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183. Keiji Sekiguchi, Yoshio Ueda, and Yoshiko Nakamori : Studies on the Method of Thermal Analysis of Organic Medicinals. III.[*1,*2] Relations between Methods of Sample Preparation and Obtained Phase Diagrams.

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The so-called "thaw-melt method" developed by Rheinboldt has long been adopted for the thermal analysis of organic binary system because of simplicity and minute amount of sample required.1) The method is often thought to be an established one, and only a few trials of modification have been attempted except the application of microscopic technique using a hot stage. Nevertheless, there are many investigators who doubt the dependability of the method. In fact, not a few phase diagrams were reported in literatures which were questionable from the Phase Rule. Although the errors were resulted partly from uncautious application of the technique without previous training or from incomplete apprehension of foundamental theories involved, the method has some weak points of its own. One of them is due to the low precision of the melting point apparatus adopted by Rheinboldt and others (Precision of measurement of binary mixture by usual method is said to be ±2～5°).2) The second source of error is attributed to the misunderstanding that a sample prepared by fusion in a crucible attains always a true equilibrium state.

In the previous paper, a simple and accurate melting point apparatus, very suitable for the visual thermal analysis of binary system was proposed.[*2] The purpose of this study is to investigate the applicability of three methods of sample preparation, among which two were modified by authors, and at the same time to discuss the results, especially the meaning of metastable eutectic points often observed in systems of compound formation. Thus, the authors believe that both reliability and applicability of the thaw-melt method are much improved, and the unreasonable reputations in the past is largely eliminated.

Experimental

Materials——Almost all of the component substances were used after recrystallization from suitable solvents once or twice. Commercial ammonium benzoate was purified by washing several times with Et_2O, and the purity was found to be 98.7% by titration of freed ammonia.

Apparatus and Measurement——A melting point apparatus reported previously was employed (Fig. 1). The thaw point is the temperature at which the solid mixture begins to liquefy, and it is measured by pressing the sample with a small glass stirrer, inserted into the melting point capillary. The temperature of the complete disappearance of the solid phase is designated the melting point which is also determined while stirring continuously. The observation of a sample during heating and the temperature reading were done with magnifiers. If possible, the kind of primary crystal was discriminated, since the information is sometimes useful for drawing liquidus curve. Usually, the heating rate near the thaw and melting point was 0.5～1°/min. For the determination of the metastable eutectic point, the rate was sometimes more rapid.

[*1] This work was presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, June 10, 1961.

[*2] Part I. H. Nogami, K. Sekiguchi : Yakugaku Zasshi, **75**, 471 (1955); Part II. K. Sekiguchi, Y. Ueda : *Ibid.*, 83, 410 (1963).

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1) H. Rheinboldt : J. prakt. Chem., **111**, 242 (1925); **112**, 187 (1926); **113**, 199 (1927).

2) E. Skau, H. Wakeham, in A. Weissberger, ed., Physical Methods of Organic Chemistry, Vol. I, 104 (1949).

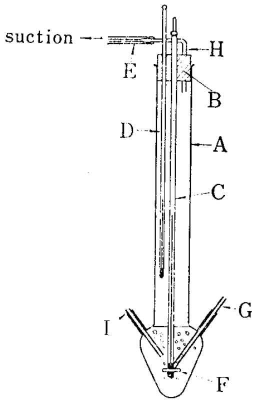

Fig. 1. Melting Point Apparatus

A : Melting point tube
B : Cork stopper
C : Thermometer
D : Thermometer for temperature correction
E : Polyvinylchloride tube
F : Support of melting point capillary
G : Melting point capillary
H : Glass tube for air outlet
I : Capillary for air inlet

Sample Preparation

Method I. The Mixture Prepared by Mechanical Mixing (**The Physical Mixture**)——Both components were weighed accurately into a small beaker or an Erlenmeyer flask in various proportions, and mixed thoroughly in an agate mortar. For each measurement, 15～25 mg. of material was introduced into the melting point capillary and pressed down so that it occupies 5～7 mm. at the bottom of the tube.

Method II. The Mixture Prepared by Fusion (**The Fused Mixture**)——The sample of the simple physical mixture in a melting point capillary was heated in the melting point apparatus, and after complete fusion, the melt was allowed to solidify. Compared with the original method using a small crucible, overheating which sometimes causes decomposition can be almost avoided. Even when one or both of the components are sublimable, the surface of sublimation in a melting point capillary is much smaller. Therefore, the change in composition caused by sublimation or evaporation will be mostly neglected. For rapid solidification, the capillary is not cooled but heated up to the temperature, several degrees below the eutectic or peritectic point. Thus, the crystallization will be much accelerated by easier migration of molecules due to reduced viscosity of the supercooled melt. From our experience concerning about 300 kinds of binary systems, this procedure was proved to be very effective, especially for systems which are apt to keep vitreous condition after fusion.

Method III. The Mixture Prepared by Dissolution and Evaporation (**The Evaporated Mixture**)——The weighed mixture of both components was heated and dissolved with a small amount of suitable solvent on a water bath. Then the solution was evaporated to dryness and yielded a solidified mass. This was triturated thoroughly and dried in vacuum. After complete evaporation of the solvent, the mass was again reduced to a fine powder. If the residue does not crystallize and keeps supercooled condition, solidification will be induced by heating in an electric oven similarly as with the fused mixture.

Results and Discussion

Aminopyrine/7-(2-Hydroxyethyl)theophylline System (Fig. 2, Table I)——Eutectic points of physical mixtures were found to be about three degrees higher than those of fused mixtures. The difference is attributed to the following reasons. (i) The interface of both components in the simple physical mixture is much smaller than that in the fused mixture, because the former consists only of gross particles of both components which are in a state of point contact, whereas, the latter is composed of primary crystals and eutectic conglomerates in which minute particles of components are mixed intimately. (ii) In the physical mixture, the air layer between particles prevents heat transmission. On the other hand, as the sample prepared by fusion does not contain air, heat is transmitted more easily. Thus, the observation of eutectic liquefaction is somewhat delayed when the physical mixture is used.

Similarly, the difference between the two melting point curves is due to the difference of the state of aggregation. The somewhat higher melting points of physical mixtures are explained by the slow rate of solution of large particles. In fused mixtures, the primary crystal is said to be in a dendrite structure of large surface area; accordingly, the phase reaction of melting occurs at the correct temperature.

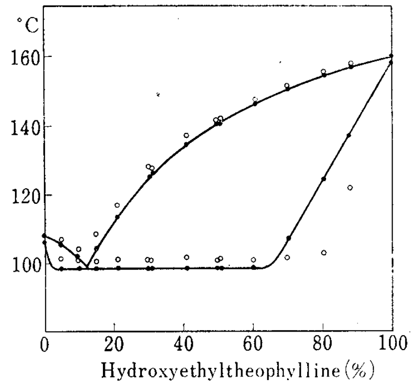

Fig. 2. Aminopyrine/Hydroxyethyltheophylline System

Closed circles : Fused mixtures
Open circles : Physical mixtures

Table I. Aminopyrine/Hydroxyethyltheophylline System[a]

HET[b] (%)	Physical mixt. (°C)		Fused mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.
0.0	106.0	108.2	106.3	108.3
5.1	101.5	107.0	98.5	105.3
10.0	100.8	104.5	98.0	102.3
15.0	100.8	108.5	98.0	104.0
20.6	101.5	117.0	98.5	113.5
30.2	101.4	128.3	98.5	125.3
30.8	101.0	127.5	98.5	126.0
40.7	101.7	137.5	98.5	134.5
49.7	101.0	141.5	98.5	140.2
50.8	101.5	142.0	98.5	140.3
60.4	101.3	147.5	98.5	145.7
70.0	101.5	151.5	107.5	150.3
80.4	103.0	155.5	124.0	154.0
88.2	121.5	158.0	137.0	156.5
100.0	158.5	160.5	158.5	160.6

a) Commercially available aminopyrine and HET were employed without further purification.
b) HET : 7-(2-Hydroxyethyl)theophylline.

***o*-Nitroaniline/*p*-Aminobenzoic Acid System** (Fig. 3, Table II)——Previously, it was reported that the original method could not be applied to this system, since marked sublimation or evaporation of *o*-nitroaniline occurred during fusion process of sample preparation in a crucible.[3] However, nearly the same diagrams could be obtained with samples prepared by the three methods. This indicates that the modified methods are more applicable than the original one.

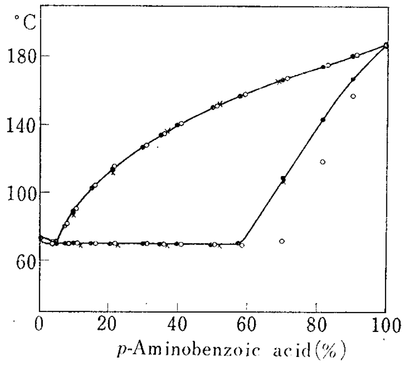

Fig. 3. *o*-Nitroaniline/*p*-Aminobenzoic Acid System

Closed circles: Fused mixtures
Open circles: Physical mixtures
Crosses: Evaporated mixtures

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3) T. Okano : Yakugaku Zasshi, **70**, 435 (1950).

Table II. *o*-Nitroaniline/*p*-Aminobenzoic Acid System

PABA[a] (%)	Physical mixt. (°C) t.p.	Physical mixt. (°C) m.p.	Fused mixt. (°C) t.p.	Fused mixt. (°C) m.p.	Evaporated mixt. (°C) t.p.	Evaporated mixt. (°C) m.p.
0.0	71.8	72.8				
5.1	70.2	71.0	69.5	70.5		
7.4	70.2	81.0	69.5	80.5		
10.0	70.2	89.3	69.5	89.0	68.5	86.5
15.0	70.3	104.0	69.5	103.5		
21.2	70.0	117.0	69.3	115.2	68.5	112.2
30.0	70.2	128.0	69.5	127.2		
35.0	70.2	134.2	69.3	134.0	68.8	134.5
39.5	70.3	141.0	69.5	140.0		
50.0	70.5	151.0	69.5	150.8	69.2	151.0
57.5	70.5	157.0	71.0	156.5		
70.0	72.5	166.5	110.5	167.0	107.8	165.5
81.5	119.0	175.0	145.0	174.5		
90.0	158.5	181.2	167.0	181.0		
100.0	187.0	187.5				

a) PABA : *p*-Aminobenzoic acid

Nicotinamide/Theophylline System (Fig. 4, Table III)——A molecular compound with incongruent melting point is formed between the two components. In a previous paper, the ratio of the compound formed was reported as 1:1 by mistake,[4] and here it is corrected to 2:1 with respect to the amide and theophylline. In the case of the simple physical mixture whose composition is somewhat greater than 44.8%, thawing was once observed at 126.5 or 127.0°, corresponding to the eutectic point. Further heating caused resolidification and at 169° the second thaw point due to peritectic reaction was again observed. However, the fused mixture of the same composition did not exhibit the first thaw point of 126.5~127.0°. The phenomenon of double thawing observed with physical mixtures is attributed to the fact that portions near nicotinamide, particles are assumed to be in smaller proportions with respect to theophylline, even when the total composition exceeds the combining ratio of 2:1. The discussion about the metastable melting point emerged in the diagram will be given in the next report.

Table III. Nicotinamide/Theophylline System

Theophylline (%)	Physical mixt. (°C) t.p.	Physical mixt. (°C) m.p.	Fused mixt. (°C) t.p.	Fused mixt. (°C) m.p,
0.0	129.5	131.0	129.6	131.2
5.0	126.5	129.5	125.5	129.0
10.0	126.5	139.0	125.5	134.0
14.6	126.5	146.5	125.5	146.0
20.0	126.5	156.5	125.5	153.5
30.3	126.5	166.5	126.0	165.5
35.0	126.5	169.2	126.0	168.5
40.0	126.5	178.0	147.5	173.0, 177.2
44.8	127.0→169.0[a]	194.0	168.0	189.2
50.0	170.0	198.0	169.2	198.8
55.0	170.0	210.0	169.5	209.2
60.0	170.5	216.5	170.0	217.0
64.8	170.5	225.0	169.5	224.5
70.0	170.5	229.5	169.5	231.0
74.8	170.5	238.0	176.5	237.0
80.0	171.5	242.5	194.5	243.5
90.0	221.5	257.0	231.5	259.0
100.0	268.0	271.5	269.0	271.8

a) arrow : Means that the sample partly liquefies at the former, resolidifies and again partly liquefies at the latter temperature.

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4) K. Sekiguchi : Yakugaku Zasshi **81**, 687 (1961).

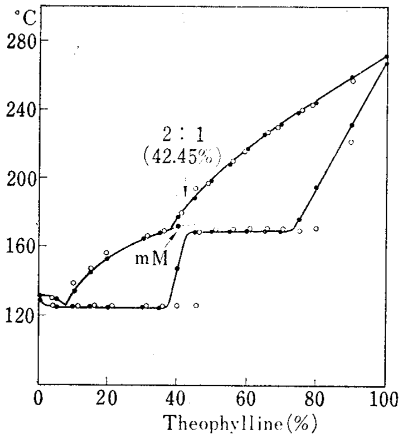

Fig. 4. Nicotinamide/Theophylline System

Closed circles: Fused mixtures
Open circles: Physical mixtures
mM Metastable melting point

Ammonium Benzoate/Benzoic Acid System (Fig. 5, Table IV)——As ammonium benzoate decomposes quickly on fusion, it was difficult to obtain reproducible results using fused mixtures. Analyses conducted with evaporated samples which were prepared from ethanol solutions gave a more distinct phase diagram of compound formation. However, the shape of the curves indicates that some decomposition still occurred during evaporation of the solvent. The physical mixtures gave more reproducible results and accordingly were the most suitable for this system. Due to the same reason as in the

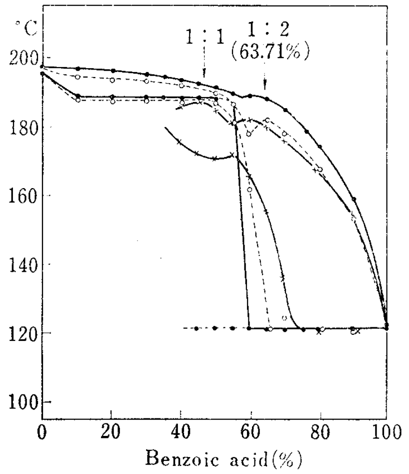

Fig. 5. Ammonium Benzoate/Benzoic Acid System

Closed circles: Physical mixtures
Open circles: Evaporated mixtures
Crosses: Fused mixtures

Table IV. Ammonium Benzoate/Benzoic Acid System

Benzoic acid (%)	Physical mixt. (°C)		Fused mixt. (°C)		Evaporated mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.	t.p.	m.p.
0.0	195.5	197.5				
10.0	189.5	197.0		188.5	188.5	194.5
20.0	188.8	196.0			187.5	194.0
30.0	188.8	195.0			187.5	193.5
35.6	188.8	194.5				
40.0	188.8	193.5	176.0	186.5	187.0	192.5
45.0	122.0→188.8	193.0	173.0	188.5		
50.0	122.0→188.5	191.5	171.0	185.0	188.0	190.0
54.8	122.0→187.5	189.5	172.0	181.5	182.0	187.5
60.0	122.0	189.5	165.5	182.5	162.0	178.5
65.0	122.0	188.5	155.0	180.5	122.0	182.5
70.0	122.0	185.0	136.0	176.5	125.0	178.5
75.6	121.5	179.0				
80.0	122.0	174.5	121.0	168.0	122.0	168.0
90.0	122.0	159.5	121.0	155.0	121.0	154.0
100.0	121.8	122.7				

former system, the double thaw point was observed. As the change of composition during the determination of thaw and melting point, could never be avoided, the combining ratio of the molecular compound could not be decided exactly, even with physical mixtures. However, if it is considered that decomposition of the benzoate makes the sample richer in benzoic acid, the ratio is supposed to be 1:2 rather than 1:1 with respect to the benzoate and benzoic acid.

Anthranilic Acid/Caffeine System (Fig. 6, Table V)——Although the jump in the solidus is small, it is evident that a one to one molecular compound with incongruent melting point is formed. This is supported by the presence of metastable eutectic points observed with simple physical mixtures. As clearly shown in the diagram, the metastable eutectic line passes through a point at which the extrapolation curves of both sides of liquidus intersect. The fact that the metastable eutectic liquefaction were observed in the physical mixture and not in the fused mixture is due apparently to the difference of molecular species of both mixtures. The fused sample is either a mixture of the acid and the molecular compound or a mixture of the molecular compound and caffeine, depending on the proportion of the components. On the other hand, the physical mixture does not contain the molecular compound at the initial state of measurement. The reaction between the solid acid and the solid caffeine is so slow that

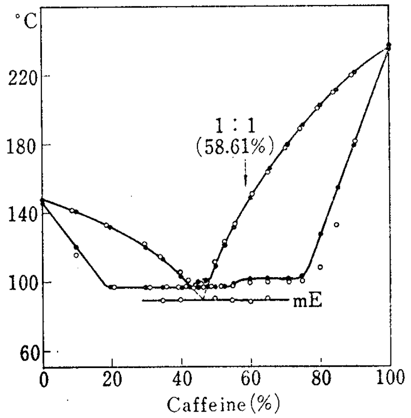

Fig. 6. Anthranilic Acid/Caffeine System

Closed circles: Fused mixtures
Open circles: Physical mixtures
mE Metastble eutectic point

Table V. Anthranilic Acid/Caffeine System

Caffeine (%)	Physical mixt. (°C)		Fused mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.
0.0	145.5	146.5		
10.0	116.0	141.0	119.5	140.5
20.0	96.5	132.5	96.5	132.0
30.0	96.5	122.5	96.0	120.5
35.0	89→96.5	114.0	95.5	113.0
40.0	89→96.5	105.0	96.0	102.5
42.3	96.5	99.8	96.0	98.5
45.0	96.5	98.5	96.0	99.5
47.6	96.5	99.5	96.3	101.0
49.9	90→96.5	111.0	96.5	108.0
52.5	96.5	122.5	97.0	121.0
55.0	89→96.5	131.0	98.0	131.0
60.0	88→99.2	147.5	100.5	147.5
65.0	ca. 90→99.5	163.0	101.5	164.5
70.8	99.2	177.0	101.5	178.5
75.0	99.5	190.0	102.5	190.5
80.0	108.0	201.0	127.0	201.5
84.7	132.0	208.5	154.0	210.0
90.0	181.0	220.5	178.5	220.5
100.0	235.5	237.0		

the sample has an opportunity to show the metastable eutectic liquefaction as if there was no reaction of compound formation between the components.

Benzoic Acid/7-(2-Hydroxyethyl)theophylline System (Fig. 7, Table VI)——The correct phase diagram is a peritectic type and the combining ratio of the compound is 1:1. With physical mixtures containing the xanthine less than 50% by weight, thawing was once observed at 94° or 95° which corresponds to the metastable eutectic point. In most cases, the liquid formed by the metastable eutectic reaction solidified quickly, and again liquefied at the constant temperature of 98° which is the eutectic point of the stable system. The liquidus curve, obtained by jointing the melting points of various physical

Table VI. Benzoic Acid/Hydroxyethyltheophylline System

HET (%)	Physical mixt. (°C)		Fused mixt. (°C)		Evaporated mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.	t.p.	m.p.
0.0	121.8	122.7	121.2	122.4		
5.1			97.8	120.4	104.0	119.8
10.0	99.0	119.0	98.0	118.5		
14.8			98.0	116.0	98.0	116.3
17.5	94.5, 98.3	115.3				
19.9	94.0→98.3	114.5	98.0	114.5		
21.9	94.0→98.2	113.2	98.0	113.5		
24.9			97.8	110.4	98.0	111.0
27.7	98.3	108.5				
29.3	95.0, 98.2	109.5				
30.0			98.0	107.3	98.0	106.9
35.0	95.0, 98.0	104.0	97.8	103.5	97.9	103.1
36.9	98.0	102.7		100.5		
37.6			97.7	100.0	98.0	100.3
39.9			97.8	98.6	98.0	99.0
40.3	94.0→98.0	103.5		100.7		
42.4			97.8	100.4	98.0	101.1
42.7	98.0	103.5	98.0	101.8		
44.8			94.0, 97.3	102.3	98.0	103.3
45.3	94.0→98.0	106.0				
47.3	94.0, 98.0	107.8	97.8	105.0		
47.7			97.8	103.8	98.0	104.5
49.9			97.7	105.2	98.0	105.8
50.0	98.0	109.0	97.8	105.5		
51.4	98.0	112.0				
52.3			97.8	106.3	98.0	106.9
54.5	98.5	116.0				
55.2			97.8	107.4	98.0	107.5
59.0	98.5	121.0				
59.9	98.0	120.5	98.0	110.0, 116.0		
60.0			99.5	108.6→116.5	98.2	117.2
62.7	98.5	124.0				
64.6			107.7	122.3	107.8	123.7
65.9	98.5→106.5	129.0				
69.2		130.5	106.5	128.8		
70.3			106.2	130.0	106.6	130.8
73.0	106.5	135.0	106.5	134.2		
74.6			106.1	136.8	106.6	137.2
77.7	106.5	144.0				
80.0	106.5	142.0	106.4	141.0		
80.1			106.4	142.4	106.6	142.3
84.7				146.9	106.6	146.5
88.4	107.0	150.5		150.0		
94.6			137.0	157.4	132.0	156.5
100.0	159.7	161.4			159.7	161.3

mixtures is not a smooth one. This is due to the fact that the heating rate (1°/min.) was too rapid for physical mixtures to attain true equilibria.

Data of suitable accuracy and reproducibility could be obtained with both fused and evaporated mixtures. Nearly all of these samples did not exhibit the metastable eutectic points. It is interesting, however, that only one fused mixture containing the xanthine 44.8% which is likely to have nearly the same composition as that of the metastable eutectic mixture, exhibited clearly the metastable eutectic point.

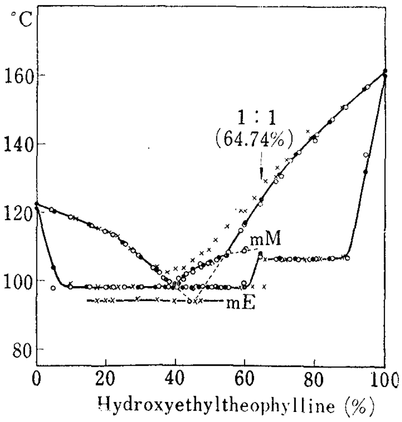

Fig. 7. Benzoic Acid/Hydroxyethyltheophylline System

Closed circles: Evaporated mixtures
Open circles: Fused mixtures
Crosses : Physical mixtures
mM Metastable melting point
mE Metastable eutectic point

***m*-Methoxybenzoic Acid/7-(2-Hydroxyethyl)theophylline System** (Fig. 8, Table VII)—— A false diagram which resembles to the simple eutectic type was obtained with physical mixtures. In this case, the higher melting points indicate the difficulty of attainment of true equilibria. Thawing could not be observed clearly as a point. This is due to the fact that the metastable and stable eutectic liquefaction were superimposed owing to the slowness of transformation of the metastable to the stable condition as compared with the rate of heating of the sample. On the other hand, thawing or melting was clearly observed as a definite point using the fused mixture. The solidus and liquidus indicate that a one to one compound with an incongruent melting point is formed between the acid and the xanthine. In the fused mixture, the transformation occurs rapidly owing to the uniform and intimate mixing of both components ; accordingly, the metastable and the stable eutectic points could be measured with sufficient accuracy.

Table VII. *m*-Methoxybenzoic Acid/Hydroxyethyltheophylline System

HET[a]	Physical mixt. (°C)		Fused mixt. (°C)	
(%)	t.p.	m.p.	t.p.	m.p.
0.0	104.0	106.5		
9.5	89~91	103.5	89.0	103.2
20.8	87~90	101.5	84.0→89.0	98.2
30.2	88~89	98.0	84.0→89.0	93.3
37.1	87~88.5	96~97	84.0→89.0	93.0
40.1	87~89	104.5	84.0→89.0	95.2
43.8	87.5~89	110	85.0→88.5	96.5
48.3	87~89	115~116	89.0	99.0, 106.2
55.3	88~89.5	121~122.5	85.0→92.0	117.0
59.7	88~89	128.5	98.0	123.0
64.4		132.5~133.5	98.0	128.8
70.2	90~91	140.0	98.0	135.3
80.5	89~91	148.0	102.5	145.5
90.0		154.0	132.0	153.4
100.0	158.5	160.5	158.5	160.6

[a] Commercially available HET was employed.

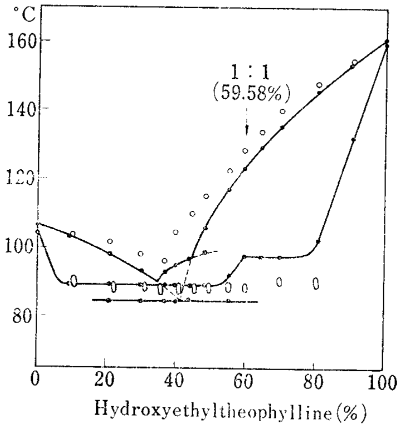

Fig. 8. *m*-Methoxybenzoic Acid/Hydroxyethyltheophylline System

Closed circles: Fused mixtures
Open circles: Physical mixtures
mM Metastable melting point
mE Metastable eutectic point

***p*-Nitroaniline/7-(2-Hydroxyethyl)theophylline System** (Fig. 9, Table Ⅷ)——Nearly the same phase diagram of peritectic type were obtained with both kinds of sample. Unlike the other systems, almost all of the samples of physical mixture showed distinctly the metastable eutectic liquefaction and solidified quickly again by further heating. Although in this case, the temperature difference is only three degrees, the discrimination between the eutectic and the peritectic point could be easily done, even with the simple physical mixture. This indicates that the reaction of compound formation takes place more rapidly in the physical mixture of this system than in the physical mixture of *m*-methoxybenzoic or benzoic acid and hydroxyethyltheophylline system.

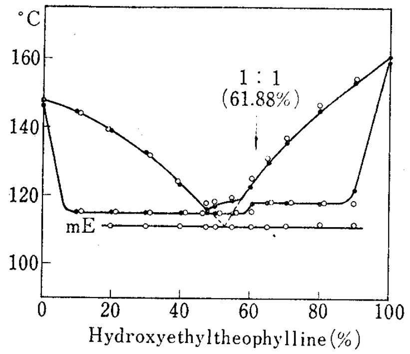

Fig. 9. *p*-Nitroaniline/Hydroxyethyltheophylline System

Closed circles: Fused mixtures
Open circles: Physical mixtures
mE Metastable eutectic point

TABLE Ⅷ. *p*-Nitroaniline/Hydroxyethyltheophylline System

HET	Physical mixt. (°C)		Fused mixt. (°C)	
(%)	t.p.	m.p.	t.p.	m.p.
0.0	146.2	147.8		
10.0	115.3	144.5	114.8	144.5
20.0	111.0→115.0	139.0	115.0	138.6
30.2	111.0→115.0	132.0	114.8	132.5
40.3	111.0→115.2	124.0	115.0	123.3
47.5	111.0→115.2	118.0	114.8	116.2
50.2	111.0→115.2	118.2	114.8	117.2
55.1	111.0→115.0	119.5	115.0	118.7
60.4	111.0→115.5	125.5	117.5	122.5
65.2	111.0→117.8	131.5	118.0	130.0
70.5	111.5→118.0	137.0	118.0	135.6
80.1	112.0→117.7	147.0	117.8	145.2
90.1	112.0→118.0	154.5	122.0	153.4
100.0	159.7	161.4		

Benzidine/7-(2-Hydroxyethyl)theophylline System (Fig. 10, Table IX)——The diagram obtained with physical mixtures resembles to that of the physical mixtures of *m*-methoxybenzoic acid and hydroxyethyltheophylline. The jump of solidus at the composition of compound formation could not be observed. This is due to the fact that the resolidification of the sample containing the xanthine more than 54.9% is delayed. In other words, the rate of the change from an unstable to a stable condition is slower than the heating rate. The melting point of the physical mixture could not be determined correctly because of the difficulty of the discrimination between primary crystals and suspending air bubbles.

When the measurement was done with the fused samples, thawing was observed at three temperatures. The lowest thaw point is due to the metastable eutectic point, which is often observed even with the samples containing the xanthine more than 54.9%. It is evident that such a partial liquefaction takes place by segregation of the xanthine. When these samples were prepared by keeping the supercooled melts at a temperature between 101° and 105°, the first and the second thaw points disappeared and only the third corresponding to the peritectic point was observed. The result of the fused mixture indicates that a molecular compound of 1:1 type is formed between the components.

Previously, the thermal analysis by the thaw-melt method was applied without regard to the possible occurrence of the double or triple thaw point. Although fusion

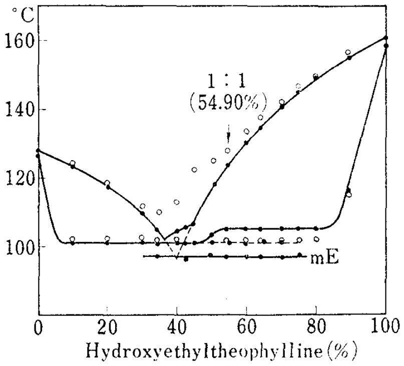

Fig. 10. Benzidine/Hydroxyethyltheophylline System

Closed circles: Fused mixtures
Open circles: Physical mixtures
mE Metastable eutectic point

Table IX. Benzidine/Hydroxyethyltheophylline System

HET[a] (%)	Physical mixt. (°C)		Fused mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.
0.0	126.5	128.5	126.5	128.1
10.0	102.0	124.5	101.0	123.5
20.0	102.5	118.5	101.2	117.5
30.0	101.7	111.5	101.0	109.5
34.4	102.0	110[b]	97.6, 100.5	105.5
40.1	102.0	113[b]	101.2	104.8
42.7			96.5, 100.8	105.9
45.1		122.5[b]	101.0	107.0
50.5		125[b]	98.0, 103.5	117.8
54.3	101.7	128[b]	97.0, 101.0, 105.7	123.5
59.9	101.8	133.5	97.0, 101.0, 105.0	130.4
63.8	101.9	138.0	98.0, 101.5, 105.0	134.5
70.3	102.0	142.0	97.0, 101.0, 105.5	140.5
75.1	102.0	146.5	98.0→104.5, 105.5	144.5
79.9	102.0	149.0	105.5	148.5
89.1	115.0	156.5	116.0	154.6
100.0	158.5	160.5	158.5	160.6

a) Commercially available HET was employed.
b) With these samples, accurate determination was rather difficult.

or some other procedure that keeps the mixture of components once in either a true or a supercooled liquid state is the necessary condition, it must be strongly emphasized that this is not the sufficient condition for preparing a correct sample. The discrimination of the three kinds of thawing which occur closely as in this system, would be difficult, if the original melting point apparatus is used, since uniform temperature distribution of the bath liquid can not be expected. On the other hand, the apparatus modified by the authors is very suitable for such a system.

Aminopyrine/Diallylbarbituric Acid System (Fig. 11 (A), 11 (B), Table X)——The phase diagram reported previously is the one obtained by combining two diagrams of physical mixtures.⁵⁾ The one is the system of aminopyrine and the molecular compound, which was isolated from the acetone solution of aminopyrine and diallylbarbituric acid. The other is the system of molecular compound and the barbiturate. As is seen in Fig. 11 (A), the shape of the curves is somewhat questionable from the standpoint of the Phase Rule. For example, a mixture represented by a point x, lying a little above the right horizontal part of solidus, must be in equilibrium between the solid and liquid phase, since the mixture is in the region divided with solidus and liquidus. However, the tie-line passing through the point, indicates that the mixture is composed of both solid (l) and solid (m). This contradiction is apparently derived from incompleteness of the analysis. Thawing at about 70° should be attributed to the metastable eutectic reaction. In order to get a true equilibrium diagram, the modified method was applied to this system. The diagram obtained by the authors with both physical and fused samples is a peritectic type. The first thaw point of 80° is clearly taken for the metastable eutectic point, since the extensions of both sides of liquidus meet together at a point of 80°. The fact that the metastable eutectic point was observed at 70° by

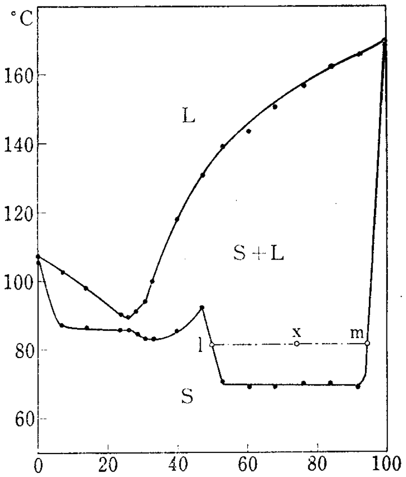

Fig. 11 (A). Reported Diagram of Aminopyrine/Diallylbarbituric Acid System

This diagram is a combination of aminopyrine/molecular compound, and molecular compound/diallylbarbituric acid system.

L : Liquid phase
S : Solid phase

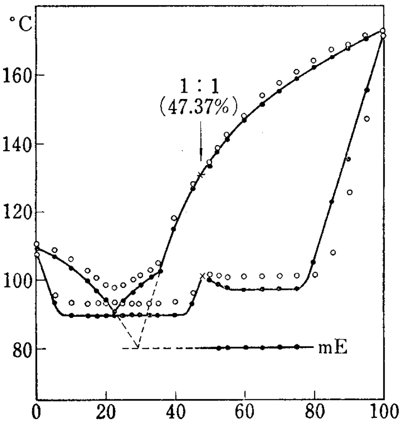

Fig. 11 (B). Aminopyrine/Diallylbarbituric Acid System

Closed circles: Fused mixtures
Open circles: Physical mixtures
Crosses: Isolated molecular compound
mE Metastable eutectic point

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5) P. Pfeiffer, E. Ochiai : J. prakt. Chem., **136**, 129 (1933); E. Ochiai, S. Kuroyanagi : Iyakuhin-ketsugo-kenkyuho (The Method of Investigation of the Combination of Medicinals), 108, (1941), Nanzando.

Pfeiffer and Ochiai is probably attributed to the presence of free aminopyrine and some decomposition products in the isolated molecular compound from acetone. It was reported that the compound used by these authors has a melting range of 92.5~131°, while the compound isolated by us from water has a thaw point of 99.5~100.2° and a melting point of 130.5°. *Anal.* Calcd. for $C_{23}H_{29}N_5$: C, 62.86; H, 6.65; N, 15.94. Found: C, 62.95; H, 6.66; N, 15.93.

When measurement was done with the physical mixtures containing the barbiturate and the compound from water, no sign of liquefaction due to the metastable eutectic reaction was observed.

Table X. Aminopyrine/Diallylbarbituric Acid System

Dial (%)	Physical mixt. (°C) t.p.	Physical mixt. (°C) m.p.	Fused mixt. (°C) t.p.	Fused mixt. (°C) m.p.
0.0	107.2	109.0	107.0	108.5
5.1	95.0	108.5	93.0	106.5
10.1	93.5	105.5	89.5	103.5
15.0	93.0	102.5	89.5	99.5
17.5	93.0	100.5	89.5	97.0
20.0	93.0	99.0	89.5	94.0
22.5	93.0	98.0	89.0	90.5
25.1	93.0	98.5	89.5	93.5
27.5	93.0	100.5	89.5	95.5
30.0	93.0	101.5	89.5	98.0
32.5	93.0	103.0	89.5	101.0
35.0	93.0	104.5	89.5	103.0
40.0	94.0	117.5	93.0	115.0
45.0	96.0	128.0	100.0	126.0
47.37[a]	99.5~100.2	130.5		
50.0	101.5	134.0	99.0	133.5
52.6	101.0	138.0	98.5	137.0
55.1	101.0	142.0	80.0→97.5	140.0
60.0	101.0	147.5	80.0→97.5	146.5
65.0	101.0	154.0	80.0→97.5	151.5
70.0	101.0	157.5	80.0→97.5	155.0
75.0	101.0	161.0	80.0→97.5	159.0
80.0	101.5	163.5	105.0	162.5
85.0	108.0	167.5	122.5	164.5
89.9	125.5	168.5	135.0	167.5
94.9	147.0	170.5	155.0	170.0
100.0	170.5	172.5	170.0	172.0

a) Molecular compound isolated from water solution.

***p*-Nitrophenol/7-(2-Hydroxyethyl)theophylline System** (Fig. 12, Table XI)——This is at present the first and the single system of the type of formation of compound with a congruent melting point that exhibits the metastable eutectic point. The assignment of the first thaw point of 57° to the metastable eutectic point was done by the fact that the two extrapolating curves of both sides of liquidus meet at a point of 57°. In addition, the existence of one metastable melting point of 72° which lies on the right extrapolating curve supports the validity of the assignment. The double thaw point observed with the fused sample containing the xanthine 52.8% is apparently due to the segregation of the component.

Hydroquinone/7-(2-Hydroxyethyl)theophylline System (Fig. 13, Table XII)——A molecular compound with congruent melting point is formed. The maximum in the liquidus and the jump in the solidus of the fused mixture indicate that the compound has a stoichiometric ratio of 3:2 with respect to the phenol and the xanthine. The liquidus curves of the physical mixture are equal to those of the fused mixture. On the other hand, the

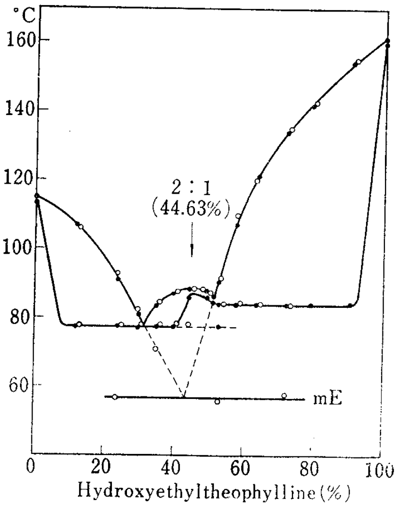

Fig. 12. *p*-Nitrophenol/Hydroxyethyltheophylline System

Closed circles: Fused mixtures
Open circles: Physical mixtures
mE Metastable eutectic point

Table XI. *p*-Nitrophenol/Hydroxyethyltheophylline System

HET (%)	Physical mixt. (°C)		Fused mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.
0.0	113.0	114.5		
11.9	78.0	107.0	77.5	107.0
23.8	57.0→78.0	93.0	77.5	91.0
29.8	78.0	82.5	77.0	81.0
35.3	78.0	72.0, 84.0	77.5	83.5
40.0	78.5	87.0	77.5	87.3
44.6	78.0	88.5	86.0	88.5
49.6		88.5	86.0	88.0
51.3		86.5	84.5	86.5
52.8	56.0, 84.5	91.0	77.5, 84.0	90.5
57.9	84.5	110.0	84.0	107.0
63.8	84.5	121.0	84.0	121.5
72.2	58.0→84.0	134.0	84.0	134.0
79.6		142.0	84.0	142.0
90.4		154.0	104.5	154.0
100.0	159.7	161.4		

solidus curves of both kinds of sample differ entirely. When fused mixture were used, the biginning of liquefaction was observed at 125° or 121°. These points are easily assigned to the first and the second eutectic point of the stable equilibrium system. With physical mixtures, thawing were observed at 121° and 113°. These findings are very interesting but is difficult to explain. Neither of them can be attributed to the metastable eutectic reaction between the two components, since the extraporations of

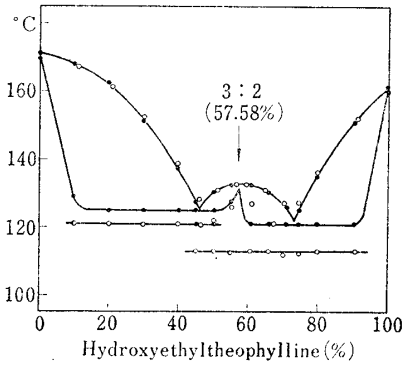

Fig. 13. Hydroquinone/Hydroxyethyltheophylline System

Closed circles: Fused mixtures
Open circles: Physical mixtures

both sides of liquidus meet at a point much lower than the two points. It is supposed that these points may probably have relation to the phase reactions in which the polymorphic form of hydroquinone or the metastable molecular compound acts as one component. Another methods of investigation, such as the differential thermal analysis and the X-ray diffraction method should be applied in order to find a solution of this problem.

Table XII. Hydroquinone/Hydroxyethyltheophylline System

HET (%)	Physical mixt. (°C)		Fused mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.
0.0	169.5	171.0		
10.0	121.0	168.0	129.0	168.3
20.0	121.0	162.0	125.0	162.5
30.0	121.0	152.5	125.0	151.0
40.1	121.0	139.0	125.0	137.5
44.9	113.0→121.0	128.0	121.0→125.0	127.5
50.3	113.0→122.0	130.8	121.0→125.0	130.5
55.3	112.5→126.0	132.5	127.5	132.5
60.8	113.0→127.0	132.5	121.0	132.5
65.8	113.0→121.0	130.5	121.0	130.5
70.7	112.0	126.0	121.0	126.0
74.5	112.4	127.5	121.0	125.0
79.7	112.0	136.5	121.0	135.0
90.4	113.0	151.5	121.0	151.0
100.0	159.7	161.4		

Conclusion

Twelve kinds of binary system, method of sample preparation, their applicability and the type of diagram are listed in Table XIII. As is seen in the phase diagrams of these systems, the thermal analysis by the thaw-melt method is not so simple as it was considered previously. However, the complexity of the result is not the factor that makes the method unreliable, but on the contrary, is the very evidence to prove both the applicability and the reliability of the thaw-melt method. The fact that not a few

Table XIII. Summary of Results and Applicability of Methods of Sample Preparation

System	Type	Applicability		
		Phys. mixt.	Fused mixt.	Evap. mixt.
Aminopyrine/HET	eutectic	applicable	applicable	
o-Nitroaniline/PABA	〃	〃	〃	applicable
Nicotinamide/theophylline	peritectic (2:1)	〃	〃	
Ammonium benzoate/ benzoic acid	compd. with congruent m.p. (2:1)	〃	questionable	applicable with care
Anthranilic acid/caffeine	peritectic (1:1)	〃	applicable	
Benzoic acid/HET	〃	applicable with care	〃	applicable
m-Methoxybenzoic acid/ HET	〃	inapplicable	〃	
p-Nitroaniline/HET	〃	applicable	〃	
Benzidine/HET	〃	inapplicable	〃	
Aminopyrine/Dial[a]	〃	applicable	〃	
p-Nitrophenol/HET	compd. with congruent m.p. (1:2)	〃	〃	
Hydroquinone/HET	compd. with congruent m.p.	〃	〃	

a) Dial : Diallylbarbituric acid.

false or incomplete diagrams were reported in literatures is clearly attributed to the uncautious preparation of samples, the use of an incomplete melting point apparatus and the erroneous interpretation of the results.

In most cases, measurement with physical mixtures should be applied as a preliminary experiment. However, as the metastable eutectic point is usually observed with the physical mixture, it is useful for the detection of compound formation between components. If the components are stable to heat, the true equilibrium diagram is obtained with both fused and evaporated mixtures. In this connection, it should be noted that even with the sample prepared by fusion or evaporation of the solvent, the attainment of a stable equilibrium is not necessarily permitted. For this reason, metastable liquefaction can take place, if the metastable solidification or segregation occurs during both process of sample preparation. In order to obtain a stable sample, solidification induced by heating the supercooled liquid was proved to be very effective, especially for those system that are apt to keep vitreous conditions.

It seems strange for the authors that the metastable eutectic point was scarcely reported in the past works by the thaw-melt method. Since the accurate measurement is difficult with the melting point apparatus of Rheinboldt, the metastable eutectic and the true eutectic point would not be measured as two definite points. The possibility of mistaking the metastable eutectic point for a stable one, or obtaining scattered values of thaw point may interprete the low precision of the method believed previously. However, if the analysis is done with the notices mentioned above, the dependability of the thaw-melt method would be much improved.

There are three methods of thermal analysis, the cooling and heating curve method, the thaw-melt method and the differential method. Among the three, the thaw-melt method is thought to be the simplest, and has the widest applicability for the two-component condensed system of organic materials. The suitable temperature range of the method is from about 30° to about 300°. The accuracy is also superior to the other two methods, because stirring of the sample for attainment of stable equilibrium is easier. Although the solubility or distribution analysis, the X-ray diffraction method, and the spectroscopic analysis are also important means of detecting the interaction between substances, they need special equipments and are not so simple as the thermal analysis. When they are applied to solid mixtures, the problem of sample preparation is as important as in the thermal analysis.

In conclusion, the thaw-melt method must be much more highly evaluated, if it is correctly applied.

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Summary

Three methods of sample preparation for the thermal analysis by the thaw-melt method were proposed. The heating procedure for solidification of the melt was proved to be very effective, especially for those samples that are apt to take vitreous states after fusion. Tests concerning both reliability and applicability the modified thaw-melt method were carried out on twelve kinds of organic binary system to which the application of the original method of Rheinboldt is thought to be difficult. The results indicate that the modified method is more accurate and reliable than the original one. The meaning and the use of the thaw point due to the metastable eutectic point in the system of compound formation were discussed.

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