On the Anomalous Melting Point and the Decomposition of Acetyl-salicylic Acid

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In Beilstein's Handbook Vol. X (1927) it is described that Bayer's aspirin is different in some respects from most preparations of acetyl-salicylic acid, namely, it has a crystalline form of plates, and shows a high melting point of 137°, while others are needles and usually melt at 135°. Some pharmaceutists,(1) having made comparative studies on a number of samples of acetyl-salicylic acid produced in France, Germany and in our country, came to the conclusion that our domestic products are not inferior to the imported ones. It was also shown(2) that the crystals of various domestic products consist of plates like those of Bayer's aspirin, although some difference is observed in crystalline habit according to makers, but, unfortunately, there lacks any description on their melting points.

Melting point Some papers have already been published(3) on the examination how the melting point of acetyl-salicylic acid varies with the solvents used for recrystallization, but the melting points described by them were always below 134°. With a view to reinvestigate this question, we have made recrystallization from various solvents and measured the melting points of the products.

The recrystallization was carried out by evaporating the solvents slowly at lower temperatures. The crystals separated out were usually plates like Bayer's aspirin, but sometimes there appeared prismatic crystals. The melting point was determined by putting a capillary tube with the sample suddenly in a bath heated up to 130° and by elevating the temperature of the bath at a rate of 4° per minute. The results are presented in Table 1, which shows that the melting point, being in most cases nearly 135°, reaches as high as 137°, when acetyl-salicylic acid is recrystallized from a hydrophobic solvent such as chloroform. Thus it may safely be concluded that Bayer's aspirin is not a special chemical substance in melting point nor in crystalline form.

Table 1

Solvent	m. p. (corr.)	Solvent	m. p. (corr.)
Chlofoform	136.3-137.4	Ethyl alcohol	135.1
Dioxan	135.7		
Acetic anhydride	135.7	Methyl alcohol	132.6-133.6
Ether	135.6	Water	131.6

Decomposition It has already been recognized that acetyl-salicylic acid undergoes decomposition before it reaches its melting point, but the extent of thermal decomposition has never been measured. Hence we have measured the quantity of salicylic acid set free by thermal decomposition(4) of acetyl-salicylic acid, employing a newly devised colorimetric method of determining salicylic acid, since none of the known methods(5) is found quite suitable fo rour purpose.

The standard solution of our new method is made by adding 0.5 cc. of a 12 per cent aqueous solution of ferric chloride hexahydrate to 20 cc. of a 0.06 per cent methanol solution of salicylic acid containing 1 g. of acetyl-salicylic acid, whereby a brown color with a violet tint is developed, and compared by a 0.001 mol/l.

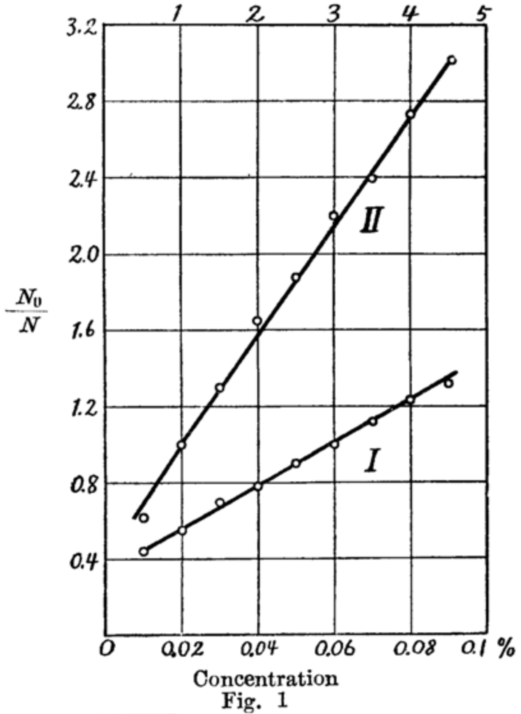

Fig. 1

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(1) H. Suzuki, I. Keimatsu and K. Ito, *Chem. Abstr.*, **29**, 5429 (1935)

(2) S. Watanabe and A. Watanabe, *Proc. Imp. Acad. Japan.*, **11**, 379 (1935)

(3) Capelli, *Pharm. Ztg.*, **65**, 800 (1920); K. Suda and H. Ogakureyama, *J. Pharm. Soc. Japan*, **No. 481**, 241 (1922) (in Japanese); Putnam, *Ind. Eng. Chem.*, **16**, 778 (1924)

(4) This expression is not quite right, the decomposition is rather hydrolysis due to moisture.

(5) Allport, "Colorimetric Analysis", p. 162 London (1947)

Duboscq colorimeter with a series of solutions of various concentrations prepared in a similar way. It has thus been found that a linear relationship exists between the concentration of salicylic acid and the ratio of the lengths of the two solutions, N_0/N, N_0 being that of the standard (I in Fig. 1). In Table 2 are shown the results of experiments made at 110° with 1 g. of acetyl-salicylic acid.

Table 2

Decomposition of acetyl-salicylic acid.

Time min.	N_0/N	Conc. %	Decomposition %	Lowering of melting point	
				obs.	calc.
5	0.613	0.025	0.65	1	0.48
15	0.672	0.031	0.79	4	0.57
25	0.925	0.053	1.38	4	1.02
35	1.093	0.068	1.77	5	1.30

In Table 3 are shown the results of measurements made at 128°. In this case 0.2 g. of acetyl-salicylic acid was used. After heating at this temperature for a definite length of time it was dissolved in 20 cc. methanol and 0.5 cc. of a 1/2 mol aqueous solution of ferric chloride was added to it. By comparing this solution colorimetrically with the standard made from a 1/1000 mol methanol solution of salicylic acid and the iron reagent, the quantity of free salicylic acid was determined by means of a relation previously established between N_0/N and concentration of salicylic acid (II in Fig. 1).(6)

Table 3

Decomposition of acetyl-salicylic acid at 128°

Time min.	N_0/N	Conc. 10^3 mol/l.	Decomposition %	Lowering of melting point (°C)	
				obs.	calc.
5	0.719	0.60	1.08	2	0.79
15	1.825	2.45	4.41	13.5	3.23
25	2.23	3.25	5.81	20.5	4.22

Lowering of melting point The difference in melting point between the original acetyl-salicylic acid and the heated is shown in the column (obs.) of the lowering of melting point in Tables 2 and 3. It is seen from this column that the melting point naturally falls with the duration of heating as well as with the elevation of temperature. We have calculated the lowering of melting point from the data of decomposition on the assumption that the depression is caused by the decomposition of acetyl-salicylic acid. For this pnrpose we measured the molecular depression of acetyl-salicylic acid by using adipic acid, salicylic acid and hydroquinone as solutes. The results of measurements are shown in Table 4.

The calculated values of lowering of melting point shown in Tables 2 and 3 were obtained from the data of decomposition by using 6.6 as the mean value of molecular depression. The observed values, as may be seen, are always incomparably larger than the calculated. Hence it seems to us that the abnormal depression of melting point of acetyl-salicylic acid is not solely due to the dissolution of both salicylic and acetic acids formed by its thermal decomposition.

Table 4

Molecular depression of acetyl-salicylic acid.

Solute	Conc. %	Depression	Molecular depression
Adipic acid	15	6.66	6.48
〃	30	13.33	6.49
Salicylic acid	13.8	6.50	6.50
〃	27.6	12.75	6.38
Hydroquinone	11	6.75	6.75
〃	22	14.00	7.00
			Mean 6.6

Anomalous melting point Such an anomalous behavior in melting point is observed not only in acetyl-salicylic acid, but also in its *p*-isomer, namely, *p*-acetoxy-benzoic acid. As the melting point of this compound is variously recorded in the literature, we have examined it with some materials obtained by recrystallizing from various solvents such as ether, acetic anhydride, ethyl alcohol, methanol, dilute alcohol, and water, and have found it to lie between 186° and 188°. The discrepancy, though much smaller than in acetyl-salicylic acid, is yet clearly seen. A sample of *p*-acetoxy-benzoic acid, once melted, shows a depression by 2° to 3°. By repeating this process fifteen times, we have realized that the melting point can be lowered finally even to 165°. This depression is undoubtedly associated with thermal decomposition of *p*-acetoxy-benzoic acid. While on the contrary, both free salicylic and free *p*-hydroxy-benzoic acids show no sign of this phenomenon. Their melting points are quite definite, exhibiting no tendency of lowering, even if repeatedly melted.

Thus it was confirmed that the lowering of melting point is exclusively due to the instability of their acetyl derivatives.

We have in the next place made comparison in stability between the *o*-and *p*-compounds, since it appers to us that acetyl-salicylic acid is more liable to decomposition than its *p*-isomer. According to the measurements of Anschütz and Motschmann(7) the velocity constants of hydrolysis of acetyl-salicylic acid in water at 100° is 0.14701 ($t=30$ min.), while that of the *p*-isomer is 0.05975. We have also found that the saponification velocity constants of *o*-and *p*-acetoxy-benzoates in boiling dilute alcohol are respectively 0.015 and 0.0015 ($t=$ min.). Thus it is clear that *p*-acetate is far

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(6) The line I is related with the lower ordinate, the line II with the upper. The concentration is exprssed in different measures, so as to fit the lines into a diagram.

(7) Ann., **392**, 116 (1912)

resistent to decomposition than acetyl-salicylic acid. Besides, in harmony with this fact, a wide difference is observed between the velocities of formation of the two acetyl derivatives, viz., it takes more than three hours to obtain the *p*-compound by boiling a mixture of hydroxy-benzoic acid and acetic anhydride, whereas it takes only one hour with acetyl-salicylic acid. Thus it is evident that acetyl-salicylic acid is more easily formed and more liable to be decomposed.

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