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# Studies on the Method of Size Reduction of Medicinal Compounds. V.[1] Size Reduction of Several Sulfonamides by Desorption of Ammonia from Their Ammonia Compounds[2]

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Compounds between four kinds of sulfonamides and $NH_3$ were prepared either by crystallization from liquid $NH_3$ or by sorption of gaseous $NH_3$. Their thermal behaviors were examined by several methods such as differential scanning calorimetry and thermogravimetry. It was found that each of sulfadiazine and sulfamerazine formed a single compound with $NH_3$ having 1:2 molecular ratio, while the other sulfonamides gave two different compounds. The combining ratios of the latters were as follows: sulfathiazole–$NH_3$, 1:2 and 2:1; and sulfamethizole–$NH_3$, 1:2 and 1:1, respectively. It was also confirmed that these compounds decomposed by heating and released $NH_3$ gas, although the heats of decomposition were comparatively large. Thus, each of the sulfonamides were recovered without loss of purity and the specific surface area of the sulfonamide particles became much larger than that of the original ones reaching to the extent of several $m^2/g$. These facts suggest that effective size reduction of sulfonamides can be accomplished by eliminating $NH_3$ from their corresponding $NH_3$ compounds.

In a series of studies, the authors developed a method of size reduction by solvation and subsequent desolvation of certain drug compounds that can form solvates with suitable solvents and investigated both the mechanisms involved in the method and appropriate conditions for desolvation.[1,4–6] Thus, ultra fine powders of griseofulvin, chloramphenicol and several steroid hormones[7] were successfully prepared.

In this study, isolation of compounds formed between $NH_3$ and four sulfonamides was attempted and their thermal behaviors were investigated by several methods. As the result, it was found that all of the sulfonamides form one or even two compounds and the desorption of $NH_3$ was accomplished by increasing the temperature below the melting point of the original sulfonamide. It was also confirmed that particles of the recovered sulfonamides had much larger specific surface areas than those of ordinary ones.

## Experimental

**Materials and Reagents**——Sulfathiazole, sulfadiazine and sulfamerazine of J.P. VII grade and sulfamethizole of J.P. VIII grade were used. Liquid $NH_3$ in a steel bomb was employed as the source of $NH_3$. The Nessler's reagent solution for detection of $NH_3$ evolved during differential scanning calorimetry was prepared by the formula in J.P. VIII.

**Preparation of $NH_3$ Compounds of the Four Sulfonamides**——1. Crystallization from Liquid $NH_3$: Each sulfonamide was placed in a flask and was cooled with the acetone–dry ice mixture. When dried $NH_3$ gas was introduced gradually into the flask, it was liquefied and dissolved the sulfonamide. The flask was

1) Part IV: I. Himuro, Y. Tsuda, K. Sekiguchi, I. Horikoshi, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), **19**, 1034 (1971).
2) Presented partly at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1968.
3) Location: *9–1, Shirokane 5-chome, Minato-ku, Tokyo.*
4) K. Ueno, T. Yamaguchi, K. Yoshida, I. Hyuga, and K. Sekiguchi, *Yakuzaigaku* (*Arch. Pract. Pharm.*), **23**, 284 (1962).
5) K. Sekiguchi, K. Ito, E. Owada, and K. Ueno, *Chem. Pharm. Bull.* (Tokyo), **12**, 1192 (1964).
6) K. Sekiguchi, I. Horikoshi, and I. Himuro, *Chem. Pharm. Bull.* (Tokyo), **16**, 2495 (1968).
7) Presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.

then immersed in an ice bath and the excess of $NH_3$ was allowed to evaporate. The $NH_3$ compound thus formed was not hygroscopic, but released its combined $NH_3$ gradually at room temperature.

2. Sorption of Gaseous $NH_3$: Dried gaseous $NH_3$ was passed through a flask containing about 3 g of finely powdered sulfonamide until no more weight increase occurred. If crystals of the sulfonamide were used in place of the powdered one, changes of appearance due to sorption were seen directly.

**Differential Scanning Calorimetry (DSC)**——A Perkin–Elmer DSC–1B differential scanning calorimeter was used. When quantitative calorimetry was conducted, the sample was weighed down to 0.01 mg with a semimicro balance. In almost all cases, evolved gas detection (EGD) was done simultaneously and if necessary, dissociated $NH_3$ was identified by introducing the gas from the DSC furnace into a test tube containing Nessler's reagent solution. For analysis under closed condition, the sample was hermetically sealed in a liquid sample pan.

**Thermogravimetry (TG)**——1. Application of Infrared Moisture Meter: At an early stage of study, a modified TG apparatus constructed with a moisture meter having a heating device of an infrared radiation lamp (Infrared–drying Moisture Content Meter, Type 1M-02, Kyoto Denshi Kogyo Co., Ltd.) and a recorder was employed. The heating rate was adjusted manually by a slidac at about 1.5°/min. Decrease in weight of the sample was recorded automatically and the temperature was measured with a small thermistor by hanging it in the sample pile. About 5 g of a sample was necessary for one measurement. Although the assembly was simple, reproducible TG data could be obtained so far as the heating rate was kept constant.

Thermobalance: A Perkin–Elmer TGS–1 thermobalance was used. The sample weight was 3—9 mg and a scanning speed from 4°/min to 16°/min was adopted. In the case of sulfadiazine-$NH_3$ compound, the sample crystals flied off easily from the pan during heating; therefore, measurement was done by wrapping them lightly in an aluminum foil. Consequently, the weight decrease occurred at somewhat higher temperature than the corresponding DSC peak. Changes in weight of the sample due to dissociation of $NH_3$ were also examined at various temperatures with the same apparatus.

**Measurement of Specific Surface Area**——A BET gas adsorption apparatus (Model 600-P, Shibata Chemical Apparatus Co., Ltd.) was used. The sample weight was 2—8 g, and the gas for adsorption was $N_2$.

## Results and Discussion

### Thermograms of $NH_3$ Compounds of Four Sulfonamides

1. $NH_3$ Compounds of Sulfathiazole: Typical patterns of simultaneous DSC and EGD curves of the crystals obtained from liquid $NH_3$ solution are shown in Fig. 1 (b) and (c). The DSC curve consists of four endothermic and one or two small exothermic peaks. The first two endothermic peaks appear successively between 50° and 100°,[8] while the third and the fourth peaks arise separately at ranges of 150—160° and 200—210°, respectively. The corresponding EGD curve shows two peaks indicating stepwise desorption of $NH_3$. The lower peak with a shoulder extends nearly the same range of temperature as that of the two endothermic DSC peaks, while the higher one appears at the temperature of the third DSC peak. The TG curve in Fig. 1 (d) shows that decrease in weight takes place in two steps. These facts indicate that two different compounds are formed between sulfathiazole and $NH_3$. The molecular ratios of both components were determined to be 1: 2 and 2: 1 with respect to the sulfonamide and $NH_3$ by the amounts of weight decrease. The difference of the $NH_3$ contents between the two compounds is also evident from the fact that the area of the first EGD peak is three times larger than that of the second peak. Because neither evolution of $NH_3$ nor decrease in weight occurs at temperature of the fourth DSC peak, and because the peak just coincides with the one due to melting of the $\beta$ form of sulfathiazole (the polymorphic form stable at higher temperature) as shown in Fig. 1 (a), it is certain that sulfathiazole is recovered by heating of the $NH_3$ compound without loss of purity.

When simultaneous measurement of DSC and EGD was done under closed condition, the 1: 2 compound exhibited two peaks and the residue in the punctured pan was melted. (Fig. 1 (e) and (f)). This will suggest that eutectic or peritectic fusion and subsequent melting

8) These peaks appeared often as three endothermic and one exothermic peaks due to delayed phase reactions.

of the compound occur during heating.[9] Therefore, the exothermic peak in Fig. 1 (b) will be ascribed to delayed crystallization of the second compound.

When sulfathiazole is exposed to gaseous $NH_3$ or the 1:2 compound is kept at about 80° for several hours, the 2:1 compound is formed as shown in the DSC and TG curves of Fig. 2 (a) and (b). This compound is more stable than the 1:2 compound and exhibits two endothermic DSC peaks, one EGD peak and one TG step. The combining ratio is determined by TG (Fig. 2 (b)) and by the elemental analysis. *Anal.* Calcd. for $C_9H_{12}O_2N_4S_2$: C, 41.31; H, 4.01; N, 18.58. Found: C, 41.25; H, 4.08; N, 18.52.

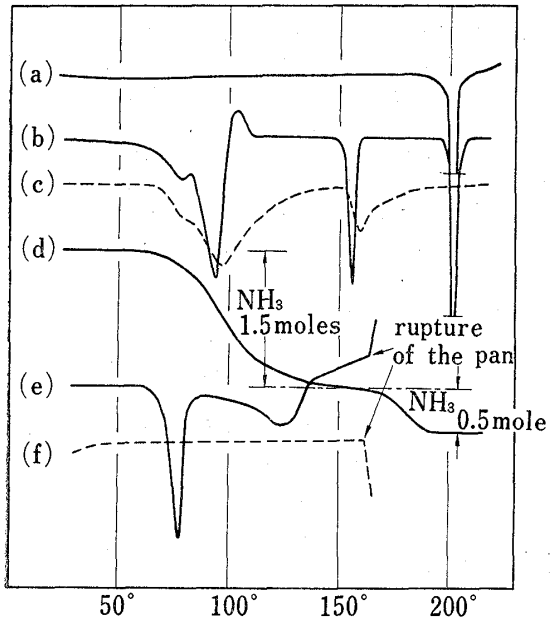


Fig. 1. Thermograms of Sulfathiazole and Its 1:2 $NH_3$ Compound prepared by Recrystallization from Liquid $NH_3$

(a):DSC curve of the $\beta$ form of sulfathiazole under semiclosed condition: sample weight 8.1 mg, heating rate 16°/min
(b) and (c):Simultaneous DSC and EGD curves of the 1:2 compound under semiclosed condition: sample weight 6.9 mg, heating rate 16°/min
(d):TG curve of the 1:2 compound: sample weight 4.433 mg, heating rate 16°/min
(e) and (f):Simultaneous DSC and EGD curves of the 1:2 compound under closed condition: sample weight 10.2 mg, heating rate 16°/min

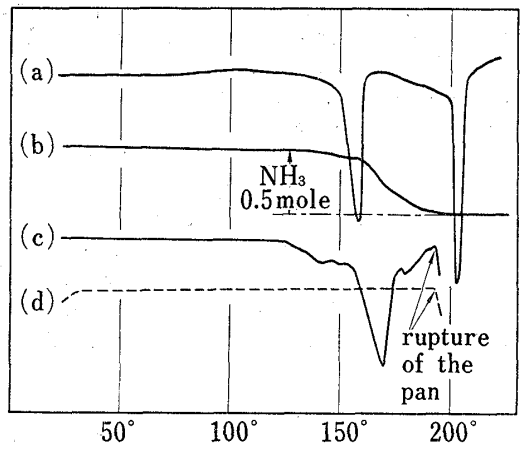


Fig. 2. Thermograms of the 2:1 $NH_3$ Compound of Sulfathiazole prepared by Sorption of Gaseous $NH_3$

(a):DSC curve of the 2:1 compound under semiclosed condition: sample weight 10.2 mg, heating rate 16°/min
(b):TG curve of the 2:1 compound: sample weight 4.279 mg, heating rate 16°/min
(c) and (d):Simultaneous DSC and EGD curves of the 2:1 compound under closed condition: sample weight 6.5 mg, heating rate 16°/min

2. $NH_3$ Compounds of Sulfamethizole: The thermograms of sulfamethizole and its compound prepared by sorption of gaseous $NH_3$ are shown in Fig. 3 (a)—(f). The second DSC peak under semiclosed condition is assigned to melting of free sulfamethizole, while the first one has its peak maximum at 165° and is attributed to desorption of $NH_3$ from the compound. The combining ratio of the compound is determined to be 1:1 from the weight decrease in the TG curve and by the elemental analysis. *Anal.* Calcd. for $C_9H_{13}O_2N_5S_2$: C, 37.93; H, 4.56; N, 24.37. Found: C, 38.18; H, 4.44; N, 23.89.

When sulfamethizole is crystallized from liquid $NH_3$ solution, colorless clustered needles are obtained. As is evident from the thermograms in Fig. 4 (a)—(c), these crystals are not stable and nearly all of them convert into the 1:1 compound by releasing $NH_3$ on standing. In this case, an additional small DSC or EGD peak and a short TG step appear in the ther-

9) Even if the system belongs to the type with a congruent melting point, some of $NH_3$ will be desorbed into the void space of the sample pan and the sample will become a mixture of 1:2 and 2:1 compounds. Accordingly, two DSC peaks due to eutectic fusion and melting will be observed.

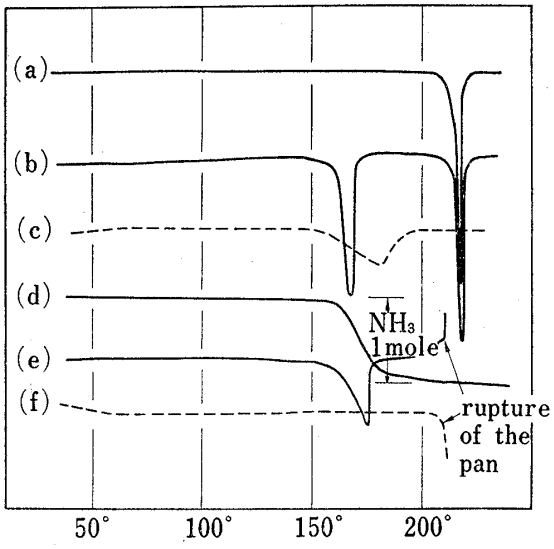


Fig. 3. Thermograms of Sulfamethizole and Its 1:1 $NH_3$ Compound prepared by Sorption of Gaseous $NH_3$

(a):DSC curve of sulfamethizole under semiclosed condition: sample weight 7.3 mg, heating rate 16°/min
(b) and (c):Simultaneous DSC and EGD curves of the 1:1 compound under semiclosed condition: sample weight 8.9 mg, heating rate 16°/min
(d):TG curve of the 1:1 compound: sample weight 4.544 mg, heating rate 16°/min
(e) and (f):Simultaneous DSC and EGD curves of the 1:1 compound under closed condition: sample weight 5.1 mg, heating rate 16°/min

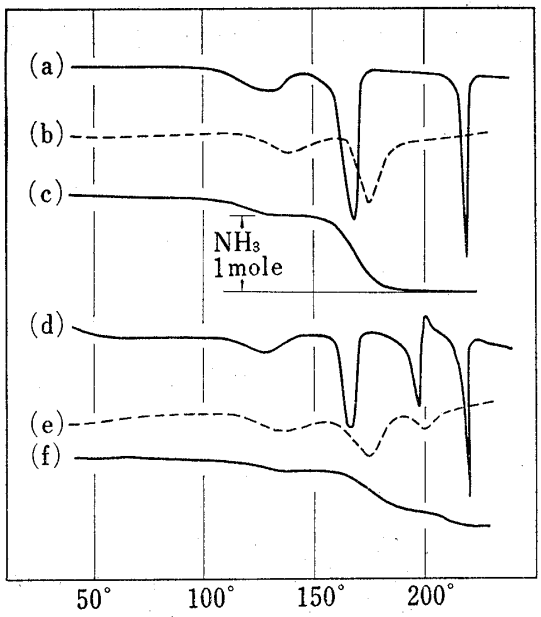


Fig. 4. Thermograms of the $NH_3$ Compound of Sulfamethizole prepared by Recrystallization from Liquid $NH_3$

(a) and (b):Simultaneous DSC and EGD curves under semiclosed condition of sample after storage of about 1 month in a refrigerator: sample weight 10.1 mg, heating rate 16°/min
(c) TG curve of the same sample as (a) and (b): sample weight 4.155 mg, heating rate 16°/min
(d) and (e) Simultaneous DSC and EGD curves of the same sample as (a) and (b) showing incomplete desorption of $NH_3$ and retarded crystallization of sulfamethizole: sample, finely pulverized in an agate mortar, sample weight 8.9 mg, heating rate 8°/min
(f) TG curve corresponding to the simultaneous DSC and EGD curves of (d) and (e): sample weight 3.995 mg, heating rate 16°/min

mograms below 150°. Further, when measurement is done with crystals immediately after preparation, the DSC and EGD peaks below 150° become larger and the total weight change approaches to the amount of 2 moles of $NH_3$. Therefore, it is likely that another compound having molecular ratio of 1:2 with respect to the sulfonamide and $NH_3$ will exist.

As shown in Fig. 4 (d)—(f), it often happens that even if the same batch of the sample from liquid $NH_3$ solution is used, the endothermic DSC peak at 210° appears at somewhat lower temperature and is divided into two endothermic and one exothermic peaks. Similar changes of thermograms are also observed with the 1:1 compound prepared by sorption. Since the corresponding EGD or TG curve shows in such cases, evolution of $NH_3$ or nonstoichiometric weight decrease, the fact will be ascribed to both incomplete evaporation of $NH_3$ from the melt and the retarded crystallization of free sulfamethizole.

3. $NH_3$ Compound of Sulfadiazine: As is evident in Fig. 5 (a)—(e), only one compound is formed by crystallization of sulfadiazine from liquid $NH_3$ solution. The compound is not stable, and the temperature at which $NH_3$ is eliminated is much lower than those of the above two sulfonamides, especially when the heating rate is slow. The combining ratio of sulfadiazine and $NH_3$ is calculated at 1:2 based on the weight decrease in the TG curve.

4. $NH_3$ Compound of Sulfamerazine: A single compound containing 2 moles of $NH_3$ per one mole of the sulfonamide is formed. Characteristic patterns of DSC, EGD and TG curves shown in Fig. 6 are nearly the same as those of the compound of sulfadiazine; however, the first DSC peak sometimes separates into two peaks. The fact is supposed to be due to

retarded crystallization of free sulfamerazine, since no liquefaction was observed at this range of temperature by visual melting point determination.

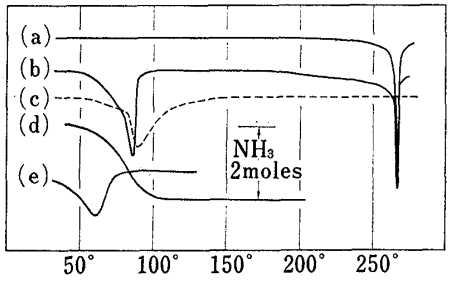


Fig. 5. Thermograms of Sulfadiazine and Its 1:2 $NH_3$ Compound prepared by Recrystallization from Liquid $NH_3$

(a):DSC curve of sulfadiazine under semiclosed condition: sample weight 10.1 mg, heating rate 16°/min
(b) and (c):Simultaneous DSC and EGD curves of the 1:2 compound under semiclosed condition: sample weight 6.6 mg, heating rate 16°/min
(d):TG curve of the 1:2 compound: sample weight 3.955 mg, heating rate 8°/min
(e):DSC curve of the 1:2 compound under semiclosed condition: sample weight 7.9 mg, heating rate 4°/min

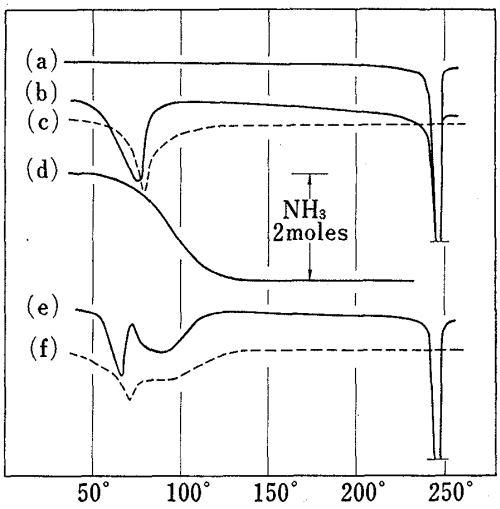


Fig. 6. Thermograms of Sulfamerazine and Its 1:2 $NH_3$ Compound prepared by Recrystallization from Liquid $NH_3$

(a):DSC curve of sulfamerazine under semiclosed condition: sample weight 9.6 mg, heating rate 16°/min
(b) and (c):Simultaneous DSC and EGD curves of the 1:2 compound under semiclosed condition: sample weight 10.5 mg, heating rate 16°/min
(d):TG curve of the 1:2 compound: sample weight 3.185 mg, heating rate 16°/min
(e) and (f):Simultaneous DSC and EGD curves of the 1:2 compound under semiclosed condition showing retarded crystallization of sulfamerazine: sample weight 11.7 mg, heating rate 16°/min

TABLE I. Heat of Decomposition and Heat of Fusion of the $NH_3$ Compounds and the Sulfonamides

| Compound | Heat of decomposition kcal/mole of sulfonamide | Heat of fusion kcal/mole |
|---|---|---|
| 1) Sulfathiazole: | | |
| the 1:2 compd. ⟶ the 2:1 compd. | 9.3±0.4 | — |
| the 2:1 compd. ⟶ sulfathiazole | 4.6±1.1 | — |
| Sulfathiazole | — | 7.5±0.2 |
| the 1:2 compd. | — | 11.3±0.1 |
| the 2:1 compd. | — | 8.2 |
| 2) Sulfamethizole: | | |
| the 1:1 compd. ⟶ sulfamethizole | 10.6±1.0 | — |
| Sulfamethizole | — | 8.0±0.1 |
| the 1:1 compd. | — | 8.8 |
| 3) Sulfadiazine: | | |
| the 1:2 compd. ⟶ sulfadiazine | 14.9±1.4 | — |
| Sulfadiazine | — | 11.8±0.2 |
| 4) Sulfamerazine: | | |
| the 1:2 compd. ⟶ sulfamerazine | 18.2±0.1 | — |
| Sulfamerazine | — | 10.5±0.1 |

### Heats of Decomposition of $NH_3$ Compounds

The heats of decomposition and fusion of the $NH_3$ compounds and the heats of fusion of the four parent sulfonamides were determined by DSC. As shown in Table I, the heats of decomposition are greater than the values for desolvation of solvates.

### Size Reduction of Sulfonamides by Desorption from Their $NH_3$ Compounds

The method of size reduction by solvation and desolvation is based on the fact that a solvate can be dissociated into solvent vapor and the original solid substance. The type of phase reaction involved in desorption of the $NH_3$ compound of the sulfonamide is thought to be similar to that of a solvate. Accordingly, conditions for desorption of $NH_3$ will influence the extent of size reduction of the parent sulfonamide as has been discussed on griseofulvin chloroformate[6] and chloramphenicol pyridinate.[1] Since the stability of each $NH_3$ compound differs considerably, it is important to determine the temperature for size reduction. It is also important for effective elimination of $NH_3$ whether the pressure should be reduced or not. For these purposes, weight changes of each $NH_3$ compound at various temperatures were measured by the thermobalance. As an example, results obtained with the 1:2 compound of sulfathiazole are shown in Fig. 7. Even if the temperature is maintained at 80°, the 1:2 compound does not convert into sulfathiazole but into the 2:1 compound. However, when the compound is held at the same temperature under reduced pressure of 15 mmHg, complete desorption is accomplished. On the other hand, the $NH_3$ compounds of sulfadiazine and sulfamerazine are much less stable, so that the combined $NH_3$ is easily eliminated by keeping the temperature at 50° or so, even under atmospheric pressure. In Table II, conditions adopted for desorption and the specific surface areas of sulfonamide particles thus obtained are given. From these data, it is clear that effective size reduction of sulfonamide is possible.

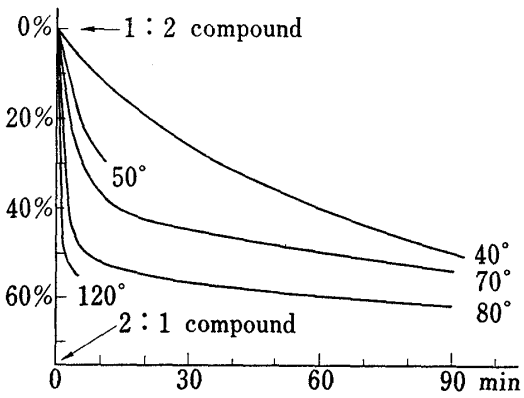


Fig. 7. Percent Release of $NH_3$ from the 1:2 $NH_3$ Compound of Sulfathiazole maintained at Various Temperatures in the DSC Furnace

Table II. Results of Size Reduction of Sulfonamides by Desorption of Their $NH_3$ Compounds under Several Conditions

| $NH_3$ Compound | Temperature and time of desorption | Pressure | Recovered sulfonamide | |
|---|---|---|---|---|
| | | | Specific surface area | Mean diameter |
| 1:2 Sulfathiazole-$NH_3$ | 1) 50—80° for 3 hr, then 140—150° for 1 hr | atmospheric | 2.0 $m^2/g$ | 2.0 $\mu$ |
| | 2) 95—100° for 1.5 hr | 1—3 mmHg | 3.1 | 1.3 |
| 1:2 Sulfamethizole-$NH_3$ | 150—160° for 2.5 hr | 1—3 mmHg | 1.8 | 2.2 |
| 1:2 Sulfadiazine-$NH_3$ | 1) 45—50° for 3 hr | atmospheric | 3.7 | 1.1 |
| | 2) 65—70° for 1.5 hr | atmospheric | 3.6 | 1.1 |
| | 3) 80—90° for 2 hr | 15 mmHg | 7.1 | 0.6 |
| | 4) 95—100° for 20 min | 1—3 mmHg | 7.4 | 0.6 |
| 1:2 Sulfamerazine-$NH_3$ | 70—80° for 2 hr | atmospheric | 3.2 | 1.3 |

## Conclusion

Although the authors expected that each of the sulfonamides would form a single equimolar compound of $NH_3$ which is bonded by ionic force, most of the compounds have a combining

ratio other than 1:1. Further, two different compounds are formed between sulfathiazole and sulfamethizole and $NH_3$. These facts will suggest that in the compounds at least one molecule of $NH_3$ is combined with the sulfonamides by other kinds of forces such as the dipole-dipole interaction and/or hydrogen bonding. It is for this reason that the authors express them by the term "$NH_3$ compounds" not by "$NH_4$ salts."

Size reduction of sulfonamides through formation of their $NH_3$ compounds is in principle a modification of the method by solvation and desolvation; however, the method will be less selective and have wider application than the latter, since it is thought that many acidic drug substances will form compounds with $NH_3$ and be recovered in the form of ultra fine particles by simple processes.

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