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Decomposition of Benzoic Acid Derivatives in Solid State

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Abstract □ A series of solid, substituted benzoic acids (p-XC_6H_4COOH), which decompose into a liquid (XC_6H_5) and carbon dioxide, were studied. For decomposition to take place below the melting point, the σ value must be less than -0.35; the decomposition then follows Bawn-type kinetics. Neither solid (k_s) nor liquid (k_l) decomposition constants show isokinetic relations at their melting points. However, log k_s is proportional to $1/T_m$, where T_m is the absolute melting temperature, much as was found for vitamin A esters.

Keyphrases □ Decomposition rates of solid compounds—p-substituted benzoic acid derivatives □ Solid-state decomposition—p-substituted benzoic acid derivatives □ Benzoic acid derivatives—solid-state decomposition, rate constants

Many studies have been conducted related to decomposition rates of solid compounds. A great majority of these have concerned inorganic salt decompositions [carbonates (1–9), oxalates (10–17), and permanganates (18–21)], and several general patterns have been proposed as primary mechanisms in the decompositions; most notable of these are the Prout–Tompkins model (21) and the power laws (22–25). Some studies have been reported in the pharmaceutical literature, notably the ones by Leeson and Mattocks (26), by Kornblum and Sciarrone (27), by Garrett *et al.* (28), and by Guillory and Higuchi (29).

Attempts to correlate decompositions in the solid state with usual substituent parameters in homologous series have not met with success. Dorko *et al.* (30) found no such correlation in a study of substituted tosylates, and Meyers *et al.* (31) found that in the reaction R′COONa + R″COOH → R′COOH + R″COONa, substituent σ values were the governing parameters in that σ' would have to be larger than σ'' for the reaction to occur; this, in essence, is paramount to the time-tested rule that "the stronger acid drives out the weaker acid." The latter two studies aimed at the importance of the chemical factors involved in reactivity in the solid state; whereas, in general, physical parameters (active sites, dislocations, *etc.*) have been the bases for proposed hypotheses.

The pharmaceutical literature has partially touched upon the importance of liquid layers as mediators of the actual decompositions (26, 29), whereas the remaining great majority of the cases cited dealt with reactions of the type solid → solid + gas. The work dealing with aspirin anhydride (28), as well as the work

Table I—Data Relating to Physical and Chemical Characteristics of *para*-Substituted Benzoic Acids, XC_6H_4COOH

X	Molecular Weight	Density, g./cm.[3]	Crystal System	σ Value	Reactivity	Melting Point
—	122.12	1.2659	Monoclinic	.0	−	122°
NH_2	137.13	—	Monoclinic	−0.66	+	188°
CH_3NH	151.15	—	—	−0.59	+	163°
$(CH_3)_2NH$	165.17	—	—	−0.83	+	241°
OH	138.12	1.443	Monoclinic	−0.36	+	215°
Cl	156.57	1.541	Triclinic	+0.23	−	243°
NO_2	167.12	1.550	Monoclinic	+0.78	− (secondary reactions)	242°
F	140.11	1.479	Monoclinic	+0.06	−	182°
OCH_3	152.14	1.385	Monoclinic	−0.27	−	184°
OC_2H_5	166.17	—	—	−0.25	−	195°
OC_4H_9	194.22	—	—	−0.32	−	148°
CH_3	136.14	—	—	−0.17	−	180°

dealing with vitamin A esters (29), pointed to the importance of liquid phases in pharmaceutically important substances. In the study reported here, reactions of the type solid → liquid + gas were selected. For instance, most acetylated compounds forming acetic acid would fall in such a category and, therefore, an insight into such a class of reactions would be valuable.

It is obvious from literature reports that crystal size, polymorphic forms, and lattice perfection are parameters of importance; in studying a series of compounds to elucidate chemical parameters, it is of importance to select a series that minimizes these nonchemical factors. For this reason, this report deals with substituted benzoic acids. These all crystallize in identical or very closely related morphological systems; particulars are given in Table I. All the reactive acids in the series decompose to a liquid and a gas; *e.g.*, *p*-aminobenzoic acid decomposes to carbon dioxide and aniline.

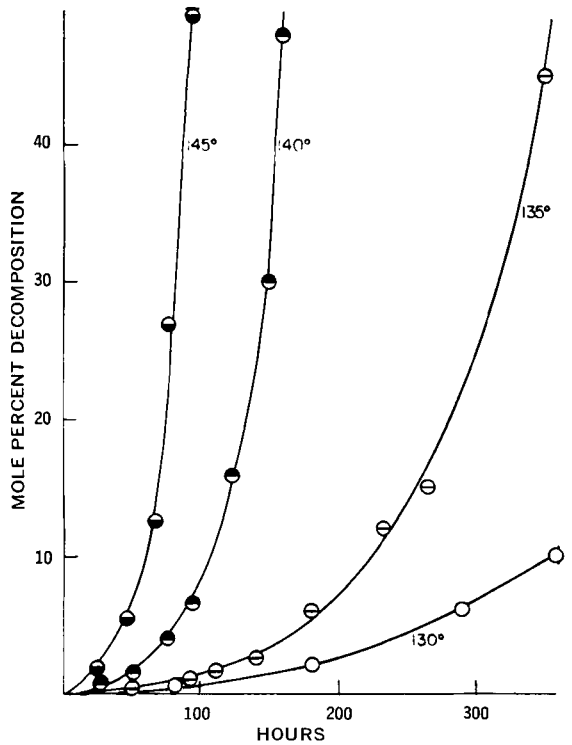

Figure 1—*Decomposition curves of* p-*aminobenzoic acid.*

EXPERIMENTAL AND RESULTS

All raw materials were used as received from the supplier[1]. The surface areas calculated from particle-size distribution of the compounds were close; *e.g.*, *p*-aminobenzoic, *p*-hydroxybenzoic, *p*-methylaminobenzoic, and *p*-dimethylaminobenzoic acids had surface areas of 0.55, 0.42, 0.36, and 0.41 m.²/g., respectively.

Conventional apparatus, such as those described by Prout and Herley (33) and Galwey (19), as well as thermal methods cannot be used in the series described here because of the sublimation tendency. For this reason, decompositions were conducted in the following manner: 10/30 joints were fused onto both ends of 8-mm. i.d. (10-mm. o.d.) breakseal tubes[2]. Then 250 mg. of the solid to be tested was weighed into the back end of the tube; this was narrowed down over a 2-cm. length and was then attached to a high vacuum rack and degassed thoroughly at less than 0.5 mTorr pressure. The back end of the breakseal tube was then sealed off at the constriction, leaving the solid in the hermetically sealed vacuum of the back end

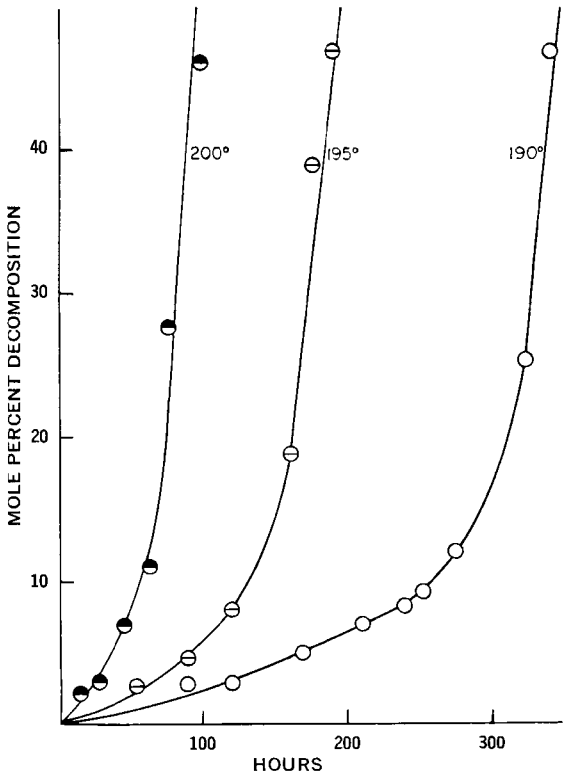

Figure 2—*Decomposition curves of* p-*dimethylaminobenzoic acid.*

[1] Aldrich Chemical Co., Inc., Milwaukee, WI 53233

[2] Catalog No. 6001, Eck and Krebs Scientific Laboratory Glass Apparatus Inc., Long Island City, NY 11101

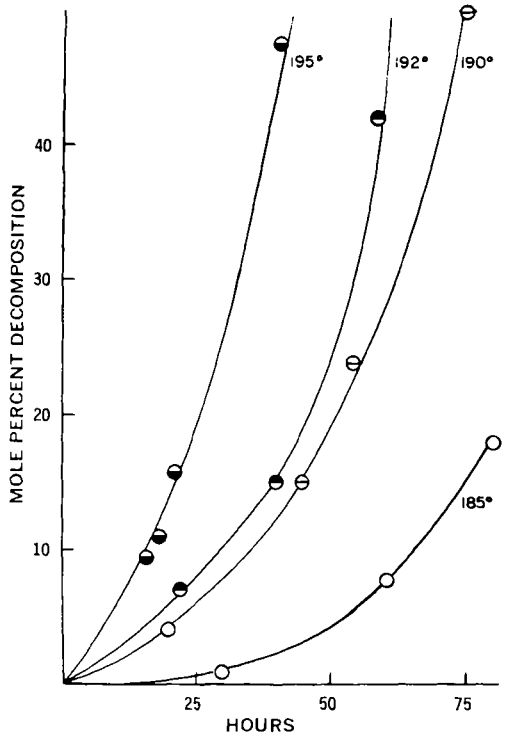

Figure 3—*Decomposition curves of* p-*hydroxybenzoic acid.*

of the tube. This was then exposed to the desired temperature for the desired length of time in thermostatically controlled ovens[3]; these ovens maintain a temperature within ±0.5°. A piece of iron metal was placed in the front (open) end of the breakseal tube, which was then attached at the 10/30 joint to the vacuum rack, and the system was thoroughly degassed. By manipulating a magnet externally to the tube, the capillary of the breakseal tube was broken and the evolved gas was allowed to escape into a space of known volume.

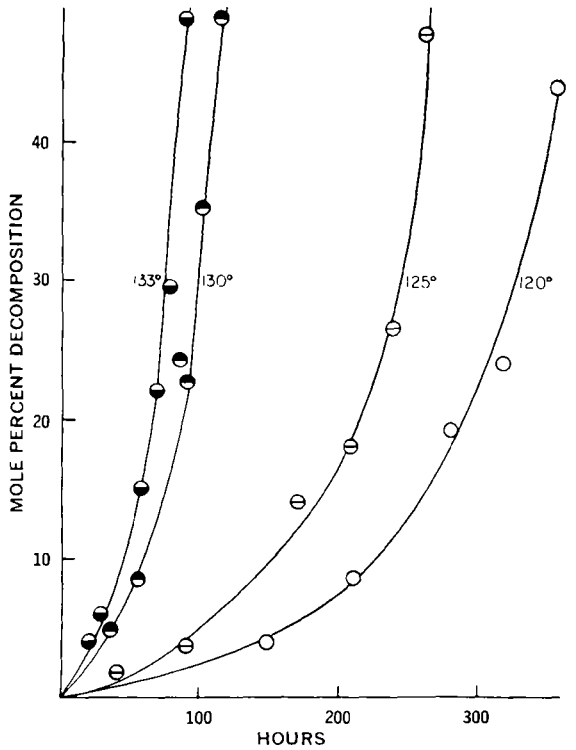

Figure 4—*Decomposition curves of* p-*methylaminobenzoic acid.*

[3] Model 1302, Hotpack Corp., Philadelphia, PA 19135

Table II—Decomposition Rate Constants for Gas Phase Decomposition at Saturation Pressure of Some Substituted Benzoic Acids

Compound	Temperature	Rate Constant, hr.$^{-1}$
p-Aminobenzoic acid	145°	0.017
p-Hydroxybenzoic acid	185°	0.007
p-Methylaminobenzoic acid	133°	0.018
p-Dimethylaminobenzoic acid	195°	0.022

Subsequent to the experiment and disassembly, the volume of the breakseal tube was determined with water calibration; these volumes were always between 7 and 8 cm.^{3}. The pressure was measured with the standard manometer of the rack or with a high compression ratio McLeod gauge (34), and the number of moles of gas evolved was calculated by the gas law. A cold finger in the setup was cooled with liquid nitrogen; the manometric pressure would return to zero, indicating that only carbon dioxide (not oxygen, nitrogen, nitric oxide, or carbon monoxide) was evolved. The decomposition was checked at one temperature for each compound *via* titration of the remaining solid; the number of moles of carbon dioxide evolved, found by gas analysis, was found to correspond to loss in titer. Several experiments were conducted for each compound where a removable cold finger was cooled with liquid nitrogen after gas analysis. Cooling was continued for 5–10 hr., and the condensate (after evaporation of carbon dioxide), usually only a drop, was checked spectrophotometrically. In each case, the spectrum matched the spectrum of the expected decomposition product.

Typical decomposition curves are shown in Figs. 1–4. The accuracy of the points, as determined by triplicate determinations, in several instances, is ±2%. Of the 12 compounds tested (Table I), only four were reactive.

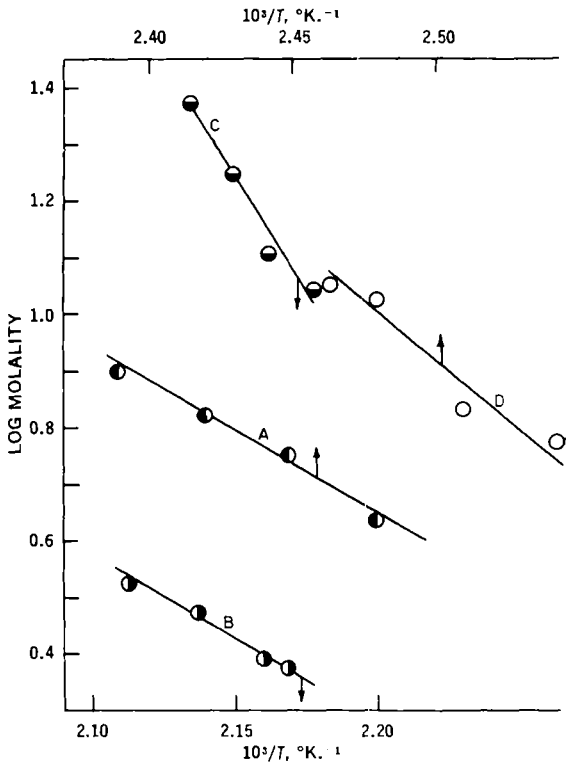

Figure 5—*Solubility as a function of temperature of a series of* para-*substituted benzoic acids: Key: A (◐), aminobenzoic acid; B (◑), dimethylaminobenzoic acid; C (◒), hydroxybenzoic acid; and D (○), methylaminobenzoic acid. Arrows denote scale to which line refers.*

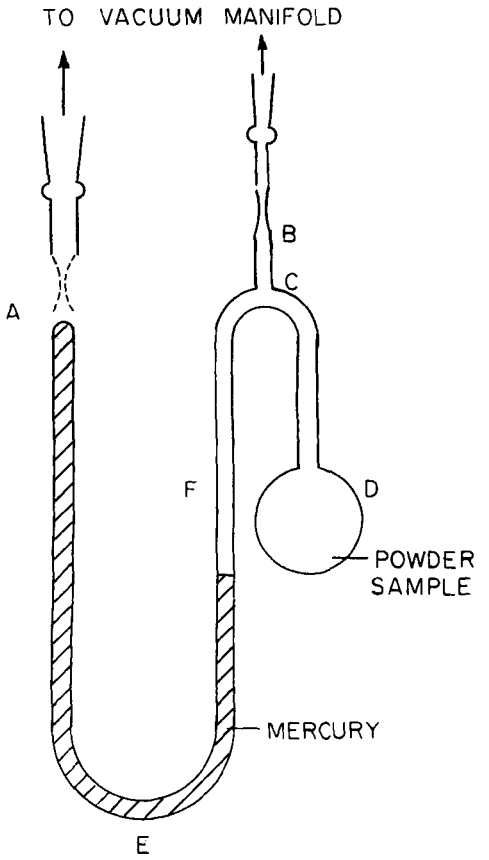

Figure 6—*Apparatus for determining vapor pressure of* para-*substituted benzoic acids. The manometer AEF is made by placing mercury in the U-tube AEF, attaching both 10/30 joints to a vacuum rack, evacuating, and sealing off at A as shown. D is the sample bulb.*

At longer decomposition times, the tubes were observed hourly and the point at which the sample was completely liquid was observed. The extent of decomposition was determined experimentally as already described, allowing calculation of the solubility of the substituted benzoic acid in its degradation product (substituted benzene). In this case, the accuracy was dependent on the fact that complete liquefaction was determined timewise, with an accuracy of 1 hr. From a knowledge of the slope of the decomposition–time curve, the accuracy can be determined. For example, the decomposition of *p*-aminobenzoic acid at 145° caused liquefaction at a time higher than 99 hr. and less than 100 hr., at which times the mole percents decomposed were, respectively, 56.2 and 57.2. The solubilities in moles of *p*-aminobenzoic acid per mole of aniline corresponding to these figures were 43.8/56.2 = 0.779 and 42.8/57.2 = 0.748; these two figures differ by 4%, so the accuracy of the solubility is of this order of magnitude. Solubilities of four acids in their decomposition products are shown in Fig. 5.

It shall become apparent in the following discussion that the possibility of gas phase-mediated decomposition cannot be discarded *a priori* as a route of decomposition. To test the extent to which decomposition in the gas phase plays a role, gas phase decompositions were conducted. Samples of the acids in vapor phase at saturation pressure were prepared in breakseal bulbs[4] by using essentially the same procedure as already described. By knowledge of the bulk volume and the saturated vapor pressure, exactly the amount of solid required to fill the space in the bulb was introduced into it. Since these amounts are small, the acid was introduced as a 1% methanol solution; the methanol was evaporated by degassing at 25° for 15 min. Model experiments showed that this length of time sufficed to evaporate the methanol and yet was not sufficient for substantial amounts of the acid to sublime off (as determined by titration). The bulb was then placed at the higher temperatures (allowing evaporation of the solid into the now closed bulb), and decomposition was determined after suitable lengths of time. The results are shown in Table II. The preceding experiment requires knowledge of the saturation vapor pressure of the acids at various temperatures. This information was obtained by attaching a sidearm with a 10/30 joint and a small sample bulb to a closed manometer, as shown in Fig. 6. The acid was placed in the sample bulb, and the tube leading to the 10/30 joint was narrowed down over a 2-cm. area. The assembly was then attached at the joint to the vacuum rack, degassed, and sealed off under vacuum. The entire assembly was submerged in mineral oil, which was then heated to various temperatures; the pressure differences were recorded by means of a precision cathetometer[5]. The difference in mercury height was then converted to difference at 25° by adjustment according to the density of mercury at the two temperatures (35). The vapor pressures adhere to a Clausius–Clapeyron relationship, within experimental error as shown in Fig. 7. The data imply that there is no phase transition in the studied temperature interval.

Table III—Liquid Decomposition Rate Constant, k_l

Compound	Temperature	k_l, hr.$^{-1}$ From Data beyond Liquefaction Point (±20%)	k_l, hr.$^{-1}$ From α (Eq. 3)
p-Aminobenzoic acid	135°	0.030	0.023
	140°	0.039	0.050
	145°	0.064	0.076
p-Hydroxybenzoic acid	185°	0.011	0.016
	190°	0.025	0.025
	192°	0.022	0.020
	195°	0.037	0.033

It has been pointed out that there is a particular point of complete liquefaction; beyond this point the substituted benzoic acid

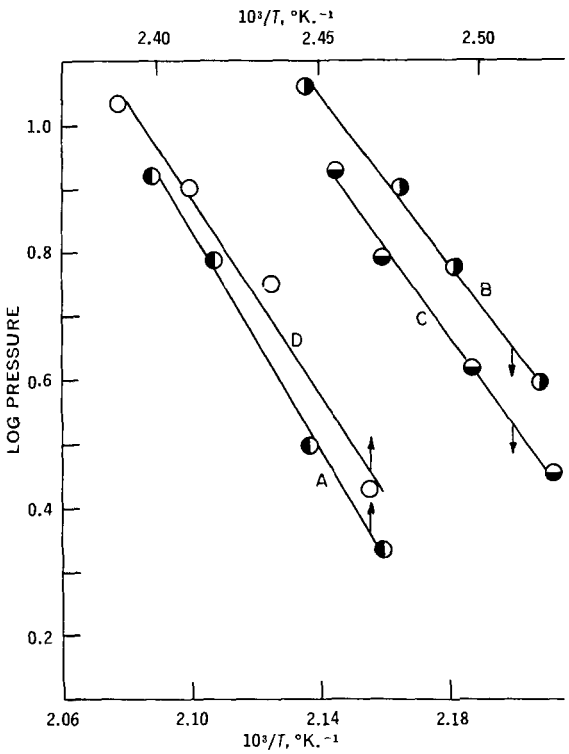

Figure 7—*Vapor pressure of a series of* para-*substituted benzoic acids (Torr). Key: A (◐), aminobenzoic acid; B (◑), dimethylaminobenzoic acid; C (◒), hydroxybenzoic acid; and D (○), methylaminobenzoic acid. Arrows denote scale to which line refers.*

[4] Catalog No. 6010, Eck and Krebs Scientific Laboratory Glass Apparatus Inc., Long Island City, NY 11101

[5] Gaertner Scientific Corp., Chicago, IL 60614, model M-911.

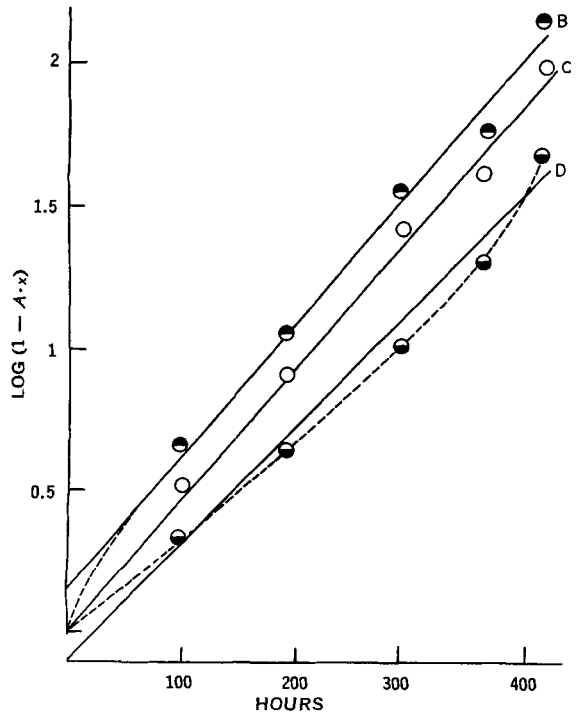

Figure 8—*Plot of log [1 — A·x] for varying values of A. Key: B (◓), A = 200; C (○), A = 426.5; and D (◒), A = 600. The compound is p-aminobenzoic acid and the temperature is 130°.*

remaining intact is in solution, and further decomposition takes place *via* simple solution kinetics. Plots of points beyond the liquefaction point show that the decomposition is pseudo-first order; the liquid decomposition rate constant, k_l, can be evaluated from such data. The k_l values estimated in this fashion are shown in Table III. Employing this approach in evaluating k_l is not gratifying, particularly since the pressure buildup in the reaction tubes becomes prohibitive; complete decomposition of 250 mg. of *p*-aminobenzoic

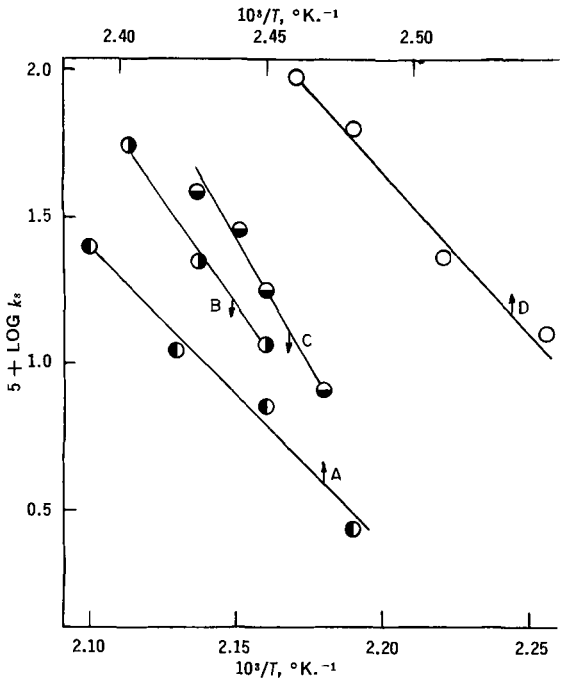

Figure 9—*Plot of the solid-state decomposition constant,* k_s, *as a function of temperature for a series of* para-*substituted benzoic acids. Key: A (◐), aminobenzoic acid; B (◑), dimethylaminobenzoic acid; C (◒), hydroxybenzoic acid; and D (○), methylaminobenzoic acid. Arrows denote scale to which line refers.*

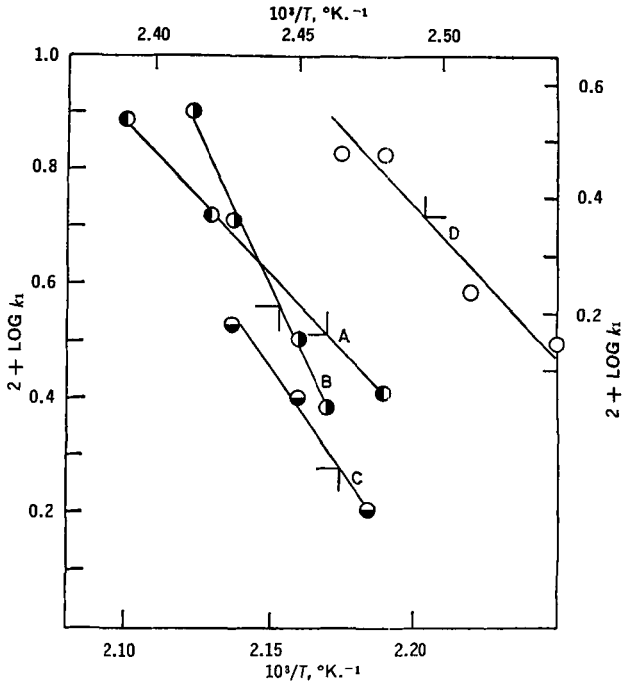

Figure 10—*Plot of the decomposition rate constant,* k_l, *of a series of* para-*substituted benzoic acids in solution in their decomposition product; log* k_l *is plotted* versus *1000* T. *Key: A (◐), aminobenzoic acid; B (◑), dimethylaminobenzoic acid; C (◒), hydroxybenzoic acid; and D (○), methylaminobenzoic acid. Arrows denote scale to which line refers.*

acid in a 7-ml. tube at 145° yields a pressure of 0.250·82·418/7·137 = 9 atm. Experiments in which solid acid and a liquid decomposition product were introduced into tubes were not successful; the initial degassing is difficult, and sealing the sample off by drawing the glass at the constriction almost invariably causes leaks in the breakseal tube.

DISCUSSION

During the decomposition of the solids in this study, there will be (after an initial lag time) liquid decomposition products present; the lag time is, of course, dependent on the vapor pressure of the decomposition product and the volume of the vessel (about 7 ml.); once decomposition exceeds the number of moles necessary to saturate the space above the solid, the liquid decomposition product will appear on the solid. Let k_s be the rate constant of the *solid* decomposition, and let k_l be the rate constant of the decomposition of the solid when in solution in its liquid decomposition product. At time t, a mole fraction x is decomposed so that there are x moles of liquid decomposition product and $(1 - x)$ moles of intact acid left; of these, $S \cdot x$ moles are in solution, where S is the solubility of the substituted benzoic acid in its decomposition product (in moles per mole). The amount left in the solid phase is, therefore, $(1 - x - S \cdot x)$ and the amount in solution is $S \cdot x$. Therefore, by assuming first-order decomposition (36):

$$\frac{dx}{dt} = k_s \cdot [1 - x - S \cdot x] + k_l \cdot S \cdot x = k_s + \alpha \cdot x \quad \text{(Eq. 1)}$$

where:

$$\alpha = S \cdot k_l - S \cdot k_s - k_s \quad \text{(Eq. 2)}$$

Integration and application of initial conditions to Eq. 1 lead to:

$$\log \left(1 + \frac{\alpha}{k_s} \cdot x\right) = \frac{\alpha}{2.3} \cdot t \quad \text{(Eq. 3)}$$

By inserting a series of arbitrary values for $A = \alpha/k_s$ and plotting log $[1 + A \cdot x]$ *versus* t, traces will result which, at high time values, will appear linear and have positive or negative y-intercepts. By

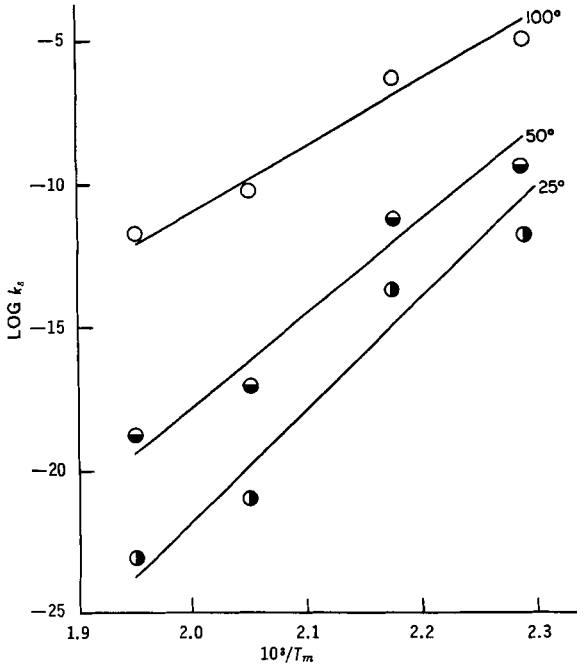

Figure 11—*Logarithm of the solid-state decomposition constant for a series of benzoic acids as a function of the reciprocal of their absolute melting temperatures.*

methodical series of choices, a value for A can be found that produces a line with zero intercept. This is exemplified in Fig. 8. The value of A yielding linearity (A = 426.5) and a zero y-intercept was found by computer[6]; only the one value of A yielding a zero y-intercept actually imparts linearity to the data; this is exemplified by insertion of the dotted lines in Fig. 8.

The value of α can now be obtained from the slope and, because A is known, k_s can be found ($k_s = \alpha/A$). Insertion of the values of k_s and S (in moles per mole) into Eq. 2 then yields the value for k_l. Both k_s and k_l adhere to an Arrhenius relation, and these plots are shown in Figs. 9 and 10.

It should be noted at this point the reactions cannot be explained by vapor phase reactions, partly because of the magnitudes of the figures in Table II and partly because such a scheme would dictate a strict zero-order relationship which is contrary to the findings. For example, it is seen (Fig. 7) that at 145° the saturation pressure for *p*-aminobenzoic acid is about 10 Torr = 1/76 atm. The vapor phase decomposition rate is given by $dC/dt = k_1C_0$, where k_1 is the first-order rate constant listed in Table II (k_1 = 0.017 hr.$^{-1}$) and where C_0 is the number of moles in the gas phase; *i.e.*, $dC/dt = 0.017 \cdot 7/(76 \cdot 82 \cdot 418) = 4.6 \cdot 10^{-8}$ mole/hr. This assumes that decomposing molecules in the gas phase are immediately replaced by sublimation from the solid phase. After 100 hr., $4.6 \cdot 10^{-3}$ mmole would, therefore, be expected to have decomposed in the gas phase, as opposed to a total of $0.5 \cdot 250/137 = 0.9$ mmole found to decompose experimentally (Fig. 1). The order of magnitude of the gas phase decomposition is, therefore, at about two orders of magnitude less than that in solid and solution in the system.

Some k_l values found from α values are listed in Table III, along with values found from decomposition determinations beyond the liquefaction point. There is agreement to within 20% of the values found one way as opposed to those found the other way; such order of magnitude of agreement is support for the views of the general decomposition scheme voiced here.

It would, therefore, appear from the data that the decomposition takes place *via* two paths: (*a*) a solid decomposition with reaction rate k_s, and (*b*) a liquid decomposition with reaction rate k_l. The original question as to whether chemical factors are of importance in a homologous series such as the one studied here can be answered directly by making reference to Table I. It is quite obvious that *only the derivatives in the benzoic acid series with* $\sigma \gtrless -0.36$ *undergo decarboxylation at temperatures below their melting point.* Although this is not the type of quantitative relationship usually encountered in Hammett linear free energy plots, it is a distinct qualitative conclusion, somewhat akin to the nature of the conclusions by Meyers *et al.* (31).

There is, however, an interesting conclusion to be drawn from the data, similar to the findings of Guillory and Higuchi (29). These authors found that for a series of vitamin A esters, the decomposition (isomerization) at 50° proceeded with a rate, k, that was related to the melting point of the compound by the equation $\log k = \theta + Q/T_m$, where T_m was the absolute melting temperature. Although the hypothesis put forth by these authors involved a liquid layer and (in the framework of this study) would relate k to k_l, and hence cannot apply to the k_s values here, it is seen from the lines in Fig. 11 that the same type of relation holds for k_s in this series.

[6] Univac model 1108.

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Opium Alkaloids XII: Quantitative Determination of Morphine in Opium by Isotope Dilution

EINAR BROCHMANN-HANSSEN

Abstract □ A method was developed for quantitative determination of morphine in opium based on the isotope dilution technique. Morphine-2-^{3}H and morphine-*N*-$^{14}CH_3$ are used as radioactive standards. A mixture of opium and the radioactive morphine standard is triturated with dimethyl sulfoxide, dispersed on diatomaceous earth and acidic aluminum oxide, and suspended in water. The aqueous suspension is transferred to a chromatographic column of acidic aluminum oxide, and the alkaloids are eluted with water. Alternatively, the mixture of opium and radioactive morphine is triturated with a little water and dispersed on diatomaceous earth, and the alkaloid bases are liberated with ammonia. The powder mixture is transferred to a column of neutral aluminum oxide and eluted with chloroform–isopropyl alcohol (3:1). Phenolic and nonphenolic alkaloids are separated by extraction at pH 13, and morphine crystallizes from the aqueous phase after adjustment of pH to 9. The crystals are collected and recrystallized to constant radioactivity. Both extraction methods gave the same results. No loss of tritium occurred during the assay, and morphine-2-^{3}H and morphine-*N*-$^{14}CH_3$ were equally satisfactory as radioactive standards. The method is specific for morphine, has good precision (0.4%), and requires no elaborate technique.

Keyphrases □ Opium alkaloids—analysis of morphine in opium by isotope dilution □ Morphine, in opium—analysis, isotope dilution method □ Isotope dilution method—analysis, morphine in opium

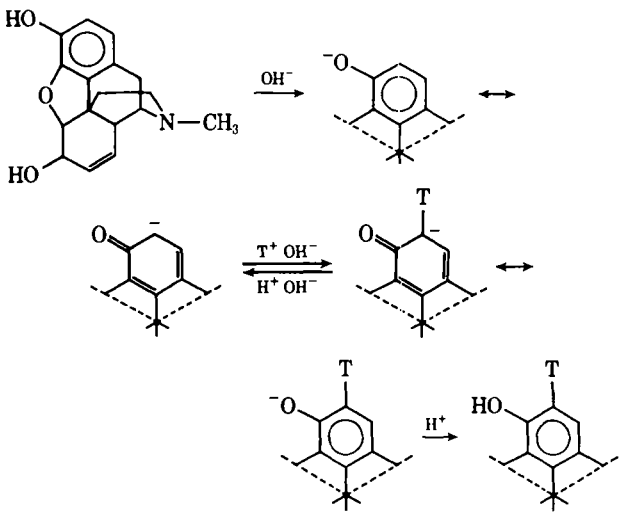
The lime method for assay of opium has remained relatively unchanged through several revisions of the USP (1). Nevertheless, it is well recognized that this method leaves much to be desired and does not give an accurate estimate of the morphine content of opium (2–4). In recent years, many attempts have been made to overcome the problems associated with the lime method and to develop assay procedures with better precision and accuracy.

DISCUSSION

Many modern pharmacopeias have adopted modifications of the method proposed by Mannich (5) in 1935, in which an aqueous solution of morphine is reacted with 1-chloro-(or fluoro)-2,4-dinitrobenzene in the presence of base. The slightly soluble dinitrophenyl ether of morphine crystallizes and can be determined gravimetrically or volumetrically. The extraction of morphine from opium is usually achieved with water or alcohol, and a partial purification is obtained by means of a chromatographic column of aluminum oxide. The many modifications of this technique were reviewed by Schultz and Schneckenburger (6). Loss of morphine may result from a slight solubility of the dinitrophenyl ether (3, 6). At the same time, the crystalline precipitate is often contaminated with minor opium alkaloids, with aluminum hydroxide, and with excess reagent or the corresponding phenol or amine (2, 3, 6, 7).

Other methods proposed for the assay of opium make use of liquid–liquid extraction techniques (8–11), ion-exchange resins (12–14), partition or adsorption chromatography (15–18), paper chromatography (19–21), TLC (22), GC (23), UV and IR spectrophotometry (17, 18, 22, 24, 25), colorimetry (11–13, 19, 20, 26, 27), and polarography (11, 28, 29). Although some of these methods may be superior to the USP lime method, no assay procedure reported to date is specific for morphine.

It is extremely difficult to obtain a complete separation of morphine from the complex mixture of alkaloids and nonalkaloidal matter associated with it without losing morphine in the process. Therefore, specificity can probably be achieved only by using a selective method for the quantitative estimation. The isotope dilution technique is such a method of exceptional selectivity. The principle of this method is to add a known amount of radioactive morphine standard to a sample of opium and then to isolate morphine and purify it to constant radioactivity. The difference in specific activity of the isolated morphine as compared to that of the radioactive



Scheme I—Base-catalyzed tritium labeling of morphine