plotted from the data should present unique characteristics. This is not obvious in the figure though the curves have attained a linear form from about this temperature to the lowest temperature investigated which was −50°. Clearly we may not describe the water which freezes only at temperatures below −22° in terms of ordinary phase equilibria. That which freezes at temperatures between zero and −22° might be so described if it is considered as compressed but other evidence indicates that orientation of the dipoles would complicate the interpretation. In conclusion it may be stated that the present data are in general agreement with the previous studies[1a,6] and while compression occurs at the solid–liquid interface, the properties of the liquid are additionally modified in this region.

Summary

By means of the calorimetric method, determinations have been made of the unfrozen water on the surface of wetted silica gel and carbon at temperatures from 0 to −50°. Basing a comparison on unit quantities of the solids, the silica binds the water more strongly than the carbon.

PULLMAN, WASHINGTON RECEIVED SEPTEMBER 10, 1940

[CONTRIBUTION FROM THE CHEMICAL SECTION, DRUG DIVISION, AND THE MICROANALYTICAL DIVISION OF THE FOOD AND DRUG ADMINISTRATION, FEDERAL SECURITY AGENCY]

The Dimorphism of Sulfathiazole

BY DONALD C. GROVE AND GEORGE L. KEENAN

The entrance of the new drug, sulfathiazole (2-sulfanilamidothiazole),[1] into the field of chemotherapy made a survey of its physical and chemical properties essential. In the course of this study, it was found that sulfathiazole occurred in two distinct crystalline forms. The conditions for the existence and isolation of these dimorphs and their physical properties are herein presented.

Hexagonal Form.—When sulfathiazole was crystallized from water, acetone, or ethyl or methyl alcohol, hexagonal prisms (Fig. 1) were formed. They were obtained easily by preparing a saturated solution of the material in ethyl alcohol on the steam-bath, removing the container from the bath and allowing to cool slowly to room temperature. The crystals were then filtered off and dried in the air.

On heating the hexagonal prisms on the Fisher micromelting point stage and observing under the microscope, part of them remained clear and melted at approximately 173 to 175°, while others suddenly turned white or opaque throughout and did not melt until the temperature reached 200–202°. This indicated that some of the crystals had undergone a transition to the higher melting form, and the extent of this transition has been found to depend to a large extent upon the rate of heating. Thus, if the stage was preheated to about 175°, it was possible to observe all the crystals melting at this temperature. On the other hand, if the temperature was raised slowly, most of the crystals would have become opaque before reaching 173°.

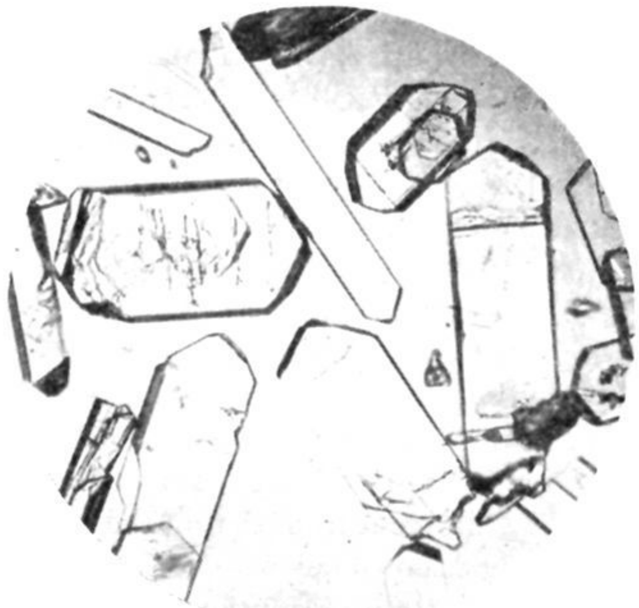

Fig. 1.—Hexagonal prisms (× 80).

Rod Form.—An attempt was made to isolate a second type of crystal by fractional crystallization from hot ethyl alcohol; however, all fractions obtained in this manner were of the hexagonal form. Consideration was then given to the fact that when the hexagonal form became opaque upon heating on the melting point stage, it had in reality undergone a structural change to the higher melting form. This opaque material then, if used as a seed crystal, should give rise to the higher melting form. Accordingly, a hot satu-

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[1] Fosbinder and Walters, THIS JOURNAL, **61**, 2032 (1939).

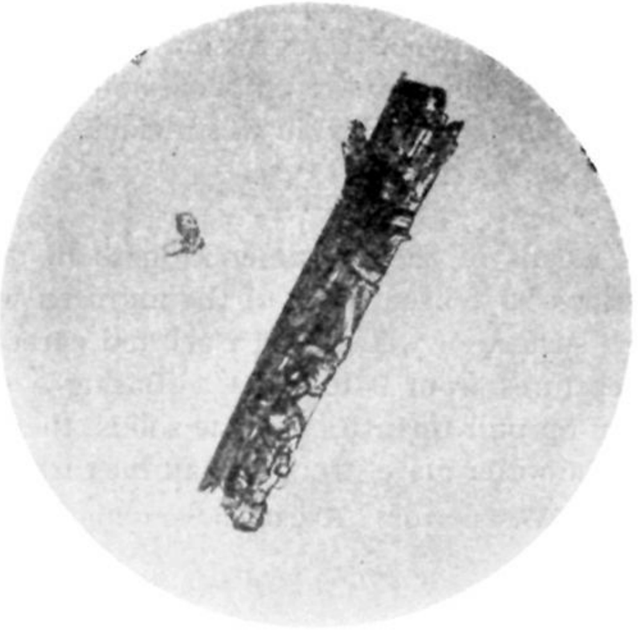

Fig. 2.—Rod changing to prisms (× 80).

Fig. 3.—Rods (× 80).

rated solution of sulfathiazole in ethyl alcohol was prepared on the steam-bath, removed from the bath and immediately seeded with some of the opaque hexagonal form (previously heated to 180°). Almost at once, rod-like crystals started to grow. When the alcohol had cooled, the crystals were filtered off and dried in the air at room temperature. As the crystals dried, it was noticed that the whole mass of material gradually turned chalky or opaque. A microscopical examination of this opaque material showed that the interior of the crystals was frequently filled with small hexagonal prisms (Fig. 2). However, there were a few crystals which had not turned opaque and these appeared as transparent prismatic rods (Fig. 3). A melting point taken on the clear rods showed no change at 173–175°, the crystals remaining clear and melting at 200–202°. Also, the minimum refractive index of these rods was markedly different from that of the hexagonal prisms as will be shown below.

Another hot saturated solution of sulfathiazole in ethyl alcohol was prepared and seeded as above. The rods that formed were not filtered off, but were allowed to remain in the alcohol at room temperature. After about two hours, it was found that the rods had all disappeared and the resulting crystals consisted entirely of hexagonal plates. This demonstrated that the rods are metastable in alcohol at room temperature, and explained why the filtered rods became chalky or opaque, in that the change to the hexagonal form had begun before they were filtered off.

In order to prepare the clear rods and prevent them from becoming opaque, *n*-propyl alcohol was used as the solvent. It has a higher boiling point than ethyl alcohol and the crystals could be removed from the hot solution before the transition took place. The following procedure was used:

A saturated solution of sulfathiazole in boiling *n*-propyl alcohol was prepared, placed on the top of the steam-bath, not directly in the steam, where the temperature was about 80–90° and seeded as described above. After a crop of the rods had formed, the hot supernatant *n*-propyl alcohol was decanted and drained off as thoroughly as possible. The crystals were then washed with ether to remove the remainder of the alcohol and allowed to dry in the air at room temperature. The prismatic rods prepared in this way were stable in the air and remained perfectly clear.

An analysis of both types of crystals for nitrogen and sulfur gave the following results:

	N, %	S, %
Hexagonal prisms	16.24	25.21
Prismatic rods	16.48	25.13
2-Sulfanilamidothiazole (theoretical)	16.46	25.12

Thus, both forms had the same composition and were free from solvent of crystallization.

The melting point of sulfathiazole, determined by the usual procedure in a capillary tube, was 201–202.5° regardless of the type of crystal used. Occasionally, a slight shrinkage was observed at 173–175°. The single melting point obtained by this procedure may be explained by the close packing of the crystals in the capillary tube. Any material melting at the lower temperature was in contact with crystals of the higher melting form, either present originally or formed during the heating process, causing it to solidify immediately and remelt at 201–202.5°. This phenomenon was observed readily under the microscope. It was occasionally possible to melt the hexagonal prisms completely in a capillary tube at 175° by preheating the bath to this temperature before introducing the tube. On cooling, this molten material solidified and would remelt at 201–202.5°.

Optical Properties.—The hexagonal prisms and plates were colorless and were broken up into angular fragments for microscopical examination (Fig. 1). *Refractive indices* (determined by the immersion method in organic oily liquids): $n_\alpha = 1.674$; $n_\beta = 1.733$; $n_\gamma = >1.733$; all ± 0.002. n_α and n_β were most often obtained. *In parallel polarized light (crossed nicols)*, the birefringence was strong. Many fragments did not extinguish sharply with crossed nicols. *In convergent polarized light (crossed nicols)*, biaxial figures were common, especially showing fragments perpendicular to the acute bisectrix with positive optical character and relatively small axial angle.

The prismatic rods, when examined in ordinary light under the microscope, showed narrow colorless elongated prisms which broke up readily into angular fragments (Fig. 3). *Refractive indices* (determined by the immersion method in organic oily liquids): $n_\alpha = 1.605$; $n_\beta = 1.733$; $n_\gamma = >1.733$; all ± 0.002. n_α and n_β were most often obtained, many of the elongated forms showing n_α crosswise, which was also readily observed on angular fragments. *In parallel polarized light (crossed nicols)*, the birefringence was strong. Extinction on the elongated prisms was parallel. *In convergent polarized light (crossed nicols)*, partial biaxial figures were frequently found, especially fragments perpendicular or inclined to an optic axis.

We wish to thank the laboratories of the American Medical Association which, through the courtesy of Dr. Leech, first brought to our attention their observation that sulfathiazole exhibited two melting points. At that time, they were of the opinion that this was due to solvent of crystallization. However, in a later communication to us, they have confirmed our observations, and agree that it is a case of dimorphism.

Summary

The new drug, sulfathiazole (2-sulfanilamidothiazole), exists in dimorphic forms. Data have been presented giving methods of preparation, melting points, optical properties, and photomicrographs.

WASHINGTON, D. C. RECEIVED OCTOBER 10, 1940

[CONTRIBUTION FROM THE SYPHILIS DIVISION OF THE DEPARTMENT OF MEDICINE, JOHNS HOPKINS MEDICAL SCHOOL, AND THE UNITED STATES PUBLIC HEALTH SERVICE]

The Preparation of Phenylarsenoxides. IV. Disubstituted Compounds

BY G. O. DOAK, H. G. STEINMAN AND HARRY EAGLE

In continuation of our studies on the relation between the chemical structure of organic arsenicals and their treponemicidal activity (*T. pallidum*), a series of disubstituted phenylarsine oxides has been prepared. The majority of the corresponding arsonic acids have been described in the older literature.

The catalytic method of Stevinson and Hamilton[1] employing Raney catalyst, has been used in preparing arsonoanilines from the corresponding nitro compounds, with yields varying between 50 and 75%. 2-Nitro-, and 2-nitro-3-hydroxyphenylarsonic acids were not reduced to amines using Raney catalyst. Unidentified amorphous products were obtained from the reduction mixture. The addition of platinic chloride or fresh Raney catalyst did not complete the reaction.

The preparation of 3,4-dihydroxyphenylarsonic acid has been reported by the oxidation of 4-arsonophenol with potassium persulfate,[2] but subsequent investigation by Balaban[3] and in this Laboratory has not confirmed this synthesis. However, we were able to prepare 3,4-dihydroxyphenyldichloroarsine by an adaptation of a method for the preparation of catechol.[4]

While Barber has stated that the reaction between sulfites and halogenated nitroarsonic acids does not proceed normally,[5] we have prepared disodium 3-nitro-4-sulfophenylarsonate by this method. The synthesis is simpler than that employed by Barber for the free acid.[6]

Experimental Part

Table I lists the new compounds prepared. All but one of the arsine oxides (*cf.* footnote *i*, Table I) were obtained by sulfur dioxide reduction of the corresponding arsonic acids. When amino-substituted arsonic acids were reduced, best results were obtained by working in concentrated hydrochloric acid solution, from which the amine hydrochloride dichloroarsines precipitated in crystalline form. Where preliminary experiments indicated that the arsine oxides were unstable in alkaline solution, no attempt was made to isolate them, since the dichloroarsines proved satisfactory for pharmacological investigation. The phenylarsine oxides and arsonous acids were obtained as amorphous powders which showed no definite melting point.

3,4-Dihydroxyphenylarsine Oxide.—Diazotized 3-amino-4-hydroxyphenylarsonic acid was added dropwise to

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(1) Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935).

(2) German Patent 271,892.

(3) Balaban, *J. Chem. Soc.*, 1088 (1929).

(4) Cumming, Hopper and Wheeler, "Systematic Organic Chemistry," Constable and Co., London, 1937, p. 206.

(5) Barber, *J. Chem. Soc.*, 2047 (1930).

(6) Barber, *ibid.*, 2556 (1931).