pyrrole with hydrogen peroxide in acetic acid according to the method of Chierici and Gardini.[3]

2,2'-Pyrrolylpyrrolidine.—The 5-(2-pyrrolyl)-2-pyrrolidone (150 mg) prepared as described above was added to a solution of 500 mg of lithium aluminum hydride in ether (25 ml). The mixture was stirred at room temperature for 1 hr and then refluxed for 15 min. Excess reducing agent was destroyed by the slow addition of water, an additional 25 ml of ether was added, and the solution was filtered. Evaporation of solvent yielded 82 mg (60%) of product, mp 86° after vacuum sublimation (lit.[8] mp 85.5–86.5°). The 2,2'-pyrrolylpyrrolidine was identical (mixture melting point and infrared) with the product prepared independently by the reduction of 2,2'-pyrrolylpyrroline using the method of Atkinson and co-workers.[8] The same product could also be obtained from fluoroborate salt IV by stirring for 1 hr with lithium aluminum hydride at room temperature followed by refluxing for 15 min.


Optical Rotatory Dispersion of Some Cyclic Sulfides[1]

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The optical rotatory dispersion (ORD) and circular dichroism properties of simple organic sulfides have not been studied in detail. Cotton effects have been measured in episulfides,[3–5] 1,3-oxathiolanes,[5,6] 1,3-dithiolanes,[6] and 1,3-oxathianes,[6] but in these compounds special electronic effects may be operative.[4–7] ORD investigations of carbohydrate sulfides[8] and of thio ether derivatives of cysteine and 4-thialysine[9] have been restricted to the range of wavelengths above 265 and ca. 300 mμ, respectively, furnishing plain dispersion curves only. In the circular dichroism of a series of D-(+)-alkylthiosuccinic acids, a first dichroic absorption band was reached with λ_{max} ca. 240 mμ (ORD peak at ca. 250 mμ),[10] but interpretation and analysis of the data are made difficult by the presence of the carboxyl chromophore which has similar transition energy.

To study the optical properties of dialkyl sulfides, we synthesized the conformationally rigid compounds 1 and 2 with known and *opposite* absolute configuration at the 5–6 ring juncture. Compound 1, (−)-

1   2
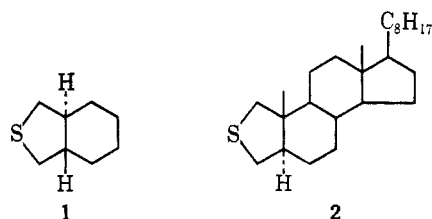
(8R,9R)-*trans*-2-thiahydrindan, was prepared from (+)-*trans*-cyclohexane-1,2-dicarboxylic acid (obtained by resolution[11] of the racemic acid) *via* reduction of the diacid to the diol, tosylation, and ring closure with sodium sulfide. Since the absolute configuration of (+)-*trans*-cyclohexane-1,2-dicarboxylic acid is known to be (S,S) by correlation with (−)-(8R,9R)-*trans*-hexahydroindan-2-one,[11] the absolute configuration of 1 is established unambiguously. Since A-nor-2-thiacholestane (2), was prepared from cholesterol *via* cholestan-3β-ol and the 2,3-secocholestane-2,3-dioic acid, the absolute configuration of 2 is that shown in the formula above.

In Figure 1 are presented the ultraviolet absorption characteristics of sulfides 1 and 2. In acetonitrile solution each compound displays two absorption bands: ca. 205 mμ (ϵ 1790) and 215 mμ (ϵ 1480) [shoulder (sh)] in 1, and ca. 205 mμ (ϵ 1810) (sh) and 215 mμ (ϵ 1370) (sh) in 2. In addition, low-intensity absorption was observed between λ ca. 230 and 260 mμ. This consistently observed feature in the ultraviolet absorption curve indicates the presence of an electronic transition at ca. 240–245 mμ (ϵ ca. 50). The presence of a low-intensity absorption band near 240 mμ in tetramethylene sulfide (tetrahydrothiophene) and other simple sulfides has been previously noted[7,12] and discussed.[12]

In a further refinement of our data, the ultraviolet spectra were decomposed by a nonlinear least-squares curve-fitting computer program[13] into component bands; the long wavelength transition thus dissected out of the tails of the shorter wavelength bands has $\lambda_{max}^{acetonitrile}$ 244.3 mμ (ϵ 53.6) (half band width 10.4 mμ) and $\lambda_{max}^{acetonitrile}$ 245.1 mμ (ϵ 67.8) (half band width 11.1 mμ) for 1 and 2, respectively. This transition proved to be strongly optically active and characteristic of configuration as detailed below.

Inspection of the ORD curve of 1 (Figure 2) reveals a strong negative Cotton effect with a midpoint at about 240 mμ (the second extremum is seen as a shoulder at ca. 230 mμ), followed by a positive effect (midpoint at about 218 mμ) and a negative one (midpoint at about 205 mμ). Decomposition of the ORD curve through use of the computer program recently described by Carver, Shechter, and Blout[14] yielded two Cotton effects, one centered at 243 mμ ($R = -3.86 \times 10^{-40}$ erg cm^3) and one at 217 mμ ($R = +3.48 \times 10^{-40}$ erg cm^3).

Inspection of the ORD curve of 2 (Figure 2) reveals two positive Cotton effects of comparable amplitudes,

(1) This work was supported by the National Science Foundation under Grant No. GP-3375.

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(3) C. Djerassi, H. Wolf, D. A. Lightner, E. Bunnenberg, K. Takeda, T. Komeno, and K. Kuriyama, *Tetrahedron*, **19**, 1547 (1963).

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(13) H. Stone, *J. Opt. Soc. Am.*, **52**, 998 (1962). We are indebted to Mr. M. Goldstein and Dr. J. Jacobus for performing the computations.

(14) J. P. Carver, E. Shechter, and E. R. Blout, *J. Am. Chem. Soc.*, **88**, 2550 (1966). We are indebted to Professor Blout for kindly providing us with details of this program prior to publication, and to Mr. M. Goldstein and Dr. J. Jacobus for performing the computations.
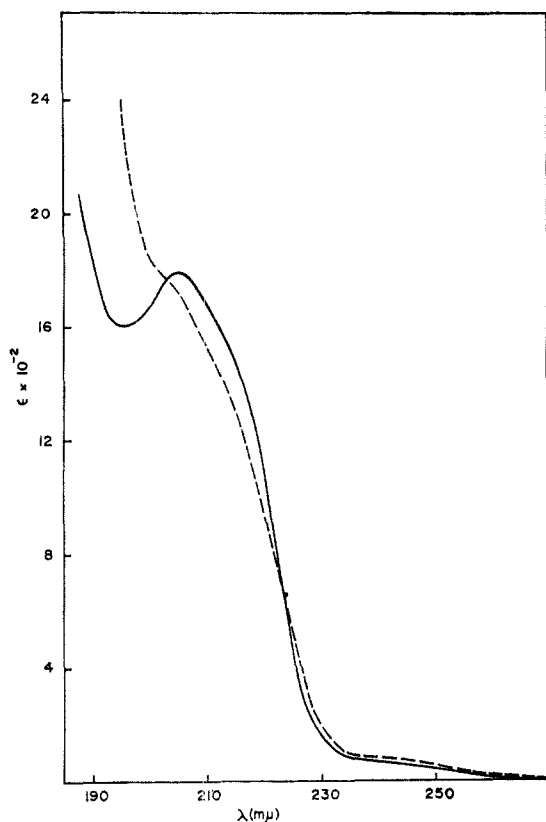
Figure 1.—Ultraviolet absorption spectra in acetonitrile of 1 (solid line) and 2 (dashed line).
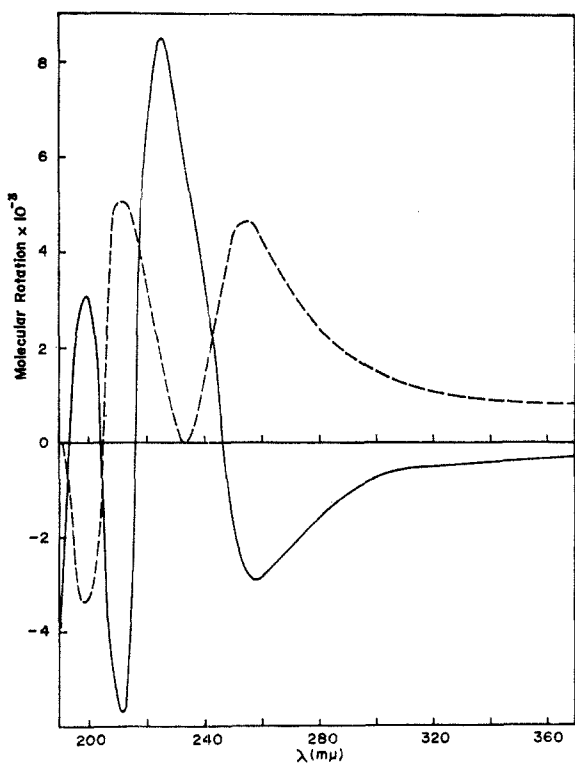

Figure 2.—Optical rotatory dispersions in acetonitrile of 1 (solid line) and 2 (dashed line).

with midpoints at about 240 and 205 mμ. Decomposition of the ORD curve by use of the curve-fitting computer program[14] also yielded two positive Cotton effects, one centered at 244 mμ (R = +3.28 × 10^{-40} erg cm³) and one at 199 mμ (R = +11.76 × 10^{-40} erg cm³), in fair agreement with observations. The

circular dichroism of 2 was in harmony with our interpretation of the ORD. Two positive Cotton effects were observed, one centered at 244 mμ (R = +3.78 × 10^{-40} erg cm³) and one at 205 mμ (R = +3.77 × 10^{-40} erg cm³).

It is thus apparent that 1 and 2 share two optically active transitions at 244 and 205 mμ, with a rotational strength of about 4 × 10^{-40} erg cm³, *whose signs reflect the chirality of the neighboring centers.* In addition, compound 1 has an optically active transition centered at about 217 mμ.

The usefulness of the sulfide chromophore for stereochemical correlations has thus been demonstrated.[14a]

Experimental Section[15]

(−)-(8R,9R)-*trans*-2-**Thiahydrindan** (1).—(±)-*trans*-Cyclohexane-1,2-dicarboxylic acid was prepared from commercially available *cis*-cyclohexane-1,2-dicarboxylic anhydride (Aldrich) according to a literature procedure[16] and resolved through the diquinine salt.[11] The (+)-*trans*-cyclohexane-1,2-dicarboxylic acid thus obtained had [α]^{25}D +20.9° (c 3.5, acetone). On the basis of the previously reported value[11] for presumably optically pure material, [α]^{25}D +22.3°, the sample was 94% optically pure. This material was reduced with lithium aluminum hydride to the bis(hydroxymethyl) derivative, which was tosylated to yield (+)-*trans*-1,2-bis(hydroxymethyl)cyclohexane bis-*p*-toluenesulfonate, mp 107–109°, [α]^{25}D +23.8° (c 2.16, benzene) (lit.[11] mp 109–109.7°, [α]^{28}D +25.0°). This compound was transformed into the sulfide by a procedure analogous to the preparation of *trans*-3-thiabicyclo[3.3.0]octane.[17] A solution of sodium sulfide nonahydrate (6 g in 6 ml of water) was added to the refluxing solution of 3.9 g of the bistosylate in 20 ml of ethanol. After refluxing for 1 hr, 80 ml of water was added and the mixture was distilled. After a forerun the distillate became cloudy and was collected until it became clear again. The distillate was extracted several times with ether and the ethereal solutions were dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residue was distilled twice (Kugelrohr), yield 0.57 g (47%), bp 80–100° (28 mm) [lit.[18] bp 104.6–105.6 (20 mm) for racemic material]. Part of this product (50 mg) was purified further by chromatography on 30 g of silica gel (Merck, neutral) with carbon tetrachloride as eluent. After distillation, the colorless liquid had [α]^{24}D −63.6° (c 0.574, acetonitrile); the infrared spectrum was identical with that of racemic material.[18] No impurities were found by gas–liquid partition chromatography.

Anal. Calcd for C$_8$H$_{14}$S: C, 67.54; H, 9.92; S, 22.54. Found: C, 67.45; H, 9.96; S, 22.75.

In a second run, the first (mainly alcoholic) part of the distillate from the reaction mixture was treated with a warm solution of mercuric chloride in absolute ethanol and the precipitate (4.5 g from 6.8 g of bistosylate) was collected and washed with ethanol giving colorless crystals, mp 207–209°. Recrystallization from 95% ethanol did not change the melting point. To decompose the complex, 4.0 g was placed into a 100-ml flask, 50 ml of 15% hydrochloric acid was added, and the flask was immersed in an oil bath preheated to 160°. The complex dissolved,

(14a) NOTE ADDED IN PROOF.—It has since been shown by P. Salvadori, L. Lardicci, G. Consiglio, and P. Pino [*Tetrahedron Letters*, 5343 (1966)] that in optically active acyclic sulfides the sign of the rotation in the long-wavelength region is related to the configuration of the asymmetric environment of the sulfur atom.

(15) Solvents for optical measurements were "spectroquality" reagents, used without further purification. All ORD data were obtained on a Cary 60 recording spectropolarimeter at varying concentrations (0.574–0.115 g/100 ml for 1, 0.162–0.110 for 2), and path lengths (10–0.1 cm); the spectral slit width was 1.0 mμ for the whole wavelength region. The cells were thermostated at 27°. Circular dichroism measurements were obtained on a Cary 60 circular dichroism attachment kindly provided by Cary Instruments Co. Ultraviolet absorption spectra were recorded on a Cary 14 spectrophotometer (nitrogen purge). Elemental analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

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(18) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954).

and the first 15 ml of distillate was collected and extracted with ether, the solvent was removed from the ether extract under reduced (150 mm) pressure, and the residue was distilled twice (Kugelrohr), yield 1.15 g, $[\alpha]^{26}$D $-73.4°$ (c 2.7, acetonitrile). This material was in all respects (except rotation) identical with that obtained above. The ORD was measured on the material with $[\alpha]$D $-63.6°$, $i.e.$, of optical purity 87–95% (as determined from the rotation of the starting material and of 1 purified by means of the complex).

A-Nor-2-thiacholestane (2).—By duplicating literature procedures,[19] cholesterol was converted into 2,3-secocholestane-2,3-dioic acid (mp 194–196°, lit.[19b] mp 196–197°) via cholestan-3β-ol. A modified Hunsdiecker reaction[20] was used to prepare 1,4-seco-1,4-dibromocholestane from the acid. To 4.34 g (10 mmoles) of the dioic acid, dissolved in 200 ml of carbon tetrachloride at reflux temperature, was added red mercuric oxide (3.24 g, 15 mmoles) while stirring vigorously. The reaction mixture was shielded from light by wrapping the system in aluminum foil, and bromine (3.2 g, 20 mmoles) was added dropwise. After 1 hr, the reaction flask was allowed to cool and the dark mixture was filtered; the filtrate was concentrated under reduced pressure; and the petroleum ether (bp 30–60°) soluble portion of the concentrate was filtered through a short column of silica gel. The crude, oily product (1.7 g, 33% yield), homogeneous to tlc, could be crystallized from methanol, mp 91–92°, $[\alpha]^{27}$D $-1.5 \pm 0.3°$ (c 0.65, chloroform). The material exhibited end absorption only in the ultraviolet spectrum: $\epsilon_{200}^{isooctane}$ 650; $\epsilon_{190}^{acetonitrile}$ 1650.

Anal. Calcd for $C_{25}H_{44}Br_2$: Br, 31.68; mol wt, 502, 504, 506. Found: Br, 31.14; mol wt (mass spectrum),[21] 502, 504, 506.

The dibromide was dissolved in 100 ml of refluxing ethanol. To this solution was added a tenfold excess of sodium sulfide nonahydrate dissolved in a minimal amount of water. Heating was continued for 24 hr; after this time, tlc (ligroin as developer) indicated complete conversion of the dibromide to product. The solvent was removed by distillation, and the residue was diluted with ether and water. In the usual work-up, a 70% yield of A-nor-2-thiacholestane (2) was obtained, mp 101–102°, $[\alpha]^{23}$D $+61°$ (c 1.04, chloroform), after recrystallization from methanol or acetonitrile.

Anal. Calcd for $C_{25}H_{44}S$: C, 79.71; H, 11.77; S, 8.51; mol wt, 376, 378. Found: C, 80.11; H, 11.75; S, 8.22; mol wt (mass spectrum),[21] 376, 378.

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(21) We thank Dr. D. A. Lightner of the University of California at Los Angeles for this measurement made with an AEI MS-9 mass spectrometer. The spectrum was determined with the direct inlet system and 70-ev ionizing energy.

Chemistry of Cephalosporin Antibiotics. IX.
Synthesis of Cephaloridine[1]

JOHN L. SPENCER, FAI Y. SIU, BILL G. JACKSON,
HARVEY M. HIGGINS, AND EDWIN H. FLYNN

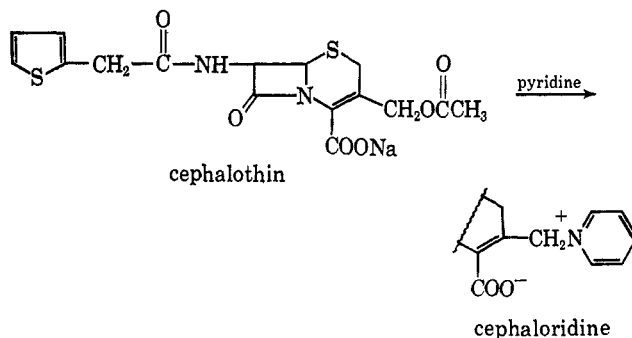The Lilly Research Laboratories, Eli Lilly and Company,
Indianapolis, Indiana

Displacement of the acetoxy group in cephalothin[2] by pyridine results in the formation of cephaloridine. This is analogous to the conversion of cephalosporin C to cephalosporin C_A (pyridine) as reported by Hale, Newton, and Abraham.[3] Initial laboratory evalua-

tions[4,5] indicated this product to be a potentially useful, broad-spectrum antibiotic. These findings have been substantiated by further laboratory and clinical investigations.[6]

cephalothin

cephaloridine

The kinetics of this reaction have been studied by Taylor,[7] and on the basis of these data he proposed a mechanism involving a carbonium ion. We wish to report that addition of certain salts to the reaction solution enhanced the conversion of cephalothin to cephaloridine. In the absence of added inorganic salts, this conversion was only 20–25% because of primary decomposition of cephalothin and secondary reactions of the product, but was increased to 75–80% by addition of potassium thiocyanate or potassium iodide. The yield enhancement was directly proportional to the amount of salt added. In addition to increasing the yield of cephaloridine, these same salts were found to increase the solubility of cephaloridine in water. This made the isolation of cephaloridine more difficult and the removal of these salts mandatory. Exchange of the thiocyanate or iodide for another anion such as acetate which has less effect on the solubility of cephaloridine was accomplished by an anion-exchange resin. This had the added advantage of removing unreacted cephalothin and many of the decomposition products. Direct crystallization of cephaloridine was effected by chilling the solution following ion exchange. This procedure was limited to reaction mixtures containing relatively small amounts of conversion-promoting salts since relatively large amounts (greater than 5 moles/mole of cephalothin) of these adjuvants required impractically large quantities of resin. In addition, the solutions became saturated with inorganic acetates which, in turn, crystallized with cephaloridine.

We found that cephaloridine formed salts with hydrothiocyanic acid and with hydriodic acid which are sparingly soluble in water. This discovery permitted maximum utilization of the beneficial effect of added thiocyanate or iodide. Acidification of such reaction mixtures gave a facile separation of cephaloridine conjugate acids which were optimally converted to the betaine using an ion-exchange resin. Over-all yields of cephaloridine by this method were twice those previously attained.

The complete role of the added ions in this reaction is not yet clear. We have found that salts such as potassium thiocyanate stabilize cephaloridine under

(1) Cephaloridine is the generic name given to 7-[α-(2-thiophene)acet-amido]-3-(1-pyridylmethyl)-3-cephem-4-carboxylic acid betaine. The trade name of cephaloridine is KEFLORDIN (cephaloridine, Lilly).

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