2500-cm^{-1} regions (OH, NH), and at 1720 (CO_2H), 1635 (amide-I), and 1565 cm^{-1} (amide-II).

Anal. Calcd for $C_{12}H_{21}NO_8$ (307.3): C, 46.90; H, 6.89; N, 4.56. Found: C, 47.00; H, 7.02; N, 4.64.

Registry No.—2, 14001-79-7; 3, 13942-26-2; 4, 13942-32-0; 5, 14001-80-0; 6, 13942-28-4; 7, 14001-81-1; 8, 14038-36-9; 9, 13942-29-5; 10, 13942-30-8; 11, 13978-01-3; 12, 13942-31-9; 13, 13942-32-0; 15, 14001-82-2; 16, 14001-83-3; 17, 13942-33-1; 19, 4603-73-0; 20, 13942-35-3; 21, 13942-36-4.

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Rearrangments of 2-(Aminoalkylthio)-2-thiazolines and -5,6-dihydro-4H-1,3-thiazines

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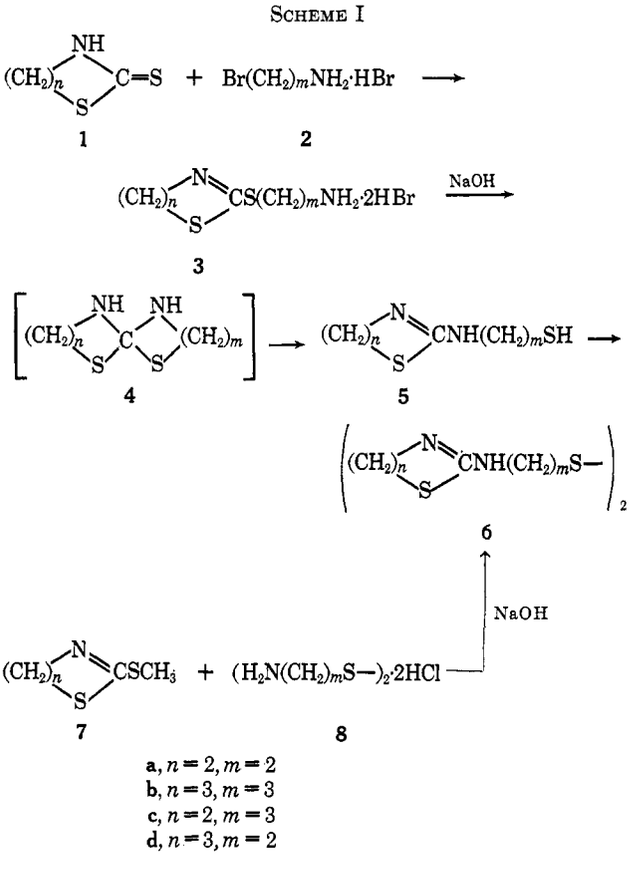
Treatment of 2-(3-aminopropylthio)-5,6-dihydro-4H-1,3-thiazine dihydrobromide (**3b**) with base yielded compound **9** by an intermolecular reaction, in addition to disulfide **6b** by rearrangement. The same amine dihydrobromide (**3c**), containing a thiazoline ring, was obtained from the aminopropylation of 2-thiazolidinethione and the aminoethylation of tetrahydro-2H-1,3-thiazine-2-thione. On rearrangement it afforded the disulfide with the five-membered heterocyclic ring, **6c**. The latter was also obtained both from the reaction of 2-methylthio-2-thiazoline with 3,3′-dithiobispropylamine and from 2-methylthio-5,6-dihydro-4H-1,3-thiazine with 2,2′-dithiobisethylamine. In rearrangements that may involve such an intermediate as **4c**, the product containing the five-membered ring is preferentially obtained.

The rearrangement of 2-(2-aminoethylthio)-2-thiazoline to 2-(2-mercaptoethylamino)-2-thiazoline through a postulated bicyclic intermediate, analogous to that proposed by Doherty, *et al.*,[1] for the conversion of 2-(2-aminoethyl)-2-thiopseudourea (AET) to 2-mercaptoethylguanidine, has been reported.[2] Similar reactions involving derivatives of 2-oxazolines, in which rearrangement can proceed through a bicyclic intermediate, have been described.[3] In the present paper the application of rearrangements of this kind to six-membered heterocyclic systems and to compounds with longer side chains is considered.

2-(3-Aminopropylthio)-5,6-dihydro-4H-1,3-thiazine dihydrobromide (**3b**) was prepared by the aminopropylation of tetrahydro-2H-1,3-thiazine-2-thione (**1b**) with 3-bromopropylamine hydrobromide. Treatment of the amine dihydrobromide with sodium hydroxide afforded two crystalline products, one of which precipitated quite rapidly. The properties of the second product, which separated slowly from the reaction mixture, indicated that it was the disulfide (**6b**) of 2-(3-mercaptopropylamino)-5,6-dihydro-4H-1,3-thiazine (**5b**), the mercaptan that would be obtained by rearrangement of **3b** through the bicyclic intermediate **4b**. The identity of the disulfide was established by its synthesis from 2-methylthio-5,6-dihydro-4H-1,3-thiazine (**7b**) and 3,3′-dithiobispropylamine dihydrochloride (**8b**) (see Scheme I).

The product that precipitated rapidly on treatment of **3b** with sodium hydroxide was found to be a base, which formed a dipicrate and which remained unchanged on further exposure to sodium hydroxide. Its infrared spectrum showed strong bands at 6.12 and 6.28 μ comparable to strong absorptions in both 2-methylamino-5,6-dihydro-4H-1,3-thiazine (6.10 μ, N=CN)

SCHEME I



and in 2-methylthio-5,6-dihydro-4H-1,3-thiazine (6.26 μ, N=CS).[4] The nmr spectrum indicated that the molecule contained six methylene groups adjacent to nitrogen or sulfur (set of signals from τ 6.1 to 7.1) and three methylene groups enclosed by methylenes (separate set of signals from τ 7.8 to 8.4). These observations and the analytical data demonstrated that

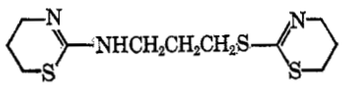
(1) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957).

(2) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *J. Org. Chem.*, **26**, 1666 (1961).

(3) (a) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *ibid.*, **28**, 1308 (1963); (b) *ibid.*, **29**, 2172 (1964).

(4) Similarly, in 2-thiazolines and 2-oxazolines[2,3] the C=N absorption is characteristically at higher wavelength in 2-alkylthio than in 2-alkylamino derivatives.

the compound was 5,6-dihydro-2-[3-(5,6-dihydro-4H-1,3-thiazin-2-ylthio)propylamino]-4H-1,3-thiazine (**9**), which can be formed from the reaction of two molecules of **3b**.



9

The formation of two products, in approximately equal yield, from **3b** on treatment with alkali is in contrast to the result obtained with 2-(2-aminoethylthio)-2-thiazoline dihydrobromide (**3a**) under similar conditions.[2] In the latter case only the rearrangement product, **6a**, was obtained in high yield. This difference can be accounted for by the greater ease of ring closure to the intermediate **4a** by the shorter side chain of **3a**[5] and the consequent smaller opportunity for the competing reaction to occur.

2-Thiazolidinethione (**1a**) reacted readily with 3-bromopropylamine hydrobromide to give a crystalline amine dihydrobromide. However, the same dihydrobromide was obtained from the reaction of tetrahydro-2H-1,3-thiazine-2-thione (**1b**) and 2-bromoethylamine hydrobromide. That this product was the five-membered heterocyclic derivative, 2-(3-aminopropylthio)-2-thiazoline dihydrobromide (**3c**),[6] rather than the isomeric six-membered heterocycle (**3d**) was demonstrated by its nmr spectrum. The spectrum showed an A_2B_2 pattern centered at τ 5.85 for the methylene groups adjacent to nitrogen and sulfur in the ring that was the same as the patterns for these groups in the spectra of 2-methylthio-2-thiazoline hydroiodide[7] and 2-(2-aminoethylthio)-2-thiazoline dihydrobromide (**3a**).[2] The chemical shifts for the corresponding methylene groups in the spectra of the analogous six-membered heterocycles are at higher field.

The amine **3c** can result from the reaction of tetrahydro-2H-1,3-thiazine-2-thione and 2-bromoethylamine hydrobromide by rearrangement of the aminoethylation product (**3d**) through the intermediate **4c**. This reaction represents the first instance observed in this work in which an amine of type **3** is obtained as a rearrangement product and it is comparable to the conversion of AET to 2-amino-2-thiazoline, rather than to 2-mercaptoethylguanidine, at pH 3.5.[1]

Treatment of 2-(3-aminopropylthio)-2-thiazoline dihydrobromide (**3c**) with 2 equiv of sodium hydroxide afforded a good yield of a disulfide of type **6**. Despite the several disulfides that might potentially be formed from the mercaptans produced in the rearrangement, thin layer chromatography indicated that the precipitate from the reaction was substantially a single substance and its structure was clearly revealed by comparison of its nmr spectrum with the spectra of 2-methylamino-2-thiazoline and 2-methylamino-5,6-dihydro-4H-1,3-thiazine. The same A_2B_2 pattern (centered at τ 6.32) for the methylene groups in the ring is contained in the spectra of 2-methylamino-2-thiazoline, the five-membered heterocyclic disulfide **6a**, and the rearrangement product; the spectra of the analogous six-membered heterocyclic compounds do not show this pattern. The rearrangement product is thus the disulfide (**6c**) of 2-(3-mercaptopropylamino)-2-thiazoline. Other spectral data (nmr and ultraviolet) are consistent with the assignment of the thiazoline structure.

The disulfide containing a thiazoline ring (**6c**) was obtained not only from the reaction of 2-methylthio-2-thiazoline (**7a**) with 3,3′-dithiobispropylamine dihydrochloride (**8b**) but also from the reaction of 2-methylthio-5,6-dihydro-4H-1,3-thiazine (**7b**) with cystamine dihydrochloride (**8a**). The reactions of **7a** and **7b** with 3-aminopropanethiol hydrochloride and 2-aminoethanethiol hydrochloride, respectively, also afforded disulfide **6c**, after oxidation of the initial reaction product. Thus in the course of the reaction the mercaptan containing the six-membered ring, **5d**, has undergone rearrangement to 2-(3-mercaptopropylamino)-2-thiazoline (**5c**). Further, since disulfide **6c** with the five-membered ring is obtained from **7b** and the disulfide **8a**, mercaptan–disulfide interchange, initiated by the methyl mercaptan formed in the reaction, apparently takes place.

In the above reactions, substantially higher yields of **6c** were obtained from 2-methylthio-5,6-dihydro-4H-1,3-thiazine than from 2-methylthio-2-thiazoline, despite the involvement of a rearrangement in the first case. This is apparently a result of the fact that the methylthiothiazine reacts more readily with amines than does the methylthiothiazoline. After equivalent periods of refluxing in the reactions with the disulfides, a considerable quantity of the latter but none of the former could be recovered. The reaction of 2-methylthio-2-thiazoline with cystamine dihydrochloride, as well as its reaction with 3,3′-dithiobispropylamine dihydrochloride, afforded a low yield. The failure to obtain a product analogous to **9** from amines **3a** and **3c** on treatment with alkali may also reflect the lower reactivity of 2-alkylthio-2-thiazolines with amines.

In the rearrangements described in this paper in which the intermediacy of such a system as **4c** may be involved, it is apparent that the product containing the five-membered ring is preferentially formed. This may be due primarily to the slower rate of recyclization of the compounds with the longer side chains[5] (mercaptopropylamino or aminopropylthio) and their consequent more rapid removal from the reacting medium (as disulfide or amine dihydrobromide), rather than to any substantial difference in the stability of the five- and six-membered heterocyclic rings of the proposed intermediate.

Experimental Section[8]

2-(3-Aminopropylthio)-5,6-dihydro-4H-1,3-thiazine Dihydrobromide (3b).—A solution of 2.66 g (0.02 mole) of tetrahydro-

(5) For a discussion of comparative ease of ring formation and ring stability, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, p 198; also, E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 114.

(6) After completion of this work, the preparation of this compound from 2-thiazolidinethione and 3-bromopropylamine hydrobromide by L. V. Pavlova and F. Yu. Rachinskii [*Biol. Aktivn. Soedin., Akad. Nauk SSSR*, 186 (1965); *Chem. Abstr.*, **63**, 18068 (1965)] was called to our attention. The abstract reports that the compound was found to undergo the transguanylation reaction but does not describe the product.

(7) A. F. McKay, D. J. Whittingham, and M.-E. Kreling, *J. Am. Chem. Soc.*, **80**, 3339 (1958).

(8) Melting points were taken in capillary tubes in a Hershberg apparatus. The nmr spectra were determined at 60 Mc with a Varian Model A-60 spectrometer; deuterium oxide was employed as a solvent for the salts with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard, and deuteriochloroform with tetramethylsilane as a standard was used for all other compounds. Plates of silica gel G were used for thin layer chromatography and the spots were visualized with iodine vapor.

2H-1,3-thiazine-2-thione[9] and 4.38 g (0.02 mole) of 3-bromopropylamine hydrobromide in 80 ml of isopropyl alcohol was refluxed for 3 hr. The mixture was cooled and the supernatant was decanted from the partially solid precipitate. Treatment of the precipitate with 70 ml of hot ethanol afforded 4.31 g (61%) of solid, mp 172–175°. Crystallization from 540 ml of absolute ethanol gave 2.58 g of colorless needles, mp 176–178°.

Anal. Calcd for $C_7H_{16}Br_2N_2S_2$: C, 23.87; H, 4.58; N, 7.96. Found: C, 23.95; H, 4.56; N, 7.97.

The nmr spectrum contained signals for CH_2N and CH_2S in the ring at τ 6.25 and 6.60, comparable to those in the spectrum of 2-methylthio-5,6-dihydro-4H-1,3-thiazine hydroiodide.[7] The dipicrate precipitated from ethanol as yellow needles, mp 163–165°.

Anal. Calcd for $C_{19}H_{20}N_8O_{14}S_2$: C, 35.19; H, 3.11; N, 17.28. Found: C, 35.30; H, 3.14; N, 16.95.

2,2′-[Dithiobis(trimethyleneimino)]bis[5,6-dihydro-4H-1,3-thiazine] (6b). A. By Rearrangement of 3b.—To a solution of 400 mg (1.14 mmole) of **3b** in 4 ml of water was added 2.3 ml of 1 *N* sodium hydroxide in an atmosphere of nitrogen. A crystalline precipitate began to form in a few minutes. After 15 min the mixture was placed in an ice bath and after 35 min it was filtered. An additional 1.5 ml of 1 *N* sodium hydroxide was added to the filtrate and an oily precipitate that gradually solidified separated on standing in the air at room temperature for 6–7 hr and at 5° for 15 hr. Filtration gave 79.5 mg (37%) of a colorless solid, mp 86–88°. Thin layer chromatography (ethanol–29% ammonium hydroxide, 10:1) demonstrated that separation of this product from the precipitate that separated rapidly was essentially complete. Crystallization from aqueous acetone afforded 59.6 mg of colorless crystals: mp 87–89°; $\lambda_{max}^{H_2O}$ 225 mμ (ε 26,100); $\lambda_{max}^{CHCl_3}$ 6.12 μ (N=CN).

Anal. Calcd for $C_{14}H_{26}N_4S_4$: C, 44.41; H, 6.92; N, 14.80. Found: C, 44.32; H, 6.95; N, 14.71.

The nmr signals for CH_2N and CH_2S in the ring are located at τ 6.40 and 6.95, as in the spectrum of 2-methylamino-5,6-dihydro-4H-1,3-thiazine. The dipicrate was obtained as small yellow crystals, mp 180–182°, from ethanol.

Anal. Calcd for $C_{26}H_{32}N_{10}O_{14}S_4$: C, 37.31; H, 3.86; N, 16.74. Found: C, 37.30; H, 3.88; N, 16.62.

B. From 2-Methylthio-5,6-dihydro-4H-1,3-thiazine (7b).—3,3′-Dithiobispropylamine dihydrochloride (**8b**), mp 232–233.5° (lit.[10] mp 220–222°), was prepared by oxidation of 3-aminopropanethiol[11] with iodine. A solution of 580 mg (3.94 mmoles) **7b**[7] and 500 mg (1.97 mmoles) of **8b** in 45 ml of methanol was refluxed for 24 hr. Removal of the solvent under reduced pressure afforded 983 mg of oily concentrate. A 416-mg portion of the concentrate was dissolved in 20 ml of water and, after clarification of the slightly cloudy solution by ether extraction, 2 ml of 10% sodium hydroxide was added. The viscous precipitate was extracted into chloroform and the chloroform solution was washed with water, dried, and concentrated. Crystallization of the concentrate from aqueous ethanol yielded 220 mg (70%) of product, mp 82–85°. The colorless crystals, mp 87.5–89.5°, obtained by recrystallization from aqueous acetone were identical (mixture melting point, infrared spectrum) with those obtained from the rearrangment of **3b**. The picrates of the samples were also identical.

5,6-Dihydro-2-[3-(5,6-dihydro-4H-1,3-thiazin-2-ylthio)propylamino]-4H-1,3-thiazine (9).—The crystals (90.7 mg, 55%) that separated rapidly on treatment of **3b** with base melted at 105–108°. Crystallization from heptane–ethyl acetate gave 59.4 mg of colorless glistening plates, mp 107–109°.

Anal. Calcd for $C_{11}H_{19}N_3S_3$: C, 45.64; H, 6.62; N, 14.52; S, 33.23. Found: C, 45.85; H, 6.52; N, 14.40; S, 33.00.

The dipicrate crystallized from ethanol as fine yellow needles, mp 161–163°.

Anal. Calcd for $C_{23}H_{25}N_9O_{14}S_3$: C, 36.94; H, 3.37; N, 16.86; S, 12.86. Found: C, 37.04; H, 3.40; N, 16.82; S, 12.75.

In another trial of this reaction, carried out on 1.00 g of **3b** in 12 ml of water, a 49% yield of **9** and 48% yield of **6b** were obtained. The relatively higher yield in this case of the product (**6b**) of the intramolecular reaction might be the result of the somewhat more dilute solution used.

2-(3-Aminopropylthio)-2-thiazoline Dihydrobromide (3c). A. From 2-Thiazolidinethione (1a).—When a solution of 4.76 g (0.04 mole) of **1a** and 8.76 g (0.04 mole) of 3-bromopropylamine hydrobromide in 100 ml of isopropyl alcohol was refluxed, a precipitate of fine needles began to separate in about 20 min. After 2.5 hr of refluxing, filtration afforded 6.76 g (50%) of crystalline product, mp 209–211°. Recrystallization from absolute ethanol gave small colorless needles: mp 209–211° (lit.[6] mp 193°, swelling); λ_{max}^{KBr} 6.40 μ (N=CS).[12]

Anal. Calcd for $C_6H_{14}Br_2N_2S_2$: C, 21.31; H, 4.17; S, 18.96. Found: C, 21.28; H, 4.18; S, 19.02.

The dipicrate separated from ethanol as slender yellow needles, mp 154–156°, which partially decomposed on attempted recrystallization.

Anal. Calcd for $C_{18}H_{18}N_8O_{14}S_2$: C, 34.07; H, 2.86; S, 10.11. Found: C, 33.88; H, 2.78; S, 10.36.

B. From Tetrahydro-2H-1,3-thiazine-2-thione (1b).—A solution of 1.80 g (0.0135 mole) of **1b** and 2.76 g (0.0135 mole) of 2-bromoethylamine hydrobromide in 40 ml of isopropyl alcohol was refluxed for 4 hr. The solid (2.74 g) that separated during the refluxing melted from 165 to 180°. Crystallization from absolute ethanol yielded 1.12 g (24%) of small needles, mp 207–209°. Identity of this product with the dihydrobromide obtained from **1a** was established by mixture melting point and infrared and nmr spectroscopy, as well as by comparison of the picrates.

2,2′-[Dithiobis(trimethylenimino)]bis-2-thiazoline (6c) by Rearrangement of 3c.—To a solution of 800 mg (2.36 mmoles) of **3c** in 8 ml of water was added 4.8 ml of 1 *N* sodium hydroxide. A viscous precipitate separated and solidified slowly on standing at room temperature with occasional stirring. Filtration of the cooled mixture after several days gave 329 mg (79%) of colorless solid, mp 86–89°, essentially homogeneous by thin layer chromatography (ethanol–29% ammonium hydroxide, 50:1). Crystallization from heptane–ethyl acetate yielded 279 mg, mp 91–93°, and further purification afforded flat needles: mp 92–94°; $\lambda_{max}^{CHCl_3}$ 6.14 μ(N=C N); $\lambda_{max}^{H_2O}$ 215 mμ (ε 25,100); for 2,2′-[dithiobis(dimethylenimino)]bis-2-thiazoline (**6a**), $\lambda_{max}^{H_2O}$ 215 mμ (ε 24,000).

Anal. Calcd for $C_{12}H_{22}N_4S_4$: C, 41.11; H, 6.33; N, 15.98. Found: C, 41.05; H, 6.06; N, 16.17.

The triplet for CH_2S (τ 7.23) in the nmr spectrum corresponds to the CH_2S signal in the mercaptopropylamino side chain of **6b** rather than to that in the mercaptoethylamino side chain of **6a** at τ 7.06. The dipicrate, mp 248–250°, was prepared in ethanol.

Anal. Calcd for $C_{24}H_{28}N_{10}O_{14}S_4$; C, 35.64; H, 3.49; N, 17.32. Found: C, 35.78; H, 3.40; N, 17.12.

Preparation of 6c. A. From Disulfides.—A solution of 330 mg (2.24 mmoles) of 2-methylthio-5,6-dihydro-4H-1,3-thiazine (**7b**) and 250 mg (1.11 mmoles) of 2,2′-dithiobisethylamine dihydrochloride (**8a**) in 25 ml of methanol was refluxed for 24 hr. After removal of the solvent under reduced pressure, 10 ml of water was added to the concentrate and the resulting cloudy solution was extracted with ether. Treatment of the clear aqueous solution with 2 ml of 10% sodium hydroxide gave 310 mg (80%) of colorless solid, mp 89–91.5°. Crystallization afforded 273 mg of flat needles, mp 92–94°. Comparison of this disulfide and its picrate with the products from the rearrangement of **3c** demonstrated their identity.

The ether extract of the aqueous solution of the reaction product was washed with dilute sodium hydroxide and water, dried (anhydrous sodium sulfate), and concentrated. Treatment of the concentrate with ethanolic picric acid yielded no picrate of **7b**.

After a solution of 770 mg (5.78 mmoles) of 2-methylthio-2-thiazoline (**7a**)[7] and 730 mg (2.88 mmoles) of 3,3′-dithiobispropylamine dihydrochloride (**8b**) in 40 ml of methanol had been refluxed for 24 hr, the concentrate from the reaction was worked up as above. From the aqueous solution there was obtained 187 mg (18%) of **6c**, mp 84–87°. Recrystallization gave 115 mg,

(9) Prepared from 3-aminopropanol by the method of H. Bluestone, [U. S. Patent 2,845,339 (July 29, 1958)] or more expeditiously from 3-bromopropylamine [F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.*, 243 (1943)].

(10) R. Lehmann and E. Grivsky, *Bull. Soc. Chim. Belges*, **55**, 52 (1946). The picrate of **8b** melted at 144–145.5°; mp 145–146° was reported by S. Gabriel and W. E. Lauer, *Ber.*, **23**, 87 (1890).

(11) We wish to thank Dr. Eric J. Hewitt of the Evans Research and Development Corporation, New York, N. Y., for a generous sample of 3-aminopropanethiol hydrochloride.

(12) In the spectrum of 2-(2-aminoethylthio)-2-thiazoline dihydrobromide (**3a**)[2] this absorption is at 6.44 μ, whereas for the six-membered heterocycle **3b** it is at 6.31 μ. Similarly, for the hydroiodides of the five- and six-membered heterocycles, **7a** and **7b**, these bands are at 6.42 and 6.28 μ, respectively.

mp 91–93°. From the ether extract there was recovered 833 mg (40%) of **7a** picrate.

B. From Mercaptans.—A solution of 416 mg (2.83 mmoles) of **7b** and 321 mg (2.83 mmoles) of 2-aminoethanethiol hydrochloride in 15 ml of methanol was refluxed for 4.5 hr. The oily concentrate from the solution was processed by the procedure used in A. Addition of sodium hydroxide afforded, on standing in the air, an 87% yield of disulfide **6c**. No **7b** could be recovered from the ether extract.

Direct treatment of the concentrate from the reaction with ethanolic picric acid gave **2-(3-mercaptopropylamino)-2-thiazoline (5c) picrate** as fine yellow crystals, mp 169.5–171.5°. Its infrared spectrum (KBr) showed a mercaptan band at 3.9 μ.

Anal. Calcd for $C_{12}H_{15}N_5O_7S_2$: C, 35.55; H, 3.73; S, 15.82. Found: C, 35.54; H, 3.70; S, 16.02.

From **7a** and 3-aminopropanethiol hydrochloride[11] there were obtained after 7 hr of refluxing a 54% yield of **6c** and a 14% recovery of **7a** as the picrate. The same mercaptan picrate, after purification by recrystallization from ethanol, was obtained from the reaction.

2-Methylamino-5,6-dihydro-4H-1,3-thiazine.—The method of Gabriel[13] for the preparation of 2-methylamino-2-thiazoline was used. A mixture of 20 ml of cold 30% potassium hydroxide, 30 ml of benzene, and 6.4 g (0.029 mole) of 3-bromopropylamine hydrobromide was shaken in a separatory funnel and the benzene layer was added to 1.8 g (0.025 mole) of methyl isothiocyanate. An aqueous solution of the viscous precipitate that separated during 3 hr at room temperature was treated with 30% potassium hydroxide. The precipitated oil was extracted into benzene and removal of the benzene afforded a solid. The latter was extracted with 20 ml of boiling hexane and 375 mg of long needles, mp 51–54°, was obtained on cooling. Recrystallization from hexane gave colorless needles: mp 57–58.5°; $\lambda_{max}^{CHCl_3}$ 6.10 μ (N=CN); $\lambda_{max}^{H_2O}$ 218 mμ (ε 12,100).[14]

Anal. Calcd for $C_5H_{10}N_2S$: C, 46.12; H, 7.74; N, 21.52. Found: C, 45.92; H, 7.69; N, 21.55.

The picrate crystallized from ethanol as fine yellow needles, mp 189–191°.

Anal. Calcd for $C_{11}H_{13}N_5O_7S$: C, 36.77; H, 3.65; N, 19.49. Found: C, 36.94; H, 3.49; N, 19.20.

(13) S. Gabriel, *Ber.*, **22**, 1139 (1889).

(14) The corresponding absorptions in 2-methylamino-2-thiazoline are at 6.13 μ and 211 mμ (ε 10,200).

Registry No.—**3b**, 13865-94-6; **3b** dipicrate, 13865-95-7; **3c**, 4786-92-9; **3c** dipicrate, 13865-97-9; **5c** picrate, 13865-98-0; **6b**, 13865-99-1; **6b** dipicrate, 13866-00-7; **6c**, 13866-01-8; **6c** dipicrate, 4787-04-6; **9**, 13866-02-9; **9** dipicrate, 13866-03-0; 2-methlamino-5,6-dihydro-4H-1,3-thiazene, picrate of 2-methylamino-5,6-dihydro-4H-1,3-thiazine, 13866-05-2.

Acknowledgment.—We are indebted to Carmine DiPietro of these laboratories for the microanalyses. We also wish to thank Dr. Martin G. Ettlinger for helpful discussions.

A Solvolytic Investigation of Cyclooctyl and *trans*-2-Hydroxycyclooctyl Bromides and *p*-Toluenesulfonates[1]

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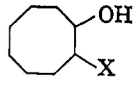
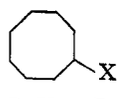
Solvolysis rates of cyclooctyl *p*-toluenesulfonate (**2T**) and bromide (**2B**) and *trans*-2-hydroxycyclooctyl bromide (**1B**) and *p*-toluenesulfonate (**1T**) have been determined in a series of solvents of varying ionizing strength. The kinetic data have been analyzed for neighboring-group, solvent, and leaving-group effects. This analysis, coupled with the partitioning of the activation parameters, suggests a parallel in mechanism between the cyclooctyl and *trans*-2-hydroxycyclooctyl derivatives. Product distribution data have been obtained for solvolysis of **1B** and **1T** in aqueous acetone and the proportions of various products exhibit some sensitivity to leaving group. Comparison with the solvolysis products of the glycol and amino alcohol suggests a product distribution sensitivity to the nature of the cationic intermediate immediately preceding product formation.

A solvolysis study of *trans*-2-hydroxycyclooctyl halides **1C** and **1B** led to the proposal that products are formed by two competing pathways, One leading largely to normal 1,2-rearrangement products and the other, largely to transannular products.[2] The alternate pathways, differing principally in the descriptions of cationic intermediates, were not specifically identified with the two groups of products, and a more detailed mechanistic investigation was needed. Because chemical kinetics is particularly useful for measuring substrate response to medium and substituent effects[3a,b] and to change in leaving group,[3c] a kinetic investigation of the solvolytic reactions of both the cyclooctyl and 2-hydroxycyclooctyl systems was undertaken. The data indicates that the reactions studied proceed through cationic intermediates and that a *trans*-2-hydroxy substituent does not alter the nature of the intermediate.



1C, X = Cl
B, X = Br
T, X = OTs



2B, X = Br
T, X = OTs

The first-order rate constants for solvolysis of **1B**, **1T**, **2B**, and **2T** in various solvents are summarized in Table I. The acetolysis reactions of **1B**, **2B**, and **1T** yielded integrated first-order rate constants that tended to decrease as the reaction progressed; consequently, the rate constant was calculated from the initial slope of a plot of log $(a - x)$ *vs.* time. All other reactions were first order in *p*-toluenesulfonate or bromide up

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(2) J. G. Trahnham and J. Schneller, *J. Am. Chem. Soc.*, **87**, 2398 (1965).

(3) (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) E. R. Thornton, "Solvolysis Mechanisms," The Ronald Press Co., New York, N. Y., 1964; (c) H. M. R. Hoffmann, *J. Chem. Soc.*, 6748, 6753, 6762 (1965).