4,4′-Dibromodiphenyldisulfimide as a Reagent for the Identification of Organic Bases II. Optical Crystallographic Properties of Derivatives of Some Antihistamines

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Optical crystallographic properties of sodium 4,4′-dibromodiphenyldisulfimide and of the 4,4′-dibromodiphenyldisulfimide derivatives of 19 antihistamines are presented. These crystallographic properties serve well as a means of identifying the 19 antihistamines.

ONE OF THE physical methods suggested for the qualitative analysis of the antihistamines is optical crystallography employing the petrographic microscope. Crystallographic properties of antihistamine salts (1–8) and colorimetric and precipitation reactions produced by various reagents and observed with a microscope have been published (1–7, 9).

In a previous paper, the authors reported the synthesis of 4,4′-dibromodiphenyldisulfimide and the preparation of disulfimide derivatives of a number of antihistamine drugs (10). The purpose of this study is to present the optical crystallographic properties of the 4,4′-dibromodiphenyldisulfimide derivatives of some antihistamines and to illustrate the use of these properties in the identification of these antihistamines.

TABLE I.—4,4′-DIBROMODIPHENYLDISULFIMIDE DERIVATIVES OF SOME ANTIHISTAMINES

	Optical Properties						Apparent Properties		
			Refractive Indices						
Derivative	System[a]	Optic Sign	α	β	γ	Elongation	Habit	Optical Orientation	Extinction Angle[b]
Antazoline	T	+	1.571	1.635	1.755	−	Lamellar	Inclined acute	6
Bromdiphenhydramine	T	+	1.582	1.623	1.721	+	Foliated	Inclined optic normal	Variable
Brompheniramine	O	+	1.644	1.655	1.668	±	Foliated	Obtuse	0
Chlorcyclizine	M	−	1.589	1.646	1.667	−	Fibrous	Inclined optic normal	0
Chlorothen	T	+	1.573	1.641	1.724	±	Fibrous	Inclined optic axis	Variable
Chlorpheniramine	O	+	1.637	1.645	1.659	±	Foliated	Obtuse	0
Cyclizine	T	+	1.573	1.620	1.728	−	Tabular	Inclined obtuse	Variable
Dexbrompheniramine	M	+	1.572	1.637	>1.785	±	Acicular	Inclined acute	Variable
Diphenhydramine	M	+	1.573	1.598	1.755	±	Tabular	Inclined acute	0
Diphenylpyraline	O	−	1.585	1.647	1.657	+	Lamellar	Optic normal	0
Doxylamine	O	+	1.538	1.621	1.727	±	Lamellar	Acute	0
Meclizine	M	−	1.567	1.661	1.665	±	Lath-shaped	Inclined optic normal	0
Methapyrilene	T	−	1.564	1.682	1.775	−	Tabular	Inclined optic normal	36
Phenyltoloxamine	T	+	1.566	1.634	1.728	±	Fibrous	Inclined optic axis	Variable
Pyrrobutamine	M	−	1.601	1.665	1.690	±	Tabular	Obtuse	5
Thenyldiamine	T	−	1.559	1.665	1.764	−	Tabular	Inclined optic normal	Variable
Thonzylamine	O	+	1.572	1.627	1.719	±	Fibrous	Variable	0
Tripelennamine	T	−	1.555	1.670	1.747	±	Tabular	Inclined acute	Variable
Zolamine	M	+	1.573	1.631	1.719	±	Lath-shaped	Inclined acute	0
Sodium-4,4′-dibromodiphenyldisulfimide	M	+	1.570	1.630	1.761	±	Lamellar	Inclined acute	0

[a] O = orthorhombic; M = monoclinic; T = triclinic. [b] Front-face view in most frequent orientation.

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The authors acknowledge supplies of antazoline (Antistine, Ciba), bromdiphenhydramine (Ambodryl, Parke Davis), brompheniramine (Dimetane, Robins), chlorcyclizine (Perazil, Burroughs Wellcome), chlorothen (Tagathen, Lederle), chlorpheniramine (Chlor-Trimeton, Schering), cyclizine (Marezine, Burroughs Wellcome), dexbrompheniramine (Disomer, White), diphenhydramine (Benadryl, Parke Davis), diphenylpyraline (Diafen, Schenley, now prepared by Riker), doxylamine (Decapryn, Merrell), meclizine (Bonine, Pfizer), methapyrilene (Histadyl, Lilly), phenyltoloxamine (Bristamine, Bristol), pyrrobutamine (Pyronil, Lilly), thenyldiamine (Thenfadil, Winthrop), thonzylamine (Neohetramine, Nepera, now prepared by Warner-Chilcott), tripelennamine (Pyribenzamine, Ciba), and zolamine (White).

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EXPERIMENTAL

The method used to obtain disulfimide derivatives was that described previously (10). Successively, 0.3 Gm. of sodium 4,4′-dibromodiphenyldisulfimide and 0.25 Gm. of the amine salt were dissolved in 20 ml. of hot ethanol–water solution (1:1). The disulfimide derivative, which precipitated within a few minutes to several hours, was filtered off and recrystallized from a minimal quantity of methanol–*n*-amyl acetate solution (1:1).

The optical crystallographic properties (Table I) were determined by methods described by Chamot and Mason (11) and Winchell (12). Diagnostic properties of crystals in their most frequently occurring orientations (Table I) were determined by procedures previously described (13, 14).

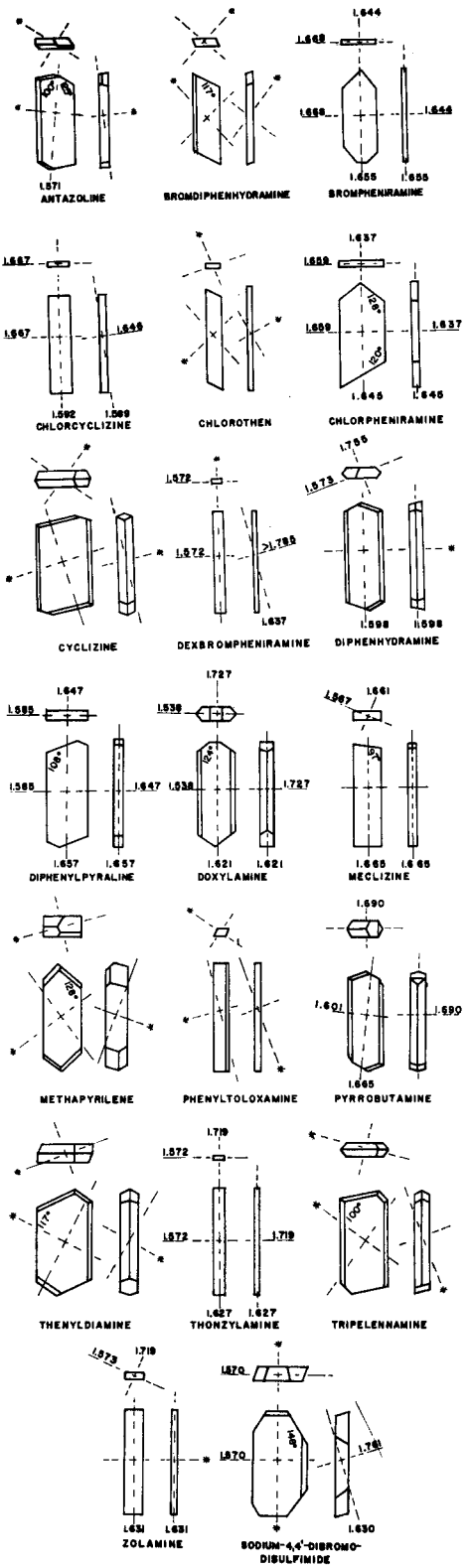

Fig. 1.—Orthographic projection drawings of typical crystals of 4,4′-dibromodiphenyldisulfimide derivatives of antihistamines.

RESULTS AND DISCUSSION

The optical properties of 4,4′-dibromodiphenyldisulfimide derivatives of some antihistamines and sodium 4,4′-dibromodiphenyldisulfimide are listed in Table I. These properties include the crystal system, the optic sign, the refractive indices, and the sign of elongation. The highest index of refraction in the authors' set of liquids was 1.785; hence, the value for gamma for dexbrompheniramine is reported as greater than 1.785. It was necessary to use crushed specimens to obtain some of the data reported. A few of the derivatives were soluble in liquids of lower index values (those containing clove oil). This solubility was of concern in determining alpha for derivatives of antazoline, bromdiphenylhydramine, chlorothen, and phenyltoloxamine. The values reported are the lowest ones found for each of these compounds.

Most of the disulfimide derivatives are so flattened that they tend to assume a common orientation on the microscope slide. In Table I are listed as apparent properties the habit and also the optical orientation and the extinction angle observed on the most frequently occurring orientations of the crystals. The optical orientation designated as acute, obtuse, or optic normal indicates that a centered interference figure is found when a crystal in its most frequently occurring orientation is examined under conoscopic vision. The descriptive term "inclined" indicates that the interference figure is not centered. Therefore, with an inclined orientation, one or both of the apparent refractive indices for the front view of the crystal usually cannot be determined within narrow limits and, if reported, would be termed variable.

In Fig. 1 are orthographic projection drawings of the crystals showing front, side, and top views. These drawings supplement the data presented in Table I and facilitate identification of the antihistamines. To determine the appearance of crystals for side and top views, the crystals were observed and rolled in Canada balsam. Dashed lines indicate the vibration directions, and refractive indices are recorded for crystals which show consistent values in these directions. An asterisk indicates the higher value on views where consistent refractive indices could not be obtained. Crystal angles measured microscopically are shown in the corners of the diagrams.

Additional discussion of properties of the reagent and derivatives will facilitate identification of the compounds by optical crystallographic methods. Derivatives of brompheniramine, chlorpheniramine, diphenylpyraline, doxylamine, and pyrrobutamine in their usual orientation present centered interference figures. Two true refractive indices can therefore be observed for each of these compounds. Seven of the compounds are so positioned in their most frequently occurring orientations that one true refractive index can be observed for each of them. Alpha can be observed for the sodium salt of the reagent and for the derivative of antazoline beta for derivatives of diphenhydramine, thonzylamine, and zolamine and gamma for derivatives of chlorcyclizine and meclizine. Derivatives of the remaining antihistamines present no true refractive index in their usual orientations.

It should be pointed out that because of the crystal habit of derivatives of chlorothen, dexbrompheniramine

mine, and thonzylamine, the crystals do not always seek a common orientation. If they assume the front view orientations shown in Fig. 1, one can observe alpha for dexbrompheniramine and thonzylamine and beta for chlorothen.

It has been mentioned that one or both refractive indices for crystals with inclined orientations cannot be determined within narrow limits. The following are approximate values of some of the intermediate indices taken from crystals in their most frequently occurring orientations: sodium 4,4′-dibromodiphenyldisulfimide, 1.635; 4,4′-dibromodiphenyldisulfimide derivatives of antazoline, 1.671; bromdiphenhydramine, 1.590 and 1.700; chlorothen, 1.661; meclizine, 1.570; methapyrilene, 1.569 and 1.751; thenyldiamine, 1.593 and 1.710; and tripelennamine, 1.570 and 1.720.

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Antimicrobial Properties of Thiosemicarbazones of Aliphatic Ketones

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The antimicrobial activity of methyl *n*-alkyl ketone thiosemicarbazones was found to be dependent upon the length of the alkyl chain. Maximum activity was obtained with the thiosemicarbazone of 2-dodecanone.

PREVIOUS INVESTIGATIONS demonstrated significant antimicrobial properties present within a group of thiosemicarbazones of aliphatic aldehydes (1, 2). These studies have been extended to include the thiosemicarbazones of aliphatic ketones.

EXPERIMENTAL AND RESULTS

A homologous series of methyl *n*-alkyl ketone thiosemicarbazones were prepared by usual methods (3). The series extended from acetone to 2-tridecanone, except for 2-hexanone. Twofold serial dilutions of the compounds were prepared in dimethylformamide and tested for antimicrobial activity by previously described procedures (2).

Results of these tests, listed in Table I, demonstrated that activity increased with increasing chain length of the molecule, reaching maximum activity at the 2-dodecanone (R = C_{10}) derivative. This structure-activity relationship, as a function of chain length, is analogous to the pattern obtained with aldehyde thiosemicarbazones (2). None of the compounds was active at 250 mcg./ml. against *Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Candida albicans, Aspergillus niger,* and *Penicillium piscarium.*

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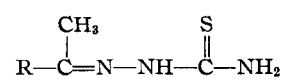
TABLE I.—ANTIMICROBIAL ACTIVITY OF THIOSEMICARBAZONES



R	Min. Concn. mcg./ml. Completely Inhibiting Growth of Organisms: *S. aureus*	*S. epidermidis*	*St. faecalis*	*A. flavus*
CH_3	x[a]	x	x	x
CH_3CH_2	x	x	x	x
$CH_3(CH_2)_2$	x	x	x	x
$CH_3(CH_2)_4$	x	x	x	x
$CH_3(CH_2)_5$	250	250	x	x
$CH_3(CH_2)_6$	62	31	125	x
$CH_3(CH_2)_7$	31	16	31	x
$CH_3(CH_2)_8$	16	8	16	31
$CH_3(CH_2)_9$	8	4	8	62
$CH_3(CH_2)_{10}$	x	x	x	x

[a] x, denotes growth at 250 mcg./ml.

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