The Synthesis and Chemistry of 2-(1-Aziridinyl)-2-oxazolines

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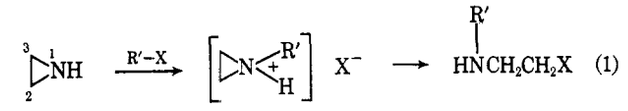
Several examples of the new 2-(1-aziridinyl)-2-oxazoline system have been synthesized by the isomerization of appropriate 1,1′-carbonylbisaziridines with catalytic amounts of tetra-*n*-butylammonium iodide. Reactions of 2-(1-aziridinyl)-2-oxazolines with Lewis and Brønsted acids indicate that complexing occurs entirely at the oxazoline nitrogen. Similar reactions with acid chlorides show that the oxazoline moiety is more nucleophilic than the aziridine function. Several novel heterocyclic systems have been synthesized from 2-(1-aziridinyl)-2-oxazolines and diacid chlorides.

Substantial and exciting developments have been reported in the area of aziridine[1] and 2-oxazoline[2] chemistry since examples in each series were first synthesized in the late 1800's. Both systems are known to undergo ring-opening reactions with a variety of reagents such as phenols, thiophenols, mineral acids, organic acids, or acid chlorides. It is generally believed that these reactions proceed by first quaternization of the nitrogen followed by nucleophilic attack by the counter ion at the 2 position of the aziridinium salt[3] (1) or at the 5 position of the oxazolinium salt[4,5] (2) to give ring-opened products as shown in eq 1 and 2. To date intermediates such as 1, where R′ is aroyl or acyl, have not been isolated; however, stable aziridinium salts have been isolated recently by several groups.[11,12] Oxazolinium salts (2), where R′ is aroyl[5] or hydrogen[9b] have been isolated and well characterized. The above reactions usually proceed in high yield to the indicated products. With this in mind it was considered of interest to incorporate these two moieties in a common molecule in an attempt to compare the relative nucleophilicities of the respective ring nitrogens when submitted to electrophiles such as mono- and diacid chlorides and to determine the preferred site of attack by Lewis and protonic acids.



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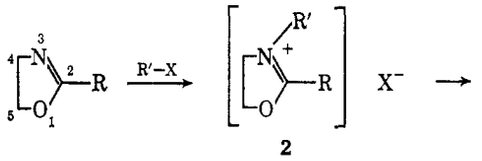

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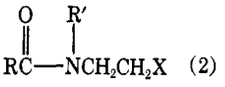
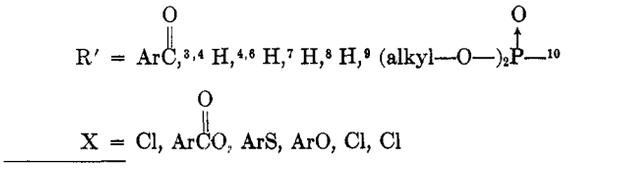
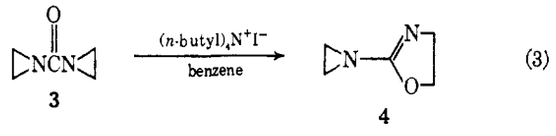




Results and Discussion

Of the three possible mono (1-aziridinyl)-2-oxazolines (*i.e.*, 2, 4, or 5 substituted), the 2-(1-aziridinyl)-2-oxazoline system appeared to be useful for this study and in fact proved to be the most convenient system to synthesize. The synthesis of 2-aziridinyl-2-oxazoline was accomplished by isomerizing one of the aziridine rings in 1,1′-carbonylbisaziridine using a catalytic amount of tetra-*n*-butylammonium iodide in benzene (eq 3).



This catalyst system offered several advantages over the usual sodium iodide–acetone or acetonitrile systems[1b] in that the solvent was much easier to dry and the amount of polymeric side products was minimized. 2-(1-Aziridinyl)-2-oxazoline was obtained in 79% yield as a low melting white solid which sublimed readily. The conversion of **3** into **4** was followed by nmr spectroscopy, wherein a singlet (−2.10 ppm) for **3** gradually disappeared as a new singlet at −2.05 ppm and a set of finely split triplets at −3.66 and −4.27 ppm ($CDCl_3$) for **4** developed. Infrared (ir) analysis also confirmed this conversion in that a strong band at 1695 cm^{-1} [>NC(=O)N<] diminished as a new band at 1661 cm^{-1}, characteristic of 2-oxazolines,[13] appeared during the course of the isomerization. This isomerization appeared to be somewhat slower than that observed for the sulfur analog [*i.e.*, 1,1′-(thiocarbonyl)bisaziridine → 2-(1-aziridinyl)-2-thiazoline].[14]

Using the method of Bestian,[3] 1,1′-carbonylbis(2-

(1) (a) H. Bestian in "Methoden Der Organischen Chemie" (Houben-Weyl), Vol. 11/2, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1958, p 223; (b) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962); (c) P. Fanta in "Chemistry of Heterocyclic Compounds," Vol. 19, part I, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 2.

(2) (a) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellman, *Angew. Chem. Intern. Ed. Engl.*, **5**, 875 (1966); (b) R. H. Wiley and L. L. Bennett, Jr., *Chem. Rev.*, **44**, 447 (1949); (c) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 377; (d) R. L. McKee in "The Chemistry of Heterocyclic Compounds," Vol. XVII, A Weissberger, Ed., John Wiley & Sons, Inc., New York–London, 1962, p 341.

(3) H. Bestian, *Ann.*, **566**, 210 (1950).

(4) E. M. Fry, *J. Org. Chem.*, **15**, 802 (1950).

(5) S. Hunig, *Angew. Chem. Intern. Ed. Engl.*, **3**, 548 (1964).

(6) G. D. Jones, *et al.*, *J. Org. Chem.*, **9**, 500 (1944).

(7) (a) G. Meguerian and L. B. Clapp, *J. Amer. Chem. Soc.*, **73**, 2121 (1951). (b) H. L. Wehrmeister, *J. Org. Chem.*, **28**, 2587 (1963).

(8) (a) L. B. Clapp, *J. Amer. Chem. Soc.*, **73**, 2584 (1951). (b) A. Jager, German Patent 1,062,253 (1959); *Chem. Abstr.*, **55**, 13380*i* (1961).

(9) (a) S. Gabriel and H. Ohle, *Ber.*, **50**, 804 (1917). (b) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948).

(10) (a) N. P. Grechkin, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.*, 538 (1956); *Chem. Abstr.*, **51**, 1933 (1957). (b) G. Greenhalgh, *Can. J. Chem.*, **41**, 1662 (1963).

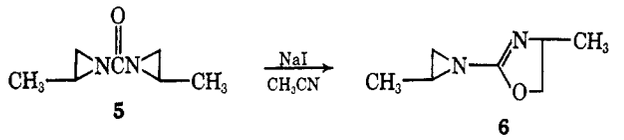
(11) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, **82**, 6418 (1960); **84**, 4806 (1962).

(12) U. Harder, E. Pfeil, and K. F. Zenner, *Ber.*, **97**, 510 (1964).

(13) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, N. Y., p 218.

(14) D. A. Tomalia, *J. Heterocycl. Chem.*, **4**, 419 (1967).

methyl)aziridine (**5**) was obtained in 36% yield as a light yellow, distillable liquid. Nmr and ir spectra were consistent with the proposed structure (See Experimental Section). Attempts to isomerize **5** in the same manner as to isomerize **3** with *n*-tetrabutylammonium iodide in benzene were unsuccessful. Isomerization of **5** to the presumed isomer **6**[15] was observed when sodium iodide in anhydrous acetonitrile was used (eq 4). Even when this catalyst system was used the

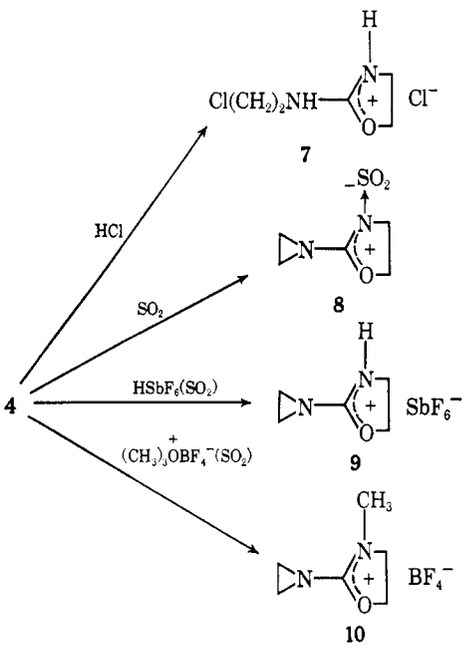


5 6 (4)

isomerization was relatively slow. The characteristic 2-oxazoline absorption was noted for the product at 1660 cm^{-1}. Although the methyl region of the nmr spectrum was too complicated by overlapping bands to determine whether both isomers were present, thin layer chromatography (tlc) indicated that a small amount of the other isomer may have been formed.

2-(1-Aziridinyl)-2-oxazoline (**4**) underwent ring opening with hydrochloric acid to yield 2-(2-chloroethylamino)-2-oxazoline hydrochloride (**7**). When the reaction was carried out with an acid possessing a nonnucleophilic counterion (*i.e.*, $HSbF_6$), with sulfur dioxide, or with trimethyloxonium tetrafluoroborate nmr analysis indicated that both rings were preserved giving in each case **8**, **9**, and **10** (Scheme I).

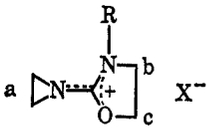
SCHEME I



Attempts to prepare the 3-acetyl-2-(1-aziridinyl)-2-oxazolinium salt (**11**) by the reaction of methyl oxocarbonium hexafluoroantimonate with **4** were unsuccessful. Ill-defined polymeric products were obtained in all cases. Nmr data supporting these structures are recorded in Table I. Further evidence for preferential electrophilic attack at the oxazoline nitrogen was obtained by allowing a model compound, 2-dimethyl-

(15) Assignment of the structure for **6** is based on the usual selectivity observed for these iodide-catalyzed isomerizations (*cf.* ref 1b).

TABLE I
NMR CHEMICAL SHIFTS (δ)
FOR 2-(1-AZIRIDINYL)-2-OXAZOLINE COMPLEXES

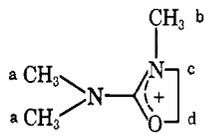


12

Compound	Solvent	Protons (a)	$\Delta\delta'^a$	Protons (b)	$\Delta\delta''^a$	Protons (c)	$\Delta\delta'''^a$
4	$CDCl_3$	−2.10 (s)		−3.66 (t)		−4.27 (t)	
8	SO_2	−2.68 (s)	0.58	−4.05 (t)	0.39	−4.93 (t)	0.66
9	SO_2	−2.76 (s)	0.66	−4.14 (t)	0.48	−5.06 (t)	0.79
10	SO_2	−2.80 (s)	0.70	−4.13 (t)	0.49	−4.94 (t)	0.67

[a] The difference in chemical shift (δ) relative to uncomplexed **4** in $CDCl_3$.

amino-2-oxazoline, to react with trimethyloxonium tetrafluoroborate. A crystalline material was isolated in high yield and was assigned the following structure,



a, −3.14 (s); b, −3.25 (s); c, −3.93 (t); d, −4.63 (t)
a:b:c:d, 5.87:2.94:2.16:2.03

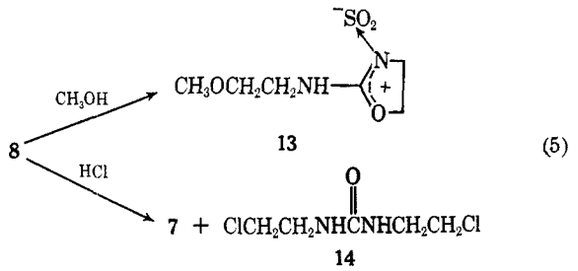
based on nmr spectral data. If quaternization had occurred at the 2-amino group one would have expected equivalent methyl groups.

The spectral data in Table I not only indicate that attachment at the oxazoline nitrogen is preferred but also suggest that the resulting complexes are best represented as resonance hybrids, as shown (Table I, **12**), whereby charge can be effectively delocalized to the aziridine ring as well as the 5 position of the oxazoline ring. The latter is apparent by comparing the amount of deshielding of these positions in the complexes relative to the uncomplexed material (*i.e.*, $\Delta\delta'$, $\Delta\delta''$, and $\Delta\delta'''$). Resonance structure **12** is not too unlike those reported for 1,3-dioxolenium cations,[16] in particular the 2-diethylamino-1,3-dioxolenium cation. Assuming that no unexpected anisotropy effects are operative, these values indicate that charge delocalization is higher at the aziridine ring and oxazoline 5 position than at the oxazoline 4 position. Just as Weinberger and Greenhalgh[17] have shown that the 2-methyl group on 2-methyl-2-oxazoline is a sensitive probe for determining the electron density on the oxazoline nitrogen, our data shows qualitatively that the aziridine ring also reflects depletion of electron density on the oxazoline nitrogen (*cf.* $\Delta\delta'$, Table I). The preferred complexing at the oxazoline nitrogen, despite the fact that aziridines[18] are usually more basic than 2-oxazolines,[10b,19] indicates that the opportunity to delocalize charge as in **12** is more important than complexation at the more basic aziridine site where charge would be localized.

Upon treatment of **8** with methanol or with anhydrous HCl, aziridine ring opening was observed, giving 2-(2-methoxyethylamino)2-oxazoline (**13**) in the first

(16) H. Hart and D. A. Tomalia, *Tetrahedron Lett.*, **15**, 1347 (1967), and previous papers.
(17) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).
(18) G. J. Buist and H. J. Lucas, *J. Amer. Chem. Soc.*, **79**, 6157 (1957).
(19) G. R. Porter, H. N. Rydon, and J. A. Schofield, *J. Chem. Soc.*, 2686 (1960).

case, whereas 2-(2-chloroethylamino)2-oxazoline hydrochloride (7) and 1,3-bis(2-chloroethyl)urea (14) were formed in the later instance (eq 5). These products were identified by comparison with authentic samples obtained by an independent method.

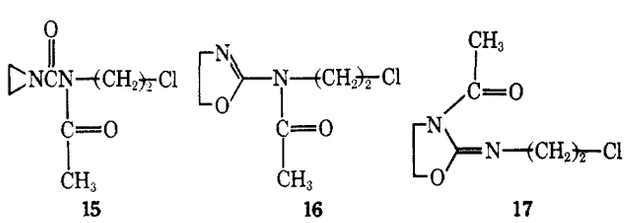


(5)

2-(1-Aziridinyl)-2-oxazoline (4) reacted exothermally with an equivalent amount of acetyl chloride to give a thermolabile, light yellow oil which analyzed for $C_7H_{11}ClN_2O_2$. Attempts to distil this material, using routine vacuum techniques, led to the formation of an orange-red polymer. Analytical samples could be obtained only by flash distillation under vacuum. This product displayed intense bands at 1722 and 1683 cm^{-1} in the ir region, whereas the nmr spectrum consisted of a singlet at −2.55, a slightly split singlet at −3.62, and an A_2B_2 pattern centered at −4.15 ppm ($CDCl_3$). These protons were present in a ratio of 3:4:4, respectively.

When the acetylation product was allowed to react with gaseous HCl, N-acetyl-1,3-bis(2-chloroethyl)urea was obtained. This material was identified by comparison with an authentic sample which was obtained from the acetylation of 1,3-bis(2-chloroethyl)-urea.

A prior consideration of opening either or both rings in 4 forces one to postulate at least three tenable structures for this product, *i.e.*, 15, 16, or 17. Although the

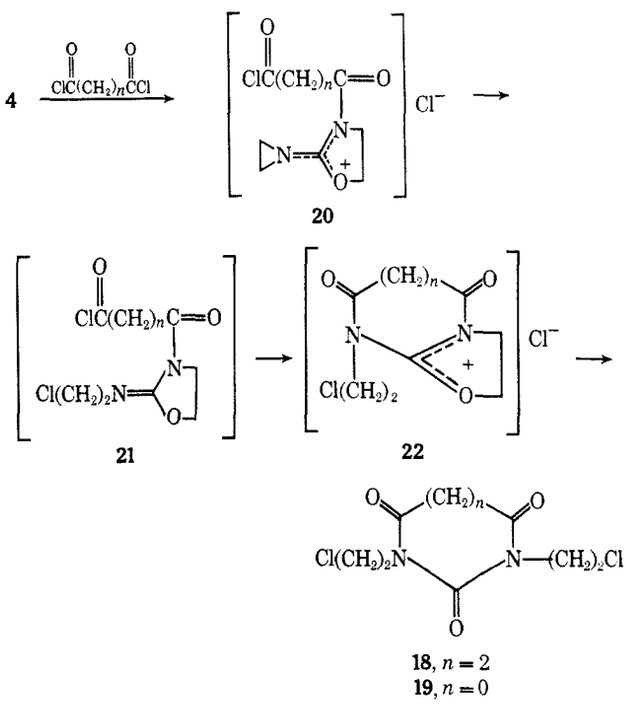


thermolability of this material is reminiscent of aziridine[1a] or oxazolidine[20] functionality, structure 15 was discounted in that no aziridine-type protons were observed in the nmr spectrum. Based on the spectroscopic data and conversion of the acetylated product into N-acetyl-1,3-bis(2-chloroethyl)urea, a choice between structures 16 and 17 cannot be decisive. In view of the spectroscopic and chemical evidence presented earlier for preferred aziridine ring opening, assignment of structure 17 to the acetylation product is favored at this time.

A survey of the literature indicated that compound 17 is a member of a relatively small class of exocyclic 2-iminooxazolidines[21] which are substituted in the 3 position with nonlabile groups such that tautomerization to a 2-amino-2-oxazoline is rendered impossible. Although related ring systems containing a labile 3 substituent[22-24] have on occasion been reported as exocyclic iminooxazolidines, more recent work has shown that the endocyclic imino tautomers usually predominate.[25]

The reaction of 4 with 2 equiv of acetyl chloride gave ill-defined products, whereas the same reaction with acetyl bromide gave a thermolabile material which was identified by nmr as 1,3-bis(2-bromoethyl)-1,3-diacetylurea. It appears that in the presence of the more nucleophilic bromide ion both the aziridine and the oxazoline moieties undergo ring opening. Despite the unsuccessful attempt to cleave both rings with 2 equiv of acetyl chloride, 4 underwent such a cleavage with diacid chlorides thus providing an interesting route to a number of heterocyclic systems. Succinyl chloride and phthaloyl chloride reacted with 4 to give the seven-membered heterocycles, 1,3-bis(2-chloroethyl)-dihydro-1H-1,3-diazepine-2,4,7(3H)-trione (18, 78%) and 2,4-bis-2-chloroethylbenzo-2,4-diazepine-1,3,5-trione (95%). These structures were confirmed by nmr, ir, and mass spectroscopy. Oxalyl chloride reacted in a similar manner with 4 to give 1,3-bis(2-chloroethyl)-imidazolidine-2,4,5-trione (19) in 92% yield. This structure was established by comparison with an authentic sample which was obtained by treating 1,3-bis-(2-chloroethyl)urea with oxalyl chloride according to the method of Blitz and Topp.[26] In each case it is believed that the cyclization occurs in four steps as outlined in Scheme II. Based on previous observations,

SCHEME II

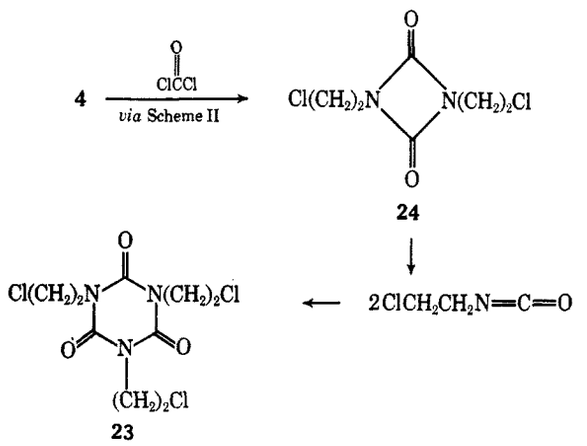


the first step probably involves formation of a 2-(1-aziridinyl)-2-oxazolinium salt (20) which then collapses to the 2-(2-chloroethyl)imino-3-acyloxazolidine derivative (21) followed by intramolecular acylation of the imino group to give the oxazolinium salt, 22. Collapse of 22 yields the heterocyclic products.

(20) E. D. Bergman, *Chem. Rev.*, **53**, 309 (1953).
(21) R. W. Leekenbaugh, U. S. Patent 2,902,356 (1959); *Chem. Abstr.*, **54**, 811*g* (1960).
(22) A. Crawshaw and A. N. Mason, *Chem. Ind.* (London), 365 (1964).
(23) E. Schmidt, F. Hitzler, and E. Lahde, *Ber.*, **71**, 1933 (1938).
(24) E. Schmidt and W. Striewsky, *ibid.*, **74**, 1285 (1941).
(25) A. R. Katritzky, *Advan. Heterocycl. Chem.*, **2**, 67 (1963).
(26) H. Blitz and E. Topp, *Ber.*, **46**, 1387 (1913).

When **4** was treated with phosgene, 1,3,5-tris(2-chloroethyl)-s-triazine-2,4,6-trione (**23**) was obtained in 28% yield rather than the expected 1,3-bis(2-chloroethyl)-2,4-uretidinedione (**24**) (Scheme III). It is quite likely that **24** is formed as a transient intermediate *via* Scheme II; however, owing to the instability of these derivatives[27] reversion to 2-chloroethyl isocyanate followed by trimerization to **23** apparently occurs.

SCHEME III



Reaction of **4** with malonyl chloride did not give the expected six-membered heterocycle *via* Scheme II. Instead, **4** functioned as a dehydrohalogenating agent, under mild conditions, to yield 2-(2-chloroethylamino)-2-oxazoline hydrochloride (**7**) and presumably carbon suboxide. Under reflux conditions 1,3-bis(2-chloroethyl)urea (**14**) was obtained. This reaction dramatizes the basicity of **4** in that it appears to parallel the well-known reaction between tertiary amines and malonyl chloride to yield carbon suboxide and tertiary amine salts.[28]

Experimental Section

Nmr spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (TMS). Ir spectra were scanned on a Perkin-Elmer 337 spectrometer. Melting points were determined in a capillary and are uncorrected unless otherwise noted.

1,1'-(Carbonyl)bisaziridine (3).—This compound was prepared according to the method of Bestian.[3] The white crystalline material, mp 38–40°, displayed a carbonyl band at 1700 (s) and aziridine (C–H stretching) at 3025 (w) and 3090 cm^{-1} (w). The nmr spectrum consisted of a singlet at −2.18 ppm (CCl_4).

2-(1-Aziridinyl)-2-oxazoline (4).—A solution of **3** (36.4 g, 0.33 mol) and tetra-*n*-butylammonium iodide (2.0 g) in 200 ml of anhydrous benzene was refluxed for 4 hr under anhydrous conditions. The solvent was removed *in vacuo* at room temperature. The light yellow residue was distilled, giving a major cut boiling at 62° (4.3 mm) which weighed 28.8 g (79%). The distillate solidified to a white crystalline material melting at 27–29°. At pressures below 1 mm this material sublimed readily. The nmr spectrum consisted of two triplets centered at −4.27 and −3.66, as well as a singlet at −2.05 ppm ($CDCl_3$) in a ratio of 1:1:2. The ir spectrum contained an intense band at 1661 cm^{-1} which is generally characteristic of 2-oxazoline.[13]

Anal. Calcd for $C_5H_8N_2O$: C, 65.18; H, 8.75; N, 30.41. Found: C, 65.21; H, 8.68; N, 30.23.

1,1'-(Carbonyl)bis(2-methylaziridine) (5).—A solution of 2-methylaziridine (28.5 g, 0.5 mol) and triethylamine (50.5 g, 0.5 mol) in 250 ml of ether was added dropwise to a stirred solution of phosgene (24.5 g, 0.25 mol) in 500 ml of ether while the reaction temperature was maintained at −5 to 0°. The addition took 4 hr and then the reaction was allowed to stir at 0 to 10° for 2 hr. Triethylamine hydrochloride was filtered off and the solvent was removed *in vacuo* at room temperature. The light yellow oily residue weighed 23.2 g and distilled to give a major fraction, bp 56° (5 mm), weighing 12.5 g (36%), $n^{25}D$ 1.4605. The nmr spectrum consisted of a multiplet at −2.73 to −2.13 and two doublets centered at −1.84 and −1.30 ppm (CCl_4) in a ratio of 2:1:3, respectively. The ir spectrum contained bands at 3075 (w), 3005 (w), and 1695 (s) cm^{-1} (neat).

2-(2-Methylaziridinyl)-4-methyl-2-oxazoline (6).—A solution of the aziridine **5** (1.24 g, 0.03 mol) and sodium iodide (0.6 g, 0.004 mol) in 25 ml of dry acetonitrile was refluxed under anhydrous conditions for 27 hr. After the solvent was removed *in vacuo* at room temperature, the residue was distilled to give 0.55 g (44%) of product boiling at 85–90° (2 mm), $n^{25}D$ 1.4650. The nmr spectrum consisted of multiplets at −4.84 to −3.66, −2.66 to −2.20, −2.05 to −1.90, and −1.48 to −1.14 ppm ($CDCl_3$) in a ratio of 3:2:1:6, respectively. A characteristic band for OC=N[13] was observed at 1656 cm^{-1} (neat).

Reaction of 4 with Hydrochloric Acid → 7.—2-(1-Aziridinyl)-2-oxazoline (1.0 g) was added to 25 ml of 12 *N* HCl, while stirring at room temperature, to give a homogeneous solution. Removal of the solvent gave 1.6 g of a white crystalline solid, mp 108–110°. This material was spectroscopically identical with an authentic sample of 2-(2-chloroethylamino)-2-oxazoline hydrochloride.[29]

2-(1-Aziridinyl)-2-oxazoline–Sulfur Dioxide Complex (8).—Under anhydrous conditions, **4** (1.0 g) was added dropwise into 20 ml of liquid sulfur dioxide. An nmr spectrum of the pale yellow solution was scanned at a probe temperature of −30°, giving the chemical shifts indicated in Table I.

Reaction of 8 with Methanol → 13.—The above solution was added to 35 ml of anhydrous methanol and allowed to stand overnight at room temperature. The excess methanol was removed *in vacuo* to give a somewhat viscous liquid residue. Nmr analysis of the residue revealed complete loss of the aziridine proton signal and the appearance of a new singlet at −3.17 ppm (d_6-DMSO) characteristic of CH_3O groups. The nmr spectrum was essentially identical with a sample of 2-(2-methoxyethylamino)-2-oxazoline prepared by the reaction of 1,3-bis(2-chloroethyl)urea with an equivalent amount of sodium methoxide in methanol.

Reaction of 8 with Hydrogen Chloride → 7 + 14.—Dry hydrogen chloride was bubbled into a solution of **8** in liquid sulfur dioxide. An equal volume of chloroform was added and the sample was allowed to stand overnight at room temperature. The solvent was removed *in vacuo* to give a solid residue. This residue was identified as a mixture of **7** and **14** by nmr and ir analysis, using authentic samples for the comparison. Authentic **14** was prepared according to the method of Bestian.[3]

2-(1-Aziridinyl)-2-oxazolinium Hexafluoroantimonate (9).—A solution of $HSbF_6$ was prepared by bubbling a stoichiometric amount of HCl gas into a solution of $AgSbF_6$ (1.72 g) in approximately 40 ml of liquid sulfur dioxide.[30] After silver chloride was removed 2-(1-aziridinyl)-2-oxazoline (0.56 g) was added while stirring (*ca.* −30°). A sample of this solution was scanned at −30° giving the chemical shifts listed in Table I.[31]

2-(1-Aziridinyl)-3-methyl-2-oxazolinium Tetrafluoroborate (10).—All operations were conducted in a N_2-filled drybox. To a stirred solution of trimethyloxonium tetrafluoroborate[32] (1.48 g, 0.01 mol) in 10 ml of SO_2 was added dropwise a homogeneous solution of 1.12 g (0.01 mol) of 2-(1-aziridinyl)-2-oxazoline in 5 ml of liquid SO_2. The resultant yellow solution was allowed to stand at −78° for 2 hr and at −20° for an additional 8 hr. An nmr spectrum of this solution with 1 drop of TMS added, was obtained and is described in the discussion section. One-half the remaining solution was evaporated to a small volume, 10 ml of dry CH_2Cl_2 was added, and a small amount (~20 mg) of trimethyloxonium tetrafluoroborate was obtained. The CH_2Cl_2 solution was diluted with dry Et_2O causing an oil to separate. Upon storage at −20° overnight the oil crystallized. The faintly yellow crystals were collected by suction filtration (0.73 g, 68%) and an nmr spectrum (SO_2) of it was essentially identical with that of the original SO_2 solution. The extremely hygroscopic nature of the solid, mp 34.1–37°, made reliable elemental analysis impractical.

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3-Acetyl-2-[(2-chloroethyl)imino]oxazolidine (17).—A solution of acetyl chloride (0.8 g, 0.01 mol) in 15 ml of chloroform was added dropwise over a period of 15 min to a solution of 2-(1-aziridinyl)-2-oxazoline (1.12 g, 0.01 mol) in 20 ml of chloroform. The reaction mixture was refluxed for 0.5 hr, followed by removal of the solvent *in vacuo* at room temperature to give 1.84 g of a pale yellow product. Attempts to use normal vacuum distillation techniques caused this material to polymerize to an orange-red polymer which was soluble in both chloroform and water. Flash distillation gave a colorless liquid, bp 120–125° (1.5 mm), $n^{25}D$ 1.5085. The nmr spectrum consisted of a singlet at −2.55, a slightly split singlet at −3.62, and an A_2B_2 pattern centered at −4.15 ppm ($CDCl_3$) in a ratio of 3:4:4. The ir spectrum displayed intense bands at 1722 and 1683 cm^{-1} (neat).

Anal. Calcd for $C_7H_{11}ClN_2O_2$: C, 44.10; H, 5.80; N, 14.7. Found: C, 44.30; H, 5.65; N, 14.7.

Reaction of 17 with Hydrogen Chloride.—Gaseous hydrogen chloride was bubbled into a solution containing 1 g of **17** in 40 ml of benzene. A white precipitate was formed and then subsequently dissolved to give a homogeneous reaction mixture. Evaporation of the solvent gave a white crystalline material, mp 53–55°. An admixture melting point of this material with authentic N-acetyl-1,3-bis(2-chloroethyl)urea was not depressed and the ir spectra for each of these materials were identical (see below).

N-Acetyl-1,3-bis(2-chloroethyl)urea.—1,3-Bis(2-chloroethyl)-urea (5 g, 0.03 mol) and pyridine (2.6 g, 0.032 mol) in 40 ml of anhydrous benzene was stirred while a solution of acetyl chloride (2.4 g, 0.03 mol) in 30 ml of benzene was added dropwise over a period of 15 min. The reaction mixture was refluxed for 3 hr and then filtered free of pyridinium hydrochloride. Concentration of the filtrate gave a white crystalline product weighing 5.9 g (90%), mp 53–55°. The nmr spectrum consisted of a multiplet at −4.24 to −3.59 and a singlet at −2.43 ppm ($CDCl_3$) in a ratio of 8:3. The ir spectrum contained a carbonyl absorption band at 1683 cm^{-1} (Fluorolube).

Reaction of 2-(1-Aziridinyl)-2-oxazoline with 2 Mol of Acetyl Bromide.—A 50-ml, three-necked, round-bottomed flask, equipped with a magnetic stirrer, an addition funnel, and a reflux condenser capped with a drying tube was charged with 1.12 g (0.01 mol) of 2-(1-aziridinyl)-2-oxazoline in 15 ml of dry CH_2Cl_2. To this was added, dropwise, with stirring 2.46 g (0.02 mol) of acetyl bromide in 15 ml of dry CH_2Cl_2 at a rate to maintain gentle reflux. Upon completion of the addition (~20 min) the clear colorless solution was heated under reflux for additional 1 hr and allowed to stand at room temperature overnight. The solvent was removed at reduced pressure to give a quantitative recovery of light yellow slightly viscous oil. The nmr spectrum ($CDCl_3$) was in agreement with the formulation of the compound as 1,3-bis(2-bromoethyl)-1,3-diacetylurea: −2.38 (s, 6), −3.54 (m, 4), −3.98 ppm (m, 4); ir (film) 1705 broad (C=O), no band near 950 cm^{-1} (oxazoline). Attempted distillation of the material at reduced pressure led to tar formation with no distillate obtained.

1,3-Bis(2-chloroethyl)dihydro-1H-1,3-diazepine-2,4,7(3H)-trione (18).—To a stirred solution of succinyl chloride (3.12 g, 0.02 mol) in 100 ml of benzene was added a solution of 2-(1-aziridinyl)-2-oxazoline (2.24 g, 0.02 mol) in 25 ml of benzene in a dropwise manner over a period of 2 hr. A slight exotherm was noted with a maximum temperature of 35°. This was accompanied by some solid precipitate. After the addition was complete, the reaction was refluxed for 3.5 hr. The homogeneous solution was concentrated to a volume of 10 ml. This residue crystallized to a white mass upon standing at room temperature. After recrystallization from absolute ethanol the white crystalline product weighed 4.2 g (78%) and melted at 82–83°. The nmr spectrum consisted of two triplets centered at −4.24 and a singlet at −2.97 ppm ($CDCl_3$) in a ratio of 1:1:1. The ir spectrum contained intense carbonyl bands at 1705 and 1667 cm^{-1} (Nujol mull). Mass spectrometry gave a parent ion peak of 266.02 (mol wt 267.11).

Anal. Calcd for $C_9H_{12}Cl_2N_2O_3$: C, 40.8; H, 4.33; N, 10.05. Found: C, 40.8; H, 4.61; N, 10.32.

Reaction of 4 with Oxalyl Chloride → 19.—A solution of 2-(1-aziridinyl)-2-oxazoline (1.12 g, 0.01 mol) in 25 ml of dry chloroform was added dropwise to a stirred solution of oxalyl chloride (1.27 g, 0.01 mol) in 25 ml of chloroform. The reaction mixture was refluxed for 1 hr and the solvent was removed *in vacuo* to yield 2.2 g (92%) of a cream-colored solid, mp 109–111°. Recrystallization from ethanol gave white needles melting at 112–113°. This material showed no depression in melting point when mixed with authentic 1,3-bis(2-chloroethyl)imidazolidine-2,4,5-trione. Similarly, reaction of 2-(1-aziridinyl)-2-oxazoline with oxalyl bromide under the same conditions gave a 97.2% recrystallized yield of the corresponding dibromo compound, mp 92.5–94.5° (from benzene–isopropyl alcohol). The nmr spectrum (acetone-d_6) consisted of a pair of multiplets at −3.69 and −4.10 ppm. The ir spectrum (Nujol mull) showed a broad carbonyl absorption at 1728 cm^{-1}.

1,3-Bis(2-chloroethyl)imidazolidine-2,4,5-trione (19).—1,3-Bis(2-chloroethyl)urea (5.55 g, 0.03 mol) in 50 ml of diethyl ether was stirred as oxalyl chloride (3.75 g, 0.03 mol) in 15 ml of ether was added dropwise. A vigorous reaction ensued and the reaction mixture was then refluxed for 30 min. During this time a white solid mass fell out of solution. The solid was filtered, washed with 2 × 10 ml of cold ether, and dried. The white, clingy product weighed 6.3 g (89%) and melted at 105–109°. Recrystallization from absolute ethanol gave white needles, mp 112–113°. The nmr consisted of an A_2M_2 pattern which was centered at −3.91 ppm ($CDCl_3$). The ir spectrum contained an intense carbonyl absorption at 1739 cm^{-1}.

Anal. Calcd for $C_7H_8Cl_2N_2O_3$: C, 35.15; H, 3.35; N, 11.71. Found: C, 35.10; H, 3.37; N, 11.60.

Preparation of 2,4-Bis-2-chloroethylbenzo-2,4-diazepine-1,3,5-trione.—Into a 250-ml, three-necked, round-bottomed flask, equipped with a reflux condenser, protected from atmospheric moisture by a calcium chloride tube, a 125-ml addition funnel, and thermometer, was placed 10.15 g (0.05 mol) of phthaloyl chloride in 50 ml of dry $CHCl_3$. To this magnetically stirred solution was added dropwise, at a rate to maintain the temperature between 40 and 50°, 5.61 g (0.05 mol) of 2-aziridinyl-2-oxazoline in an additional 50 ml of dry $CHCl_3$. Upon completion of the addition the solution was heated under reflux (~78°) for 1 hr. The $CHCl_3$ was removed at reduced pressure to give a viscous yellow liquid which was, with some difficulty, induced to crystallize (crude mp 75–79°), yield 14.98 g (95%). One recrystallization from hot isopropyl alcohol gave 9.01 g (57%) of fine, white needles, mp 87.5–89°. The nmr spectrum ($CDCl_3$) showed the typical A_2B_2 pattern for the group NCH_2CH_2Cl at −3.84 (4.12 H) and −4.46 (3.92 H) and a complex multiplet at −7.94 ppm (3.94 H) for the aromatic protons. The ir spectrum (CCl_4, CS_2) showed carbonyl bands at 1730 and 1680 (doublet), and aromatic absorptions at 1603 and 1596 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}N_2O_3Cl$: C, 49.54; H, 3.84; N, 8,89. Found: C, 49.4; H, 4.03; N, 8.89.

1,3,5-Tris(2-chloroethyl)-*s*-triazine-2,4,6-trione (23.)—A solution of **4** (2.24 g, 0.02 mol) in 40 ml of benzene was added dropwise to a stirred solution of phosgene (2.07 g, 0.02 mol) in 75 ml of benzene over a period of 0.5 hr. The reaction temperature was maintained at 0–10° during the addition; the mixture was then stirred at room temperature for 0.5 hr, followed by refluxing for 3 hr. After removal of the solvent by using vacuum at room temperature a somewhat viscous liquid residue was obtained which crystallized out of absolute ethanol giving 1.2 g (28%) of product. Several recrystallizations from diethyl ether gave a white crystalline material melting at 96–97°. The nmr spectrum contained two triplets centered at −4.27 and −3.73 ppm ($CDCl_3$) in a ratio of 1:1, whereas the ir spectrum displayed an intense carbonyl band at 1683 cm^{-1}. Mass spectroscopy confirmed this structure in that three chloride ion peaks were observed and a parent ion peak of 314.99 was obtained (mol wt 316.58).

Anal. Calcd for $C_9H_{12}Cl_3N_3O_3$: C, 34.2; H, 3.90; N, 13.3. Found: C, 34.4; H, 3.80; N, 13.1.

Reaction of 4 with Malonyl Chloride → 7.—A solution of the aziridine **4** (2.8 g, 0.025 mol) in 20 ml of anhydrous ether was added dropwise to a stirred solution of freshly distilled malonyl chloride (3.5 g, 0.025 mol) in 100 ml of ether. After reflux for 0.5 hr and filtration, a brilliant yellow powder (4.63 g) was obtained which melted over a range of 82–96°. Recrystallization of this material from a mixture of acetonitrile and ether gave a white crystalline product which exhibited a double melting point at 109–111° and 126–127°. This material was spectroscopically identical with 2(2-chloroethylamino)-2-oxazoline hydrochloride which had been prepared by an alternate method.[29]

1,1-Dimethyl-3-(2-chloroethyl)urea.—To a stirred solution of 26.89 g (0.25 mol) of dimethylcarbamoyl chloride in 100 ml of dry CH_2Cl_2 was added dropwise 10.77 g (0.25 mol) of aziridine in an additional 100 ml of dry CH_2Cl_2 with protection against moisture. The cloudy solution was heated under reflux for 1 hr and decanted from a small amount of resinous material. The solvent was evaporated at reduced pressure to give a quantitative recovery of yellow oil which slowly solidified to a yellow semisolid.

The nmr spectrum indicated it to be a 1:2 mixture of 2-dimethylamino-2-oxazolinium hydrochloride and the desired product: nmr ($CDCl_3$) −2.95 (s, 6), −3.62 (m, 4), −3.29 (s, 3), −4.08 (m, 1), −4.91 (m, 1). Since the materials are isomeric and both require 1 mol of base to generate 2-dimethylamino-2-oxazoline, the mixture was used without further purification in the next step.

2-Dimethylamino-2-oxazoline.—To 24.15 g (0.16 mol) of N,N-dimethyl-N′-(2-chloroethyl)urea dissolved in 50 ml of methanol was added, all at once, 160 ml of 1.000 *N* potassium methoxide in methanol. An immediate precipitate of potassium chloride was noted and the mixture was heated under reflux with magnetic stirring for 1.5 hr. The precipitated potassium chloride was removed by suction filtration. The methanol was removed from the filtrate at reduced pressure and 50 ml of CH_2Cl_2 was added to precipitate the remaining KCl, which was filtered off (total weight of KCl, 11.90 g; 99.8%). The CH_2Cl_2 solution was dried over $CaSO_4$ for 3 hr and filtered and the CH_2Cl_2 was removed at reduced pressure to give 18.13 g (99.4%) of crude product. Distillation at reduced pressure gave 10.42 g of colorless, mobile liquid, bp 96–98.5° (80 mm). The nmr spectrum contained a sharp singlet at −2.965 (6 H) and an A_2B_2 multiplet at −3.79 (2 H) and −4.315 ppm (2 H), in accord with the proposed structure. The ir spectrum (CCl_4, CS_2) showed 1670 (N=CO) and 936 cm^{-1}, characteristic of the oxazoline ring.

2-Dimethylamino-2-oxazolinium Tetrafluoroborate.—In a nitrogen-filled drybox 1.48 g (0.01 mol) of trimethyloxonium tetrafluoroborate was slurried in 20 ml of dry CH_2Cl_2. To this stirred slurry was added dropwise 1.14 g (0.01 mol) of 2-dimethylamino-2-oxazoline in 10 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 hr. The CH_2Cl_2 solution was concentrated at reduced pressure to a small volume causing the formation of a white precipitate, which was collected by suction filtration to give 1.66 g (77%) of small white crystals: mp 168.5–169.5° dec; nmr (CD_3CN) −3.14 (s, 6), −3.25 (s, 3), −3.93 (m, 2), −4.63 (m, 2); ir (Nujol mull) 1700 (broad, NC^+O) and 1170 cm^{-1} (very broad, BF_4^-).

Registry No.—**4,** 19587-77-0; **5,** 7259-82-7; **6,** 19587-79-2; **8,** 19587-80-5; **9,** 19598-91-5; **10,** 12344-31-9; **17,** 19587-81-6; **18,** 19587-82-7; **19,** 19587-83-8; **23,** 6299-37-2; 1,3-bis(2-bromoethyl)imidazolidine-2,4,5-dione, 19587-84-9; N-acetyl-1,3-bis(2-chloroethyl)urea, 19587-85-0; 2,4-bis(2-chloroethyl)benzo-2,4-diazepine-1,3,5-trione, 19587-86-1; 2-dimethylamino-2-oxazoline, 19587-87-2; 2-dimethylamino-2-oxazolinium tetrafluoroborate, 19598-92-6.

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Base-Catalyzed Hydrogen–Deuterium Exchange in Some Pyridine N-Oxides. Chloro and N-Oxide Rate Factors and Mechanism[1,2]

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Rates of deuterium–hydrogen exchange for deuterated pyridine N-oxide (I) and 3-chloro- (II) and 3,5-dichloropyridine N-oxide (III) in CH_3ONa–CH_3OH were obtained by nmr methods. At 138° relative rates for I-4, I-3,5, and I-2,6 are 1.0, 10, and 1500, respectively. At 50° relative rates for II-4, I-2,6, II-6, III-4, II-2, and III-2,6 are 0.37, 1.0, 12.2, 1370, 1840, and 11800. Log rate factors (relative to benzene) at 50° for Cl and N-oxide groups are *o*-Cl = 3.27 ± 0.24; *p*-Cl = 0.95 ± 0.14; *o*-NO = 9.58, and *p*-NO = 5.88. The N-oxide group is one of the most strongly activating groups for carbanion formation yet reported; its effect appears to be largely inductive. Exchange proceeds by direct deprotonation to give carbanions.

Base-catalyzed hydrogen exchange reactions in aromatic carbocyclic systems have been studied in considerable detail[4] and continue to draw interest as the fine points of the reaction mechanism become clearer.[5,6] Considerable attention has recently been directed to exchange in heteroaromatic ring systems, particularly five-membered-ring systems forming ylidic intermediates.[7] Information relating to exchange at annular positions in the six-membered heterocycles is more sparse.[2,8,9]

An intriguing problem is posed by the mechanism of base-catalyzed hydrogen–deuterium exchange on six-membered heteroaromatic substrates since they readily add nucleophiles.[10] For such compounds hydrogen exchange could take place on the adduct which results from the addition of base to the ring (addition–deprotonation pathway) or it could result from attack of base directly on a ring hydrogen.

This paper is one of several reporting a systematic study of hydrogen–deuterium exchange in heteroaromatic systems. This study is an attempt to elucidate the effects of heteroatoms on the position and rate of exchange and on the mechanism. We report a kinetic study of sodium methoxide catalyzed H–D exchange of deuterated forms of pyridine N-oxide (I) and of 3-chloro-(II) and 3,5-dichloropyridine N-oxide (III) in methanol. Chlorine substituents were chosen since they activate aromatic rings for hydrogen exchange. Moreover, methoxide ion catalyzed hydrogen exchange

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(2) A preliminary account of this work has appeared: J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).

(3) Member of the 1966–1968 National Science Foundation Summer Research Participation Program for College Teachers.

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