Synthesis of Specifically Deuterium Labeled Sulfur and Oxygen Ether Side-Chain-Extended Antileukemic (2-Chloroethyl)nitrosoureas and Study of Their Products and Pathways of Decomposition under Physiological Conditions[1a]

J. William Lown,* R. Rao Koganty, and Alummoottil V. Joshua

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Received October 29, 1981

The synthesis of certain specifically deuterium labeled ether and thioether side-chain-extended (2-chloroethyl)nitrosoureas is described. Controlled aqueous decomposition of α-d_2-S-CENU and β-d_2-S-CENU under physiological conditions affords six products including 2-chloroethyl vinyl ether, bis(2-chloroethyl) thioether, and 1,2-dihydrothiophenes. The reactions, which are dominated by elimination under these conditions, the products, and the distribution of isotopic labels are consistent with the formation of thiiranium intermediates which are then subject to ring opening and ring expansion. Similar decomposition of α-d_2-O-CENU and β-d_2-O-CENU affords seven products including the 2-chloroethyl vinyl ether, acetaldehyde, vinyl chloride, and bis(2-chloroethyl) ether but no dihydrofuran. The products and isotope distributions in these cases are consistent with an oxiranium species formed at the demand of the incipient cationic center but not formed at the ω-position. The rates of aqueous decomposition of α-d_2-S-CENU, and α-d_2-O-CENU show no isotope effects in accord with the suggested rate-determining step. In contrast, the 2-chloroethyl vinyl ether (or thioether) product distributions, corresponding to elimination of a proton or deuteron, of 4:1 for α-d_2-S-CENU and 15:1 for α-d_2-O-CENU are in accord with large primary isotope effects at the stage of the intermediate thiiranium or oxiranium ions. The overall results are in accord with the observed property of S-CENU to cross-link DNA readily due to sulfur participation at two sites unlike O-CENU which only alkylates and does not cross-link DNA. These results may relate to the superior antileukemic activity of S-CENU.

(2-Chloroethyl)nitrosoureas (CENUs) including 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), 1-(2-chloroethyl)-3-(4-*trans*-methylcyclohexyl)-1-nitrosourea (MeCCNU), and chlorozotocin have an established place in the clinical treatment of a range of malignant diseases.[1b,2] CENUs decompose spontaneously under physiological conditions to generate electrophiles, and pharmacological evidence suggests that the latter, which include the (2-chloroethyl)diazohydroxide, attack macromolecules, principally DNA, causing both alkylation and interstrand cross-linking.[3-9] The latter lesion is expected to be a cytotoxic event because it is difficult to repair.[10] We designed and synthesized certain mustard side-chain-modified CENUs in order to promote the tendency to form DNA cross-links and to prevent the formation of certain potentially carcinogenic byproducts such as carbamates.[11] These new types of CENUs proved to be highly effective in animal test neoplasms[11] and prompted the present study of their chemical reactivity.

Table I. Products of Aqueous Decomposition of S-CENU and O-CENU[a]

product	% theoretical yield S-CENU	% theoretical yield O-CENU
cyclohexyl isocyanate	80	75
dicyclohexylurea	2	2
2-chloroethyl vinyl (thio)ether	72	68
2-hydroxylethyl vinyl (thio)ether	tr	tr
acetaldehyde		1
vinyl chloride		1
2,3-dihydrothiophene	4	
bis(2-chloroethyl) (thio)ether	1	1

[a] Based on ca. 10% recovery of unreacted CENU after 48 h from a 1-mM solution of S-CENU or O-CENU at 37 °C and pH 7.2.

Accordingly, we report the synthesis of certain specifically deuterium labeled sulfur and oxygen ether side-chain CENUs, an investigation of their chemical reactivity, and their products and pathways of decomposition under physiological conditions.

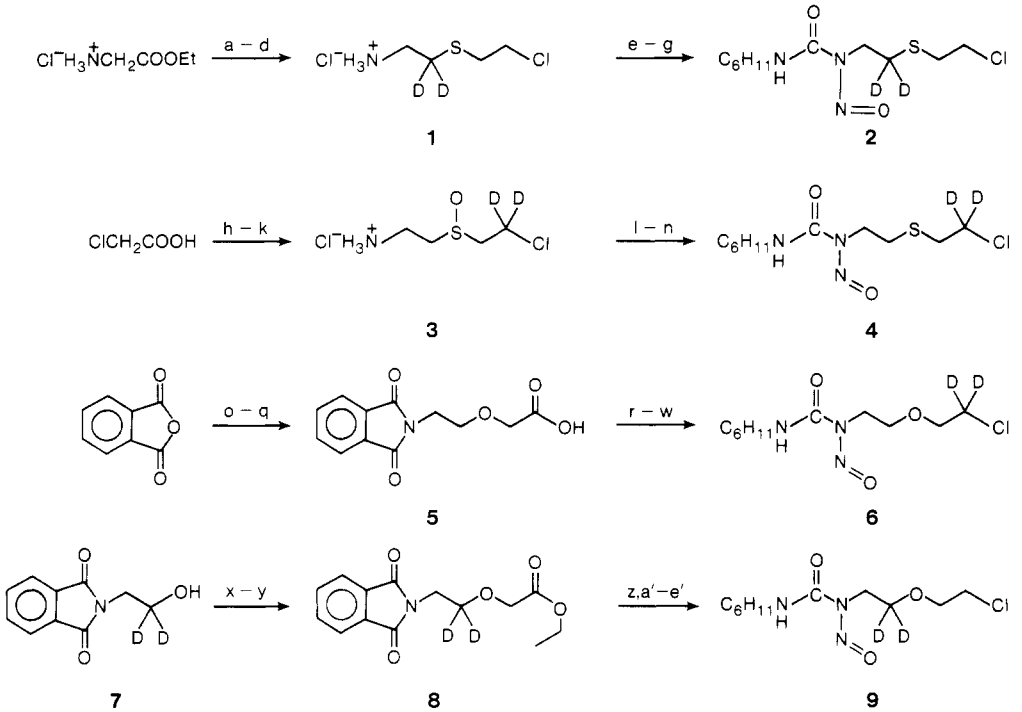
Synthesis of Deuterium-Labeled CENUs

The synthetic schemes developed to prepare the parent protium compounds[11] were adapted to provide the required specifically deuterium-labeled derivatives as shown in Scheme I. Some modifications in the synthetic procedures were necessary, however. For example, in Scheme I the use of formic acid in the nitrosation step ensures regioselective nitrosation on the desired less-hindered side of the nitrosoureas.[12] In Scheme I (4) it was necessary to protect the sulfur of the intermediate thioether by forming the *S*-oxide to prevent premature deuterium-label scrambling. After conversion to the labeled chloro derivative of the *S*-oxide, the sulfoxide was deoxygenated under mild conditions by treatment with phosphorus triiodide[13] and

(1) (a) CENU, 1-(2-chloroethyl)-3-alkyl-1-nitrosourea; BCNU, bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; S-CENU, 1[2-[(2-chloroethyl)thio]ethyl]-3-cyclohexyl-1-nitrosourea: O-CENU, 1-[2-[(2-chloroethyl)oxy]ethyl]-3-cyclohexyl-1-nitrosourea; α-d_2-S-CENU, 1-[[2-(2-chloroethyl)thio]-2,2-dideuterioethyl]-3-cyclohexyl-1-nitrosourea; β-d_2-S-CENU, 1-[2-[(2-chloro-2,2-dideuterioethyl)thio]ethyl]-3-cyclohexyl-1-nitrosourea; α-d_2-O-CENU, 1-[2-(2-chloroethoxy)-2,2-dideuterioethyl]-3-cyclohexyl-1-nitrosourea; β-d_2-O-CENU, 1-[2-(2-chloro-2,2-dideuterioethoxy)ethyl]-3-cyclohexyl-1-nitrosourea. (b) Wheeler, G. D. *ACS Symp. Ser.* **1978**, *No. 30*, 87-119.
(2) De Vita, D.; Carbone, P.; Owens, A.; Gold, G. L.; Kraut, M. J.; Edmonson, J. *Cancer Res.* **1965**, *25*, 1876.
(3) Montgomery, J. A.; James, R.; McCaleb, G. S.; Kirgk, M. C.; Johnston, T. P. *J. Med. Chem.* **1975**, *18*, 568.
(4) Brundrett, R. B.; Cowens, J. W.; Colvin, M.; Jardine, I. *J. Med. Chem.* **1976**, *19*, 958.
(5) Gombar, C. T.; Tong, W. P.; Ludlum, D. B. *Biochem. Pharmacol.* **1980**, *29*, 2639.
(6) Chatterjii, D. C.; Green, R. F.; Gallelli, S. F. *J. Pharm. Sci.* **1978**, *67*, 1527.
(7) Brundrett, R. B. *J. Med. Chem.* **1980**, *23*, 1245.
(8) Lown, J. W.; Chauhan, S. M. S. *J. Med. Chem.* **1981**, *24*, 270.
(9) Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1981**, *46*, 2479.
(10) Ludlum, D. B. In "Cancer. A Comprehensive Treatise"; Becker, F. F., Ed.; Plenum Press: New York, 1975; Vol. 5, p 285 ff.
(11) Lown, J. W.; Joshua, A. V.; McLaughlin, L. W. *J. Med. Chem.* **1980**, *23*, 798.
(12) Johnston, T. P.; McCaleb, G. S.; Opliger, P. S.; Montgomery, J. A. *J. Med. Chem.* **1966**, *9*, 892.

0022-3263/82/1947-2027$01.25/0

Scheme I[a]



[a] (a) $LiAlD_4$, THF, 0 °C; (b) $SOCl_2$, $CHCl_3$; (c) $HSCH_2CH_2OH$, KOH, EtOH; (d) $SOCl_2$, $CHCl_3$; (e) NEt_3, CH_2Cl_2; (f) $C_6H_{11}NCO$; (g) $NaNO_2$, HCO_2H, 0 °C; (h) $LiAlD_4$, THF, 0 °C; (i) $Cl^-{}^+H_3NCH_2CH_2SH$, KOH, EtOH; (j) MCPB, $CHCl_3$; (k) $SOCl_2$, $CHCl_3$; (l) PI_3, NEt_3, CH_2Cl_2, −70 °C; (m) $C_6H_{11}NCO$; (n) $NaNO_2$, HCO_2H, 0 °C; (o) $H_2NCH_2CH_2OCH_2CH_2OH$, $CH_3C_6H_5$, reflux; (p) H_2CrO_4, CH_3COCH_3, −20 °C; (q) $KMnO_4$, H_2SO_4; (r) H_2NNH_2 EtOH; (s) HCl; (t) $LiAlD_4$, THF, 0 °C; (u) $SOCl_2$, $CHCl_3$; (v) NEt_3, CH_2Cl_2 then $C_6H_{11}NCO$; (w) $NaNO_2$, HCO_2H, 0 °C; (x) NaH, DMF; (y) $ClCH_2COOEt$; (z) H_2NNH H_2NNH_2, EtOH; (a′) HCl; (b′) $LiAlH_4$, THF, 0 °C; (c′) $SOCl_2$, $CHCl_3$; (d′) NEt_3, CH_2Cl_2 then $C_6H_{11}NCO$; (e′) $NaNO_2$, HCO_2H, 0 °C.

triethylamine in methylene chloride at −70 °C. The position and extent of deuterium incorporation was determined by both high-field ^1H NMR and mass spectrometry. It was confirmed that no scrambling of the labels had occurred.

The synthesis of the corresponding deuterium-labeled oxygen ether nitrosoureas (O-CENUs) is shown in Scheme I (**6** and **9**). Incorporation of the amino ether into a phthalimide moiety facilitated the syntheses. In these cases also it was determined that the required deuterium isotopes had been incorporated in the desired positions to the extent of 97% and with no evidence of label scrambling from ^1H NMR and mass spectrometry.

Results

The parent protium S-CENU was allowed to decompose in 40 mM potassium phosphate buffer, pH 7.2 at 37 °C for 48 h, and both volatile and nonvolatile products were analyzed, identified, and quantified by GC, GC/MS and CIMS techniques. The results expressed as the percent of the theoretical yield of individual products are presented in Table I. Six compounds were identified, with cyclohexyl isocyanate and 2-chloroethyl vinyl thioether representing the major products. In addition, smaller amounts of dicyclohexylurea, 2,3-dihydrothiophene, and bis(2-chloroethyl) thioether were identified by comparison with authentic samples and a trace of 2-hydroxyethyl vinyl thioether. No detectable quantities of vinyl chloride or acetaldehyde, which are common products of CENUs,[3-9] were found.

Similar controlled decomposition of O-CENU under physiological conditions afforded seven products (Table I). The major products were cyclohexyl isocyanate and 2-chloroethyl vinyl ether. A small amount of the bis(2-chloroethyl) ether and a trace of the 2-hydroxyethyl vinyl ether were found. Additional products, not detected from S-CENUs, were acetaldehyde and vinyl chloride whereas no product corresponding to the dihydrothiophene was formed.

Decomposition of α-d_2-S-CENU afforded a (1:4) mixture of the 2-*d* (monodeuterated) and 1-d_2 (dideuterated) differentially vinyl group labeled 2-chloroethyl vinyl ethers together with a similar mixture of the 5-*d* and 4-*d* 2,3-dihydrothiophenes. Some α-d_2 bis(2-chloroethyl) thioether and traces of the mixture of vinyl-2-*d* and -1-d_2 group labeled 2-hydroxyethyl vinyl ethers were obtained.

Similar decomposition of β-d_2-S-CENU afforded 2-chloro-2,2-dideuterioethyl vinyl thioether in addition to a mixture of the 2,2-dideuterio- and 3,3-dideuterio-2,3-dihydrothiophenes. Some bis(2-chloroethyl)vinyl-β-d_2 thioether and traces of a mixture of 2-hydroxy-2,2-dideuterioethyl vinyl thioether and 2-hydroxy-1,1-dideuterioethyl vinyl thioether were also obtained.

Aqueous decomposition of α-d_2-O-CENU under physiological conditions gave formyl-*d* labeled acetaldehyde and a 15:1 mixture of the vinyl-1-d_2 and vinyl-2-*d* labeled 2-chloroethyl vinyl ethers together with some bis(2-chloroethyl)-α-d_2 vinyl ether. Comparable controlled decomposition of β-d_2-O-CENU gave acetaldehyde singly labeled with deuterium in the methyl group and 2-chloro-2,2-dideuterioethyl vinyl ether with no evidence in this case of isotope scrambling. A small quantity of bis(2-chloroethyl)-β-d_2 ether was also obtained.

The half-lives and unimolecular rate constants for decomposition of S-CENU and O-CENU and their specifically deuterium labeled counterparts compared with those of CCNU are given in Table II.

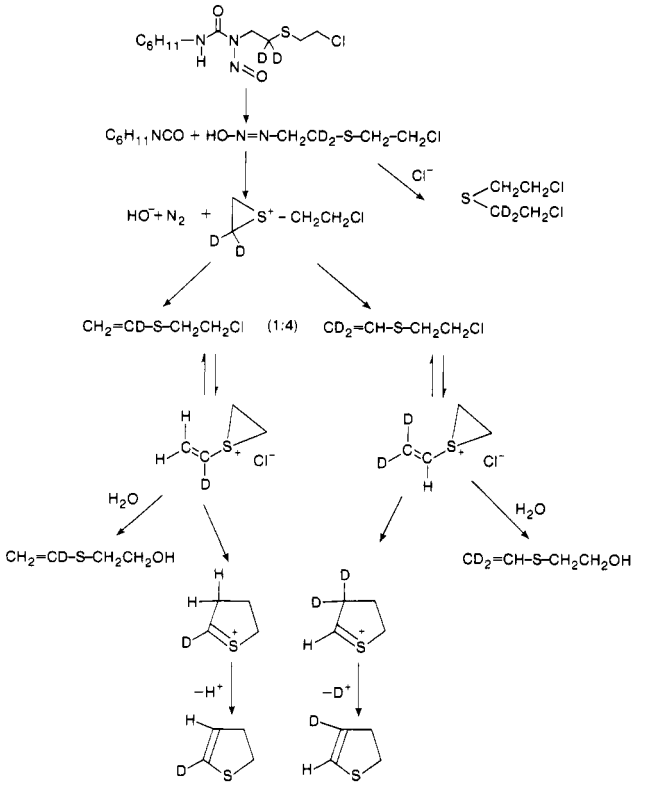
(13) Denis, J. N.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1980**, 544.

Table II. Rates of Unimolecular Decomposition of (2-Chloroethyl)-1-nitrosoureas at pH 7.1 and 37 °C

CENU	$E_{1/2}(1)$,[a] V	$E_{1/2}(2)$,[a] V	$10^{-3}k$, min^{-1}	$T_{1/2}$
CCNU	−0.853	−1.168	10.0	69 ± 1
S-CENU	−0.945	−1.265	2.03	341 ± 10
α-d_2-S-CENU	−0.935	−1.250	1.98	349 ± 12
O-CENU	−0.930	−1.270	2.17	319 ± 12
α-d_2-O-CENU	−0.930	−1.250	2.30	301 ± 12

[a] Polarographic half-wave potentials measured in 5% aqueous CH_3CN in 10^{-2} M potassium phosphate buffer with potassium chloride as a supporting electrolyte.

Scheme II. Decomposition of Deuterium-Labeled α-d_2-S-CENU

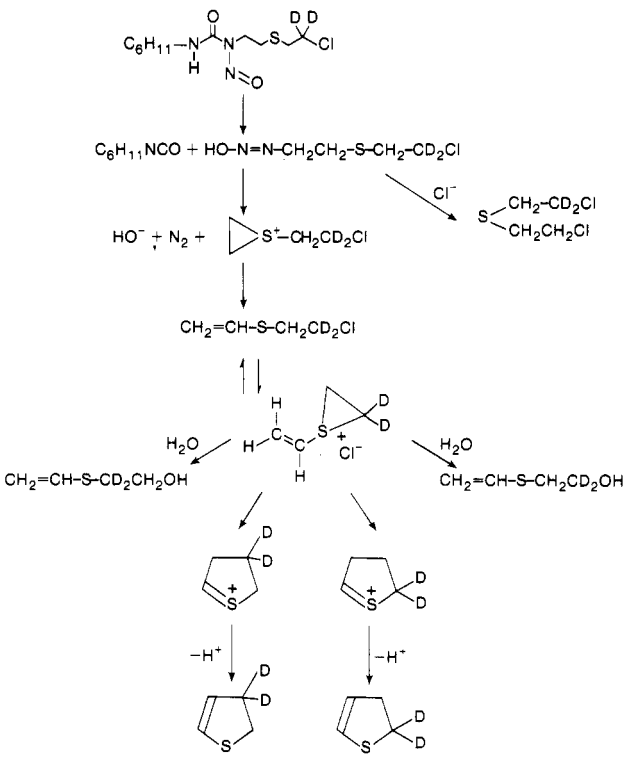


Discussion

The nature of the products of aqueous decomposition of S-CENU together with the disposition of the deuterium labels in the products from α-d_2-S-CENU and β-d_2-S-CENU are in accord with the reaction pathways shown in Schemes II and III. The observation of label scrambling in both cases implicates thiiranium intermediates both from the incipient cation derived from the diazo hydroxide and subsequently from the elimination product. The absence of any significant deuterium isotope effect in the rates of decomposition of α-d_2-S-CENU and β-d_2-S-CENU compared with that of S-CENU is compatible with the indicated initial rate-determining step.

Formation of the 1,2-dihydrothiophene as a minor product suggests that at some stage in the decomposition a ring expansion has taken place from a thiiranium intermediate. Evidence in support of the contention that this is the *S*-vinylthiiranium species is obtained from the observed position and extent of deuterium incorporation in the 1,2-dihydrothiophenes obtained from α-d_2-S-CENU and β-d_2-S-CENU, respectively, as well as from the detection in each case of the labeled 2-hydroxyethyl vinyl thioethers anticipated. The number of the deuteriums and, as far as was possible, their positions in the 1,2-dihydrothiophenes were determined by examination of characteristic electron-impact fragments such as $CH{\equiv}S^+$ and $CD{\equiv}S^+$ in the mass spectra. Thiiranium ion intermediates have been proposed to account, for example, for the rearrangement of a thiirane following treatment with acetyl chloride,[14] and S-alkylated thiiranium salts have been isolated.[15] It is apparent that under the present reaction conditions the major reaction following the formation of the thiiranium ion is elimination whereas the S-CENU in the presence of DNA forms interstrand cross-links extremely efficiently in a process that undoubtedly involves nucleophilic substitution.[11] The preferred elimination pathway observed for both S-CENU and O-CENU under the present conditions may be explained on the basis of a neutral reaction medium which is devoid of strongly nucleophilic species.

Scheme III. Decomposition of Deuterium-Labeled β-d_2-S-CENU

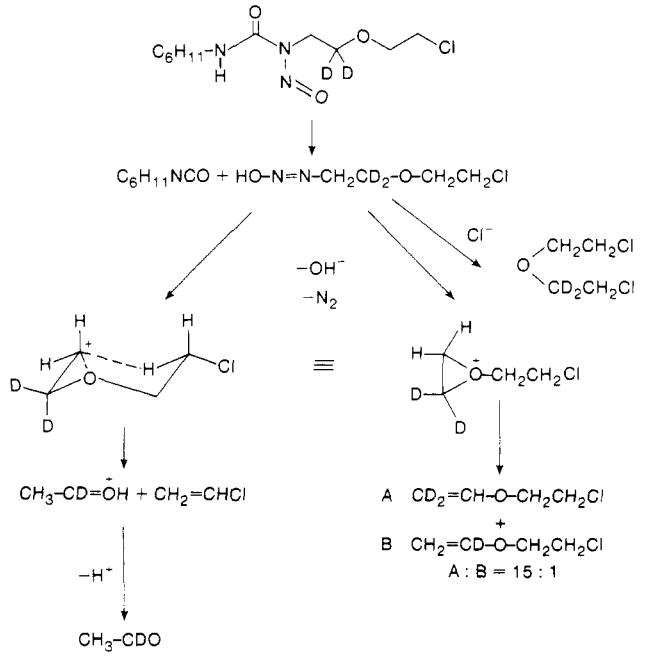


Although neighboring-group participation by oxygen in the O-CENU case was not anticipated to the same extent as for sulfur,[16] the evidence from the 2-chloroethyl vinyl ethers obtained as products and in particular the deuterium label exchange observed for α-d_2-O-CENU provides strong support for the intermediacy of an oxiranium ion formed at the demand of the incipient cationic center. As anticipated, however, there was no deuterium exchange in the case of β-d_2-O-CENU. Oxiranium salts have been identified in solution, for example, by treatment of oxirane with BF_3 at −78 °C[17] and have also been suggested as intermediates in the acid and Lewis acid catalyzed rearrangement of oxiranes.[17]

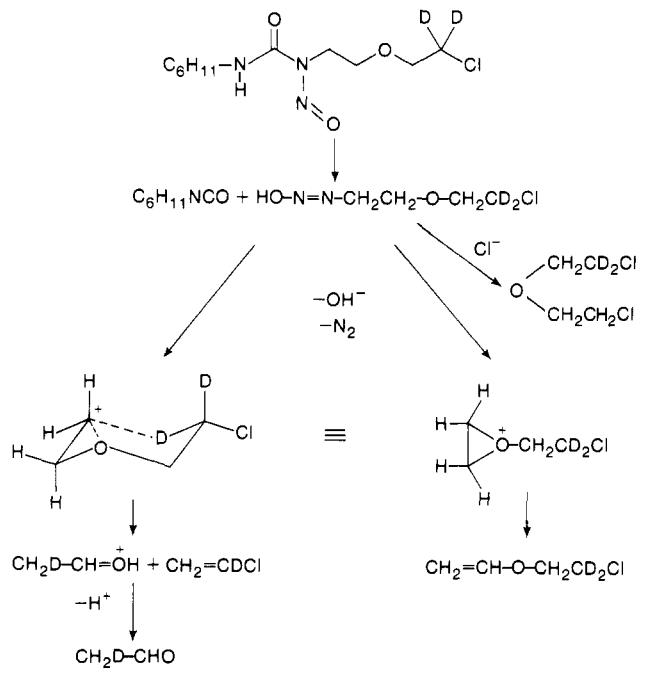
The formation of small quantities of acetaldehyde and vinyl chloride obtained from O-CENU decomposition is

(14) Davies, W.; Savige, E. W. *J. Chem. Soc.* **1950**, 317.
(15) Owsley, D. C.; Holmkamp, G. K.; Rettig, M. F. *J. Am. Chem. Soc.* **1969**, *91*, 5239.
(16) Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, *3*, 1.
(17) Levsen, K.; Heimbach, H.; Van de Sande, C. C.; Monstrey, J. *Tetrahedron* **1977**, *33*, 1785.

Scheme IV. Decomposition of Deuterium-Labeled α-d_2-O-CENU



Scheme V. Decomposition of Deuterium-Labeled β-d_2-O-CENU



rationalized by an internal hydride transfer involving the intermediate *O*-(2-chloroethyl)oxiranium ion in a six-centred cyclic transition state (Scheme V). This suggested intramolecular hydride transfer is further substantiated by the decomposition of β-d_2-O-CENU which requires the corresponding transfer of deuterium which is detected in the methyl group of the acetaldehyde produced (Scheme V).

It is apparent that the deuteriums incorporated in the starting materials are retained to a very large extent in the elimination products. This implies preferential proton loss from the thiiranium or oxiranium intermediates or that elimination is dominated in both cases by large primary isotope effects. Formation of these three-membered-ring intermediates is favored entropically. Since they are relatively stable, the transition states leading to their formation must involve similar configurations in which the hydrogens and deuterium atoms on the ring are virtually symmetrically positioned. Therefore, their differences in zero-point energies will be retained throughout the process of activation. It follows that in the activation process in order for the C–D vibration to become translational the transition state must cross a point where the C–H vibration also becomes translational. Under these circumstances the differences in zero-point energies between C–H and C–D bonds, amounting to ca. 1.15 kcal/mol,[18] becomes significant and translates into a rate ratio of k_H/k_D of ≥ 7. Certain types of E_2 elimination are known[19] in which the absence of a deuterium isotope effect was explained by invoking Hammond's postulate[20] which proposes a common intermediate that mediates between the two transition states, one involving a stretched C–D bond with a slightly higher activation energy and the other involving a stretched C–H bond with a somewhat lower energy of activation. In the present case such a mediating species is the oxiranium or thiiranium ions[18] which can be expected to have substantially lower energy than either of the transition states. Therefore, the interconversion of **2** and **4** via. **1** (Scheme VI) would involve rather larger energy changes, including deactivation of one transition state and activation to the other. Other contributions such as eclipsing effects may be expected to be small, owing to the small sizes of the substituents.[21] The transition states **2** and **4** will resemble their respective elimination products **3** and **5** since they contain a partially formed double bond. For this reason the differences in the energies of the transition states **2** and **4** will be significant, and this predicts the predominant formation of product **3**.

In conclusion, the present results are in accord with a suggested unimolecular decomposition in aqueous solution of S-CENU and O-CENU to afford initially symmetrical heteroatom-stabilized electrophilic species. The subsequent products from the S-CENU are compatible with formation of a second thiiranium ion promoting a second nucleophilic substitution and in agreement with its extremely efficient DNA cross-linking properties. In contrast, the oxiranium intermediate from O-CENU leads to fragmentation products which is compatible with its ability to alkylate but not to cross-link DNA.[11] These events may be related to the superior in vivo antileukemic properties of S-CENU compared with O-CENU.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ^{1}H NMR spectra of the intermediates were recorded on a Varian HA-100 or a Bruker WH-200 or WH-400 analytical spectrometer. Mass spectra were determined on an Associated Electrical Industries (AEI MS-9) double-focussing high-resolution mass spectrometer with ionization energies at 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15 000 on an AEI MS-50 spectrometer.

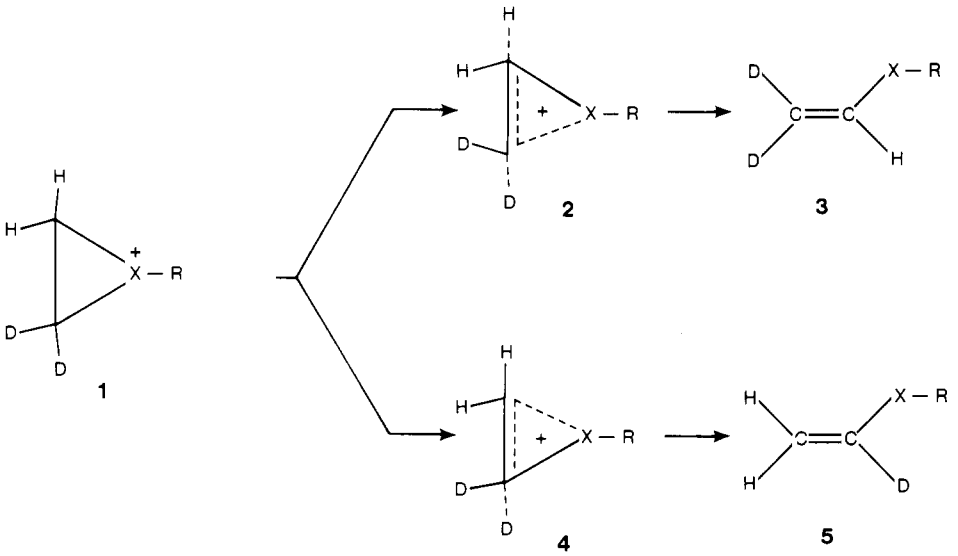
GC analyses were performed on a Hewlett-Packard 5840A gas chromatograph equipped with a flame-ionization detector. GC/MS analyses were performed on an AEI MS-12 spectrometer.

Infrared spectra were recorded on a Nicolet 7199 FT spectrophotometer.

Electrochemical measurements were made with a Princeton Applied Research 17KA polarograph.

(18) Westheimer, F. H. *Chem. Soc. Rev.* **1960**, 265.
(19) Lewis, E. S.; Boozer, C. E. *J. Am. Chem. Soc.* **1954**, *76*, 791.
(20) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 337.
(21) Cram, D. J.; Greene, F. D.; Depuy, C. H. *J. Am. Chem. Soc.* **1956**, *78*, 790.

Scheme VI



Materials. Ethyl glycinate hydrochloride, 2-(2-aminoethyl)-ethanol, chloroacetic acid, and lithium aluminum deuteride were obtained from Aldrich Chemical Co.

2-[(2-Hydroxyethyl)thio]-2,2-dideuterioethylamine. A solution of 0.78 g (10 mmol) of 2-mercaptoethanol and 1.2 g of potassium hydroxide in 25 mL of 50% aqueous ethanol was heated under reflux for 2 h. A solution of 1.17 g (10 mmol) of 2-chloro-2,2-dideuterioethylamine[4] hydrochloride in 15 mL of 50% aqueous ethanol was added to the pale yellow solution, and refluxing was continued for a further 30 min. The solution was cooled and the solvent removed in vacuo. The residual oil was taken up in 25 mL of methanol, the solution filtered, the solvent removed in vacuo, and the product purified by distillation under reduced pressure: 0.9 g (73% yield); bp 141–143 °C (1 mm) [lit.[22] bp 105–108 °C (0.15 mm)]; ^{1}H NMR ($CDCl_3$) δ 2.5–3.1 (m, 7 H), 3.73 (t, 2 H).

1-[2-[(2-Chloroethyl)thio]-2,2-dideuterioethyl]-3-cyclohexylurea (2). A solution of 1.23 g (10 mmol) of 2-[(2-hydroxyethyl)thio]-2,2-dideuterioethylamine was cooled to 0 °C, and 1.5 g (12 mmol) of freshly distilled thionyl chloride was added dropwise with stirring. Stirring was continued at room temperature for 48 h, and then the solvent and excess of thionyl chloride were removed under vacuum. The residual solid was thoroughly washed with ether and dried, affording 2-[(2-chloroethyl)thio]-2,2-dideuterioethylamine hydrochloride (1).

A solution of 0.884 g (5 mmol) of 2-[(2-chloroethyl)thio]-2,2-dideuterioethylamine hydrochloride in 50 mL of dichloromethane was cooled to 0 °C. A mixture of 0.51 g (5 mmol) of triethylamine and 0.625 g (5 mmol) of cyclohexyl isocyanate was added with stirring. Stirring was continued overnight at room temperature, the solvent was removed under vacuum, and the residual solid washed with cold water and recrystallized from chloroform/petroleum ether, affording 1.2 g (80% yield) of the urea as a white crystalline powder: mp 122–124 °C (lit.[11] mp 124 °C); ^{1}H NMR ($CDCl_3$) δ 1.0–2.04 (m, 10 H), 2.89 (t, 2 H), 3.37 (d, 2 H), 3.5 (m, 1 H), 3.66 (t, 2 H), 4.66 (d, 1 H), 5.08 (t, 1 H).

1-[2-[(2-Chloroethyl)thio]-1,1-dideuterioethyl]-3-cyclohexyl-1-nitrosourea. The nitrosourea was prepared from the urea by following the literature procedure for the protium compound[11] in 85% yield as a pale yellow oil: ^{1}H NMR δ 1.02–2.2 (m, 10 H), 2.89 (t, 2 H), 3.65 (t, 2 H), 3.84 (m, 1 H), 4.0 (s, 2 H), 6.79 (d, 1 H).

2-Chloro-1,1-dideuterioethanol. Vacuum-dried chloroacetic acid (1.84 g, 20 mmol) was added in small portions to a stirring cold slurry of 0.570 g (15 mmol) of lithium aluminum deuteride in 100 mL of dry tetrahydrofuran. The temperature was maintained at gentle reflux for 15 min, and stirring was continued for 4 h. The solution was cooled, the excess of lithium aluminum deuteride discharged by the cautious addition of water, and the product isolated by continuous ether extraction. Distillation afforded pure 2-chloro-1,1-dideuterioethanol: 1.0 g (60% yield); bp 127–128 °C (lit.[11] bp 129 °C); ^{1}H NMR ($CDCl_3$) δ 3.64 (3, 2 H), 3.7 (br s, 1 H).

2-[(2-Aminoethyl)thio]-1,1-dideuterioethanol. A solution of 0.56 g (5 mmol) of 2-mercaptoethylamine hydrochloride and 0.65 g (10 mmol) of 85% potassium hydroxide in 10 mL of 50% ethanol was heated under reflux for 1 h. 2-Chloro-1,1-dideuterioethanol (0.4 g, 5 mmol) was added and refluxing continued for a further 30 min. The solution was cooled and the solvent removed in vacuo. Methanol (30 mL) was added and the solution filtered to remove precipitated potassium chloride. The filtrate was concentrated and the residual oil distilled under reduced pressure, affording the 2-[(2-aminoethyl)thio]-1,1-dideuterioethanol as a colorless liquid: 0.4 g (68% yield); bp 102–105 °C (0.2 mm) [lit.[22] bp 105–108 °C (0.15 mm)]; ^{1}H NMR ($CDCl_3$) δ 2.48–3.08 (m, 8 H), 3.6 (s, 1 H).

1-[2-[(2-Chloro-2,2-dideuterioethyl)thio]ethyl]-3-cyclohexylurea. *m*-Chloroperbenzoic acid (2.25 g, 11 mmol, of 80%) was added in small quantities to a stirred ice-cold solution of 1.2 g (10 mmol) of 2-[2-hydroxy-2,2-dideuterioethyl)thio]ethylamine in 75 mL of chloroform. Stirring was continued for 2 h, and then the solution was washed (3 × 50 mL) with 10% aqueous sodium hydrogen carbonate. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to ca. 35 mL while cooling in an ice bath. Freshly distilled thionyl chloride (1.5 g, 13 mmol) was added dropwise with continuous stirring, and the solution was maintained under gentle reflux for 30 min and stirred for 12 h at room temperature. The solution of 3 was cooled and the excess of reagent and solvent removed in vacuo. The residual solid (3) was washed several times with dry ether and dichloromethane. A suspension of the solid in 100 mL of dry dichloromethane was cooled to –60 °C and stirred, and 2.1 g (20 mmol) of triethylamine was added followed by 4.2 g (10 mmol) of phosphorus triiodide.[13] Stirring was continued for 1 h during which time the temperature was allowed to reach 25 °C, and then the solution was stirred for a further 30 min. The organic layer was removed, washed with water, dried (Na_2SO_4), filtered, and saturated with dry hydrogen chloride gas. The resulting 2-[(2-chloro-2,2-dideuterioethyl)-thio]ethylamine hydrochloride (0.43 g, 25% yield) was collected and purified by washing with dry ether and then was vacuum dried.

The title urea was prepared from 2-[(2-chloro-2,2-dideuterioethyl)thio]ethylamine hydrochloride by using the literature procedure described previously: 55% yield; mp 118–120 °C (lit.[11] mp 122–124 °C); ^{1}H NMR ($CDCl_3$) δ 1.04–2.0 (m, 10 H), 2.72 (t, 2 H), 2.92 (s, 2 H), 3.49 (m, 1 H), 3.37 (m, 2 H), 4.53 (d, 1 H), 4.96 (t, 1 H).

1-[2-[(2-chloro-2,2-dideuterioethyl)thio]ethyl]-3-cyclohexyl-1-nitrosourea (4). The title nitrosourea was prepared in

(22) Klopping, H. L. U. S. Patent 2 824 887; *Chem. Abstr.* **1958**, *52*, 11911*d*.

60% yield, by nitrosation of the urea in formic acid following the literature procedure, as an oil: ^{1}H NMR ($CDCl_3$) δ 1.06–2.08 (m, 10 H), 2.5 (t, 2 H), 2.8 (s, 2 H), 3.78 (m, 1 H), 3.92 (t, 2 H), 6.83 (d, 1 H).

2-(Phthalimidoethoxy)ethanol. A solution of 14.8 g (0.1 mol) of phthalic anhydride and 10.5 g (0.1 mol) of diglycolamine in 250 mL of toluene was heated under reflux for 4 h. The solvent was removed under vacuum, and the residue solidified upon cooling. Crystallization from chloroform gave 2-(2-phthalimidoethoxy)ethanol as a pale yellow solid: 20 g (85% yield); mp 64 °C; ^{1}H NMR ($CDCl_3$) δ 3.39 (br s, 1 H), 3.5–4.05 (m, 8 H), 7.6–7.98 (m, 4 H); mass spectrum, m/e 235 (M^+). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.6; N, 5.95. Found: C, 60.8; H, 5.62; N, 6.00.

(2-Phthalimidoethoxy)acetaldehyde. To 11.8 g (50 mmol) of 2-(2-phthalimidoethoxy)ethanol in 150 mL of acetone at 15–20 °C was added 14 mL of Jones reagent[23] dropwise with stirring. After being stirred 2 h, the solution was filtered and evaporated to dryness. Crystallization of the residue from chloroform–petroleum ether (1:1) gave 9.5 g (80% yield) of (2-phthalimidoethoxy)acetaldehyde: mp 117–120 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (m, 4 H), 4.11 (s, 2 H), 7.8 (m, 4 H), 8.26 (br s, 1 H); mass spectrum, m/e 233 (M^+). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.3; H, 4.72; N, 6.00. Found: C, 61.0; H, 4.76; N, 5.8.

(2-Phthalimidoethoxy)acetic Acid (5). Powdered potassium permanganate (3.5 g, 21 mmol) was added over a period of 2 h to a stirred solution of 6.9 g (30 mmol) of (2-phthalimidoethoxy)acetaldehyde in 3.5 mL of 96% sulfuric acid and 27 mL of water. After the permanganate was consumed (pink color does not spread on filter paper), 150 mL of warm acetone was added, the solution was filtered, and the collected precipitate was washed with acetone. The acetone was distilled off, and the residue was crystallized from chloroform/petroleum ether (1:1), affording (2-phthalimidoethoxy)acetic acid (5): 5 g (65% yield); mp 125–129 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (m, 4 H), 4.07 (s, 2 H), 7.75 (m, 4 H), 8.0–10.0 (vbr s, 1 H). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.4; N, 5.6. Found: C, 57.7; H, 4.70; N, 5.6.

2-(2-Aminoethoxy)-1,1-dideuterioethanol. A solution of 5 g (20 mmol) of (2-phthalimidoethoxy)acetic acid and 2.5 g (25 mmol of hydrazine hydrate in 30 mL of 95% ethanol was heated under reflux for 30 min. The precipitated solids were collected, and the filtrate was saturated with hydrogen chloride gas. The resulting precipitate was collected and the filtrate concentrated. The residual solid was dried under vacuum, giving (2-aminoethoxy)acetic acid hydrochloride (2.3 g, 75% yield). The salt (2.3 g, 15 mmol) was added in portions to an ice-cold slurry of 1.0 g (24 mmol) of lithium aluminum deuteride in 100 mL of dry tetrahydrofuran. The solution was heated and maintained at a gentle reflux for 6 h. The metal complex and the excess of lithium aluminum deuteride were decomposed by cautiously adding a 10% aqueous solution of ammonium chloride with cooling in an ice bath. The granular hydroxides were extracted in a Soxhlet for 48 h. The pure alcohol was isolated by distillation of the concentrated extract: 0.85 g (40% yield); bp 120–124 °C (2 mm) (lit.[24] bp 218–224 °C); ^{1}H NMR ($CDCl_3$) δ 2.56 (br s, 1 H), 2.88 (t, 2 H), 3.4–3.8 (m, 6 H).

1-[2-(2-Chloro-2,2-dideuterioethoxy)ethyl]-3-cyclohexylurea. A solution of 0.84 g (5.4 mmol) of thionyl chloride in 5 mL of chloroform was added dropwise to an ice-cold stirred solution of 0.55 g (5 mmol) of 2-(2-aminoethoxy)-1,1-dideuterioethanol in 15 mL of chloroform. The solution was refluxed gently for 3 h, and the excess of thionyl chloride and solvent were removed in vacuo, giving 0.70 g (95% yield) of the chloroethyl salt. The latter compound (0.78 g, 4.5 mmol) was dried under vacuum and suspended in 25 mL of methylene chloride, and 0.5 g (50 mmol) of triethylamine was added followed by 0.63 g (50 mmol) of cyclohexyl isocyanate with continuous stirring. Stirring was continued for 12 h, and then the solvent was removed under vacuum. The residual solid was recrystallized from chloroform/petroleum ether (1:1), giving 0.800 g (80%) of the urea as a crystalline solid: mp 83–84 °C (lit.[11] mp 84–86 °C); ^{1}H NMR ($CDCl_3$) δ 1.0–2.04 (m, 10 H), 3.39 (q, 2 H), 3.51 (m, 1 H), 3.6 (t, 2 H), 3.74 (s, 2 H), 4.86 (d, 1 H), 5.15 (t, 1 H); mass spectrum, m/e 250 (M^+).

1-[2-(2-Chloro-2,2-dideuterioethoxy)ethyl]-3-cyclohexyl-1-nitrosourea (6). The nitrosourea was prepared by following the literature procedure:[11] 80% yield; ^{1}H NMR ($CDCl_3$) δ 1.04–2.06 (m, 10 H), 3.48 (t, 2 H), 3.62 (s, 2 H), 3.8 (m, 1 H), 4.02 (t, 2 H), 6.78 (d, 1 H); mass spectrum, m/e 279 (M^+).

1,1-Dideuterio-2-phthalimidoethanol (7). A solution of 5 g (80 mmol) of 2-amino-1,1-dideuterioethanol[24] and 11.84 g (80 mmol) of phthalic anhydride in 100 mL of toluene was heated under reflux for 3 h. The solvent was removed in vacuo, and the residue was crystallized from chloroform/petroleum ether to give the product (7): 12 g (75% yield); mp 124 °C (lit.[11] mp 124–126 °C); ^{1}H NMR ($CDCl_3$) δ 2.6 (br s, 1 H), 3.86 (s, 2 H), 7.6–8.0 (m, 4 H); mass spectrum, m/e 193 (M^+).

2-(2-Amino-1,1-dideuterioethoxy)ethanol. Sodium hydride (1.0 g, 30 mmol, of 80%) was gradually added to a solution of 3.86 g (20 mmol) of 1,1-dideuterio-2-phthalimidoethanol in 100 mL of dry tetrahydrofuran at room temperature. The mixture was gently refluxed for 2 h with continuous stirring. Ethyl chloroacetate (2.45 g, 20 mmol) was added dropwise to the refluxing solution, and the solution was stirred for 12 h at room temperature. The solvent was removed in vacuo, 50 mL of water added, and the residue extracted with chloroform (3 × 30 mL). The chloroform layer was dried and the solvent removed in vacuo. The residue was then heated under reflux with 2 g of hydrazine hydrate in 25 mL of ethanol. The precipitated phthaloyl hydrazide was collected and the cold filtrate saturated with hydrogen chloride gas. The hot ethanolic solution was filtered to remove precipitated solids, and the filtrate was concentrated to 5 mL and then passed through a short column of silica gel. This provided 1.8 g (40% yield) of a semisolid consisting of a mixture of hydrochloride salts of the acid and ethyl ester (8) of (2-amino-1,1-dideuterioethoxy)acetic acid. This mixture was then directly reduced by its addition to an ice-cold slurry of 0.75 g (18 mmol) of lithium aluminum hydride in 100 mL of dry tetrahydrofuran. The temperature of the solution was raised to a gentle reflux and maintained thus for 4 h. The metal complex and an excess of metal hydride were decomposed by cautiously adding a 10% aqueous solution of ammonium chloride while cooling in an ice bath. The granular hydroxides were extracted in a Soxhlet apparatus with THF for 48 h. Drying and evaporation of the extract gave 0.8 g (38% overall yield) of 2-(2-amino-1,1-dideuterioethoxy)ethanol purified by distillation: bp 120–124 °C (2 mm) (lit.[24] bp 218–224 °C); ^{1}H NMR ($CDCl_3$) δ 2.6 (br, 3 H), 3.45–3.88 (m, 6 H); mass spectrum m/e 107 (M^+).

1-[2-(2-Chloroethoxy)-2,2-dideuterioethyl]-3-cyclohexylurea. 2-(2-Amino-1,1-dideuterioethoxy)ethanol was chlorinated with thionyl chloride in chloroform. The resulting 2-(2-chloroethoxy)-2,2-dideuterioethylamine hydrochloride (0.6 g, 75% yield) was dried in vacuo and then suspended in 25 mL of methylene chloride. Triethylamine (0.5 g, 50 mmol) was added followed by 0.63 g (50 mmol) of cyclohexyl isocyanate with continuous stirring. Stirring was continued at room temperature for 12 h and the solvent removed in vacuo. The residual urea was purified by recrystallization from chloroform/petroleum ether: 0.8 g (65% yield); mp 84 °C (lit.[11] mp 84–86 °C); ^{1}H NMR ($CDCl_3$) δ 1.0–2.0 (m, 10 H), 3.36 (d, 2 H), 3.5 (m, 1 H), 3.64 (t, 2 H), 3.74 (t, 2 H), 4.97 (d, 1 H), 5.26 (t, 1 H); mass spectrum, m/e 250 (M^+).

1-[2-(2-Chloroethoxy)-2,2-dideuterioethyl]-3-cyclohexyl-1-nitrosourea (9). The corresponding nitrosourea was prepared in 80% yield by nitrosation in formic acid following a previously described procedure as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.16–2.14 (m, 10 H), 3.56 (t, 2 H), 3.68 (t, 2 H), 3.88 (m, 1 H), 4.08 (s, 2 H), 6.82 (d, 1 H); mass spectrum, m/e 279 (M^+).

General Procedure for Analysis of Aqueous Decomposition Products of S-CENU and O-CENUs. Solutions of the nitrosoureas (0.1 mmol/mL) in 40 mM potassium phosphate buffer (pH 7.2) in 3-mL air-tight Reacti-vials equipped with Teflon septums were thermostated at 37 °C. At intervals the gaseous fractions were withdrawn with a 2-mL hypodermic syringe and were injected into the Hewlett-Packard gas chromatograph for analysis of volatile products. Samples were analyzed on a 6-ft 10% Carbowax 20M 80-100 WAW-DMCS 5830 column with the helium flow at 22 mL/min. The column was heated at 70 °C to detect acetaldehyde, vinyl chloride, and 1,2-dihydrothiophene and

(23) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 142.
(24) "Aldrich Chemical Catalog"; Aldrich Chemical Co.: Milwaukee, WI, 1981; p 51.

was heated further at a rate of 5 °C/min up to 120 °C for 30 min to detect the 2-chloroethyl vinyl ether, the thioethers, and the corresponding 2-hydroxyethyl compounds.

The aqueous layer was extracted thoroughly with Spectrograde chloroform and dried (Na_2SO_4), and the extract was similarly analyzed by GC and GC/MS.

Polarographic Measurement of Rates of Decompositon. Kinetic measurements of the rates of aqueous decomposition of S-CENU and O-CENU were made by differential pulse polarography following the disappearance of the electrochemically active nitroso group as described previously.[25] Measurements were made in a PAR 174A polarograph using a three-electrode cell thermostated at 37 °C. All solutions contained 50 mM potassium phosphate buffer (pH 7.2) and 10^{-2} M potassium chloride as the supporting electrolyte together with 10^{-4} M nitrosourea with 5% acetonitrile. Polarographic potentials were measured and are recorded with respect to the saturated calomel electrode.

Acknowledgment. This investigation was supported by Grant 1-R01-CA21488-01 awarded by the National Cancer Institute, DHEW, and by a grant from the Alberta Provincial Cancer Hospitals Board. We thank Dr. Alan Hogg and his associates for the mass spectral determinations.

Registry No. *S*-CENU, 66929-50-8; αd_2-*S*-CENU, 81141-99-3; βd_2-*S*-CENU, 81142-00-9; *O*-CENU, 73944-53-3; αd_2-*O*-CENU, 81142-01-0; βd_2-*O*-CENU, 81177-94-8; CCNU, 13010-47-4; dicyclohexylurea, 2387-23-7; 2,3-dihydrothiophene, 1120-59-8; cyclohexyl isocyanate, 3173-53-3; 2-chloroethyl vinyl thioether, 81142-02-1; 2,2′-dichlorodiethyl sulfide, 505-60-2; 2-hydroxyethyl vinyl sulfide, 3090-56-0; acetaldehyde, 75-07-0; vinyl chloride, 75-01-4; 2-chloroethyl vinyl ether, 110-75-8; 2,2′-dichlorodiethyl ether, 111-44-4; 2-hydroxyethyl-2′-chloroethyl ether, 628-89-7; 2,3-dihydrothiophene-*5-d*, 81142-03-2; 2,3-dihydrothiophene-*4-d*, 81142-04-3; 2,2-dideuterio-2,3-dihydrothiophene, 81142-05-4; 3,3-dideuterio-2,3-dihydrothiophene, 81142-06-5; 2-[(2-hydroxyethyl)thio]-2,2-dideuterioethylamine, 81142-07-6; 2-mercaptoethanol, 60-24-2; 2-chloro-2,2-dideuterioethylamine hydrochloride, 78604-36-1; 2-[(2-chloroethyl)thio]-2,2-dideuterioethylamine HCl, 81142-08-7; 1-[2-[(2-chloroethyl)thio]-2,2-dideuterioethyl]-3-cyclohexylurea, 81157-74-6; 1-[2-[(2-chloroethyl)thio]-1,1-dideuterioethyl-3-cyclohexyl-1-nitrosourea, 81142-09-8; chloroacetic acid, 79-11-8; 2-chloro-1,1-dideuterioethanol, 77081-40-4; 2-[(2-aminoethyl)thio]-1,1-dideuterioethanol, 81142-10-1; 2-mercaptoethylamine hydrochloride, 156-57-0; 1-[2-[(2-chloro-2,2-dideuterioethyl)thio]ethyl]-3-cyclohexylurea, 81142-11-2; 2-[(-2-chloro-2,2-dideuterioethyl)sulfinyl]ethanamine hydrochloride, 81142-12-3; 2-[(2-chloro-2,2-dideuterioethyl)thio]-ethylamine hydrochloride, 81142-13-4; phthalic anhydride, 85-44-9; diglycolamine, 929-06-6; 2-(2-phthalimidoethoxy)ethanol, 69676-63-7; (2-phthalimidoethoxy)acetaldehyde, 81142-14-5; (2-phthalimidoethoxy)acetic acid, 69676-65-9; 2-(2-aminoethoxy)-1,1-dideuterioethanol, 81142-15-6; (2-aminoethoxy)acetic acid hydrochloride, 81142-16-7; 1-[2-(2-chloro-2,2-dideuterioethoxy)ethyl]-3-cyclohexylurea, 81142-17-8; 2-amino-1,1-dideuterioethanol, 59099-87-5; 1,1-dideuterio-2-phthalimidoethanol, 81142-18-9; 2-(2-amino-1,1-dideuterioethoxy)-ethanol, 81142-19-0; ethyl chloroacetate, 105-39-5; (2-phthalimido-1,1-dideuterioethoxy)acetic acid, 81142-20-3; ethyl (2-phthalimido-1,1-dideuterioethoxy)acetate hydrochloride, 81142-21-4; 1-[2-(2-chloroethoxy)-2,2-dideuterioethyl]-3-cyclohexylurea, 81142-22-5; $ClCH_2CH_2OCD_2CH_2Cl$, 81142-23-6; $CD_2{=}CHOCH_2CH_2Cl$, 81157-75-7; $CH_2{=}CDOCH_2CH_2Cl$, 81142-24-7; CH_3CDO, 4122-13-8; $ClCH_2CH_2SCD_2CH_2Cl$, 81142-25-8; $CH_2{=}CDSCH_2CH_2Cl$, 81142-26-9; $CD_2{=}CHSCH_2CH_2Cl$, 81157-76-8; $CD_2{=}CHSCH_2CH_2OH$, 81157-77-9; $ClCD_2CH_2SCH_2CH_2Cl$, 81142-27-0; $CH_2{=}CHSCH_2CD_2Cl$, 81142-28-1; $ClCD_2CH_2OCH_2CH_2Cl$, 81142-29-2; $CH_2{=}CDCl$, 4984-12-7; $CH_2{=}CHOCH_2CD_2Cl$, 81142-30-5; CH_2DCHO, 7086-00-2.

Supplementary Material Available: Table III containing aqueous decomposition and mass spectral data for the CENUs (3 pages). Ordering information is given on any current masthead page.

(25) Lown, J. W.; McLaughlin, L. W.; Plambeck, J. A. *Biochem. Pharmacol.* **1979**, *28*, 2115.

Chemistry of 2-Carbenabicyclo[3.2.1]octadiene[1]

Peter K. Freeman* and Karl E. Swenson

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

Received August 4, 1981

Pyrolytic decomposition of the lithium or potassium salt of the tosylhydrazone of bicyclo[3.2.1]octa-3,6-dien-2-one (**11**) or photolysis of the lithium salt of **11** results in the formation of bicyclo[3.2.1]octa-2,6-diene (**12**), tricyclo[3.2.1.$0^{2,7}$]oct-3-ene (**13**), tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane (**14**), semibullvalene (**15**), 5-ethynyl-1,3-cyclohexadiene (**16**), and *endo*-6-ethynylbicyclo[3.1.0]hex-2-ene (**17**). The formation of the C_8H_8 fraction (**15–17**) is ascribed to insertion and rearrangement reactions of singlet 2-carbenabicyclo[3.2.1]octadiene, whereas the formation of the C_8H_{10} fraction (**12–14**) appears to be the result of hydrogen abstraction reactions of the corresponding triplet carbene or closely related species.

Homoaromatic character for the bicyclo[3.2.1]octadienyl carbanion **1** has been proposed by Brown[2,3] and Winstein,[4,5] evidence supporting antiaromaticity of the related carbocation **2** (Chart I) has been provided by Diaz,[6] and studies have been carried out on the related free radical.[7] In recent molecular orbital studies, Grutzner[8] and Schleyer[9] conclude, however, that homoaromaticity is not important in the bicyclo[3.2.1]octadienyl anion and similar systems. Our interests in homoaromatic carbenes and in systems with potential for carbene to carbene rearrangements provided the impetus to consider the chemistry of 2-carbenabicyclo[3.2.1]octa-3,6-diene (**3**). Qualitative MO

(1) Reported in preliminary form: Freeman, P. K.; Swenson, K. E. 33rd Northwest Regional Meeting of the American Chemical Society, Seattle, WA, June 1978; American Chemical Society: Washington, DC, 1978; Abstract No. 198.

(2) Brown, J. M.; Occolowitz, J. L. *Chem. Commun.* **1965**, 376.

(3) Brown, J. M. *Chem. Commun.* **1967**, 638.

(4) Winstein, S.; Ogliaruso, M.; Sakai, M.; Nicholson, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 3656.

(5) See also: Bos, H.; Klumpp, G. W. *Tetrahedron Lett.* **1978**, 1865. Trimitsis, G. B.; Tuncay, A. *J. Am. Chem. Soc.* **1976**, *98*, 1997. Trimitsis, G. B.; Tuncay, A. *Ibid.* **1975**, *97*, 7193. Dauben, W. G.; Tweig, R. J. *Tetrahedron Lett.* **1974**, 531. Moncur, M. V.; Grutzner, J. B. *J. Am. Chem. Soc.* **1973**, *95*, 6449. Goldstein, M. J.; Natowsky, S. *Ibid.* **1973**, *95*, 6451.

(6) Diaz, A. F.; Sakai, M.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 7477. See also: Jefford, C. W.; Mareda, J.; Perlberger, J.-C.; Burger, U. *Ibid.* **1979**, 1370.

(7) Japenga, J.; Klumpp, G. W.; Stapersma, J. *Tetrahedron* **1977**, *33*, 2847.

(8) Grutzner, J. B.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1981**, *103*, 1372.

(9) Kaufmann, E.; Mayr, H.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1375.

0022-3263/82/1947-2033$01.25/0