

cinenic acid rearrangement; to Dr. Herbert Weissbach for samples of DBC and BC; to Dr. Arnold Pratt for advice concerning gas manipula-

tion; and to Dr. Roscoe Brady for making available before publication the method for preparation of methylmalonyl CoA.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA, LINCOLN 8, NEBR.]

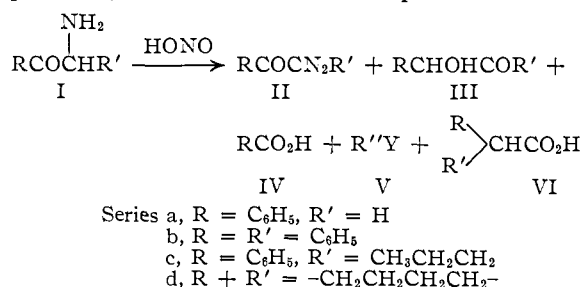
Reactions of Amines. VII. The Reactions of α -Amino Ketones with Nitrous Acid^{1,2}

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RECEIVED JUNE 21, 1960

The reactions of several α -amino ketones, $\text{RCOCH}(\text{NH}_2)\text{R}'$, with nitrous acid yielded, in addition to α -hydroxy ketones and α -diazo ketones, acidic products, RCO_2H and $\text{RR}'\text{CHCO}_2\text{H}$. When $\text{R}' = \text{H}$ only *cleavage* product RCO_2H was formed but when $\text{R}' \neq \text{H}$ both the *cleavage* acid and the *rearrangement* product $\text{RR}'\text{CHCO}_2\text{H}$ were formed. The remaining *cleavage* fragments appear to be the alcohols or olefins to be expected from the acid-catalyzed decomposition of the diazo hydrocarbon intermediate, $\text{R}'\text{CHN}_2$. Mechanisms to explain these observations are given.

Based on the work of previous investigators and on theoretical considerations one would predict that α -amino ketones should react with nitrous acid to give any or all of four feasible products (or sets of products), as illustrated in the sequence $\text{I} \rightarrow \text{VI}$.



The reaction of I with nitrous acid to give a diazoketone (II) was first described by Schiff and Maissen⁴ and later was used with modest success by Angeli.⁵ The formation of benzoin from desylamine is an example of the formation of a product of type III.⁶ Apparently the only report of the formation of an acid of type IV is that of Angeli,^{5c} who reported the formation of benzoic acid (IVa) when phenacylamine (Ia) was treated with nitrous acid. Angeli suggested two possible sources of the benzoic acid, oxidation of the diazoketone IIa to the acid plus an unspecified fragment V and hydrolytic cleavage of the diazoketone to the acid plus diazomethane (V, $\text{R}'' = \text{CH}_2$, $\text{Y} = \text{N}_2$). Very recently Edwards and Lesage⁷ reported the first example of the formation of a product of type VI, cyclopentanecarboxylic acid (VIId), from the reaction of α -aminocyclohexanone with nitrous acid. The latter communication prompts us to report the results of an examination of the reaction of a number of α -amino ketones with nitrous acid, which has been and is being carried out in this Laboratory.

Our completed studies have been restricted largely to investigations of the *cleavage reaction* (I

$\rightarrow \text{IV} + \text{V}$) and of the *rearrangement reaction* (I $\rightarrow \text{VI}$); therefore, we have little to contribute at this time relative to the formation of products like II and III other than that their presence was noted in almost every experiment (by infrared techniques) and that yields of II seem to be better when $\text{R}' \neq \text{H}$. Reactions leading to these products will be ignored in the following discussion and comparisons will be made between only the *cleavage* and *rearrangement* reactions.

α -Amino ketones (I) for which $\text{R} = \text{aryl}$ and $\text{R}' = \text{H}$ appear to give only *cleavage* products (IV + V). Rigorous examination of this generalization has been made only for phenacylamine (Ia), but in the examination of a number of substituted phenacylamines no evidence has been obtained for the presence of other acidic products (Table I). In the case of phenacylamine, the expected acidic products would be benzoic (IVa) and phenylacetic acids (VIa). In model experiments mixtures of these acids could be converted to the methyl esters and the latter separated by gas chromatography in such a manner as to permit the facile determination of less than 1% of phenylacetic acid in the presence of benzoic acid. When the crude acid obtained from the reaction of phenacylamine with nitrous acid was converted into the methyl ester and the ester examined by gas chromatography, no peak corresponding to methyl phenylacetate was present. This result indicates that either the *rearrangement* reaction does not occur with phenacylamine under the conditions used or that it occurs to the extent of well below 1% of the total acid product. Examination of a number of crude acid fractions with infrared techniques tended to confirm this observation.

A relatively large number of experiments were carried out with phenacylamine to determine the optimum conditions for the *cleavage* reaction. These appeared to involve the slow addition of acid (sulfuric, hydrochloric or acetic acid) to an aqueous solution of phenacylamine hydrochloride and three equivalents of sodium nitrite at room temperature.⁸ Under these optimum conditions the yield of benzoic acid was as high as 68%. A number of substituted phenacylamines were examined under the same conditions and gave yields in the range 70–78% (Table I).

(1) Paper VI, THIS JOURNAL, **82**, 4422 (1960).

(2) The work was supported in part by grant G-3689 of the National Science Foundation.

(3) Abstracted from the Ph.D. thesis of C. H. A., June, 1959.

(4) R. Schiff and P. Maissen, *Gazz. chim. ital.*, **11**, 471 (1881).

(5) (a) A. Angeli, *Ber.*, **26**, 1715 (1893); (b) A. Angeli, *Gazz. chim. ital.*, **23II**, 345 (1893); (c) A. Angeli and G. Malagnini, *ibid.*, **24II**, 318 (1894); (d) A. Angeli, *ibid.*, **25II**, 394 (1895).

(6) P. W. Neber and G. Huh, *Ann.*, **515**, 283 (1935).

(7) O. E. Edwards and M. Lesage, *J. Org. Chem.*, **24**, 2071 (1959).

(8) Cf. D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 838 (1934).

TABLE I
REACTION OF α -AMINO KETONES WITH NITROUS ACID

X	$p\text{-XC}_6\text{H}_4\text{COCH}_2\text{NH}_2\text{Cl} \xrightarrow{\text{HNO}_2} p\text{XC}_6\text{H}_4\text{CO}_2\text{H}$		
	Yield, %	M.p., °C. ^a	Yield ^b ether-sol. product, g.
H	68	122-122.5	1.47
Br	72	253-255	1.69
Cl	76	239-241	1.95
CH ₃ O	73	182.5-184	1.57
NO ₂	70	236-239	1.64
CH ₃	78	177.5-179	1.49

^a M.p.'s reported in ref. 23: 122°, 251-253°, 243°, 184.2°, 238° and 181°, respectively. ^b Neutral material from 0.05 mole of amino ketone.

In the cleavage reaction of phenacylamine there must be a one-carbon fragment (V) formed in addition to the benzoic acid. Although Angeli^{6c} suggested that this fragment might be diazomethane, no evidence was offered to this effect. Actually three fairly reasonable mechanisms can be written for the cleavage reaction leading to the formation of formic acid, hydrogen cyanide or diazomethane, respectively. Misled at first by the apparent odor of cyanide, which often appears with this reaction, we carried out a rather rigorous examination for the presence of hydrogen cyanide in the products. None was found. However, after this work was completed Yates and Shapiro⁹ reported that diazoacetophenone was cleaved by sequential treatment with aqueous alkali and mineral acid into benzoic acid, hydrogen cyanide and hydroxylamine. Since there was a reasonable possibility that the cleavage reaction of α -amino ketones with nitrous acid and the base-catalyzed cleavage of diazoketones might proceed by the same or similar mechanisms, we repeated our search for evidence of cyanide. Although we were able to detect readily the presence of deliberately added sodium cyanide (corresponding to a 12% yield benzoic acid), only negative tests for cyanide were obtained in the absence of added cyanide ion. Tests for hydroxylamine were not made, for preliminary experiments showed that it reacted too rapidly with nitrous acid for detection by the usual techniques.¹⁰

These results appear to indicate that, when R' = H, the mechanisms of the cleavage reactions of diazoketones (RCOCN₂R') with base and of I with nitrous acid cannot be the same.

If Angeli's early speculation was correct, it seemed probable that any diazomethane formed slowly in mildly acidic solution would be hydrolyzed to methanol and nitrogen. Therefore, a series of quantitative assays for methanol was run (based on model experiments). The details of these experiments are given in the Experimental section. In a typical experiment in which the yield of benzoic acid was 58%, the analysis indicated a 40% yield of methanol. Very possibly some of the diazomethane unaccounted for may have escaped hydrolysis or

(9) P. Yates and B. L. Shapiro, *THIS JOURNAL*, **81**, 212 (1959).

(10) Presumably any hydroxylamine present could be identified by gas chromatographic analysis of the effluent gases for nitrous oxide (N₂O) using an appropriate column. This experiment was not attempted because of the negative tests for cyanide ion. The major portion of the effluent gas was shown to be nitrogen by analysis using molecular sieve, type 13X, packing.

have reacted with other species present in the solution to give other products. In any event, the above result appears to indicate that the primary cleavage products are benzoic acid and diazomethane.

Those α -amino ketones (I) studied for which R, R' \neq H gave both the cleavage and rearrangement reactions. Thus, α -aminovalerophenone (IIc) reacted with nitrous acid to give a 38% yield of the rearrangement product, α -phenylvaleric acid (VIc), and a 27.5% yield of the cleavage product, benzoic acid (IVc), as indicated by partition chromatographic analysis on a silicic acid column. Desylamine (Ib) gave only 5% of the rearranged product, diphenylacetic acid (VIb), and 77% of the cleavage product, benzoic acid (IVb). In partial accord with the recent results of Edwards and Lesage,⁷ who reported obtaining from the reaction of α -aminocyclohexanone (IVd) with nitrous acid as much as 57% of a *carboxylic acid* at least part of which was cyclopentanecarboxylic acid (VI d), we obtained a 21% yield of cyclopentanecarboxylic acid, which was identified by its neutralization equivalent, gas chromatographic analysis and its amide derivative. In this specific example, other acidic material was obtained, tentatively identified by gas chromatography and infrared spectra as the cleavage product ϵ -hydroxycaproic acid and 5-hexenoic acid.

Only rather general mechanistic rationalizations for the above reactions can be given at this time, for the same uncertainties that are current objects of investigation in the reactions of simple aliphatic amines with nitrous acid¹¹ are evident, at least in part, in the reactions of the α -amino ketones. Studies on the aliphatic amine-nitrous acid reactions have indicated that either the aliphatic diazonium ion or the carbonium ion derived from it may be considered as the branching point from which the several diverse reactions proceed. Thus far, the possibility that the aliphatic diazoic acid may share, in some examples, in this role has not been popular, although recent studies in the aromatic series¹² indicate that its potentialities should not be ignored.

For the cleavage reaction it has been noted (*vide supra*) that at least three unrelated mechanisms can be written to account for the acid fragment. Assuming, however, that the by-product methanol has been correctly identified from the reaction of phenacylamine, the following mechanism (a) or some variation of it is suggested as explaining the present observations.

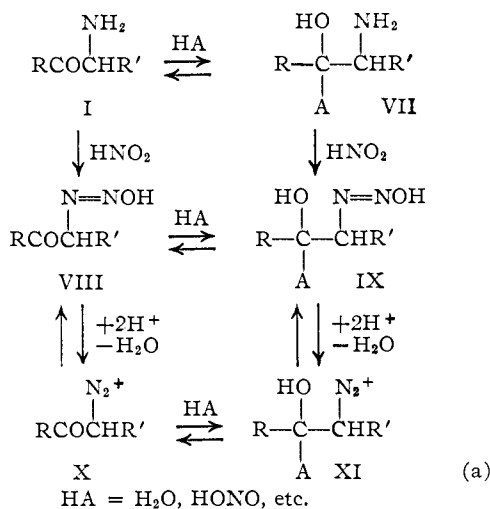
The key intermediates in the proposed scheme are IX and XI, which may be formed from I (or, more probably, a salt of I)¹³ as in the equilibrium¹⁴

(11) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957).

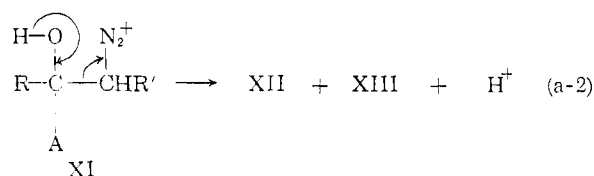
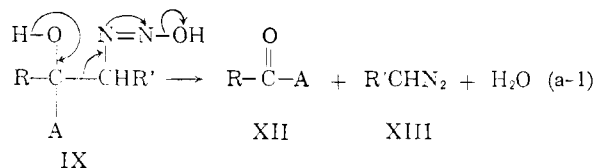
(12) E. S. Lewis and M. D. Johnson, Abstracts Cleveland, Ohio, Meeting of the American Chemical Society, April 5-14, 1960, p. 49-O.

(13) When solutions of Ia in a limited amount of water were treated with sodium nitrite at low temperatures, a salt, presumably the nitrite salt of Ia, precipitated. Attempts to isolate the salt were not successful, for it quickly decomposed during the attempted isolation to benzoic acid and α -diazoacetophenone.

(14) The possibility that a major portion of the product might arise from the reaction of α -diazoacetophenone with nitrous acid appears remote in view of the observation that, under the conditions used, the yield of benzoic acid from α -diazoacetophenone was quite low (even with a generous allowance (0.12 g.) for the benzoic acid not recovered



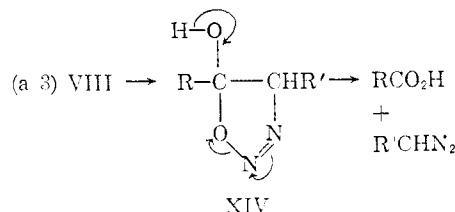
Subsequently the changes indicated by the curved arrows in a-1 and a-2 occur yielding the cleavage acid XII (or a readily hydrolyzed derivative) and the aliphatic diazohydrocarbon XIII.



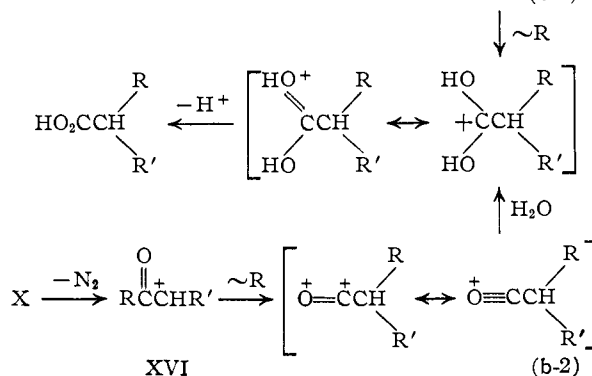
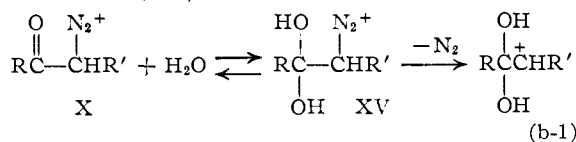
In the mildly acid solution the latter (XIII) would be converted into the aliphatic diazonium ion, which could then undergo the several reactions expected of this species to form isomeric olefins and alcohols. Where $\text{R}' = \text{H}$, it would be expected that the predominant, if not sole, product of the further reaction of X would be methanol.

Alternatively the keto diazoic acid VIII may cleave by a cyclic mechanism as indicated in a-3.¹⁵ from the various solutions, the yield would be below 6-7%). This observation could be interpreted also as vitiating the sequence $\text{I} \rightarrow \text{VIII} \rightarrow \text{X} \rightarrow \text{XI}$, for the reaction of α -diazooacetophenone with acid probably proceeds through X. However, in the reaction of I with nitrous acid very probably all of the reacting species are in the aqueous phase, whereas in the reaction of α -diazooacetophenone with nitrous acid most of the former is in the organic phase (at least at the start) and there is no evidence available as yet to indicate whether the reaction takes place in the organic phase, in the aqueous phase or at the interface. The fate of X could very well be determined by its surroundings at the time of its formation. Thus, it may be noted that U. S. Seth and S. S. Deshpande (*J. Indian Chem. Soc.*, **29**, 539 (1952)) obtained at least a 17% yield of *p*-chlorobenzoic acid from the treatment of *p*-chloro- α -diazooacetophenone with a trace of sulfuric acid in ethanol solution.

(15) Under the conditions of the reaction any or all of species VII-XI (as well as their conjugate acids or bases) may be present in equilibrium. These brief mechanistic summaries merely show that any of the species could be involved but no preference for any one is required by the available evidence nor are the details of each limited by the equations given. For example, acid catalysis may play a part in a-1, facilitating the departure of OH (as H_2O), or in a-3, promoting the cleavage to RCO_2H . However, acid catalysis does not appear to be required, for a-1 is similar to the mechanism proposed by Yates and



Although the rearrangement reaction may also involve intermediates such as IX, XI or XIV, it will be written as proceeding from the hydrated keto diazonium (XV) or keto carbonium (XVI) ion.



In either instance the rearrangement step may be concerted with the elimination of nitrogen, a possibility that seems highly desirable in sequence b-2, which otherwise would involve the rather unstable ion XVI. It will be seen that the sequence b-1 is quite similar to that involved in the semipinacol rearrangement.

A more detailed rationalization and intercomparison of the reactions of the individual amino ketones will be deferred until needed further experiments have been performed.

Experimental¹⁶

The Reaction of Phenacylamine Hydrochloride with Nitrous Acid. A.—A procedure similar to that of Womack and Nelson¹⁷ for the preparation of ethyl diazoacetate was used.

To a solution of 17.1 g. (0.1 mole) of phenacylamine hydrochloride in 200 ml. of water cooled to 0° was added a cold solution of 8.0 g. (0.115 mole) of sodium nitrite in 20 ml. of water. After the mixture was again cooled to 0°, 100 ml. of ether and 0.5 ml. of dilute sulfuric acid (6 g. of concentrated sulfuric acid in 100 ml. of water) were added, and the mixture was stirred vigorously for 5 min. The ether layer was separated and washed with 10% aqueous sodium carbonate. The lower aqueous layer was returned to the chilled reaction beaker. The following procedure was then repeated many times (*ca.* 20). To the reaction mixture was added 25 ml. of ether and 2.5 ml. of the dilute sulfuric acid solution. The mixture was stirred vigorously for 3 minutes, always maintaining the temperature below 5°. The layers were

Shapiro¹ for the cleavage reaction of azibenzil with strong aqueous base, a reaction that would appear not to involve a-2 but might proceed at least in part by a-3 (wherein the conjugate bases of VIII and XIV rather than VIII and XIV would be involved).

(16) Melting points are corrected, boiling points are not. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(17) E. B. Womack and A. B. Nelson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 392.

separated in a separatory funnel and the ether layer was washed with a 10% sodium carbonate solution. The water layer was recycled through this procedure until the ether layer became colorless.

All of the ether portions were combined and dried over anhydrous magnesium sulfate overnight. The ether solution was evaporated to dryness and the residue was recrystallized from ether-petroleum ether. The yield of α -diazacetophenone was 2.34 g. (16%), m.p. 47–48.5° (lit.¹⁸ m.p. 49–50°).

All of the sodium carbonate fractions were combined and neutralized with concentrated hydrochloric acid. The white solid that formed was removed by filtration. The yield of benzoic acid was 3.9 g. (32%), m.p. 121.5–122°, mixture m.p. with pure benzoic acid, m.p. 121–122°.

B. 1.—In a three-necked flask, equipped with a mechanical stirrer and a dropping funnel, were placed 8.58 g. (0.05 mole) of phenacylamine hydrochloride, 150 ml. of water and 100 ml. of ether. To this was added, with stirring, 10.35 g. (0.15 mole) of sodium nitrite in 25 ml. of water. Then 125 ml. of a dilute sulfuric acid solution (6 g. of concentrated sulfuric acid in 100 ml. of water) was added slowly (approximately 10 drops per minute). The reaction mixture was allowed to stir for 24 hours at room temperature. The ether and water layers were then separated and the water layer was extracted with two 50-ml. portions of ether. The combined ether layers were extracted with one 25-ml. portion and two 10-ml. portions of a 10% sodium carbonate solution. The sodium carbonate extract was acidified with concentrated hydrochloric acid. After chilling in the ice-box overnight, the white precipitate was collected by filtration. The yield of benzoic acid was 4.12 g. (68%), m.p. 122–122.5°.

The ether layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The yield of ether-soluble product was 1.47 g.

Experiments using only one equivalent of sodium nitrite produced a maximum yield of 52%. In addition, the use of this lesser amount of sodium nitrite gave inconsistent results.

When these conditions were employed, but substituting phenylacetic acid, benzaldehyde, phenacyl alcohol, isonitrosoacetophenone or phenacyl chloride for phenacylamine hydrochloride, no benzoic acid was obtained.

2.—Phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated as in procedure B-1 with the exception that dilute hydrochloric acid was substituted for the dilute sulfuric acid (the molarity of the dilute hydrochloric acid was equal to that of the dilute sulfuric acid solution). The yield of benzoic acid was 1.49 g. (61%), m.p. 121.5–122.5°.

3.—Phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated as in procedure B-1 with the exception that dilute acetic acid was substituted for the dilute sulfuric acid (the molarity of the dilute acetic acid was equal to that of the dilute sulfuric acid solution). The yield of benzoic acid was 1.44 g. (59%), m.p. 122–123°.

4.—Phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated with 4.14 g. (0.02 mole) of sodium nitrite as in procedure B-1 with the exception that only 1 ml. of dilute sulfuric acid was initially added to the reaction mixture. After 24 hours, the remainder of the 50 ml. of acid was added dropwise and the reaction was allowed to continue for an additional 24 hours. The yield of benzoic acid was 1.41 g. (58%), m.p. 122–123°.

Determination of Absence of Hydrogen Cyanide.—Phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated as in procedure B-1 with the exception that nitrogen was bubbled through the reaction mixture and the escaping gases were scrubbed with 400 ml. of 1 *N* potassium hydroxide. The yield of benzoic acid was 1.51 g. (62%), m.p. 122–123°. The potassium hydroxide solution gave a negative test for cyanide with copper sulfide paper.¹⁹

A sample of phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated exactly as above with the exception that 0.16 g. (0.0024 mole) of potassium cyanide was added to the reaction mixture. The yield of benzoic acid was 1.42 g. (58%), m.p. 122–123°. The potassium hydroxide solution gave a positive test with copper sulfide paper, turning colorless the portion of paper in contact with the drop.

(18) L. Wolff, *Ann.*, **325**, 129 (1902).

(19) F. Feigl, "Spot Tests," Elsevier Publishing Co., New York, N. Y., 1954, Vol. 1, p. 290.

Analysis for Methanol. Qualitative.—Phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated as in procedure B-1 with the exception that no ether was used. After a 5-hr. reaction period, the reaction mixture was distilled at atmospheric pressure and 4 ml. of distillate was collected. To 2 ml. of distillate was added 2 ml. of Schiff aldehyde reagent. The resulting solution remained colorless even after 1 hour, indicating the absence of aldehydes or any other interfering substances in the distillate. To the remaining 2 ml. of distillate was added 1 ml. of a potassium permanganate-phosphoric acid solution.²⁰ After standing for 10 min., the mixture was decolorized by the addition of 1 ml. of an oxalic acid-sulfuric acid solution.²⁰ After decolorization, 2 ml. of Schiff aldehyde reagent was added. In a few minutes, a violet color developed, indicating the presence of methyl alcohol in the distillate.²⁰

Blanks were run on all of the starting materials, phenacylamine hydrochloride, sodium nitrite and dilute sulfuric acid and one possible product, phenacyl alcohol. Negative tests were obtained in all cases.

Quantitative.—Phenacylamine hydrochloride (3.43 g., 0.02 mole) was treated as in the preceding procedure. The yield of benzoic acid was 1.42 g. (58%), m.p. 122–123°. The reaction mixture was distilled to dryness at atmospheric pressure. The distillate was diluted to 250 ml. in a volumetric flask. The test for methyl alcohol²⁰ outlined in the preceding procedure was used on 2 ml. of diluted distillate. A set of standard samples of aqueous methyl alcohol also were treated by the methyl alcohol test procedure outlined above. After 1 hour, the intensities of violet color obtained with both the unknown and the standards were compared at 590 $m\mu$ by use of a visible spectrometer. According to the comparison the unknown sample contained 0.102 g. of methanol per 100 ml. of solution. Therefore, the yield of methyl alcohol was 0.255 g. (40%).

Analysis for Phenylacetic Acid.—The procedure of Clinton Laskowski²¹ for the esterification of carboxylic acids was used. A mixture of 30 ml. of ethylene dichloride, 9.6 g. (12.0 ml., 0.3 mole) of methyl alcohol, 1.5 ml. of sulfuric acid, 12.08 g. (0.099 mole) of benzoic acid and 0.12 g. (0.001 mole) of phenylacetic acid was heated under reflux overnight. The reaction mixture was washed with one 50-ml. and two 25-ml. portions of water, one 50-ml. and two 25-ml. portions of a 5% aqueous sodium bicarbonate solution and one 50-ml. and two 25-ml. portions of water, in that order. The ethylene dichloride solution was dried overnight over anhydrous magnesium sulfate.

Following the procedure outlined above 3.25 g. of acid, obtained from the reaction of phenacylamine hydrochloride with nitrous acid, was converted to the methyl ester.

A 0.04-ml. sample of the ethylene dichloride solution of the esters obtained by the esterification of the standard acid mixture was injected into a Perkin-Elmer Vapor Fractometer, model 154B, which was operated at 15 p.s.i. pressure of helium and a column temperature of 174° and which used a 0.25-in. column, 2 m. in length, packed with Perkin-Elmer packing B (20% di-(2-ethylhexyl) sebacate on 60–80 mesh Chromosorb R). After an initial peak due to the solvent ethylene dichloride, a large peak was observed, followed by a small peak. The retention times of these latter two peaks corresponded to those of pure methyl benzoate and methyl phenylacetate, respectively. Thus, the method was easily capable of detecting the presence of 1% phenylacetic acid in benzoic acid.

A 0.04-ml. sample of the ethylene dichloride solution of the esters obtained by the esterification of the reaction mixture acid was injected into the Fractometer. After an initial peak of the solvent, ethylene dichloride, a large peak (corresponding to that of pure methyl benzoate) was observed. No other peaks were obtained, even though the column was operated for a much longer time than would be needed for a methyl phenylacetate peak to appear.

Reaction of *p*-Substituted Phenacylamine Hydrochlorides with Nitrous Acid.—The procedure followed is illustrated by that used with *p*-methylphenacylamine hydrochloride.

In a three-necked flask, equipped with a mechanical stirrer and a dropping funnel, were placed 9.18 g. (0.05 mole) of

(20) F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1937, Vol. II, p. 18.

(21) R. O. Clinton and S. C. Laskowski, *This Journal*, **70**, 3135 (1948).

p-methylphenacylamine hydrochloride, 150 ml. of water and 100 ml. of ether. To this was added with stirring, 10.35 g. (0.15 mole) of sodium nitrite in 25 ml. of water. Then 125 ml. of a dilute sulfuric acid solution (6 g. of sulfuric acid in 100 ml. of water) was added slowly (approximately 10 drops per minute). The reaction mixture was stirred for 24 hr. at room temperature. The ether and water layers were separated and the water layer was extracted with two 50-ml. portions of ether. The combined ether layers were extracted with 25-ml. portions of a 10% sodium carbonate solution until no additional acid was obtained (as evidenced by evolution of carbon dioxide). The sodium carbonate extract was acidified with concentrated hydrochloric acid. After the solution had been chilled in the ice-box overnight, the white precipitate was collected by filtration. The yield of *p*-toluic acid was 5.31 g. (78%), m.p. 176–178° (lit.²² m.p. 181°). The product was recrystallized from a water-ethanol mixture, m.p. 178–179°, mixture m.p. with pure *p*-toluic acid, 177.5–179°.

The ether layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The yield of ether-soluble product was 1.49 g.

The Reaction of α -Diazoacetophenone with Nitrous Acid.—To a mixture of 2.81 g. (0.02 mole) of α -diazoacetophenone (washed with a cold 10% aqueous sodium carbonate solution to remove any benzoic acid present), 2.76 g. (0.04 mole) of sodium nitrite, 110 ml. of water and 50 ml. of ether, 60 ml. of 1 *N* hydrochloric acid was added dropwise. The reaction mixture was stirred for 24 hr. at room temperature. The ether and water layers were then separated and the water layer extracted with two 50-ml. portions of ether. The combined ether layers were extracted with one 15-ml. portion and two 5-ml. portions of a 10% aqueous sodium carbonate solution. The sodium carbonate extract was acidified with concentrated hydrochloric acid. After chilling in the ice-box overnight, the white precipitate was collected by filtration. The yield of benzoic acid was 0.03 g. (1.2%), m.p. 124–125°.

When the same procedure was employed with the exception that 0.02 mole of phenacylamine hydrochloride was substituted for α -diazoacetophenone, 1.35–1.50 g. (55–61%) of benzoic acid was obtained.

To a solution of 4.14 g. (0.06 mole) of sodium nitrite in 100 ml. of water were slowly added, simultaneously, a solution of 2.81 g. (0.02 mole) of α -diazoacetophenone (washed with a 10% aqueous sodium carbonate solution) in 50 ml. of ether and 50 ml. of dilute sulfuric acid (6 g. of sulfuric acid in 100 ml. of water). The ethereal solution of α -diazoacetophenone was added slightly faster than the sulfuric acid solution, in order to maintain a slight excess of α -diazoacetophenone in the reaction mixture. The ether and water layers were then separated and water layer was extracted with two 25-ml. portions of ether. The combined ether extracts were extracted with one 25-ml. portion and two 10-ml. portions of a 10% sodium carbonate solution. The sodium carbonate extract was acidified with concentrated hydrochloric acid. After chilling in the ice-box overnight, the white precipitate was collected by filtration. The yield of benzoic acid was 0.04 g. (1.6%), m.p. 118–120°, mixture m.p. with authentic benzoic acid, 124–126°.

When the same procedure was employed with the exception that 0.02 mole of phenacylamine hydrochloride was substituted for α -diazoacetophenone, 1.46 g. (60%) of benzoic acid was obtained.

α -Phenyl-*n*-pentylamine.—The procedure of Ingersoll, *et al.*,²³ for the preparation of α -*p*-chlorophenylethylamine was followed using an initial charge of 81 g. (0.5 mole) of valerophenone, 126 g. (2.0 moles) of ammonium formate and 25 ml. of 90% formic acid. On heating this mixture the temperature rose rapidly to about 125°, then slowly, over a period of 3.5 hr., to about 165° at which time the mixture become homogeneous and ebullition began. The solution was refluxed for 16.5 hours, the temperature being maintained between 175 and 185°, and the distillate (water + ketone) was collected as specified.²³ In order to maintain a slightly acidic reaction mixture, 15-ml. portions of 90% formic acid were added whenever ammonia was detected at the take-off connection (total formic acid added = 220 ml.). Any ketone that distilled out with the water was separated

and returned to the reaction mixture. The heating process was interrupted and resumed several times.

On cooling, the reaction mixture separated into two layers. The red upper layer was separated and heated under reflux with 100 ml. of concentrated hydrochloric acid for 1.5 hr. To the resulting mixture was added enough water (presumably) to dissolve the amine hydrochloride. The solution was extracted with two 50-ml. portions of benzene and two 50-ml. portions of ether. The aqueous layer was neutralized with 33% potassium hydroxide and extracted with three 50-ml. portions of ether. The ether extract was dried over anhydrous magnesium sulfate and the ether removed by distillation. The amount of amine obtained was quite small.

The benzene and ether used to extract the acidic hydrolysis mixture was evaporated to dryness and the solid obtained, which appeared to be amine hydrochloride, was dissolved in 2 *N* hydrochloric acid. This solution was extracted with two 50-ml. portions of ether. The aqueous layer was neutralized with 33% potassium hydroxide and then extracted with three 50-ml. portions of ether. The ethereal extract was dried over anhydrous magnesium sulfate and the ether was then removed by distillation. The amine was combined with the small amount of amine obtained above and distilled under reduced pressure. The yield of α -phenyl-*n*-pentylamine was 61.0 g. (75%), b.p. 116–118° (15 mm.). The product was dried over potassium hydroxide pellets and redistilled twice under reduced pressure, b.p. 83° (1.6 mm.), *n*_D²⁰ 1.5090. An additional experiment gave a 74% yield.

Anal. Calcd. for C₁₁H₁₇N: C, 80.92; H, 10.50; N, 8.58. Found: C, 81.17; H, 10.62; N, 8.59.

Although it appeared that the crude amine hydrochloride was soluble in the benzene and/or ether fractions on extraction of the acidic hydrolysis mixture and although the evaporation of the ether and benzene fractions yielded crude amine hydrochloride, the somewhat purer amine hydrochloride, after being dissolved in 2 *N* hydrochloric acid, was insoluble in ether.

α -Aminovalerophenone Hydrochloride.—The procedure of Baumgarten and Petersen¹ for the preparation of phenacylamine hydrochloride was followed.

Using 42.7 g. (74.4 ml., 0.2 mole) of α -phenyl-*n*-pentylamine and 44.7 g. (49.2 ml., 0.4 mole) of *t*-butyl hypochlorite in the first step of the reaction and 13.8 g. (0.6 g. atom) of sodium and 140 ml. of anhydrous methanol in the second, a 30-min. reflux period was required before a test with acidified starch-iodide paper was negative. The reaction mixture was cooled in an ice-water-bath and the precipitated sodium chloride was removed by filtration. The filter cake was washed with three 25-ml. portions of dry benzene. The combined filtrates were extracted with one 150-ml. and three 50-ml. portions of 2 *N* hydrochloric acid. The combined acid extracts were washed twice with 50-ml. portions of ether. The ether extracts were discarded.

The pale yellow aqueous solution was evaporated to dryness in a rotating evaporator at 40°. The residue was extracted with one 50-ml. portion and two 25-ml. portions of hot isopropyl alcohol-hydrochloric acid solution (1 ml. of hydrochloric acid per 100 ml. of isopropyl alcohol). The residual sodium chloride was discarded. Chilling the alcohol extracts yielded one crop of colorless crystals which were collected by filtration. Four volumes of anhydrous ether were added to the filtrate and a second crop was obtained. The combined yield was 27.8 g. (65%), m.p. 156–158°. Recrystallization from isopropyl alcohol-ether yielded a product, m.p. 156.5–158°. An additional experiment gave a 66% yield.

Anal. Calcd. for C₁₁H₁₆ClNO: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.88; H, 7.56; N, 6.19.

The Reaction of α -Aminovalerophenone Hydrochloride with Nitrous Acid.— α -Aminovalerophenone hydrochloride (21.35 g., 0.1 mole) was treated with nitrous acid as in procedure A. On acidification of the sodium carbonate extract, an oil was obtained. The resulting oil was extracted with ether and the ethereal extract was dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue was distilled at reduced pressure, yielding 5.56 g. (31%) of α -phenylvaleric acid, b.p. 136–140° (3.0 mm.), m.p. 48–52°. The product was recrystallized from petroleum ether, m.p. 53–55° (lit.²⁴ m.p. 52°). Its neutralization equivalent was 180.5 (calcd. 178.2).

(22) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953, p. 520.

(23) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp and G. Jennings, *This Journal*, **58**, 1808 (1936).

(24) R. H. Pickard and J. Yates, *J. Chem. Soc.*, **96**, 1011 (1909).

An additional experiment with 4.27 g. (0.02 mole) of α -aminovalerophenone hydrochloride yielded 2.03 g. of crude acid mixture. A small sample (0.00861 g.) of the crude acid was dissolved in an ethyl acetate-Skelly-Solve B mixture and placed on a 1.5 \times 35 cm. silicic acid chromatographic column using the procedure of Bhargava and Heidelberger²⁵ for the separation of carboxylic acids.

The eluent was collected in 3.5-ml. samples, diluted with 3.5 ml. of water and 0.4 ml. of *n*-butyl alcohol and titrated with 0.005 *N* sodium hydroxide (phenol red indicator). Two peaks resulted, the first peak (corresponding to that of pure α -phenylvaleric acid) using 59% of the total volume of alkali and the second peak (corresponding to that of pure benzoic acid) using 41% of the total volume of alkali. Thus the yields in the original acid sample were 1.36 g. (38%) of α -phenylvaleric acid and 0.67 g. (27.5%) of benzoic acid.

A mixture of 1.0 g. (0.0056 mole) of the supposed α -phenylvaleric acid and 5 ml. of thionyl chloride was refluxed for 30 min. and then poured into 15 ml. of ice-cold concentrated ammonia. The precipitated amide was collected by filtration. The yield of α -phenylvaleramide was 0.49 g. (49%), m.p. 82.5–84°. The product was recrystallized from a water-ethanol mixture, m.p. 83.5–85° (lit.²⁶ m.p. 83–85°).

The Reaction of Desylamine Hydrochloride with Nitrous Acid.—Desylamine hydrochloride (4.93 g. 0.02 mole) was treated with nitrous acid as in procedure A. On acidification of the sodium carbonate extract, 2.10 g. of solid was obtained. A small sample (0.00496 g.) of the crude acid was dissolved in an ethyl acetate-Skelly-Solve B mixture and placed on the silicic acid chromatographic column described above. Two peaks resulted, the first peak (corresponding to that of pure diphenylacetic acid) using 6.5% of the total volume of alkali and the second peak (corresponding to that of pure benzoic acid) using 93.5% of the total volume of alkali. Thus, the yields in the original acid sample were 0.22 g. (5%) of diphenylacetic acid and 1.88 g. (77%) of benzoic acid.

The Reaction of α -Aminocyclohexanone Hydrochloride with Nitrous Acid.— α -Aminocyclohexanone hydrochloride (14.95 g., 0.1 mole) was treated with nitrous acid as in procedure A. After neutralization the solution was extracted with ether and the ethereal extract was dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue was distilled at reduced pressure yielding 2.40 g. (21%) of cyclopentanecarboxylic acid, b.p. 76° (2.8 mm.) (lit.²⁷ b.p. 104° (11 mm.)). Its neutralization equivalent was 119.2 (calcd. 114.1).

(25) P. M. Bhargava and C. Heidelberger, *THIS JOURNAL*, **77**, 166 (1955).

(26) Bayer & Co., German Patent 249,241; *Chem. Zentr.*, **83**, 396 (1912).

A second experiment with 2.99 g. (0.02 mole) of α -aminocyclohexanone hydrochloride yielded 0.74 g. of crude acid mixture. A small sample (0.00494 g.) of the crude acid was dissolved in an ethyl acetate-Skelly-Solve B mixture and placed on the silicic acid chromatographic column described above. Only one peak resulted (corresponding to that of pure cyclopentanecarboxylic acid). Only 56% of the acid was eluted leaving 44% of the crude acid which was not accounted for.

A mixture of 1.0 g. (0.0088 mole) of the supposed cyclopentanecarboxylic acid and 5 ml. of thionyl chloride was refluxed for 30 min. and then poured into 15 ml. of ice-cold concentrated ammonia. The precipitated amide was collected by filtration. The yield of cyclopentanecarboxamide was 0.51 g. (51%), m.p. 175–178°. The product was recrystallized from a water-ethanol mixture, m.p. 178–179° (lit.²⁷ m.p. 179°).

In a third experiment α -aminocyclohexanone hydrochloride (7.5 g., 0.05 mole) was treated with nitrous acid as in procedure B-1 except that the combined ether layers were washed only with water and dried over magnesium sulfate. The ether was removed by distillation and the residue was heated under reflux for 4 hr. with 50 ml. of anhydrous methanol and 10 g. of ion exchange resin Amberlite IR-120, which had been washed thoroughly with methanol and dried *in vacuo*. The methanol was evaporated, the residue was picked up in methylene chloride and the solution was washed with 5% sodium carbonate and with water and dried over magnesium sulfate. Examination of the solution by gas chromatography using the column and procedure described above showed the probable presence of methyl cyclopentanecarboxylate, methyl 5-hexenoate and methyl 6-hydroxyhexanoate, as well as other neutral material.²⁸ The presence of the latter two esters was inferred from the agreement of retention times with those observed for a crude mixture of esters and neutral materials obtained under the same conditions from the reaction of 6-aminohexanoic acid with nitrous acid. This tentative identification was supported by comparison of the infrared spectra of the two methylene chloride solutions, both of which showed the bands expected for compounds containing the hydroxyl (3490 (w)), ester carbonyl (1835(s)) and terminal vinyl group (1640(w), 915(s) cm.⁻¹).²⁹

(27) N. Zelinsky, *Ber.*, **41**, 2627 (1908).

(28) Based on incomplete experiments with other α -amino ketones; other materials probably present include α -hydroxycyclohexanone and 1,2-cyclohexanedione, the latter resulting from the oxidation of the former.

(29) In view of the announced intentions of Edwards and Lesage⁷ to study this particular reaction in detail, at the moment we plan no experiments with α -aminocyclohexanone beyond those described here.

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE, AMHERST, MASS.]

The Effect of the Nature of the Leaving Group upon Relative Solvolytic Reactivity¹

BY MARC S. SILVER

RECEIVED JUNE 27, 1960

A series of substituted benzhydryl *p*-nitrobenzoates have been prepared and the rates of the acid-catalyzed and neutral solvolyses of these compounds in aqueous acetone have been determined. It has been established that alkyl-oxygen fission occurs, primarily by correlating the solvolysis rates with σ^+ . The ρ -values for the neutral solvolysis (–4.12 to –3.69) are appreciably different from those for the acid-catalyzed reaction (–2.65 to –2.33). The significance of this difference is discussed briefly.

Perusal of several articles on the general nature of the solvolysis reaction^{2–4} reveals that relatively little attention has been focused on the effect of the

leaving group X upon the solvolytic behavior of RX. In 1957, however, Fainberg and Winstein⁵ systematically studied variations in the ratios of solvolysis rates for bromides to chlorides [$k(\text{RBr})/k(\text{RCI})$, R = *t*-butyl, neophyl, α -phenylethyl and benzhydryl] as a function of solvent composition.

(1) Supported by a Frederick Gardner Cottrell grant from the Research Corporation.

(2) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, chapter VII.

(4) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, chapters 5, 6.

(5) (a) A. H. Fainberg and S. Winstein, *THIS JOURNAL*, **79**, 1597, 1602, 1608 (1957); (b) S. Winstein, A. H. Fainberg and E. Grunwald, *ibid.*, **79**, 4146 (1957).