THE MELTING POINT OF ACETYLSALICYLIC ACID.

BY T. S. CARSWELL.

I. INTRODUCTION.

In a recent article upon the physical constants of acetylsalicylic acid, Hayman, Wagener and Holden (JOUR. A. PH. A. 14, 388–392 (1925)) show that the melting point of the product varies when crystallized from different solvents, although the crystals obtained from different solvents are identical in optical properties and crystal form. They also state that the temperature at which acetylsalicylic acid melts is apparently not a true melting point.

In the course of some work in this laboratory on acetylsalicylic acid, it became apparent that consistent results for the melting point of this substance could be obtained only when the conditions under which the melting point was taken were rigidly standardized. Attention was first given to the rate of heating, and it was found that in order to obtain check results even upon the same sample it was necessary to control the rate of heating by a stop-watch. Even when the rate of heating was carefully controlled, variations in the melting point were noticed which could not be attributed to errors on the part of the manipulator. Crystallizations of the same product from different solvents gave varying melting points, and in this respect checked the observations of Hayman, Wagener and Holden.

A further study of the matter showed that the irregular variations in melting points were due to some physical differences in the crystals, and when the physical differences were eliminated or equalized by grinding the products to a uniform degree of fineness, the irregularities to a large extent disappeared.

Three methods of determining the melting point are at the present time in general use:

(1) The U. S. P. X method in which the sample is inserted in a bath preheated to 120°, and the temperature raised 3° per minute until melting begins, when the rate is lowered to 0.5° per minute;

(2) The method of Dahm (*Ind. Eng. Chem.* 11, 29–30 (1919)), in which the sample is inserted in a bath preheated to 130°, and the temperature raised 1° per minute;

(3) The method of the new German Pharmacopœia, in which the sample is inserted in a bath preheated to 125°, and the temperature raised so that not more than 10 to 15 seconds are required to cause a rise in temperature for each successive degree.

These methods all give different values for the melting point, a result which is to be expected, since practical experience, as well as a study of the literature, leaves no doubt that aspirin melts with decomposition, and that what is really determined is a combination of the true melting point with the decomposition point. The latter has no exact value, but is a function of the time and temperature. The longer the period of heating below the true melting point, the more the observed value approaches a decomposition rather than a melting point. It is interesting to tabulate the approximate melting points by these various methods, together with the time and average temperature of heating.

	Approx. m. p.	Average temp.	Time.
U. S. P. X Method	132°	126°	4
Dahm Method	134°	132°	4
German Pharmacopœia Method	135°	130°	2

It is evident that the nearest approach to the true melting point will be given by the German Pharmacopœia Method while the U. S. P. X will more nearly approach a decomposition point. It must be noted that none of the above methods specifies the fineness to which the sample must be reduced before the determination. The U. S. P. X under general remarks says that the substance shall be reduced to a very fine powder but makes no other specification.

II. EXPERIMENTAL WORK.

High grade samples of commercial aspirin were used as the starting material. The purity as determined by assay according to the U. S. P. X was 99.8 to 99.9%. The data given below are taken from determinations on one sample from one manufacturer, but similar data were obtained upon different samples from different manufacturers. As has been previously stated, the temperature rise in all determinations was held at the specified rate with a stop-watch. The melting point apparatus of Dahm (*loc. cit.*) was used. In taking melting points by the German Pharmacopœia the temperature was raised exactly 5° per minute.

The melting point as given under "unground" was taken by crushing the crystals roughly with a spatula upon a clean piece of cardboard, the value given under "ground" was taken by crushing the crystals in a mortar and passing through a 200-mesh screen. The portion remaining on the screen was crushed and resifted, and the operation repeated until the entire sample passed through the screen.

The starting material gave the following values:

	Not ground.	Ground.
U. S. P. X Method	131.2–132.2	130.8–131.8
Dahm Method	133.0–134.8	132.4–134.0
German Pharmacopœia Method	133.8–135.0	132.8–134.8

After crystallization from chloroform the following values were obtained:

	Not ground.	Ground.
U. S. P. X Method	130.6–132.1	129.7–130.5
Dahm Method	132.4–132.8	131.6–132.7
German Pharmacopœia Method	134.8–136.8	133.2–135.0

It is interesting to note that the crystals from chloroform melted higher than the original product by the method of the German Pharmacopœia, although lower by the U. S. P. and Dahm methods. The latter results agree with those of Hayman, Wagener and Holden who obtained a slightly lower melting point after chloroform crystallization. Allen ("Commercial Organic Analysis," Edition V, Vol. 3, p. 527) states that acetylsalicylic acid recrystallized from benzene or chloroform melted sharply at 136–137°, but he does not give the method by which the melting point was taken. It will be noted that in our experiment the melting point on the "ground" basis dropped to a normal value. Although the experiment we quote here gave us a higher apparent melting point by the method of the German Pharmacopœia, we have also observed cases in which crystallization from chloro-

form gave a lower melting point on the "not ground" basis. Even in these cases, grinding of the product showed a normal melting point.

After crystallization from benzene, the following values were obtained:

	Not ground.	Ground.
U. S. P. X Method	131.6–132.6	130.0–130.6
Dahm Method	133.2–134.0	132.2–133.4
German Pharmacopœia Method	135.6–136.6	133.0–134.9

Crystallization from acetone gave the following values:

	Not ground.	Ground.
U. S. P. X Method	131.0–132.0	131.2–132.0
Dahm Method	132.8–133.8	133.0–134.4
German Pharmacopœia Method	133.0–135.6	133.4–135.2

Crystallization from ethyl alcohol gave the following values:

	Not ground.	Ground.
U. S. P. X Method	130.2–131.6	130.6–131.6
Dahm Method	133.0–135.0	132.6–134.2
German Pharmacopœia Method	134.2–136.0	133.6–135.2

III. DISCUSSION OF RESULTS.

Inspection of the above tables shows that the fineness of the material in the melting point tube greatly influences the observed melting point. The normal effect of increasing fineness is to decrease the melting point. Since this is the case, it is evident that a reliable method for taking the melting point should specify the fineness of the product, and not leave this to chance. The writer believes that a specification should be adopted, requiring grinding to pass 200 mesh. Such a specification will eliminate variations due to crystal size and structure.

The above tables also show that the melting point after grinding, when taken by the method of the German Pharmacopœia, approaches the constant value of 135°, although by the other methods varying results are obtained. Fifteen determinations on different samples of commercial ground acetylsalicylic acid by the method of the Pharmacopœia gave an average final melting point of 135.0°, with maximum variations of ± 0.2°. Determinations of the melting point by the U. S. P. procedure on the same samples (ground to 200 mesh) gave an average final melting point of 131.2, with maximum variations of ± 0.7°.

This data indicates that the method of the German Pharmacopœia gives more nearly the true melting point of acetylsalicylic acid, since it approaches an exact value, reproducible within narrow limits. The method of the U. S. P. X gives a "decomposition point," which is subject to rather wide fluctuations, depending on the external conditions, such as the size of the tube, compactness of the powder and the physical state of the powder.

CONCLUSIONS.

1. The melting point of acetylsalicylic acid is dependent upon the size of the particles in the melting-point tube, and to obtain uniform results grinding to a standard fineness must be adopted.

2. The nearest approach to the true melting point of acetylsalicylic acid is given by the method of the new German Pharmacopœia, after grinding to 200 mesh.

3. Variations in the melting point of acetylsalicylic acid after crystallization from different solvents are caused by differences in the physical structure of the crystals, since grinding to a fine powder gives a uniform melting point.

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NITROSYL CHLORIDE AND KETONES.

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Since the review (1) published more than a year ago, covering the chemical action of nitrosyl chloride, our attention was called to a report (2) of Rheinboldt and Schmitz-Dumont which had appeared but a short time before. They found that certain ketones were converted by this gas into chlorinated isonitroso compounds, R—CO—C(=NOH)Cl. The exact mechanism of this change is not clear, but it is difficult to interpret it in any other way than simple chlorination. Because the intermediate isonitroso compounds could be isolated in some cases and because they could then be converted by further action under the same conditions, producing two molecules of nitric oxide, the authors express the opinion that the reaction proceeds in two steps:

(1) $R—CO—CH_3 + NOCl \longrightarrow R—CO—CH{=}NOH + HCl$
(2) $R—CO—CH{=}NOH + 2NOCl \longrightarrow R—CO—C(=NOH)Cl + 2NO + HCl$

The second stage could be expressed by production of a hypothetical HNO:

$$R—CO—CH{=}NOH + NOCl \longrightarrow R—CO—CH(=NOH)Cl + HNO$$
$$HNO + NOCl \longrightarrow HCl + 2NO$$

Acetone, methyl propyl ketone, methyl isopropyl ketone, pinacoline, levulinic acid, methyl *p*-tolyl ketone, benzal acetone and anisal acetone gave, in this way, chlorisonitroso derivatives, *p*-chloracetophenone and phenylacetone gave merely the isonitroso compound, while anisalacetone yielded both forms. Acetophenone, under the conditions gave no reaction, but vapors of the reagents reacted to give chlorisonitrosoacetophenone. The nitrosyl chloride compound of stannic chloride carried the reaction only as far as the isonitrosoacetophenone.

Our experiments, started some time ago, have led to results which are somewhat at variance with these and which open up a fertile field of investigation. With acetone undiluted, there is an immediate and quiet reaction in the cold to give isonitrosoacetone and phorone, the latter being subsequently converted into mono, and probably a dinitrosochloride. No trace of a chlorinated product could be separated, nor was there any indication of nitric oxide evolution. If, however, the acetone is previously diluted with carbon tetrachloride, the results of Rheinboldt and Schmitz-Dumont are confirmed. It seems rather remarkable that undiluted acetone should react to give less complete action than does the diluted substance, and we are now engaged in studying this phase. The natural supposition would be to attribute this to the fact that the process requires a longer time when the acetone is first dissolved, but our experience indicates that this is by no means a satisfactory explanation.