Polymorphism in Sulfonamides

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Abstract □ An evaluation of entropies and enthalpies of transition and fusion and a comparison of X-ray diffraction patterns and IR spectra of polymorphic forms of structurally related compounds were undertaken to obtain information which might prove useful in correlating the frequency of occurrence of polymorphism with certain aspects of chemical structure. Sixteen sulfonamides were selected for study. The screening procedures used in this research identified polymorphism in eight compounds and solvates in two compounds. The *p*-amino group, the acidic N^1-hydrogen atom, and the oxygens of the sulfonamide group have been implicated in the various hydrogen-bonding arrangements which distinguish one polymorphic form from another. It is postulated that electron-withdrawing and electron-donating groups at the N^1-position influence the strength of the hydrogen bonds which form and, hence, the tendency of these compounds to exhibit more than one crystalline form. In some cases, however, minor alterations in structure result in disproportionate changes in the compactness of the crystal lattice, and this fact makes it difficult to develop broad generalizations applicable to large groups of compounds.

Keyphrases □ Polymorphism—evaluation of 16 sulfonamides, hydrogen-bonding arrangements, crystal compactness □ Sulfonamides—studied for polymorphism, correlation of frequency of occurrence with chemical structure, X-ray diffraction patterns compared to IR spectra, entropy and enthalpy comparisons

During the past few years, there have been frequent demonstrations of the fact that the appropriate selection of the most suitable crystalline modification, polymorph, amorphous form, or crystalline solvate can influence significantly the medicinal value of a given chemical agent. Although polymorphic forms of a compound dissolve to give identical solutions, these forms differ with respect to their thermodynamic activities, equilibrium solubilities, and rates of dissolution. Therefore, the rate of release of a polymorph from a solid dosage form, whether *in vivo* or *in vitro*, should depend on which form is present, provided the rate of release is diffusion controlled.

In some cases, it may be desirable to employ a polymorphic form of a compound exhibiting a high thermodynamic activity in order to provide therapeutic blood levels of an otherwise inactive drug formulation. In other instances, it may be advisable to use the more stable polymorph. If, for example, a suspension of a drug in an aqueous vehicle is prepared using a metastable polymorph, reversion to a more stable form might occur under certain conditions of storage. This reversion might lead to crystal growth in the formulation, with subsequent caking. It might also lead to a wide range of dose-to-dose drug availability for the patient.

Given the possible consequences of an injudicious choice of a particular polymorphic form employed in the formulation of a medicinal agent, and given the estimate that fully one-third of all organic compounds are likely to exhibit polymorphism (1), it seems reasonable to propose that some kind of screening procedure should be used routinely to detect this phenomenon in potential pharmaceuticals. Furthermore, it would be helpful to know what types of structural characteristics, if any, predispose a compound to exhibit polymorphism. This study was undertaken to obtain information which could be useful in the detection of, and in predicting the occurrence of, polymorphism in organic compounds. It was proposed that an evaluation of entropies and enthalpies of transition and fusion and a comparison of IR spectra and X-ray diffraction patterns of a series of structurally related chemical compounds might yield information useful in correlating the frequency of occurrence of polymorphism with certain aspects of chemical structure.

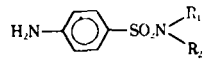
With these aims in mind, a group of compounds with closely related structures, the sulfonamides, was selected for study. The polymorphism of sulfonamides received wide attention in the early 1940's when sulfonamide chemotherapy was at its peak. The discovery of new crystal forms of sulfonamides was, in most cases, completely accidental and, for many years, there was no concerted attempt to study the polymorphism of these compounds as a group.

The first report of polymorphism in a sulfonamide was the observation reported by Zyp (2) in 1938 that sulfanilamide appears in several distinct crystalline forms when it is crystallized from a drop of water and examined under the microscope. In 1941, Watanabe (3) reported three polymorphic modifications of sulfanilamide and published their X-ray diffraction patterns. This work apparently escaped the attention of Yakowitz (4), who confirmed Watanabe's results and reported refractive indexes and heats of solution for the three forms. A fourth form of sulfanilamide was reported by McLachlan (5) in his book on X-ray crystal structure.

The crystal structures of three of the forms of sulfanilamide were determined using X-ray and neutron diffraction studies (6). Inoue and Saito (7) used differential thermal analysis (DTA) to obtain thermograms of the various forms of sulfanilamide, but they did not obtain quantitative data on the heats of transition of the compound. Lin and Guillory (8) employed DTA calorimetry to detect polymorphism in sulfanilamide-d_4, and they reported the thermograms and heats of fusion and transition for this compound's four crystal forms as well as for nondeuterated sulfanilamide.

Another sulfonamide that has been studied extensively is sulfathiazole. Grove and Keenan (9) discovered two polymorphs of sulfathiazole, one of which undergoes transition at 175° and melts at 202°; the other melts at 202° without undergoing transition. A third form was reported by Miyazaki (10), who supplied X-ray diffraction patterns for the polymorphs. The heat of transition for sulfathiazole was reported by Milosovich (11), who studied the dissolution rate of two of the polymorphs. The method used to determine the heat of transition was a modification of the solubility method previously used by Higuchi *et al.* (12). The heat of

Table I—Solvents Used for Recrystallization of Sulfonamides



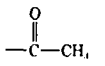
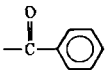
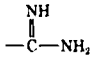
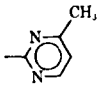
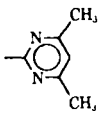
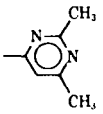
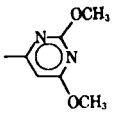
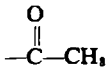
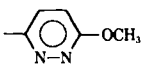
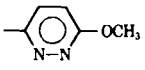
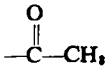
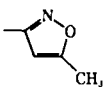
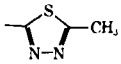
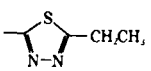
Compound	R_1	R_2	Acetone	Methanol	Ethanol	*n*-Butanol	*n*-Pentanol	Other
Sulfacetamide	H		×	×	×	×	×	—
Sulfabenzamide	H		×	×	×	×	×	H_2O at RT, *n*-propanol, isopropanol, isobutanol
Sulfaguanidine	H		×	×	×	×	×	—
Sulfapyridine	H		×	×	×	×	×	$CHCl_3$, *n*-propanol, isopropanol, H_2O, isobutanol, ethanol–isooctane mixture
Sulfadiazine	H		×	×	×	×	×	—
Sulfamerazine	H		×	×	×	×	×	—
Sulfamethazine	H		×	×	×	×	×	—
Sulfisomidine	H		×	×	×	×	×	—
Sulfadimethoxine	H		×	×	×	×	×	H_2O
N^1-Acetyl sulfamethoxypyridazine			×	×	×	×	×	—
Sulfamethoxypyridazine	H		×	×	×	×	×	H_2O, ethanol–isooctane mixture
Acetyl sulfisoxazole			×	×	×	×	×	—
Sulfisoxazole	H		×	×	×	×	×	H_2O
Sulfamethoxazole	H		×	×	×	×	×	*n*-Propanol, H_2O at RT, H_2O at dry ice–acetone temperature
Sulfamethizole	H		×	×	×	×	×	—
Sulfaethidole	H		×	×	×	×	×	*n*-Propanol

Table II—Thermal Data for Eight Sulfonamides in Which Polymorphism Was Not Found

Compounds	Solvents Used for Recrystallization	Heat of Fusion, kcal./mole	Fusion Temperature	Entropy of Fusion, e.u.
Sulfacetamide	Original powder	5.35 ± 2.0%	183°	11.7
Sulfadiazine	Original powder	9.74 ± 2.3%	259°	18.3
Sulfamerazine	Original powder	8.68 ± 2.8%	236°	17.1
Sulfisomidine	Original powder	10.81 ± 1.7%	244°	20.9
Sulfadimethoxine	Methanol	7.12 ± 2.1%	204°	14.9
N^1-Acetyl sulfamethoxypyridazine	Methanol	1.72 ± 0.2%	187°	3.7
Acetyl sulfisoxazole	Original powder	8.16 ± 1.6%	197°	17.3
Sulfamethizole	Ethanol	6.42 ± 1.9%	207°	13.4

transition of sulfathiazole and its heat of fusion were reported by Guillory (13), who used DTA calorimetry, and by Moustafa and Carless (14), who used differential scanning calorimetry (DSC). The crystal structure of sulfathiazole II was reported in 1971 by Kruger and Gafner (15).

Five crystalline forms of sulfapyridine were reported by Castle and Witt (16), who also determined the optical properties and the melting points of these forms. Another sulfonamide exhibiting multiple crystalline forms is phthalylsulfacetamide, which can be obtained in four forms when dissolved in dilute aqueous sodium hydroxide and precipitated by the addition of dilute hydrochloric acid at various controlled temperatures (17).

In the course of a micromelting-point determination on 28 sulfanilamide derivatives, Reimers (18) found that a number of the derivatives, obtained by treating sulfonamides with silver nitrate and then with ethyl iodide, were polymorphous. Recently, Mesley and Houghton (19) employed IR spectroscopy to screen 18 pharmaceutically important sulfonamides for the existence of polymorphism; Kuhnert-Brandstätter and Wunsch (20) concluded that of the 50 sulfonamides and related compounds which they examined by thermomicroscopic methods, 60% were polymorphic. In some instances, the polymorphs were so unstable that they could be identified only by use of binary phase diagrams.

Although the work done on polymorphism in sulfonamides to date is considerable, there has been no systematic study of the heats of transition and fusion of these compounds. For many sulfonamides, there is a controversy concerning the number of polymorphic forms that actually do exist. This work was undertaken to obtain a better understanding of the phenomenon of polymorphism. Sulfonamides were chosen for study because of their clinical importance, their structural simplicity, their similarity, and because their solubilities are critical with respect to the development of crystalluria.

EXPERIMENTAL

Materials—Sixteen sulfonamides were selected for study: sulfacetamide[1], sulfaguanidine[1], sulfamethazine[1], sulfapyridine[1], sulfabenzamide[2], sulfadiazine[2], sulfisoxazole[2], acetyl sulfisoxazole[3], sulfadimethoxine[3], sulfamethoxazole[3], acetyl sulfamethoxypyridazine[4], sulfamethoxypyridazine[4], sulfamerazine[5], sulfisomidine[6], sulfamethizole[7], and sulfaethidole[8].

The solvents used were: reagent grade *n*-pentanol[9], isooctane[9], and *n*-propanol[9]; analytical grade *n*-butanol[10], acetone[10], methanol[10], and isopropanol[10]; and dehydrated alcohol USP. IR quality potassium bromide[11] powder was employed in the preparation of pellets for IR analysis. Metals for calibration of the DTA equipment were supplied by the manufacturer[12].

Methods and Instrumentation—Polymorphic forms of the sulfonamides were prepared by recrystallization from the solvents listed in Table I. Hot, saturated solutions were prepared and cooled to ice-water temperature, to room temperature, or to acetone–dry ice temperature. Crystals were collected and dried in a vacuum desiccator overnight.

The DTA instrument[13] employed in quantitative measurements of heats of transition and fusion was equipped with a calorimeter cell. The cell was calibrated with gallium, indium, tin, and zinc following the procedure used by Guillory (13). A pair of cold junction thermocouples in an ice bath was used to establish the reference temperature. Six samples of each of the standard metals were weighed on an electrobalance[14] to ±0.002 mg. The aluminum foil cups, which served as liners for the sample holder, were fashioned with the aid of a dowel pin from aluminum sheets 0.003 cm. (0.001 in.) thick. No liner was employed in the reference holder. Sample sizes were selected to produce fusion peaks whose areas could be measured with an error of not more than 3%. Samples of indium, tin, and zinc were each heated in the calorimeter cell from room temperature to about 30° above the melting points. Samples of gallium were cooled to about −40° with the aid of a dry ice-acetone mixture and then heated to 20° above the melting point at a heating rate of 10°/min. In each case, the thermogram of differential temperature *versus* reference temperature was obtained with a single endothermic peak corresponding to fusion. The areas of these endothermic peaks were found by drawing a line from the point where the thermogram first departed from the baseline (onset) to the point where the baseline was resumed following fusion (recovery). The areas were determined by use of a compensating polar planimeter[15]. The fusion temperature for each material was taken as the extrapolated onset temperature of the endothermic peak. The lower temperature side of the fusion peak was extrapolated to the prefusion baseline. The fusion temperatures (obtained to the nearest ±0.5°) were corrected for the nonlinear temperature response of the chromel–alumel thermocouples employed.

Calibration coefficients were calculated from the equation:

$$E = \frac{\Delta HMa}{AT_s \Delta T_s} \qquad \text{(Eq. 1)}$$

[1] City Chemical Co., New York, N. Y.
[2] Nutritional Biochemicals Co., Cleveland, Ohio.
[3] Hoffmann-La Roche Inc., Nutley, N. J.
[4] Parke, Davis & Co., Detroit, Mich.
[5] American Cyanamid Co., Pearl River, N. Y.
[6] Ciba Pharmaceutical Co., Summit, N. J.
[7] Ayerst Laboratories, New York, N. Y.
[8] Smith Kline & French Laboratories, Philadelphia, Pa.
[9] Fisher Scientific Co., Pittsburgh, Pa.
[10] Mallinckrodt Chemical Works, St. Louis, Mo.
[11] Matheson, Coleman & Bell, East Rutherford, N. J.
[12] E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.
[13] DuPont 900, E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.
[14] Cahn Instrument Co., Paramount, Calif.
[15] Model 620005, Keuffel & Esser Co., New York, N. Y.

Table III – X-Ray Powder Diffraction Data

Sulfacetamide		Sulfadiazine	
d, Å	I/I_1	*d*, Å	I/I_1
7.3	100	12.0	---
5.8	26	10.5	10
5.3	30	7.6	19
4.6	58	6.8	70
4.15	20	6.2	14
3.85	48	5.4	90
3.5	27	4.7	85
3.25	10	4.2	41
3.0	7	3.85	100
2.65	11	3.65	16
2.55	14	3.45	22
2.45	10	3.18	41
2.25	12	3.05	25
2.20	6	2.75	4
2.15	8	2.48	10
		2.35	13
		2.10	7

Sulfamerazine		Sulfisomidine	
d, Å	I/I_1	*d*, Å	I/I_1
7.2	100	11.0	58
6.1	48	8.5	7
5.6	16	7.0	3
5.1	27	6.3	100
4.4	32	5.2	17
4.1	35	4.7	50
3.9	44	4.2	21
3.65	42	3.85	14
3.25	8	3.6	50
2.90	10	3.4	15
2.75	8	3.15	17
2.55	2	2.95	14
2.35	7	2.65	4
1.96	3	2.50	3
		2.35	1
		2.25	2
		2.15	4
		2.07	7
		2.02	4
		1.92	3
		1.84	3

Sulfadimethoxine		N^1-Acetyl Sulfamethoxypyridazine	
d, Å	I/I_1	*d*, Å	I/I_1
8.5	48	11	55
7.3	69	8	15
6.4	99	6.8	26
5.8	53	6.2	47
5.2	4	5.7	82
4.7	62	5.1	56
4.2	100	4.7	35
3.85	20	4.2	43
3.55	89	3.65	100
3.15	18	3.5	49
2.75	19	3.3	25
2.55	10	3.1	41
2.40	5	2.9	4
2.25	10	2.75	4
2.01	20	2.45	3
1.95	10	2.27	5
1.73	9	2.08	5
		2.00	2
		1.86	5
		1.83	4

Acetyl Sulfisoxazole		Sulfamethizole	
d, Å	I/I_1	*d*, Å	I/I_1
11.5	6	10.5	86
7.0	100	7.3	34
6.3	87	5.6	13
5.4	10	5.1	10
4.8	76	4.5	100
4.2	38	4.05	20
3.9	21	3.6	8
3.5	45	3.4	24

Table III—*Continued*

Acetyl Sulfisoxazole		Sulfamethizole	
d, Å	I/I_1	*d*, Å	I/I_1
3.2	8	3.3	29
2.9	8	3.2	26
2.7	6	2.95	9
2.55	10	2.6	9
2.45	10	2.3	5
2.2	4		
2.05	4		

where:

E = calibration coefficient, mcal. deg.$^{-1}$ min.$^{-1}$
ΔH = heat of fusion, mcal. mg.$^{-1}$
M = sample mass, mg.
a = heating rate, deg.$^{-1}$ min.$^{-1}$, 10° min.$^{-1}$
A = peak area, in.^{2}
T_s = X-axis sensitivity, deg.$^{-1}$ in.$^{-1}$, 20° in.$^{-1}$ (except for zinc, 50° in.$^{-1}$)
ΔT_s = Y-axis sensitivity, deg.$^{-1}$ in.$^{-1}$, 0.5° in.$^{-1}$

The calibration coefficients and fusion temperatures obtained, respectively, were as follows: gallium, 7.61 mcal. deg.$^{-1}$ min.$^{-1}$ and 30.2°; indium, 9.86 mcal. deg.$^{-1}$ min.$^{-1}$ and 156.6°; tin, 11.3 mcal. deg.$^{-1}$ min.$^{-1}$ and 232.1°; and zinc, 16.3 mcal. deg.$^{-1}$ min.$^{-1}$ and 41.6°. A plot of these data gave a smooth line from which the calibration coefficient of the required temperature could be obtained. The reliability of the calibration curve was checked using benzoic acid and silver nitrate. Heats of fusion obtained for these compounds were within 2% of the reported literature values.

Measurements of heats of transition and fusion for sulfonamides were determined in essentially the same way. Six samples of each polymorphic form were weighed into aluminum sample holder liners, and thermograms were obtained. The sample size and differential temperature (ΔT) setting were selected to produce a peak area which could be measured with an error of not more than 3%. Heating rates of 10°/min. were employed. Heats of transition and fusion were calculated from the measured peak area using the equation for the calibration coefficient.

The DTA instrument, equipped with a standard cell, was also used to record polymorphic transitions and fusion temperatures in all cases. Glass tubes, 2 mm. in diameter, were filled with sample to a depth of about 2 mm., and a thermocouple was inserted in the sample so that the junction was in contact with the bottom of the tube. For the standard and reference tubes, a volume of glass beads approximately equal to that of the sample was employed. Settings of 0.5° in.$^{-1}$ for ΔT and 20° in.$^{-1}$ for the T scale were used in all cases. Air inside the cell assembly was flushed out with nitrogen gas to protect the samples from oxidation. A pair of cold junction thermocouples in an ice bath was employed to establish the reference temperature. A heating rate of 10°/min. was employed in this study so that the results obtained from conventional DTA would be consistent with those obtained from the calorimeter cell. All samples were heated from room temperature up to several degrees above their melting points.

IR spectra of the polymorphs were taken as potassium bromide pellets on a spectrophotometer[16]. The sample and potassium bromide were triturated in an agate mortar for about 15 min. The sample–KBr ratio was 0.5–1.2 mg.:350 mg. if the potassium bromide die (Beckman) and hydraulic press (Pasadena) were employed, and a pressure of 20 tons was used. A sample–KBr ratio of 0.5–1.0 mg.:100 mg. was used if the Wilk's Mini-Press was employed. The spectra obtained by the two methods are essentially identical. Spectra were recorded in the range of 4000–300 cm.$^{-1}$, and polystyrene film was used to calibrate the wave number axis.

Phase transitions were also observed using the thermomicroscopic technique. A small amount of sample was placed between a slide and cover glass. The slide was put on the Kofler micro hot stage and examined using polarized light to observe polymorphic transitions as heat was applied at a uniform heating rate of 10° min.$^{-1}$.

[16] Beckman IR-10 IR spectrophotometer.

Table IV—Thermal Data for Various Forms of Sulfabenzamide

Form	Solvent Used for Recrystallization	Transition Temperature	Heat of Transition	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy of Fusion, e.u.
I	Methanol	—	—	181°	6.42 ± 1.1%	14.1
II	Ethanol	—	—	182°	6.39 ± 1.5%	14.0
III	H_2O	*endo* 172°, 173° *exo* 176°	—	181°	6.99 ± 2.4%	15.4
IV	Isobutanol and heated to 96°	173°	—	182°	5.79 ± 1.5%	12.7
SI	*n*-Butanol	71°, 119°	—	181°	6.06 ± 1.6%	13.3
SII	*n*-Pentanol	58°, 80°, 143°	—	182°	6.18 ± 2.2%	13.6
SIII	Isobutanol	77°, 108°, 172°	—	181°	—	—

The thermogravimetric analyzer (TGA)[17] was employed to distinguish between polymorphs and solvates. A nitrogen gas purge and cold junction thermocouples in an ice bath were also employed with this instrument. Samples ranging in size from 10 to 20 mg. were employed; thermograms, representing weight as a function of temperature, were obtained. The amount of solvent contained in a given sample was obtained directly from the *Y*-axis of the thermograms.

The X-ray powder diffraction method was employed for obtaining diffraction diagrams of all polymorphic forms studied. Samples were placed in 0.5-mm. diameter capillary tubes, and a Debye-Scherrer powder camera (114.6 mm. in diameter) with asymmetric film mount was used. CuKα radiation with $\lambda = 1.5418$ Å was employed. The interplanar spacings, *d* values, in Angstroms were obtained by direct measurement of the diagrams, and their relative intensities were estimated using an Enraf-Nonius densitometer. In some regions, *d* values were obtained to the nearest tenth of an Angstrom unit. The relative intensities are probably reliable to about ±10%.

RESULTS AND DISCUSSION

Of the 16 sulfonamides studied, eight were found to exhibit polymorphism under the conditions used. Table II summarizes the thermal data for sulfonamides in which polymorphism was not detected in this study. The interplanar spacings, *d* values, and relative intensities of X-ray diffraction measurements for each of the compounds are listed in Table III.

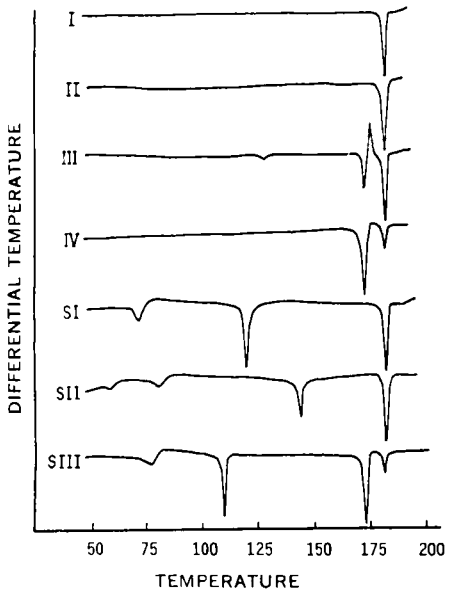


Figure 1—*Differential thermograms of various forms of sulfabenzamide.*

[17] DuPont model 950.

It should not be inferred that polymorphs of these compounds will never be found. Rather, under the solvent recrystallization techniques used in this research, polymorphs sufficiently stable to be characterized were not obtained. Indeed, in three instances (acetyl sulfisoxazole, sulfamerazine, and sulfamethizole) Kuhnert-Brandstätter and Wunsch (20) reported thermomicroscopic evidence of polymorphism. In the case of sulfamethizole, Form II was so unstable that it could only be detected in a binary system with sulfaethidole. Similarly, Form III of acetyl sulfisoxazole was obtained as a stable intermediate phase only in a binary system with sulfamethoxazole. Form II of acetyl sulfisoxazole and Form II of sulfamerazine arise under circumstances that suggest partial decomposition of the sulfonamide. In none of these instances could corroborative DTA, X-ray, or IR spectroscopic evidence of polymorphism be obtained in this study.

From the last column of Table II, it can be seen that N^1-acetylsulfamethoxypyridazine has an unusually low entropy of fusion. If this compound is recrystallized from *n*-butanol or *n*-pentanol, it undergoes deacetylation to sulfamethoxypyridazine. The crystal form of the deacetylated compound which is obtained is the same as that obtained by recrystallization of sulfamethoxypyridazine from *n*-butanol or *n*-pentanol.

Mesley and Houghton (19) reported that only one crystalline form of sulfisomidine could be obtained by the recrystallization methods they employed. They did, however, occasionally isolate mixtures of this form and an amorphous form by evaporation of solutions of the compound in ethanol and methanol. Repeated attempts to obtain an amorphous form by this method failed. Only by heating the compound to fusion temperature and then allowing the sample to cool could sulfisomidine be obtained in an amorphous form.

Sunwoo and Eisen (21) used DTA to obtain heats of fusion of some sulfonamides during a study of solubility parameters. Three of the compounds they studied (sulfadiazine, sulfisomidine, and sulfamerazine) are among those in which polymorphism could not be detected. The melting points reported (21) for these compounds are 6.6, 6.4, and 6° higher, respectively, than those obtained in this investigation. They are also higher than the melting points reported

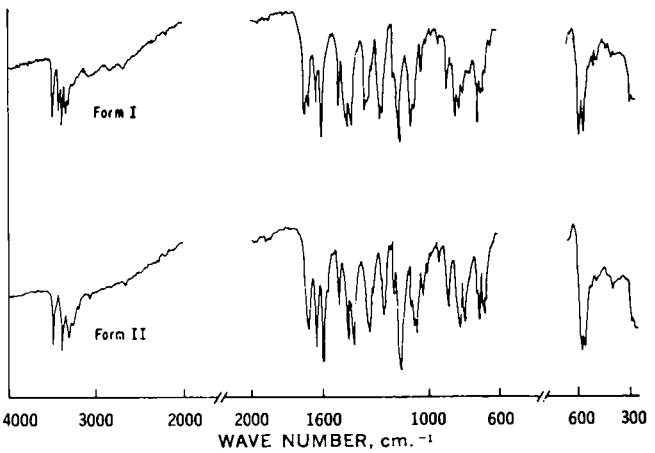


Figure 2—*IR spectra of two forms of sulfabenzamide.*

Table V—X-Ray Powder Diffraction Data for Sulfabenzamide

Form I		Form II	
d, Å	I/I_1	*d*, Å	I/I_1
16	2	17.0	25
9.7	28	9.8	16
8.0	36	8.0	55
7.1	49	7.2	69
6.3	59	6.3	73
5.7	6	5.7	5
5.3	19	5.3	16
5.1	42	5.1	17
4.85	54	4.85	81
4.6	100	4.6	100
4.4	78	4.4	87
4.2	54	4.2	78
4.05	29	4.05	21
3.85	43	3.9	66
3.75	85	3.75	44
3.45	60	3.60	54
3.3	46	3.50	5
3.15	14	3.25	40
3.05	15	3.15	22
2.85	7	3.05	4
2.66	18	2.95	2
2.46	17	2.88	6
2.38	6	2.77	12
2.33	4	2.67	11
2.12	6	2.57	8
1.98	12	2.47	16
1.70	3	2.32	9
1.62	2	2.20	10
		2.12	11
		2.02	5
		1.98	12

Form III		Form IV	
d, Å	I/I_1	*d*, Å	I/I_1
12.7	7	18.0	47
8.0	15	10.0	33
7.2	66	8.2	34
6.5	8	7.2	41
5.1	60	6.5	55
4.8	24	5.9	6
4.5	27	5.5	17
4.3	34	5.2	45
4.15	45	close	
3.96	23	5.0	44
3.75	100	4.7	100
3.60	25	4.5	64
3.40	8	4.3	34
3.25	47	4.2	23
3.10	16	3.8	82
2.99	3	3.6	46
2.80	28	3.4	40
2.70	7	3.15	12
2.60	12	2.95	9
2.45	3	2.75	19
2.40	4	2.55	16
2.30	3	2.45	8
2.25	1	2.30	4
2.20	5	2.15	6
2.12	7	2.00	9
2.04	6		
1.98	2		
1.88	4		

Form SI		Form SII	
d, Å	I/I_1	*d*, Å	I/I_1
16.0	24	16.0	56
9.8	17	9.8	27
8.0	41	8.2	29
7.2	49	7.2	32
6.4	50	6.4	37
5.4	12	5.1	41
4.7	100	4.6	100
4.3	75	4.4	39
3.85	59	4.2	34
3.55	44	4.0	20
3.30	25	3.75	73
2.70	6	3.50	41

Table V—*Continued*

Form SI		Form SII	
d, Å	I/I_1	*d*, Å	I/I_1
2.50	9	3.30	34
2.35	5	3.05	11
2.15	4	2.85	6
1.98	5	2.65	17
		2.45	14
		2.35	6
		2.25	3
		2.10	5
		1.98	8

Form SIII	
d, Å	I/I_1
16.0	59
10.8	26
9.5	45
8.0	32
7.1	53
6.4	51
5.8	5
5.4	28
5.0	51
4.6	100
4.25	49
4.00	44
3.75	86
3.50	58
3.30	46
3.05	15
2.85	6
2.68	21
2.48	21
2.37	9
2.23	3
2.13	8
1.98	10

in "The Merck Index" (22). The heats of fusion reported by these authors are 23, 6, and 13% lower, respectively, than those obtained in the present study.

Sulfabenzamide—Sulfabenzamide exists in four crystalline forms (I, II, III, and IV). Three solvated crystalline forms also have been obtained (SI, SII, and SIII). The thermograms and thermal data obtained for these forms are summarized in Fig. 1 and Table IV, respectively.

From an examination of the thermograms, it can be seen that Forms I and II have identical DTA patterns and similar heats of fusion, but differences in the IR spectra of these two modifications can be seen in Fig. 2, particularly in the N—H stretching vibration region (3410 $cm.^{-1}$ and 3320–3250 $cm.^{-1}$). These two forms also show different X-ray diffraction patterns (Table V).

It was observed that Form III can be transformed to Form I by trituration and, hence, gives the same IR spectrum as Form I. Form III does exhibit a different X-ray diffraction pattern and also displays an additional small endothermic peak at 125° in the DTA thermogram. The heat of transition associated with this peak is too small to be measured accurately. The second endothermic peak and the exothermic peak which follows it are so close to the fusion peak that the transition energies cannot be measured separately.

Experiments reveal that Form IV is transformed to Form III and then to Form I by trituration. Therefore, the same IR spectrum and virtually the same diffraction pattern are obtained for Form IV as for Form I.

Form IV exhibits the lowest heat of fusion of the four polymorphic forms of sulfabenzamide. Furthermore, its fusion peak is preceded by a large endothermic peak, indicating that it is transformed into a highly disordered state prior to fusion. The transition temperature is so close to the fusion temperature that it is difficult to obtain an accurate measure of the heat of transition. The sum of the heat of transition and the heat of fusion is recorded in the table for this form.

Three endothermic peaks are observed in the conventional DTA thermogram of Form SI, at 71, 119, and 181°. The first two peaks correspond to loss of solvent; the third represents fusion. When TGA was employed, it was found that the weight loss from this sample

Table VI—Thermal Data for Crystal Forms of Sulfaguanidine

Form	Solvent of Recrystallization	Transition Temperature	Heat of Transition, kcal./mole	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy, e.u. Transition	Entropy, e.u. Fusion
SI	Original powder	133–143°	10.32	191°	5.78 ± 1.3%	25.4	12.5
II	Acetone	—	—	191°	5.35 ± 3.6%	—	11.5
III	Methanol	—	—	191°	6.20 ± 3.0%	—	13.4
IV	*n*-Butanol	160°	0.73	192°	5.64 ± 1.9%	1.68	12.1
V	*n*-Pentanol	169°	0.82	191°	5.05 ± 1.5%	1.85	10.9

occurred over the temperature range from 65 to 86°, with no further weight loss at 119°. From the TGA experiment, it can be estimated that 0.83 mole of solvent (*n*-butanol) is bound to each mole of sulfabenzamide.

When a sample of Form SI was heated to 106° in the TGA apparatus, allowed to cool to room temperature, and then subjected to DTA, the sample did not exhibit a peak at 119°. It seems likely, then, that the first endothermic peak observed in DTA corresponds to the energy required to break the hydrogen bonds formed between solvent and sulfabenzamide molecules. When this experiment is performed with the crystals exposed to a steady stream of nitrogen, as they are in the TGA apparatus, the solvent escapes rapidly from the surface of the crystals. When the sample is packed into a capillary tube, however, the solvent does not vaporize until its boiling point (117–118°) is exceeded.

There are four endothermic peaks in the DTA thermogram of Form SII. The peaks occur at 58, 80, 143, and 182°. The first three endothermic peaks disappear from the DTA thermogram when crystals of Form SII are heated to 114° in an oven or in the TGA apparatus. The peak at 182° corresponds to fusion. In the TGA apparatus, weight loss occurs in two stages. Over the temperature range from 50 to 74°, the sample loses 5.95% of its weight. Over the temperature range from 74 to 104°, the sample loses an additional 12.12% of its weight. From that point to fusion, the sample weight remains constant. When these results are compared with those obtained using DTA, it appears obvious that the first two peaks correspond to loss of solvent from the crystal structure, and the third peak corresponds to vaporization of the solvent when its boiling point (138°) is exceeded. It was found that 0.69 mole of solvent is bound to each mole of sulfabenzamide.

There are four endothermic peaks in the DTA thermogram of Form SIII, at 76, 108, 172, and 181°. When subjected to TGA, Form SIII loses weight between 70 and 88°. When heated to 96° in an oven and then subjected to DTA, Form SIII exhibits the same DTA thermogram as Form IV. The peak at 76° apparently represents release of solvent from the crystal structure; that at 108° corresponds to the boiling point of isobutanol (108°).

When solvents are removed from Forms SI and SII, the IR spectra obtained are identical with that of Form II. Form SIII, after solvent removal, exhibits the same IR spectrum as Forms I and IV. The X-ray diffraction patterns reveal that SI has the same crystal structure as Form II; SII and SIII have the same crystal structure as Form I.

Sulfaguanidine—Five crystalline forms, SI, II, III, IV, and V, are obtained for sulfaguanidine. DTA thermograms and thermal data are summarized for these forms in Fig. 3 and Table VI, respectively. Forms IV and V have identical IR spectra; therefore, only four spectra are shown in Fig. 4. Also, only four different X-ray diffraction patterns are obtained (Table VII), since Forms IV and V have superimposable patterns.

It has been confirmed by TGA that Form SI is a monohydrate which undergoes dehydration over the temperature range 133–143°. The dehydration peak on the DTA curve is actually a doublet. When the sample is triturated, the shape of the doublet is changed. The higher temperature peak is reduced in size and finally merges into a single, rather broad peak. This can be interpreted to mean that the lower temperature dehydration peak corresponds to the energy required to break the hydrogen bonds formed between water molecules and sulfaguanidine molecules. This energy can be supplied by trituration. The higher temperature peak corresponds to the energy required for vaporization of the water. After vaporization, only one peak remains in the DTA thermogram, and this is the fusion peak. The heat required for dehydration of sulfaguanidine monohydrate is 10.32 kcal./mole. Since the heat of vaporization of water is only 9.97 kcal./mole at 100°, the measured heat of dehydration includes the energy required both for breaking the hydrogen

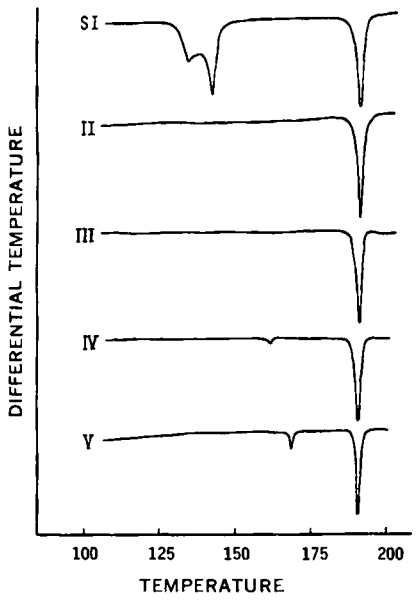


Figure 3—*Differential thermograms of various forms of sulfaguanidine.*

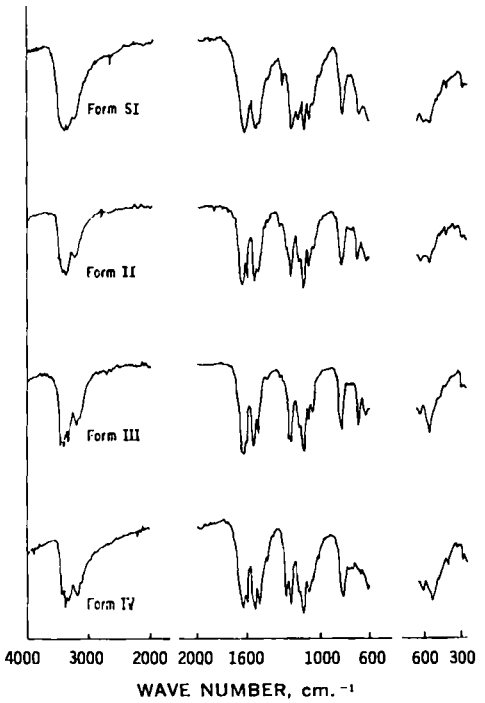


Figure 4—*IR spectra of four forms of sulfaguanidine.*

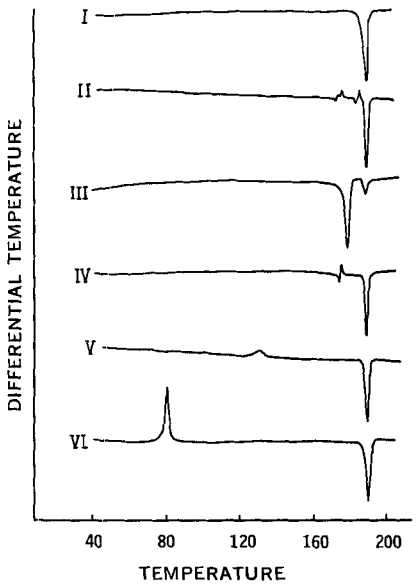


Figure 5—*Differential thermograms of various forms of sulfapyridine.*

bonds of water to sulfaguanidine and for vaporizing the water molecules.

The DTA thermograms of Forms II and III appear to be almost identical, but these forms exhibit different heats of fusion, different IR spectra, and different X-ray diffraction patterns.

In spite of the small heats of transition associated with Forms IV and V, these polymorphs are sufficiently stable so that they do not undergo transformation to other forms on trituration.

Brandstätter-Kuhnert (23) first reported that sulfaguanidine exists in two forms and, subsequently (20), that there are three forms whose melting points are: I, 187–191°; II, 174–176°; and III, 143–145°. Form II was reported to arise, in part, following loss of water from the monohydrate. IR spectral data were later reported (24) only for Forms I, II, and the monohydrate since, with the techniques used, Form III could only be obtained in the presence of II. From the data reported for the aniline NH_2 group absorption, it appears

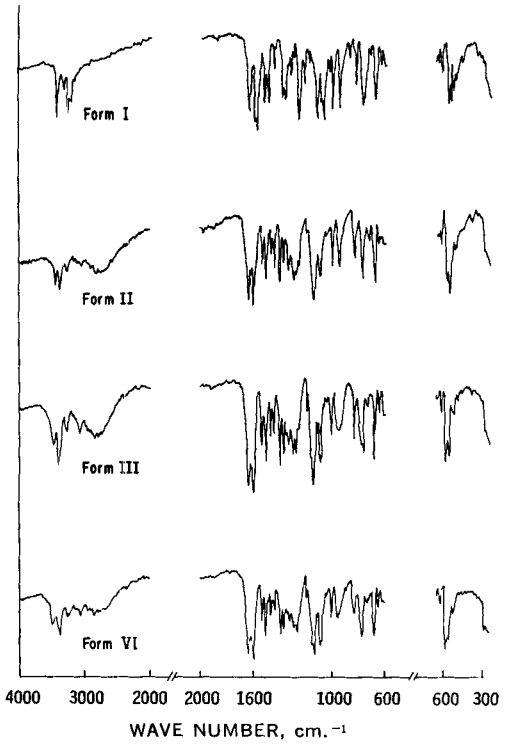


Figure 6—*IR spectra of four forms of sulfapyridine.*

Table VII—X-Ray Powder Diffraction Data for Sulfaguanidine

Form I		Form II	
d, Å	I/I_1	*d*, Å	I/I_1
12.0	17	12.0	16
7.3	4	10.0	11
6.4	100	8.5	5
5.4	31	6.5	100
4.4	81	6.0	20
4.1	77	5.4	37
3.7	59	4.75	47
3.1	50	4.4	89
2.9	20	4.1	93
close		3.8	65
2.8	26	3.55	61
2.65	16	3.25	10
2.5	10	3.10	49
2.35	27	2.85	15
2.20	10	2.65	13
2.07	10	2.45	11
1.96	5	2.35	9
1.82	6	2.15	9
1.73	4	2.05	4
1.64	4		
1.59	4		

Form III		Form IV	
d, Å	I/I_1	*d*, Å	I/I_1
10.0	46	12.5	23
6.6	26	10.0	17
5.8	14	7.0	4
5.15	96	6.6	92
4.9	48	6.0	36
4.6	37	5.5	31
4.3	100	4.8	63
4.1	67	4.4	81
3.4	21	4.1	100
3.15	66	3.7	70
2.9	18	3.3	27
2.8	6	3.1	60
2.65	14	2.85	32
2.45	8	2.60	10
2.25	13	2.45	11
2.10	12	2.35	6
1.98	7	2.20	11
1.84	4	2.05	9
		1.88	9
		1.72	6

Form V		
d, Å		I/I_1
12.0		10
9.8		10
7.2		2
6.6		62
5.9		29
5.4		25
4.8		100
4.4		54
4.1		54
3.7	band	52
3.3	band	14
3.1		37
2.85		22
2.65		5
2.45		8
2.35		6
2.25		7
	close	
2.15		7
1.86		7
1.77		7
1.70	band	4

that Form I most closely resembles Form III of this study, and Form II resembles Form IV (or V) of this study.

Mesley and Houghton (19), using IR techniques, identified one amorphous and four crystalline forms of sulfaguanidine. A comparison of the data obtained in this study with their results suggests that their Form A corresponds to Form SI. It is likely that their

Table VIII—Thermal Data for Various Forms of Sulfapyridine

Form	Solvent Used for Recrystallization	Transition Temperature	Heat of Transition, cal./mole	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy, e.u. Transition	Entropy, e.u. Fusion
I	Original powder, hot water, acetone, ethanol–isooctane mixture	—	—	192°	7.71 ± 1.4 %	—	16.6
II	*n*-Propanol	174–176° 185–186°	— —	191°	7.42 ± 2.1 %	—	16.0
III	Isobutanol	179°	—	189°	5.26 ± 0.64%	—	11.4
IV	*n*-Butanol	*endo* 175° *exo* 176°	— —	191°	7.55 ± 1.6 %	—	16.3
V	Ethanol	*exo* 129°	−517.5 ± 2.3%	191°	8.08 ± 2.1 %	−1.29	17.4
VI	Molten	*exo* 81°	—	191°	7.56 ± 3.0 %	—	16.3

Forms B and C correspond to Forms III and II, respectively. Unfortunately, they did not publish the IR spectra for these two forms. Nevertheless, the solvents used for recrystallization of Forms B and C are the same as those used to obtain Forms III and II.

Form V was prepared by recrystallization from *n*-pentanol. The DTA thermogram for this polymorph was identical with that of Form D, as obtained by evaporation of an ethanol solution on a water bath. The fact that Forms IV and V have identical IR spectra and similar powder diagrams suggests that Form IV might be a mixture of Form V and an amorphous form. Mesley and Houghton (19) observed that the process used in obtaining Form D gave a mixture of D and an amorphous form. The facts that Form IV has a higher heat of fusion than Form V, however, and that it exhibits an endothermic transition at a temperature 9° below that of Form V constitute evidence that Form IV is another polymorph and not a mixture. Neither form loses weight when heated from room temperature to fusion, so the possibility that these forms are solvates also can be ruled out.

Table IX—X-Ray Powder Diffraction Data for Sulfapyridine

Form I		Form II	
d, Å	I/I_1	*d*, Å	I/I_1
7.6	40	7.6	46
6.4	24	6.4	44
5.8	43	5.8	62
5.4	100	5.5	28
4.5	34	4.8	32
4.0	67	4.5	43
3.8	67	4.3	23
3.6	81	4.0	71
3.4	20	3.8	100
3.2	18	3.5	94
2.9	15	3.4	22
2.7	17	3.2	23
2.5	8	3.08	17
2.35	10	2.95	18
2.25	5	2.72	26
2.15	6	2.48	14
2.00	10	2.35	10
1.94	10	2.25	5
1.72	5	2.15	7
		2.02	15
		1.92	16
		1.86	8
		1.78	4
		1.72	9

Form III	
d, Å	I/I_1
7.7	12
6.5	100
5.1	67
4.5	34
4.2	58
3.9	78
3.8	79
3.0	22
2.75	8

Form IV		Form V	
d, Å	I/I_1	*d*, Å	I/I_1
12.0	3	12.5	7
7.2	30	10.5	10
6.4	48	7.5	23

Table IX—*Continued*

Form IV		Form V	
d, Å	I/I_1	*d*, Å	I/I_1
5.8	100	6.5	55
4.8	86	5.7	100
4.4	44	4.8	62
4.1	44	4.35	25
3.8	88	4.05	34
3.6	33	3.85	89
3.3	38	3.6	49
3.1	61	3.25	23
2.95	37	3.1	38
2.75	9	2.95	20
2.60	4	2.75	8
2.5	8	2.5	10
2.25	8	2.32	4
2.15	7	2.22	6
2.05	10	2.15	3
1.90	5		
1.80	7		
1.70	4		
1.62	4		

Form VI	
d, Å	I/I_1
7.6	49
6.5	19
5.6	100
5.4	28
4.5	27
4.1	36
3.9	72
3.65	68
3.25	18
3.1	12
3.0	10
2.8	18
2.65	8
2.55	4
2.45	6
2.35	4
2.25	7
2.05	5
1.96	10
1.90	8
1.76	3
1.70	2

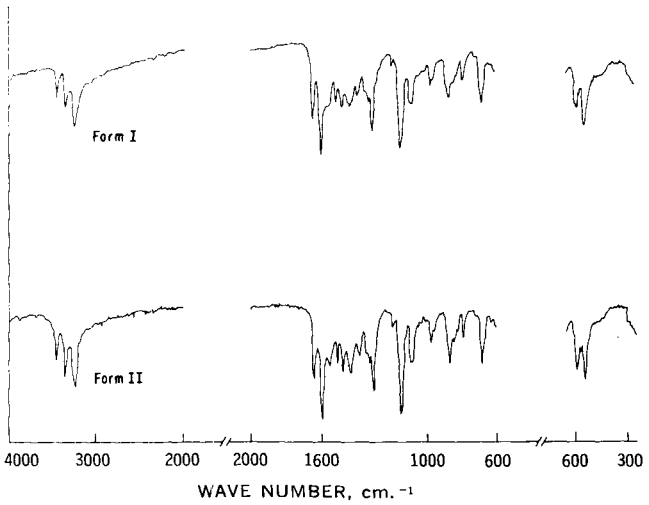


Figure 7—*IR spectra of two forms of sulfamethazine.*

Table XI—X-Ray Powder Diffraction Data for Sulfamethazine

Form I		Form II	
d, Å	I/I_1	*d*, Å	I/I_1
9.4	100	9.4	100
8.0	7	8.0	9
6.8	5	6.8	5
5.8	34	5.8	27
5.2	9	5.2	11
4.8	26	4.8	38
4.4	50	4.45	58
4.1	4	4.2	6
3.8	2	3.8	5
3.6	86	3.6	79
3.35	17	3.4	20
3.1	24	3.1	27
2.85	5	2.85	5
2.6 (band)	4	2.6	5
2.4	3	2.4	—
2.2	4	2.2	3
2.05 (band)	6	2.05	—
1.84	4	1.84	3
1.72	3	1.72	3

The IR spectrum published by Hayden (25) is similar to that of Form SI. The X-ray diffraction data published in the ASTM "Index" (26) also correspond to data obtained from Form SI.

Sulfapyridine—Five polymorphs, I, II, III, IV, and V, and one amorphous form, VI, were obtained for sulfapyridine. Thermograms and thermal data are shown in Fig. 5 and Table VIII, respectively.

The transition peaks for Forms II and IV are too small to be measured accurately. The transition peak for Form III is 11 times as large as the fusion peak. The transition temperature is so close to the fusion peak that the heat of transition cannot be measured separately, and the two quantities are combined in the value reported as the heat of fusion. This crystalline form appears to meet Timmermans' criteria (27) for a "plastically crystalline" substance.

Form VI is extremely unstable. In spite of repeated attempts, it was impossible to obtain reproducible measurements of the heat of transition of this species.

The IR spectra obtained from Forms II, IV, and V were identical, so only four IR spectra are shown in Fig. 6. Forms I, II, and III differ both in their IR spectra and in their X-ray diffraction patterns (Table IX). Forms IV and V have identical IR spectra and very similar X-ray diffraction patterns. Form II has the same IR spectrum as Forms IV and V but has a completely different X-ray diffraction pattern. Forms IV and V are considered to be different primarily on the basis of dissimilarities in their DTA thermograms.

Castle and Witt (16), using thermomicroscopic techniques, detected five crystalline forms of sulfapyridine, but they were able to isolate only four of these in the pure state. The melting points they reported for the four forms are: I, 191.5–192°; II, 181–182°; III, 177°; and IV, 174.5–175°. The melts of Phases II and IV were reported to undergo partial resolidification, with subsequent melting. From these data, it is likely that Forms I–IV obtained in this study correspond to Phases I–IV of Castle and Witt (16). It appears, however, that Form II may be contaminated with a small amount of Form IV. The latter undergoes a transition at 175°, which is also observed in Form II. Castle and Witt (16) reported that many recrystallizations were required before Form II could be obtained completely free of Form IV, and that Form II is unstable even when dried and stored in a well-stoppered bottle.

With respect to the IR data, it is difficult to compare the results of the present investigation with those of Mesley and Houghton (19) since these authors used somewhat different solvents, and they did not publish their spectra or report thermal data. They reported that the spectrum published by Sheinker and Kuznetsova (28) is their Form A. This spectrum does not resemble any recorded in the present study. The spectrum reported in a paper by Hayden (25), however, is that of Form I. In addition, the X-ray powder diffraction data published by Lennox (29) correspond to data obtained in this investigation for Form I.

Kuhnert-Brandstätter and Wunsch (20) were able to detect seven forms of sulfapyridine, one of which could be obtained only in a binary system with sulfamethoxydiazine. Three forms were obtained in sufficient purity by thermomicroscopic techniques to warrant spectroscopic examination (30). From a comparison of melting points and IR spectra, it appears that Form I of this study corresponds to their Form I, II to their Form III, and III to their Form IV.

Sulfamethazine—Mesley and Houghton (19) observed two solid forms of sulfamethazine, one crystalline and one amorphous, when they examined this compound by IR spectroscopy. Following their procedure, two crystalline forms, designated Forms I and II, were obtained. There is only a minor difference in the IR spectra of these forms, at 1550 $cm.^{-1}$ (Fig. 7). This band can be assigned (31) to the amide N—H bending vibration.

It is unlikely that the "amorphous form" reported by Mesley and Houghton (19) is stable at room temperature. When Form I is heated to fusion and the melt is cooled to room temperature, reheating produces a fusion peak of precisely the same area as was obtained at the first fusion.

The IR spectrum reproduced in *Reference 32* is apparently that of Form I. The spectrum obtained by Hayden (25) and identified by Mesley and Houghton (19) as the amorphous form resembles that of Form II, although there are some differences in peak intensities.

Form II was obtained from Form I by trituration. Its heat of fusion is somewhat less than that of Form I (Table X). Since the two forms exhibit identical DTA thermograms, displaying only a fusion peak, these are not reproduced here. The data from X-ray diffraction patterns of the two forms show many similarities (Table XI).

Although Kuhnert-Brandstätter and Wunsch (20) reported that they were able to detect four forms of sulfamethazine (sulfadimidin) by thermomicroscopic methods, it is possible that they were unable to obtain these in the pure state since no IR spectra of these forms were published in subsequent reports. The heat of fusion reported for sulfamethazine by Sunwoo and Eisen (21), 7438 ± 170

Table X—Thermal Data for Two Forms of Sulfamethazine

Form	Solvent Used for Recrystallization	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy of Fusion, e.u.
I	Ethanol, methanol	197°	7.84 ± 3.9%	16.7
II	Trituration of Form I	196°	7.55 ± 2.1%	16.1

Table XII—Thermal Data for Various Forms of Sulfamethoxypyridazine

Form	Solvent Used for Recrystallization	Transition Temperature	Heat of Transition, kcal./mole	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy, e.u. Transition	Entropy, e.u. Fusion
I	Acetone, methanol, ethanol–isooctane	—	—	180°	6.94 ± 2.4%	—	15.3
II	*n*-Butanol	*endo* 154°	1.59 ± 4.5%	180°	6.82 ± 1.4%	3.7	15.0
	n-Pentanol	*exo* 157°	−1.59 ± 5.2%			3.7	
III	H_2O	*exo* 160°	—	180°	6.09 ± 1.1%	—	13.4
II*[a]	*n*-Butanol	*endo* 149°	0.66 ± 2.6%	181°	6.03 ± 2.8%	1.6	13.3
	n-Pentanol	*exo* 153°	−0.76 ± 4.7%	—	—	1.8	—

[a] II* is the deacetylated N^1-acetylsulfamethoxypyridazone through recrystallization from *n*-butanol or *n*-pentanol.

cal./mole, is similar to that of Form II. The melting point, 198.5°, reported by these authors is, however, higher than that obtained in this study for either Form I or II.

Sulfamethoxypyridazine—Using IR spectroscopy, Mesley and Houghton (19) reported the isolation of one amorphous and two crystalline forms of sulfamethoxypyridazine. They indicated that the original form, which is crystalline, was not recovered by any of the solvent treatments they used. A second form was occasionally obtained by recrystallization from mixtures of ethanol and isooctane. They reported that the IR spectrum reproduced by Chouteau *et al.* (33) is a mixture of Form B (ethanol–isooctane) and the amorphous form.

In the present work, three crystalline forms were obtained. No amorphous forms resulted from recrystallization, although it was noted that following fusion the melt resolidified as a glass. The original powder obtained from the manufacturer and the crystals obtained from acetone and methanol solutions, as well as those obtained from ethanol–isooctane, were designated as Form I. This form gives an IR spectrum identical with that reproduced by Chouteau *et al.* (33) and Hayden (25). The thermograms and thermal data for the three polymorphs are summarized in Fig. 8 and Table XII, respectively.

Form II absorbs heat at 154° and releases approximately the same quantity of heat as it undergoes transformation to Form I. Form III also exhibits an exothermic peak, but the peak is too small to obtain a quantitative estimate of the heat of transition. The latter peak is not preceded by an endothermic peak. The possibility that Form III might be a mixture of Forms I and II can be excluded since its IR spectrum (Fig. 9) and X-ray diffraction pattern (Table XIII) are completely different from those of the latter two forms.

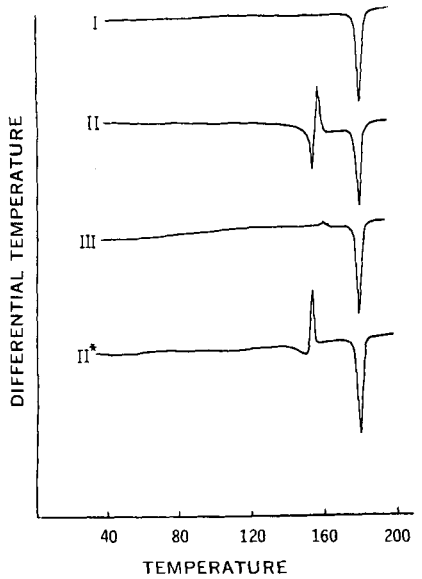


Figure 8—*Differential thermograms of various forms of sulfamethoxypyridazine. II* is the thermogram for deacetylated* N^1*-acetyl sulfamethoxypyridazine.*

When Form II is heated to 160° and when it is subjected to prolonged vigorous trituration, it is transformed completely to Form I. The trituration required for solid-state sampling in IR spectroscopy and X-ray diffraction is apparently insufficient to produce this complete transformation.

The form designated II* was obtained by recrystallization of N^1-acetyl sulfamethoxypyridazine from *n*-butanol or *n*-pentanol. By use of IR spectra, TLC, and X-ray diffraction diagrams, it was found that N^1-acetyl sulfamethoxypyridazine can be completely deacetylated to sulfamethoxypyridazine. The crystal form resulting from this deacetylation corresponds to that obtained when sulfamethoxypyridazine itself is recrystallized from the same solvents. The heats of transition and fusion of Form II*, however, are somewhat lower than those of the corresponding Form II. The X-ray diffraction pattern for Form II* suggests the presence of some amorphous sulfamethoxypyridazine, and this would account for the lower heat of fusion.

Kuhnert-Brandstätter and Wunsch (20) also obtained three forms of sulfamethoxypyridazine, but the third form could be induced to crystallize only from contact preparations with sulfamethoxydiazine. No IR data were reported.

Sulfisoxazole—Mesley and Houghton (19) found no evidence of polymorphism in sulfisoxazole. In this investigation, two polymorphs of the compound were obtained. Thermograms and thermal data are shown in Fig. 10 and Table XIV, respectively.

An examination of the thermal data reveals that Form I, obtained by recrystallization from water at room temperature, exhibits a transition peak at 145°, with a heat of transition of 294 cal./mole and a melting point at 196° with a heat of fusion of 7.46 kcal./mole. Form I can be transformed to Form II by simple trituration. Because

Table XIII—X-Ray Powder Diffraction Data for Sulfamethoxypyridazine

Form I		Form II		Form III	
d, Å	I/I_1	*d*, Å	I/I_1	*d*, Å	I/I_1
14	12	8.2	16	9.2	34
11	12	7.3	41	7.7	21
8.5	26	6.6	8	6.8	34
6.8	95	5.6	19	5.7	20
5.8	16	5.2	86	5.1	41
5.2	63	4.9	59	4.7	52
4.8	100	4.7	88	4.3	100
4.4	41	4.2	10	3.8	69
3.9	65	3.9	61	3.35	24
3.65	46	3.75	100	3.05	9
3.4	37	3.45	14	2.85	17
3.05	5	3.30	65	2.65	14
2.8	11	2.95	7	2.30	5
2.6	7	2.80	18	2.15	4
		2.55	13		
		2.37	4		
		2.27	5		
		2.13	4		
		2.00	7		
		1.88	4		
		1.74	5		
		1.69	5		
		1.62	3		
		1.54	3		

Table XIV—Thermal Data for Polymorphs of Sulfisoxazole

Form	Solvent Used for Recrystallization	Transition Temperature	Heat of Transition, cal./mole	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy, e.u. Transition	Entropy, e.u. Fusion
I	H_2O at RT	145°	294.0 ± 3.8%	196°	7.46 ± 0.9%	0.7	15.9
II	*n*-Pentanol and others	—	—	196°	7.55 ± 2.5%	—	16.1

of the relative ease with which this transformation occurs, both forms show identical IR spectra (not reproduced here) and identical X-ray diffraction diagrams (Table XV).

Kuhnert-Brandstätter and Wunsch (20) also observed two forms of sulfisoxazole (sulfafurazole) using thermomicroscopy. No IR data were reported.

Sulfamethoxazole—Three polymorphic forms, I, II, and III, were identified. Mixtures of Forms I and II were obtained by recrystallization from solvents other than those listed in Table XVI. The thermograms and thermal data for the various polymorphic forms are summarized in Fig. 11 and Table XVI, respectively.

Form II undergoes an endothermic transition at 166°. This transition temperature is so close to the fusion temperature that the heat of transition cannot be determined independently by DTA calorimetry. The approximate ratio of the transition peak to the fusion peak area is 1 : 6, as estimated from the conventional DTA thermogram. Thus, the total energy measured includes the heat of transition, approximately 1 kcal./mole, and the heat of fusion, approximately 5 kcal./mole.

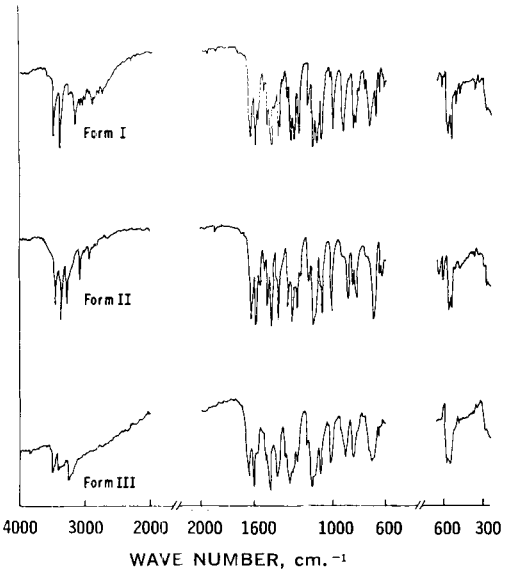


Figure 9—*IR spectra of three forms of sulfamethoxypyridazine.*

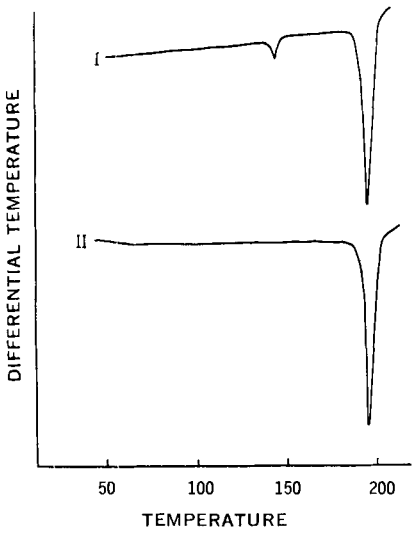


Figure 10—*Differential thermograms of two forms of sulfisoxazole.*

The IR spectra of Forms I and II are reproduced in Fig. 12. The spectrum published by Chouteau *et al.* (33) is that of Form I. Form II exhibits less intense bands at 3300 and 3150 cm.$^{-1}$ than does Form I, and it also exhibits additional bands at somewhat lower wave numbers: 3080, 2990, and 1640 cm.$^{-1}$. The latter bands are not present in the spectrum of Form I. Differences in the spectra are also found at 1395, 1330, and 1150 cm.$^{-1}$. The absorption bands at 3300 and 3150 cm.$^{-1}$ have been attributed (34) to the amide N—H stretching vibration. The 1640-cm.$^{-1}$ band is due to an N—H bending vibration (34), and the 1330- and 1158-cm.$^{-1}$ bands have been assigned to asymmetrical and symmetrical S—O stretching vibrations, respectively (35). These assignments suggest that the more strongly bonded N—H is present in Form II.

After Form II is heated to about 164°, its IR spectrum becomes identical with that of Form I. The X-ray diffraction patterns (Table XVII) for these two forms show some similarities. Apparently, Form II can be transformed to Form I, but this transformation requires more energy than is available from trituration.

The estimated heat of fusion of Form II, about 5 kcal./mole, is somewhat less than that of Form I. The X-ray diffraction pattern for Form II is much less distinct than that of Form I, and this could be due to the presence of some amorphous sulfamethoxazole in the sample. This might also account for the lower heat of fusion observed in Form II.

Although Kuhnert-Brandstätter and Wunsch (20) were able to identify three polymorphs of this compound by thermomicroscopic methods, only two forms could be obtained in sufficient purity to warrant IR investigation (29). The spectra for Forms I and III reported by Kuhnert-Brandstätter and Bachleitner-Hofmann (30) are similar to those of Forms I and II of this study.

Interestingly, the thermogram of sulfamethoxazole reproduced in the paper by Sunwoo and Eisen (21) has only one endothermic peak; this peak is at 166.3°, the temperature of transition, rather than the normal melting point, 170°.

Sulfaethidole—Two polymorphic modifications, I and II, were obtained for this compound. Form I undergoes a transition at 181°, and the peak area associated with this transition is approximately 10 times as great as that associated with the fusion peak at 187° (Fig. 13). Apparently, Form I absorbs enough heat energy during its phase transition to become highly disordered, and only a small

Table XV—X-Ray Powder Diffraction Data for Sulfisoxazole

Form I		Form II	
d, Å	I/I_1	*d*, Å	I/I_1
7.3	98	7.4	100
6.6	43	6.7	63
5.8	53	5.8	56
5.1	76	5.1	84
4.4	33	4.3	33
3.85	100	3.9	86
3.3	89	3.30	90
2.95	10	2.95	12
2.65	12	2.65	13
2.45	5	2.45	12
2.32	10	2.33	5
2.22	8	2.25	6
2.17	9	2.18	3
2.10	9	2.10	10
2.02	5	2.03	7
1.90	5	1.96	7
		1.90	6

Table XVI—Thermal Data for Three Polymorphs of Sulfamethoxazole

Form	Solvent Used for Recrystallization	Transition Temperature	Heat of Transition, cal./mole	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy, e.u. Transition	Entropy, e.u. Fusion
I	*n*-Butanol, acetone, methanol	—	—	170°	5.86 ± 2.0%	—	13.2
II	H_2O at dry ice–acetone mixture temperature	166°	—	170°	6.03 ± 6.1%	—	13.6
III	H_2O at RT	123°	457 ± 2.3%	170°	5.48 ± 2.6%	1.1	12.4

amount of heat energy is subsequently required for the fusion step.

Thermal data for these modifications are summarized in Table XVIII. The transition peak is so near the fusion peak for Form I that DTA calorimetry cannot resolve them. The measured heat of fusion is the sum of the heat of transition (approximately 5 kcal./mole) and the heat of fusion (approximately 0.5 kcal./mole). The heat of fusion of Form II is considerably higher than this, 6.58 kcal./mole.

Figure 14 illustrates the IR spectra of these two forms. Form I has a stronger bonded N—H stretching vibration band at about 3200 cm.$^{-1}$ (34). There are also differences in the regions of 1630–1620, 1320–1270, and 1140–1120 cm.$^{-1}$. These peaks show that the N—H bending vibrations and both the asymmetrical and symmetrical S—O vibrations (35) are quite different in the two forms. Marked differences are also apparent in the X-ray diffraction diagrams of Forms I and II (Table XIX).

Kuhnert-Brandstätter and Wunsch (20) observed three forms of sulfaethidole, but the third form was obtained in a binary system with sulfamethizole and was not isolable alone. The melting characteristics (20) and IR spectra (29) reported for Forms I and II correspond to those of Forms II and I, respectively, in this study.

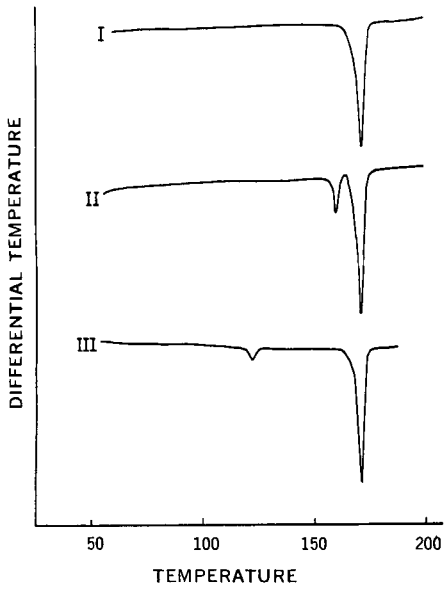


Figure 11—*Differential thermograms of three forms of sulfamethoxazole.*

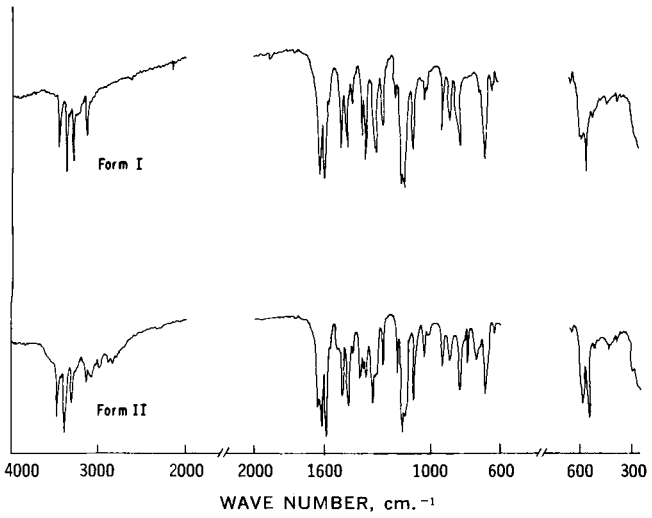


Figure 12—*IR spectra of two forms of sulfamethoxazole.*

CONCLUSIONS

It was observed in this study that the major differences in the IR spectra of different modifications of the same compound are in the regions of $—NH_2$ and —NH stretching vibrations and asymmetric and symmetric $—SO_2$ stretching vibrations. Pronounced changes in IR spectra are known to occur on formation of a hydrogen bond of the A—H- - -B type. The A—H stretching frequency shifts to lower frequencies; the A—H bending frequency shifts to higher frequencies, and the width and intensity of the A—H stretching frequency increase markedly (36). Apparently, the *p*-amino group, the acidic N^1-hydrogen atom, and the oxygen of the S—O group are involved in intermolecular hydrogen bonding in molecular crystals of sulfonamides.

That this is, indeed, the case has been confirmed for one sulfonamide for which extensive X-ray and neutron diffraction data are available, sulfanilamide. The crystal structures of three forms of sulfanilamide have been determined. α-Sulfanilamide, for example, is an orthorhombic crystal with eight molecules in one unit cell. The molecules are packed into layers parallel to the *c*-axis. Each molecule forms bonds to four others in the layer by means of two strong (2.94 Å) and two very weak (3.12 Å) hydrogen bonds (NH- - -O type). The stronger bonds form a chain of molecules in the *x*-direction and, together with the van der Waals forces in the

Table XVII—X-Ray Powder Diffraction Data for Sulfamethoxazole

Form I		Form II		Form III	
d, Å	I/I_1	*d*, Å	I/I_1	*d*, Å	I/I_1
8.1	35	11.0	26	13	21
7.2	67	8.5	18	8.0	40
5.1	79	7.2	46	7.2	75
4.4	26	5.6	36	6.4	17
4.2	40	5.0	77	5.05	80
4.0	39	4.2	62	4.4	32
3.7	100	3.7	100	4.2	56
3.3	43	3.3	48	4.08	43
3.15	53	3.2	71	3.70	100
3.0	14	3.0	24	3.30	25
2.8	20	2.75	41	3.15	30
2.7	20	2.40	—	3.0	12
2.6	13	2.05	—	2.8	13
2.5	13			2.7	27
				2.6	11
				2.5	7
				2.4	8
				2.3	6
				2.2	7
				2.12	8
				2.02	5
				1.97	4

Table XVIII—Thermal Data for Two Polymorphic Forms of Sulfaethidole

Form	Solvent Used for Recrystallization	Transition Temperature	Heat of Transition	Fusion Temperature	Heat of Fusion, kcal./mole	Entropy of Fusion, e.u.
I	*n*-Butanol	181°	—	187°	5.50 ± 2.6%	11.9
II	*n*-Propanol Methanol Ethanol	-	—	188°	6.58 ± 2.2%	14.3

same direction, the layers of molecules are linked by weak (3.06 Å) N—H ···O bonds (6).

Both β-sulfanilamide and γ-sulfanilamide are monoclinic. Each has a unit cell consisting of four molecules. Each forms hydrogen bonds whose lengths differ from those formed in α-sulfanilamide (6).

Kuhnert-Brandstätter and Bachleitner-Hofmann (30) also commented on the significance of hydrogen bonding to polymorphism in sulfonamides. They have proposed the general rule that modifications stable at room temperature can be expected to exhibit lower aniline N—H frequencies than unstable forms. As a corollary, the stable modifications have stronger hydrogen bonds.

The substitution of functional groups for one of the hydrogen atoms on N^1 would be expected to influence the ease with which the second hydrogen atom can participate in hydrogen bonding. This influence may be partly steric and partly electronic. Bulky functional groups might be expected to hinder the close approach of an amide hydrogen to the sulfonamide oxygen of a neighboring molecule. In some instances, however, the functional group may, through an inductive effect or through a resonance effect, increase or reduce the electron density on the amide nitrogen, consequently affecting the strength of the hydrogen bonds that might form. The combination of steric effects and inductive or resonance effects may be sufficient in some substituted sulfonamides to preclude hydrogen-bond formation involving the amide hydrogen. In these molecules, polymorphism might still be manifested if a variety of arrangements of the hydrogen bonds formed by the N^4-hydrogens is possible, or if van der Waals' interactions of different types can be formed.

Sulfacetamide, whose acetyl group at N^1 greatly increases the acidity of the amide function as compared with sulfanilamide, was found not to exhibit polymorphism. If sulfacetamide does not form polymorphs, their absence can possibly be attributed to the fact that significantly stronger hydrogen bonds are formed by the amide hydrogen in this molecule. The hydrogen bonds which are formed are not readily stretched or broken to form alternate crystalline arrangements. When sufficient heat is absorbed by the crystal to break the hydrogen bonds, the crystal collapses and the compound melts. The melting point and heat of fusion of sulfacetamide, 183° and 5.35 kcal./mole, respectively, are higher than those of sulfanilamide, 166° and 5.27 kcal./mole, in agreement with this line of reasoning. Within the entire sulfonamide series it was found that, as a rule, compounds which do not exhibit polymorphism have somewhat higher melting points and heats of fusion than compounds which are polymorphic.

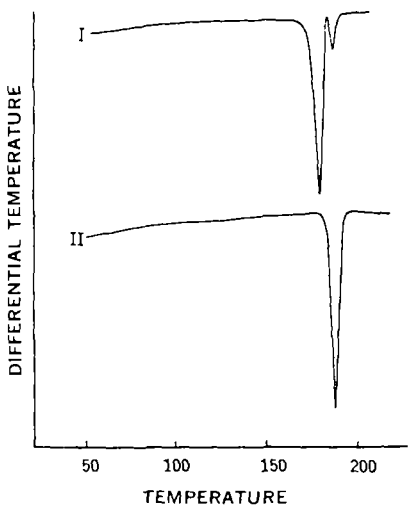
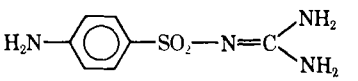


Figure 13—*Differential thermograms of two forms of sulfaethidole.*

The importance of the N^1-hydrogen's contribution to the polymorphism of sulfonamides is seen in the case of sulfisoxazole and sulfamethoxypyridazine and their acetylated derivatives. The parent compounds form polymorphs which are stable at room temperature; their acetyl derivatives apparently do not. The amide hydrogen is not, however, absolutely essential for the formation of polymorphs. There are cases in which this atom is absent and the derivative exhibits polymorphism. For example, sodium sulfacetamide was reported (19) to exhibit three crystal forms. Presumably, in this case, the different hydrogen-bonding arrangements are associated with N^4-hydrogens.

Another compound which lacks amide hydrogens is sulfaguanidine. As a result of NMR and IR spectroscopic studies, the structure of this compound is reported (7) as shown here. This symmetrical



sulfaguanidine

molecular structure has three free amino groups, increasing the number of possible hydrogen-bonding combinations. In this study, sulfaguanidine was found to exhibit four polymorphic forms and a solvate.

In the case of sulfabenzamide, the carbonyl group apparently participates in hydrogen bonding in one crystalline form to a greater degree than in others. The absorption band of the carbonyl group in this compound shifts to a lower frequency (1690 *versus* 1680 $cm.^{-1}$) and also changes somewhat in shape as the hydrogen bond formed to the carbonyl group becomes stronger. Participation of the carbonyl group of sulfabenzamide in such hydrogen-bonding interactions is presumably made more feasible through a conjugative shift of electrons from the benzene ring to the oxygen of the carbonyl.

Interestingly, sulfamethizole and sulfaethidole differ only in the lateral group on the N^1-substituted ring. In the latter, the group is ethyl; in the former, it is methyl. Sulfaethidole is polymorphic, but no polymorphs of sulfamethizole sufficiently stable to be characterized were found. A comparison of the melting points reveals that sulfamethizole melts at 207°, while sulfaethidole melts at 187°. This implies that the sulfamethizole molecules are arranged somewhat more compactly in the crystal lattice than are those of sulfaethidole.

Table XIX—X-Ray Powder Diffraction Data for Sulfaethidole

Form I		Form II	
d, Å	I/I_1	*d*, Å	I/I_1
10.8	100	10.8	100
8.5	60	9.2	60
7.5	13	7.7	12
5.8	87	4.9	91
4.9	99	4.4	8
4.4	39	4.1	38
4.15	78	3.6	79
3.65	71	3.3	26
3.55	59	2.9	30
3.3	34	2.25	11
2.95	38	2.17	7
2.65	22	2.02	5
		1.95	7
		1.88	10
		1.83	10

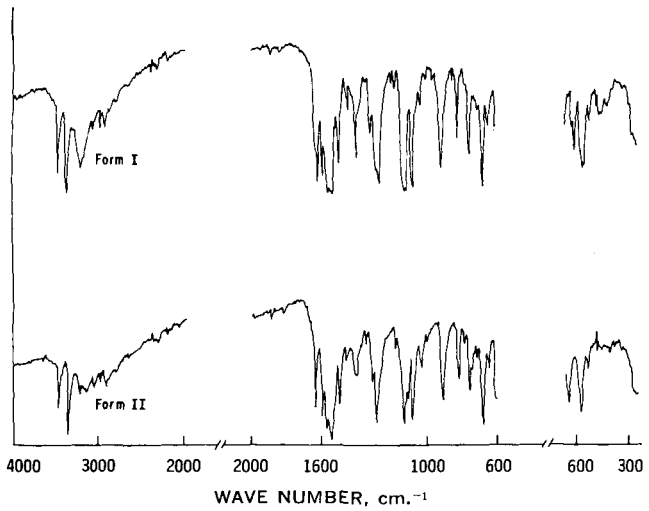


Figure 14—*IR spectra of two forms of sulfaethidole.*

Therefore, it is difficult to predict the existence of polymorphs simply from a knowledge of the chemical structure of a compound.

The thermograms and thermal data obtained in this study indicate that N^1-acetyl sulfamethoxypyridazine and some crystalline forms of sulfabenzamide, sulfapyridine, and sulfaethidole exhibit the type of thermal behavior characteristic of plastically crystalline substances. Such compounds have very small entropies of fusion (less than 5 e.u.). This is probably indicative of the fact that the crystal structure of these compounds immediately prior to melting closely resembles the structure of the liquid state. Only a small amount of additional disordering is required to destroy the crystal lattice completely.

While a few generalizations can be made concerning the influence of structural modifications on the tendency of sulfonamides to exhibit polymorphism, a complete understanding of this problem awaits the total structure determinations of each crystal form of each polymorphic sulfonamide.

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