Reactions of Aziridines. Preparation and Properties of 2-Thiazolinium Salts (I)

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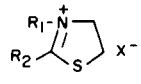
Received October 16, 1970

Reaction of 1-substituted aziridines with thioamides in the presence of perchloric acid has provided a facile route to 2-thiazolinium salts. Thioformamide was used in this reaction to give the 2-unsubstituted 2-thiazolinium salts 3-[4-(2,6-xylyloxy)butyl]-2-thiazolinium perchlorate (IIa) and 3-(2-cyclohexylbutyl)-2-thiazolinium perchlorate (IIc). A study of the rates of hydrolytic breakdown of IIc and 3-(2-cyclohexylbutyl)-2-methyl-2-thiazolinium perchlorate (IId) showed that the 2-unsubstituted compound (IIc) was considerably less stable than the 2-methyl analog (IId) over the entire *p*H range. Use of 1-substituted aziridines in ring-opening reactions, previously applied only to 1-unsubstituted aziridines, has given expected products when thiocyanate ion or thiourea was the nucleophile.

The highly reactive intermediate ethylenimine has been employed in many and varied types of ring-opening, ring-preserving, and degradation reactions leading to open chain and heterocyclic compounds (2). Ring-opening reactions, in contrast with ring-preserving reactions generally, also are applicable to 1-substituted aziridines. An attempt was made in this work to broaden the scope of aziridine ring-opening reactions by using 1-substituted aziridines in cases previously limited to ethylenimines.

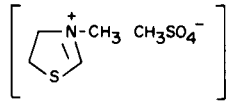
A reaction which differentiates between hydrogen and alkyl or aryl groups at the 1-position of aziridine is that of thioamides with ethylenimine to form 2-thiazolines (3). 1-Substituted aziridines (I) would be expected to give either a 2-thiazolinium salt (II) or in the absence of cyclization an *N*-(2-mercaptoethyl)amidine (III) (Scheme I). In the present work 2-thiazolinium salts (II) were prepared from 1-substituted aziridines (I) and thioacetamide or thioformamide in the presence of perchloric acid (4). Moderate yields of purified products were obtained from these reactions using hexamethylphosphoric triamide as solvent. No other solvent was tried. Crystalline products were not obtained in this reaction with 1-aziridineethanol, 1-aziridinepentanol (5) and 1-[4-(*p*-methoxyphenyl)butyl]aziridine (6).

2-Substituted 2-thiazolines (IV, R ≠ H) and the corresponding 2-thiazolinium salts (II, R_2 ≠ H) are found in large numbers in the chemical literature. 2-Unsubstituted 2-thiazolines (IV, R = H) are rare (7,8), and 2-unsubstituted 2-thiazolinium salts (II, R_2 = H) are even more rare. The single example of II (R_2 = H) is that of a crude solid product (V) isolated from a reaction of 2-thiazoline (IV, R = H) with dimethyl sulfate (9). This material was reported to be very unstable, and therefore only a partially purified degradation product (VI) was characterized. Synthetic methods leading to 2-substituted 2-thiazolinium salts (II, R_2 ≠ H) have been limited to quaternization reactions (10,11) using reactive alkylating agents. The apparent instability of 2-unsubstituted 2-thiazolinium salts (II, R_2 = H) limits the usefulness of vigorous alkylation techniques in this series. It is therefore significant that the present study has provided a facile route to 2-thiazolinium salts (II). It has been found further that thioformamide can be employed in the reaction to give the heretofore elusive 2-unsubstituted 2-thiazolinium salts (II, R_2 = H). The selection of nitrogen substituents was based on an extensive study in these laboratories of substituted *S*-2-aminoethyl hydrogen thiosulfates as antiradiation agents (12). Other workers have reported the synthesis and antiradiation properties of 2-thiazolines (13) and 2-thiazolinium salts (11) with 2-substituents in all cases. Some of the 2-thiazolines possessed antiradiation properties. All com-



II

IV



V

$CH_3SCH_2CH_2N(CH_3)CHO$

VI

TABLE I

Stability of 2-Thiazolinium Salts IIc and IId as a Function of *p*H

	Half-life (a)						
No.	*p*H 0	*p*H 1	*p*H 3	*p*H 5	*p*H 7	*p*H 9	*p*H 10
IIc (R_2 = H)	13 hrs.	2 hrs. (b)	15 min.	9.5 min.	24 sec. (c)	<5 sec. (c)	(d)
IId (R_2 = Me)	460 hrs.	350 hrs. (b)	140 hrs.	67 hrs.	4.2 hrs.	5 min.	<5 sec.

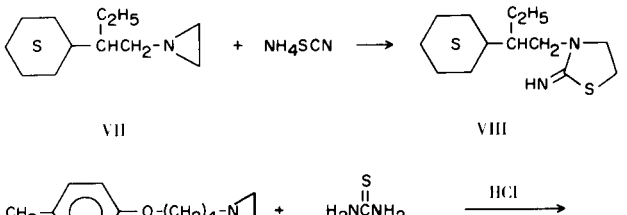
(a) Half-life values were determined spectrophotometrically in 10% aqueous methanol, except for 2 cases using 25% methanol. (b) Straight-line plots were obtained in all cases except at *p*H 1. With IIc, the semi-log plot of percent intact compound versus time dropped off rapidly at first, and then gradually became almost tangential to the 50% decomposition line at 2 hours. After this time it decomposed in normal straight-line mode. With IId at *p*H 1, the semi-log plot was curved also, but to a much smaller degree. (c) 25% aqueous methanol for solubility. (d) Hydrolysis was too rapid for measurement.

pounds described in this report were inactive as antiradiation agents (14).

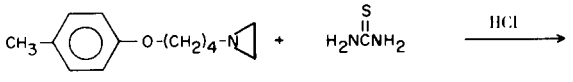
The 2-thiazoline structure has been found in a number of biologically important compounds (15). Much attention, therefore, has been given to the properties of 2-thiazolines, including the kinetics of hydrolysis which provide rationales for the behavior of this system in compounds of biological interest (15,16). In alkaline solvents, 2-substituted 2-thiazolines undergo general base catalysis to *N*-acyl-2-aminoethanethiols. In acid, analysis of kinetic data is more complex, but *S*-acyl-2-aminoethanethiols have been proposed as end products (15,16).

A study of the hydrolytic breakdown of IIc and IId gave data (Table I) consistent with the earlier work (17, 18). The 2-unsubstituted 2-thiazolinium salt (IIc) is considerably more labile than the 2-methyl analog (IId) over the entire *p*H range. The relative stability of the 2-methyl derivative *versus* the unsubstituted compound varies from 35:1 in 1 *N* hydrochloric acid to 630:1 at *p*H 7. In alkaline media the stabilities are not precise because both salts hydrolyzed rapidly. The very weak ultraviolet absorption of decomposed material contrasts with the relatively intense absorption ($\epsilon > 8000$) of the intact salts, giving precise and reproducible data.

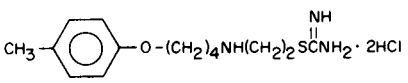
Two more examples of reactions using 1-substituted aziridines in cases previously limited to ethylenimines were explored. Thus, a 2-iminothiazolidine (VIII) (19,20) was isolated in a reaction of 1-(2-cyclohexylbutyl)aziridine (VII) with ammonium thiocyanate, and reaction of thiourea with 1-[4-(*p*-tolyloxy)butyl]aziridine (IX) resulted in 2-thio-2-[[2-[[4-(*p*-tolyloxy)butyl]amino]ethyl]pseudourea dihydrochloride (X) (21).



VII VIII

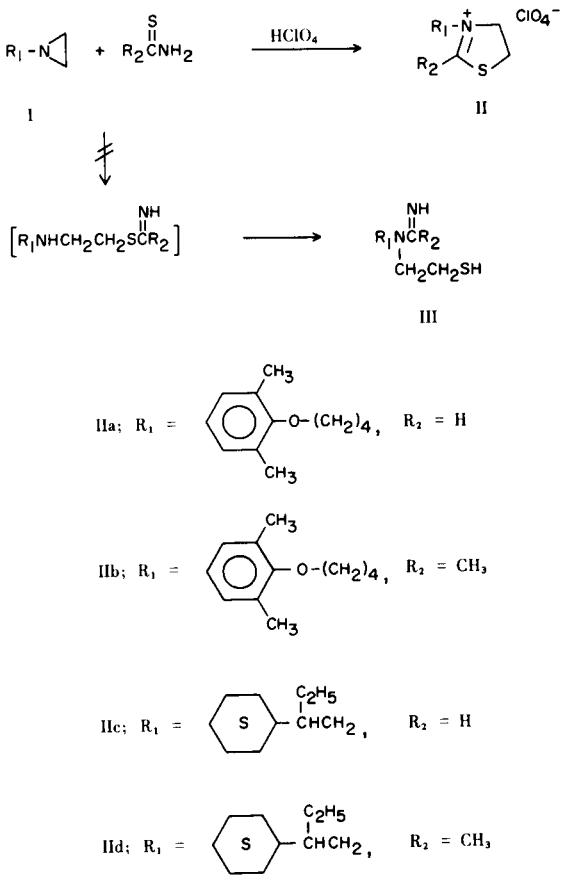


IX



X

SCHEME I



Use of 1-substituted aziridines in ring-opening reactions, previously applied only to 1-unsubstituted aziridines, has given expected products when thiocyanate ion or thiourea was the nucleophile. Acid-catalyzed ring-opening of 1-substituted aziridines with thioformamide and thioacetamide resulted in a method for preparing 2-unsubstituted 2-thiazolinium compounds in addition to another synthesis of 2,3-disubstituted thiazolinium salts. The new procedure avoids the vigorous alkylation techniques normally required to prepare quaternary salts. The method is convenient in the case of 2,3-disubstituted 2-thiazolinium salts, and it is possibly the only practical route yet developed for 2-unsubstituted 2-thiazolinium salts. A consideration of the importance of the 2-thiazoline structure in biological systems and the large differences in stability between the 2-unsubstituted and 2-substituted 2-thiazolinium salts may lead by means of this synthetic development to compounds having unique biological properties.

EXPERIMENTAL (22)

3-[4-(2,6-Xylyloxy)butyl]-2-thiazolinium Perchlorate (IIa).

To a well stirred solution of 12 g. (0.055 mole) of 1-[4-(2,6-xylyloxy)butyl]aziridine (23) and 7.0 g. (0.11 mole) of thioformamide in 60 ml. of hexamethylphosphoric triamide cooled to -15° was slowly added dropwise 30 ml. of 71% perchloric acid. The temperature was maintained below -10° during the addition. The ice bath was removed and the solution was stirred for 3 hours at room temperature. 1-Butanol (100 ml.) was added and the resulting mixture was chilled overnight to give crystalline product. The solid was separated and washed with ether, a small volume of water, and again with ether. Two recrystallizations from absolute ethanol gave 6.7 g. (33%) of IIa: m.p. 114-117°; ir (potassium bromide) 1625 cm^{-1} ($C{=}N^+$); nmr (DMSO-d_6) δ 9.67 ppm (s, 1, S-C*H*=N^+).

Anal. Calcd. for $C_{15}H_{22}ClNO_5S$: C, 49.50; H, 6.09; Cl, 9.75; N, 3.85; S, 8.81. Found: C, 49.62; H, 5.91; Cl, 9.89; N, 3.95; S, 8.92.

2-Methyl-3-[4-(2,6-xylyloxy)butyl]-2-thiazolinium Perchlorate (IIb).

Reaction of 4.0 g. (0.018 mole) of 1-[4-(2,6-xylyloxy)butyl]-aziridine, 2.7 g. (0.036 mole) of thioacetamide, and 1.0 ml. of 71% perchloric acid in 20 ml. of hexamethylphosphoric triamide under the conditions used for IIa gave 4.5 g. (67%) of IIb, m.p. 118-120°. Recrystallization from 1-butanol, water, and again from 1-butanol gave 1.4 g. (21%) of IIb as glistening platelets: m.p. 120-123°; ir (potassium bromide) 1620 cm^{-1} ($C{=}N^+$); nmr (deuteriochloroform) δ 2.74 ppm (s, 3, C*H*$_3$C=N^+); uv max (methanol) 267 nm (ε, 8240).

Anal. Calcd. for $C_{16}H_{24}ClNO_5S$: C, 50.86; H, 6.40; N, 3.71. Found: C, 50.94; H, 6.45; N, 3.48.

3-(2-Cyclohexylbutyl)-2-thiazolinium Perchlorate (IIc).

Reaction of 10 g. (0.055 mole) of 1-(2-cyclohexylbutyl)-aziridine (23), 7.0 g. (0.11 mole) of thioformamide, and 30 ml. of 71% perchloric acid in 60 ml. of hexamethylphosphoric triamide under the conditions used for IIa gave solid product after the addition of 150 ml. of 1-butanol. The crude product was taken up in chloroform and the mixture was filtered to remove some insoluble material. The chloroform filtrate was concentrated to dryness under vacuum, and the residue was recrystallized twice from absolute ethanol to give 4.7 g. (26%) of IIc: m.p. 137-140°; ir (potassium bromide) 1612 cm^{-1} ($C{=}N^+$); nmr (deuteriochloroform) δ 9.30 ppm (s, 1, S-C*H*=N^+).

Anal. Calcd. for $C_{13}H_{24}ClNO_4S$: C, 47.91; H, 7.42; Cl, 10.88; N, 4.30; S, 9.84. Found: C, 48.17; H, 7.34; Cl, 11.08; N, 4.19; S, 10.00.

3-(2-Cyclohexylbutyl)-2-methyl-2-thiazolinium Perchlorate (IId).

Reaction of 15 g. (0.082 mole) of 1-(2-cyclohexylbutyl)-aziridine, 12.8 g. (0.17 mole) of thioacetamide, and 50 ml. of 71% perchloric acid in 100 ml. of hexamethylphosphoric triamide under the conditions used for IIa gave 10.2 g. of crude product. One recrystallization from 1-butanol followed by two recrystallizations from absolute ethanol gave 7.4 g. (27%) of IId: m.p. 113-116°; ir (potassium bromide) 1610 cm^{-1} ($C{=}N^+$); nmr (deuteriochloroform) δ 2.59 ppm (s, 3, C*H*$_3$C=N^+); uv max (methanol) 268 nm (ε, 8330) (24). The uv absorption at 268 nm disappears on addition of strong base, an observation consistent with the known susceptibility to ring opening of 2-thiazolines in the presence of base (16b).

Anal. Calcd. for $C_{14}H_{26}ClNO_4S$: C, 49.46; H, 7.71; Cl, 10.43; N, 4.12; S, 9.43. Found: C, 49.42; H, 7.45; Cl, 10.73; N, 4.21; S, 9.56.

A 0.2-g. sample of IId was dissolved in 100 ml. of 50% aqueous methanol containing *ca.* 1 ml. of 1 *N* sodium hydroxide. The solution, immediately giving a strong nitroprusside test for thiol, was allowed to stand for 10 minutes before adding 0.2 ml. of 30% hydrogen peroxide. The nitroprusside test for thiol was then negative, and the mixture was concentrated under vacuum to remove the methanol. The product was extracted into ether, the extract was dried over magnesium sulfate and concentrated to give 0.1 g. (66%) of oily residue; ir (liquid film) 1650 cm^{-1}, indicating a simple amide. Thus, the structure of IId was substantiated because it is known (16b) that 2-thiazolinium salts undergo base-catalyzed hydrolysis to give *N*-acyl-2-aminoethanethiols. In this case the thiol was oxidized to disulfide for ease of handling.

3-(2-Cyclohexylbutyl)-2-iminothiazolidine (VIII).

A mixture of 1.3 g. (0.016 mole) of ammonium thiocyanate and 3 g. (0.016 mole) of 1-(2-cyclohexylbutyl)aziridine in 10 ml. of hexamethylphosphoric triamide was heated in a steam bath for 24 hours. The mixture was poured into 150 ml. of saturated sodium bicarbonate, and the product was extracted with 3 30-ml. portions of ether. The combined extracts were dried over magnesium sulfate and then treated with hydrogen chloride gas, precipitating a cream-colored solid. The crude material was recrystallized from 2-propanol to give 0.6 g. (14%) of VIII, m.p. 251-253° dec.

Anal. Calcd. for $C_{13}H_{24}N_2S{\cdot}HCl$: C, 56.39; H, 9.10; N, 10.12; S, 11.59. Found: C, 56.58; H, 9.15; N, 10.19; S, 11.53.

Compound VIII was synthesized independently, using a method of Klayman and Milne (25), from 5.5 g. (0.03 mole) of S-2-[(2-cyclohexylbutyl)amino]ethyl hydrogen thiosulfate (12), 1.5 g. (0.03 mole) of sodium cyanide, and 1.2 g. (0.03 mole) of sodium hydroxide in 60 ml. of water. The crude product as the hydrochloride salt was recrystallized from 2-propanol acetonitrile to give 2.8 g. (33%) of VIII, m.p. 253-254° dec. The ir spectra of the two preparations were identical.

2-Thio-2-[[2-[[4-(*p*-tolyloxy)butyl]amino]ethyl]pseudourea Dihydrochloride (X).

A solution containing 5.5 g. (0.07 mole) of thiourea and 15 g. (0.07 mole) of 1-[4-(*p*-tolyloxy)butyl]aziridine (23) in 250 ml. of

absolute ethanol was treated by a very slow dropwise addition at 5-10° of 48 ml. of 5.2 *N* hydrogen chloride in 2-propanol. The mixture was stirred in the cold for 2 hours after complete addition of the acid. The solvent was removed under reduced pressure and the solid residue was triturated with 250 ml. of boiling acetonitrile. The solid was then recrystallized twice from absolute ethanol to give 5.4 g. (21%) of X, m.p. 169-171°; ir (potassium bromide) 1653 cm^{-1} (C=NH).

Anal. Calcd. for $C_{14}H_{23}N_3OS \cdot 2HCl$: C, 47.46; H, 7.12; N, 11.86; S, 9.05; SH, 0.00. Found: C, 47.24; H, 7.25; N, 11.94; S, 9.16; SH, 0.33.

Aqueous Stability of IIc and IId as a Function of *p*H.

Samples were dissolved in methanol (concentration, 0.090%) and diluted 10 times into aqueous solvent (concentration, 0.0090%) over a broad *p*H range. The ultraviolet spectrum was taken immediately upon dilution, and periodically with time. The amount of decomposition followed directly the decrease in absorption of the wavelength maximum, since hydrolysis products had no significant absorption at the initial wavelength. Spectral data taken immediately upon dilution were as follows:

No.	Solvent	λ max, nm	ε
IIc	MeOH	271	8,000
IIc	1 *N* HCl (a)	272	8,100
IId	MeOH	267	8,100
IId	1 *N* HCl (a)	267	8,300

(a) Contained 10% methanol.

Irradiation experiments showed that both IIc and IId were very resistant to visible and ultraviolet light exposure, indicating that room light would not appreciably affect the results obtained. Samples were stored at room temperature on the desk top in diffuse light. Half-life values (Table I) were obtained from semi-log plots of percent intact sample remaining *versus* time. At *p*H values where decomposition proceeded rapidly, spectrophotometric readings were taken at minimum time after dilution (*ca.* 20 seconds), followed by readings at short time intervals.

Acknowledgment.

The authors are especially indebted to Dr. J. R. Dice for encouragement and advice, and to Mrs. Carola H. Spurlock for some of the spectrophotometric data. Microanalyses were performed by Mr. C. E. Childs and associates, and nuclear magnetic resonance and infrared spectra were obtained by Mr. R. B. Scott and Mr. E. J. Schoeb. Miss Marie M. Grenan of Walter Reed Army Institute of Research performed the antiradiation tests, and we are grateful to Dr. D. L. Klayman of that Institute for helpful discussions.

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