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Optical Crystallographic Properties of Drugs of Abuse: Commonly Used Amine Street Drugs

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Received July 1, 1980, from the **School of Pharmacy, University of Wyoming, Laramie, WY 82071*, and the ‡*School of Pharmacy, University of Washington, Seattle, WA 98195.* Accepted for publication November 21, 1980.

Abstract □ The optical crystallographic properties of the diliturate derivatives of amine drugs found in illicit street drug preparations known as "white crosses," "mini-bennies," or "whites" were determined. The crystallographic properties, especially the crystal morphology, extinction angles, and indexes of refraction, identify the drug substances found in the white cross suite. These data can be used with UV and IR spectroscopic and chromatographic evaluations for drug identification.

Keyphrases □ Drugs of abuse—substance identification by optical crystallographic properties of diliturate derivatives of amine drugs □ Optical crystallography—substance identification of diliturate derivatives of amine drugs □ Amphetamines—drugs of abuse, identification of drug substance by optical crystallographic properties

Optical chemical crystallography is a physical method for rapid drug identification (1–3). Microchemical properties of amine drug salts have been determined with various reagents (4), but few studies (5, 6) concentrated on the optical crystallographic properties.

The present study reports the optical crystallographic data and constants for the diliturate derivatives of amine drugs found in illicit street drug preparations entitled "white crosses" or "mini-bennies." These preparations are so termed because of the physical shape of the small, white, cross-scored tablets purported to contain 2–8 mg of *d*-methamphetamine (7, 8). However, other drugs have been freely substituted for dextroamphetamine in these street preparations since the 1970 Drug Enforcement Administration Controlled Substances Act made the amphetamines difficult to procure for the street market (8).

EXPERIMENTAL

Materials—The drugs used to prepare the diliturate derivatives were obtained from pharmaceutical manufacturers and chemical supply

Table I—Optical Properties of Drug Diliturates

Derivative[a] (Optic Sign)	System[b]	Optical Orientation	Refractive Indexes			2V by Nomogram[c] Method	Elongation	Habit	Extinction Angle
			α	β	γ				
dl-Amphetamine (−)	O	Obtuse	1.470	1.645	1.698	53°	(±)	Acicular	Parallel
Dextroamphetamine (−)	O	Obtuse	1.471	1.653	1.704	52°	(±)	Tabular	Parallel
dl-Chlorpheniramine (−)	M	Inclined obtuse	1.512	1.682	1.732	52°	(±)	Lamellar	15°
Diphenhydramine (−)	M	Inclined acute	1.582	1.608	1.624	75°	(+)	Tabular	42°
l-Ephedrine (−)	O	Optic normal	1.544	1.619	1.655	66°	(−)	Lamellar	Parallel
dl-Ephedrine (−)	T	Inclined optic axis	1.537	1.662	1.731	67°	(±)	Tabular	38°
Mephentermine (−)	M	Inclined optic normal	1.488	1.659	1.688	40°	(−)	Acicular	27°
dl-Methamphetamine (−)	M	Inclined obtuse	1.482	1.654	1.656	8°	(−)	Acicular	24°
d-Methamphetamine (−)	M	Acute	1.545	1.648	1.705	70°	(±)	Tabular	33°
Methapyrilene (−)	M	Inclined obtuse	1.548	1.689	1.723	48°	(±)	Lamellar	33°
Papaverine (−)	T	Inclined optic normal	1.493	1.742	1.785	41°	(+)	Prismatic	27°
Phentermine (−)	O	Obtuse	1.495	1.665	1.688	36°	(−)	Acicular	Parallel
Phenylephrine (−)	T	Inclined obtuse	1.520	1.664	1.752	70°	(±)	Prismatic	42°
dl-Phenylpropanolamine (lath) (−)	O	Obtuse	1.461	1.678	1.708	36°	(−)	Lath	Parallel
dl-Phenylpropanolamine (lam) (−)	O	Obtuse	1.471	1.663	1.685	34°	(−)	Lamellar	Parallel
Propoxyphene (−)	M	Inclined obtuse	1.495	1.618	1.658	55°	(±)	Acicular	15°
Pseudoephedrine (−)	O	Optic normal	1.520	1.622	1.640	36°	(+)	Prismatic	Parallel
Dilituric acid (−)	M	Inclined obtuse	1.388	1.684	>1.785	50° est.	(−)	Tabular	9°

[a] The authors acknowledge supplies of *dl*-chlorpheniramine (Chlortrimeton, Schering), mephentermine (Wyamine, Wyeth), methapyrilene (Histadyl, Lilly), phentermine (Ionamine, Penwalt), propoxyphene (Darvon, Lilly), and pseudoephedrine (Sudafed, Burroughs Wellcome) and express their appreciation to the manufacturers who supplied the amine salts.

[b] O = orthorhombic, M = monoclinic, and T = triclinic. [c] Determined by the method of Hartshorne and Stuart (11).

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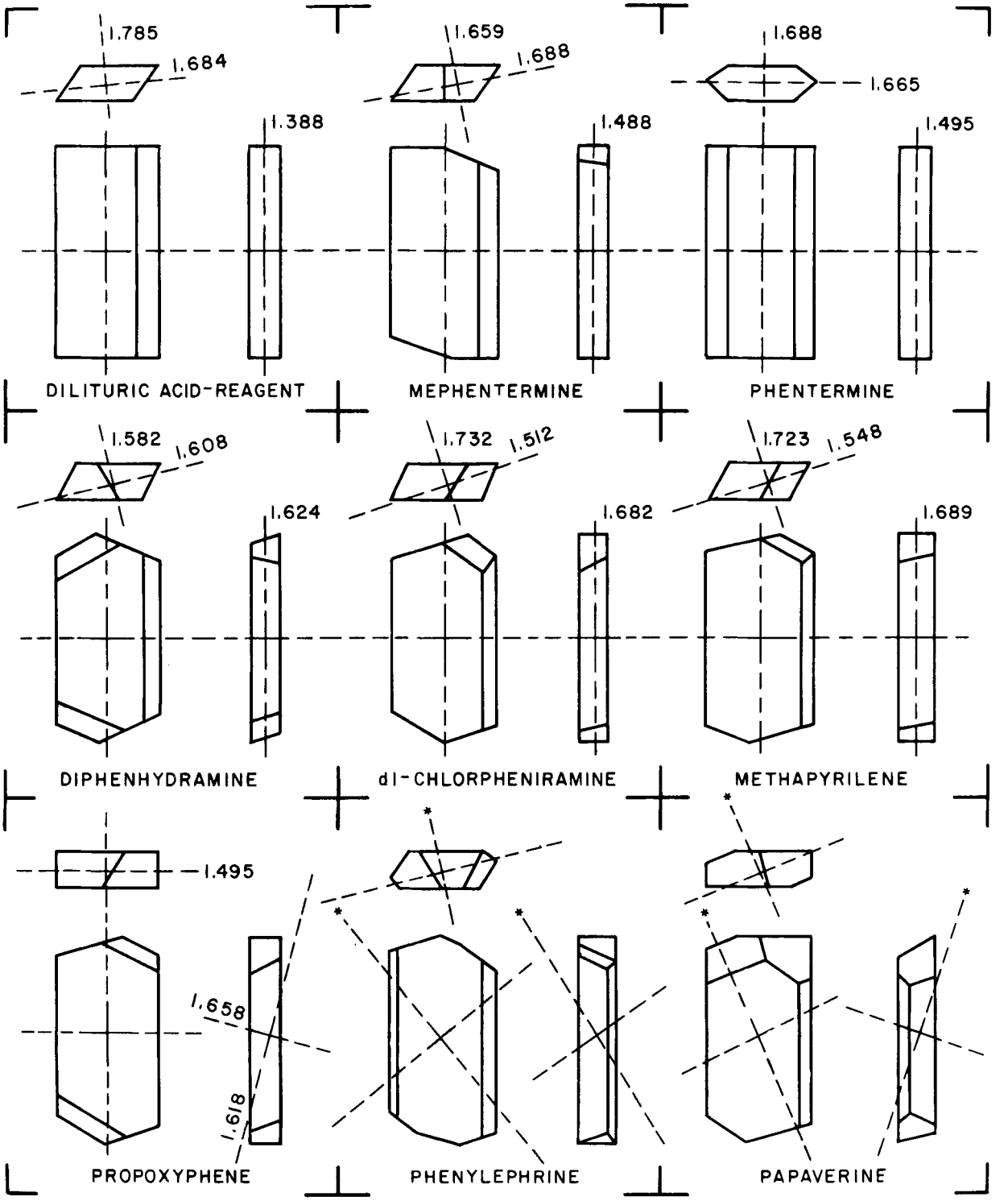

Figure 1—*Drawings of amine dilituratates: white cross suite.*

houses. The index of refraction standards[1,2] and the dilituric acid[3] (5-nitrobarbituric acid) used to prepare the crystalline derivatives also were purchased commercially.

Methods—The method utilized to prepare dilituric acid derivatives of the amine salts was that of Plein and Dewey (9). Briefly, 100 mg of the amine salt was dissolved in a minimum of water, and 10 ml of a hot, 1% aqueous solution of dilituric acid was added. The dilituratates of the amines crystallized out upon cooling in most cases, and the crystalline derivatives were recrystallized from water one to several times until compounds with sharp melting points were obtained. The purity of the salts was established by determination of percent nitrogen. All compounds analyzed for nitrogen were within 0.3% of the calculated theoretical values.

The optical data for the dilituratates of the white cross amines were determined using literature methods (9–11). The highest index of refraction liquid standard in the authors' sets of liquids was 1.785, so no value above this figure is reported. Crushed specimens were necessary to obtain some refractive indexes.

In this study, the $2V$ values were determined by a nomogram method (11). Briefly, the nomogram was utilized as a base upon which the three known refractive indexes were used to determine the fourth variable V ($V = \cos^2 \theta$).

[1] R. P. Cargille Co., Cedar Grove, N.J.
[2] Series n = 1.400–1.785 in increments of n = 0.002 at 25°.
[3] EK-2502, Eastman Kodak Co., Rochester, N.Y.

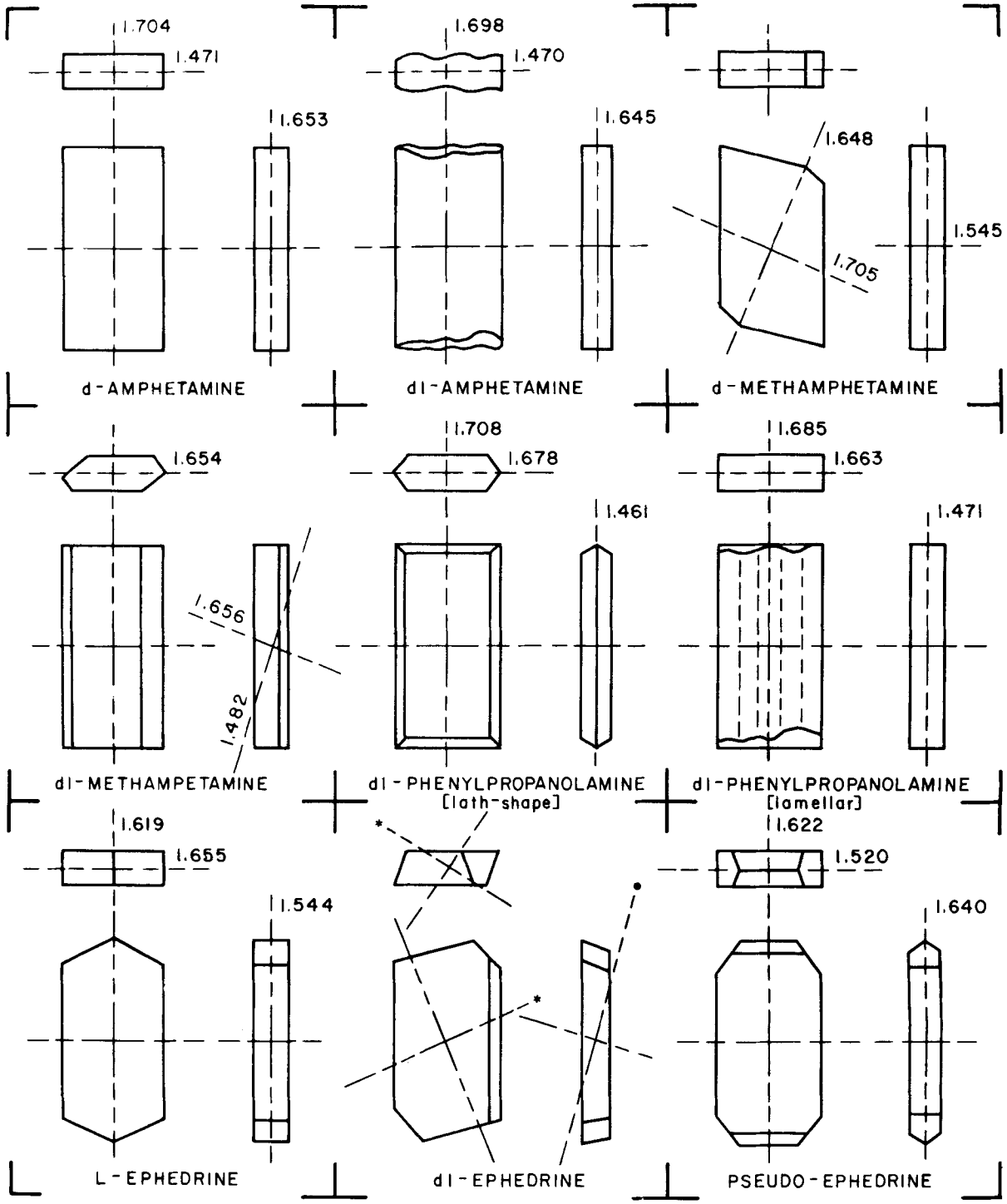

Figure 2—*Drawings of more amine dilituratés: white cross suite.*

RESULTS AND DISCUSSION

The crystallographic properties of the amine dilituratés are reported in Table I and are shown in Figs. 1 and 2. Many of the crystal derivatives are so flattened that they tend to assume a common orientation when immersed in the index oils on the microscope slide. The apparent properties of habit, optical orientation, and extinction angle of each crystalline derivative as observed on the most frequently occurring orientation are listed in Table I. The optical orientations designated as acute, obtuse, and optic normal indicate that a "centered" interference figure was observed upon an uncrushed crystal in its most frequently occurring orientation. The descriptive term "inclined" denotes that centered figures were not observed on the usual orientation of the crystal; therefore, one or both refractive indexes of the front face of the crystal would be variable.

Additional optical crystallographic properties reported in Table I are the three refractive indexes, crystal system, optic sign, elongation, and optic axial angle ($2V$). The $2V$ value is an optical parameter that can distinguish between two or more similar crystals, *e.g.*, *dl*-chlorpheniramine ($2V = 52°$) and diphenhydramine ($2V = 75°$).

Figures 1 and 2 present orthographic projection drawings of the crystals showing the front, side, and top views. These drawings supplement the data appearing in Table I and the text, and they facilitate the identification of the crystalline derivatives. Dashed lines represent the vibration directions, and refractive indexes are recorded for crystals that show consistent indexes in these directions. An asterisk indicates the higher index value on views in which consistent refractive indexes 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 by optical crystallographic methods. Dilituric acid rarely crystallized out of the reaction solution in the concentration utilized; however, dilituric acid crystals appeared as small square- to rectangular-shaped tablets with a low α index (n = 1.388), running parallel to the crystal length and showing a low extinction angle (9°) on the top face.

Dextroamphetamine crystallized out as thin rectangular platelets that showed bright first- to second-order polarization colors under crossed nicols as compared to its *dl*-isomer, which was observed as poorly formed acicular prisms showing a high birefringence. *d*-Methamphetamine appeared as large, well-formed, lamellar platelets twinned on 001, showing bright polarization colors and a front face extinction angle of 33°. Its *dl*-isomer occurred as bundles of elongated rods with a notably small $2V$ = 8°. Both isomers are monoclinic crystals as compared to the two amphetamine isomers which show orthorhombic symmetry.

Derivatives of *l*-ephedrine, racephedrine, *dl*-chlorpheniramine, methapyrilene, and diphenhydramine crystallized out as six-sided platelets. The two ephedrine isomers crystallized out as large hexagonal platelets. *l*-Ephedrine showed orthorhombic symmetry, while racephedrine crystallized out as a large, yellow, triclinic platelet with a 38° extinction angle on the front face. *dl*-Chlorpheniramine had a crystal size smaller than the ephedrines and also showed monoclinic symmetry with an extinction angle of 15° on the top face. Methapyrilene and diphenhydramine appeared as monoclinic crystals with extinction angles of 33 and 42°, respectively, on the top face. However, diphenhydramine occurred as stellate rosettes, and the crystals showed a large $2V$ = 75°; methapyrilene appeared as a diamond-shaped crystal with a moderate $2V$ = 48°.

Propoxyphene dilituratе occurred as long, acicular, monoclinic crystals that crystallized out in stellate rosettes. The side face of this crystal showed a 15° extinction angle. The mephentermine derivative was a long, acicular, monoclinic crystal with an extinction angle of 27° appearing on the top face; the phentermine dilituratе, which was of the same crystal habit, showed orthorhombic symmetry.

Pseudoephedrine, phenylephrine, and papaverine dilituratеs crystallized out as prisms. Derivatives of both pseudoephedrine and phenylephrine were elongated in form but were distinguished easily from each other since pseudoephedrine had an orthorhombic symmetry and a low $2V$ = 36° while phenylephrine appeared as a triclinic crystal with a $2V$ = 70° and a front face extinction angle of 42°. The papaverine dilituratе was observed as an almost equant triclinic prism with multifaceted sides.

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High-Pressure Liquid Chromatographic Analysis of Phenylpropanolamine in Human Plasma following Derivatization with *O*-Phthalaldehyde

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Abstract □ A high-pressure liquid chromatographic analysis of phenylpropanolamine in human plasma following extraction, back-extraction, and *O*-phthalaldehyde derivatization is presented. Using fluorescence detection, the method was sufficiently sensitive to quantitate as little as 5 ng of drug/ml of plasma; the coefficient of variation below 100 ng/ml ranged between 5.7 and 2.8%. Plasma concentration data following a single 25-mg dose of phenylpropanolamine hydrochloride in 12 healthy volunteers demonstrate the application of the analytical method.

Keyphrases □ High-pressure liquid chromatography—phenylpropanolamine analysis in human plasma, *O*-phthalaldehyde derivatization □ Phenylpropanolamine—high-pressure liquid chromatographic analysis in human plasma, *O*-phthalaldehyde derivatization □ Derivatization—*O*-phthalaldehyde, high-pressure liquid chromatographic analysis in human plasma

There is great interest in measuring plasma phenylpropanolamine concentrations following single therapeutic doses (25 mg of phenylpropanolamine hydrochloride) of this sympathomimetic agent. GLC following formation of a heptafluorobutyryl derivative (1) was used previously (2, 3) to study phenylpropanolamine pharmacokinetics and was adequate when doses of 60 mg or more were administered or when plasma concentrations were >40 ng/ml and 2 ml of plasma was available for each determination. TLC following acetylation with tritiated acetic anhydride (4) suffers from a high coefficient of variation and nonlinearity.

After preliminary studies of GLC and liquid chromatography with absorbance detection were found to have inadequate specificity and sensitivity, the present method was developed. Previous investigators (5–7) showed that *O*-phthalaldehyde, in the presence of 2-mercaptoethanol, reacts with primary amines to form highly fluorescent products, 1-alkylthio-2-alkyl-substituted isoindoles (8). Replacing 2-mercaptoethanol with ethanethiol was reported to provide a more stable product (9), but the latter is difficult to work with due to its unpleasant odor.

A procedure for extraction of phenylpropanolamine and an internal standard from plasma, derivatization with *O*-phthalaldehyde, separation by high-pressure liquid chromatography (HPLC), and detection by fluorescence

0022-3549/81/0600-0707$01.00/0