It is suggested that not quite all of the simple silicic acid condenses to form the large polysilicic acids, but remains in equilibrium with the products of condensation. It is able to diffuse through the membrane, upsetting the equilibrium and forming more simple acid molecules. This probably explains the attack of sodium hydroxide solution upon the gel.

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The Polymorphism of Sulfapyridine

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In the course of the determination of the optical crystallographic properties of some of the sulfanilamide drugs and their derivatives, five polymorphic forms of sulfapyridine (2-sulfanilamidopyridine) were discovered.[2]

The methods of preparation of these forms, their melting points and analyses (Table I), their optical crystallographic properties (Table II), and their photomicrographs (Figs. 1–5) are presented.

Experimental

Preparation of the Forms of Sulfapyridine

Sulfapyridine, Phase I.—This form of sulfapyridine was obtained by crystallization from hot water or methanol, and is the form occurring in commercial preparations of sulfapyridine. This form appears to be the stable modification at room temperature because all other forms (except Phase IV[3]) have been observed to change into Phase I on standing at room temperature in the dry state, well protected from light and moisture.

Fig. 1.—Sulfapyridine, Phase I (× 56).

Sulfapyridine, Phase II.—In order to prepare this form of sulfapyridine, a slightly less than saturated solution of sulfapyridine in hot *n*-propyl alcohol was allowed to stand on the steam-bath at about 80°, until crystals began to form. The solution was allowed to cool slowly undisturbed to about 40°, then rapidly filtered, and the crystals were washed with ether and air dried at room temperature. Usually this method gave a preparation consisting of pure Phase II. However, it was necessary to exercise great care with this procedure or the product was a mixture of Phases II and IV, the latter predominating. When difficulty was experienced in obtaining Phase II in pure form, a process of selective seeding was applied. A crop of crystals containing a mixture of Phases II and IV was used to seed the hot *n*-propyl alcohol solution. The conditions described above were followed and the crop of crystals filtered, dried and examined microscopically. By repeating this process of selective seeding with crops of crystals successively richer in Phase II, a pure preparation was obtained.

Fig. 2.—Sulfapyridine, Phase II (× 56).

When crystals of Phase II from *n*-propyl alcohol were allowed to stand in contact with the mother liquor, a mixture of Phase I and Phase IV was obtained. Phase II slowly changed into Phase I at room temperature, even when carefully dried and stored in well-stoppered bottles protected from light.

Sulfapyridine, Phase III.—This form of sulfapyridine was prepared by allowing a hot saturated solution of sulfapyridine in *n*-butyl, isobutyl, or *n*-amyl alcohol to cool undistrubed to about 35°. The solution was filtered rapidly, and the crystals were washed with ether, and air dried at room temperature.

Crystals of Phase III changed completely into crystals of Phase I on standing in contact with the mother liquor for two days at room temperature. Crystals of Phase III changed into crystals of Phase I at a fairly rapid rate even when perfectly dry. The crystals of Phase III were found to be somewhat soluble in the immersion liquids used in studying the optical properties. After crystals of Phase

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(1a) From a portion of the Ph.D. thesis, Department of Chemistry, University of Colorado.

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(2) After this work on sulfapyridine was completed, an abstract of the work of F. Reimers appeared: *C. A.*, **38**, 2250 (1944).

(3) Phase IV changes into Phase I after melting (174–175°).

III dissolved in the immersion liquids crystals of Phase I appeared.

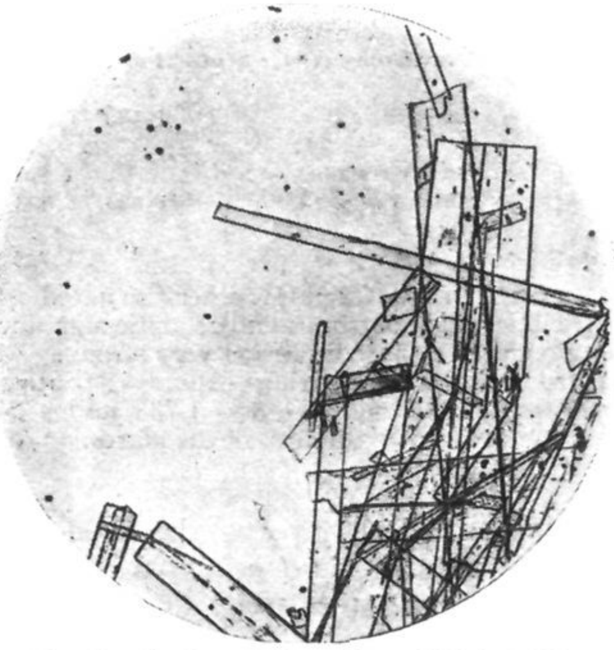

Fig. 3.—Sulfapyridine, Phase III (× 56).

Sulfapyridine, Phase IV.—This form of sulfapyridine was prepared from a hot saturated solution of sulfapyridine in *n*-propyl alcohol. The solution was cooled quite rapidly without shaking. The solution was filtered rapidly, and the crystals were washed with ether and air dried at room temperature. This form also was obtained nearly pure from isopropyl alcohol under similar conditions. Preparations from ethyl alcohol contained appreciable quantities of this phase in addition to Phase I. At room temperature Phase IV appeared to have no tendency to change into Phase I either at contact with *n*- or isopropyl alcohol solutions of sulfapyridine or when perfectly dry.

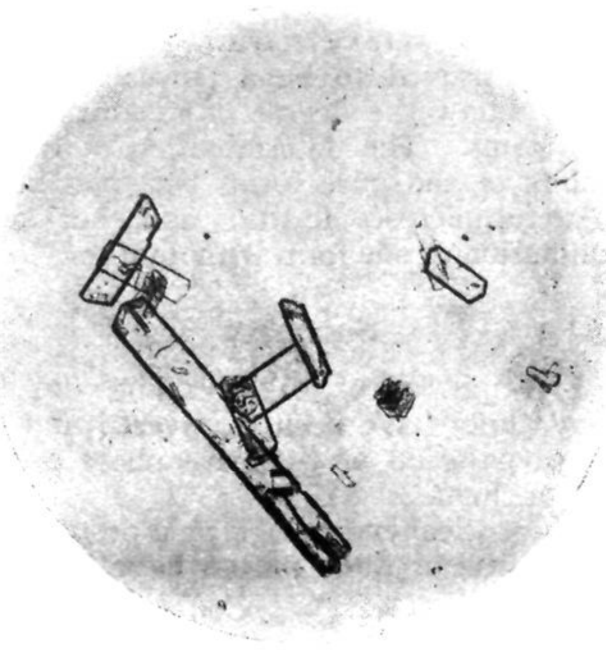

Fig. 4.—Sulfapyridine, Phase IV (× 56).

Sulfapyridine, Phase V.—Attempts to prepare this phase in the pure state were unsuccessful. It frequently occurred in moderate amounts in preparations from *n*- and isopropyl alcohol solutions when they were allowed to stand undisturbed a few hours. Crystals of Phase V when allowed to stand for long periods of time in contact with the mother liquor (*n*- or isopropyl solutions of sulfapyridine) disappear and crystals of Phases I and IV are found. Attempts to obtain a pure preparation by selective seeding failed. Preparations containing appreciable quantities of this phase have been analyzed, and the results indicated that it was sulfapyridine and that it did not contain solvent of crystallization.

Fig. 5.—Sulfapyridine, Phase V (× 56).

Melting Points and Analyses

The melting points were determined on the Maquenne block apparatus which facilitated the placing of crystals on the block as the temperature was increased. All melting points are corrected.

The melting points and analyses of the five polymorphic forms of sulfapyridine are summarized in Table I.

TABLE I

MELTING POINTS AND ANALYSES OF THE POLYMORPHIC FORMS OF SULFAPYRIDINE

Phase	M. p. cor., °C.	Analyses, % nitrogen	
Sulfapyridine		Calcd.,	16.86
Phase I	191.5–192, Sl. dec.	16.75	16.74
Phase II	181–182[a]	16.69	16.69
Phase III	177	16.94	16.97
Phase IV	174.5–175[b]	16.91	16.95
Phase V	[c]	[c]	

[a] Part of the melt solidified on increasing the temperature. [b] Part of the melt solidified and remelted at 186–190°. [c] No melting point determinations or analyses were made.

Optical and Crystallographic Properties

Apparatus and Technique.—A Leitz petrographic microscope Model No. 30CM was used in the present research. The light source was a fluorescent lamp equipped with a 15-watt G. E. Mazda fluorescent tube, 3500° white.

The principal refractive indices α, β and γ at 25 ± 1°, were determined by the immersion method, using interference figures as a guide in selecting correctly oriented crystals. The immersion liquids were those described by Winchell[4a]

(4) (a) Winchell, "Elements of Optical Mineralogy," 5th ed., John Wiley and Sons, Inc., New York, N. Y., 1937, p. 81. (b) Larsen and Berman, "The Microscopic Determination of Nonopaque Minerals," 2nd ed., U. S. Department of the Interior, Geological Survey Bulletin No. 848, Washington, D. C., 1934, p. 12.

TABLE II

OPTICAL CRYSTALLOGRAPHIC PROPERTIES OF THE POLYMORPHIC FORMS OF SULFAPYRIDINE

Phase	Habit	Crystal system	Extinction	Elongation	2V[a]	Optic sign	Dispersion	Refractive indices[b] α	β	γ
I	Tabular to equant	Monoclinic[c]	$Y \| b, Z \wedge c = 39°$[d]	±	88°	+	Very strong axial, $r > v$[e]	1.670	1.736	1.813[f]
II	Lath shaped	Monoclinic	$Y \| b, X \wedge c = 38°$[g]	Parallel to b, (±)	36°	−	Inclined, $v > r$	1.585	1.722	1.739
III	Lamellar	Orthorhombic	$X = a, Y = b, Z = c$	±	Very large	+	Strong rhombic, $v > r$	[h]	1.697	1.721
IV	Tabular	Monoclinic	$Y \| b, Z \wedge c = 44°$[g]	Parallel to b, (±)	74°	+	Axial, $r > v$	1.625	1.693	1.835[i]
V	Equant	Triclinic (?)	?	?	Very small	−	Strong, $r > v$[j]	[k]	1.745	1.761

[a] Calcd. for α, β, and γ. [b] The values of the refractive indices are accurate to ±0.002 unless otherwise noted. [c] Prien and Frondel, *J. Urol.*, **46**, 756 (1941), reported the following data: triclinic, pseudoorthorhombic; optic sign uncertain, probably negative; $2V = 90°$; $\alpha = c = 1.673$, $\gamma = 1.770$; crystals elongated laths; dispersion very strong. [d] Extinction position shows residual blue violet color. [e] The dispersion is so strong that a purple fringe extends the entire length of the isogyre. [f] Keenan, *J. Assoc. Official Agr. Chem.*, **27**, 153 (1944), reported $\alpha = 1.680$, $\beta = 1.733$, and $\gamma > 1.733$. [g] Common orientation shows parallel extinction. [h] Indeterminate due to the extreme thinness of the plates. [i] Accuracy probably not greater than ±0.005. [j] Anomalous dispersion. [k] Indeterminable.

and Larsen and Berman.[4b] The optic axial angle 2V was calculated from the refractive indices α, β and γ, using the more exact formula suggested by Larsen and Berman.[5]

The optical constants of the five phases of sulfapyridine are summarized in Table II.

Characteristic Details.—An inclined optic axis interference figure is obtained on the commonly observed orientation of crystals of Phase I. Thus the indices of refraction obtained on the common orientation are near β but are variable. The dispersion of the refractive indices is great, especially β.

An optic axis interference figure inclined toward the obtuse bisectrix is obtained on the commonly observed orientation of crystals of Phase II. Thus β is the only principal index of refraction obtained on the common orientation. Crystals showing a centered acute bisectrix interference figure do not extinguish sharply and the interference colors are abnormal blue and yellow.

The commonly observed orientation of crystals of Phase III yields a centered obtuse bisectrix interference figure. This orientation gives the principal indices of refraction β and γ. The polarization colors are an abnormal shade of yellow. An abnormal shade of violet is occasionally observed.

The commonly observed orientation of crystals of Phase IV yields an incline optic axis interference figure. This orientation gives β and a fairly constant value between β and γ.

The most commonly observed orientation of crystals of Phase V yields an interference figure in which one brush sweeps the field of view. From this orientation no principal indices of refraction are obtainable. The interference figure shows strong dispersion of an anomalous character. When the trace of the axial plane is in the three-nine o'clock position, the dispersion appears to be horizontal. However, in the 45° position, the dispersion appears to be inclined, showing a red fringe on the concave side of one isogyre and on the convex side of the other.

It is significant that the existence of more than one form of sulfapyridine was detected first by the different degree of dispersion, observed on the interference figures of crystals of Phase I and IV. A subsequent determination of the β indices of refraction showed the values to be widely different. In attempting to isolate the two forms, the other forms were detected. The petrographic microscope proved to be a powerful tool with which to follow the degree of separation of the various forms. The determination of the melting points of the pure forms was possible only after careful microscopic study as a check against contamination of one form with another.

Summary

1. Five phases of sulfapyridine (2-sulfanilamidopyridine) have been discovered and methods of preparation of the pure phase described for four of them.

2. The optical crystallographic properties and melting points of these phases have been determined.

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(5) Ref. 4b, p. 6.