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CHEMICAL STUDIES ON FUNGICIDES

PART VII–RESOLUTION OF THE CIS-TRANS DI(BROMOACETATE) OF 1,4-CYCLOHEXANEDIOL

Joseph P. LaRocca and Warren E. Weaver

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Approved by:

Dr. A. L. Alexander, Head, Protective Coatings Branch
Dr. P. Borgstrom, Superintendent, Chemistry Division

NAVAL RESEARCH LABORATORY

CAPTAIN F. R. FURTH, USN, DIRECTOR

WASHINGTON, D.C.

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ABSTRACT

In order to correlate geometric structure with fungicidal activity, it was of interest to study the cis and trans isomers of some compound such as the di(bromoacetate) of 1,4-cyclohexanediol. Since the acetate of this diol has been separated into its cis-trans isomers, it was reasonable that the di(bromoacetate) (chosen in view of the excellent fungicidal properties of the alpha bromoacetamides) could also be resolved. The separation of the cis-trans isomers of 1,4-cyclohexanediol di(bromoacetate) was accomplished and the resolution is described.

PROBLEM STATUS

This is an interim report; work on the problem is continuing.

AUTHORIZATION

NRL Problem C03-06R
NR 403-060

CHEMICAL STUDIES ON FUNGICIDES
PART VII–RESOLUTION OF THE CIS-TRANS DI(BROMOACETATE) OF 1,4-CYCLOHEXANEDIOL

INTRODUCTION

Deterioration caused by fungi in tropic environments has stimulated efforts toward preventing this destruction by either "passive" (careful packaging and dehumidifying procedures) or "active" measures utilizing fungicidal materials applied on or into the material being protected. The latter method is desirable because it provides for protection after equipment is unpackaged and is in use. While the use of fungicidal materials is desirable, relatively little has been done to study fungicides except to examine heterogeneous groups of compounds for specific activity and utility.

This Laboratory has undertaken a systematic examination of organic substances so that fungicidal activity may be correlated with chemical structure. The salient feature of this attempt is the evaluation of all potential fungicides against standard organisms using the same technique without immediate regard to utility of the compounds under examination. Those substances showing promise are then examined more closely both as to fungicidity and end use. The difficulty in correlating structure with activity, however, lies beyond the realm of simple observation of toxicity and involves the actual mechanism of action of toxic substances. Since this latter field is only slowly being evolved (and necessarily so because of the complexities involved) current work more profitably and justifiably is directed toward more thorough exploration of those compounds which show toxicity in direct tests.

An intriguing feature of all work involving physiological activity of any type is the variation in activity caused by slight changes in molecular structure, especially optical or geometric isomers. With optical isomers there are startling examples of wide variation in physiological reaction between laevo and dextro compounds, a classic case being the response to the optical isomers of epinephrine.[1]

Less has been reported concerning geometric isomers, although variation in activity should be as marked as with optical isomers. This is all the more remarkable when one considers that geometric isomers have different chemical and physical properties whereas optical isomers vary only in their ability to rotate a plane of polarized light. For geometric isomers, then, it is most unexpected that so little has been reported about their physiological activity. It has been observed that maleic and fumaric acids (cis and trans respectively) have reversible effects toward bacteria depending on the temperature at which the test is operated.[2] In addition, these acids also have different tastes and affect certain enzymes in different degrees. This Laboratory has shown that maleic acid and fumaric acid also have different toxic effects against fungi.[3]

After consideration of these phenomena, work was initiated in this Laboratory with the object of investigating and evaluating other possible geometric isomers, especially those geometric isomers not dependent on a double bond for cis-trans configuration. This report concerns the

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[1]Tainter, M. L. J. Pharmacol., 40, 43-63 (1930).

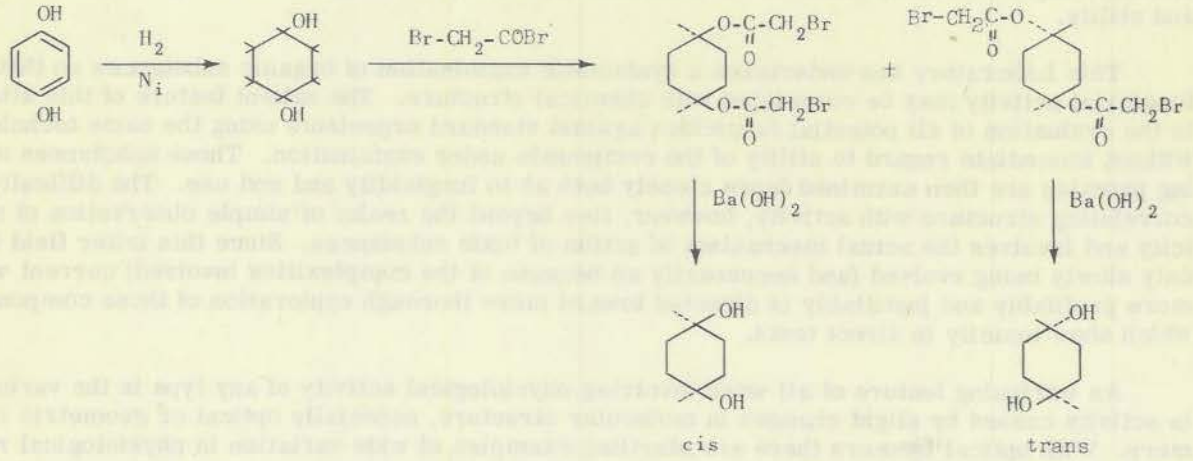
[2]Jenkins, G. L. and Hartung, W. H. The Chemistry of Organic Medicinal Products, p. 613. New York, Wiley (1943).

[3]Leonard, J. M. and Weaver, W. E. Fungus Inhibitive Properties of Organic Compounds. Part II. Aliphatic Alcohols, Acids and Esters. NRL Report C-3403, March 1949.

synthesis and resolution of one set of geometric isomers which are to be investigated for variation in fungicidal activity.

BACKGROUND

In order to detect any variation in fungicidal properties, it is necessary to synthesize compounds that would ordinarily exert a fair level of fungicidity irrespective of isomeric considerations. For this work, the di(bromoacetate) of 1,4-cyclohexanediol was chosen since the alpha bromine atom would be expected to be activated (and the compound fungicidal) analogously to the alpha bromoacetamides.[4] Moreover, since the acetate of 1,4-cyclohexanediol has been resolved by Olberg et al,[5] the bromoacetate was expected to be similarly resolvable. These workers were able to prepare the acetate and, after separation of the isomers, hydrolyze to the cis and trans 1,4-cyclohexanediol. Knowing the melting points of the isomers of the diol, a similar procedure was used for the bromoacetates. The scheme may be pictured thus:



The hydrolysis is merely a means of proving the isomer separation.

EXPERIMENTAL

The reduction of hydroquinone was carried out in a glass-lined high-pressure reaction bomb of the type manufactured by the American Instrument Company. The procedure was essentially that of Adkins and Cramer.[6] Two and one-half moles (275 g.) of hydroquinone was dissolved in 500 ml. of 95% ethanol. To this solution was added 18 g. of Raney nickel catalyst. The reduction mixture was then placed in the bomb under an initial hydrogen pressure of 2000 lb. The temperature was raised initially to 150°, and when agitation was started, it reached a maximum of 178° with a hydrogen pressure of 2880 lb. After 15 hours the reaction was complete and the pressure in the bomb had dropped to 300 lb. (room temperature). The reduction mixture was removed from the bomb, the catalyst filtered off, and the solvent was distilled. The white solid remaining (212 g.) represented a 75% yield.

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[4] Leonard, J. M. and Blackford, V. L. Fungus Inhibitive Properties of Organic Compounds. Part III. Bromoacetamides. NRL Report C-3413, March 1949.

[5] Olberg, R. C., Pines, H. and Ipatieff, V. N. J. Am. Chem. Soc., 66, 1096-99 (1944).

[6] Adkins, H. and Cramer, H. I. J. Am. Chem. Soc., 52, 4349-58 (1930).

The 1,4-cyclohexanediol, so obtained, was esterified by dissolving one-half mole (57 g.) in 2000 ml. of benzene and adding dropwise one mole (202 g.) of bromoacetyl bromide. After the addition was completed, the mixture was maintained at gentle reflux for 5 hours (or until evolution of hydrogen bromide ceased) whereupon the benzene was removed by distillation. A brown residue weighing 152 g. (97% of theoretical) remained.

The crude di(bromoacetate) was recrystallized from hot alcohol, and a white crystalline solid containing both isomers was obtained. This material was washed with ether to remove the cis form selectively, leaving on the filter the more insoluble trans isomer. The trans isomer was repeatedly recrystallized from ethanol until a constant melting point of 137° was obtained. Ten grams of the trans di(bromoacetate) was refluxed for three hours with a solution containing 19 g. of barium hydroxide. The solution was evaporated to dryness, extracted with hot acetone, and the acetone solution concentrated and cooled. One gram of white crystals (33% yield) was obtained (m.p. 143.5-145°). This agrees substantially with Olberg's value of 142°, confirming the assignment of the trans form to the di(bromoacetate) melting at 137°.

The ether solution of impure cis isomer (contaminated with trans in the separation) was evaporated to dryness; and the brown crystalline residue was dissolved in acetone, decolorized with Nuchar, and cooled in a dry ice-isopropanol bath. A white solid was obtained which melted at 114-115° even after repeated recrystallizations. Recrystallization from a benzene-ligroin solvent mixture failed to raise the melting point above this value.

An insufficient amount of material remained to carry out the hydrolysis to the cis 1,4-cyclohexanediol. However, the definite melting points of the two fractions of the di(bromoacetate) along with confirmatory hydrolysis to the known trans 1,4-diol is presumptive evidence that separation was accomplished. The melting points of the two isomers also agree with the generalization that a cis isomer usually melts lower than the trans.

SUMMARY

The synthesis and separation of the cis-trans isomers of the di(bromoacetate) of 1,4-cyclohexanediol has been described. These two isomers will be studied for toxic effects against fungi to determine whether there is any variation in fungicidal activity. This evaluation represents the initial effort of this Laboratory toward establishing correlation of geometric configuration with fungicidity.

NAVY-DPPO PRNC. WASH., D.C.