peaks and the fact that it was present in only small amount if at all. There could have been as much as 3% of this constituent without a clear indication of its presence.

The results obtained are tabulated below. The evidence for near-complete exchange is clear in every instance. Experiments 7 and 8 show unmistakably that there is no appreciable difference in the rates of CH_4 and CH_3D exchange.

Expt. no.	2	3	4	5	6	7	8
Temp., °C.	360	340	342	365	370	350	350
Reactant methanes, %							
CH_4	100	100	100	0	0	50	33
CH_3D	0	0	0	100	100	50	67
Product methanes, %							
CH_4	39	50	52	0	0	26	16
CH_3D	3	3	2	53	53	25	34
CH_2D_2	0	0	0	0	0	0	0
CHD_3	8	6	4	8	7	11	10
CD_4	50	41	42	39	40	38	40

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A Kinetic Study of the Perkin Condensation[1]

BY ROBERT E. BUCKLES AND KEITH G. BREMER

RECEIVED NOVEMBER 7, 1952

Base-catalyzed, aldol-type condensations of carbonyl compounds with weak secondary acids capable of losing a proton have been studied to some extent from the standpoint of kinetics and mechanisms.[2] No kinetic studies have been made on the Perkin condensation, but its mechanism has been formulated as an aldol-type condensation of an acid anhydride with an aromatic aldehyde.[2a]

The present investigation is concerned with the kinetics of the base-catalyzed condensation of benzaldehyde with phenylacetic acid in acetic anhydride. This particular condensation is of interest as a starting point in the study of the effect of substituents on the benzene ring of both the benzaldehyde and the phenylacetic acid.

Experimental

Reagents.—Commercial benzaldehyde was washed with 10% aqueous sodium carbonate and then with water. It was dried over magnesium sulfate and distilled at reduced pressure (below 30 mm.) in the presence of a little hydroquinone. The acetic anhydride was distilled at 745 mm., and the fraction boiling 137–139° was used. Both of these reagents were purified in small quantities and were used as soon as possible.

The anhydrous amines were obtained from Sharples Chemicals, Inc. The phenylacetic acid was a recrystallized commercial preparation of m.p. 76–77°.

Product Isolation.—The condensation of 54.6 g. of phenylacetic acid and 42.4 g. of benzaldehyde in 80 ml. of acetic anhydride containing 40 ml. of triethylamine was carried out as described before.[3] From the reaction mixture was isolated 60–67 g. (67–75%) of crude α-phenylcinnamic acid of m.p. around 156°. From this crude product 48–52 g. (54–58%) of product of m.p. 172–173° could be obtained by crystallization from 50% ethyl alcohol.

In a similar experiment carried out at room temperature for six days a 63% yield of crude product was obtained.

Kinetic Measurements.—The reactions were carried out in an all-glass apparatus consisting of a 500-ml. three-necked flask fitted with a long air condenser, protected from atmospheric water vapor, and a True-Bore glass stirrer. The reaction flask was immersed in a thermostatically controlled oil-bath whose heating element was contained in the wall of the bath. The temperature was kept constant to within 0.1° at the temperatures used. Varying amounts of phenylacetic acid in 150 ml. of acetic anhydride were added to the reaction flask and allowed to remain in the bath overnight. The benzaldehyde and the amine catalyst were then added with stirring. An initial 5-ml. sample was withdrawn into a pipet fitted with a hypodermic syringe as soon as the mixture was homogeneous. Further samples were taken at regular intervals of time thereafter. The analysis for benzaldehyde was carried out by a modification of the procedure described for the determination of carbonyl compounds in the presence of carboxylic acids.[4] A 5-ml. sample was added to 100 ml. of 90% aqueous methanol and the mixture was allowed to stand for 15 minutes so that the anhydride would be destroyed. The *p*H of the solution was then adjusted to 2.5 with 0.5 *N* aqueous hydrochloric acid and 25 ml. of the 0.5 *N* hydroxylamine hydrochloride in 80% ethyl alcohol (*p*H 2.5) was then added. After a reaction period of 15 minutes the hydrochloric acid formed was titrated with 0.463 *N* carbonate-free sodium hydroxide in 80% methanol to an end-point of *p*H 2.5. The results of the titration of the initial samples coupled with the initial mole ratios of the reagents added were used to calculate the initial concentrations of the runs. Satisfactory agreement within experimental error was obtained in a number of duplicate determinations. The runs with variations in concentrations, catalyst and temperature are summarized in Table I.

TABLE I

SUMMARY OF BASE CATALYZED CONDENSATIONS OF PHENYLACETIC ACID WITH BENZALDEHYDE IN ACETIC ANHYDRIDE AT 100°

	Concentrations of reagents, *M*			
Run	PhCHO	$PhCH_2COOH$	Et_3N	$k \times 10^5$
1	1.058	1.058	0.000	. . .
2	1.002	1.002	.577	7.6
3	0.972	1.944	.560	6.2
4	1.889	0.964	.550	5.7
5	1.032	1.032	.297	7.5
6	1.007	1.007	.580[a]	6.9
7	0.978	0.978	.564[b]	5.9
8	1.076	1.076	.620[c]	5.1
9	1.198	1.198[d]	.690	0.18
10	1.261	0.000	.000	. . .
11	1.256	0.000	.723	0.15
12[e]	1.060	1.060	.611	1.04
13[f]	1.001	1.001	.577	6.3
14[g]	1.014	1.014	.584	10.2

[a] Tri-*n*-propylamine was used as a catalyst. [b] Tri-*n*-butylamine was used as a catalyst. [c] Potassium acetate was used as a catalyst. [d] Acetic acid was added in place of phenylacetic acid. [e] The reaction was carried out at 26°. [f] The reaction was carried out at 80°. [g] The reaction was carried out at 120°.

Results and Discussion

The various runs carried out and their results are summarized in Table I. Typical titration data for

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[1] From the Ph.D. thesis of Keith G. Bremer. Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., September, 1952.

[2] (a) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 9, (b) J. D. Gettler and L. P. Hammett, THIS JOURNAL, **65**, 1824 (1943). (c) E. F. Pratt and E. Werble, *ibid.*, **72**, 4638 (1950). (d) T. I. Crowell and F. A. Ramirez, *ibid.*, **73**, 2268 (1951).

[3] R. E. Buckles, M. P. Bellis and W. D. Coder, Jr., *ibid.*, **73**, 4972 (1951).

[4] D. M. Smith and J. Mitchell, Jr., *Anal. Chem.*, **22**, 750 (1950).

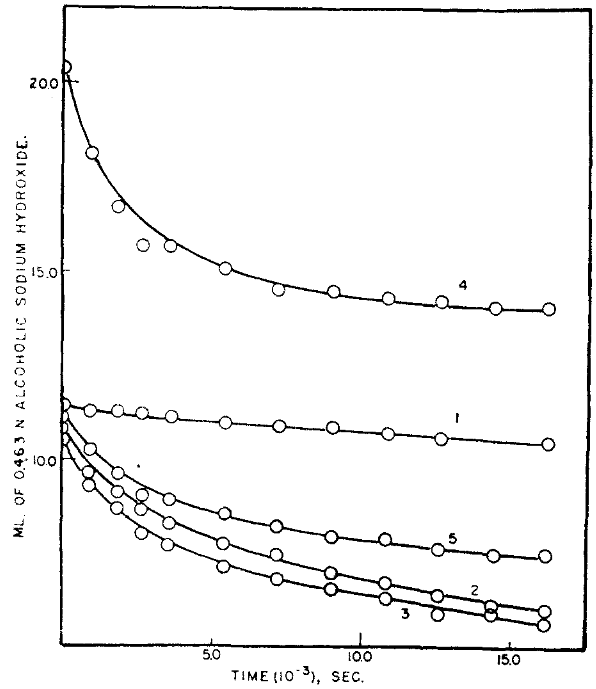


Fig. 1.—Representative titration curves for some of the runs listed in Table I.

several runs are shown graphically in Fig. 1. The slow disappearance of benzaldehyde presumably caused by autoxidation is illustrated in run 1 in which added catalyst was absent. A similar result was obtained when both catalyst and phenylacetic acid were absent (run 10). Of more consequence as a competing reaction was the condensation of benzaldehyde with acetic anhydride as shown in runs 9 and 11. This was a slower reaction than the apparent condensation of benzaldehyde with phenylacetic acid as shown by the kinetic results as well as by the fact that α-phenylcinnamic acid was isolated in a crude yield of 75% when the latter condensation was carried out in the presence of an excess of acetic anhydride. As a first approximation in the determination of specific rate constants for the apparent condensation of benzaldehyde with phenylacetic acid, these competing reactions of benzaldehyde were ignored.

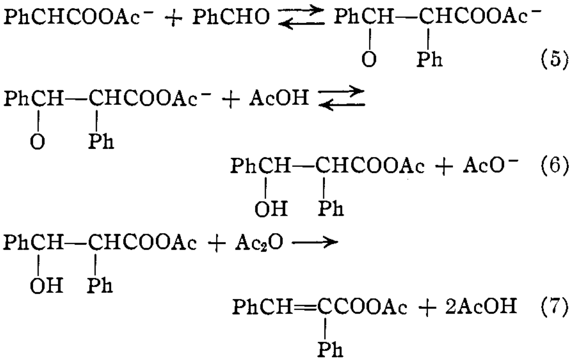
The rate law found to be most consistent with changes in the rate of reaction arising from changes in concentrations of the various reactants as well as from changes in the identity of the catalyst is given in equation (1). This equation can be derived from a mechanism such as that outlined in equations (2) through (7) if it be assumed that equation (5) represents the rate-determining step. Such a mechanism is consistent with results for aldol-type condensations.[2] The steps preceding (5) are considered to be essentially at equilibrium. It would be expected, however, that step (2) would be fairly complete to the right in the presence of the large excess of acetic anhydride, that step (3) would also be far in favor of the forward reaction as shown by a consideration of the relative acid and base strengths of acetic acid and the trialkylamines, and that step (4) would be far in favor of the reverse reaction. Thus, it can be assumed that the initial concentration of phenylacetic acid is equal to that of the mixed anhydride of phenylacetic and acetic acids, and also to the initial concentration of acetic acid. When the initial concentration of the amine is equal to or less than that of the phenylacetic acid plus any acetic acid (from step (7)), the concentration of acetate ion will be equal to the initial concentration of the amine.

$$\frac{dx}{dt} = \frac{k(\mathrm{PhCHO})(\mathrm{PhCH_2COOH})(\mathrm{AcO^-})}{(\mathrm{AcOH})} \quad (1)$$

$$\mathrm{PhCH_2COOH + Ac_2O \rightleftharpoons PhCH_2COOAc + AcOH} \quad (2)$$

$$\mathrm{R_3N + AcOH \rightleftharpoons R_3NH^+ + AcO^-} \quad (3)$$

$$\mathrm{PhCH_2COOAc + AcO^- \rightleftharpoons PhCHCOOAc^-} \quad (4)$$



$$\mathrm{PhCHCOOAc^- + PhCHO \rightleftharpoons \underset{O}{PhCH}—\underset{Ph}{CHCOOAc^-}} \quad (5)$$

$$\mathrm{\underset{O}{PhCH}—\underset{Ph}{CHCOOAc^-} + AcOH \rightleftharpoons \underset{OH}{PhCH}—\underset{Ph}{CHCOOAc} + AcO^-} \quad (6)$$

$$\mathrm{\underset{OH}{PhCH}—\underset{Ph}{CHCOOAc} + Ac_2O \longrightarrow PhCH{=}\underset{Ph}{C}COOAc + 2AcOH} \quad (7)$$

Steps analogous to (4), (5), (6) and (7) would be expected for the condensation of benzaldehyde with acetic anhydride. If this competing reaction is considered, the rate law is equation (8) where k' is the specific rate constant of the reaction with acetic anhydride.

$$\frac{dx}{dt} = \frac{k(\mathrm{PhCHO})(\mathrm{AcO^-})}{(\mathrm{HOAc})}\left[(\mathrm{PhCH_2COOH}) + \frac{k'}{k}(\mathrm{Ac_2O})\right] \quad (8)$$

A first approximation of the value of k, the specific rate constant of the apparent condensation of benzaldehyde with phenylacetic acid was obtained by the use of equation (1). The approximate value of k as well as that of k', which was obtained similarly, was used in a second approximation by means of equation (8). The approximate values obtained are given in Table I. The average value of the specific rate constant at 100° was $(6.4 \pm 0.9) \times 10^{-5}$ liter per mole per second ($\pm 0.9 \times 10^{-5}$ determines the 95% confidence limits of the average). Considering the assumptions made and the difficulties encountered in following the reaction, the observed standard deviation of 8–14% for individual specific rate constants is not believed to be excessive. The effect of varying the concentrations of the reagents and the identity of the catalyst on the rate certainly lends support to the type of mechanism proposed. The reaction exhibits specific acetate ion catalysis when it is carried out in a large excess of acetic anhydride as a medium. Wide variations in yield reported[5] with different catalysts for this type of condensation would not be caused by differences in the initial rate of condensation, but by differences in side reactions,

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(5) M. Bakunin and D. Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935); R. E. Buckles and E. A. Hausman, THIS JOURNAL, **70**, 415 (1948).

product decomposition, and other factors affecting the isolation of a product.

Variation of the specific rate constant with temperature is also shown in Table I (runs 13, 14 and 15). The reaction has a low temperature coefficient which is not particularly surprising for an aldol-type condensation.[2b]

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The Isolation of the Toxic Principles of Mamey

BY M. P. MORRIS AND C. PAGÁN

RECEIVED AUGUST 1, 1952

The insecticidal properties of the various parts of the mamey tree (*Mammea americana* L.) have been recognized for many years.[1] Although the seeds from the fruit of this tree have been the subject of numerous investigations,[2] the isolation of the toxic compounds in pure form has not been previously reported.

Outlined below is a procedure which led to the isolation of one pure, toxic, crystalline compound and to one toxic amorphous solid. These two substances were highly toxic to several species of insects and accounted for 81% of the toxicity of mamey extract. Their powerful action as fish poisons facilitated their isolation since this permitted the use of guppies as the bioassay test animal.

Experimental

Seeds of mature fruit were sectioned, dried at 45° in a forced-draft oven for 24 hours, ground to 80 mesh, and extracted for 8 hours with petroleum ether in a soxhlet type extractor. A light-red, sticky, semi-solid mass, representing 5% of the dried powder, was obtained after evaporation of the solvent. Heating under high vacuum for 2 hours at 100° was required for the removal of the last traces of solvent. Other non-polar solvents served as well as petroleum ether for this extraction. This semi-solid mass was dissolved in the minimum amount of acetone and placed in an ice-bath for 24 hours. A non-toxic white, powdery solid, melting sharply at 78°, was obtained. The yield was 1.5% of the dried extract. The acetone in the filtrate was evaporated under reduced pressure and the residue dissolved in petroleum ether to give a 10% solution. Fifty ml. of this solution, equivalent to 5.0 g. of dried extract, was placed on a 75 × 150 mm. column prepared with silicic acid (Merck 200 mesh) and developed with a 1:10 mixture of ether and petroleum ether. After the initial band had separated into three distinct bands, the silicic acid was extruded, sectioned, and the three bands extracted with ether. The immobile band at the top of the column was not toxic and was discarded. The procedure was repeated five times and the corresponding extracts of the two mobile toxic bands were combined. This gave a preliminary separation.

The ether solution of the leading toxic band was partially evaporated and the remaining ether gradually replaced with petroleum ether while boiling on a steam-bath. Cooling in an ice-bath for 24 hours produced 2.3 g. of well-formed, colorless crystals, representing several crystalline modifications. Numerous recrystallizations from ether–petroleum ether showed these crystals to be a mixture of compound A, m.p. 130–131° (2.1 g.), and several other crystalline compounds which have not yet been obtained in pure form. Compound A showed approximately the same LD_{50} as the original extract, *i.e.*, 1.5 p.p.m., and thus accounted for 7% of the toxicity of the original extract. The mother liquors when combined and partially evaporated yielded 0.5 g. of light-yellow crystals, m.p. 70–90°. This mixture was resolved into three crystalline substances, melting at 82–84°, 101–102° and 114–115°. These last three substances appeared to be solvates, for they effervesced strongly at their melting points.

Compound A dissolved readily in dilute alkali to give a yellow solution and gave positive phenolic tests. This compound added methylmagnesium bromide readily, but did not liberate methane in the Zerewitinoff apparatus. The ultraviolet absorption spectrum obtained with a Beckman model DU spectrophotometer, using 95% alcohol as the solvent, showed maxima at 244, 249, 255, 261 and 334 mμ.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.26; H, 7.33. Found: C, 71.15, 71.10; H, 7.62, 7.56.

The ether solution of the middle toxic band was evaporated and a light-red oil was obtained which was extracted several times with petroleum ether. The tacky residue that remained was taken up in a 1:10 ether–petroleum ether mixture and rechromatographed three times on a silicic acid column as described above. This led to the isolation of 3.1 g. of a highly toxic material. The LD_{50} of this golden-yellow amorphous substance which softened at 170–175°, was 0.25 p.p.m. by the guppy bioassay method[3] and accounted for 74% of the toxicity of the original extract. This LD_{50} of 0.25 p.p.m. indicated that this substance was approximately 20% as toxic as rotenone under the same conditions. The molecular structures of the toxic compounds described above are now being investigated by Professor J. L. E. Erickson, Louisiana State University. A report of this work will be submitted from his laboratory to THIS JOURNAL at a later date.

During the past year this Laboratory received several requests for samples of these pure toxic compounds, indicating a widespread interest in these potential insecticides. A recent press release[4] from the University of Puerto Rico stated that mamey extract contained "antibiotic substances which were active *in vitro* against one or more bacteria."

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[1] D. de Grosourdy, "El Médico Botánico Criollo," Vol. II(2), Paris, (1864), p. 511.

[2] M. A. Jones and H. K. Plank, THIS JOURNAL, **67**, 2262 (1945); H. K. Plank, *J. Econ. Entomol.*, **37** (6), 737 (1944), and refs. cited.

[3] C. Pagán, *ibid.*, **41** (6), 942 (1948).

[4] "Información Oficial," Núm. **19**, Oct. 4, 1951, Universidad de Puerto Rico.

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An Investigation of the Hammick Reaction

BY NELSON H. CANTWELL AND ELLIS V. BROWN

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In an attempt to elucidate the nature of the Hammick reaction[1,2] with a view to extending it, we varied the character of the carbonyl reactant by introducing substituents into its nucleus.

The various carbonyl compounds which were successfully coupled with picolinic acid upon decarboxylation are listed in Table I. In initial investigations various solvents such as dibromobenzene, nitrotoluene, bromoanisole, xylene and *p*-cymene, equivalent in amount to the aldehyde used were added to the reaction mixture to determine what effect they might have on the yield. This proved to be very practical for the yield of carbinol was increased in every case. The best yields were ob-

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[1] D. Ll. Hammick and P. Dyson, *J. Chem. Soc.*, 1724 (1937); 809 (1939).

[2] D. Ll. Hammick and B. R. Brown, *ibid.*, 173 (1949); 659 (1949).