1,1′-Phenyl-1,1′-(dithiodiethylene)diguanidine (XIX)——To *N* NaOH (32.5 ml.) was added Ⅳ (12.2 g.) and the pH of the solution was adjusted to 8.0 by the addition of *N* NaOH (1 ml.), and H_2O (130 ml.) was added to the solution to dissolve the separated solid. The clear solution was oxidized with air until SH test by Na-nitroprusside had become negative (24 hr.). The reaction mixture was evaporated *in vacuo* to leave a colorless oily residue which was extracted with iso-PrOH. Removal of the iso-PrOH left a crude XIX 2HBr (4.6 g., 48.9 %) as colorless crystals, m.p. 168～169°, which was recrystallized from iso-PrOH-iso-Pr_2O to afford XIX 2HBr, m.p. 220～225°.

In the similar way a crude XXI 2HBr (6.6 g., 89%, after one recrystallization) was obtained from Ⅶ (10.0 g.) by the air oxidation for 48 hr. And a crude XXII (6.4 g., 54.7%) was obtained from Ⅸ (14.5 g.) by the air oxidation for 58 hr.

The authors' thanks are due to Mr. M. Uoji and Miss Y. Shibanuma for IR and NMR data, and to the members of the analytical center of Research Laboratory of Tanabe Seiyaku Co., Ltd. for microanalytical data.

Summary

Ten kinds of N-substituted-2-(2-aminoethyl)thiopseudoureas (AETs) were prepared. 1′-Phenyl-AET (Ⅵ) gave 2-aminothiazoline derivative (XXIII) with one equivalent of alkali, while other AETs having at least one hydrogen atom at the amino nitrogen underwent intramolecular rearrangement to give MEGs. GEDs were prepared from these MEGs by mild oxidation.

The NMR and IR spectra of these compounds were also discussed.

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164. Tohru Hino, Katsuko Tana-ami, Kazuko Yamada, and Sanya Akaboshi : Radiation-protective Agents. Ⅱ.*1 The Transformation of 2-(2-Aminoethyl)thiopseudoureas to 2-Amino-2-thiazolines.

(*Department of Pharmaceutical Sciences, National Institute of Radiological Sciences**2)

In the preceding paper the authors described the synthesis of 2-(2-aminoethyl)-thiopseudoureas dihydrobromides (AETs) and their transguanylation reaction with a base.*1 AET was known[1] to be converted to 2-aminothiazoline hydrobromide (2-AT) in an aqueous solution *via* the same cyclic intermediate as that supposed in the case of the transguanylation.

The present paper describes the transformation of AETs described in the previous paper to 2-ATs, and discussed the effect of the substituents of AET on this transformation. 2-Aminothiazoline was obtained in good yield when AET was refluxed in an aqueous solution or a buffered solution (pH 4.5). The same transformation was also observed when its aqueous solution was kept at room temperature. The formation of 2-AT was observed by the thin-layer chromatography (TLC) after 12 hr. at room

*1 Part Ⅰ. This Bulletin, **14**, 1193 (1966).

*2 Anagawa, Chiba-shi (日野 亨, 田名網和子, 山田和子, 赤星三弥).

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

temperature and AET disappeared after 6 to 7 days. However, this transformation was inhibited by the addition of one equivalent of hydrochloric acid and AET was still found by TLC after standing of its aqueous solution at room temperature for 10 days.*3 These results supported the Doherty's proposal[1] on the mechanism of the transformation.

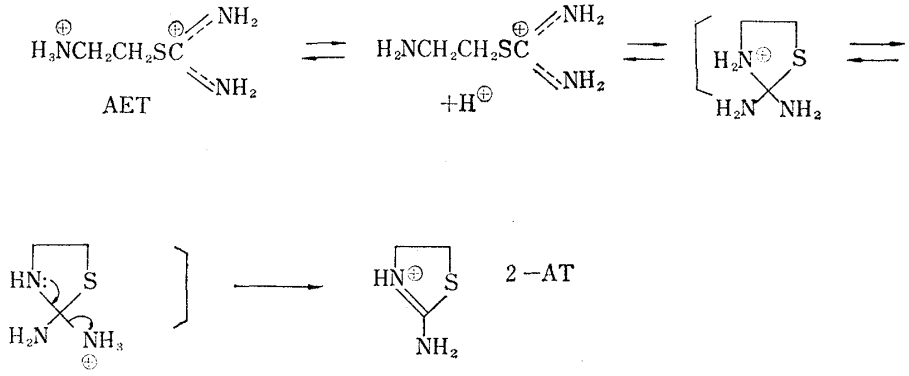


Chart 1.

In the cases of AETs which possessed a substituent at the amino nitrogen, 3-substituted 2-amino-2-thiazolines and ammonium bromide were obtained by refluxing their aqueous solutions.

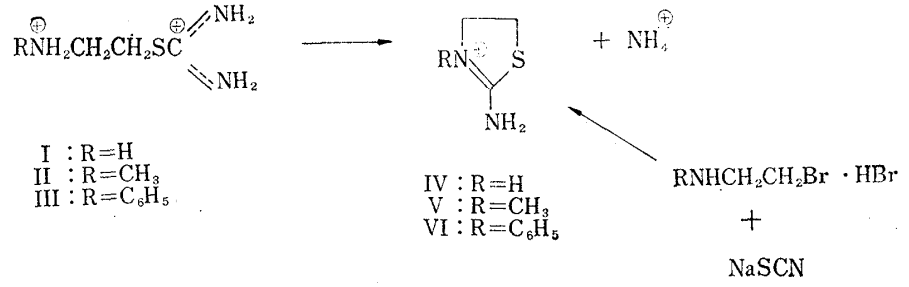


Chart 2.

The structures of V and VI were proved by the direct comparison with the authentic samples prepared by the alternative synthesis from bromoethylamine.[2] This transformation could be followed also by the nuclear magnetic resonance (NMR) spectra in deuterium oxide solution. The NMR spectra of 2-ATs are summarized in Table I. Two methylene groups in the thiazoline ring gave two separate triplets (about 3.60 and 4.10 p.p.m.) and this feature was different from that of AET*1 derivatives. The lower triplet of 2-ATs could be clearly distinguished from the A_2B_2 spectrum of AET and this made possible to estimate the ratio of AETs to the corresponding 2-ATs in the mixture.

To find out the ease of the formation of 2-ATs, deuterium oxide solutions of I, II and III were warmed respectively in a water bath for one hour and their NMR spectra were taken to integrate the signals. The ratios of AETs to 2-ATs were 0.09 for I, 0.43 for II and 0.16 for III. These results indicated the parent AET was the fastest in the formation of 2-AT, the middle was the N-phenyl derivative and N-methyl derivative was relatively slow.

In the cases of AETs having a substituent on the nitrogen atom of the thiourea, the transformation would give the mixture of products as shown in Chart 3.

*3 The same reaction was analyzed quantitatively by the spectrometric method and essentially the same result was obtained. Cf. A. Hanaki, T. Hino, S. Akaboshi: This Bulletin, in preparation.

2) *a*) W. Marckwald, O. Frobenius: Ber., **34**, 3549 (1901). *b*) S. Gabriel: *Ibid.*, **22**, 1139 (1889).

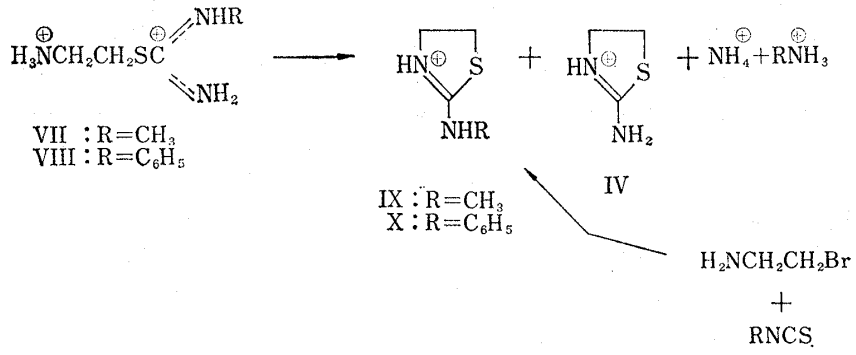
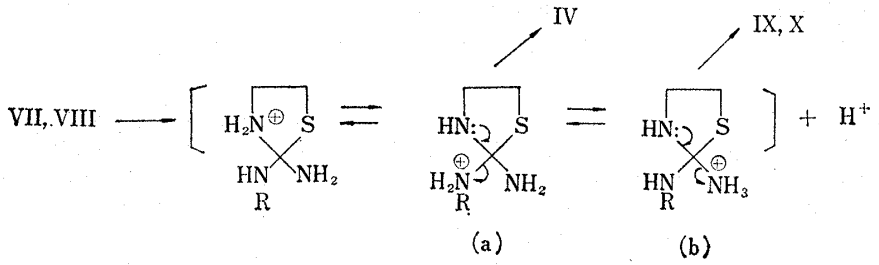


Chart 3.

Doherty[1] has reported that the mixture of 2-ATs was obtained when Ⅶ was treated with various buffered solutions, but he did not investigate further. When an aqueous solution of Ⅶ was refluxed until no more starting material was recognized, 2-methylamino-2-thiazoline (Ⅸ), and 2-amino-2-thiazoline (Ⅳ) were found in the reaction mixture. Separation of the products by the preparative TLC method, gave 2-AT (Ⅳ) as the main product and Ⅸ as the minor which was identical with the authentic sample prepared by the known method.[2] For further estimation of the ratio of the both compounds, N-methyl signals of Ⅸ and methylammonium bromide in the NMR spectrum of the crude product were utilized. The N-methyl signal of the latter which should be produced in the equimolar amount to Ⅳ was clearly separated from that of Ⅸ, and the ratio of both signals obtained indicated that the rough molar ratio of the formation of Ⅳ : Ⅸ was about 2:1.

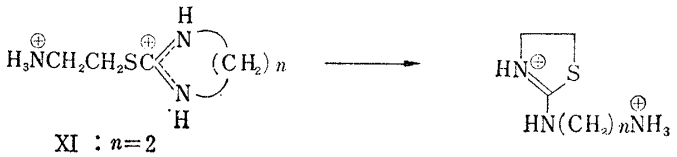
The crude product which was obtained by refluxing an aqueous solution of Ⅷ, showed the presence of both Ⅳ and X on TLC. The NMR spectrum of the crude mixture was not useful for the estimation of the ratio of the both compounds in this case. The isolation of Ⅳ and Ⅸ as free bases was carried out, utilizing the insolubility of the free base of X in water. The structure of X was proved by the alternative synthesis[3] from phenyl isothiocyanate. In contrast to the case of Ⅶ, X was the main product and the ratio of X and Ⅳ was nearly 10:1 in weight. These results were conceivable when the positive charge in the hypothetical intermediate was supposed to be mainly on the more basic nitrogen. In the case of Ⅶ the positive charge would be mainly on the methyl-substituted nitrogen (a, R=CH_3) and the nitrogen lone-pair would shift as shown in (a) to afford Ⅳ as the main product. On the other hand in the case of Ⅷ, positive charge could retain on NH (b,R=C_6H_5) and the reaction would proceed with the electron shift as shown in (b) to afford X as the main product.



3) *a*) E. Menne : Ber., **33**, 659 (1900). *b*) Y. Iwakura, A. Nabeya : Nippon Kagaku Zasshi, **77**, 773 (1956). *c*) A. S. Deutsch, P. E. Fanta : J. Org. Chem., **21**, 892 (1956). *d*) H. Najer, R. Giudicelli : Bull. soc. chim. France, **1960**, 960.

Main infrared bands of these 2-ATs are summarized in Table I and II. As the hydrobromides of 2-ATs were considered to be the cyclic thiuronium salts, their infrared spectra were similar to those of AET,*[1] though the infrared spectra of 2-ATs and the corresponding AETs were distinguishable in the wave numbers of the main bands and the fine structures. Spectral data of the free bases of 2-ATs are summarized in Table II. In V* and VI*,*[4] the C=N double bonds are fixed to an exocyclic position, and the stretching vibration of the C=N double bonds of V* and VI* in chloroform solution were observed in 1600 and 1610 cm^{-1} respectively. The C=N stretching vibration of IV*, however, appeared at higher wave number, 1640 cm^{-1}, suggesting the presence of an endocyclic C=N double bond.[4] Another evidence of the endocyclic double bond in IV* was obtained by two stretching vibrations (3520 and 3430 cm^{-1}) of free NH in dilute solution which showed NH_2 form instead of two NH. The stretching vibration of the C=N in X* was observed at 1630 cm^{-1}, and closer to that of IV*. The ultraviolet spectrum of X* showed the same absorption maximum as that of VI*, λ_{max} 257 mμ, and this would suggest that both VI* and X* have the same conjugated system, and the C=N double bond in X* would be in an endocyclic position. These results suggested that C=N double bond of IV* and X* would be in an endocyclic position. The location of the C=N double bond in IX* was not clear from the position of its stretching vibration band (1625 cm^{-1}). The NMR spectra of these free bases showed two triplets which had been shifted to higher field than those of the corresponding salts. It was rather difficult to deduce the position of the C=N double bond from the chemical shift, since the substituents at 3-position would strongly affect the chemical shift of the methylene at 4-position.*[5]

The transformation of XI and XII proceeded in a different way from previous cases, and the amine residue was not split off. On the contrary to Doherty's report that the cleavage of imidazoline ring in the hypothetical intermediate for XI was not conceivable, XIII was obtained in a good yield when a methanol-acetic acid solution of XI was kept overnight at room temperature or when its aqueous solution was refluxed.



XI : $n=2$
XII : $n=3$

XIII : $n=2$
XIV : $n=3$

The product (XIII) was clearly distinguished from the starting material and mercaptoethylguanidine derivative or its disulfide which were the other possible transformation products by the comparison of the physical properties (the melting point, infrared and NMR spectra). The presence of thiazoline ring in XIII was supported by the NMR spectrum which showed the two triplets at 3.64 and 4.06 p.p.m. similar to the other

*[4] The stared compound numbers mean the free base form of the corresponding 2-ATs.

[5] In the cases of the compounds (IV, IX*, and X*) having no substituent at 3-position signals for two methylenes in the thiazoline ring were very close each other in the chemical shift, and this suggested that the position of the C=N double bond would be in the same, an endocyclic position. And these signals were rather simple, and showed no significant indication of the presence of tautomers except the case that the speed of the equilibrium was too fast to recognize two isomers as separate signals.

4) W. Otting, F. Drwert : Chem. Ber., **88**, 1469 (1955); J. Fabian, M. Legrand, P. Poirier : Bull. soc. chim. France, **1956**, 1499; K. K. Kuz'mina, N. G. Ostroumona, Yu. V. Markova, M. N. Shchukina : Zh. Obshch. Khim., **32**, 3215 (1962) (C. A., **58**, 11341 (1963)); Yu. N. Sheinker, E. M. Peresleni, A. I. Kol'tson, N. M. Bazhenov, M. V. Vol'kensktein : Dokl. Akad. Nauk SSSR, **148**, 878 (1963) (C. A., **59**, 3746 (1963)); E. N. Persleni, Yu. N. Sheinker, N. P. Zosimova, Yu. I. Pomerantsen : Zh. Fiz. Khim., **39**, 92 (1965) (C. A., **62**, 16224 (1965)); L.C. King, E. W. Stern : J. Org. Chem., **30**, 3222 (1965).

thiazoline derivatives (see Table I). The compound, XII, transformed in the same way with XI into XIV when an aqueous solution of XII was refluxed. The NMR spectrum of XIV showed rather complicated signals at between 3 and 4 p.p.m. due to overlapping of four methylenes adjacent to nitrogen or sulfur atoms, but the signals of two methylenes in thiazoline were clearly revealed by the decoupling method (Table I). The formation of XIII was found to be more rapid than that of XIV: *i.e.*, XII was not changed while XI was mostly converted to XIII when the aqueous solutions of XI and XII were kept at room temperature for 24 hr. respectively and then refluxed for a half hour.

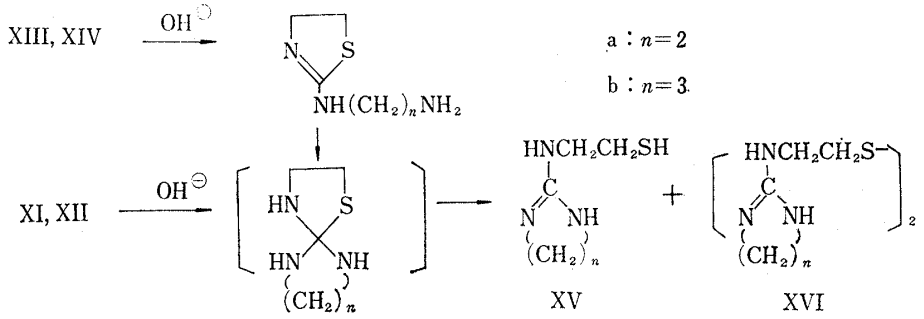


TABLE I. Infrared and Nuclear Magnetic Resonance Data of 2-ATs Salts (HBr salts)

Compound No.	IR in KBr Disk 3100 cm^{-1}	IR in KBr Disk 1700～1500 cm^{-1}	NMR c.p.s. from DSS in D_2O NCH_2CH_2S in thiazoline rings
IV	3300, 3260, 3200	1658 s, 1650 s, 1580 m	3.60(t), 4.00(t)
V	3240	1660 s, 1620 s	3.51(t), 4.11(t), 3.15(s, N-CH_3)
VI	3300	1635 s, 1572 m	3.70(t), 4.44(t), 7.4～7.7(m, phenyl)
IX	3400, 3240	1640 s, 1580 w, 1550 w	3.61(t), 4.02(t), 3.02(s, N-CH_3)
X	3150	1635 s, 1600 s, 1550 w, 1500 m	3.64(t), 4.06(t), 7.3～7.7(m, phenyl)
XIII	3260, 3200	1650 s, 1550 m	3.64(t), 4.06(t), 3.30, 3.74(two triplets, NCH_2CH_2N)
XIV	3250, 3110	1645 s, 1608 m, 1580 w, 1555 w, 1515 m	3.62(t), 4.02(t), 2.03(quintet, CCH_2C), 3.10, 3.48(two triplets, NCH_2CCH_2N)

Remarks: s, strong in IR and singlet in NMR; m, medium in IR and multiplet in NMR; w, weak; t, triplet.

TABLE II. Infrared and Nuclear Magnetic Resonance Data of 2-ATs (Free Bases)

Compound No.	IR in KBr Disk 1700～1500 cm^{-1}	IR in $CHCl_3$ solution 3200 cm^{-1}	IR in $CHCl_3$ solution 1700～1500 cm^{-1}	NMR in $CDCl_3$(c.p.s. from TMS) NCH_2CH_2S in thiazoline rings
IV	1630 s	3510 s, 3420 s, 3350 s, 3200 b,s	1640 s, 1600 sh	3.35(t), 3.96(t), 5.27(s, NH)
V	1605 s [a]	3375 m, 3250 w	1600 b, s	3.15(t), 3.58(t), 5.89(s, NH), 2.91(s, N-CH_3)
VI	1605 s, 1590 s	3380 w	1610 s, 1588 s	3.25(t), 4.07(t), 7.1～7.4(m, phenyl)
IX	1630 sh, 1615 s, 1550 m	3490 w, 3290 w, 3230 w	1625 s, 1502 w	3.33(t), 4.03(t), 4.58(s, NH), 2.93(s, N-CH_3)
X	1625 s, 1585 s	3600 m, 3450 m	1630 s, 1595 s	3.28(t), 3.82(t), 7.0～7.4(m, phenyl)

Remarks: s, strong in IR and singlet in NMR; m, medium in IR and multiplet in NMR; w, weak; t, triplet; sh, shoulder; b, broad.

a) In a liquid film

The free bases of 2-ATs (IV, V, VI, IX, and X) were stable and easily purified, though IV was known to convert to N-(2-mercaptoethyl)urea[5] by warming its alkaline solution. Free bases of XIII and XIV, however, could not be isolated as pure forms and converted to MEG derivative (XV) during the purification or on standing. The original hydrobromide (XIII) was again obtained from the crude free base of XIII by the addition of hydrobromic acid, and the crude free base gave its N-phthaloyl derivative. On standing the crude base for several days or during the purification some other compounds were observed by TLC and the NMR spectrum. In aqueous solution the change was rapid and no 2-AT (XIII) was observed by TLC after one day. From the TLC and NMR data the products were MEG (XVa) and GED (XVIa), and this was further proved by the direct comparison of the authentic sample of GED (XVIa)*1 when the mixture was oxidized with air. The similar behavior was observed in the case of XIV. Thus in cases of XIII and XIV the free bases were rather unstable and underwent a rearrangement probably *via* a spiran intermediate to afford MEG (XV) which was obtained directly from AETs (XI and XII) by an alkaline. This rearrangement was possible only in 2-ATs which were transformed from AETs without removal of an amine. The similar type of rearrangement has been reported on 2-mercaptoethylamino-oxazoline and 2-aminoethylthio-2-thiazoline.[6]

Experimental*6

2-Amino-2-thiazoline (IV)——2-AT HBr was obtained from an aqueous solution of AET (I) following Doherty's procedure, m.p. 173° (reported m.p. 175~176°[1], 172°[7], 170~171°[8]). Free base, m.p. 80~81° (reported m.p. 84~85°,[3a] 79~80°,[9] 86°[7]). Picrate, m.p. 241~243° (reported m.p. 235°[5]).

The Formation of IV from I in an Aqueous Solution at Room Temperature——An aqueous solution of AET (I, 10^{-2} molar solution) was kept at room temperature, and the reaction mixture was submitted to TLC.*7 For the first 6 hr., I was the only compound observed on TLC and the second spot corresponding to IV appeared after 12 hr., beside that of I. After standing for 150 hr. AET (I) disappeared. When an aqueous solution of I (10^{-2} molar solution containing one equivalent of HCl) was allowed to stand at room temperature, the spot corresponding to IV appeared after 75 hr., and the spot corresponding to I did not disappear even after 150 hr.

The Formation of IV in Other Solvents——a) In AcOH. AET (I, 1.5 g.) was dissolved in AcOH (210 ml.) and the solution was heated at 90° (bath temperature) for 7.5 hr. On cooling the mixture was filtered to remove some insoluble materials, and the filtrate was distilled *in vacuo* to leave a crude IV, m.p. 163~165° (1.4 g.). The crude product was recrystallized twice from AcOH, and then once from iso-PrOH to afford pure IV HBr, m.p. 171~173°, which was identical with the sample obtained above.

b) In EtOH. AET (I, 50 mg.) in EtOH (10 ml.) was refluxed for 3 hr. The reaction mixture was found to contain AET and IV by TLC.*7 After refluxing for 5 hr. the solution gave only one spot corresponding to IV by the same TLC.

2-Amino-3-methyl-2-thiazoline (V)——i) In H_2O. N-Methyl-AET (II, 10.0 g.) was dissolved in H_2O (250 ml.) and the solution was refluxed for 28.5 hr. The solvent was removed *in vacuo* to leave a white solid which was extracted with hot iso-PrOH to remove inorganic materials.

The extracts were evaporated *in vacuo* and the residual crude V HBr was recrystallized three times

*6 All melting points are uncorrected. The IR spectra were taken with a JASCO-DS-301 spectrophotometer, and the UV spectra were measured with a Perkin-Elmer 202 spectrophotometer, and the NMR spectra were measured with a Varian Associates HR-100 spectrometer.

*7 Samples were developed in a solvent system (EtOH-iso-PrOH-*N* HCl 3:3:2), on a Silica-gel plate prepared with *N* HCl instead of distilled water and the spots were detected by I_2 vapor or spraying with NaOH-sodium nitroprusside solution.

5) A. Schoberl, M. Kawohl: Angew. Chem., **63**, 268 (1951); Monatsh. Chem., **88**, 478 (1957); A. Schoberl, G. Hansen: Chem. Ber., **91**, 1055 (1958).
6) R.C. Clapp, L. Long, T. Hasselstrom: J. Org. Chem., **29**, 2172 (1964); **28**, 1308 (1963); **26**, 1666 (1961).
7) A. Schoberl, H. Kawohl, R. Hamm: Chem. Ber., **84**, 571 (1951).
8) A. Schoberl, G. Hansen: *Ibid.*, **91**, 1239 (1958).
9) L. Geodman, L.O. Ross, B.R. Baker: J. Org. Chem., **23**, 1954 (1958).

from iso-PrOH to afford V HBr (3.5 g., 45%), m.p. 160~161.5°. *Anal.* Calcd. for $C_4H_{11}N_3SBr$: C, 24.37; H, 4.60; N, 14.21; S, 16.27; Br, 40.54. Found: C, 24.50; H, 4.44; N, 14.12; S, 16.05; Br, 40.59. This sample was identical with the one obtained from N-(2-bromoethyl)methylamine HBr and NaSCN following Marckwald's procedure[2b] in which chloromethylmethylamine was used instead of the bromide.

Picrate: Yellow crystals, m.p. 202~205° (reported[2b] m.p. 200~203°). Free base was obtained as an oil from the hydrobromide, and was purified by column chromatography.

ii) In AcOH——N-Methyl AET (II, 1.0 g.) was dissolved in AcOH (85 ml.), and after being kept at room temperature for 4 days the solution was heated at 80° for 14 hr. After cooled, the solvent was evaporated and the residue (1.0 g.) was treated with AcOH to remove insoluble inorganic materials and the AcOH was again evaporated *in vacuo* to leave a white solid which was recrystallized from iso-PrOH to give V HBr, m.p. 160~160.5°, which showed no depression of the melting point on admixture with the sample obtained above. The both samples were also identical in IR spectra and TLC.

iii) From IV——2-AT (IV free base, 102 mg.) and CH_3I (222 mg.) was dissolved in acetone (10 ml.) and the mixture was kept at room temperature overnight. The crystals (174 mg.) were collected and recrystallized from iso-PrOH to afford V HI, m.p. 162~163° (reported m.p. 159~160°[2b]). The picrate prepared from this hydroiodide, m.p. 204~205°, showed no depression of the melting point on admixture with the sample obtained above. The IR spectra of both samples were also identical. When IV in DMF solution was treated with CH_3I, V was also obtained. A new spot was also observed on TLC in the both reaction mixture, but it could not be isolated as a pure form.

2-Amino-3-phenyl-2-thiazoline (VI)——i) An aqueous solution (20 ml.) of III (1.0 g.) was refluxed for 30 hr. until SH-test by Na nitropruside had become negative. The solvent was evaporated *in vacuo*, and the residue (0.7 g.), m.p. 191~192°, was recrystallized from iso-PrOH-iso-Pr_2O to afford VI HBr, m.p. 221~222°. *Anal.* Calcd. for $C_9H_{11}N_2SBr$: C, 41.71; H, 4.28; N, 10.81; S, 12.37; Br, 30.83. Found: C, 41.59; H, 4.02; N, 10.59; S, 12.20; Br, 30.14. UV: $\lambda_{shoulder}^{95\%\ EtOH}$ 240 mμ (ε: 7500) The mixed melting point test and IR spectra proved this hydrobromide to be identical with the sample obtained by the following method ii). Free base: From the above HBr (1.3 g.) a crude free base (0.73 g.), m.p. 47~48°, was obtained by the usual method and was recrystallized from iso-Pr_2O to afford pure free base, m.p. 54~54.5°. *Anal.* Calcd. for $C_9H_{10}N_2S$: C, 60.64; H, 5.65 N, 15.72; S, 17.99. Found: C, 60.61; H, 5.67; N, 16.05; S, 17.62. UV: $\lambda_{max}^{95\%\ EtOH}$ 257 mμ (ε: 7300). Picrate: Yellow crystals, m.p. 166~167° (from water). *Anal.* Calcd. for $C_{15}H_{13}N_5O_7S$: C, 44.23; H, 3.22; N, 17.19; S, 7.87. Found: C, 44.18; H, 3.15; N, 17.14; S, 7.79.

ii) From bromoethylaniline[2]——To a warm aqueous solution of bromoethylaniline HBr (8.4 g. in H_2O 10 ml.) was added NaSCN (2.7 g.) in H_2O (5 ml.). The mixture was refluxed for 1.5 hr., and the solvent was evaporated *in vacuo* to leave a solid which was extracted with hot iso-PrOH. The solvent was evaporated to afford a crude VI HBr (5.9 g., 76%), m.p. 221~223°, which was recrystallized from iso-PrOH to give VI HBr, m.p. 221~222°.

Formation of 2-ATs from AETs in D_2O——Each of 50 mg. of I, II, and III was dissolved in 0.5 ml. D_2O in an NMR sample tube respectively and heated at 95° (bath temperature) for 1 hr. And NMR spectra of these sample were taken at room temperature and all the signals were integrated. The ratio of AET/2-AT was determined by that of 2A/B-A where A was the area of the lower triplet of 2-ATs and B was that of the signals of AET overlapped with the higher field triplet of 2-ATs. (In the case of II, N-methyl signal of II and V were also useful to measure the ratio of the mixture.)

	AET/2-AT	95°,	1 hr.
I	0.09		
II	0.43		
III	0.16		

2-Methylaminothiazoline (IX)——i) From bromoethylamine HBr[2b]. To a mixture of 33% aq. KOH (80 ml.) and benzene (80 ml.) was added bromoethylamine HBr (25 g.) with stirring. The benzene layer was separated and the aqueous layer was extracted with benzene (40 ml. × 2). To the combined benzene solution was added dropwise methylisothiocyanate (14.6 g.) under ice-cooling, and then the mixture was refluxed for 2.5 hr. A viscous oily layer produced during the reaction was separated from the benzene layer and the benzene layer was extracted with H_2O. The aqueous solution was combined with the viscous oil, and the aqueous solution was evaporated *in vacuo* to leave a crude IX HBr (16.4 g.) as a viscous oil. A part of the oil (12.0 g.) was treated with conc. NaOH and extracted with benzene. The benzene solution was evaporated *in vacuo* to leave a white solid (5.32 g.), which was recrystallized from cyclohexane to afford IX, m.p. 88~88.5° (reported m.p. 90°[2b]). Another part of the crude HBr salt was recrystallized from iso-PrOH-iso-Pr_2O to afford IX HBr, m.p. 115~120°. *Anal.* Calcd. for $C_4H_9N_2SBr$: C, 24.37; H, 4.60; N, 14.21; S, 16.27. Found: C, 23.88; H, 4.60; N, 14.68; S, 15.97.

ii) From VII. An aqueous solution of VII (100 mg. in 5 ml. H_2O) was heated at 90° for 21 hr. and refluxed for 3 hr. until VII had no longer been recognized by TLC. The mixture was evaporated *in vacuo*

to leave a white solid (100 mg.). The solid showed 2 spots on TLC*8 which were corresponded to that of authentic samples of Ⅳ and Ⅸ respectively. However, Ⅳ was obtained as the main product which was isolated by a preparative TLC. The minor product gave the same Rf value with the authentic sample of Ⅸ on TLC. The NMR spectrum of the crude mixture in D_2O solution showed two N-methyl signals (3.02 and 2.59 p.p.m.), the one was corresponding to the N-methyl of Ⅶ HBr (3.02) and the other was that of $CH_3NH_2 \cdot HBr$. The ratio of the area of the two signals was about 2:1, which showed the ratio of Ⅳ and Ⅸ was roughly 2:1.

2-Anilino-2-thiazoline (X)——i) From bromoethylamine. By following the procedure of Menne[3a] the free base of X was obtained as colorless crystals, m.p. 162~163° (reported m.p. 159~160°[3a], 162°[3d], 160°[3b], 158~160°[3c]). UV: $\lambda_{max}^{95\% EtOH}$ 257 mμ (ε: 12000). Hydrobromide: m.p. 125~126° (from iso-PrOH). *Anal.* Calcd. for $C_9H_{11}N_2SBr$: C, 41.71; H, 4.28; N, 10.81; S, 12.37; Br, 30.83. Found: C, 41.82; H, 4.01; N, 10.97; S, 12.16; Br, 30.60. UV: $\lambda_{max}^{95\% EtOH}$ 245 mμ (ε: 11000).

ii) From Ⅷ. An aqueous solution of Ⅷ HBr (7.0 g in H_2O 70 ml.) was refluxed for 37.5 hr. and the mixture was evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH to remove inorganic salts, and the EtOH was evaporated *in vacuo* to leave a mixture of Ⅳ and X HBr (5.2 g.) as a white solid. The presence of Ⅳ and X was proved by TLC*8. A part of this mixture (4.17 g.) was dissolved in H_2O (5 ml.) and basified with 33% aq. NaOH (10 ml.) under ice-cooling. The separated solid (2.2 g.), m.p. 148~154°, showed one spot corresponding to X on TLC, and was recrystallized from 50% aq. EtOH to give X, m.p. 163~164°, which was confirmed to be identical in IR spectra with the authentic sample obtained from i) and gave no depression of the melting point on admixture with the authentic sample. The alkaline filtrate was extracted with $CHCl_3$ (15 ml. × 10 times), and the combined extracts were dried over $MgSO_4$ and evaporated *in vacuo* to leave an oil (230 mg.), which gave two spots corresponding to Ⅳ and X on TLC. The oil was dissolved in $CHCl_3$ and chromatographed over Al_2O_3. From the effluent with AcOEt-EtOH (1:1) was obtained a partially crystallized oil (200 mg.), which gave single spot corresponding to Ⅳ on TLC. One recrystallization of the crude Ⅳ from benzene-petr. ether gave a colorless crystal, m.p. 73~74°, which was confirmed to be identical with Ⅳ in IR spectra.

In a repeated experiment Ⅷ HBr (9.0 g.) gave free base of X (3.4 g., 76%), m.p. 162~163°, after one recrystallization.

2-(2-Aminoethylamino)-2-thiazoline Dihydrobromide (XIII)——A solution of Ⅺ (10.0 g.) in MeOH-AcOH (1:1) was allowed to stand overnight at room temperature. The crystals (8.8 g.), m.p. 228~232°, were collected, and recrystallized from MeOH-benzene to give XIII 2HBr, m.p. 232~234°. *Anal.* Calcd. for $C_5H_{13}N_3SBr_2$: C, 19.56; H, 4.27; N, 13.68; S, 10.44; Br, 52.05. Found: C, 20.02; H, 3.89; N, 13.88; S, 10.24; Br, 52.44. Picrate: Yellow crystals, m.p. 208~210° (from MeOH). *Anal.* Calcd. for $C_5H_{11}N_3S \cdot 2C_6H_3N_3O_6$: C, 33.84; H, 2.84; N, 20.89; S, 5.31. Found: C, 33.79; H, 2.72; N, 21.15; S, 5.24.

Free Base of XIII——An aqueous solution of XIII HBr (3.0 g.) was basified with 30% aq. NaOH under cooling and the cloudy solution was extracted with $CHCl_3$, and the extracts were dried over $MgSO_4$ and evaporated *in vacuo* to leave a semi-solid (A) (1.37 g).

NMR (in $CDCl_3$, p.p.m. from TMS as an internal standard). 2.79 (t), 3.21 (t), 3.27 (t), 3.91 (t), 2.6 (broad, NH).

Phthaloyl derivative; (Prepared from the fresh crude free base (A) and phthalic anhydride in AcOH) white crystals, m.p. 176~178° (from EtOH). *Anal.* Calcd. for $C_{13}H_{13}N_3SO_2$: C, 56.71; H, 4.76; N, 15.26; S, 11.65. Found: C, 56.66; H, 4.58; N, 15.02; S, 11.39.

A part of the fresh crude base (A) was treated with HBr in EtOH to give the original XIII HBr. On standing the crude base (A) gave three spots on TLC which were corresponded to XIII, XVa and XVIa. When an aqueous solution of the crude base (A) was kept at room temperature for 24 hr., the spot corresponding to XIII disappeared. A portion of the crude base (A) was extracted with $CHCl_3$, and the insoluble residue which was mostly XVa, was dissolved in H_2O and oxidized with air. The reaction mixture was evaporated *in vacuo* after the addition of HBr to give a colorless solid which showed only one spot corresponding to XVIa on TLC. The crude XVIa was recrystallized from EtOH to give pure XVIa, m.p. 214~216°, which was proved to be identical with the authentic sample by the mixed melting point test and comparison of their IR spectra and NMR spectra. From the $CHCl_3$ extracts, XIII was again obtained and proved as picrate.

2-(3-Aminopropylamino)-2-thiazoline Dihydrobromide (XIV)——2-(2-Aminoethylthio)-3,4,5,6-tetrahydropyrimidine (XII 2HBr, 9.7 g.) was dissolved in H_2O (150 ml.), and the mixture was refluxed for 88 hr. The mixture was evaporated *in vacuo* to leave a white solid (8.0 g.), m.p. 190~205°, which showed melting point depression to 182~200° on admixture with the starting material. The crude product was recrystallized from EtOH-MeOH (1:1) once and then from EtOH containing a small amount of MeOH several times to give XIV 2HBr, m.p. 226~228°, which was very hygroscopic. *Anal.* Calcd. for $C_6H_{15}N_3SBr_2$: C, 22.44; H, 4.71; N, 13.09; S, 9.99; Br, 49.77, Found: C, 22.47; H, 4.43; N, 13.43; S, 9.92; Br, 50.03.

*8 The samples were developed on a Al_2O_3-plate in a solvent system (MeOH-acetone 2:3).

Picrate; Yellow crystals, m.p. 183~185° (from MeOH). *Anal.* Calcd. for $C_6H_{13}N_3S \cdot 2C_6H_3N_3O_7$: C, 35.01; H, 3.10; N, 20.42; S, 5.19. Found : C, 35.42; H, 3.03; N, 20.66; S, 5.29.

The HBr salt (2.3 g.) was dissolved in H_2O (7 ml.) and the solution was basified with 30% aq. NaOH under cooling, and the cloudy solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with a saturated NaCl solution and dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to leave a viscous oil (900 mg.) which gave one spot on TLC.*9

NMR (in $CDCl_3$) 1.68 (quintet, $NCCH_2CN$), 2.80 (triplet, $-CH_2S$). 3.30, 3.38 (two overlapped triplets, NCH_2CCH_2N) 3.99 (triplet, NCH_2CS). A part of the viscous oil was converted to the picrate and the crude picrate, m.p. 144~170°, which was recrystallized from MeOH to give XIV picrate, m.p. 184~185°. The picrate was confirmed to be identical with that prepared from XIV HBr directly by the mixed melting point test and in IR spectra. When the crude free base was left at room temperature for a long time*10 (ca. two months), four spots were detected on TLC, and the NMR spectra indicated the absence of XIV and the presence of XVb and XVIb. The mixture (370 mg.) was dissolved in H_2O and the pH of the solution was adjusted to 8.6 with 10% HBr and was oxidized with air for 3 hr. The solution was acidified with a small amount of HBr and evaporated *in vacuo* to leave viscous oil, which showed one spot corresponding to XVIb besides a small amount of impurities at the start line on TLC. Its NMR spectrum was identical with that of authentic sample of the disulfide (XVIb).*1

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Summary

The cyclization of N-substituted 2-(2-aminoethyl)thiopseudoureas (AETs) to 2-aminothiazolines (2-ATs) was investigated. The AETs (I, II and III) having a substituent at the amino nitrogen afforded a simple 3-substituted 2-ATs. The phenyl derivative was cyclized easier than the corresponding methyl derivative. The AETs (VII and VIII) having a substituent at the nitrogen atom of the thiourea, however, afforded the mixture of products, IV (2-aminothiazoline) and a 2-(substituted-amino)-2-thiazoline. 2-Aminothiazoline (IV) was the main product in the case of methyl derivative (VII), while substituted 2-AT was the main product in the case of phenyl derivative (VIII). The AETs (XI and XII) in which the both nitrogens of thiourea were linked with two or three methylenes afforded 2-ATs (XIII and XIV) without removal of an amine, and the free bases of these 2-ATs were unstable and underwent a rearrangement to give 2-(2-mercaptoethylamino)imidazoline or -tetrahydropyrimidine.

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*9 The samples were developed on a Al_2O_3-plate in the solvent system (MeOH-AcOH-H_2O 1:1:1).

*10 This change was rapid in an aqueous solution and no XIV was found on TLC in the mixture after standing one day at room temperature.