zation from ethanol–ether gave pure *endo* alcohol hydrochloride, mp 270° dec.

Anal. Calcd for $C_{11}H_{20}ClNO$: C, 60.67; H, 9.26; N, 6.43. Found: C, 60.76; H, 9.25; N, 6.48.

A sample of the hydrochloride salt was dissolved in water and the solution was basified with 30% sodium hydroxide solution. The solution was extracted with chloroform, and the combined organic layers were dried, filtered, and evaporated to give a white solid. Sublimation of this material gave white needles of pure *endo* alcohol **14**, mp 87.5–88.5°.[31]

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.94; H, 10.61; N, 7.71; $pK^*_{mcs} = 8.11$.

B. **With Sodium Borohydride.** A solution of 2.0 g (0.0115 mole) of **2** in 45 ml of methanol was added to a solution of 455 mg (0.012 mole) of sodium borohydride in 40 ml of water and the resulting mixture was slowly stirred at room temperature for 3 hr. After the excess of borohydride had been destroyed by the addition of acetic acid, 3 ml of concentrated hydrochloric acid was added and the mixture was concentrated, made basic with aqueous sodium hydroxide, and extracted with ether. The ethereal extract was dried, filtered and evaporated, and the residue was sublimed to give 1.85 g of solid, mp 43–49°.

A solution of 1.72 g (9.50 mmoles) of this crude solid and 1.90 g (10.25 mmoles) of *p*-nitrobenzoyl chloride in 25 ml of chloroform was allowed to stand at room temperature for 61 hr. The same work-up as above afforded a white solid which could be fractionally crystallized from ethanol to give 350 mg of **2** hydrochloride (from incomplete reduction), mp 235–240° dec, and 1.3 g of *endo* alcohol hydrochloride, mp 250–265° dec. The latter substance was further recrystallized from ethanol–ether to give pure *endo* alcohol hydrochloride, mp 270° dec, identical in all respects with the sample of part A.

C. **With Sodium and Isopropyl Alcohol.** To a stirred mixture of 1.73 g (0.075 g-atom) of sodium metal in 35 ml of toluene was added rapidly a solution of 3.0 g (0.0167 mole) of **2** in 11 g of isopropyl alcohol. After the resulting mixture had been refluxed for 3.5 hr (at which time all the sodium had reacted), it was cooled and extracted with three 30-ml portions of 4 *N* hydrochloric acid. The acid extracts were made basic by the addition of sodium hydroxide pellets and the resulting oily mixture was extracted with pentane. The pentane solution was dried, filtered, and evaporated, and the residual solid was sublimed to give 2.4 g of amino alcohol mixture, mp 82–101°.

A solution of 2.28 g (12.60 mmoles) of this solid and 2.50 g (13.45 mmoles) of *p*-nitrobenzoyl chloride in 30 ml of chloroform was allowed to stand at room temperature for 61 hr. The same work-up as above afforded a white solid which was fractionally crystallized from absolute ethanol to give three crops: A, 1.95 g of the *p*-nitrobenzoate ester hydrochloride of the *exo* alcohol **15**, mp 248–249° dec; B, 150 mg of a mixture, mp *ca.* 230° (indefinite melting region); C, 1.25 g of *endo* alcohol hydrochloride, mp 255–268° dec. Further recrystallization of the C fraction from ethanol–ether raised the melting point to 270° dec. This material was identical with the sample prepared above.

Fraction A was recrystallized several times from ethanol to give pure *exo* alcohol *p*-nitrobenzoate hydrochloride as white platelets, mp 253–254° dec.

Anal. Calcd for $C_{18}H_{23}ClN_2O_4$: C, 58.93; H, 6.32; N, 7.64. Found: C, 58.83; H, 6.36; N, 7.52.

A mixture of 1.2 g (3.27 mmoles) of this ester hydrochloride and 10 ml of 20% hydrochloric acid was refluxed for 6 hr and cooled. The precipitated *p*-nitrobenzoic acid was removed by filtration and the filtrate was basified with 30% sodium hydroxide solution and extracted with chloroform. The combined organic layers were dried, filtered, and evaporated to give a white solid. Sublimation of this material gave white needles of pure *exo* alcohol **15**, mp 104–104.5°.[32]

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.98; H, 10.61; N, 7.66; $pK^*_{mcs} = 8.09$.

(31) The reduction of **2** was also reported by Alder, *et al.*[5] The melting point of their amino alcohol (*ca.* 75°) is indicative of a mixture of epimers.

(32) All preliminary attempts to separate **14** and **15** on a variety of gas chromatographic columns were without success in our hands.

The Stereochemistry of Δ^2-Thiazoline Formation from Episulfides

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Abstract: Stereochemical evidence is presented in support of the previously proposed mechanism for the acid-promoted reaction of episulfides with nitriles to form Δ^2-thiazolines. Ring opening of propylene sulfide by acetonitrile takes place at the more substituted carbon, resulting in the formation of 2,4-dimethyl-Δ^2-thiazoline without detectable amounts of the 2,5 isomer. That the ring opens in a *trans* manner is demonstrated by the preparation of *trans*-2-phenyl-3a,4,5,6,7,7a-hexahydrobenzthiazole from cyclohexene sulfide, which can only have the *cis* configuration. (4*R*:5*S*)-(−)-*cis*-2,4,5-Trimethyl-Δ^2-thiazoline has been prepared from (*SS*)-(−)-*trans*-2-butene episulfide, which was prepared from (*RR*)-(+)-*trans*-2,3-epoxybutane. The same epoxide can be converted to (*SS*)-(−)-*trans*-2,3-dimethylaziridine, from which the enantiomer of the above optically active thiazoline can be obtained by treatment with thioacetamide.

We have elsewhere reported[1] a general, stereospecific route to Δ^2-thiazolines, by treatment of an episulfide with a nitrile in the presence of a strong acid. At that time we proposed a mechanism for this reaction which involved protonation of the episulfide, ring opening by nucleophilic attack by the nitrile, and ring closure to form the thiazoline salt. We have now found the stereochemistry of this reaction to be in complete accord with the proposed mechanism.

To demonstrate that reaction involved one inversion, it was desirable to convert an episulfide of known configuration to one of a pair of isomers, both of which had been previously characterized. The preparation of *trans*-2-phenyl-3a,4,5,6,7,7a-hexahydrobenzthiazole from cyclohexene sulfide was admirably suited for these purposes. The episulfide can have only the *cis* configuration, and both the *cis* and *trans* thiazole isomers have been prepared[2] together with their picrates,[2]

(1) G. K. Helmkamp, D. J. Pettitt, J. R. Lowell, Jr., W. R. Mabey, and R. G. Wolcott, *J. Am. Chem. Soc.*, **88**, in press.

(2) (a) T. Taguchi and M. Kojima, *ibid.*, **78**, 1464, (1956); (b) M. Kojima, *Yakugaku Zasshi*, **79**, 1 (1959); *Chem. Abstr.*, **53**, 10183*h* (1959).

methiodides, and ethiodides.[3] When cyclohexene sulfide was added to a solution of concentrated sulfuric acid in benzonitrile, *trans*-2-phenyl-3a,4,5,6,7,7a-hexahydrobenzthiazole was obtained in 52% yield. The melting points of the free base and its picrate, methiodide, and ethiodide are all in excellent agreement with the values reported by Kojima and co-workers.[2,3] These data are made even more conclusive by the large difference in melting points between the *cis* and *trans* derivatives; the reported[2,3] melting points of the picrates, methiodides, and ethiodides differ by 64, 102, and 32°, respectively.

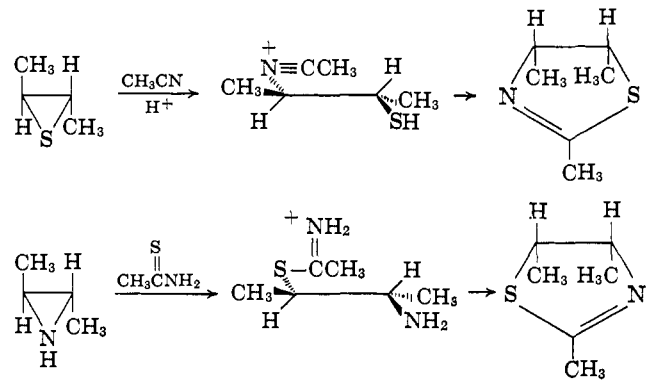
The nmr spectrum of the free base is in agreement with the assigned structure. The aromatic protons appear as two multiplets, δ 7.2–7.5 and 7.7–8.0, areas 3 and 2. The 3a and 7a protons give rise to a broad multiplet at 3.2–3.5, area 2, and the other protons on the six-membered ring occur as a series of broad multiplets, 1.0–2.8, total area 8. The infrared spectrum is rather unusual in the 6.1–6.3-μ region, in which the C=N stretching band is usually observed.[1,4] The lowered intensity and longer wavelengths for this band may be due to a combination of conjugation with the aromatic ring and the considerable amount of strain due to the *trans*-fused five- and six-membered rings.

The direction of ring opening was determined from the reaction of propylene sulfide with acetonitrile and sulfuric acid. A dimethylthiazoline was isolated from the reaction mixture in 17% yield. Analysis by vpc gave only a single peak in addition to that due to some remaining acetonitrile. The nmr spectrum of the collected sample was consistent only with that expected for the 2,4 isomer, with no detectable contamination from the 2,5 isomer. A doublet at δ 2.15, J = 1.5 cps, area 3, was assigned to the 2-methyl group. Roggero and Metzger[5] have reported that protons on a 2-alkyl group of Δ^2-thiazolines couple with the 4 protons, but not with the 5 protons, and that the coupling constant for this "homoallylic" coupling is 2.2 cps. Thus 2,5-dimethylthiazoline would show a triplet for the 2-methyl group, and two 4 protons would be split by the 2-methyl group as well as the 5 proton. The observed doublet for the 2-methyl group, and the fact that the two similar ring protons appear at δ 3.07 and 3.20 as overlapping quadruplets, J_1 = 32 cps, J_2 = 10 cps, rule out the 2,5-dimethyl structure for the product. The doublet at δ 1.31, J = 5.5 cps, area 3, can thus be assigned to the 4-methyl group; the quadruplets at 3.07 and 3.20 can be assigned to the 5 protons; and the multiplet, area 1, at 4.4 can be assigned to the 4 proton.

The above assignments are consistent with the nmr spectra reported in another paper,[1] in which all of the 2-alkyl-4,5-dimethyl-Δ^2-thiazolines show the 4 proton between δ 4.00 and 4.19 and the 5 proton between 3.33 and 3.83. Assignment of the δ 1.31 doublet to the 4-methyl group provides justification for the assignment of the 4- and 5-methyl resonances in Table III in another paper.[1] The doublets for the 4- and 5-methyl groups in the 2-alkyl derivatives fall into two regions, δ 1.12–1.18 and 1.27–1.33. The fact that the 4-methyl group appears at δ 1.31 provides strong evidence that the downfield methyl group is that on the 4 position.

Opening of the episulfide ring at the more substituted position is in accord with ring opening of epoxides in acidic media and with other ring opening reactions of episulfides. Epoxides are opened at the less substituted carbon atom in base, and at the more substituted carbon atom under acid conditions.[6] The reaction of isobutylene sulfide with primary alcohols and with primary thiols has been studied by Snyder and coworkers.[7] In the presence of boron trifluoride, the ratio of primary to tertiary thiol was approximately 50:50 in the case of reaction with 1-butanethiol. With 1-butanol, in the presence of boron trifluoride, the predominant product was primary thiol (from attack at the more substituted carbon atom), and only traces of tertiary thiol were found in the product. These observations are easily explained in terms of a transition state for SN2 attack in which "bond breaking" becomes more important as the nucleophilicity of the attacking molecule decreases. Thus the thiol is less discriminating in its attack than is the more weakly nucleophilic alcohol. The much less nucleophilic nitrile should be even more discriminating than the alcohol. The isolated dimethylthiazoline supports this contention. Although the yield of thiazoline is only 17%, there is no reason to believe that the 2,4-dimethyl isomer should survive the isolation procedure better than the 2,5 isomer. It appears that reaction took place, as far as our methods (vpc, nmr) could detect, only at the more substituted carbon atom.

Preparation of (4*R*:5*S*)-(−)-*cis*-2,4,5-trimethyl-Δ^2-thiazoline[8] from (*SS*)-(−)-*trans*-2-butene episulfide demonstrated that the reaction proceeds without racemization. Since this episulfide is prepared from (*RR*)-(+)-*trans*-2,3-epoxybutane, the novel possibility presented itself of preparing the enantiomeric *cis*-thiazoline from the same epoxide, *via* (*SS*)-*trans*-2,3-dimethylaziridine. When the imine was treated with thioacetamide in refluxing benzene, (4*S*:5*R*)-(+)-*cis*-2,4,5-trimethyl-Δ^2-thiazoline was isolated in 24% yield. After purification by vpc the optical rotations of the two isomers were compared. The episulfide product showed $[\alpha]^{25}D$ −66.24° (10.39%, hexane), while the product from the aziridine had $[\alpha]^{25}D$ +72.67° (11.22%, hexane).



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(8) Optically active compounds are described by the (*R*, *S*) system of R. S. Kahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

The results presented here conclusively show that the formation of Δ^2-thiazolines from episulfides and nitriles occurs with a single inversion, as does the reaction of aziridines with thioamides. The stereochemistry of the reaction is most consistent with the previously suggested mechanism, consisting of nucleophilic attack by the nitrile on a carbon atom of the protonated episulfide, followed by ring closure of the intermediate nitrilium salt to the Δ^2-thiazoline.

Experimental Section

Purification of Solvents and Preparation of Starting Materials. Practical grade acetonitrile was dried over anhydrous magnesium sulfate and distilled from phosphorus pentoxide, bp 80.3–81° (737 mm). The dry acetonitrile was stored over molecular sieves. Reagent grade benzene was distilled through a simple distillation apparatus, discarding the first 100 ml, and was stored over sodium wire. *dl-trans*-2-Butene episulfide was prepared by the method of Bordwell and Andersen,[9] bp 89–91° (737 mm). (*SS*)-(−)-*trans*-2-Butene episulfide was prepared in the same manner, bp 89–91° (736 mm), $[\alpha]^{25}D$ −132.9° (neat) (highest previously reported value, $[\alpha]^{24}D$ −134.8°, neat[10]), from (*RR*)-(+)-*trans*-2,3-epoxybutane, $[\alpha]^{25}D$ +45.75°. The latter compound was prepared from (*RR*)-(−)-2,3-butanediol (from the action of *Aerobacillus polymyxa*[11,12] on glucose) by published methods.[13,14] (*SS*)-(−)-*trans*-2,3-Dimethylaziridine was prepared by the published method[15] from the same optically active epoxide, bp 73.5–74.5°, $[\alpha]^{25}D$ −99.87° (neat) (lit.[15] −103.8°). Other materials were reagent grade, and were used without purification.

Optical rotations were determined on a Zeiss 0.005° photoelectric polarimeter, in 50- and 100-mm tubes of all glass construction except for quartz windows. Infrared spectra were determined on a Perkin-Elmer Model 421 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined with a Varian Model A-60 spectrometer on carbon tetrachloride solutions containing tetramethylsilane as an internal standard. Vapor phase chromatographic (vpc) analyses were made on 5 and 8 ft × 0.25 in. columns of silicone (GE SF 96) on Fluoropak or firebrick. Elemental analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif.

trans-**2-Phenyl-3a,4,5,6,7,7a-hexahydrobenzthiazole.** This compound was prepared from 5.0 g (0.044 mole) of cyclohexene sulfide by the sulfuric acid procedure of the previous paper,[1] using excess benzonitrile as solvent. The thiazole was separated from benzamide by treatment with hot hexane and removal of the insoluble amide by filtration. On cooling, the solution deposited the product in crops of 2.55, 1.46, and 0.92 g (total 4.93 g, 52%), mp 48–52°, raised to 52–53.5° by one recrystallization from hexane (lit.[2a] 51–52°).

The picrate precipitated from ether and was recrystallized once from 95% ethanol, mp 197–199° (lit.[2a] 195–196°).

The methiodide was prepared by refluxing the thiazole with excess methyl iodide in benzene. The salt was isolated in low yield, mp 224–226° after washing twice with ether and air drying (lit.[3] 225–226°).

The ethiodide was prepared according to Kojima.[3] After washing with benzene until free from a reddish coloration, it melted at 181–183° (lit.[3] 181–182°).

The 2,4,6-trinitrobenzenesulfonate (TNBS) salt was prepared in the usual manner,[1] and recrystallized from 95% ethanol, mp 208–209°.

2,4-Dimethyl-Δ^2-thiazoline. The reaction of propylene sulfide with acetonitrile was carried out by the same sulfuric acid procedure, using 5.0 g (0.068 mole) of episulfide, with excess acetonitrile as solvent. The yield of thiazoline was 1.32 g. Analysis by vpc gave only one peak in addition to that due to remaining acetonitrile. The sample for nmr and elemental analysis was prepared by vpc, $n^{25}D$ 1.4953.

Anal. Calcd for C_5H_9NS: C, 52.13; H, 7.88. Found: C, 52.20; H, 7.86.

The picrate precipitated from ether, and was recrystallized four times from 95% ethanol, mp 145.5–147° (reported melting point for the picrate of 2,5-dimethyl-Δ^2-thiazoline, 126°[16]).

Anal. Calcd for $C_{11}H_{12}N_4O_7S$: C, 38.37; H, 3.51. Found: C, 38.39; H, 3.67.

The TNBS salt crystallized from 95% ethanol; after one recrystallization from the same solvent, it melted at 163–165°.

(**4***R*:**5***S*)-(−)-*cis*-**2,4,5-Dimethyl-Δ^2-thiazoline.** Preparation of the optically active compound from (*SS*)-(−)-*trans*-2-butene episulfide was by the same procedure, using 5.30 g (0.06 mole) of episulfide. The thiazoline, isolated by the usual procedure, weighed 5.86 g, 75% yield. The crude material was distilled through a 10-cm Vigreux column, bp 68° (25 mm). A center cut, d_{25} 0.9871, $n^{25}D$ 1.4935, exhibited $[\alpha]^{25}D$ −64.67° (neat). For comparison with the enantiomer, below, the rotation was also determined in hexane, $[\alpha]^{25}D$ −66.24° (10.39%, hexane).

The picrate precipitated from ether, mp 149–151° after recrystallization from 95% ethanol.

The TNBS salt crystallized from 95% ethanol. After one recrystallization from 95% ethanol, it melted at 124–126°, solidified, and melted again at 147–148°.

The nmr spectrum of the free base was virtually identical with the spectrum of its *dl* isomer.

(**4***S*:**5***R*)-(+)-*cis*-**2,4,5-Trimethyl-Δ^2-thiazoline.** This thiazoline was prepared by the method reported in the previous paper[1] for synthesis of *trans*-2,4,5-trimethyl-Δ^2-thiazoline from *cis*-2,3-dimethylaziridine and thioacetamide. From 1.10 g (0.016 mole) of (*SS*)-(−)-2,3-dimethylaziridine and 2.0 g (0.027 mole) of thioacetamide was obtained 0.48 g of colorless oil, which was purified by vpc, $n^{25}D$ 1.4921, $[\alpha]^{25}D$ +72.67° (11.22%, hexane).

The picrate, precipitated from ether and recrystallized from 95% ethanol, melted at 150.5–151.5°.

The TNBS salt crystallized from 95% ethanol; after one recrystallization from the same solvent, it melted at 149–150°.

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