Synthesis and Biological Properties of Certain Trichloromethyl Compounds

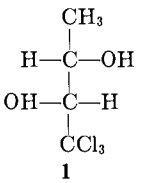
LASZLO L. DARKO

Department of Organic Chemistry, Geigy Pharmaceuticals, Division of Ciba-Geigy Corporation, Ardsley, New York 10502

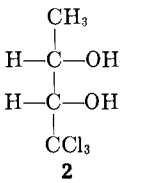
Received October 30, 1970

Four trichloromethylalkanediols have been prepared and tested for sedative-hypnotic activity. The stereochemistry of the *threo*- and *erythro*-1,1,1-trichlorobutane-2,3-diol was established based upon ir spectra measurements and dipole moment studies. Pharmacological evaluations showed the threo and erythro isomers of potency similar to that of chloral hydrate upon ip administration. Upon oral administration the threo isomer proved to be more potent than the erythro isomer or chloral hydrate.

As part of an effort to develop a new sedative–hypnotic agent, a series of compounds was prepared in which the CCl_3 group is adjacent to an alkane diol group. The target compounds were obtained by chlorination of $Hg(OAc)_2$ complexes of terminal acetylenes using a slight modification of a literature procedure[1] followed by LAH reduction of the α-acetoxy ketones so obtained. In this way but-1-yn-3-ol was converted into 1,1,1-trichloroacetoin which was then reduced to 1,1,1-trichlorobutane-2,3-diol. This compound was obtained as a mixture of threo and erythro isomers, **1** and **2**. Similarly 3-methylbut-1-yn-3-ol



1

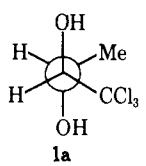


2

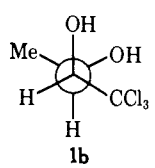
and hex-1-yn-3-ol were converted into 1,1,1-trichloro-3-methylbutane-2,3-diol [$Cl_3CCHOHCOH(CH_3)_2$] (**3**) and 1,1,1-trichlorohexane-2,3-diol ($Cl_3CCHOHCHOH$-$CH_2CH_2CH_3$) (**4**), respectively. Compound **4** was obtained as a single isomer.

As we stated previously, LAH reduction of the CO of the trichloroacetoin occurred from both possible directions, and a mixture of the *threo*- (**1**) and *erythro*- (**2**) 1,1,1-trichlorobutane-2,3-diol was obtained. The isomers were separated (see Experimental Section) from $CHCl_3$. Vpc analysis showed that the threo isomer was obtained in 99.8% purity and the erythro isomer in 98.2% purity.

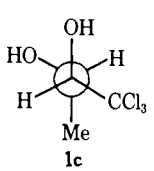
The stereochemical assignments were based on ir spectra measurements and on dipole moment studies. The nmr spectra of the isomers were in agreement with the assigned structures.



1a



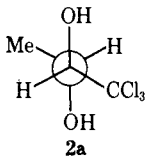
1b



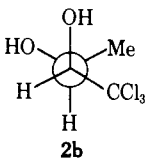
1c

Of the three relatively stable conformations of the threo isomer (**1a**, **1b**, **1c**) the contribution of rotamers **1a** and **1c** in which the 4 large groups are adjacent to each other would not be expected to be high. The staggered interactions of rotamer **1b** are fewer, and the interaction between the Me and CCl_3 groups could be further reduced as a result of intramolecular H bonding between the two OH groups. Therefore, we consider the structure **1b** to be that of the predominant rotamer. This rotamer would be expected to show strong intramolecular H bonding.

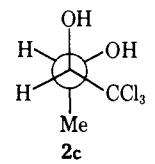
Similarly the erythro isomer **2** could exist in three stable rotamers, **2a**, **2b**, and **2c**.



2a



2b



2c

Again rotamers **2b** and **2c**, having the 4 large groups adjacent to each other, would not be expected to be predominant; in these cases interaction between the Me and CCl_3 would be increased by intramolecular H bonding of the OH groups. The predominant structure would be expected to be **2a**, possessing two pairs of staggered interactions between large groups. This places the OH groups trans to each other, and intramolecular H bonding between them would be impossible with this species.

The relative intensities of the bonded (3500 cm^{-1}) and nonbonded (free) (3600 cm^{-1}) OH stretching vibrations in the ir spectrum of the lower melting isomer measured in CCl_4 were unaffected by changes in concentration. This indicated that intermolecular H bonding is insignificant in this species. These findings are in agreement with structure **1b**; therefore, this is the threo isomer.

In dil CCl_4 soln, the higher melting isomer shows only nonbonded (3600 cm^{-1}) OH stretching bands. With increasing concentration a second bonded OH stretching band appears at 3440 cm^{-1}, and the free OH bond decreases in intensity indicating intermolecular H bonding. This is in agreement with structure **2a**; thus, the higher melting compound is the erythro isomer.

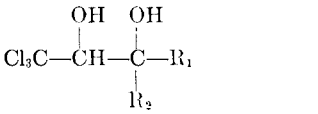
Dipole moment measurements of the isomers in PhH confirmed our assignment unambiguously. The value for the threo isomer in which the OH groups are at an angle of 30° to one another would be expected to be greater than that of the erythro isomer in which the dipoles of the two OH groups are opposed. The measured values were 3.16 D for the threo (**1**) and 2.40 D for the erythro (**2**) isomer.

Pharmacology.—All 4 compounds were tested for loss of the righting reflex in mice. Male CF_1S mice were used. Each mouse was tested over a 30-min period by placing him on his back. The reflex was judged blocked if the mouse failed to right himself within 30 sec. Five to ten mice were used for each dose of each drug. All compounds were dissolved in distd H_2O and injected ip or administered orally in a vol of

(1) R. E. Bowman, A. C. White, and W. R. N. Williamson, *J. Chem. Soc.*, 1086 (1964).

0.1 ml/10 g of body weight. The ED_{50}'s were derived from "eye-fit" linear plots on probit paper. The results of these tests are listed in Table I.

TABLE I
PHARMACOLOGICAL SCREENING RESULTS[a]



Test compounds	R_1	R_2	Isomer	ED_{50}, mg/kg Ip	ED_{50}, mg/kg Po	LD_{50}, mg/kg Ip	LD_{50}, mg/kg Po
Chloral hydrate				317	510	1050	1500
1	CH_3	H	Threo	280	310	>640	1180
2	CH_3	H	Erythro	250	480	>640	1400
3	CH_3	CH_3		480		>640	
4	C_3H_7	H		450		>640	

[a] One of the more significant findings was that the *threo*-1,1,1-trichlorobutane-2,3-diol (**1**) was as potent orally as ip.

Experimental Section

Melting points, obtained on a Thomas-Hoover capillary melting point apparatus, are uncorrected. Ir spectra were recorded on a Perkin-Elmer 137 ir spectrometer. The dipole moments were determined in PhH using a Sargent oscillometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

***threo*- and *erythro*-1,1,1-Trichlorobutane-2,3-diols (1 and 2).**—To a suspension of LAH (43.5 g, 1.14 moles) in Et_2O (2.5 l) was added a soln of 1,1,1-trichloro-3-acetoxybutan-2-one (296.85 g, 1.27 moles) in Et_2O (500 ml). After the completed addition the reaction mixt was stirred at reflux temp for 24 hr. Usual work-up yielded 232.0 g of dark oil. Vpc analysis indicated the presence of 2 major components, present to the extent of 61.2% and 28.7%. These components were separated by fractional distn using a 12.5-cm column filled with glass helices followed by fractional crystns. In this way the threo isomer **1** was isolated from $CHCl_3$ in 99.8% purity [bp 72.5° (1.45 mm), mp 62–63°] and the erythro isomer **2** in 98.2% purity [bp 76° (1.2 mm), mp 85.5–87°] measured by vpc analysis: threo isomer **1**, *anal.* ($C_4H_7Cl_3O_2$) C, H, Cl; erythro isomer **2**, *anal.* ($C_4H_7Cl_3O_2$) C, H, Cl.

1,1,1-Trichloro-3-methylbutane-2,3-diol (3).—To a suspension of LAH (slight excess) in Et_2O (400 ml) was added a soln of 1,1,1-trichloro-3-acetoxy-3-methylbutan-2-one[1] (90 g, 0.037 mole) in Et_2O (100 ml), and the reaction mixt was stirred at room temp for 40 hr. The oil obtained from the work-up was purified first by distn, bp 68–72° (0.1 mm), then by recrystn of the solidified distillate from CCl_4-heptane (1:1). The diol **3** melted at 57–58° and weighed 5.2 g (68% yield). *Anal.* ($C_5H_9Cl_3O_2$) C, H, Cl.

1,1,1-Trichlorohexane-2,3-diol (4).—To a suspension of LAH (slight excess) in Et_2O (400 ml) was added a soln of 1,1,1-trichloro-3-acetoxyhexan-2-one [prepd from hex-1-yn-3-ol by the same method as reported by Bowman and coworkers, bp 48.5° (0.035 mm)] (15.0 g, 0.0575 mole) in Et_2O (100 ml). After the completed addition (20 min), the reaction mixt was stirred at room temp for an additional 30 min and acidified with HCl, the org layer was sepd, dried ($MgSO_4$), concd, distd, and, when the distillate solidified, crystd from CCl_4 giving 1.2 g of **4**, bp 94–105° (0.5–0.6 mm), mp 75–77.5°. *Anal.* ($C_6H_{11}Cl_3O_2$) C, H, Cl.

Acknowledgments.—The author wishes to thank Dr. K. Doebel for many helpful discussions, Dr. P. Nicolson and associates of the Analytical Research Department for the microanalytical and spectral results, and Dr. J. Saelens of the Pharmacology Department for the pharmacological results. The author is also indebted to Mr. H. Tomaselli and Mrs. V. Bedenko for their technical assistance.

Synthesis and Antimicrobial Evaluation of Some 5-(5-Nitrofurylidene)rhodanines, 5-(5-Nitrofurylidene)thiazolidine-2,4-diones, and Their Vinylogs[1]

S. K. MALLICK,* A. R. MARTIN,

College of Pharmacy, Washington State University, Pullman, Washington 99163

AND R. G. LINGARD

School of Pharmacy, Chelsea College of Science and Technology, London, S. W. 3, England

Received January 11, 1971

This paper describes the synthesis and antimicrobial evaluation of 5-(5-nitrofurylidene)rhodanines and 5-(5-nitrofurylidene)thiazolidine-2,4-diones substituted in the 3 position with the object of modifying the solubility, physical properties, and microbial reduction pattern in the series. Some vinylogs of these compounds were also prepared. The antibacterial, antiprotozoal, and antifungal activities of these compounds were compared with those of some commercially available drugs and correlations of structure with the activity in this series of compounds are discussed.

The synthesis of 5-(5-nitrofurylidene)rhodanine (**1**) was reported by Sasaki[2] in 1954. Owing to its poor water solubility **1** appeared to lack promise as an antibacterial agent. Later, however, Koschucharoff[3] found it to be the most active of a series of 5-nitrofurylidene derivatives tested against a variety of fungi, including *Candida albicans*, *Trichophyton*, *Epidermophyton*, and *Microspora*. Antibacterial activity of **1** against *Escherichia coli* and *Staphylococcus aureus* with dilutions of 1:4000 to 1:8000 was also observed. This paper describes the synthesis and microbiological evaluation of 5-(5-nitro-2-furylidene)rhodanines substituted in the 3 position with the object of modifying the solubility, physical properties, and microbial reduction of the NO_2 group of **1**.[4] Further modification in the sta-

(1) Abstracted in part from the Ph.D. Thesis of S. K. Mallick, Chelsea College of Science, University of London, London, England, 1966.

(2) T. Sasaki, *Chem. Pharm. Bull.*, **2**, 104 (1954).

(3) (a) P. Koschucharoff, *Pharmazie*, **15**, 492 (1960); (b) P. Koschucharoff and T. Harisanova, *ibid.*, **17**, 134 (1962).

(4) Subsequent to the completion of this work, E. Jeney and T. Z. Solnai, *Arch. Exp. Veterinaermed.*, **21**, 259 (1967), reported **2**, **3**, **7**, **8**, and **12** (Table 1) to possess no appreciable activity against *Staph. aureus*, *Strep. pyogenes*, *Staph. albus*, *Sh. dysenteriae*, *Sal. typhosa*, *E. coli*, *A. aerogenes*, and *P. vulgaris*. The yields of these compounds were low and some of the melting points did not agree to those made in our laboratory. The comparative data are presented in footnote *b*, Table 1.