J. Pharm. Pharmac., 1967, **19**, 295–304 Received November 25, 1966

Infrared identification of pharmaceutically important sulphonamides with particular reference to the occurrence of polymorphism

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The infrared absorption spectra of sulphonamides, when compared with the spectra of Authentic Specimens, provide a simple and complete means of identification, provided the effects of polymorphism are excluded. Of 18 substances examined, twelve showed evidence of polymorphism. Limited solubility prevents the use of solution spectra, and specified solvent treatments, details of which are given, may therefore be necessary with these substances to ensure reproducible spectra.

IN a number of monographs in the British Pharmacopoeia and the British Pharmaceutical Codex an identification test is included in which the infrared absorption spectrum of the sample under examination is compared with that of an Authentic Specimen, supplied for this purpose. The original collection of Authentic Specimens consisted mainly of steroids, but is being extended to include a number of sulphonamides and other substances. For the purposes of this comparison of spectra, it was necessary to establish conditions whereby different forms of a substance, should they exist, might be converted to a single form thus eliminating differences in solid-state infrared spectra.

Polymorphism occurs frequently in complex compounds, particularly with those molecules in which hydrogen bond formation is possible, and in general the polymorphic variations of a substance give rise to different infrared spectra. Means of overcoming this difficulty have already been proposed for a number of steroids (Mesley & Johnson, 1965) and barbiturates (Cleverley, 1960). Amongst sulphonamides, polymorphism has been reported with sulphanilamide (Watanabe, 1942) and sulphathiazole (Grove & Keenan, 1941; Miyazaki, 1947), and infrared spectra of two forms of sulphanilamide have been published by Barnes, Liddel & Williams (1942).

Experimental

MATERIALS

The samples of sulphadiazine sodium, sulphadimethoxine, sulphaguanidine, sulphanilamide, sulphaphenazole and sulphathiazole were the Authentic Specimens of the British Pharmaceutical Codex. Samples of the remaining substances were supplied by Mr. C. A. Johnson of the British Pharmacopoeia Commission. Solvents used were of B.P. or A.R. quality.

SOLVENT TREATMENTS

To obtain as many forms of each substance as possible, the following treatments were used: evaporation to dryness of solutions in water,

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ethanol, methanol, acetone and chloroform, normally on a water-bath but in some instances also at room temperature; precipitation from alkaline solution by addition of acid, or vice versa; heating at temperatures up to 140°. The solubility of the substances in the different solvents varied widely and not all of these treatments could be used with each substance. Where the existence of further forms was suspected, or where these treatments failed to give crystalline products, other treatments were tried, including the use of mixed solvents and true recrystallization by allowing saturated solutions to cool.

INFRARED ABSORPTION SPECTRA*

Samples were prepared for infrared examination both as mulls in liquid paraffin (Nujol) and as pressed alkali halide discs using the technique previously described (Mesley & Johnson, 1965). The low solubility of the sulphonamides precluded the use of solutions for obtaining spectra.

Spectra of all the forms were recorded using a Grubb Parsons GS 2 or Spectromaster grating spectrometer. The recommended solvent treatments were repeated independently using spectra recorded on a Unicam SP 200 spectrometer with sodium chloride prism or a Perkin-Elmer 237 grating spectrometer.

X-ray powder diffraction patterns of five forms of sulphadimidine sodium were obtained (by Mr. K. Goodhead) using a Philips generator with a Unicam 9 cm camera and copper Kα radiation.

Results and discussion

Table 1 lists the substances examined and the number of solid forms of each substance found. These are not necessarily all crystalline, as in many instances an amorphous form was obtained from certain treatments. From the point of view of obtaining consistent spectra, this was as troublesome as the true polymorphic variations. The list also includes some forms detected in alkali halide discs, though they were not always isolated in the free state.

TABLE 1. INCIDENCE OF POLYMORPHISM IN THE 18 SULPHONAMIDES EXAMINED

Substance	No. of solid forms encountered	Substance	No. of solid forms encountered
Phthalylsulphathiazole	2	Sulphaguanidine	5
Succinylsulphathiazole	5	Sulphamethizole	1
Sulphacetamide sodium	3	Sulphamethoxydiazine	4
Sulphadiazine	1	Sulphamethoxypyridazine	3
Sulphadiazine sodium	1	Sulphanilamide	3
Sulphadimethoxine	1	Sulphaphenazole	1
Sulphadimidine	2	Sulphapyridine	7
Sulphadimidine sodium	7	Sulphasomidine	2
Sulphafurazole	1	Sulphathiazole	4

* Throughout the paper the use of the word "spectrum" refers to the infrared absorption spectrum.

The purpose of using Authentic Specimens is to avoid dependence on published spectra, particularly where different spectra may be obtained from the same substance. Even in those instances where no evidence of polymorphism was found, the existence of other forms cannot be ruled out, and no spectra are therefore included in this report. In fact spectra of most of the substances in this category have already been published elsewhere. A survey of all the forms encountered and a review of published spectra are given below.

Phthalylsulphathiazole. Only one crystalline form was obtained as a result of the various solvent treatments used, but the original sample showed certain additional absorptions which may have been due to a second crystalline form. The spectrum obtained from a potassium bromide disc was distinctly different from that of a liquid paraffin mull, presumably due to the production of an amorphous form. The Sadtler Standard collection includes spectra of both potassium bromide disc and Nujol mull, which agree with those obtained in this work.

Succinylsulphathiazole. The original form (A) was a monohydrate, and was not recovered from any of the solvent treatments used. On heating it gave form D. Evaporation at room temperature of an acetone solution prepared from either of these forms gave form B. Evaporation of similar solutions on a water-bath gave variously forms C and D and the amorphous form, or mixtures of any two of these. Alcoholic solvents tended to give only the amorphous form. Form B was consistently recovered when the material was dissolved in dilute sodium hydroxide solution and precipitated by addition of dilute hydrochloric acid. This form was not stable on grinding with potassium bromide, the resulting spectrum being predominantly that of the amorphous form. The Sadtler Standard collection includes a Nujol mull spectrum of form A and a potassium bromide disc spectrum which is mainly that of the amorphous form.

Sulphacetamide sodium. The original form (A) was a monohydrate, and was recovered by recrystallization from aqueous solution. Evaporation of solutions in ethanol and methanol normally gave the amorphous form, but on occasions this crystallized to give the anhydrous form B. A potassium bromide disc prepared from form B showed the presence of some form A, presumably due to traces of moisture in the potassium bromide. A spectrum of this substance in the Sadtler Pharmaceutical collection, recorded as a potassium bromide disc, shows a mixture of form A with the amorphous form.

Sulphadiazine. No evidence of polymorphism was found. The spectrum agreed with those previously published by Hayden, Sammul, Selzer & Carol (1962), Sheinker & Kuznetsova (1957) and in the Sadtler Standard and Pharmaceutical collections.

Sulphadiazine sodium. No evidence of polymorphism was found. The spectrum agreed with that in the Sadtler Pharmaceutical collection.

Sulphadimethoxine. No evidence of polymorphism was found. The

spectrum agreed with those published by Bellomonte, Calo & Cardini (1959) and by Chouteau, Davidovics & Defretin (1963). A spectrum in the Sadtler Pharmaceutical collection shows only broad bands of low intensity and is not recognizable as sulphadimethoxine.

Sulphadimidine. Only one crystalline form was detected. Prolonged grinding with potassium bromide gives an amorphous form with a different spectrum, and partial conversion to this was observed when the material was ground alone in a mechanical mill for 15 min and then examined as a Nujol mull. Spectra of the two forms have been published: in the Sadtler Standard collection (Nujol mull) and by Hayden & others (1962) (potassium bromide disc). A potassium bromide disc spectrum in the Sadtler Pharmaceutical collection shows a mixture of the two forms.

Sulphadimidine sodium. Only solutions in water, ethanol and methanol were investigated, but under various conditions these yielded one amorphous and at least six crystalline forms. The infrared spectra of some of these forms were very similar, though they could be distinguished by their X-ray diffraction patterns, and at least two of the crystalline forms contained residual solvent. All were converted to the same form on heating, provided that no amorphous material was present, though temperatures in excess of 140° were sometimes necessary. No spectrum of this substance has been published.

Sulphafurazole. No evidence of polymorphism was found. The spectrum agreed with those published by Hayden & others (1962) and in the Sadtler Pharmaceutical collection.

Sulphaguanidine. One amorphous and four crystalline forms were identified. The original form (A) was a hydrate, and was recovered by recrystallization from aqueous solution. Form B was sometimes obtained from form A by evaporation of a methanol solution on a water-bath, though on some occasions form A was recovered. Form C was sometimes obtained from form A by evaporation of acetone solution on a water-bath, though more often a mixture of B and C was obtained. On the other hand form D (obtained from B by evaporation of ethanol solution on a water-bath), when treated in the same way, gave a mixture of form D and the amorphous form. The leaflet issued with the B.P.C. Authentic Specimen recommends evaporation of an acetone solution, without specifying any temperature. Under varying conditions this has yielded all five forms, so this is obviously not a good choice of solvent. A potassium bromide disc prepared from form B gave the spectrum of form A (presumably due to moisture in the potassium bromide). After heating this disc the spectrum was intermediate between those of form D and the amorphous form. A spectrum in the Sadtler Pharmaceutical collection is of form A.

Sulphamethizole. No evidence of polymorphism was found in this work, and the spectrum obtained agreed with spectra of two samples published in the Sadtler Pharmaceutical collection. It differed, however, in several respects from that published by Sammul, Brannon & Hayden

(1964), said to be of a potassium bromide disc prepared from material recrystallized from a mixture of ethanol and iso-octane. This solvent treatment was tried but produced no change in spectrum. Another spectrum which differs from both of these has been published by Sheinker, Postovskii, Voronina & Kushkin (1957).

Sulphamethoxydiazine. One amorphous and three crystalline forms were obtained. The original form (A) could usually be recovered by recrystallization from aqueous ethanol. Recrystallization from aqueous solution gave form B, which was converted to form A by heating. Precipitation from acetone solution by addition of water, or from alkaline solution by addition of acid, gave form C. Evaporation of a methanol solution gave the amorphous form, and this was also present in potassium bromide discs prepared from all three crystalline forms. A spectrum of such a disc, corresponding to that prepared from form A, has been published by Chouteau & others (1963).

Sulphamethoxypyridazine. One amorphous and two crystalline forms were identified. The original form (A) was not recovered from any of the solvent treatments used. A second crystalline form (B) was normally obtained by recrystallization from a mixture of ethanol and iso-octane. Most other treatments gave the glassy form, which was also present in potassium bromide discs prepared from forms A and B. Spectra of potassium bromide discs published by Hayden & others (1962) and by Chouteau & others (1963) show mixtures of form B and the amorphous form. A Nujol mull spectrum of form A has been published by Bellomonte & others (1959). The potassium bromide disc spectrum in the Sadtler Pharmaceutical collection shows the presence of all three forms.

Sulphanilamide. The existence of three forms of sulphanilamide was reported by Watanabe (1942) and methods of preparation were described by Yakowitz (1948). Spectra of two forms described as B and C were published by Barnes & others (1943). The Authentic Specimen as received gave the spectrum of form B, and was converted to form C by heating or by evaporation of ethanol solution on a water-bath. A third form (presumably A) was obtained together with form B when a methanol solution was evaporated to dryness in a stream of air at room temperature. This form was not obtained in a pure state. The leaflet issued with the B.P.C. Authentic Specimen recommends evaporation of an acetone solution. This normally gives a mixture of forms B and C. Apart from the spectra of Barnes & others (1943), spectra of form B have been published by Chouteau & others (1963) and in the Sadtler Standard and Pharmaceutical collections. A spectrum published by Hayden & others (1962) corresponds to a mixture in which form C predominates.

Sulphaphenazole. No evidence of polymorphism was found. The spectrum agreed with those of Bellomonte & others (1959) and of Sammul & others (1964).

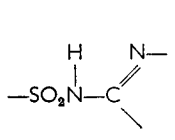
Sulphapyridine. One amorphous and six crystalline forms were identified. The first sample examined consisted mainly of form A, together with a small amount of another form, designated F, which was not otherwise encountered; a second sample was entirely form A. Pure form A was obtained by heating forms B, D and F to 140°. Form C was only partially converted to A and the effect of heat on form E was not investigated. Form B was obtained from A by recrystallization from a mixture of ethanol and iso-octane, but other forms gave either form C or mixtures. Form C was obtained on one occasion when a chloroform solution of form A was allowed to evaporate overnight. Evaporation of a similar chloroform solution in a current of air at room temperature gave form D. Form E was obtained when a solution of form C in acetone was evaporated in a similar manner; when form A was treated in this way a mixture of forms A and B was obtained. Forms A, B and C were not affected by grinding with potassium bromide, but a potassium bromide disc prepared from form D gave the spectrum of the amorphous form. Spectra published by Sheinker & Kuznetsova (1957) and in the Sadtler Pharmaceutical collection are of form A.

Sulphasomidine. Only one crystalline form was encountered, and this could be recovered by recrystallization from aqueous solution. Evaporation of solutions in ethanol and methanol sometimes gave an amorphous form, and other treatments were liable to produce mixtures. No spectrum of this substance has been published.

Sulphathiazole. Two crystalline forms of sulphathiazole were reported by Grove & Keenan (1941) and three by Miyazaki (1947). In the present work an amorphous form and three crystalline forms were encountered, and from their manner of preparation the forms now designated A, B and C appear to correspond to Miyazaki's α, β and α'. Carless & Foster (1966) have recently shown by differential thermal calorimetry that the material distributed by the Pharmaceutical Society of Great Britain, i.e. the B.P.C. Authentic Specimen, contains two or more forms. The presence of forms A and C has been confirmed, though their infrared spectra are in fact very similar. From this mixture, form A was recovered by recrystallization from a mixture of acetone and chloroform and form C was obtained by recrystallization from dilute ammonia solution. Recrystallization from ethanol, n-propanol or isobutanol gave substantially form B. Evaporation of an ethanol solution to dryness, recommended in the leaflet accompanying the B.P.C. Authentic Specimen, gave the amorphous form, which on standing was liable to crystallize spontaneously as either form B or form C. Evaporation of a methanol solution of the original mixture gave form C, but the same treatment with a solution of form B gave form B unchanged. Spectra published in the Sadtler Standard and Pharmaceutical collections are both of form A; that given by Sheinker & others (1957) appears to be substantially form C.

General discussion

The incidence of polymorphism amongst these sulphonamides appears to be even more prevalent than with the steroids (Mesley & Johnson, 1965) or barbiturates (Cleverley & Williams, 1959). Moreover, reproducible interconversion between different forms is more difficult to achieve than in the instance of the steroids. It has been shown (Mesley, 1966) that the polymorphic forms of the steroids frequently differ in the type of hydrogen bonding between the molecules in the lattice, and similar differences might be expected with the sulphonamides. However, in many of the sulphonamides tautomerism can also occur, between the amide form (I) and the imide form (II), and both forms are known to



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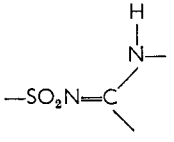

II

occur in solution. On the basis of their infrared spectra, Sheinker & others (1957) postulated that sulphamethizole and sulphathiazole both exist in the solid state in the imide form, and Sheinker & Kuznetsova (1957) suggested that sulphadiazine and sulphapyridine were also imides, whereas sulphacetamide has the amide structure. These infrared assignments were disputed by Uno, Machida, Hanai & others (1963), who used deuteration to show that sulphadiazine was in fact an amide, although they agreed with the imide structure for sulphapyridine and sulphathaziole. Schwenker (1962) has shown that sulphaguanidine also has the imide structure in the solid phase.

In the light of these findings it might be anticipated that where polymorphism occurs some forms might be amides whilst others are imides. However, no spectral differences have been observed between polymorphic forms of the same substance which could be ascribed to amide–imide tautomerism, and it must therefore be assumed that the high incidence of polymorphism amongst the sulphonamides is due mainly to the variety of hydrogen bonding possibilities.

With a number of these substances it was found that individual forms responded differently to the same solvent treatment. This is difficult to explain without assuming that particular types of association between molecules can persist in solution. In fact, association of sulphonamide molecules in solution has been demonstrated by Chaplin & Hunter (1937) and by Baxter, Cymerman-Craig & Willis (1955), though in very dilute solution the proportion of associated molecules is usually small. Nevertheless these associated molecules probably form nuclei round which crystals are formed and thus dictate the form in which the substance crystallizes. When different crystalline forms are dissolved in the same solvent it may be possible for the two types of association to persist in solution, giving rise to different solid forms (usually, but not necessarily, those with which one started) when the solid is evaporated. This behavi-

our was noticed with prednisolone (Mesley & Johnson, 1965) and has now been observed with succinylsulphathiazole, sulphadimidine sodium, sulphaguanidine, sulphamethoxydiazine, sulphanilamide, sulphapyridine and sulphathiazole. Although in most of these cases the solutions were evaporated to dryness, in some instances this effect was also found when saturated solutions were allowed to crystallize.

Difficulty was also encountered in obtaining reproducible results when solutions of the same form were evaporated to dryness. In some instances this was due to the solid initially appearing as a glass which subsequently crystallized spontaneously in one of two or more forms. In others the temperature at which crystals were produced or to which they were subsequently heated may have been critical. This trouble may be overcome by recrystallizing from a saturated solution rather than evaporating the solution to dryness.

RECOMMENDED PROCEDURES

In establishing a procedure for obtaining a consistent solid form, it is desirable that the whole of the material should be recovered, so that impurities, if present in the sample, will still be present when the infrared spectrum is recorded. Owing to the behaviour mentioned above this is not always possible, and recrystallization may be necessary, with a possible loss of impurities. In a few instances particular forms are so stable that they can only be converted to a common form by chemically altering the molecule (e.g. by forming the sodium derivative) and then recovering the substance by precipitation.

When two samples of the same substance are to be compared, in most instances it will be found that they give the same infrared spectrum without any recourse to solvent treatment. If two samples give different spectra but are thought to be of the same substance, then both should be subjected to the treatment suggested below for that substance. These treatments were found to be effective for all the forms obtained in this work; there is a possibility that other forms may be encountered, and whilst these treatments would probably still be effective, this cannot be guaranteed.

Phthalylsulphathiazole. Dissolve in minimum of sodium hydroxide solution, neutralize with dilute hydrochloric acid, filter, wash precipitate with water and dry. Examine as Nujol mull.

Succinylsulphathiazole. Dissolve in minimum of sodium hydroxide solution, neutralize with dilute hydrochloric acid, filter, wash precipitate with water and dry without heating above 100°. Examine as Nujol mull.

Sulphacetamide sodium. Recrystallize from water. Dry without heating above 100°. Examine as Nujol mull or halide disc.

Sulphadimidine. Dissolve in ethanol, acetone or chloroform and evaporate solution to dryness on water-bath. Examine as Nujol mull.

Sulphadimidine sodium. Dissolve in water and evaporate solution to dryness. If spectra still differ, convert to sulphadimidine by addition of

dilute hydrochloric acid to aqueous solution, filter, wash precipitate with water and dry. Examine as Nujol mull.

Sulphaguanidine. Recrystallize from water, filter and dry crystals at room temperature in current of air or under vacuum. Examine as Nujol mull or halide disc.

Sulphamethoxydiazine. Recrystallize from 50% aqueous ethanol. If spectra still differ, heat to 140° for 15 min. Examine as Nujol mull.

Sulphamethoxypyridazine. Dissolve in minimum amount of hot ethanol, add an equal volume of iso-octane (2,2,4-trimethylpentane) and evaporate to dryness on water-bath. The product should be white (a yellow colour indicates the presence of amorphous material, in which case the treatment should be repeated). Examine as Nujol mull.

Sulphanilamide. Dissolve in ethanol, evaporate solution to dryness on water-bath. Examine as Nujol mull.

Sulphapyridine. Heat to 140° for 15 min. If spectra still differ, dissolve in minimum of sodium hydroxide solution, add dilute hydrochloric acid dropwise until neutral to litmus paper (material is soluble in excess acid), filter, wash precipitate with a little cold water and dry. Examine as Nujol mull.

Sulphasomidine. Recrystallize from water. Examine as Nujol mull or halide disc.

Sulphathiazole. Recrystallize from n-propanol. Examine as Nujol mull or halide disc.

It will be noted that in many of these suggested treatments it is recommended that the substance be examined as a mull. This is due to the instability of many of the crystalline forms when ground and pressed with potassium bromide. Indeed, of the twelve substances listed above, ten showed changes in the spectrum of at least one form when examined as potassium bromide discs.

Acknowledgements. Thanks are due to Mr. C. A. Johnson of the British Pharmacopoeia Commission for confirming many of the results.

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