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A Study of Intermolecular Compounds*

By Helmut M. Haendler with L. Wait Rising†

The residual affinity possessed by various organic compounds, whatever its origin, is a property somewhat difficult, if not impossible, to measure quantitatively. To attempt the prediction of the possibility of formation of an intermolecular compound on the basis of present evidence is useless. In most cases the procedure is somewhat empirical; solutions of the compounds are mixed and an effort made to isolate any crystalline products. The application of melting point curves, however, simplifies the method considerably, and with the collection of sufficient data the prediction as to the possibility of forming intermolecular compounds can be expected to become more definitive.

Knowledge of this sort would be particularly helpful in the field of pharmaceutical chemistry, where the preparation and chemotherapy of new compounds is of great value. Consequently, it was decided to study certain pharmaceutical combinations to determine, if possible, what compounds in particular exhibit a tendency to combine in this fashion.

The "thaw-melting point" curve (1) offers the quickest and most reliable method for this type of study. It is possible to tell directly whether a compound is formed or whether the two components merely formed a eutectic mixture. As the temperature of a mechanical mixture of the two components is raised, a point is reached where the material appears to soften or "thaw." Further heating causes complete melting, and the temperatures at which these two phenomena occur are plotted against mol percentages of various mixtures of the two substances.

EXPERIMENTAL

The combinations of acetanilid, in particular, and of several other pharmaceuticals were studied. Varying amounts of the two U. S. P. chemicals of each system, dried in a vacuum desiccator, were weighed into small test-tubes, melted in an oil bath, allowed to solidify, pulverized and the melting points taken. An aluminum block, drilled for a thermometer and a capillary tube, heated by a micro burner, and equipped with a viewing microscope, was used for the measurements.

In general, one of two types of curves is obtained. In the case of a eutectic mixture, the curve is represented as in (*a*) of Fig. 1; in the event that a compound is formed, the shape assumed is that of (*b*). The point at which the thawing curve, which is the lower of the two, intersects the melting curve represents the eutectic point in the first case (*a*); the three intersections represent the two eutectics and the melting point of the compound formed, if such is the case, as in (*b*).

None of the systems observed have given evidence of compound formation. The observational data for each system studied are given in Tables I to XII. In these tables, the mol percentage of one component is given, followed by the observed thawing temperature and the final observed melting point. From graphical consideration of these data, the

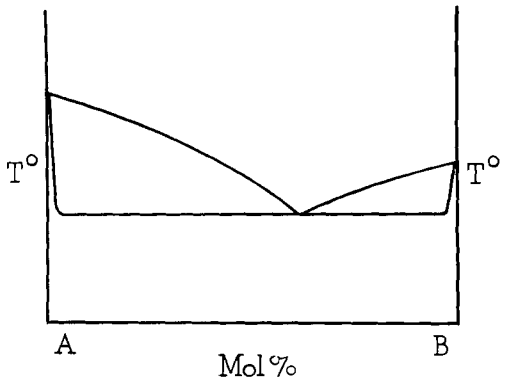

Fig. 1 (*a*).—Thaw-Melting Point Curve for a Eutectic.

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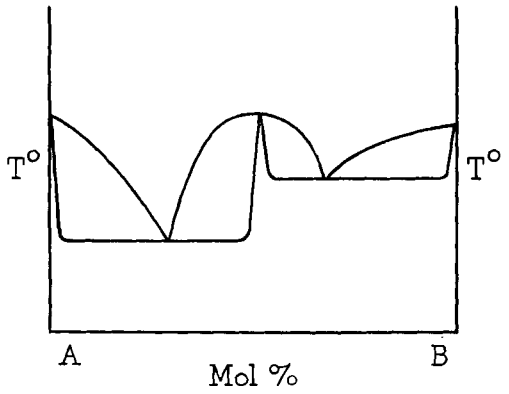

Fig. 1 (*b*).—Thaw-Melting Point Curve for a Compound.

composition and melting point of the eutectics were obtained.

Table I.—Acetanilid-Antipyrine

No compound; eutectic at 52% acetanilid with m. p. of 56° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	111	112
11.44	68	106.5
17.30	56	103
30.65	56	90
40.07	56	79
50.66	56	60.5
54.32	55	63
63.74	56	79
75.88	56	93
83.15	56	101
93.53	68	111
100.00	114	115

Table II.—Acetanilid-Mandelic Acid

No compound; eutectic at 55% acetanilid with m. p. of 58.5° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	117	119
10.04	68	112.5
19.64	58.5	107
29.46	59	99.5
40.31	58.5	86.5
50.50	58	72.5
59.20	58	71.5
71.09	58.5	91.5
79.59	59	101
90.60	58.5	109
100.00	114	115

Table III.—Acetanilid-Betanaphthol

No compound; eutectic at 52.5% acetanilid with m. p. of 59° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	121.5	122.5
9.98	60.5	115
19.94	59	107
30.57	59.5	93.5
39.93	59	80
51.18	59	61.5
60.70	59	76
73.91	59	95.5
81.24	59	101.5
91.78	60	110
100.00	114	115

Table IV.—Acetanilid-Phenacetin

No compound; eutectic at 66% acetanilid with m. p. of 83° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	136	137
10.02	83	130
20.09	83	124.5
30.11	84	118
39.91	84	112.5
49.82	83	105
58.94	83	96.5
69.81	83	91
78.76	84	98
90.23	85	107
100.00	114	115

Table V.—Acetanilid-Pyramidon

No compound; eutectic at 55% acetanilid with m. p. of 58° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	106	107
14.45	60	100
29.65	59	92
39.45	58.5	83
50.33	58.5	67.5
58.57	58	71
69.56	58	91
81.02	58	104
88.94	58	109.5
100.00	114	115

Table VI.—Acetanilid-Sulfonal

No compound; eutectic at 64% acetanilid with m. p. of 90° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	125	126
14.57	91	120.5
19.64	89.5	119
28.60	90	114.5
39.18	89.5	110
49.35	90	103.5
59.28	90	96
70.32	90.5	96
78.38	89.5	103
89.54	91.5	109.5
100.00	114	115

Table VII.—Acetanilid-Trional

No compound; eutectic at 33% acetanilid with m. p. of 61° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	74.5	75.5
9.79	61.5	71.5
20.45	61	67
29.27	61	63.5
39.45	60	71
49.24	61	82
60.76	61.5	92
69.86	61	99
78.53	61	103
85.39	61	107
100.00	114	115

Table VIII.—Antipyrine-Phenacetin

No compound; eutectic at 62% antipyrine with m. p. of 76° C.

Mol % Antipyrine	Thaw Point, ° C.	Melting Point, ° C.
0.00	136	137
8.12	78	131.5
20.87	76.5	122.5
25.91	76	120
39.73	76	105
46.86	76	97
59.03	76.5	81
72.55	76	91
78.30	76	97
90.05	76	106.5
100.00	111	112

Table IX.—Mandelic Acid-Betanaphthol

No compound; eutectic at 53% mandelic acid with m. p. of 88.5° C.

Mol % Mandelic Acid	Thaw Point, ° C.	Melting Point, ° C.
0.00	121.5	122.5
9.90	91	117
19.65	90	111.5
30.35	88.5	105.5
39.94	89	99.5
50.49	89	91
59.91	88	96.5
71.26	88	105
79.64	88	109.5
90.78	90	115
100.00	117	119

Table X.—Mandelic Acid-Phenacetin

No compound; eutectic at 56.5% mandelic acid with m. p. 79° C.

Mol % Mandelic Acid	Thaw Point, ° C.	Melting Point ° C.
0.00	136	137
9.96	79	130
19.92	79	123
30.00	79	115
39.06	79	106
49.35	79	92
60.01	79	84.5
70.86	79	97.5
80.30	78.5	106
87.05	78.5	112
100.0	117	119

Table XI.—Mandelic Acid-Sulfonal

No compound; eutectic at 57% mandelic acid with m. p. of 86° C.

Mol % Mandelic Acid	Thaw Point, ° C.	Melting Point, ° C.
0.00	125	126
9.97	88.5	122
19.72	86	118.5
30.11	86	112
39.74	86	105
50.14	86	96
59.78	86	90.5
69.89	86	98.5
78.36	86.5	105.5
90.53	87.5	113.5
100.00	117	119

Table XII.—Betanaphthol-Phenacetin

No compound; eutectic at 61% betanaphthol with m. p. of 70° C.

Mol % Betanaphthol	Thaw Point, ° C.	Melting Point, ° C.
0.00	136	137
10.09	71	131
19.78	70	124
29.79	70	114
40.26	70	103
50.05	70	91
60.48	70	72
70.15	70	89
79.61	70	103
89.50	72	114
100.00	121.5	122.5

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Report on the Vanadium Oxytrichloride Colorimetric Method for the Determination of Capsaicin in Capsicum

By Alice Hayden and C. B. Jordan**

In July 1933 L. F. Tice (1) published in the *American Journal of Pharmacy* an article on "A Simplified and More Efficient Method for the Extraction of Capsaicin Together with the Colorimetric Method for Its Quantitative Determination in Capsicum Fruit and Oleoresin." The colorimetric assay as described in the above publication was later modified as follows (2):

ASSAY PROPER

"The sample to be assayed would be representative of the whole lot of capsicum and not having an abnormal ratio of any one of the fruit parts. It should be powdered and dried in a desiccator to remove moisture.

"Shake 1 Gm. of the dried and powdered capsicum with 50 cc. of dry acetone in a dry glass-stoppered flask, allow the mixture to stand with occasional agitation for from one-half to one hour and filter.

"Add from 0.2 to 0.3 per cent of dried, non-pungent paprika to about 100 cc. of dried acetone, in another flask, shake it well and filter. Then adjust the color to match that of the acetone extract of the capsicum already prepared, diluting it with sufficient acetone. Use this paprika extract to prepare the standard, by dissolving 7 mg. of capsaicin, accurately weighed, in 50 cc. of the colored acetone.

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