Mechanism of Thietane Formation from the Reaction of 1,3-Dioxan-2-ones with Thiocyanate Ion. A Stereochemical Investigation

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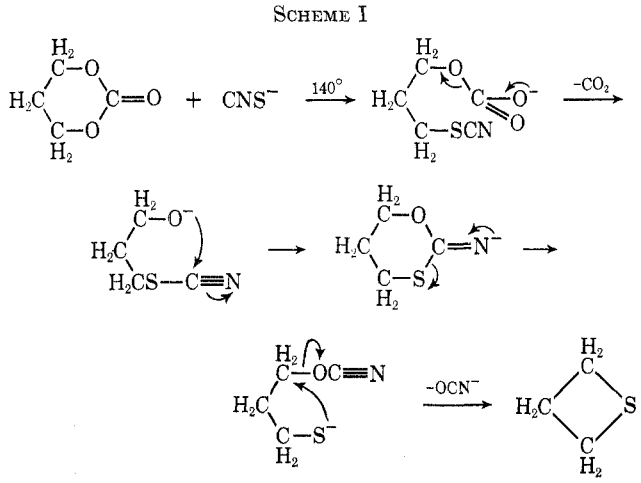
The stereochemical fate of C-4 in a 1,3-dioxan-2-one in its decomposition to a 2-substituted thietane has been examined. Lithium aluminum hydride reduction of (*R*)-(−)-3-acetoxybutyric acid, obtained from quinine resolution of β-hydroxybutyric acid, afforded (*R*)-(−)-1,3-butanediol. This diol was then converted to (*R*)-(−)-4-methyl-1,3-dioxan-2-one, which was in turn heated with potassium thiocyanate at 170–180°. The resulting thietane was oxidized to give (*S*)-(−)-2-methylthietane 1,1-dioxide with a high degree of stereospecificity. The absolute configuration of this sulfone was established in the following manner. (*R*)-(−)-1,3-Dibromobutane was prepared by hydride reduction of (*S*)-(+)-3-acetoxybutyric acid, dimesylation of the resulting (*S*)-(+)-1,3-butanediol, and treatment of the dimesylate with lithium bromide in hot dioxane. Cyclization of the dibromide with thiourea and base, followed by oxidation of the cyclic sulfide, gave (*S*)-(−)-2-methylthietane 1,1-dioxide. The *S* absolute configuration is demanded by the double displacement incurred in passing from the dimesylate to the cyclic sulfone. Assessment of the magnitude of the stereoselectivity was gained by resolving (with *d*-camphor-10-sulfonic acid) *trans*-2-methyl-3-piperidinothietane 1,1-dioxide followed by carefully controlled Hofmann degradation of its methiodide. Hydrogenation of the (*R*)-(−)-4-methylthiete 1,1-dioxide so produced gave (*R*)-(+)-2-methylthietane 1,1-dioxide of maximum rotation. From these data, the stereospecificity realized in the 1,3-dioxan-2-one to thietane conversion was very high. The overall stereochemical course provides compelling support for the mechanism advanced earlier. The stereochemical interconversions have also demonstrated that both possible antipodes of a 2-substituted thietane can be cleanly prepared from a single enantiomer of a disymmetric 1,3-diol.

In 1958, Searles and Lutz discovered that fusion of equimolar quantities of potassium thiocyanate and the cyclic carbonate ester of a 1,3-diol (a 1,3-dioxan-2-one) resulted in formation of carbon dioxide and the related thietane.[2a] Subsequently, this same group established that the scope of this thietane synthesis is rather wide;[2b] in actuality, the simplicity of the method and ready availability of the starting materials has given this reaction considerable importance as a practical synthesis of this four-membered heterocyclic system.[3] The mechanism which has been advanced in explanation of this transformation is illustrated for the simplest case in Scheme I. The intervention of hydroxy thiocyanates

SCHEME I



(as the alkoxide ions) was thought to take place by analogy to the mechanism by which 1,3-dioxol-2-ones[4] and epoxides[5] are converted to episulfides with thiocyanate ion. Some measure of further support for the scheme was derived from the observation that higher temperatures (~200°) are required for the reaction as the level of steric hindrance at the α-carbon atoms of the 1,3-dioxan-2-one is increased. A direct relationship between the degree of steric hindrance at the α positions and the per cent of oxetane by-product produced was also noted. However, all of the evidence to date has been inferential.

The purpose of this study was twofold: (a) to obtain evidence relating to the mechanism of the title reaction by examining the stereochemical course of the process, and (b) to determine if the synthesis of optically active thietanes could be achieved by this method.

The first consideration was the preparation of an optically active 1,3-dioxan-2-one of known absolute configuration. To this end, commercially available *dl*-β-hydroxybutyric acid was acetylated and partially resolved with quinine. Lithium aluminum hydride reduction of the liberated (*R*)-(−)-3-acetoxybutyric acid (**1**)[6] afforded (*R*)-(−)-1, 3-butanediol (**2**), $[\alpha]^{22}D$ −8.2 ± 0.8° (*c* 5.385, C_2H_5OH).[7] This series of transformations (Scheme II) was completed by conversion of **2** to (*R*)-(−)-4-methyl-1,3-dioxan-2-one (**3**), $[\alpha]^{22}D$ −9.4 ± 0.5° (*c* 10.310, C_2H_5OH). Fusion of **3** with an equimolar quantity of potassium thiocyanate at 170–180° afforded 2-methylthietane (**4**) which was directly oxidized with *m*-chloroperbenzoic acid for the purpose of characterization. The pure 2-methylthietane 1,1-dioxide (**5**) so obtained exhibited $[\alpha]^{21}D$ −5.8 ± 1.7° (*c* 2.410, C_2H_5OH) and gave infrared and nmr spectra which were superimposable upon those of an optically inactive sample (see Experimental Section).

(1) American Chemical Society Petroleum Research Fund Graduate Fellow, 1968–1969; National Science Foundation Graduate Fellow, 1966–1968.

(2) (a) S. Searles, Jr., and E. F. Lutz, *J. Amer. Chem. Soc.*, **80**, 3168 (1958); (b) S. Searles, Jr., H. R. Hays, and E. F. Lutz, *J. Org. Chem.*, **27**, 2828 (1962).

(3) Y. Etienne, R. Soulas, and H. Lumbroso in "The Chemistry of Heterocyclic Compounds," Vol. 19, Part II, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, pp 686, 687.

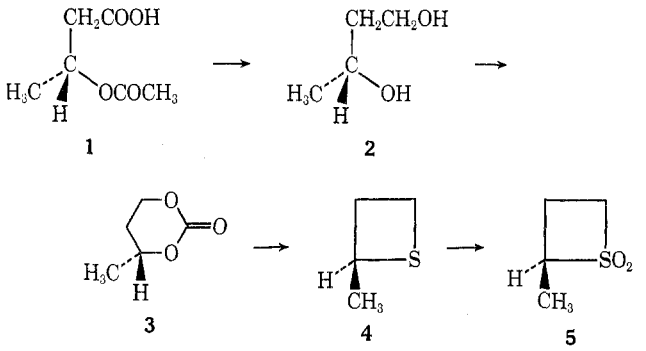
(4) S. Searles, Jr., H. R. Haynes, and E. F. Lutz, *J. Org. Chem.*, **27**, 2832 (1962).

(5) E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 3444 (1951); C. C. Price and P. F. Kirk, *ibid.*, **75**, 2396 (1953).

(6) For the absolute configurational assignment, see (a) K. Serck-Hanssen, *Ark. Kemi*, **8**, 401 (1955); (b) K. Serck-Hanssen, S. Stallberg-Stenhagen, and E. Stenhagen, *ibid.*, **5**, 203 (1953).

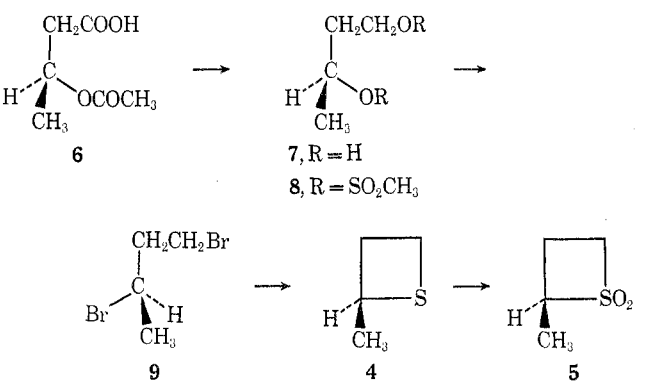
(7) 1,3-Butanediol possessing a maximum rotation of $[\alpha]^{23}D$ +27.3 ± 0.5° (*c* 5, C_2H_5OH) has been shown to be of the (*S*)-(+) configuration.[6a]

SCHEME II



The optical activity of **5** clearly signaled that total racemization was not occurring in the passage from **3** to **4**. To reveal whether net retention or inversion had taken place at C-4 in **3**, determination of the absolute configurations of (+)- and (−)-2-methylthietane 1,1-dioxides was made. For this purpose, partially resolved (*S*)- (+)-3-acetoxybutyric acid (**6**) was reduced by means of lithium aluminum hydride to (*S*)-(+)-1,3-butanediol (**7**), $[\alpha]^{24}D$ +10.1 ± 0.5° (*c* 10.17, $CHCl_3$).[6a,8] Treatment of **7** with methanesulfonyl chloride in pyridine gave dimesylate **8** which was directly exposed to the action of lithium bromide in refluxing dioxane (Scheme III). Cyclization of **9** with thiourea in

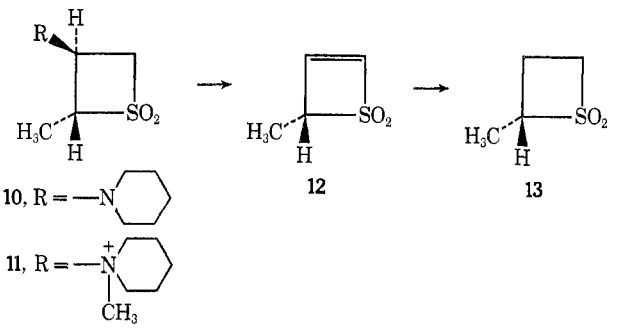
SCHEME III



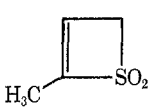
aqueous sodium hydroxide and oxidation of the resulting sulfide afforded 2-methylthietane 1,1-dioxide possessing $[\alpha]^{24}D$ −8.4 ± 0.7° (*c* 5.620, C_2H_5OH).[9] In view of the double SN2 displacement which intervenes in the passage from **8** to the thietane, the asymmetric carbon in the derived sulfone must be of the *S* configuration. Because **5** is likewise levorotatory, it now follows that the chemical change at C-4 in **3** occurs with inversion of configuration.

In the final attack on this mechanistic question, assessment of the magnitude of the stereospecificity realized in the production of **4** from **3** was highly desirable. The synthesis of 2-methylthietane 1,1-dioxide of maximum rotation began with the preparation of *trans*-2-methyl-3-piperidinothietane 1,1-dioxide *d*-camphor-10-sulfonate. Four successive recrystallizations of this salt from absolute ethanol gave a solid of mp 244.5–246° dec, from which pure **10**, $[\alpha]^{22}D$ + 70.0 ± 0.3° (*c* 3.100, C_2H_5OH), was obtained. Additional recrystallizations of the diastereomeric salt from ethanol and acetonitrile failed to increase further its melting point or the optical rotation of free amine **10**. Quaternization of this material gave in essentially quantitative yield the methiodide **11**, $[\alpha]^{21}D$ +21.6 ± 0.2° (*c* 4.829, H_2O) (Scheme IV). Hofman elimination of **11** was achieved

SCHEME IV



readily by means of dry silver oxide in anhydrous tetrahydrofuran to which had been added some calcium sulfate. This modification of the standard Hofmann procedure was devised in order to maximize the yield of 4-methylthiete 1,1-dioxide (**12**). Under the stated conditions, **12** containing no more than 7 ± 1% (nmr analysis) of the more stable but optically inactive 2-methylthiete 1,1-dioxide (**14**), could be routinely prepared.



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In contrast, **14** is readily available as the major product from the silver oxide induced Hofmann elimination of *dl*-**11** in water solution. Submission of pure **12**, $[\alpha]^{21.5}D$ −21.2 ± 0.4° (*c* 5.995, $CHCl_3$), to catalytic hydrogenation afforded optically pure **13**, $[\alpha]^{21.5}D$ +21.0 ± 0.2° (*c* 9.740, C_2H_5OH).

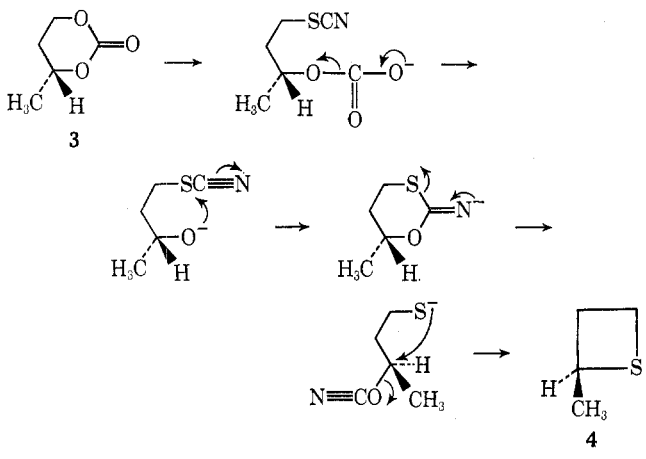
On this basis, the 2-methylthietane 1,1-dioxide obtained from chiral 1,3-dioxan-2-one **3** was approximately 28% optically pure. Since the (*R*)-(−)-1,3-butanediol employed in Scheme II was of 30% optical purity, the stereospecificity realized in this experiment is clearly very high.

The overall stereochemical course of the 1,3-dioxan-2-one to thietane conversion substantiates the previously proposed mechanism (Scheme I) and parallels that found in the analogous reaction of thiocyanate ion with 1,3-dioxol-2-ones to give episulfides.[3b] Thus, the requirement that a Walden inversion at C-4 in **3** necessarily accompany the substitution of oxygen by sulfur can be attributed to the operation of an SN2 process at this site. Because of the unsymmetrical nature of **3**, this inversion of configuration could occur in either step 1 or 5 (Scheme I). It would seem most reasonable from steric considerations that attack by thiocyanate ion at the lesser substituted α carbon, *i.e.*, C-6, would be kinetically preferred. This would imply that the intramolecular displacement of cyanate ion by mercaptide is the principal stereochemical step in the present instance (Scheme V).

(8) R. Lukes, J. Jary, and J. Nemec, *Collect. Czech. Chem. Commun.*, **27**, 735 (1962).

(9) For a preliminary account of this synthesis in a different context, see L. A. Paquette and J. P. Freeman, *J. Amer. Chem. Soc.*, **91**, 7548 (1969).

SCHEME V



Of added significance, the stereochemical interrelationships uncovered in the present study have also demonstrated that a single enantiomer of a dissymmetric 1,3-diol can be cleanly converted into the *R* or *S* antipode of a 2-substituted thietane either by decomposition of the 1,3-dioxan-2-one derivative (single inversion, Scheme II) or cyclization of the derived 1,3-dibromide with thiourea (double inversion, Scheme III). However, for ease in the resolution method and for the yields obtained, the sulfene route (Scheme IV) is superior for synthetic access to chiral thietane derivatives which are needed in further stereochemical studies currently in progress.

Experimental Section

All melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Nuclear magnetic resonance spectra were taken with Varian Associates A-60 and A-60A spectrometers.

(±)-3-Acetoxybutyric Acid.[6b]—(±)-3-Hydroxybutyric acid (50.0 g, 0.485 mol) was stirred into an ice-cooled solution of 68 ml (0.709 mol) of acetic anhydride in 97 ml of pyridine. Stirring was continued until the ice melted and at room temperature for an additional 6 hr. The reaction mixture was stored at 0° for 8 hr and then concentrated by removal of 127 ml of liquid (mostly pyridine) at 35–49° and 15 mm. The residue was cooled, 50 ml of 6 *N* hydrochloric acid was added, and the mixture was extracted four times with ether. Concentration of the combined dried ether extracts and distillation of the residue afforded 36.9 g (52%) of (±)-3-acetoxybutyric acid, bp 102–105° (0.03 mm), n^{28}D 1.4283 [lit.[6b] bp 80–85° (0.25 mm), n^{25}D 1.4270]. The lower boiling fractions contained considerable amounts of crotonic acid. The infrared spectrum of the product exhibited strong infrared absorption at 1730 and 1242 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.28 (sextet, J = 6.4 Hz, H-3), 2.63 (d of d, J = 6.4 Hz, H-2), 2.04 (s, CH_3CO–), and 1.32 (d, J = 6.4 Hz, CH_3–).

(*R*)-(−)- and (*S*)-(+)-3-Acetoxybutyric Acid (1 and 6).—(±)-3-Acetoxybutyric acid (31.89 g, 0.218 mol) was mixed in ethyl acetate (*ca.* 100 ml) with 70.8 g (0.218 mol) of anhydrous quinine, and the mixture was heated until most of the quinine had dissolved. The quinine residue was removed by filtration through a glass wool plug. The filtrate was reheated to near the boiling point and petroleum ether (bp 60–110°) was added until cloudiness persisted. The solution was again rewarmed to produce homogeneity, seeded, and cooled to room temperature and then to 0°. After 3 days at 0°, the white crystalline salt was filtered and washed twice with ethyl acetate–petroleum ether (1:1). Fractional crystallization of this solid from ethyl acetate–petroleum ether gave 20 g of quinine salt, mp 101.5–104°.

(*S*)-(+)-3-Acetoxybutyric acid (6) was recovered quantitatively by treatment of this quinine salt with 5% hydrochloric acid, saturation of the solution with sodium chloride, extraction with ether, and concentration of the combined organic extracts. Molecular distillation at 70° (0.01 mm) gave a colorless oil, $[\alpha]^{24}$D +3.6 ± 0.3° (*c* 10.175, C_2H_5OH) [lit.[6b] $[\alpha]^{23}$D +2.78° (homogeneous, *l* 1)].

(*R*)-(−)-3-Acetoxybutyric acid (1) was obtained similarly from the mother liquor residues from several resolutions by treatment with 5% hydrochloric acid and extraction in the above manner. The concentrated oil was distilled at 95–99° (0.05 mm) and there was obtained 25.4 g of 1. This acid was reduced directly to 2 for measurement of optical rotation.

(*R*)-(−)-1,3-Butanediol (2).—To a stirred slurry of 19.8 g (0.522 mol) of lithium aluminum hydride in 150 ml of anhydrous tetrahydrofuran was added dropwise a solution of 25.4 g (0.174 mol) of 1 in 75 ml of the same solvent at such a rate that gentle reflux was maintained. The reaction mixture was stirred at reflux for 9 hr and cooled, and the hydride was decomposed by cautiously adding 19.8 ml of water, 19.8 ml of 12% sodium hydroxide solution, and 60 ml of water. The solid aluminates were removed by filtration, the filter pad was carefully washed with tetrahydrofuran, and the combined filtrates were dried and evaporated. Distillation of the residue gave 14.13 g (90%) of 2, bp 64.5–74° (0.03 mm), $[\alpha]^{22}$D −8.2 ± 0.8° (*c* 5.385, C_2H_5OH),[7] with a satisfactory infrared spectrum.

(*S*)-(+)-1,3-Butanediol (7) was prepared as above from 4.01 g (0.0274 mol) of 6 and 3.12 g (0.082 mol) of hydride. Work-up and distillation led to the isolation of 1.38 g (56%) of 7, bp 52–56° (0.01 mm), $[\alpha]^{24}$D + 13.0 ± 0.6° (*c* 10.01, $CHCl_3$),[6a,7] with an infrared spectrum identical with that of racemic diol. An additional 1.09 g of diol was obtained from the pot residue by molecular distillation. The total yield was quantitative.

(*R*)-(−)-4-Methyl-1,3-dioxan-2-one (3).—Into a three-necked flask equipped with a mechanical stirrer, addition funnel, and Claisen head was added 14.13 g (0.157 mol) of 2 and a catalytic amount of sodium ethoxide. When the external oil-bath temperature reached 90°, 20.40 g (0.173 mol) of diethyl carbonate was added dropwise. Heating was continued along with the carbonate addition and continued until the theoretical amount of ethanol had been distilled. Ether (50 ml) was added to the cooled residue and this solution was extracted twice with water. The aqueous extracts were saturated with sodium chloride and reextracted with ether. The combined organic layers were dried, concentrated, and distilled to give 2.14 g of 3, bp 62–79° (0.04 mm) [lit.[10] bp 100–110° (0.8 mm)], $[\alpha]^{22}$D −9.4 ± 0.5° (*c* 10.310, C_2H_5OH). Vpc analysis indicated this sample to be of *ca.* 85% purity.

(*S*)-(−)-2-Methylthietane 1,1-Dioxide (5) from 3.—Using the procedure of Searles, Hays, and Lutz,[3] 2.68 g (0.0276 mol) of potassium thiocyanate and 2.14 g of 3 (85% purity) were allowed to react at 170–180°. The total yield of thietane–oxetane mixture was 0.83 g. This material was oxidized directly with 1.82 g of *m*-chloroperbenzoic acid in 17 ml of methylene chloride for 20 min at −10° and for 10 hr at room temperature. Purification of the mixture by molecular distillation at 55–60° (0.03 mm) gave 70 mg (4%) of 5 as a colorless liquid, $[\alpha]^{21}$D −5.8 ± 1.7° (*c* 2.410, C_2H_5OH). The infrared and nmr spectrum of this material were superimposable on those of an analytical sample of (±)-2-methylthietane 1,1-dioxide (see below).

(±)-1,3-Butanediol Dimethanesulfonate.—Neat methanesulfonyl chloride (4.65 g, 0.0406 mol) was added dropwise to a stirred solution of 1.83 g (0.0203 mol) of (±)-1,3-butanediol in 9 ml of pyridine at −10 to −5°. The reaction mixture was stored at 0° for 20 hr, poured onto twice its volume of crushed ice, and extracted with methylene chloride. To this organic solution was added ice-cold 5% hydrochloric acid solution with shaking until the aqueous layer remained acidic. The organic layer was separated, dried, and evaporated to give 4.49 g of a yellow oil. Absolute ethanol (*ca.* 2.5 ml) was added followed by the dropwise addition of chloroform until the mixture became homogeneous. After a few minutes, crystallization began. The flask was cooled in ice and the solid was filtered. After rinsing the solid with cold absolute ethanol and drying, there was obtained 3.60 g (72%) of white crystalline dimesylate: mp 41.5–43° (lit.[11] mp 40–41°); $\nu_{max}^{CHCl_3}$ 1360 and 1175 cm^{-1} (–SO_2–); $\delta_{TMS}^{CHCl_3}$ 4.87 (sextet, J = 6.2 Hz, H-3), 4.28 (t, J = 6.0 Hz, H-1), 3.05 (s, 6, CH_3SO_2–), 2.07 (q, J = ~6.1 Hz, H-2), and 1.47 (d, J = 6.2 Hz, CH_3–).

(10) S. Searles, Jr., D. G. Hummel, S. Nukina, and P. E. Throckmorton, *J. Amer. Chem. Soc.*, **82**, 2928 (1960).

(11) A. G. Kostsova and L. B. Leout'eva, *J. Gen. Chem. USSR*, **30**, 3508 (1960).

(*S*)-**1,3-Butanediol dimethanesulfonate** (**8**) was prepared in analogous fashion from a 3.03-g (0.0336 mol) sample of **7**, $[\alpha]^{22}D$ +10.1 ± 95° (*c* 10.170, $CHCl_3$), and 7.70 g (0.0672 mol) of methanesulfonyl chloride in 27 ml of pyridine. There was obtained 7.14 g (86%) of **8** with spectral characteristics identical with those of the racemic material.

(*R*)-(−)-**1,3-Dibromobutane** (**9**).—To a slurry of 12.6 g (0.145 mol) of lithium bromide (dried 2 days *in vacuo* at 80° over phosphorus pentoxide) in 50 ml of dry dioxane was added the 7.14 g (0.0289 mol) of **8** prepared above, and the heterogeneous mixture was allowed to stir at reflux for 5 hr. After cooling and standing at room temperature overnight, the mixture was poured into 150 ml of water and extracted with five portions of pentane. The combined pentane layers were washed four times with water and the combined aqueous layers reextracted once with pentane. The combined pentane extracts were shaken with brine, dried, and evaporated to give 5.25 g of **9** of *ca.* 92% purity by vpc analysis (77%), $[\alpha]^{25}D$ −29.9 ± 0.5° (*c* 17.780, $CHCl_3$). The spectral properties of **9** were identical with those of the *dl* mixture.

(*S*)-(−)-**2-Methylthietane 1,1-Dioxide** (**5**) **from 9**.—The 5.02-g sample of **9** (92% purity, 0.0214 mol), prepared above, was added to a prewarmed (60°) solution of 1.95 g (0.0257 mol) of thiourea and 3.09 g (0.0771 mol) of sodium hydroxide in 25 ml of water. The mixture was heated at reflux for 1.2 hr, 10 ml more water was added, and the volatile organic components were steam distilled. The steam distillate was extracted with four small portions of methylene chloride and the combined extracts were dried; the thietane was oxidized directly as above with 8.44 g of 87.5% *m*-chloroperbenzoic acid (0.0428 mol) in 55 ml of methylene chloride at −10°. Upon molecular distillation of the residual crude product at 55–63° (0.03 mm), there was obtained 0.54 g (21%) of **5**, $[\alpha]^{24}D$ −8.3 ± 0.4° (*c* 10.615, C_2H_5OH), whose spectra perfectly matched those of analytically pure (±)-2-methylthietane 1,1-dioxide (see below).

(±)-*trans*-**2-Methyl-3-piperidinothietane, 1,1-Dioxide** [(±)-**10**].—N-Propenylpiperidine[12] (7.40 g, 0.059 mol) and 5.97 g (0.059 mol) of triethylamine were dissolved in 250 ml of ether and the solution was cooled to −5° with stirring under nitrogen. Methanesulfonyl chloride (6.75 g, 0.059 mol) in 50 ml of ether was added at such a rate that the temperature remained below −5°. Stirring was continued at room temperature for 7 hr, the triethylammonium hydrochloride was filtered off through Celite, and the filtrate was evaporated; 11.57 g of orange oil remained.

This crude amine was redissolved in ether and precipitated as the hydrochloride salt by the addition of ethereal hydrogen chloride: yield, 12.06 g (85%). Recrystallization from ethanol and acetonitrile gave colorless crystals, mp 215–216° dec (lit.[13] mp 210–211°). Liberation of the free base with aqueous potassium carbonate gave the sulfone as a white crystalline solid: mp 41–43° (lit.[13] mp 17–23°); $\nu_{max}^{CCl_4}$ 2950, 1440, 1320, 1198, and 1135 cm^{-1}; $\delta_{TMS}^{CCl_4}$4 .22 (q, *J* = 7.0 Hz, H-2), 3.98 (d, *J* = 3 Hz, one H-4), 3.83 (d, *J* = 1.5 Hz, other H-4), 2.1–2.8 (m, 5, H-3 and α-piperidino), 1.4–1.7 (m, 6, other methylenes), and 1.45 (d, *J* = 7.0 Hz, $-CH_3$).

Resolution of *trans*-**2-Methyl-3-piperidinothietane 1,1-Dioxide.**—A 15.00-g (73.8 mmol) sample of amino sulfone (±)-**10** was dissolved in 150 ml of acetone and mixed with a solution of 17.15 g (73.8 mmol) of *d*-camphor-10-sulfonic acid in 130 ml of the same solvent. After 5 hr the precipitated solid was filtered and dried, 27.72 g (86%), mp 231.5–233° dec. Four successive recrystallizations of this salt from absolute ethanol produced crystals of mp 244.5–246° dec. Liberation of the free base with aqueous potassium carbonate solution afforded pure **10**, mp 54.5–56.0°, $[\alpha]^{22}D$ +70.0 ± 0.3° (*c* 3.100, C_2H_5OH). The melting point of the salt and the optical rotation of the base failed to increase after further recrystallizations of the former substance from both ethanol and acetonitrile.

Methiodide of (±)-*trans*-**2-Methyl-3-piperidinothietane 1,1-Dioxide** [(±)-**11**].—To 3.00 g (14.8 mmol) of amino sulfone (±)-**10** dissolved in 15 ml of reagent grade acetone was added 4.20 g (29.6 mmol) of methyl iodide, and the solution was heated (55°) for 6 hr with stirring. An additional 4.20 g of methyl iodide was then added and heating was continued for an additional 12 hr. Cooling of the mixture to 0° and filtration gave 5.00 g (98%) of white, powdery solid, mp 163–169° dec. Recrystallization of this material from absolute ethanol gave pure methiodide, mp 169–175° dec.

Anal. Calcd for $C_{10}H_{20}INO_2S$: C, 34.79; H, 5.84; S, 9.29. Found: C, 34.90; H, 5.88; S, 9.32.

The (+)-methiodide **11** was prepared analogously from 3.10 g (15.25 mmol) of **10** to give 5.17 g (98%) of flat, white needles, mp 196–197.5° dec, $[\alpha]^{21}D$ +21.6 ± 0.2° (*c* 4.829, H_2O).

(±)-**4-Methylthiete 1,1-Dioxide** [(±)-**12**].—A 2% excess (8.87 mmol) of silver oxide was prepared by treating 3.02 g (17.75 mmol) of silver nitrate with 0.71 g (17.75 mmol) of sodium hydroxide in water solution. The resulting solid was repeatedly washed with water until the washings were neutral. The silver oxide was then washed with absolute ethanol, acetone, and ether; the last traces of solvent were removed *in vacuo*.

The powdery solid was shaken in anhydrous diethyl ether (25 ml) for 15 min with 3.00 g (8.70 mmol) of 2-methyl-3-piperidinothietane 1,1-dioxide methiodide. The initially heterogeneous black and white mixture of solids was soon replaced by a grayish, flocculent precipitate. The ether was evaporated and the residue was heated in a rotary evaporator at 80° to decompose the quaternary hydroxide and to remove methylpiperidine byproduct. The residue was extracted with ether, dried, and evaporated. The yellowish oil so obtained exhibited an nmr spectrum which denoted a product mixture of 94 ± 1% of 4-methylthiete 1,1-dioxide and 6 ± 1% of the 2-methyl isomer **14**: yield 0.55 g (53%); $n^{24.5}D$ 1.4813; bp 67–72° (0.05 mm); $\nu_{max}^{CCl_4}$ 1320, 1300, 1188, and 1145 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.10 (dd, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 1.5 Hz, H-3), 6.71 (d, *J* = 4.0 Hz, H-2), 4.85 (qd, *J* = 1.5 and 6.9 Hz, H-4), and 1.51 (d, *J* = 6.9 Hz, $-CH_3$).

Anal. Calcd for $C_4H_6O_2S$: C, 40.66; H, 5.12; S, 27.14. Found: C, 40.72; H, 5.23; S, 26.75.

(*R*)-(−)-**4-Methylthiete 1,1-Dioxide** (**12**).—Silver oxide (50 mmol) was prepared as above from 4.00 g of sodium hydroxide and 17.00 g of silver nitrate. A slurry of the silver oxide, 13.3 g of fine mesh anhydrous calcium sulfate, 16.88 g of **11**, and 50 ml of dry tetrahydrofuran was heated at reflux for 2 hr. After cooling, the solvent was removed on a rotary evaporator and the solids were heated on a steam bath *in vacuo* for 1 hr. The resulting mass was extracted three times with ether, and the combined organic layers were filtered and evaporated to give 4.23 g of crude product. Sublimation of this material at 55° and 0.05 mm gave 3.91 g (68%) of **12** as a white solid, mp 59–61°, $[\alpha]^{25}D$ −20.4 ± 0.2° (*c* 4.802, $CHCl_3$). Recrystallization from petroleum ether–chloroform afforded thick cubic crystals, mp 59.5–16.5°, $[\alpha]^{21.5}D$ −21.2 ± 0.4° (*c* 5.995, $CHCl_3$. Infrared and nmr analyses revealed no trace of the 2-methyl isomer **14**.

2-Methylthiete 1,1-Dioxide (**14**).[14]—To a slurry of 300 g (1.43 mol) of silver oxide in 200 ml of water was added a solution of 264.8 g (0.72 mol) of (±)-*trans*-2-methyl-3-piperidinothietane 1,1-dioxide methiodide in 700 ml of water. The mixture was stirred for 15 min and filtered. The filtrate was heated on a steam bath for 30 min and then evaporated to three-fourths its original volume *in vacuo*. After cooling, the remaining solution was extracted continuously with ether overnight. The ether solution was dried and evaporated to give 51.4 g (64%) of an oil which by nmr analysis was found to be a mixture of **14** (67%) and 4-methylthiete 1,1-dioxide (33%). After standing at −16° for 2 days, this material partially solidified. The solid was separated by filtration, washed with cold ether, and recrystallized from ether to afford 20.7 g (25.8%) of **14**: mp 51.5–52.5°; $\nu_{max}^{CHCl_3}$ 1310 and 1135 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.77 (q, 1, *J* = 1.8 Hz, H-2), 4.38 (m, 2, H-4), and 2.03 (m, 3, $-CH_3$).

Anal. Calcd for $C_4H_6O_2S$: C, 40.67; H, 5.08; S, 27.15. Found: C, 40.74; H, 5.12; S, 26.76.

(±)-**2-Methylthietane 1,1-Dioxide.**—A 68:32 mixture of 4-methyl- and 2-methylthiete 1,1-dioxides (1.7 g) dissolved in 50 ml of absolute methanol was shaken on a Parr apparatus for 5.5 hr under 50 psig of hydrogen in the presence of 0.2 g of 10% palladium on carbon. After filtration, the solvent was evaporated and the residue was molecularly distilled at 39° and 0.05 mm to give 1.03 g (61%) of mobile, water-white liquid, $n^{24.5}D$ 1.4680, which was homogeneous on vpc analysis and thin layer chromatography: $\nu_{max}^{CCl_4}$ 1332, 1217, 1163, and 1135 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.6–4.8 (m, 3, α-sulfonyl), 1.6–2.8 (m, 2, H-3), and 1.45 (d, *J* = 7.2 Hz, $-CH_3$).

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 39.96; H, 6.70; S, 26.48.

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(14) The authors thank Mr. R. W. Houser for this preparation.

(*R*)-(+)-2-Methylthietane 1,1-dioxide (13) was prepared similarly from 12, 85% yield, $n^{26.5}$D 1.4689; $[\alpha]^{25}$D +21.0 ± 0.2° (*c* 9.740, C_2H_5OH).

Registry No.—(±)-3-Acetoxybutyric acid, 24621-58-7; (±)-1,3-butanediol dimethanesulfonate, 24605-74-1; (±)-2-methylthietane 1,1-dioxide, 24609-83-4; **2**, 6290-03-5; **5**, 24621-60-1; **7**, 24621-61-2; **9**, 24621-62-3; (+)-**10**, 24621-63-4; (±)-**10**, 24621-64-5; (+)-**11**, 24621-65-6; (±)-**11**, 24621-66-7; (−)-**12**, 24621-67-8; (±)-**12**, 24605-75-2; **13**, 24605-76-3; **14**, 24621-57-6;

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Chemistry of Isocyanurates. I. Synthesis of Disubstituted Isocyanuric Acids from the Reaction of Alkali Metal Cyanates with Organic Isocyanates[1]

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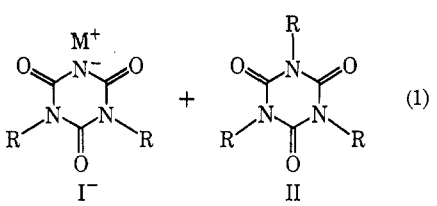
Cyanate ion, unlike other anions, reacts with organic isocyanates to give salts of disubstituted isocyanurates (I^-) which are readily converted to the corresponding acid (I). Trimerization of the isocyanate to the trisubstituted isocyanurate (II) is a competing reaction which can seriously detract from the yield of I. The selectivity to I^- was found to be sensitive to the concentration of cyanate ion, temperature, solvent type, isocyanate structure, concentration of isocyanate, and ionic strength of medium. The mechanistic implication of these parameters on selectivity is discussed.

In the course of a recent investigation into the mechanism by which cyanate ion (NCO^-) reacts with organic halides, a new and convenient synthesis of disubstituted isocyanuric acids (I) evolved.[3] Thus, it was shown that alkali metal cyanates (MOCN) in dipolar aprotic media react with organic isocyanates (RNCO) to give the salt (I^-) of the corresponding disubstituted isocyanuric acid (eq 1). The singular

R—NCO + MOCN ⟶



(1)

by-product is the trisubstituted isocyanurate (II), a product anticipated in view of the ease with which isocyanates undergo base-catalyzed trimerization.[4,5]

Salt I^- is readily separated from trimer II by extracting the solvent-free reaction mixture with water (II is insoluble); subsequent acidification of the aqueous salt solution with hydrochloric acid precipitates the acid I. The present paper deals with the scope of the reaction of eq 1 in terms of the parameters governing the selectivity to I^-.

Results

Although the preparation of disubstituted isocyanurates from RNCO and MOCN is quite general, the selectivity to I^- is dependent on a number of reaction variables. The following parameters were shown to have a marked influence on the competition between trimerization and salt formation.

Isocyanate Structure.—As shown in Table I, a large number of structurally divergent isocyanates are applicable in this synthesis. It is clear that the nature of R has a profound influence on selectivity. The order in decreasing selectivity is aryl > benzyl, allyl ≫ alkyl. This is the same order of reactivity reported for the reaction of RNCO with amines to form ureas;[6] the most electrophilic isocyanate gives the highest selectivity.

Concentration of RNCO.—Selectivity varies inversely with the initial concentration of RNCO. As shown in Table II, a tenfold increase in the initial isocyanate concentration reduced the selectivity by nearly 50%.

Solvent.—A modest study was undertaken to determine the effect of solvent on selectivity. As shown in Table III, the dipolar solvents, such as dimethylformamide (DMF), afford the highest selectivities in addition to rate acceleration. These findings probably reflect changes in KNCO solubility (*vide infra*) rather than changes in dielectric constant or solvent polarity. DMF was employed throughout this study because of its availability and ease of purification.

Temperature.—At moderate temperatures, the selectivity gradually increases with temperature reaching a plateau at 75°. Unfortunately, the temperature effect is complicated by the fact that increasing the reaction temperature also increases the solubility of the metal cyanate (see Table IV).

Concentration of NCO^-.—Owing to the limited solubilities of NaOCN and KOCN (the only readily available alkali metal cyanates), the NCO^- concentra-

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