The Synthesis of 2-Methyl-5,5′-gem-Disubstituted-△²-Thiazolines

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2-Methyl-5,5′-gem-Disubstituted-△²-Thiazoline系 化合物의 合成

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The synthesis of 2—methyl—5, 5′—gem—disubstituted—⊿²—thiazolines has been undertaken by two methods. The first involves the preparation of gem-disubstituted N- or S-acetylamino mercaptan intermediates by ring opening of the corresponding thiiranes with ammonia. The second consists of the ring opening of gem-disubstituted ethylene imines using thiolacetic acid. The thiirane rings have never been opened under conditions as vigorous as that of using sodium amide in liquid ammonia. This is probably due to retardation by the gem-disubstituents. In contrast to this, the corresponding ethylene imine ring opens easily, in spite of the same stereochemical situation. The stabilization of gem-disubstituted cyclic compounds has been discussed from a stereochemical point of view. It has been concluded from the results of this work that the compression effect of gem-disubstitution is not due to bond angle deformation, which was observed by Thorpe and Ingold, but mostly to an electronic bond interaction of the gem-disubstituents and to the hetero atom(s), if any.

要 約

2-Methyl-5, 5′-gem-disubstituted-⊿²-thiazoline系 化合物의 合成을 1, 1′-gem-disubstituted thiiranes의 三員環을 ammonia로 開環하여 該當하는 N- 또는 S-acetyl-amino mercaptan을 얻고 그것을 다시 閉環하는 方法과 또 하나는 같은 三員環인 gem-disubstituted imines을 thiolacetic acid로 開環하고 그것을 直接 다시 閉環하여 얻는 두가지 方法에 의하여 硏究하였다. 前者의 thiirane ring은 gem-disubstitution의 compression 効果에 의하여 極히 安定化되어 여러가지 强力한 反應條件下에서의 sodium amide를 利用한 ammonia nuclephile에 頑强한 抵抗을 나타냈으며 反對로 後者의 三員環 imine은 같은 gem-disubstitution 効果를 받음에도 不拘하고 容易하게 開環하였다. 이 gem-disubstitution 効果에 의한 環狀化合物의 開環阻止性과 閉環促進性을 立體化學的인 見地에서 考察하였으며 本硏究로서 環狀化合物의 安定性에 미치는 gem-disubstitution의 compression 効果는 所謂 Thorpe-Ingold의 bond angle deformation에 緣由하는 것이 아니고 오히려 gem-disubstituents와 異節環狀化合物內의 hetero atom(s)이 미치는 bond interaction에 起因한다는 結論을 얻었다.

Introduction

The importance of the structure of 2-methyl-⊿²-thiazoline in native proteins has been recognized by many workers since Linderstrm-Lang and Jacobsen reported the easy opening of the thiazoline ring. After the fact that Bacitracin-A contains a thiazoline ring had been demonstrated[2], Calvir[3] proposed that the thiazoline ring forms in strongly acidic solutions of glutathione; this has been further supported.[4] These findings are in apparent contradiction to each other. Recently, Martin and his coworkers[5] investigated the rate of hydrolysis of the compound as a function of pH and concluded that the molecule is quite stable in concentrated HCl, and hydrolyzes very slowly in neutral solution.

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Since stereochemical factors often affect the stability of ring compounds profoundly, in the consideration of the stability of the thiazoline ring one must survey the problem in a stereochemical method. For example, there is a strong possibility that the thiazoline ring could be stabilized by a compression effect. And it is well-known that ring compounds are highly stabilized by gem-disubstitution.[6] Therefore, it seems possible that gem-disubstituents on the thiazoline ring could be especially stabilizing. Concerning the problem of 2-methyl-Δ^2-thiazoline, it can be easily seen from the steric configuration of the compound that there would not be any compression effect in the thiazoline ring. To date, no report dealing with the effect of steric factors on the stability of gem-disubstituted thiazoline derivatives is available.

Not only would such an effect be of interest, but also the synthesis of geminally disubstituted amino mercaptans, through which the thiazoline ring can be formed, is of importance, the reason being that the geminally disubstituted amino mercaptans are known the most effective radiation screening protection.

In this paper the syntheses of such sterically compressed thiazoline compounds as 2-methyl-5,5′-gem-disubstituted-Δ^2-thiazolines are described and their stability discussed in the light of steric considerations.

Experimental

1,1′-Dimethyl ethylene oxide.[7]—To 11g., 0.20 mole, of isobutylene gas (Methison Co. Inc.) which had been dissolved in 100 m*l*. of diethyl ether with external cooling were added 28g., 0.20 mole, of perbenzoic acid dissolved in 300 m*l*. of diethyl ether. The perbenzoic acid was prepared by the method of Braun.[8] At the end of the reaction the perbenzoic acid which remained in solution was analyzed by iodometric titration; only a slight amount of the perbenzoic acid was unreacted. The perbenzoic acid in the mixture was extracted from the ether solution by using an excess of aqueous 10% NaOH. The ether solution was neutral, and then dried over anhydrous sodium sulfate. The product, 1,1′-dimethyl ethylene oxide, was then purified by fractional distillation; b. p. 50–54° (lit.[9] 50–53°). The yield was 9–10g., 64–70% of theoretical. Infrared spectrum: 9.30, 9.59, 10.70 and 11.05μ.

Titration of perbenzoic acid.[8]—In order to estimate the amount of active oxygen in diethyl ether solution, a 10 m*l*. aliquot of the solution was added to a solution consisting of 1.5g. of sodium iodide in 50 m*l*. of water and 5 m*l*. of glacial acetic acid in 5 m*l*. of diethyl ether with vigorous shaking. The iodine liberated was titrated using 0.1N sodium thiosulfate solution. One m*l*. of sodium thiosulfate is equivalent to 0.0069g. of perbenzoic acid.

1,1′-Diethyl ethylene oxide.—To 23g., 0.17 mole, of perbenzoic acid in 340 m*l*. of chloroform were added 14g., 0.16 mole, of 1,1′-diethyl ethylene (purchased from Matheson Coleman & Bell Co., and redistilled at 66.2–66.7°) while keeping the temperature below 0°.[6] The mixture was shaken frequently during the first hour, and was then kept in an ice box for 24 hrs. The complete reaction of perbenzoic acid was ascertained by the iodometric titration. The mixture was colored slightly yellow at the end of the reaction. It was treated the same way as in the case of 1,1′-dimethyl ethylene oxide. The crude product was purified by distillation, b. p. 102–107° (lit.[10] 104–107°). The yield was 10g. (65%). Infrared spectrum: 8.21, 9.02, 9.23, 10.20 and 11.05μ, (Fig. 1-a).

1,1′-Diphenyl ethylene oxide.—To 23g., 0.17 mole, of perbenzoic acid in about 300 m*l*. of chloroform were added 27.4g., 0.15 mole, of 1,1′-diphenyl ethylene (Eastman Chemicals) at below zero temperature. Since the temperature of the reaction mixture raised suddenly during initial period, the mixture was cooled by means of ice-salt bath and then kept in an ice-box at below zero for more than 30 hrs. Liberated benzoic acid was removed with an excess of 10% NaOH solution which was itself removed by washing with water. The crude product was isolated by distilling off all the chloroform and chilling the residue. It was recrystallized from 95% ethanol; m. p. 54–56° (lit.[11] 56°); the yield 15g. (54%); infrared spectrum: 5.78, 6.01, 6.24, 6.68, 7.82 and 8.50μ.

1,1′-Dimethyl ethylene sulfide.—To a solution of 25g., 0.33 mole, of thiourea in 100 m*l*. of methanol were added 24g., 0.33 mole, of 1,1′-dimethyl ethylene oxide. The mixture was stirred vigorously in a round bottom flask at room temperature for 17.5hrs. and the contents then poured into about 500m*l*. of water; the unreacted thiourea was dissolved completely. After standing five to ten minutes in a separatory fun-

nel, a colorless heavy oily liquid formed, was separated, washed three times with water, and dried over sodium sulfate. The crude product was purified by distillation, b. p. 82-85° (lit.[12] 84-86°); the yield 9.2g. (30%).

1,1′-Diethyl ethylene sulfide.—This compound was prepared by the mothod described above; b. p. 70-71°/73mm.; n_D^{25} 1.3330; infrared spectrum: 7.72, 9.18, 9.69 and 11.25μ.

Anal.[13] Calcd. for $C_6H_{12}S$: C 62.00; H 10.41; S 27.59. Found: C 61.90; H 10.35; S 27.40.

1,1′-Diphenyl ethylene sulfide.—1,1′-Diphenyl ethylene oxide was treated with thiourea in methanol solution similar to the method used for the preparation of 1,1′-dimethyl ethylene sulfide. The crude product was extracted with chloroform, which was washed several times with water in order to remove unreacted thiourea. The chloroform solution containing the product was evaporated to yield a sticky oil. This was then distilled, and the white crystals which formed in the distillate was recrystallized from an acetone and water mixture three times; m. p. 136-8°, white micro needle type crystal; infrared spectrum: 5.85, 6.20, 7.85, 8.95, 9.36 and 10.60μ, (cf. Fig. 1-b).

Anal. Calcd. for $C_{14}H_{12}S$: C 79.19; H 5.70; Found: C 79.34; H 5.64.

1,1′-Dimethyl ethylene imine.—To a solution of 100g., 1.1 mole, of 2-methyl-2-amino-1-propanol in 200 ml. of water were added 110g., 1.1 mole, of sulfuric acid in 200ml. of water with shaking. The solution was distilled at atmospheric pressure until the temperature of the reaction mixture reached 115°; it was then heated to 170° under 20-30mm. pressure. Care must be taken not to over-heat the reaction mixture. When the temperature rose above 180° the mixture changed into a brown clear paste, which was allowed, to cool by standing at room temperature. A slightly brown crystalline mass was obtained to which was added excess 40% sodium hydroxide solution. The mixture was distilled until the temperature of the vapor reached 100°. After saturating the distillate with potassium hydroxide pellets, an upper organic layer formed, was separated, dried over KOH and distilled twice; b. p. 69-73° (lit.[14] 66-70°); obnoxious order; the yield 46g. (65%); infrared spectrum: 3.04, 7.49, 9.05, 9.85 and 11.20μ, (cf. Fig 1-c).

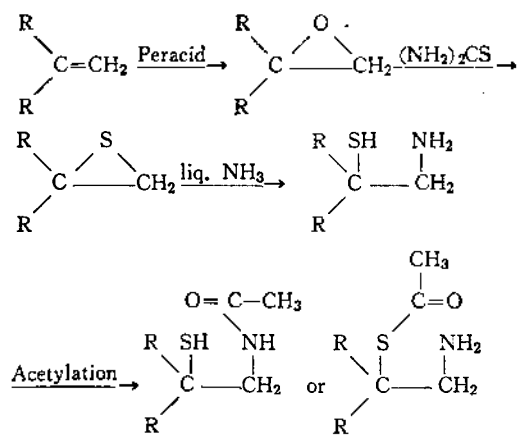
1,1′-Dimethyl-2-acetyl-aminomercaptan.—To 50g., 0.65 mole, of thiolacetic acid were added dropwise 46g., 0.65 mole, of 1,1′-dimethyl ethylene imine in 340 ml. of methanol at 5-10°. The addition of the 1,1′-dimethyl ethylene imine took 15 minutes. The mixture then solidified. The yield was more than 95%, and the product was soluble in water; less soluble in ethanol, diethyl ether and acetone. It was recrystallized from diethyl ether; m. p. 72-73°. A sodium nitroprusside test for SH and ninhydrin test for NH_2 were both positive. Infrared spectrum: 2.99, 6.00, 6.41, 7.75, 8.50 and 9.65μ. (cf. Fig. 1-d).

Anal. Calcd. for $C_6H_{13}NOS$: C 48.94; H 8.90; N 9.51; S 21.77. Found: C 48.94; H 9.03; N 9.41; S 21.75.

2-Methyl-5,5′-dimethyl-⊿²-thiazoline (Ring closure of 1,1′-dimethyl-2-acetylamino mercaptan).—Into 500 ml. round bottom flask connected with a condenser were placed 2g. of 1,1′-dimethyl-2-acetylamino mercaptan and 2g. of phosphorous pentoxide without solvent. The mixture was then heated on a water bath for an hour, and was turned to dark brown at the end of the period. It was extracted with diethyl ether which was dried over sodium sulfate and evaporated to yield a dark brown oil; this was vacuum distilled; b. p. 50-51°/10mm.; ultraviolet spectrum: λ max. =256 mμ.

Results and Discussion

Preparation of 2-methyl-5, 5′-dialkyl-⊿²-thiazolines and 2-methyl-5, 5′-diphenyl-⊿²-thiazoline has been attempted by the following general scheme:



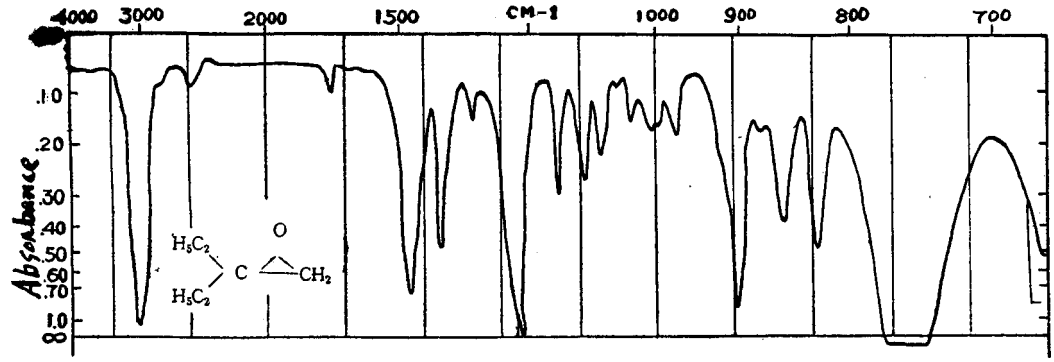


Fig. 1—a

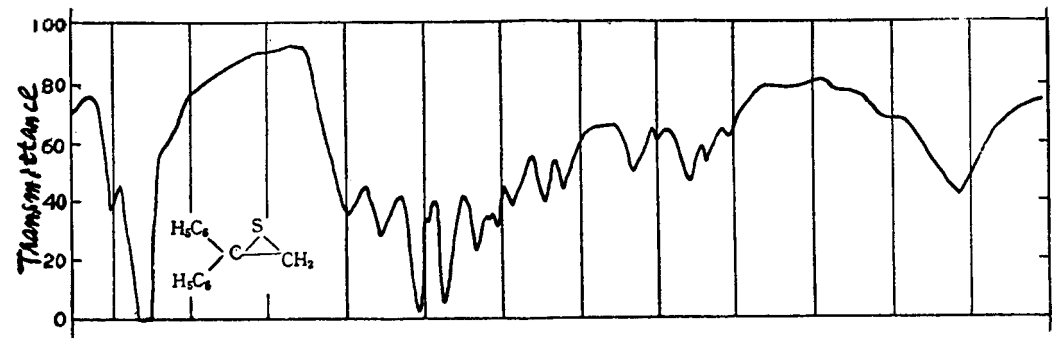


Fig. 1—b

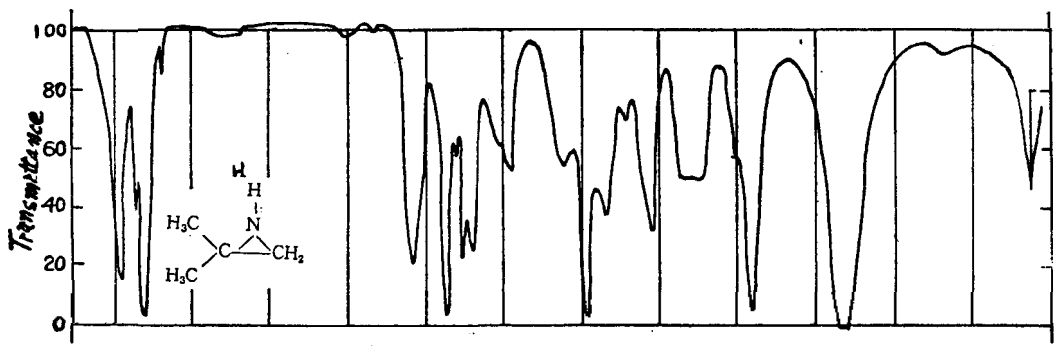


Fig. 1—c

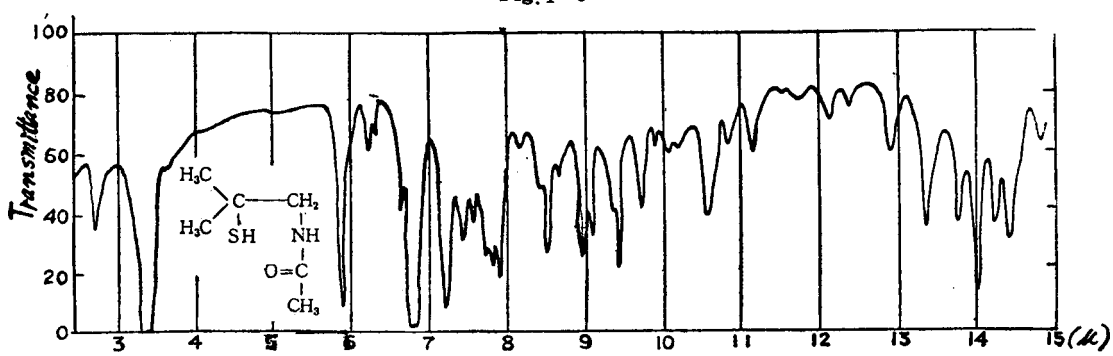
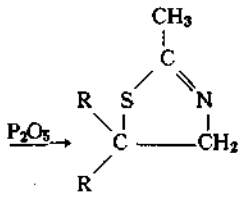
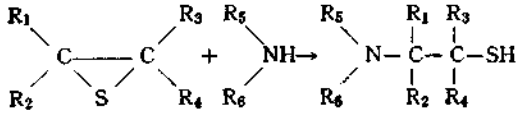


Fig. 1—d



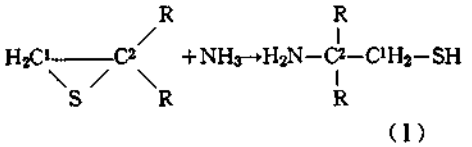
(R=$-CH_3$, $-C_2H_5$, $-C_6H_5$) ……(1)

Gem-disubstituted ethylene oxides (oxiranes) were obtained by the reaction of perbenzoic acid and the appropriate 1,1′-disubstituted ethylene, followed by conversion to the corresponding ethylene sulfides using thiourea or potassium thiocyanate. The reactions proceeded with a good yield and without any difficulties when R was a methyl, ethyl or phenyl group. These substances were identified by comparison of their transition points with those which are known, or by elemental microanalysis for those which were unknown. The infrared spectra of all substances synthesized showed the characteristic band for every specific bond. The infrared spectra of 1,1′-diethyl ethylene oxide and 1, 1′-diphenyl ethylene sulfide are shown in Fig. 1 as being representative of the oxiranes and the thiiranes. In general, the reaction between olefin sulfides such as ethylene sulfide and propylene sulfide, and primary or secondary amines, has been used for the preparation of a number of new amino mercaptans.[16] Recently, Snyder et al[17] have demonstrated the reactivity of various amines with symmetrically and unsymmetrically substituted ethylene sulfides at relatively high temperature and have obtained reasonably good results. In the present work, Snyder's general scheme has utilized in an attempt to prepare 1,1′-disubstituted-2-aminoethyl mercaptans by opening of the thiiranes with the NH_3 nucleophile.

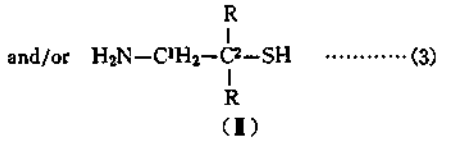


……(2)

Here, R_1, R_2, R_5 and R_6 are all hydrogen. One might expect to obtain two possible isomeric products in the reaction of unsymmetrically disubstituted thiiranes with ammonia, i.e.

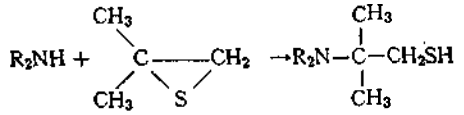


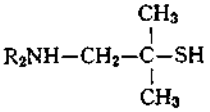
(I)

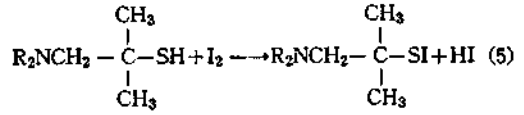
and/or  ……(3)

(II)

Product (I) would be obtained by attack of the NH^-_2 nucleophile on the C^2 atom followed by cleavage of the S—C^2 bond. Product (II) might be formed by a similar attack on the S—C^1 bond. However, considering the hyperconjugation effect of the alkyl substituents and electron repelling ability of the phenyl groups on the ring, it can be predicted that a higher electron density would be localized on the C^2 atom than C^1 atom. This means that the C^1 atom would be positively polarized; thus, the nucleophile must attack C^1 to yield product (II). The validity of this reasoning has been demonstrated by Snyder et al; i.e., they have tested the product obtained from the reaction of 1,1′-dimethyl ethylene sulfide with amines (eq. 4), using Rheinbold test,[18] and found that the main products are sulfenyl iodides (eq. 5), tertiary mercaptans, rather than primary mercaptanes. This is the evidence for the expectation of the S—C^1 bond cleavage in the reaction of the thiirane ring opening. Futhermore, the S—C^1 bond cleavage seems to be more favorable from the stereochemical point of view. Considering the bulkiness of gem-disubstituents on C^2 atom, it is quiet obvious that nucleophile would more easily approach to C^1 atom rather than C^2 atom.



and/or  (4)



(5)

Since the compounds of type (II) are an interme-

diate of those sought, and the facts mentioned above are favorable for the preparation of 1,1′-dimethyl-2-aminoethyl mercaptanes, the first sequence used was that indicated by eq. (3). Sodium amide was used ocassionally in order to increase the nucleophilicity of the liquid ammonia. For example, to 1,1′-dimethyl ethylene sulfide in an excess of liquid ammonia was added the equivalent amount of sodium amide. The mixture was sealed in a steel-lined, thick pyrex tube which was kept cold in a trichloroethylene dry-ice bath and then shaken at room temperature for more than 36 hrs. in a bomb room. The tube was again cooled, opened with extreme care, and the equivalent amount of ammonium chloride added. The ammonia gas evaporated on standing at room temperature, the residue was treated with diethyl ether to extract ammonium salt out of the amino mercaptan, and the ether was saturated with anhydrous hydrogen chloride gas, which produced a tar-like black product. Various organic solvents were all unsatisfactory for recrystallization. The residue from the ether extraction was treated with aqueous hydrogen chloride solution; a vigorous reaction occurred. Possibly, the hydrogen chloride solution might have reacted with unreacted sodium amide and formed sodium chloride, which was identified by a metal fusion test and its transition point. A number of the ammonolizations, that is ring opening of the gem-disubstituted thiiranes (gem-dimethyl, gem-diethyl and gem-diphenyl) with ammonia, have been carried out under various conditions. The results in every case were unsatisfactory; these are summarized in Table I.

In contrast with Snyder's work, in which primary and secondary amines were used as nucleophile, the thiirane ring openings with ammonia were not preferable as the results in Table I show. One might suggest the reason for such unreactivity is due to the reaction conditions. Indeed, the reaction temperature of the mixture consists of the thiirane and ammonia was not be able to raise higher than 60°, at which the container was exploded as the experiment No. 4. The reaction temperature was kept low at the initial, due to the necessity of keeping liquid phase of ammonia and to avoid undesirable detonation in the first halves of the experiments, though it was possible to raise the temperature up to 300° in the cases of amines as Snyder reported.[17] However, based on the results of experiment No. 7 below in Table I, it seems unlikely that the temperature dependence on the reactivity is main factor which determines the easiness of the S—C[1] bond cleavage.

Such unexpectedly strong resistence of the gem-disubstituted thiirane against ammonia is most probably due to stereochemical factors. Thorpe and Ingold[19-22] have investigated the geminal disubstitution effect on the reactivity of cyclic compounds, and have proposed that gem-disubstituents retard the ring opening. This idea has been further supported by workers who, along with Thorpe and Ingold, attribute the geminal disubstitution effect to the deformation of the bond angle θ, not to bond interaction of the geminal substituents. Recently, Searles[23] has also demonstrated evidence of the gem-disubstitution effect in 2-oxaspirane which he also attributed to a decrease of bond angle.

Although Snyder, in the gem-disubstituted thiirane system, pointed out the fact that retardation of the ring opening is apparent, the results of the present work indicate that such extream retardation is unlikely to be due to bond angle deformation only. Assuming that the reaction of the thiiranes with ammonia is not feasible, an alternate method was adopted for the next attempted preparation of 2-methyl-5,5′-dimethyl-Δ^2- thiazoline:

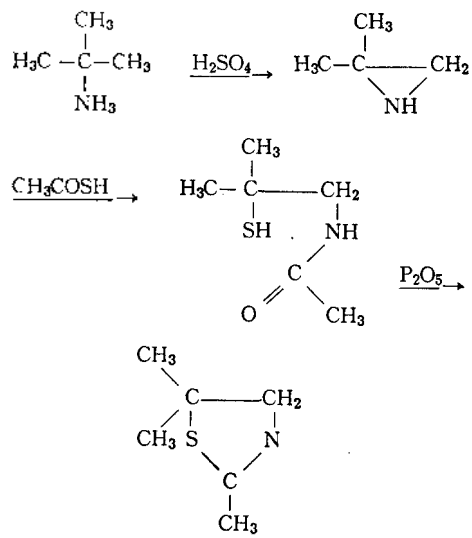


Table I

Ammonolization of gem-Disubstituted Ethylene Sulfide

Expt. No.	Substituent (R=)	Nucleophile(s) Solvent	Temp.	Time (hrs.)	Product or Results
1	CH_3	liq. NH_3	Rm.	36	Tar, NaCl & inorganic materials
2	CH_3	liq. NH_3	Rm.	48	Same as above
3	C_2H_5	liq. NH_3	Rm.	20	White granular solid, m.p. 93-5° Anal. for $C_6H_{15}NS$: Calcd. C 54.08; H 11.35; N 10.51; S 24.06. Found: C 60.93; H 10.34; N 1.98; S 27.34. I.R.; no C-N, N-H band
4	C_2H_5	liq. NH_3	60	20	Exploded
5	C_2H_5	liq. NH_3	Rm.	20	HCl salt, m.p. 162-4° Metal fusion test; no N and S contained Anal. for $C_6H_{16}ClNS$: Calcd. C 42.46; H 9.51; Cl 20.89; N 8.25; S 18.89 Found: C 57.83; H 10.03; Cl 5.49; N 1.92; S 24.40
6	C_2H_5	liq. NH_3, $CHCl_3$	Rm.	24	Mix. of inorganic compounds
7	C_2H_5	Reflux by cooling condenser with liq. NH_3		8	Ninhydrin test for NH_2 & sodium nitroprusside test for SH were both negative
8	C_6H_5	liq. NH_3, $CHCl_3$ under N_2 gas	Rm.	24	Electropholysis test for NH_2 was negative; I.R. analysis & m.p. (141°, original one 138°) proved the starting material recovered
9	C_6H_5	liq. NH_3, $NaNH_2$.	Reflux in triethyl amine (b.p. 89.5°)	12	Mix. of inorganic compounds
10	C_6H_5	Bubbled NH_3 gas in $CHCl_3$ under N_2 gas	Rm.	24	Recovered starting material
11	C_6H_5	Bubbled NH_3 gas	Reflux in $CHCl_3$ (b.p. 61°) under N_2 gas	24	Recovered starting material
12	C_6H_5	Bubbled NH_3 gas	Reflux in DMF (b.p. 153°) under N_2 gas	24	Recovered starting material
13	C_6H_5	$NaNH_2$ in liq. NH_3 and $CHCl_3$	Reflux	12	Recovered starting material

1,1′-Dimethyl ethylene imine was obtained from the reaction of 2-methyl-2-amino-propanol with sulfuric acid in good yield. The imine ring, entirely different from the thiiranes, was opened with thiolacetic acid exothermically in more than 95% yield. The product, 1,1′-dimethyl-2-acetyl-amino mercaptan, was identified by elemental analysis and infrared spectrum (Fig. 1-d). The ring closing reaction of 1,1′-dimethyl-2-acetylamino-mercaptan to give 2-methyl-5,5′-dimethyl-Δ^2-thiazoline proceeded smoothly using phosphorous pentoxide fusion.

Comparing analogous compounds of geminally disubstituted thiiranes and ethylene imines, the two would be expected to be identical from a stereochemical point of view. However, considering the atomic radius of the nitrogen and sulfur atoms in the two compounds, the gem-disubstituted ethylene imines would be more sensitive to bond angle deformation. As a consequence, the ethylene imine ring should open more difficultly than the corresponding thiirane. The reverse should hold true if the prediction that the retardation of ring opening was due only to bond angle deformation. Neverthless, the experimental fact that the imine ring opened easily is apparently in contrast to the above expectation.

This is evidence that the stabilization of such cyclic compounds is not due to a decrease of bond angle, but to bond interaction of the geminally disubstituted groups and the hetero atom(s). It seems most likely that the stabilization of ring structure is rather due to

bond interaction, such as, the departing ability of atoms expected to be cleaved in the transition state. Recently, Bruice and Pandit [24] supported this proposal in an investigation of the rates of the intramolecular catalysis of the hydrolysis of substituted monoesters of dibasic acids. Thus, the proposal of bond angle deformation to account for the retardation of the opening of gem-disubstituted rings seems no longer accurate.

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