body weight were made twice weekly. At the 29th day after initiation of the therapy, the animals were killed, the body weights were determined, and the uteri, ovaries, and adrenal glands were removed and weighed after having been treated as mentioned above.

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Supplementary Material Available: ^{1}H NMR data (Tables V and VI) and elemental analyses (Table VII) of compounds **7–32** (3 pages). Ordering information is given on any current masthead page.

Synthesis of Nitrosourea Derivatives of Pyridine and Piperidine as Potential Anticancer Agents

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Nitrosourea derivatives **18–22** which utilize either a piperidine or pyridine ring as a carrier group were synthesized and evaluated for anticancer activity. *N'*-(1-Benzyl-4-piperidinyl)-*N*-(2-chloroethyl)-*N*-nitrosourea hydrogen maleate (**19**) exhibited good activity against intracranial L1210 leukemia as well as the mouse ependymoblastoma brain tumor system. Compound **19** exhibited comparable activity in the Lewis lung carcinoma system to *N,N'*-bis(2-chloroethyl)-*N*-nitrosourea. Replacement of the *N*-benzyl group in both the 3-piperidinyl- and 4-piperidinylnitrosoureas resulted in less active compounds in all tumor systems tested. The 3-pyridylnitrosourea **22** was inactive in the L-1210 leukemia system.

The synthesis of a variety of nitrosoureas[2-5] have been described, many of which are highly active in mice against murine leukemia L1210 implanted either intraperitoneally[3-6] or intracerebrally.[4-6] Several nitrosoureas, including *N,N'*-bis(2-chloroethyl)-*N*-nitrosourea (BCNU, carmustine), *N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea (CCNU, lomustine), and *N*-(2-chloroethyl)-*N'*-(*trans*-4-methylcyclohexyl)-*N*-nitrosourea (MeCCNU, semustine), are currently undergoing extensive clinical trials.[7]

In a previous report, the synthesis and antileukemic activity of two ergoline nitrosoureas were described.[8] These compounds were designed in an attempt to combine antiprolactin and antitumor activity in the same molecule.

Based on the antitumor activity of these compounds, we have synthesized a series of related (based on the ergoline D ring) nitrosoureas which contain the pyridine and piperidine ring systems as carrier groups. These compounds are of considerable interest, since (a) they may be considered as nitrogen analogues of CCNU; (b) they form stable, water-soluble, crystalline salts; (c) the N-substituent may be altered in order to vary the lipophilicity of the compounds; and (d) they are less leukopenic than BCNU at equitoxic doses.

Chemistry. Piperidines containing the *N*-(2-chloroethyl)-*N*-nitrosourea group substituted at the 4 position of the ring (Table III) were prepared starting from ethyl isonipecotate. Precursors to the compound containing the nitrosourea group attached at the 4 position of the piperidine ring are given with their physical properties in Table I. The desired nitrosoureas **19** and **20** were prepared by nitrosation of the corresponding chloroethylureas **12** and **14** with sodium nitrite in 99% formic acid.[3] Isomeric purity was established by NMR spectroscopy (Table IV). The spectral symmetry[3] of the $ClCH_2CH_2N(NO)$ group (A_2B_2 system) is clearly shown in Table IV.

N-(1-Benzyl-3-piperidinyl)-*N*-(2-chloroethylurea) hydrogen maleate (**18**) was prepared starting from 3-acetamidopyridine (**7**). Catalytic reduction of **7** followed by alkylation with benzyl chloride and removal of the *N*-acetyl protecting group, gave the intermediate amine, **10**. The nitrosourea **18** was prepared by nitrosation of **11**.

A direct relationship between the lipophilicity of the N-substiuent and the yield of the nitrosourea seems apparent (Table III). A water-soluble hydrochloride of *N*-(2-chloroethyl)-*N'*-(1-methyl-4-piperidinyl)-*N*-nitrosourea has been reported.[9] However, our attempts to prepare nitrosoureas with a methyl group on the piperidine nitrogen gave unstable, highly water soluble products. The piperidinylchloroethylureas containing an *N*-ethyl or *N*-butyl group likewise gave complex reaction mixtures upon nitrosation.

Derivatives in which a (2-chloroethyl)urea group is substituted at the 2, 3, or 4 positions of pyridine were prepared in the normal manner, and their properties are given in Table II. Only *N*-(2-chloroethyl)-*N'*-(3-pyridyl)-*N*-nitrosourea (**22**) could be obtained by nitrosa-

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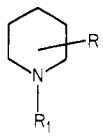
Table I. Physical and Chemical Data of Piperidine Derivatives



no.	R	R_1	mp, °C	method	recrystn solvent	yield, %	formula	anal.[a]
1	4-CO_2Et	$(CH_2)_3CH_3$	175-176.5	A	EtOH-Et_2O	50[b]	$C_{12}H_{23}NO_{20}$·HCl	C, H, N
2	4-CO_2Et	$CH_2C_6H_5$	oil[c]	A		89	$C_{15}H_{21}NO_2$	
3	4-$CONHNH_2$	$(CH_2)_3CH_3$	116-118	B	C_6H_6	91	$C_{10}H_{21}N_3O$	C, H, N
4	4-$CONHNH_2$	$CH_2C_6H_5$	119-122	B	C_6H_6	81	$C_{13}H_{19}N_3O$	C, H, N
5	4-NH_2	$(CH_2)_3CH_3$	253-255.5	C	EtOH-Et_2O	78	$C_9H_{20}N_2$·2HCl	C, H, N
6	4-NH_2	$CH_2C_6H_5$	270-273[d]	C	EtOH	43	$C_{12}H_{18}N_2$·2HCl	
8	3-NHAc	H	oil[e]			47	$C_7H_{14}N_2O$	
9	3-NHAc	$CH_2C_6H_5$	97-98		Et_2O	78	$C_{14}H_{20}N_2O$	C, H, N
10	3-NH_2	$CH_2C_6H_5$	265-266		EtOH	67	$C_{12}H_{18}N_2$·2HCl	C, H, N

[a] All new compounds were analyzed for the elements shown in parentheses and were within ±0.4% of the calculated value. [b] Yield of the free base. [c] Lit.[12] mp 76-77 °C. [d] Lit.[13] mp 273-274 °C. [e] Lit.[14] mp 75-80 °C.

Table II. (2-Chloroethyl)ureas

$RNH_2 \longrightarrow RNHCONHCH_2CH_2Cl$

no.	R	mp, °C	method	recrystn solvent	yield, %	IR (KBr), cm^{-1} NH	C=O	CNH	formula	anal.[a]
11	1-benzyl-3-piperidyl	141-143	D	EtOH-Et_2O	28[b]				$C_{19}H_{26}ClN_3O_5$	C, H, N
12	1-benzyl-4-piperidyl	125.5-127.5	D	C_6H_6	50	3210	1620	1580	$C_{15}H_{22}ClN_3O$	C, H, N
13	1-ethyl-3-piperidyl	112.5-114.5	E	EtOH-Et_2O	82[b]	3245	1615	1580	$C_{14}H_{24}ClN_3O_5$	C, H, N
14	1-butyl-4-piperidyl	105.5-107	E	C_6H_6-petr ether	41	3295	1615	1570	$C_{12}H_{24}ClN_3O$	H, N; C[c]
15	2-pyridyl	116.5-117.5	E	EtOAc	47	3195	1670	1530	$C_8H_{10}ClN_3O$	C, H, N
16	3-pyridyl	137.5-138.5[d]	E	EtOAc	81	3300	1670	1560	$C_8H_{10}ClN_3O$	C, H, N
17	4-pyridyl	164-165	E	EtOH	49[b]	3230	1710	1620	$C_{12}H_{14}ClN_3O_5$[e]	C, H, N

[a] All new compounds were analyzed for the elements shown in parentheses and were within ±0.4% of the calculated value unless otherwise specified. [b] Yield of the free base. [c] C: calcd, 55.04; found, 54.23. [d] Lit.[3] mp 155 °C. [e] Maleate salt.

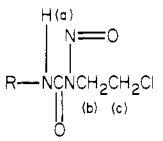
Table III. (2-Chloroethyl)nitrosoureas

$RNHCONHCH_2CH_2Cl \xrightarrow{\text{method F}} RNHCON(NO)CH_2CH_2Cl$

no.	R	mp, °C	recrystn solvent	yield, %	formula	anal.[a]
18	1-benzyl-3-piperidyl	128.5-129	EtOAc	51	$C_{19}H_{25}ClN_4O_6$[b]	C, H, N
19	1-benzyl-4-piperidyl	122-125	EtOH-Et_2O	79[c]	$C_{19}H_{25}ClN_4O_6$[b]	C, H, Cl, N
20	1-butyl-4-piperidyl	97.5-99.5	EtOAc-Et_2O	39	$C_{16}H_{27}ClN_4O_6$[b]	C, H, N
21	1-ethyl-3-piperidyl	126-127	EtOH-Et_2O	15	$C_{14}H_{23}ClN_4O_6$[b]	C, H, N
22	3-pyridyl	89-90	Et_2O	49	$C_8H_9ClN_4O_2$	C, H, Cl, N

[a] All of the compounds were analyzed for the elements shown and were within ±0.4% of the theoretical values. [b] Maleate salt. [c] Yield of the free base.

Table IV. NMR and IR Data for Nitrosoureas 18-22



no.	NMR,[a] δ H_b	H_c	H_a	IR (KBr), cm^{-1} NH	C=O	CNH	N=O
18[b]	3.61 (t, 6)	4.17 (t, 6)	c	3310	1690	1550	1470
19[d]	3.47 (t, 6)	4.17 (t, 6)	6.90 (d)	3390	1710	1575	1485
20[e]	3.67 (t, 6)	4.13 (t, 6)	8.93 (d)	3290	1720	1580	1480
21[e]	3.67 (t, 7)	4.17 (t, 7)	9.03 (d)	3220	1695	1570	1480
22	3.60 (t, 6)	4.28 (t, 6)	9.33 (br s)	3240	1730	1555	1500

[a] Chemical shifts are expressed as δ with multiplicity and coupling constants (Hz) in parentheses. [b] Spectrum recorded in Me_2SO-d_6/D_2O. [c] NHCO exchanged. [d] Spectrum recorded in $CDCl_3$ on the free base. [e] Spectrum recorded in Me_2SO-d_6.

Table V. Effect of Nitrosoureas on Mouse Leukemia[a]

no.	tumor	dose range, mg/kg[b]	opt dose[c]	toxicity-day survivors[d]	animal wt diff, g: T - C	% T/C (cures)[e]
18	L-1210[f]	100-6.25	100	6/6	-5.3	340 (3)
	L-1210[g]	200-12.5	100	6/6	-0.8	192
19	L-1210[f]	200-12.5	100	6/6	-4.8	379 (5)
	L-1210[g]	200-12.5	100	6/6	-1.0	151
	P-388[f]	200-6.25	100	6/6	-4.5	361 (1)
20	L-1210[f]	256-16	64	6/6	-3.9	197
21	L-1210[f]	256-16	128	6/6	-5.9	235 (1)
22	L-1210[f]	400-12.5	12.5	5/5	-7.2	126

[a] Tests were carried out by A. D. Little under National Cancer Institute auspices. For a detailed description of the test protocol, see R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 3(2), 1(1972). [b] Single intraperitoneal injection on day 1. [c] Optimum dose. [d] Recorded on the 5th day after injection of the compound. [e] A cure in this assay represents a 30-day survivor. [f] Intraperitoneally implanted. [g] Intracerebrally implanted.

Table VI. Effect of Nitrosoureas on 3EM 37 Mouse Ependymoblastoma[a]

compd	dose range, mg/kg[b]	opt dose[c]	toxicity-day survivors[d]	animal wt diff, g: T - C	% T/C (cures)[e]
18	200-12.5	100	10/10	-0.9	223 (1)
19	200-12.5	100	10/10	-1.2	242 (1)
MeCCNU	256-16	128	9/10	+1.0	204

[a] Tests were performed by I. Wodinsky at A. D. Little under National Cancer Institute auspices. See footnote *a*, Table V, for test protocol. This test measures the ability of the compound to penetrate the CNS and exert antitumor activity. [b] Single intraperitoneal injection on day 1. [c] Optimum dose. [d] Recorded on the fifth day after initial injection of the compound. [e] A cure in this assay represents a 30-day survivor.

Table VII. Effect of Nitrosoureas on Lewis Lung Carcinoma[a]

compd	dose range, mg/kg[b]	opt dose[c]	animal wt diff, g: T - C	% T/C (cures)[d]
18	64-2	64	-3.7	259 (1)
19	64-2	64	-2.9	>353 (3)
BCNU	64-2	32	-3.5	>353 (5)

[a] See footnote *a*, Table V, for test protocol. [b] Single intraperitoneal injection on day 1. [c] Optimum dose. [d] A cure in this assay represents a 60-day survivor.

Table VIII. Effect of Nitrosoureas on Total White Blood Cell Count[a]

compd	dose, mg/kg[b]	% change from control[c] day 3	day 5	day 7
BCNU	90.5	-68[d]	-48[d]	[c]
	40.25	-46[d]	-22[d]	-41[d]
	22.63	-33[d]	-28[d]	+42[d]
	11.31	-47[d]	-42[d]	+2
18	75	-63[d]	-45[d]	+11
	37.5	-20	+16	+60[e]
	18.75	-26	-5	+40[e]
	8.38	-19[d]	+15	+23
19	106	-67[d]	-35[d]	+1
	53	-22	-5	+14
	26.5	+12	+5	+7
	13.25	+3	+18[e]	+8

[a] For a detailed description of the test protocol, see W. T. Bradner, J. E. Schurig, J. B. Huftalen, and G. J. Doyle, *Cancer Chemother Pharmacol.*, in press (1980). [b] Treatment given intraperitoneally; 10 mice per group. Control based on predose value. [c] All animals dead. [d] Significant change $p \leq 0.05$. [e] Significant change $p \leq 0.01$.

tion of the corresponding (2-chloroethyl)urea **16**. Attempted nitrosation of **15** and **17** gave reaction mixtures which could not be characterized.

Biological Activity. Earlier studies by Montgomery[10] had indicated that introduction of heteroatoms (not including N) into the cyclohexane ring of CCNU was detrimental to activity against Lewis lung carcinoma. In this investigation, an attempt was made to increase the hydrophobic character of the piperidine analogues by attaching a benzyl group (π value = 2.63)[11] to the ring nitrogen. The resulting *N*-benzyl derivatives **18** and **19** were found to be stable, lipophilic compounds with a broad spectrum of potent antitumor activity. In mouse leukemia systems, P-388 and L-1210 (Table V), these compounds showed a T/C > 300 at high doses. However, some toxicity (weight loss greater than 4 g) was present. The compounds were injected as their water-soluble salts; however, each showed good activity vs. intracranial L1210 and another CNS tumor, 3EM37 (Table VI), which has been used to select among nitrosoureas active against the mouse leukemias. In addition, both compounds showed good activity in the Lewis lung system (Table VII) and here potency compared favorably to that exhibited by BCNU. Again the 4 isomer, **19**, appeared to be more active. Replacement of the *N*-benzyl group in **19** with *N*-butyl resulted in, **20**, a more water-soluble, less active compound in L1210. The same result occurred when the *N*-benzyl group in **18** was replaced by *N*-ethyl to yield **21**, a less active compound. Replacement of the piperidine group with pyridine resulted in a highly toxic, relatively inactive derivative, **22**.

Initial results (Table VIII) indicate that both **18** and **19** are less leukopenic than BCNU at equitoxic doses. Further studies are in progress to compare **18** and **19** to chlorozotocin, which is reported to be relatively nontoxic to bone marrow. The synthesis of additional *N*-benzylpiperidino analogues is planned to evaluate compounds which may have increased potency.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets with a Beckman IR-33 spectrophotomer. Mass spectra (MS) were obtained on a Dupont 21-492B double-focusing low-resolution spectrometer; *m/e* values are reported with relative intensity. NMR spectra (60 MHz) were recorded in $CDCl_3$, unless otherwise specified, with a Varian Associates EM-360 spectrometer. Chemical shifts are reported in parts per million (δ). The IR and

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NMR of all new compounds were consistent with the expected structures. Analytical data were obtained from the Microanalysis Laboratory, Department of Chemistry, Purdue University. TLC was performed on precoated silica gel plastic sheets (Machery-Nagel, SIL G/UV_{254}, 0.25-mm thickness) developing with $CHCl_3$–MeOH (9:1). Column chromatography was carried out using as the adsorbents MN-Kielselgel, 70–325 mesh, and Al_2O_3 (Merck) basic, activity I.

Method A. The synthesis of 1-butyl-4-(ethoxycarbonyl)piperidine hydrochloride (1) is representative of the general method. A suspension of ethyl isonipecotate (10.0 g, 64.0 mmol) and anhydrous $NaHCO_3$ (5.38 g, 64.0 mmol) in dry DMF (50 mL) was treated with 1-bromobutane (8.77 g, 64.0 mmol) in dry DMF (25 mL). After the solution was stirred at room temperature for 17 h, the solvent was removed under reduced pressure to afford a yellow oily residue. The oil was partitioned between EtOAc (50 mL) and H_2O (250 mL). The EtOAc layer was separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield a light yellow oil. Vacuum distillation afforded 7.68 g (50%) of colorless oil: bp 74–79 °C (0.01 mmHg). The hydrochloride was prepared and recrystallized from EtOH–Et_2O to give the analytical sample, mp 175–176.5 °C.

Method B. The preparation of 1-butyl-4-piperidinecarboxylic acid hydrazide (3) is representative of the general method. A mixture of **1** (6.68 g, 36.0 mmol) and 85% hydrazine hydrate (35 mL) was refluxed for 3 h and cooled, and the solid was filtered. The solid was washed several times with hexane and dried in vacuo at 60 °C to give 6.50 g of **3**. An analytical sample was obtained by recrystallization of a small sample from C_6H_6.

Method C. The synthesis of 4-amino-1-butylpiperidine dihydrochloride (5) is representative of the general method. A solution of **3** (3.21 g, 16.1 mmol) in 0.4 N HCl (40 mL, 16 mmol), cooled at 0–5 °C, was treated with $NaNO_2$ powder (1.11 g, 16.1 mmol). After the solution was stirred for a few minutes, 0.4 N HCl (81 mL, 32 mmol) was added to the solution. The mixture was cooled to 0–5 °C for 3 h, during which time the acid azide hydrochloride precipitated from solution. After warming to room temperature, the mixture was heated strongly in an oil bath until N_2 evolution ceased. The mixture was cooled, basified with NaOH pellets, and extracted with $CHCl_3$ (2 × 100 mL) and EtOAc (1 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield a colorless oil. The oil was treated with ethanolic hydrogen chloride. Evaporation of the solvent afforded 2.88 g of **6**. Recrystallization of the dihydrochloride from EtOH–Et_2O gave an analytical sample.

3-Acetamidopyridine (7). 3-Aminopyridine (Eastman Kodak; 9.41 g, 100 mmol) was dissolved in THF (50 mL) and Ac_2O (12.3 g, 120 mmol) was added dropwise as the temperature of the reaction mixture was maintained at 0–5 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 17 h under N_2. The mixture was neutralized with solid Na_2CO_3 and diluted with H_2O (100 mL), and the THF layer was separated. The aqueous phase was extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were washed with saturated NaCl solution (1 × 100 mL), dried (Na_2SO_4), filtered, and evaporated to afford 9.77 g (72%) of **7**: mp 131–135 °C (lit.[12] mp 133 °C).

3-Acetamidopiperidine (8). A mixture of **7** (12.2 g, 89.5 mmol), PtO_2 (500 mg), and EtOH (175 mL) containing concentrated HCl (7.5 mL) was shaken on the Parr hydrogenator for 42 h. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to afford an oil. The oil was dissolved in H_2O (50 mL) and basified with 1 N NaOH. The aqueous solution was extracted with $CHCl_3$ (3 × 75 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and evaporated to yield 6.03 g of **8**. The compound was used directly without further purification: NMR δ 1.33–4.92 (m, including s, at δ 2.00, $NCOCH_3$, 13 H), 6.53 (d, 1 H, NHCO).

3-Acetamido-1-benzylpiperidine (9). 3-Acetamidopiperidine (5.76 g, 40.5 mmol) was dissolved in DMF (20 mL) and $NaHCO_3$ (3.41 g, 40.5 mmol) was added to the stirred solution. The mixture was cooled to 0–5 °C and $C_6H_5CH_2Cl$ (5.13 g, 40.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 15 h. The solvent was removed under reduced pressure to afford a yellow solid. The solid was triturated with H_2O (50 mL), and the H_2O-insoluble material was collected by suction filtration. The white solid was dried to give 7.35 g of **9**, mp 96–98 °C. An analytical sample was obtained by recrystallization of a small amount from Et_2O to give pure **9**, mp 97–98 °C.

3-Amino-1-benzylpiperidine Dihydrochloride (10). 3-Acetamido-1-benzylpiperidine (1.09 g, 4.69 mmol) was dissolved in 6 N HCl (10 mL) and heated at reflux for 1 h. The reaction mixture was cooled, basified with 6 N NH_4OH, and extracted with $CHCl_3$ (4 × 50 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and evaporated to give an oil. The oil was converted to a crystalline dihydrochloride salt, which was recrystallized from EtOH to yield 833 mg of **10**.

Method D. The synthesis of *N'*-(1-benzyl-3-piperidinyl)-*N*-(2-chloroethyl)urea hydrogen maleate (11) is descriptive of the general procedure. A mixture of **10** (1.90 g, 7.22 mmol) and Et_3N (1.46 g, 14.4 mmol) in dry $CHCl_3$ (50 mL) was stirred until neutralization of the dihydrochloride had occurred (0.5 h). To the solution was added via syringe $ClCH_2CH_2NCO$ (Eastman Kodak; 762 mg, 7.22 mmol), and stirring was continued for 16 h. The solvent was removed under reduced pressure, and the residue was partitioned between $CHCl_3$ (150 mL) and H_2O (50 mL). The $CHCl_3$ layer was washed with 5% $NaHCO_3$ solution (100 mL), dried (Na_2SO_4), filtered, and evaporated to give an oil. Column chromatography of the oil on silica gel using a $CHCl_3$–MeOH (9:1) solvent system gave 604 mg of an oil: TLC (homogeneous) R_f 0.49. The oil was converted to a crystalline hydrogen maleate salt which was recrystallized from EtOH–Et_2O to afford 375 mg (13% based on **10**) of **11**.

Method E. The synthesis of *N*-(2-chloroethyl)-*N'*-(1-ethyl-3-piperidinyl)urea hydrogen maleate (13) is typical of the general procedure. A solution of 3-amino-1-ethylpiperidine (Aldrich; 5.00 g, 39.0 mmol) in THF (50 mL) was treated dropwise at 0–5 °C with $ClCH_2CH_2NCO$ (4.12 g, 39.0 mmol) in THF (10 mL). The reaction mixture was allowed to warm to room temperature and stir for 1.5 h. Removal of the solvent under reduced pressure afforded a white solid. Recrystallization of the solid from C_6H_6 gave 7.50 g (82%) of the free base, mp 116–117 °C.

Method F. The synthesis of *N'*-(1-benzyl-3-piperidinyl)-*N*-(2-chloroethyl)-*N*-nitrosourea hydrogen maleate (18) is representative of the general method. To a solution of **11** (364 mg, 0.884 mmol) in 99% HCOOH (5 mL) cooled at 0–5 °C was added dry $NaNO_2$ powder (183 mg, 2.65 mmol). The dark yellow solution was stirred for 0.5 h at 0–5 °C, diluted with H_2O (5 mL), and stirred for an additional 0.5 h. The reaction mixture was basified with 6 N NH_4OH and extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and evaporated to give a yellow oil. Chromatography of the oil on silica gel (60 g) using $CHCl_3$ as the eluent gave 234 mg (82%) of a yellow oil. A crystalline hydrogen maleate salt was prepared and recrystallized from EtOAc to afford 200 mg (51% based on **11**) of crystalline **18**.

***N*-(2-Chloroethyl)-*N'*-(3-pyridyl)-*N*-nitrosourea (22).** A solution of **16** (2.22 g, 11.1 mmol) in 99% HCOOH (15 mL) was cooled to 0–5 °C and treated with $NaNO_2$ (2.30 g, 33.3 mmol) in small portions. The reaction mixture was stirred for 0.5 h at 0–5 °C and then neutralized (pH 7) with 10% NaOH solution. The mixture was extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and evaporated to afford a dark brown oil. The oil was column chromatographed on silica gel (50 g) using a $CHCl_3$–EtOAc (1:1) solvent system. Removal of the solvents gave 1.20 g of a yellow solid. An analytical sample was prepared by recrystallization of a small sample from Et_2O to give pure **22**: mp 89–90 °C; MS (low resolution) *m/e* 231 (M^+ + 2.5), 229 (M^+, 14), 201 (6), 193 (M^+ – Cl, 25), 164 (M^+ – CH_2CH_2Cl, 9), 121 (M^+ – $N(NO)CH_2CH_2Cl$).

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