A Comparative Bacteriostatic Evaluation of the Optical Isomers of *threo*-2-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol

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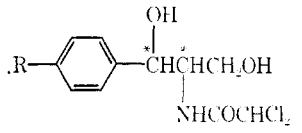
Some years ago, the synthesis of racemic *threo*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol (**1a**) and the corresponding methylsulfonyl analog (**1b**) was reported from this laboratory.[1,2] The 1*S*,2*R* isomer[3] in each series proved to be a potent antibacterial agent in both *in vitro* and *in vivo* applications against a wide variety of organisms.[4,5] On the other hand, the 1*R*,2*S* isomers were essentially inactive.



l-threo

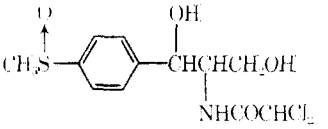
1a, R = CH_3S
b, R = CH_3SO_2
c, R = CH_3SO

* refers to asymmetric centers

More recently, it was found that the sulfone **1b** exhibited great promise as a chemotherapeutic agent in the animal health field for the treatment of a variety of poultry and mammalian diseases such as fowl cholera.[6] This prompted the development of a more satisfactory procedure for converting the sulfide **1a** to the sulfone **1b** than that described in the original publication.[1a] In the revised procedure, the reaction with peracetic acid was carried out in an aqueous medium instead of in acetone. Although physical yields were excellent, examination of the resulting product by means of thin layer chromatography indicated that, in addition to the sulfone **1b**, a second more polar component was present whose concentration varied inversely as the temperature at which the reaction was run. Thus, about 20% of the second component was formed when the reaction temperature was maintained at 30–35°, whereas none could be detected when the temperature was allowed to rise to 50°. Preparative chromatography on silica gel produced, in addition to the sulfone **1b**, a white crystalline solid, mp 117–122°, which proved to be a mixture of the isomeric sulfoxides **1c**.

The fact that sulfoxides may possess optical activity and are resolvable has been amply demonstrated.[7–10] The stereospecific synthesis of sulfoxides by oxidation of sulfides with optically active peracids has also been studied,[11,12] as well as their racemization.[13] Since the presence of a sulfoxide moiety in the molecule **1c** creates an additional asymmetric center, one would expect that four optically active isomeric forms of **1c** could be derived from the racemic *threo* form of **1a**. Thus it appeared that the mixture of sulfoxides (mp 117–122°) which had been eluted from the silica gel column might contain all four isomeric forms.

This investigation, therefore, deals with the preparation, isolation, and examination of the properties of each of the four possible optically active isomers of *threo*-2-dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (**2a–d**).[14]



2a, 1*S*,2*R* (*R* or *S*) (+)
b, 1*S*,2*R* (*S* or *R*) (−)
c, 1*R*,2*S* (*R* or *S*) (+)
d, 1*R*,2*S* (*S* or *R*) (−)

The preparation and resolution of **3** in Scheme I has been described previously.[1a] The optically active amines **3a** and **b** were converted to the corresponding sulfoxides in either of two ways as described in the reaction sequence in Scheme I. Treatment of the resolved amine **3a** with methyl dichloroacetate (MDA) in refluxing 2-propanol afforded the dichloroacetamide **4**. Oxidation of **4** with H_2O_2 in acetic acid gave a mixture of the enantiomeric sulfoxides **6** and **7**.

Initially, attempts were made to separate **6** and **7** by column chromatography. Although there was evidence that some separation had occurred, this approach was abandoned as being impractical. Fractional crystallization was also unsuccessful. Finally, it was decided to explore the properties of the amine **5** in the hope that fractional crystallization could be employed at this stage. The amine **3a** was oxidized with H_2O_2 in 6 *N* HCl to produce a mixture of the enantiomeric 1*S*,2*R*-sulfoxides (**5a** + **5b**). Treatment of the latter with hot 2-propanol yielded a solid which proved to be the isomer **5a**. The free base from this salt was converted to the dichloroacetyl derivative **6**. The more soluble amine hydrochloride proved to be the other isomer

(1) (a) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952); (b) R. A. Cutler and C. M. Suter, U. S. Patent 2,759,971 (1956); (c) C. M. Suter, U. S. Patent 2,759,972 (1956).

(2) C. M. Suter, S. Schalit, and R. A. Cutler, *J. Am. Chem. Soc.*, **75**, 4336 (1953).

(3) In the previous papers,[1,2] the D- and L-*threo* designations were used to denote the absolute configuration of the optically active forms of **1a** and **1b**. In the present paper the absolute configuration of the molecules will be referred to in accord with the Ingold rule [R. S. Kahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956)]. As indicated in ref 1, the designation of the absolute configuration of each of the optically active forms of **1a** and **1b** was based on the comparison of the rotation of the free bases derived therefrom with that of 1*S*,2*R*-2-amino-1-phenyl-1-propanol [D-(−)-norpseudoephedrine]. A similar comparison was made by M. C. Rebstock, H. M. Crooks, Jr., J. Controulis, and Q. R. Bartz [*J. Am. Chem. Soc.*, **71**, 2458 (1949)] with the free base derived from chloramphenicol.

(4) For example, (a) O. Feinsilver, *Am. Practitioner Dig. Treat.*, **6**, 34 (1955); (b) C. A. Messih, *J. Egypt. Public Health Assoc.*, 9 (1954); (c) C. M. Kunin and M. Finland, *Proc. Soc. Exptl. Biol. Med.*, **103**, 246 (1960).

(5) The 1*S*,2*R* isomer of the sulfone **1b** is currently produced and sold by Zambon of Italy under the name Thiophenicol®.

(6) The generic name of the sulfone **1b** is racemophenidol.

(7) P. W. B. Harrison, F. Kenyon, and H. Phillips, *J. Chem. Soc.*, 2079 (1926).

(8) E. V. Bell and G. M. Bennett, *ibid.*, 1798 (1927).

(9) K. Mislow, M. Green, P. Laur, J. Melillo, T. Simmons, and H. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965).

(10) A. C. Cope and E. A. Caress, *ibid.*, **88**, 1711 (1966).

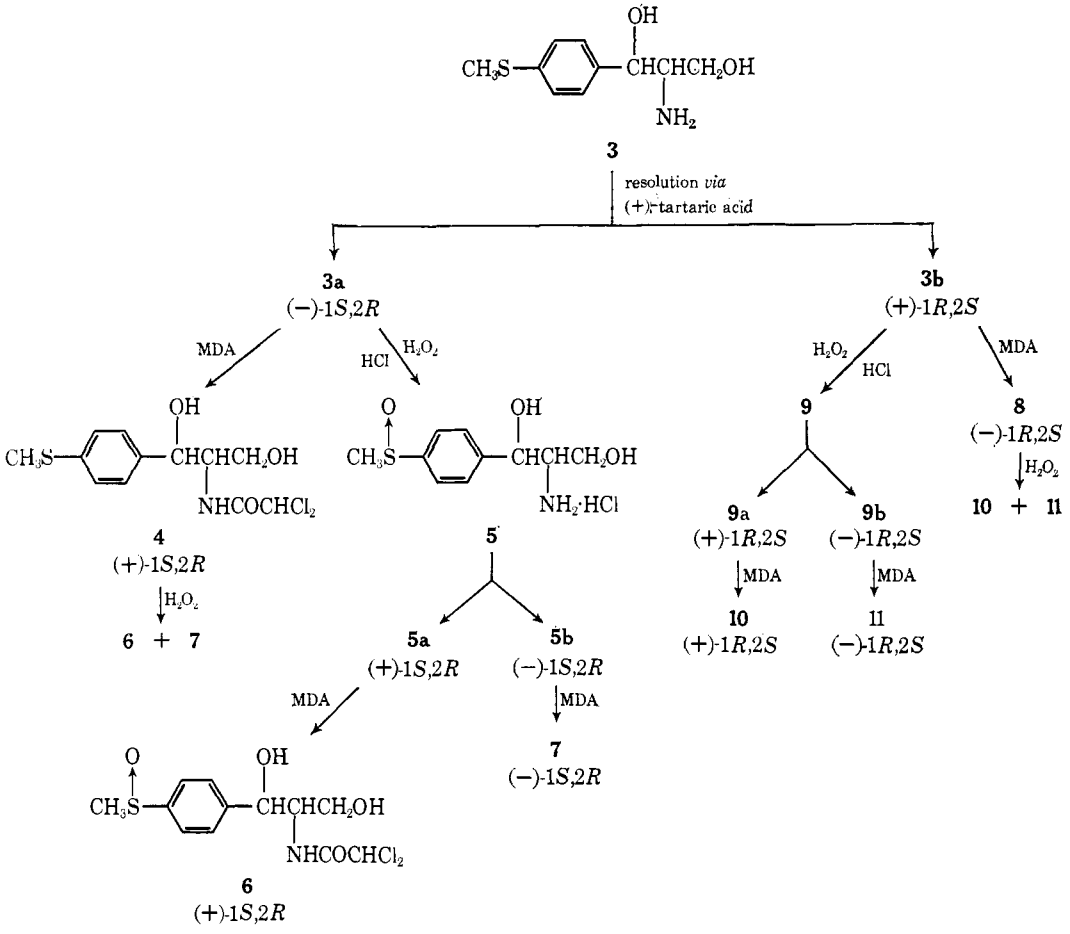
(11) A. Maccioni, F. Montanari, M. Secci, and M. Tramontini, *Tetrahedron Letters*, 607 (1961).

(12) A. Mayr, F. Montanari, and M. Tramontini, *Gazz. Chim. Ital.*, **90**, 739 (1960).

(13) D. R. Rayner, E. G. Miller, P. Beckart, A. J. Gordon, and K. Mislow, *J. Am. Chem. Soc.*, **88**, 3138 (1966).

(14) Since the absolute configuration at the sulfur atom is unknown, it is designated as *R* or *S*. The (+) or (−) following the configuration assignment refers to the specific rotation of the molecule. An investigation is underway to establish the absolute configuration and the results will be published at a later date.

SCHEME I



(**5b**). This material could not be crystallized and was converted directly to the amide (**7**) without further purification.

The foregoing procedure was repeated in the 1*R*,2*S* series. As one might have anticipated, the solubilities of the isomeric salts **9a** and **b** were reversed in comparison to **5a** and **b**. In this case, ethanol was used to separate the isomers.

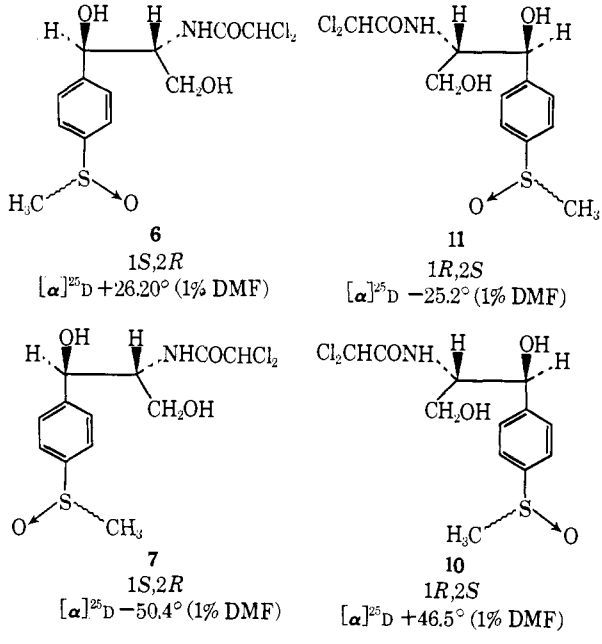
The absolute configurations of the various isomers are illustrated in Scheme II along with their optical rotations. There appears to be some discrepancy between the actual values of the optical rotation of the enantiomeric mixture **6** and **7** and **10** and **11** (Scheme I) and those predicted from the rotations of the optically pure isomers. Since the composition of these mixtures is unknown one can assume that they are not 1:1 mixtures of both amides.

Biological Activity.—The *in vitro* antibacterial activity of each of the isomeric sulfoxides was determined by a standard broth dilution test whereby the bacteria were exposed to varying concentrations of the respective drugs for 18–20 hr at 37°.[15] The bacteriostatic activity of each was compared directly with that of the sulfide (**1**), the sulfone (**1b**), and chloramphenicol against *Pasteurella multocida* Harvard No. 1, *Staphylococcus aureus* 209, *Escherichia coli* 198, *Proteus vulgaris* 9920, and *Pseudomonas aeruginosa* 211. The results are shown in Table I.

The difference in antibacterial activity between the

(15) R. A. Cutler, G. D. Diana, and S. Schalit, *Soap Chem. Specialties*, **42** (2), 45 (1966).

SCHEME II
THE ABSOLUTE CONFIGURATION OF *threo*-2-DICHLOROACETAMIDO-1-(4-METHYLSULFONYLPHENYL)-1,3-PROPANEDIOL ISOMERS



1*S*,2*R* and 1*R*,2*S* isomers in the sulfoxide series is comparable to that found in the *threo*-2-dichloroacetamido-1-[4-methylsulfonyl- (and 4-methylthio-) phenyl]-1,3-propanediol series. It is apparent that the configuration of the methylsulfinyl moiety does not affect the bacte-

TABLE I
COMPARATIVE BACTERIOSTATIC ACTIVITY

Compd	Configuration	Min inhibitory conc, ppm: *P. multocida* Harvard No. 1	*S. aureus* 209	*E. coli* 198	*P. vulgaris* 5920	*Ps. aeruginosa* 211
6	1*S*,2*R* (*R* or *S*)	2.5	50	100	100	100
7	1*S*,2*R* (*R* or *S*)	2.5	100	100	100	100
10	1*R*,2*S* (*R* or *S*)	>100	>100	>100	100	100
11	1*R*,2*S* (*R* or *S*)	>100	>100	>100	100	100
1a	1*S*,2*R*	2.5	50	7.5	100	100
1b	1*S*,2*R*	2.5	25	50	100	100
Chloramphenicol		0.5	7.5	2.5	100	100

riostatic activity of the compounds. It is further evident from Table I that the sulfone (**1b**), the methylthio homolog (**1a**), and the sulfoxides (**6** and **7**) had the same degree of antibacterial potency against *P. multocida* and *S. aureus* and that **1a** is more active against *E. coli*. In this type of test, all of these compounds were less active than chloramphenicol against these three organisms. Finally, none of the compounds in Table I exhibited any degree of activity against *P. vulgaris* and *Ps. aeruginosa*.

Experimental Section[16]

(+)- and (−)-1*S*,2*R*-2-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (6 and 7).—To a solution of 83.2 g (0.257 mole) of 1*S*,2*R*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol (**4**) in 400 ml of Me_2CO was added dropwise 7.5 ml (0.18 mole) of 84.2% H_2O_2. During the addition, the solution was maintained at −40°. After the addition was complete (20 min), the reaction mixture was allowed to warm to 0°, placed in the refrigerator overnight, and then left at room temperature for 24 hr. The solution was concentrated to half its volume, treated with EtOAc until slight turbidity appeared, and then passed through a silicic acid chromatographic column. Forty grams of material consisting of a mixture of **6** and **7** was obtained after crystallization from acetone–pentane: mp 121–125.4°, $[\alpha]^{25}D$ −23.8° (1% DMF). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) Cl, S.

(+)- and (−)-1*S*,2*R*-2-Amino-1-(4-methylsulfinylphenyl)-1,3-propanediol Hydrochloride (5).—To a solution of 63.9 g (0.3 mole) of **3a** and 25 ml of 6 *N* HCl in 500 ml of H_2O was added 30 ml (0.264 mole) of 30% H_2O_2. The reaction mixture was kept at 0° during the addition and for 2 additional days. Finally, after remaining at room temperature for 18 hr the mixture was evaporated leaving a yellow oil.

(+)-1*S*,2*R*-2-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (6).—The oily mixture of enantiomers obtained in the previous experiment was treated with hot *i*-PrOH whereupon a white solid separated. This material was collected, dried, and recrystallized from H_2O–*i*-PrOH. The amine hydrochloride (**5a**) was obtained as a solid (15.4 g), mp 229–230°, $[\alpha]^{25}D$ +32.7° (1% H_2O). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) Cl, O.

To a solution of 1.3 g (0.0581 g-atom) of Na in 40 ml of MeOH was added 15.4 g (0.0581 mole) of **5a**. A white milky precipitate of NaCl formed. Methyl dichloroacetate (9.43 g, 0.066 mole) was added and the mixture was allowed to stand at room temperature for 18 hr. The precipitate was removed by filtration and the filtrate was evaporated to dryness. A colorless glasslike material remained which gradually solidified. Recrystallization from 50 ml of H_2O gave **6** as white needles, yield 15.7 g, mp 157.5–158°, $[\alpha]^{25}D$ +26.2 (1% DMF). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) Cl, O, S.

(−)-1*S*,2*R*-2-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (7).—The *i*-PrOH filtrate obtained from the separation of the (+)-1*S*,2*R*-amine hydrochloride in the preceding experiment was evaporated to dryness. The gummy residue was dissolved in 100 ml of cold *i*-PrOH and the solid which separated (**5a**) was removed by filtration and discarded. The filtrate was concentrated to dryness and the procedure was repeated until no additional solid separated. The gum which was finally obtained after concentration of the filtrate could not be induced to crystallize. This material was dichloroacetylated in the same manner as described for **6**. The material was chromatographed on silicic acid to give, after recrystallization from acetone–pentane, 8.3 g of **7** as a white solid, mp 116.2–118°, $[\alpha]^{25}D$ −50.4 (1% DMF). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) Cl.

(+)- and (−)-1*R*,2*S*-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (10 and 11).—To a solution of 5 g (0.0154 mole) of 1*R*,2*S*-2-dichloroacetamido-1-(4-methylmercaptophenyl-1,3-propanediol) (**8**), in 45 ml of AcOH, was added 1.2 ml (0.0118 mole) of 30% H_2O_2. The solution was cooled to maintain the reaction temperature at 15–20°. After the addition was complete, the solution was left at room temperature overnight and then concentrated to dryness at 60°. The residue was chromatographed on silicic acid. Two grams of white solid was collected after elution with 60% EtOAc and 40% Me_2CO and recrystallized from acetone–pentane: mp 119.8–123.5°, $[\alpha]^{25}D$ +24.3° (1% DMF). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) S.

(−)-1*R*,2*S*-2-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (11). The amine hydrochloride (**9b**) was prepared from 10 g (0.047 mole) of **3b**, 80 ml of H_2O, 4.64 ml of 6 *N* HCl, and 6.5 ml (0.0573 mole) of 30% H_2O_2. After the addition was complete, the solution was left at 5° for 2 days and then overnight at room temperature. The material was recrystallized several times from absolute EtOH to give **9b**, mp 219–221°, $[\alpha]^{25}D$ −43.5° (1% MeOH).

The amine hydrochloride (1.42 g, 0.00535 mole) was dichloroacetylated in the usual manner with 839 mg (0.00586 mole) of methyl dichloroacetate. The material was chromatographed on silicic acid. The fractions obtained by elution with 60% EtOAc and 40% Me_2CO, corresponding to the sulfoxide, solidified on standing. The combined fractions were recrystallized (Me_2CO); yield 1 g of **11**, mp 157.6–160.2°, $[\alpha]^{25}D$ −25.2° (1% DMF). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) S.

(+)-1*R*,2*S*-2-Dichloroacetamido-1-(4-methylsulfinylphenyl)-1,3-propanediol (10).—The filtrate obtained from the previous experiment was concentrated to dryness. The gummy residue was redissolved in absolute EtOH and the solid which separated was removed by filtration and discarded. The procedure was repeated until no more solid separated. After removal of the solvent, the amine hydrochloride (**9a**) was obtained as a gum.

The resulting gum (4 g, 0.015 mole) was dichloroacetylated with 2.3 g (0.015 mole) of methyl dichloroacetate in the usual manner. Chromatography of the residual oil on silicic acid with 60% ethyl acetate and 40% acetone produced crystalline **10** which was recrystallized with Me_2CO and pentane to give 2.5 g, mp 118.7–119.4°, $[\alpha]^{25}D$ +46.5° (1% DMF). *Anal.* ($C_{12}H_{15}Cl_2NO_4S$) S.

(16) All melting points were run according to the U. S. P. procedure and are corrected. Optical rotations were run on a Rudolph photoelectric polarimeter Model 200. Analyses, melting points, and optical rotations were performed by the staffs of M. E. Auerbach and K. D. Fleischer. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.