lation of data for the acid hydrolysis of ZCONHX in water at 75 °C with

$$\log k = \psi_1 \upsilon_Z + \psi_2 \upsilon_{NHX} + h \quad (17)$$

The data used were a combination of set 2 in Table I and set 4 of ref 8. Results of the correlation are: multiple correlation coefficient, 0.969; F test for significance of regression, 176.8 (99.9% CL); s_{est}, 0.126; s_{ψ_1}, 0.109 (99.9% CL); s_{ψ_2}, 0.128 (99.9% CL); s_h, 0.125 (99.9% CL); partial correlation coefficient of υ_Z on υ_{NHX}, 0.497 (98.0% CL); $\psi_1 = -1.93$; $\psi_2 = -1.82$; $h = 2.73$; number of points in the set, 26; range in log k, 1.84. The high confidence level for the correlation of υ_Z on υ_{NHX} indicates that the separation of steric effects is less than is desirable. It seems probable, however, that rates of hydrolysis of amides substituted in both the acyl and amino moieties can be successfully correlated by eq 17.

Supplementary Material Available. The results of the correlations with eq 10, values of σ_I and σ_R for alkyl groups, and complete statistics for the correlation of the data in Table I with eq 11 (3 pages). Ordering information is given on any current masthead page.

Registry No.—Methyl acetate, 79-20-9; piperonal, 120-57-0.

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Chemistry of Nitrosoureas. Decomposition of 1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-Bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea

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1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea were synthesized and decomposed in buffered water. The products were analyzed by GC and GC/MS. The stereochemistry of the product 3-chloro-2-butanols and 2-chloro-2-butenes indicates that a significant fraction of these products are formed via reactions of 3-chloro-2-butyldiazo hydroxide with S_N2 and E2 stereochemistry, as well as by S_N1 and El reactions involving the secondary 3-chloro-2-butyl carbonium ion. Since primary carbonium ions are higher energy species than secondary ones, we predict that the decomposition of the antitumor agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) to 2-chloroethanol and vinyl chloride occurs predominantly by way of S_N2 and E2 reactions of 2-chloroethyldiazo hydroxide and not by way of S_N1 and E1 reactions involving the primary 2-chloroethyl carbonium ion.

BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea] is a useful agent for the treatment of certain malignant diseases. The major products of the decomposition of BCNU in buffered aqueous solution (pH 7.4) are vinyl chloride, acetaldehyde, 1,2-dichloroethane, and 2-chloroethanol.[1] Recently, we reported the synthesis and decomposition of specifically deuterated BCNUs.[2] The results excluded the intermediacy of diazochloroethane and the vinyl carbonium ion and were consistent with the intermediacy of the 2-chloroethyl carbonium ion. However, the results did not definitively distinguish between the S_N1–E1 path through the 2-chloroethyl carbonium ion and the S_N2–E2 path in which the various reactions and rearrangements occur concerted with the loss of nitrogen from the 2-chloroethyldiazo hydroxide. Because the decomposition of BCNU to 2-chloroethanol involves a primary carbon atom, there is no stereochemistry by which an S_N1 process could be distinguished from an S_N2 process. We report here the synthesis and decomposition of the substituted BCNU derivatives 1,3-bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea in which there is stereochemistry to follow.

Chemistry. 1,3-Bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea (*erythro*-BCBNU, **5**) was synthesized as shown in Scheme I. 1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea (*threo*-BCBNU) was synthesized by the same route, only starting from *cis*-2-butene. The unnitrosated ureas can exist as a mixture of a meso compound and a *dl* pair and the nitrosated ureas as a mixture of two *dl* pairs, but these facts do not affect any of the stereochemistry in this paper. The first three steps of the syntheses are known stereospecific reactions[3] and the last step does not involve making or breaking any bonds to carbon atoms. The remaining step, the reaction of dimethylaziridine with phosgene, is expected to go with one inversion by analogy with other aziridine ring openings.[4] This

Scheme I

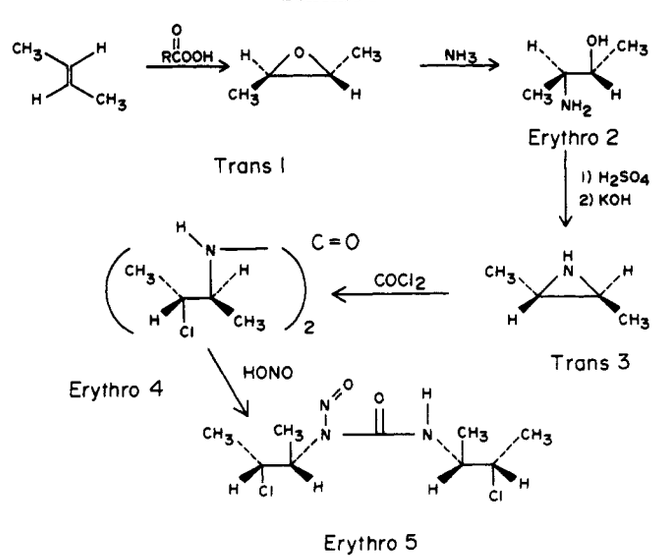
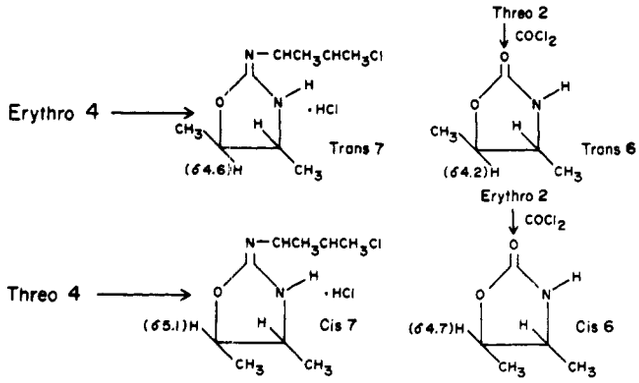


Table I. Products from BCBNU Decomposition

Product	Yield from BCBNU %[a] erythro	threo	GC retention time, min
Isobutyraldehyde	16	7	2.4
Butanone	43	29	3.8
1-Buten-3-ol	8	10	5.6
trans-2-Chloro-2-butene	3	17	7.0
cis-2-Chloro-2-butene	6	2	8.6
2-Buten-1-ol	6	7	12.0
threo-3-Chloro-2-butanol[b]	12	10	18.8
erythro-3-Chloro-2-butanol[c]	6	18	20.0

[a] Mole percent of identified products. Total product recovery was 80% of theoretical. [b] MS *m/e* (% base): 45 (100), 27 (18), 29 (12), 43 (11), 55 (7), 57 (5). [c] MS *m/e* (% base): 45 (100), 27 (12), 43 (10), 29 (8), 55 (5), 57 (4).

Scheme II



expectation was checked by converting the ureas to the oxazolines (Scheme II). If this reaction goes with one inversion, the *erythro*-urea should give the *trans*-oxazoline and the *threo*-urea should give the *cis*-oxazoline. That the ureas gave the expected oxazolines was determined by comparing the NMRs to those of *cis*- and *trans*-4,5-dimethyloxazolidone. The *cis*-oxazolidone and the oxazoline from *threo*-4 both have the absorption of the C-5 hydrogen farthest downfield.

Results

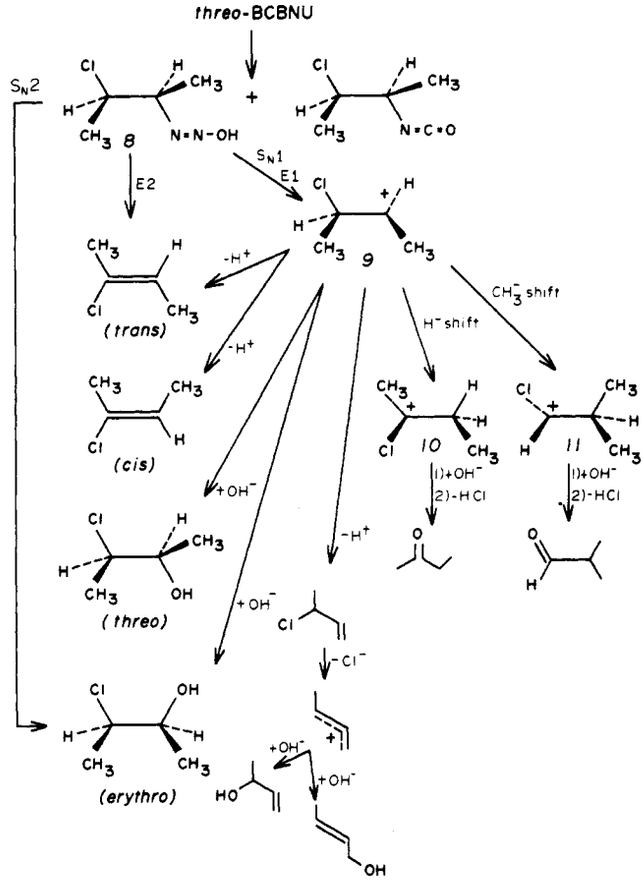
threo- and *erythro*-BCBNU were allowed to decompose at 37 °C in phosphate-buffered water (pH 7.4) in a gas-tight vial, and the products were analyzed by both GC and GC/MS. The products were identified by comparison of the GC retention times and the mass spectra to authentic standards. The results are shown in Table I. Of the eight products identified, four contain stereochemical information—*cis*- and *trans*-2-chloro-2-butene, and *threo*- and *erythro*-3-chloro-2-butanol. *erythro*-BCBNU gives predominantly *threo*-3-chloro-2-butanol and *cis*-2-chloro-2-butene, while *threo*-BCBNU gives predominantly the *erythro*-butanol and the *trans*-butene.

Discussion

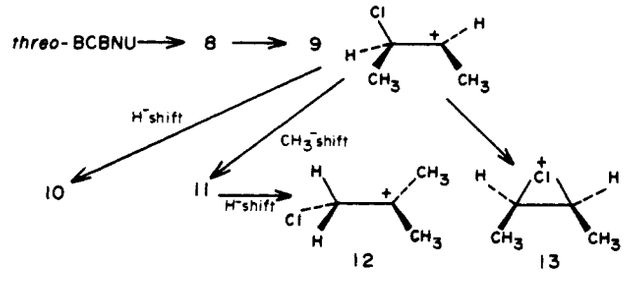
The products from the decomposition of the two BCBNUs can be explained by the mechanism shown in Scheme III for *threo*-BCBNU (the analogous mechanism explains the decomposition of the erythro isomer). In this mechanism, BCBNU decomposes to a isocyanate and a diazo hydroxide. The isocyanate half, by analogy to BCNU,[5] probably forms a mixture of 3-chloro-2-butylamine and bis(3-chloro-2-butyl)urea. These compounds are not volatile enough to pass through the GC column used. The products seen arise from the diazo hydroxide half of the BCBNU molecule.

In the mechanism shown in Scheme III, the 3-chloro-2-butanol arises in part (ca. ⅔) by an S_N1 reaction which gives

Scheme III



Scheme IV



equal amounts of the threo and erythro alcohols and in part (ca. ⅓) by an S_N2 mechanism which gives the inverted erythro alcohol (the predominant stereoisomer formed). The stereochemistry of the chlorobutanols can also be explained by a rapid stepwise mechanism. In this mechanism the diazo hydroxide decomposes to a nitrogen separated ion pair which can either collapse to predominantly retained alcohol or react with a solvent molecule (on the back side, since the front side is blocked by the nitrogen) to give mostly inverted alcohol. To prevent total racemization, this second step must occur faster than the ion can rotate and expose its front side to solvent.

Some of the alcohol may arise via a cyclic chloronium ion (**13**, Scheme IV) not considered in Scheme III. If this ion is formed by collapse of chlorine trans to the nitrogen either concerted with the loss of nitrogen or so rapidly after the loss of nitrogen that the newly formed carbonium ion cannot rotate, the chloronium ion will be formed with one inversion. The opening of this ion by water will occur with one inversion to give, overall, the retained threo alcohol. Some participation by the chloronium ion **13** is likely, since in the decomposition of BCNU 10% of the chloroethanol comes from a chloronium ion.[2] At the extreme of minimum chloronium ion participation, the threo alcohol will be derived primarily via an S_N1

mechanism as outlined in Scheme III. At the extreme of maximum chloronium ion participation, all of the threo alcohol would arise via **13** and no S_N1 mechanism would be operative. Here an S_N2 mechanism would account for all of the erythro alcohol produced which is about ⅔ of the total chlorobutanol. Thus, the amount of actual inversion is probably greater than the ⅓ indicated.

The 3-chloro-2-butanols are unstable at 37 °C in the buffer used for the nitrosourea decomposition. The two isomers decompose at about the same rate with about 25% of each reacted after 4 days. The major product is 2,3-epoxybutane with smaller amounts of 2,3-butanediol, 2-butanone, and isobutyraldehyde also formed. 2,3-Epoxybutane and 2,3-butanediol are minor products in the nitrosourea decomposition mixture. Because the threo and erythro isomers decompose at about the same rate, the final threo/erythro ratio observed should reflect the relative amounts of the two isomers actually formed.

The 2-chloro-2-butene arises in part by an E1 mechanism which gives a mixture of *cis*- and *trans*-butenes and in part by a reaction with E2 stereochemistry which gives the *trans*-butene (the predominant stereoisomer formed). This reaction could involve the loss of the β hydrogen trans to the nitrogen either concerted with the loss of the nitrogen (E2 mechanism) or so rapidly after the loss of nitrogen that the newly formed ion cannot undergo an internal ratation. The predominant formation of the *trans*-butene is not due simple to relative stability of the products, because *erythro*-BCBNU gives predominantly the *cis*-butene. The standard used to identify the 2-chloro-2-butenes was a mixture of nearly equal amounts of the cis and trans isomers. To make sure the first isomer off of the GC column was the lower boiling trans isomer, the mixture was fractionally distilled. The distillate was found to be enriched in the first isomer, the pot residue was enriched in the second isomer off the GC column. For the purpose of quantitating products, the two isomers were assumed to have equal detectability by flame ionization. The two isomers are unstable at 37 °C in the buffer used. Equal amounts of the isomers (~50%) are reacted after 4 days. No product could be identified. Because the cis and trans isomers decompose at about the same rate, the final cis/trans ratio observed should reflect the relative amounts of the two isomers actually formed.

The allylic alcohols, 1-buten-3-ol and 2-buten-1-ol, are formed by hydrolysis of the 3-chloro-1-butene which is the other possible elimination product. This elimination is probably a mixture of an E1 reaction and a reaction with E2 stereochemistry as is the elimination to form the 2-chloro-2-butenes. The hydrolysis of 3-chloro-1-butene under the conditions of the decomposition gives the two alcohols in the same ratio as the nitrosourea decomposition. The two butenols are stable at 37 °C in the buffer used.

The butanone is formed by a hydride shift followed by a reaction of hydroxide with the resulting 2-chloro-2-butyl carbonium ion and loss of hydrochloric acid. The isobutyraldehyde is formed by a methyl shift followed by reaction of hydroxide with the resulting 1-chloro-2-methyl-1-propyl carbonium ion and loss of HCl. Both of these rearrangements probably involve primarily the migration of a group trans to the nitrogen and occur either concerted with the loss of nitrogen or so rapidly after the loss of nitrogen that the newly formed carbonium ion cannot rotate. Both isobutyraldehyde and butanone are stable at 37 °C in the buffer used.

Some of the chlorobutyl carbonium ions which may be involved in the decomposition of BCBNU are shown in Scheme IV. Theroretical calculations predict that the order of stability is **12** (lowest energy), **13, 10, 9,** and **11** (highest energy).[6] Ionization of 2,3-dichlorobutane in "magic acid," which should initially give ion **9**, gives a 40:60 mixture of **12** and **10**.[7] Ion **11** is most probably an intermediate in the transformation of **9** to **12**, In the decomposition of BCBNU, products were seen from **10** (2-butanone) and **11** (isobutyraldehyde), but none were seen from **12** (2-chloromethyl-2-propanol). The failure to observe products from ion **12** indicates that the capture of ion **11** by water is much faster than the rearrangement of **11** to **12**. If the capture of ion **11** by water is much faster than its rearrangement to **12** (the energetically most favorable rearrangement in Scheme IV), then the other carbonium-ion rearrangements may also be unable to compete with capture by water. Since products are seen from the rearranged ions **10** and **11**, these rearrangements may be occurring concerted with the loss of nitrogen from **8** rather than from the free ion **9**. The concertedness of these rearrangements may also be indicated by the fact that products are seen from ion **11**. Since the theoretical calculations predict that the rearrangement of **9** to **11** is endothermic,[6] this reaction should not be able to compete with the exothermic rearrangement of **9** to **10**.[6] Thus, the products formed are probably controlled primarily by the conformation of the molecule and its solvent shell at the time the nitrogen leaves rather than by relative nucleophilicities, migratory aptitudes, and product stabilities. For a more detailed discussion of the possible role of nitrogen separated ion triplets and concerted vs. rapid stepwise reaction mechanisms one should see the excellent reviews of deamination by White[8] and by Moss.[9]

The mechanism proposed to explain the products seen from the decomposition of the two BCBNU isomers is similar to that for the decomposition of BCNU. Both mechanisms involve substitutions, eliminations, and rearrangements, reactions which are typical of carbonium ions. However, the stereochemistry of the products shows that a significant fraction of the substitution reaction to give 3-chloro-2-butanol is S_N2 in nature and that there is significant E2 character in the elimination reaction to give 2-chloro-2-butene. The carbonium ion produced by BCBNU is secondary and hence a more energetically favorable species than the primary carbonium ion that BCNU would produce. Therefore,the decomposition of BCNU would be expected to involve S_N2–E2 reactions to a much greater extent. The deamination of optically active 1-deuteriobutylamine, a reaction involving a primary carbon, gives predominant inversion of configuration.[10] For these reasons, we postulate that the decomposition of BCNU is predominantly S_N2–E2 in character.

A knowledge of the exact nature of this decomposition is important because the cytotoxic activity of the clinically useful antitumor agent, BCNU, is apparently due to its ability to alkylate with a 2-chloroethyl group. In several recent publications, evidence has been presented that indicates the antitumor effects of the nitrosoureas are due to the alkylating properties of the molecule.[11] In particular, it has been shown that cytosine is alkylated by BCNU and the products are consistent with alkylation with 2-chloroethyl groups.[12] We have recently presented evidence that alkylating species generated from BCNU are either the 2-chloroethyl carbonium ion, the cyclic chloronium ion, and/or 2-chloroethyldiazo hydroxide.[2] The predominant inversion of configuration found in these studies of the decomposition of BCBNU leads us to postulate that the alkylating reaction of BCNU is predominantly S_N2 in character. Thus, the ultimate cytotoxic alkylating species generated by BCNU is probably 2-chloroethyldiazo hydroxide with a short but finite lifetime inside the target cell.

Experimental Section

NMR spectra were obtained on a Varian A-60 instrument. Gas chromatography was performed on a Varian 2700 instrument. Gas chromatography/mass spectrometry was performed on a DuPont 491 instrument.

2,3-Epoxybutane (1). The cis isomer was prepared from *cis*-2-

butene and the trans isomer from *trans*-2-butene by epoxidation with *m*-chloroperbenzoic acid following the procedure of Pasto and Cumbo.[3a] *cis*-**1**: bp 60 °C (lit.[3a] 56–59 °C); NMR ($CDCl_3$) δ 3.0 (2 H, m), 1.2 (6 H, d). *trans*-**1**: bp 54 °C (lit.[3a] 52–53 °C); NMR ($CDCl_3$) δ 2.7 (2 H, m), 1.3 (6 H, d).

3-Amino-2-butanol (2). The threo isomer was prepared from *cis*-**1** and the erythro isomer was prepared from *trans*-**1** by reaction with excess aqueous ammonia following the procedure of Dickey, Fickett, and Lucas.[3b] *threo*-**2**: bp 77 °C at 30 mm (lit.[3b] 69–70 °C at 20 mm); NMR (Me_2SO-d_6) δ 3.3 (1 H, pentet), 2.7 (3 H, br s), 2.5 (1 H, pentet), 1.0 (6 H, t). *erythro*-**1**: bp 82 °C at 30 mm (lit.[3b] 75–75.5 °C at 20 mm); NMR (Me_2SO-d_6) δ 3.4 (1 H, m), 2.7 (3 H, br s), 2.5 (1 H, m), 0.9 (6 H, two d's).

2,3-Dimethylaziridine (3). The cis isomer was prepared from *threo*-**2** and the trans isomer was prepared from *erythro*-**2** by reacting the hydrogen sulfate ester with base following the procedure of Dickey, Fickett, and Lucas.[3b] *cis*-**3**: bp 83 °C (lit.[13] 81.1–81.5 at 739 mm); NMR ($CDCl_3$) δ 2.0 (2 H, m), 1.1 (6 H, d), 0.5 (1 H, br s). *trans*-**3**: bp 75 °C (lit.[13] 73.8–73.9 at 739 mm); NMR ($CDCl_3$) δ 1.6 (2 H, m), 1.2 (6 H, d), 0.3 (1 H, br s).

1,3-Bis(3-chloro-2-butyl)urea (4). The threo isomer was prepared from *cis*-**3** and the erythro isomer was prepared from *trans*-**3**. A solution of the 2,3-dimethylaziridine (3.6 g, 0.05 mol) in acetone (25 mL) was added slowly to a solution of phosgene (2.5 g, 0.025 mol) in acetone (60 mL) at 0 °C. The mixture was allowed to stir at 25 °C overnight, and then the solvent was removed under vacuum. Chromatography (ethyl acetate on alumina) and crystallization gave a 50% yield of product. *threo*-**4**: mp 135–137 °C (from benzene); NMR ($CDCl_3$) δ 5.5 (2 H, br d), 4.2 (4 H, m), 1.5 (6 H, d), 1.2 (6 H, d); MS M^+ 240, 242, and 244, $M^+ - HCl$ 204 and 206, $M^+ - ClCHCH_3$ 177 and 179. *erythro*-**4**: mp 110–112 °C (from hexanes); NMR ($CDCl_3$) 5.6 (2 H, br d), 4.2 (4 H, m), 1.5 (6 H, d), 1.1 (6 H, d); MS M^+ 240, 242, and 244, $M^+ - HCl$ 204 and 206, $M^+ - ClCHCH_3$ 177 and 179.

1,3-Bis(3-chloro-2-butyl)-1-nitrosourea (5). The threo isomer was prepared from *threo*-**4** and the erythro isomer was prepared from *erythro*-**4**. To a solution of 1,3-bis(3-chloro-2-butyl)urea (240 mg, 1 mmol) in formic acid (3 mL) at 0 °C was added dropwise with stirring a solution of sodium nitrite (140 mg, 2 mmol) in water (1 mL). After stirring for 1 h, the mixture was dissolved in ether, and the ether solution was washed three times with iced water and dried. Removal of the ether gave a 90% yield of product as a yellow oil. *erythro*-**5**: NMR ($CDCl_3$) δ 7.2 (1 H, br s), 5.2–4.0 (4 H, m), 1.4 (12 H, m). *threo*-**5**: NMR ($CDCl_3$) δ 7.0 (1 H, br s), 5.3–3.9 (4 H, m), 1.4 (12 H, m).

4,5-Dimethyloxazolidone (6). The cis isomer was prepared from *erythro*-**2** and the trans isomer was prepared from *threo*-**2**. Phosgene was bubbled slowly through a vigorously stirred mixture of 3-amino-2-butanol (1.5 g, 0.017 mol), powdered NaOH (2.0 g, 0.05 mol), powdered anhydrous sodium sulfate (4.0 g), and methylene chloride (100 mL) until the liquid phase remained acidic to wet litmus for 5 min after the phosgene adition was stopped (~1 h). The mixture was filtered and the solvent removed under vacuum. Chromatography (ethyl acetate on silica gel) separated a more mobile impurity to give a 60% yield of the product as a colorless oil. *cis*-**6**: NMR ($CDCl_3$) δ 6.9 (1 H, br s), 4.7 (1 H, pentet), 4.0 (1 H, pentet), 1.3 (3 H, d), 1.1 (3 H, d); MS M^+ 115, $M^+ - CO$ 87. *trans*-**6**: NMR ($CDCl_3$) δ 6.9 (1 H, br s), 4.2 (1 H, pentet), 3.5 (1 H, pentet), 1.4 (3 H, d), 1.3 (3 H, d); MS M^+ 115, $M^+ - CO$ 87.

2-(3-Chloro-2-butylimino)-4,5-dimethyl-2-oxazoline Hydrochloride (7). This synthesis is based on the synthesis of 2-(2-chloroethylamino)-2-oxazoline from 1,3-bis(2-chloroethyl)urea.[14] 1,3-Bis(3-chloro-2-butyl)urea (240 mg, 1 mmol) was refluxed with water (10 mL) until all solid has dissolved. The solvent was removed, the residue dissolved in D_2O (1 mL), and the solvent again removed under vacuum to give a white solid. **7** from *threo*-**4**: NMR (D_2O) δ 5.1 (1 H, m), 4.6 (exchangeable H, s), 4.4–3.2 (3 H, m), 1.2 (12 H, m). **7** from *erythro*-**4**: NMR (D_2O) δ 4.6 (1 H, m), 4.5 (exchangeable H, s), 4.4–3.5 (3 H, m), 1.2 (12 H, m).

3-Chloro-2-butanol (8). The erythro alcohol was prepared from *trans*-**1** and the threo alcohol was prepared from *cis*-**1** by reaction with aqueous HCl following the method of Lucas and Gould.[15] *erythro*-**8**: bp 136 °C (lit.[12] 135.4 °C at 748 mm). *threo*-**8**: bp 132 °C (lit.[12] 130.8 °C at 748 mm).

Decompositions. A mixture of nitrosourea (13.5 mg, 0.05 mmol) and 0.1 *m* phosphate buffer at pH 7.4 (1 mL) was shaken at 37 °C for 4 days in a gas-tight vial fitted with a Teflon-lined septum. Then methylene chloride (1 mL) was injected into the vial, and both the aqueous and organic layers were analyzed by GC using a 6-ft glass column packed with 0.4% Carbowax 1500 on Carbopack A. The column temperature was kept at 50 °C for 7 min and then raised at a rate of 4 °C/min.

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Registry No.—*cis*-**1**, 1758-33-4; *trans*-**1**, 21490-63-1; *erythro*-**2**, 40285-24-3; *threo*-**2**, 40285-23-2; *cis*-**3**, 930-19-8; *trans*-**3**, 930-20-1; **4**, 63548-65-2; **5**, 63548-66-3; *cis*-**6**, 19190-97-7; *trans*-**6**, 19190-96-6; **7**, 63609-37-0; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6.

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