O absorption at 1733 cm^{-1}. This proved the nitrone linkage remained intact during the esterification.[5]

Compd **25** exhibited polymorphism. Two forms were isolated with melting points of 93–95° and 120–121°. When the low-melting isomer was ground thoroughly alone or with the high-melting isomer the resulting material melted at 120–121°. After the initial prepn of **25** the low-melting isomer was never again detected.

The hemisuccinate of **4** (**26**) was converted into its Na salt **27** by treatment with the calcd amount of warm aq $NaHCO_3$ soln.

The hydroxylamines employed in this synthesis were prepared by diborane reduction of the corresponding nitro salts according to Feuer, *et al.*,[6] by the catalytic reduction of nitro alcohols using 10% Pd/C,[7] or by dissolving metal reductions, *e.g.*, Al(Hg)[8] and Na(Hg),[9] of nitro alcohols. Catalytic reduction of nitro alcohols was the most convenient and economical method (Table II) except that hydroxylamines could not be obtained from 2-methyl-2-nitro-1-propanol, 1-(4-pyridyl)-2-nitroethanol,[10] and 1-nitrocyclohexanemethanol[11] using this method. Our results indicate that *tert*-alkylnitro compounds containing a β-OH function cannot be catalytically reduced to the hydroxylamine. This difficulty was overcome by employing the AlHg reduction method. For example, 2-methyl-2-nitro-1-propanol was readily converted into its corresponding hydroxylamine by this procedure.

3-Nitropropanol (**38**) and 6-nitrohexanol (**39**) were prepared by diborane reduction of 3-nitropropionic[12] and 6-nitrocaproic[13] acids in 32 and 28% yields, respectively. O-Alkylation of 2-nitroethanol with triethyloxonium tetrafluoroborate[14] followed by neutralization with aq $NaHCO_3$ gave ethyl 2-nitroethyl ether (**40**) in 63% yield.

The ir spectra of all the nitrones showed bands indicative of CH=N→O, NO_2, and furan ether groups. The nmr spectra were also consistent with the nitrone structure.

Structure–Activity Relationships.[15]—These compounds possess broad spectrum *in vitro* antibacterial activity against representative bacteria as shown in

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(3) (a) G. C. Lancini, E. Lazzari, V. Arioli, and P. Bellani, *J. Med. Chem.*, **12**, 775 (1969); (b) D. A. Berberian, E. W. Dennis, E. Freele, D. Rosi, T. R. Lewis, R. Lorenz, and S. Archer, *ibid.*, **12**, 607 (1969); (c) J. R. Valenta, J. R. E. Hoover, and J. F. Pagano, *Antimicrob. Ag. Chemother.*, 453 (1966); *Chem. Abstr.*, **67**, 80856 (1967); (d) E. W. McChesney, E. J. Froelich, G. Y. Lesher, A. V. R. Crain, and D. Rosi, *Toxicol. Appl. Pharmacol.*, **6**, 292 (1964); *Chem. Abstr.*, **62**, 2115 (1965); (e) J. Francis, J. K. Landquist, A. A. Levi, J. A. Silk, and J. M. Thorp, *Biochem. J.*, **63**, 455 (1956); *Chem. Abstr.*, **50**, 15696 (1956).

(4) Dainippon Pharmaceutical Co., Ltd., British Patent 1,105,007; *Chem. Abstr.*, **69**, 86809 (1968).

(5) F. Kröhnke [*Justus Liebigs Ann. Chem.*, **604**, 203 (1957)] reported that aldonitrones are converted into secondary amides by the acylating agents such as Ac_2O.

(6) H. Feuer, R. S. Bartlett, B. F. Vincent, Jr., and R. S. Anderson, *J. Org. Chem.*, **30**, 2880 (1965).

(7) We found that the desired hydroxylamine was not obtained by use of Pd-$BaSO_4$ according to the literature procedure [R. Wilkendorf and M. Trénel, *Ber.*, **56**, 611 (1923)].

(8) I. Vogel, *J. Chem. Soc.*, 594 (1927).

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(12) T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick, F. T. Fiedorek, R. A. Bankert, J. T. Gregory, and W. L. Bears, *ibid.*, **74**, 1323 (1952).

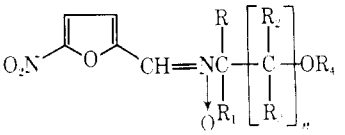
(13) A. S. Matlack and D. S. Breslow, *J. Org. Chem.*, **32**, 1995 (1967).

(14) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(15) The *in vitro* and *in vivo* biological data were obtained using methods described previously.[1]

TABLE I

α-(5-NITRO-2-FURYL)-*N*-HYDROXYALKYLNITRONES AND THEIR DERIVATIVES

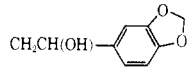
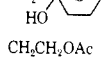
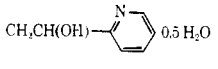


No.	R	R_1	R_2	R_3	R_4	*n*	Prepn method	Mp, °C	Recrystn solvent	Yield,[a] %	Formula[b]
4	H	H	H	H	H	1	A, B	150–151[c]	EtOH	72, 77	$C_7H_8N_2O_5$
5	H	CH_2OH	H	H	H	1	A	136–138[d]	$CHCl_3$	39	$C_8H_{10}N_2O_6$
6	Et	CH_2OH	H	H	H	1	A	115–118	$CHCl_3$	20	$C_{10}H_{14}N_2O_6$
7	CH_2OH	CH_2OH	H	H	H	1	A	171–172	EtOH	62	$C_9H_{12}N_2O_7$
8	H	CH_3	H	H	H	1	A, B	134–136[e]	MeOH	67, 77	$C_8H_{10}N_2O_5$
9	H	Et	H	H	H	1	A	110–111	EtOH	39	$C_9H_{12}N_2O_5$
10	Me	Me	H	H	H	1	A	133–135	EtOH	31	$C_9H_{12}N_2O_5$
11	H	H	H	Me	H	1	A, B	147–148[f]	EtOH	63, 89	$C_8H_{10}N_2O_5$
12	H	H	Me	Me	H	1	B	114–115	EtOH	78	$C_9H_{12}N_2O_5$
13	H	H	H	C_6H_5	H	1	B	156–158	EtOH	53	$C_{13}H_{12}N_2O_5$
14	H	H	H	4-$CH_3OC_6H_4$	H	1	B	176–178	EtOH	27	$C_{14}H_{14}N_2O_6$
15	H	H	H	3,4-$OCH_2OC_6H_3$	H	1	B	187–188	EtOH	69	$C_{14}H_{12}N_2O_7$
16	H	H	H	2-Pyridyl	H	1	B	157–159	$CHCl_3$–CCl_4	14	$C_{12}H_{11}N_3O_5$
17	H	H		$(CH_2)_5$[g]	H	1	B	122–124	EtOH	37	$C_{12}H_{16}N_2O_5$
18	H	H	H	H	H	2	B	80–81	CCl_4	42	$C_8H_{10}N_2O_5$
19	H	H	H	H	H	5	B	77–79	C_6H_6–cyclohexane	74	$C_{11}H_{16}N_2O_5$
20	H	H	H	H	Et	1	B	79–81	C_6H_6–petr ether (bp 60–70°)	50	$C_9H_{12}N_2O_5$
21	H	H	H	H	COMe	1	B, *h*	113–115	C_6H_6–petr ether (bp 60–70°)	28, 78	$C_9H_{10}N_2O_6$
22	H	H	H	Me	COMe	1	*h*	134–135	$CHCl_3$–CCl_4	93	$C_{10}H_{12}N_2O_6$
23	H	Me	H	H	COMe	1	*h*	94–96	$CHCl_3$–CCl_4	86	$C_{10}H_{12}N_2O_6$
24	H	H	H	H	$COCHCl_2$	1	*h*	122–123	C_6H_6	72	$C_9H_8Cl_2N_2O_6$
25	H	CH_2OAc	H	H	COMe	1	*h*	93–95[i]	C_6H_6–petr ether (bp 60–70°)	93	$C_{12}H_{14}N_2O_8$
26	H	H	H	H	$C(O)(CH_2)_2CO_2H$	1	*h*	135–137	*i*-PrOH	89	$C_{11}H_{12}N_2O_8$
27	H	H	H	H	$C(O)(CH_2)_2CO_2Na$	1	*j*	108–111 dec	EtOH	100	*k*

[a] Yield is of purified product. [b] All compds were analyzed for C, H, N, and where applicable Cl; analytical results obtained were within ±0.4% of the calcd values. [c] Lit.[4] mp 151–152°. [d] Lit.[4] mp 138–139°. [e] Lit.[4] mp 135–136°. [f] Lit.[4] mp 147–149°. [g] CR_2R_3–OR_4 is 1-hydroxycyclohexyl. [h] Obtained by esterification of the alcohol. [i] When ground thoroughly mp was raised to 120–121°. [j] Obtained by neutralization of the acid. [k] Not analyzed; ir in accord with structure.

TABLE II

HYDROXYLAMINO ALCOHOL OXALATE $(RNHOH)_2(CO_2H)_2$

No.	R	Mp, °C	Yield,[a] %	Formula[b]
28	CH_2CH_2OH	122–124 dec[c]	93	$C_6H_{16}N_2O_8$
29	$(CH_2)_3OH$	51–53	90	$C_8H_{20}N_2O_8$[d]
30	$CH(CH_3)CH_2OH$	101–103	70	$C_8H_{20}N_2O_8$
31	$CH_2C(CH_3)_2OH$	151–153 dec	73	$C_{10}H_{24}N_2O_8$
32	$CH(Et)CH_2OH$	144–145 dec	52	$C_{10}H_{24}N_2O_8$
33		167–168 dec	26	$C_{20}H_{24}N_2O_{12}$
34	$(CH_2)_5OH$	112–114	45	$C_{14}H_{32}N_2O_8$
35		159–161 dec	42	$C_{16}H_{32}N_2O_8$
36	CH_2CH_2OAc	108–110	69	$C_{10}H_{20}N_2O_{10}$
37		105–108	88	$C_9H_{13}N_2O_{6.5}$[e]

[a] Yield is of purified product. All products were recrystd from EtOH. [b] All compds were analyzed for C, H, N; analytical results obtained were within ±0.4% of the calcd values. [c] Lit.[7] mp 121–123° dec. [d] H: calcd, 7.40; found, 7.97. [e] C: calcd, 42.69; found, 43.38. H: calcd, 5.17; found, 4.68; calcd as $RNHOH(CO_2H)_2$.

Table III. The *in vitro* antifungal activity shown by the *N*-alkyl- and *N*-cycloalkylnitrones[1] disappeared in this series.

Hydroxylation of the *N*-ethyl group of **2**[1] caused an approximately fivefold enhancement of antibacterial activity in mice. However, no enhancement was shown in hydroxylation of α-(5-nitro-2-furyl)-*N*-propylnitrone (**3**).[1]

The antibacterial activity of the hydroxyalkylnitrones against a *Salmonella choleraesuis* variety Kunzendorf (ATCC 12011) infection in mice relative to **1** (assigned activity of 1.00) is shown in Table III. Drugs were administered in the feed. In general, the *in vivo* antibacterial activity in mice was greatest when the *N*-hydroxyalkyl group was 2-hydroxyethyl (**4**); the activity decreased with increasing chain length. The activity decreased in the order: 2-hydroxyethyl (**4**) > 3-hydroxypropyl (**18**) > 6-hydroxyhexyl (**19**). The activity of **4** was superior to that of **1** which was reported previously.[1] The *in vitro* antibacterial activity of **18** was slightly greater than that of **4** toward representative Gram-positive and Gram-negative microorganisms, but that of **19** was much less than that of either **4** or **18** (Table III).

TABLE III
BIOLOGICAL SCREENING DATA

No.	*In vivo* antibacterial activity relative to **1**	*In vitro* antibacterial and antifungal activity — Min inhib concn, μg/ml											
		SG[a]	ST	SA	SAG	PsA	PrM	EI	BS	EC	PM	AF	CA
1	1.00	*b*											
2	0.50	*b*											
3	0.67	*b*											
4	2.37	1	10	1	1	>100	100	1	1	10	1	100	100
5	<0.40	10	10	10	1	>100	100	1	10	10	1	>100	>100
6	<0.40	100	100	1	1	>100	>100	10	1	10	10	>100	>100
7	<0.40	100	100	10	10	>100	>100	10	100	100	10	>100	
8	<0.80	10	10	10	10	>100	100	10	1	100		>100	100
9	>0.60	10	10	10	10	>100	100	100	1	100	10	100	
10	<0.60	10	100	10	10	>100	100	100	1	100	10	>100	>100
11	<0.50	10	10	1	10	>100	100	0.1	10	10	1	100	100
12	0.85		10	100	100		>100			100			100
13	≪0.40	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
14	≪0.40												
15	≪0.40												
16	≪0.40	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
17	≪0.40	>100	>100	100	100	>100	>100	>100	10	>100	100	100	100
18	≪0.40	1	1	1	1		100	1	0.1	10	1	100	100
19	≪0.40	10	10	10	1	>100	>100	10	10	10	10	100	100
20	2.29	100	100	100	100	>100	>100	100	>100	100	100	>100	>100
21	>0.50	100	10	10	100	>100	100	10	10	100	10	100	100
22	1.19		100	100	100		>100			100			100
23	1.14		10	10	10		100			100			>100
25		>100	>100	10	100	>100	>100	10	1	>100	1	>100	>100
26	1.66	100	100	100	100	>100	>100	100	100	>100	>100	>100	>100
27	0.90	100	100	100	100	>100	>100	100	100	>100	0.1	>100	>100

[a] SG = *Salmonella gallinarum*, ST = *Salmonella typhimurium*, SA = *Staphylococcus aureus*, SAG = *Streptococcus agalactiae*, PsA = *Pseudomonas aeruginosa*, PrM = *Proteus mirabilis*, EI = *Erysipelothrix insidosa*, BS = *Bacillus subtilis*, EC = *Escherichia coli*, PM = *Pasteurella multocida*, AF = *Aspergillus fumigatus*, CA = *Candida albicans*. [b] See ref 1.

Replacement of the 2-hydroxyethyl moiety with 1,3-dihydroxy-2-propyl (**5**), tris(hydroxymethyl)methyl (**7**), and 2-ethyl-1,3-dihydroxy-2-propyl (**6**) groups caused a significant decrease in both *in vitro* and *in vivo* antibacterial activity. Introduction of alkyl, cycloalkyl, substituted aryl, and heterocyclic groups into the 2-hydroxyethyl moiety at position 1 or 2 also caused a decrease in biological activity.

Among the derivatives of **4**, the ether, α-(5-nitro-2-furyl)-*N*-(2-ethoxyethyl)nitrone (**20**), was the most active antibacterial agent: being comparable with **4**. Of the ester derivatives of **4**, the hemisuccinate **26** was the most active, but it was less active than **4**. It is interesting to note that the esters **22** and **23** were more active than the corresponding hydroxyalkylnitrones **11** and **8**.

The potency of **4** relative to furazolidone[16] was 0.56[1] when administered in a feed medication. However, the activity of **4** as a water medication against a standardized *Salmonella choleraesuis* infection in mice did not differ significantly from that of a furazolidone medication.

The LD_{50} of **4** was found to be 220 mg/kg in mice, while that of furazolidone was 1150 mg/kg in mice.

Five compounds in the series (**4**, **8**, **9**, **11**, **12**) were effective in preventing a *Histomonas melagridis* infection in turkeys when administered at as low a level as 0.011% in the diet. Compound **4** was also very effective against the acute phase of the infection when added to drinking water at the rate of 100 mg/l.

Compound **4** at a level of 0.033% in the feed significantly protected chickens against mortality caused by *Eimeria tenella*.

(16) Furazolidone, 3-(5-nitrofurfurylidendamino)-2-oxazolidinone.

Experimental Section[17]

Reagents.—The 1 *M* soln of borane in THF was used as received from Metal Hydrides Division, Ventron Corp., Beverly, Mass.

Starting Materials. 3-Nitropropanol (38).—To a soln of 3-nitropropionic acid[12] (47.63 g, 0.40 mole) in anhyd THF (300 ml) at 0° was introduced dropwise 528 ml of a 1 *M* soln of borane in THF, at such a rate that the temp did not exceed 10°. The reaction temp was brought to ambient over 3 hr; the mixt was stirred, poured onto crushed ice, and extd with Et_2O. The combined Et_2O exts were washed with satd aq $NaHCO_3$ and dried ($MgSO_4$), the solvent was removed, and the residue (31 g) was distd through a 15.2-cm Vigreux column to give a colorless liquid: yield 13.50 g (32%); bp 75–76° (0.8 mm); ν_{max} 3333 (OH), 1550 and 1387 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.59 (t, 2 H, J = 6 cps, CH_2NO_2), 3.78 (t, 2 H J = 6 cps, CH_2O), 2.78 (s, 1 H, OH, exchangeable with D_2O), and 2.25 (quin, 2 H, J = 6 cps, CH_2). *Anal.* ($C_3H_7NO_3$) C, H, N.

6-Nitrohexanol (39) was obtained from 6-nitrocaproic acid[13] as above in 28% yield: bp 106–107° (0.65 mm); ν_{max} 3300 (OH), 1550, and 1383 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.40 (t, 2 H, J = 7 cps, CH_2NO_2), 3.64 (un t, 2 H, CH_2O), 2.85, 2.05, and 1.46 (un m, 9 H, OH plus $(CH_2)_4$). *Anal.* ($C_6H_{13}NO_3$) C, H, N.

Ethyl 2-Nitroethyl Ether (40).—A mixt of 2-nitroethanol (36.43 g, 0.40 mole), triethyloxonium tetrafluoroborate[14] in Et_2O (80 g, 0.42 mole), and CH_2Cl_2 (500 ml) was stirred for 18 hr

(17) Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus, and are uncorrected. Elemental analysis were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Ir spectra were obtained with a Beckman IR-5 infrared spectrophotometer (KBr). Nmr spectra were obtained with a Varian A-60 spectrometer (Me_4Si): s, signifies singlet; t, triplet; q, quartet; quin, quintet; m, multiplet; and un, unresolved. Evapn of solvents was done under reduced pressure using a rotary evaporator.

at room temp. The soln was washed twice with satd $NaHCO_3$ soln (500 ml). The solvent was removed, and the residue was distd through a 10.2-cm column packed with Raschig rings to give a colorless liquid: 29.70 g (62%); bp 70° (4 mm) [lit.[18] bp 46° (1 mm) and 72° (12 mm)]; ν_{max} 1563, 1374 (NO_2), and 1124 cm^{-1} (CO); nmr (CCl_4) δ 4.48 (t, 2 H, CH_2NO_2), 3.95 (t, 2 H, CH_2O), 3.56 (q, 2 H, J = 7 cps, CH_2), and 1.18 (t, 3 H, J = 7 cps, CH_3).

The other nitro alcohols and their derivatives not listed in this report were either purchased or prepared according to the methods described previously.

Hydroxyamino Alcohols. Method A. Catalytic Reduction of Nitro Alcohols (Table II).—A soln of the nitro alcohol (0.20 mole) in a mixt (185 ml) of 95% EtOH and H_2O (15:22) contg oxalic acid dihydrate (17.65 g, 0.14 mole) was hydrogenated at room temperature under 4.2 kg/cm^2 pressure in the presence of 10% Pd/C (0.5–1.0 g) until the calcd amount of H_2 was absorbed. During the reduction, the reaction temp rose to 37°. The reaction mixt was filtd to remove the catalyst, and the filtrate was concd to 0.25 of the original vol. Addn of abs EtOH (150 ml) followed by cooling at *ca.* 0° gave a white solid. Results are shown in Table II.

Similarly 2-ethoxyethylhydroxylamine oxalate was obtained by reducing ethyl 2-nitroethyl ether (11.91 g, 0.1 mole). It was not characterized and was used without purification to prepare **20**.

Method B. Diborane Reduction of Disodium 2-Hydroxyethylnitronate.—An ice-cooled soln contg Na (45.99 g, 2.0 g-atoms) and abs EtOH (600 ml) was added in 1 portion to an ice-cold soln of 2-nitroethanol (91.07 g, 1.0 mole) in abs EtOH (200 ml). Immediately a white ppt was formed. After standing at room temp for 4 hr, anhyd Et_2O (600 ml) was added to ppt the disodium 2-hydroxyethylnitronate. This material was quickly removed by filtration, washed well with 3 portions of Et_2O (100 ml), and dried in a desiccator *in vacuo* to yield 130 g (96%) of the salt. To disodium 2-hydroxyethylnitronate (33.76 g 0.25 mole) suspended in anhyd THF (125 ml) at 0° was introduced dropwise 579 ml of 1 *M* soln of borane in THF at such a rate that the temp did not exceed 10°. The reaction mixt was stirred at this temp for *ca.* 5 hr, and then reaction temp was allowed to rise to room temp. The solvent was removed, and the temp of the residue was lowered to 0°. To the cooled mixt was added aq HCl [220 ml; H_2O–HCl (1:1.2)] at such a rate that the temp did not exceed 5°. The reaction mixt was refluxed for 1 hr, while maintaining pH 1. After evapn of the solvent to dryness, the white residue was dissolved in abs EtOH (500 ml). The insol solid was collected, and the filtrate was evapd almost to dryness. The residue was triturated with Et_2O (150 ml), a white solid was removed by filtration, and the solvent was removed to obtain 2-hydroxylaminoethanol·HCl (**28**·HCl) as a viscous oil (14.44 g, 51%). It gave a positive Tollen's test.

Method C. Al(Hg) Reduction of Nitro Alcohols. (A) 2-Hydroxylaminoethanol·HCl (28·HCl).—To 2-nitroethanol (18.21 g, 0.20 mole) in THF (150 ml) was added Al(Hg)[8] [prepared from Al foil strips (12 g) and 2% $HgCl_2$ soln] under Et_2O (600 ml). H_2O (20 ml) was added dropwise to the stirred mixt, which was then heated to boiling. The heating bath was removed, and Et_2O was allowed to reflux for an additional 15 min. More H_2O (20 ml) was added and after further warming (15 min), the mixt was stirred at room temp for 45 min. It was filtered, and the filter cake was washed with warm H_2O (3 l.). After sepn from the org phase, the aq filtrate and washings were combined, acidified with concd HCl, and evapd to dryness at 50–60°. The residue was dissolved in abs EtOH (100 ml), and the soln was evapd to give a brown viscous oil (21.7 g). On the basis of the yield (15%) of **4** from this impure material the actual yield of product was estimated as 14%.

(B) 2-Hydroxylamino-2-methylpropanol·HCl.—This compd was prepared in a manner similar to that described for **28**·HCl, using 2-methyl-2-nitro-1-propanol (23.82 g, 0.20 mole). From the nonaqueous phase after drying over anhyd $MgSO_4$, an oily product (11.00 g) was obtd. An additional 4.30 g was obtd from the aq phase. Both products (15.3 g) were combined and converted into the HCl salt (21.2 g) in the usual manner. On the basis of the yield (31%) of **10** from the crude hydrochloride, the yield of hydroxylamine was estimated as 23%.

(C) 2-Ethyl-2-hydroxylamino-1,3-propanediol·HCl was prepd in a manner similar to that described for **28**·HCl, using 2-ethyl-2-nitro-1,3-propanediol (29.83 g, 0.20 mole). After removal of the solvent including both aq and nonaqueous phase, a syrupy residue (26.90 g) was obtd and converted into its HCl salt (34.42 g) in the usual manner. On the basis of the yield (20%) of **6** from the crude hydrochloride, the yield of hydroxylamine was estimated as 20%.

Method D. NaHg Reduction of Nitro Alcohol. Tris(hydroxymethyl)methylhydroxylamine·HCl.—The hydroxylamino alcohol (6.75 g, 38%) was prepd from tris(hydroxymethyl)nitromethane (19.65 g, 0.13 mole) according to the procedure of Cason and Pront[9] using NaHg as a reducing agent. Its HCl salt was prepared by treatment with ethereal HCl in an ice bath. After removal of the solvent, a hygroscopic viscous residue was used for the synthesis of 7 without further purification.

α-(5-Nitro-2-furyl)-*N*-hydroxyalkylnitrones and Their Derivatives. Method A.—The corresponding hydroxylamino alcohol·HCl (0.1 mole) was added portionwise to a warm soln of 5-nitrofurfural (14.11 g, 0.1 mole) in 95% EtOH (200 ml) contg $NaHCO_3$ (0.2 mole) and stirred for *ca.* 4 hr. The mixture was filtd. The filter cake was taken up in hot 95% EtOH (200 ml), treated with charcoal, and filtd. Cooling the filtrate gave the bright yellow nitrones. Results are shown in Table I.

Method B.—The same procedure as above was used except that 5 molar equiv of hydroxylamino alcohol oxalate was used.

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