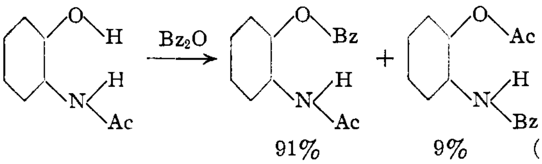
[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY OF LOUISIANA STATE UNIVERSITY]

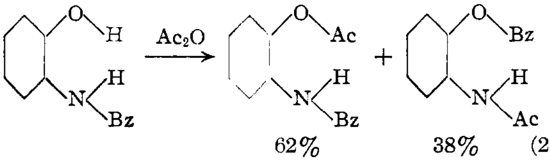
The Migration of Acetyl and Benzoyl Groups in *o*-Aminophenol. II. Hydrolysis Products of the Mixed Diacyl Derivatives and Theory of the Migrations

BY ARTHUR L. LEROSEN AND EDGAR D. SMITH

In a recent article by the present authors[1] it was shown that when acetyl and benzoyl groups were introduced into the *o*-aminophenol molecule to form the so-called "mixed diacyl" derivative, the predominant isomer formed was that one which would be expected if no rearrangement occurred. However, some rearrangement or "migration" did occur and the extent of the rearrangement varied according to the acylation sequence used. These facts were firmly established by a combination of chromatographic separations and ultraviolet spectrophotometry and are summarized by equations (1) and (2).



(1)



(2)

The two pure isomers were isolated and further study showed that, under the influence of certain solvents or of heat, they were interconvertible and tended toward an equilibrium mixture. This was the first time that these two pure isomers had been isolated, it being generally believed up to this time that only one mixed diacyl was produced by this reaction and others of this general type.

All of the workers who have attempted the preparation of the mixed acetyl–benzoyl derivatives of *o*-aminophenol have reported that on hydrolysis only the N-benzoylate was obtained.[2,3] It is the purpose of this paper to report the results of a careful chromatographic separation of the hydrolysis products of these pure and mixed isomeric diacyls, and to present some details of a new theory of the mechanism of these acyl migrations.

Table I summarizes the results of the hydrolysis of various mixtures of the two isomeric mixed diacyls in aqueous sodium hydroxide solutions. It will be noted from this tabulation that, regardless of the relative percentages of the two isomeric mixed diacyls in the sample hydrolyzed, the resulting hydrolysis mixture contained about the same proportions of 63% *o*-benzoylaminophenol to 37% *o*-acetylaminophenol. Obviously the fractional crystallization procedures used by the earlier workers in this field were ineffective and gave completely misleading results!

TABLE I

ANALYSIS OF MIXED DIACYL HYDROLYSIS PRODUCTS

Sample hydrolyzed	First crop NA,[a] %	First crop NB,[b] %	First crop Yield,[b] %	Second crop NA, %	Second crop NB, %	Second crop Yield,[c] %	Totals NA, %	Totals NB, %	Totals Yield, %
Pure NA	29	71	69	41	10	20	41	59	89
93% NA	37	63	98	..	..	..	37	63	98
65% NA	31	69	86	2.5	1	4	33	67	90
28% NA	36	64	90	..	..	..	36	64	90
Pure NB	23	77	63	41	10	21	38	62	84

[a] N-Acetyl-*o*-aminophenol. [b] N-Benzoyl-*o*-aminophenol. [c] Yields shown are based on the assumption that the relative amounts of the two monoacyls was as indicated in the "Totals" column.

The results discussed above indicate to us that the "migrations" which have been observed with mixed diacyl derivatives of *o*-aminophenol are not true migrations occurring during the preparation of the mixed diacyl derivatives, but are rather isomerizations of the normally expected product caused by the catalytic effect of the reaction media used. The isomerizations are probably instances of general acid and base catalysis[4] and hence should be expected to take place in both alcohol or water (acids), and in pyridine (base). A schematic representation of the isomerization mechanism which we believe occurs in alcohol solutions is given in Fig. 1. The dotted lines

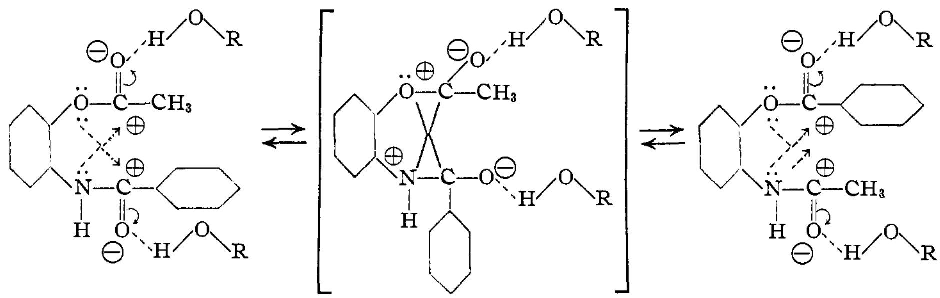


Fig. 1.—Suggested mechanism for the general acid catalyzed migration of acyl groups in *o*-aminophenol.

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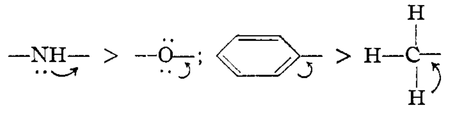
(1) A. L. LeRosen and E. D. Smith, THIS JOURNAL, **70**, 2705 (1948).

(2) L. C. Raiford, *ibid.*, **41**, 2068 (1919).

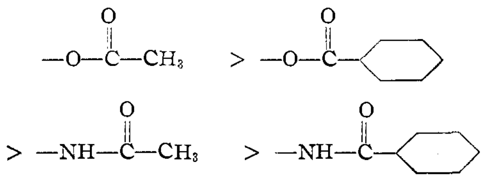
(3) Frank Bell, *J. Chem. Soc.*, 2966 (1931).

(4) L. P. Hammett, "Physical Organic Chemistry," 1st ed., McGraw-Hill Book Co., New York, N. Y., 1940, pp. 215–227.

represent the hydrogen bonds formed between the solvent and the diacyl, the dotted arrows represent the chelation tendencies in the molecules (augmented by the hydrogen bonding), and the circled plus and minus signs are intended to show the nature of the charges conferred on the two carbonyl carbon atoms as a result of the resonance and inductive effects within the molecules concerned. In assigning the relative charges in the above molecules we have assumed the following decreasing order of + T effects (Ingold's notation)



If it be further assumed that the + I effect of the methyl group is not great in comparison with the above effects, the following decreasing order of positive charges on the carbonyl carbon atoms must result.



As indicated by the double arrows in Fig. 1, the steps shown therein are reversible and so should result id an equilibrium mixture of the two isomeric mixed diacyls. It is possible to make an approximate prediction of the composition of this equilibrium mixture on the basis of what we have termed "the principle of minimum charge concentration." According to this concept the more stable of the two isomers will be that one having the better distribution of charge over its reactive centers so that there is no one point of strong positive or negative charge. For example, in Fig. 1 it will be seen that the N-acetyl-O-benzoyl form of the isomers has the better equalization of charge over its molecule and hence is the one which should predominate in the equilibrium mixture.

Pyridine solutions have most commonly been used by workers in preparing and studying the mixed acetyl–benzoyl derivatives of *o*-aminophenol and so, in Fig. 2, a summary is made of the steps and intermediates which we believe are involved in forming the various products which have been found in such solutions. While only those materials not bracketed have been isolated, this schematic representation seems to qualitatively explain the formation of all of the products which have been observed. For example, a mechanism is shown in this figure for the seemingly anomalous replacement of a benzoyl group by acetyl during a second acylation using a large excess of acetic anhydride, and also the co-existence of a mono- and a triacetyl derivative in the same strongly acetylating solution.[5] (It is of interest to note that this same type of phenomena was observed in this work when a small quantity of *o*-diacetylaminophenol was dissolved in pyridine. In this case crystals of starting material and of the monoacetyl derivative were obtained on evaporating the pyridine under vacuum.)

From Table I it will be seen that approximately the same mixture of monoacylated products was obtained regardless of the relative amounts of isomeric mixed diacyls hydrolyzed. This would appear at first glance to indicate that the diacyls first isomerized to an equilibrium mixture and then hydrolyzed to yield approximately identical mixtures. That this is not true, however, is shown by the fact that the *o*-benzoylaminophenol predominates in the hydrolysis mixtures rather than the *o*-acetylaminophenol which form is present in greater quantity in the equilibrium mixture. This behavior can readily be explained in terms of the present theory of the migration phenomena. Since hydrolysis in sodium hydroxide solution is a nucleophilic attack by hydroxyl ions on the most positive center of the molecule, it follows that the acyl group attached to oxygen will be the one which is more readily attacked by these ions. The N-benzoyl-O-acetyl form should therefore hydrolyze much more rapidly than its isomeride and, since hydrolysis of this type is irreversible, this greater hydrolysis rate should lead to a predominance of the *o*-benzoylaminophenol in the hydrolysis mixture. However, this isomeric form of the diacyl is the one present in smaller quantity in the equilibrium mixture so that this predominance is reduced and might conceivably be negated entirely depending on the relative rates of hydrolysis and isomerization. Since the same factor which causes the N-benzoyl-O-acetyl form to hydrolyze rapidly, *i. e.*, the strong positive charge on its phenolic carbonyl carbon atom, also causes this isomer to be relatively unstable in aqueous solution and consequently present to a smaller extent than its isomeride, it follows that in all such hydrolyses of mixed diacyl derivatives a mixture of the two possible monoacylated products must be obtained. If isomerization is considered to be fast as compared with hydrolysis, then one should expect to obtain essentially the same ratio of monoacylated products regardless of the starting proportions of the two isomeric mixed diacyls. This appears to be the case with the acetyl–benzoyl derivatives studied in this work.

In similar fashion many of the other related phenomena which have been observed in acyl migration studies, such as the formation of benzoxazolones[6] may be satisfactorily explained in terms of modern theory. A careful study of all experimental data reported in the literature on this

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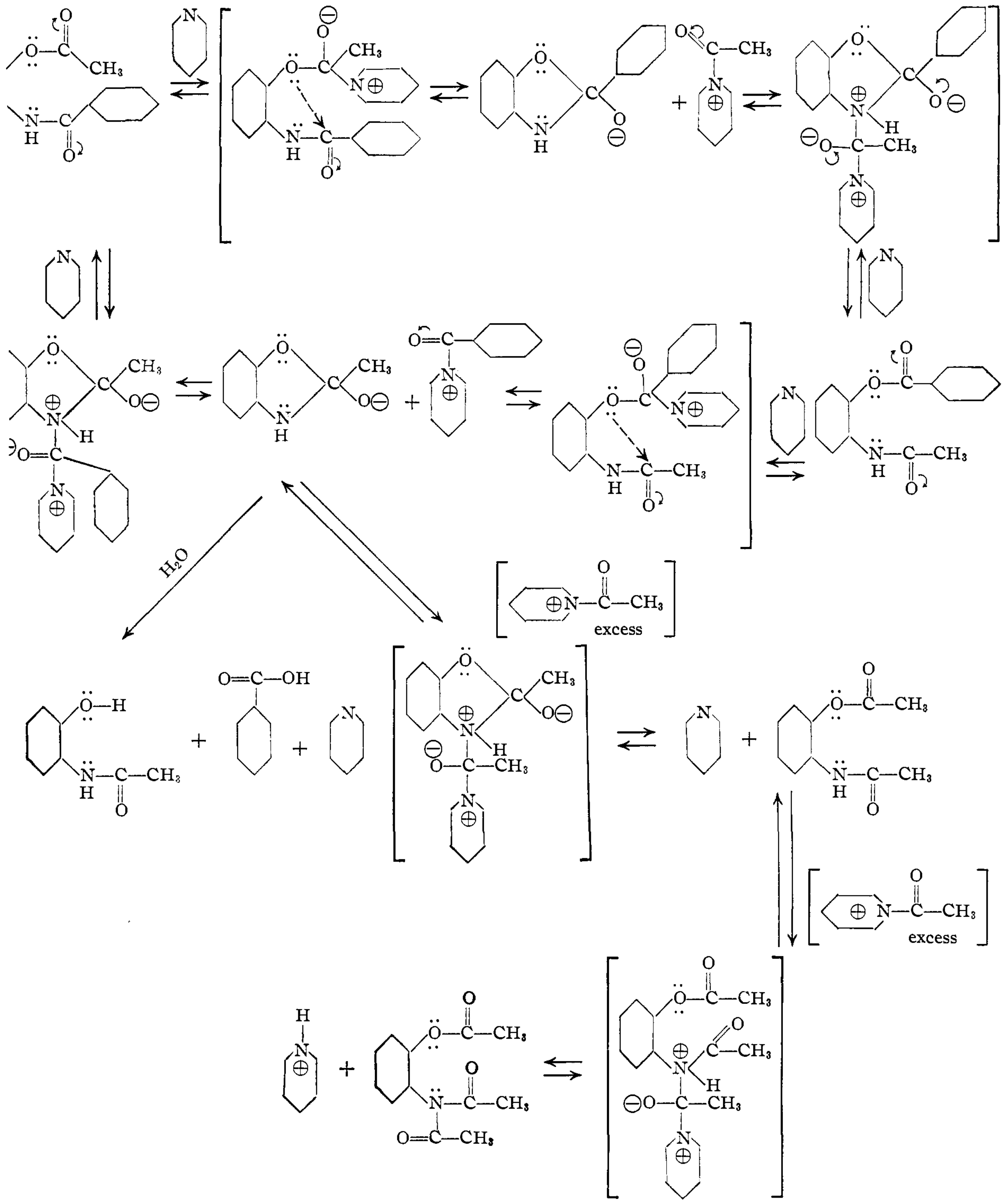
(5) L. C. Raiford and A. L. LeRosen, THIS JOURNAL, **67**, 2163 (1945).

(6) L. C. Raiford and G. O. Inman, *ibid.*, **56**, 1586 (1934).



2.—Suggested mechanism for general base catalyzed migration of acyl groups in *o*-aminophenol and other associated phenomena.

neral subject of acyl migrations shows generally od agreement with the results which would be redicted on the basis of the theory of the migraons outlined in this paper. In most instances here the theory appears to fail, a close study of the experimental data such as melting points, yields and crystallization solvents, indicates that this apparent conflict between theory and experiment is probably due to incomplete recovery of products, or to the recovery of impure products by these earlier workers. It is our opinion that much of this work must be re-investigated on a quantitative basis as outlined in this and in the preceding article of this series. We are now engaged in work of this nature in these laboratories.

Experimental

Hydrolysis of the Diacyls.—The hydrolyses of the mixed diacyls were carried out in aqueous sodium hydroxide solution using an excess of sodium hydroxide. The pure mixed diacyls both went into solution slowly, but there was a noticeably greater rate of solution on the part of the N-benzoyl-O-acetyl isomer. After solution was made complete by stirring and warming to 50°, the solutions were allowed to cool and the monoacylated products precipitated by the addition of 6 *N* hydrochloric acid dropwise until the solution was slightly acid to Hydrion paper. The precipitates were filtered off and dried, and in most cases a second crop of crystals was obtained by evaporation of the filtrates to dryness under vacuum. The first crop material was a light tan solid melting at about 150° over a range of 4–5°. There was no observable physical difference between the products obtained in this way from the two isomeric mixed diacyls.

Analysis of the Hydrolysis Products.—The analysis method used was essentially the same as that described in ref. (1) for the mixed diacyls. Using the same system of adsorbents and developing agents it was found that the *o*-acetylaminophenol was adsorbed near the top of the column while the *o*-benzoylaminophenol moved fairly rapidly down the chromatographic column. The same streak reagent was also effective in locating these adsorbate zones. The ultraviolet absorption peak at 284 mμ was used for quantitative estimation of the monoacetyl compound, and the absorption peak at 296 mμ was used for the monobenzoyl material. By using these wave lengths rather than the shorter wave length maxima, interference due to benzoic acid, which was found to contaminate the *o*-benzoylaminophenol adsorbate zone, was practically eliminated.

Summary

1. Contrary to previously published reports, the hydrolysis of the mixed acetyl–benzoyl diacyl derivatives of *o*-aminophenol in aqueous sodium hydroxide solution has been shown to yield both *o*-acetylaminophenol and *o*-benzoylaminophenol. Mixtures of these two products containing about 63% of the N-benzoylate were obtained irrespective of the relative amounts of the two isomeric mixed diacyls in the sample hydrolyzed.

2. The basic outlines of a new theory of the mechanism of acyl migrations has been given. This theory is based on modern organic theory involving a consideration of the relative inductive and resonance effects in the molecules concerned and good agreement has been found between the results reported in the literature and those predicted by theory.

3. A new principle has been developed for predicting which of several isomers will be the most stable. This principle has been called "the principle of minimum charge concentration" and states that the most stable isomer will be that one having the best distribution of charge over its reactive centers so that there is no one point of strong positive or negative charge.

4. In the light of our findings in this, and in the preceding article of this series, it seems desirable to re-examine much of the past work in this field.

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[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

A Synthesis of DL-Proline

BY NOEL F. ALBERTSON AND JEANNE L. FILLMAN[1]

Perhaps no amino acid is easier to synthesize—on paper—than proline. However, the reported solubility of proline in alcohol makes its isolation and purification somewhat more difficult than is the case with other amino acids. All of the recorded syntheses of proline make use of silver salts to remove halide ions, and most of the methods also make use of the copper salt of proline in the purification. This makes the preparation of proline both tedious and somewhat expensive. In addition, some of the methods previously reported did not give crystalline intermediates so that the final product in some instances also contained glycine or glutamic acid. In fact, in a chapter on amino acids published recently[2] Dunn and Rockland point out that there is at present no satisfactory laboratory procedure for the preparation of proline and that, "even today, the physical properties of analytically pure DL or L-proline have not been determined."

The method reported here affords a simple and practical synthesis of pure DL-proline, through the reactions diagrammed.

The over-all yield is approximately 20% when a single batch of starting material is carried all the way through to proline.[3]

The use of bromine in place of sulfuryl chloride to give the 3-bromo-3-carbethoxy-2-piperidone led to unsatisfactory results since the sodium bromide subsequently formed was difficult to remove (*cf.* ref. 13).

Amberlite resin may be used to liberate proline from its hydrochloride, but the method is not as satisfactory as the use of triethylamine.

It is interesting to note that we were unable to

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(1) Present address: Mrs. M. Silvestrone, Scotia High School, Scotia, New York.

(2) Anson and Edsall, "Advances in Protein Chemistry," Vol. III, Academic Press, Inc., New York, N. Y., 1947, p. 322.

(3) Mikeska, in U. S. Patent 2,461,336 which became available to us during the revision of this manuscript, reports the preparation of I in 88% yield using equimolar quantities of malonic ester and acrylonitrile. This would give a 29% over-all yield of proline.