**Identification of the Precipitate Obtained on Heating Reagent A.**[2]—As heating of reagent A progressed more and more of a very hygroscopic white to yellow solid separated on the walls of the reaction vessel. Solution in water followed by usual inorganic qualitative analysis showed the precipitate to be rich in zinc and bromide, as expected, but the presence of ethoxide could only be shown by the high alkalinity of the aqueous solution prior to acidification with dilute nitric acid. Consequently a carefully washed (toluene) sample of the precipitate was dissolved in *n*-butyl alcohol. The butanol solution was then subjected to v.p.c. analysis, and ethanol was identified by its retention time, which was found to differ from that of any other known components of the system. The only other "peaks" were very small (scarcely more than "blips") and they corresponded in retention times to the usual esters and a trace of toluene. The ethanol peak was substantial, and with the butanol peak constituted the only real absorptions in the chromatograms.

**Ethyl γ-Bromoisobutyrylisobutyrate.**—The following procedure is modified from directions for ketone bromination by Corey and Sneen.[26,27] A solution of 28.8 g. of reagent grade bromine (3% excess) in 100 ml. of glacial acetic acid was added dropwise to a solution of ethyl isobutyrylisobutyrate[12] (99.5% purity by v.p.c.) in 300 ml. of anhydrous ether and 60 ml. of glacial acetic acid. After refluxing for *ca.* 22 hr., water was added to the mixture until two layers formed, and then lithium bromide was added and the layers were separated. The solvents were distilled off on the steam bath under aspirator pressure, and the residual liquid was fractionated at 0.50–0.55 mm. A fraction boiling at 150° amounted to *ca.* 80% of the expected product. This was redistilled and the fraction boiling at 64° (0.25 mm.) was collected, 20.4 g. (45%).

*Anal.* Calcd. for $C_{10}H_{17}BrO_3$: C, 45.29; H, 6.46; Br, 30.14. Found: C, 45.43; H, 6.07; Br, 30.36.

(26) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

(27) This procedure carried out by Mr. H. P. Knoess.

# Studies on the Acid-Catalyzed Esterification of Substituted *o*-Benzoylbenzoic Acids in Methanol*,[1]

MELVIN S. NEWMAN AND CONSTANTINOS COURDUVELIS

*The Evans Chemistry Laboratory of The Ohio State University, Columbus, Ohio 43210*

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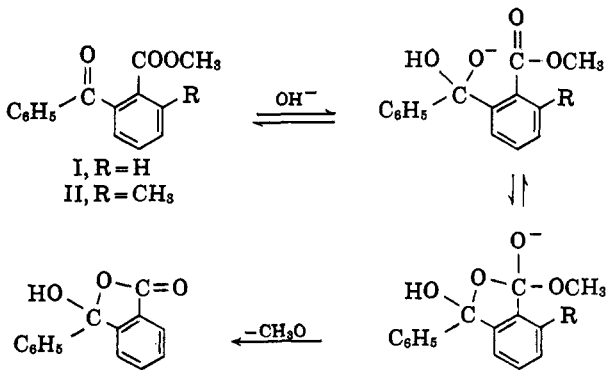
Studies on the acid-catalyzed esterification of a number of methylated *o*-benzoylbenzoic acids in methanol show that the composition of the esters formed under kinetic control is different from that formed under thermodynamic control in almost all cases. For the parent *o*-benzoylbenzoic acid *pseudo ester is formed more rapidly than normal ester* and the normal ester is formed almost exclusively under thermodynamic control. Four different routes of esterification are outlined and discussed.

The surprising fact that methyl 2-benzoyl-6-methylbenzoate (II) is hydrolyzed by alkali more rapidly than methyl *o*-benzoylbenzoate (I) was explained by a mechanism which involved primary attack of the hydroxide ion at the ketonic carbonyl group followed by intramolecular elimination of a methoxide ion.[2] The rate of this (intramolecular) reaction is greater than that of a similar reaction in the unsubstituted case because the methyl group in the 6-position causes the carbonyl group of the carbomethoxy group of II to be more favorably oriented for intramolecular attack than that in I. The conventional mechanism for ester hydrolysis, that involving attack of hydroxide ion at the carbonyl group of the carbomethoxy group, could also be involved. However, in the case of II the presence of two *ortho* substituents would be expected to decrease greatly the probability of such an attack. In the case of I both mechanisms are likely. How much hydrolysis takes place by each path is not known.




In view of the above analysis a re-examination of the acid-catalyzed esterification of *o*-benzoylbenzoic acids with methanol seemed in order. In previous work, the proportions of normal and pseudo methyl esters obtained from a number of methylated *o*-benzoylbenzoic acids were determined.[3] However, these esters were those present after lengthy periods of esterification at reflux in methanol and, hence, the proportions were more likely those controlled by the various equilibria involved (see Scheme I[4]) and not the kinetically controlled ones.

Examination of this scheme reveals that normal ester $I_n$ might be formed by route A directly from the keto acid I or by route B–C involving prior formation of pseudo ester $I_p$, or partly by each route. Similarly, pseudo ester $I_p$ might be formed directly from I by route B, or *via* route A–C involving prior formation of $I_n$, or partly by each route.

We now find that when I is heated with methanolic hydrogen chloride at 55.5° the ester isolated in 13.5% yield after 15 min. contains about 51% of $I_n$ and 49%

* That this article should appear in an issue honoring Professor Louis F. Fieser is particularly fitting because of the fact that my (M. S. N.) interest in *o*-benzoylbenzoic acid chemistry first arose in connection with synthetic work done while serving as a postdoctoral fellow at Harvard in 1935–1936.

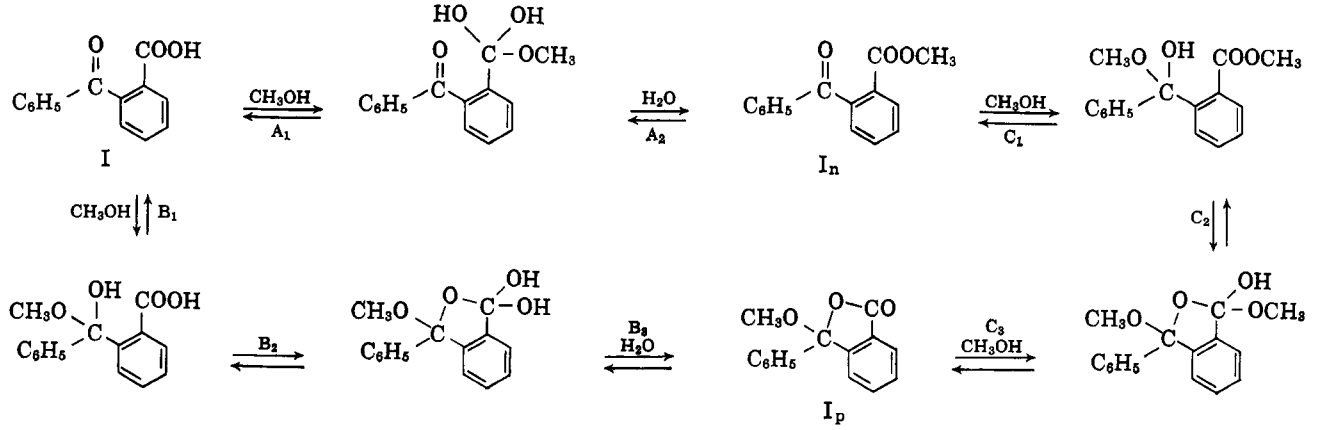
(1) This research was supported by Grant GP-718 from the National Science Foundation.

(2) M. S. Newman and S. Hishida *J. Am. Chem. Soc.*, **84**, 3582 (1962).

(3) M. S. Newman and C. W. Muth, *ibid.* **73**, 4627 (1951), Table I.

(4) The notations $I_n$ and $I_p$, etc., mean normal and pseudo ester and will be used throughout this paper for all of the esters involved. No attempt has been made to show the catalytic protons. Throughout the discussion of mechanisms of esterification we have avoided routes which involve acylium ions of the type described by M. S. Newman [*ibid.* **64**, 2324 (1942)]. Such ions are present in about 100% sulfuric acid, but we do not believe they play an appreciable role in the methanolic solutions of the present study.

SCHEME I



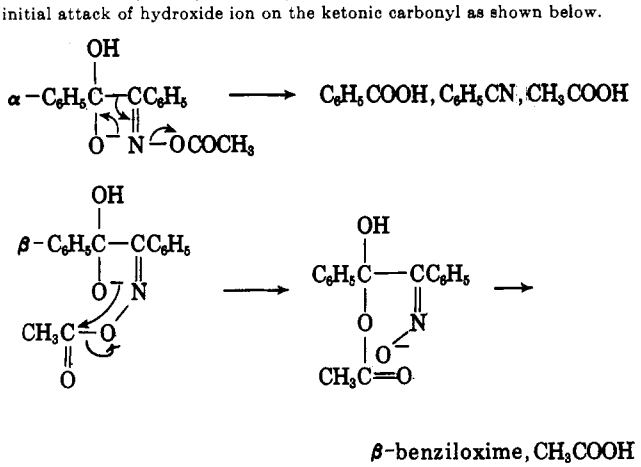
of $I_p$.[5] Under exactly comparable conditions $I_p$ is converted into a mixture of 39% of $I_n$ and 61% of $I_p$. Furthermore the composition of the equilibrium mixture of esters is 98% $I_n$ and 2% $I_p$ (see Table I).[6] These facts prove that I first forms mainly pseudo ester $I_p$ by route B. $I_p$ is then rapidly converted into $I_n$ by route C. A small amount of $I_n$ is formed from I *via* route A but accurate kinetic measurements would be required to determine this. Thus the mechanism of acid-catalyzed esterification of *o*-benzoylbenzoic acid (I) is comparable to the cyclic mechanism (route 2 in ref. 2) for alkaline hydrolysis[7] of normal esters in that the first attack of methanol is mainly at the ketonic function.

In view of the above results we decided to study the relative rates of esterification of the entire series of substituted *o*-benzoylbenzoic acids[3] under the same conditions and to determine the amounts of normal and pseudo esters formed under kinetic and thermodynamic control. In Table I are listed the amounts of normal and pseudo methyl esters found after 15 min. (mainly kinetic control) and 5 hr. (thermodynamic control). Since uniform conditions were used, the yield of ester produced in the 15-min. runs gives an approximate measure of the relative rates of esterification.[8]

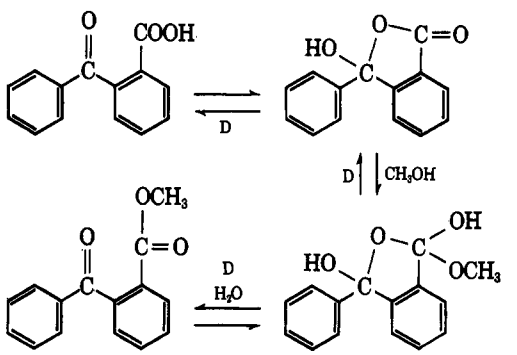
(5) In the preliminary announcement of this work [M. S. Newman and C. Courduvelis, *J. Am. Chem. Soc.* **86**, 1893 (1964)] the proportion of $I_n$ to $I_p$ was said to be 7:3. This result was in error: see Experimental part.

(6) The composition of all ester mixtures was determined by n.m.r.: see P. T. Lansbury and J. F. Bieron, *J. Org. Chem.*, **28**, 3564 (1963).

(7) For similar examples, see M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962); F. Ramirez, B. Hansen, and N. B. Desai, *ibid.*, **84**, 4588 (1962). The differing behaviors of the acetates of α- and β-benzilmonoxime toward aqueous sodium hydroxide [A. H. Blatt and R. P. Barnes, *ibid.* **58**, 1148 (1934)] may be similarly accounted for by postulating initial attack of hydroxide ion on the ketonic carbonyl as shown below.




The two acids which esterify at rates greater than that of the parent acid I are II and VI. In order to rationalize both the increased rates of esterification and the proportions of normal and pseudo esters formed in these cases, another route for esterification must be considered as shown below (route D).



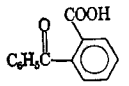
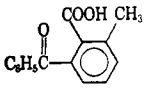
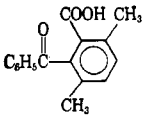
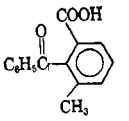
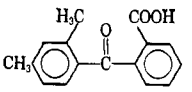
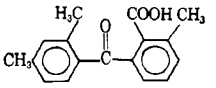
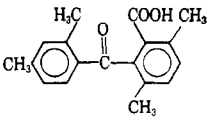
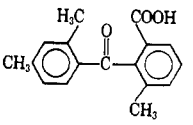
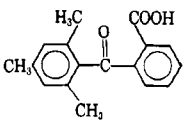
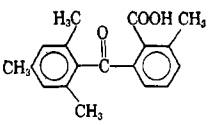
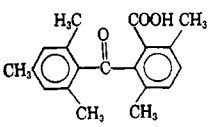
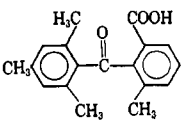
The extent to which route D is involved is dependent on the equilibrium of the keto acid and hydroxy lactone forms of the acid in question,[9] the rate of interconversion of these forms, and the rate of esterification of each. In the following paragraphs the experimental facts relating to the 15-min. runs are rationalized.

**Esterification of 2-Benzoyl-6-methylbenzoic Acid (II).**—Since II has a methyl group in position 6, esterification by route A would be expected to be extremely slow. However, in 15 min., a 46% yield of esters, 40% $II_n$ and 60% $II_p$, is formed. Route D leading to $II_n$ must be significantly involved, for, if esterification were only by route B, the ester produced would be entirely $II_p$. Furthermore, when $II_p$ was subjected to the 15-min. run conditions, 20% was converted into $II_n$. From these facts, it can be argued that II esterifies more by route B than by route D and that the 6-methyl group is important in its effect on the rates involved. The portion which esterifies by route B does so at a rate greater than that in the case of I because the 6-methyl group assists the cyclization step ($B_2$ in the diagram) by causing the carbonyl group of the carboxy function to be favorably oriented to intra-

(8) The rate of more than one reaction may be involved in determining both the total amount of acid esterified and the proportions of normal and pseudo esters produced in the 15-min. experiments.

(9) The per cent of acid in the keto acid and hydroxy lactone form was determined by ultraviolet spectral analysis and is shown in Table I; see also ref. 3.

TABLE I
ESTERIFICATION RESULTS

| Acid | Structure | % keto acid in $CH_3OH$[a] | 15-min. expt.[b] Yield, % | 15-min. expt.[b] N ester, %[c] | % of N ester at equil.[c,d] | % of N ester from P ester, 15 min.[e,d] |
|---|---|---|---|---|---|---|
| I |  | 100 | 13.5 | 51[f] | 98 | 39 |
| II |  | 26 | 46.0 | 40 | 63 | 20 |
| III |  | 7 | 6.5 | 82 | 15 | 0[g] |
| IV |  | 82 | 5.5 | 81 | 94 | 17 |
| V |  | 88 | 8.5 | 64 | 100 | 39 |
| VI |  | 80 | 19.0 | 26 | 93 | 13 |
| VII |  | 25 | 6.0 | 72 | 61 | 0[h] |
| VIII |  | 98 | 3.5 | 92 | 100 | 16 |
| IX |  | 97 | 5.5 | 100 | 100 | |
| X |  | 99 | 0 | | 100[i] | |
| XI |  | 99 | 0.5 | 88 | 100[j] | |
| XII |  | 96 | 2.0 | 100 | 100 | |

[a] Per cent determined by ultraviolet spectral analysis, assuming that log $\epsilon$ in the 325–240-m$\mu$ range for the keto acid form has the same value as that of the normal methyl ester. [b] All reactions run with 0.01 mole acid in 0.2 *N* methanolic HCl. [c] Composition determined by n.m.r. analysis; see Experimental part. [d] Yields all above 95% except for acids X and XI. Runs at longer times showed that equilibrium was reached. [e] 0.2 g. of pseudo ester used in each case. [f] This value corrects that reported in ref. 5. [g] $III_n$ under similar conditions was converted in 13% yield into $III_p$. [h] $VII_n$ under similar conditions was recovered unchanged. [i] Only 3% ester formed after 20 hr. [j] Only 28% ester formed in 5 hr.

molecular addition[10] as in the similar case for alkaline hydrolysis.[2] The portion which esterifies by route D represents a reaction which probably does not occur at all (or to a very small extent) in the case of I. Ultraviolet spectral analysis shows that II exists in the hydroxy lactone form to the extent of 75%, whereas I exists entirely in the keto acid form. To rationalize our results, we must conclude that the rate of route D in the case of II is slower than the rate of route B since the

(10) The assumption that the rate-determining step is the cyclization seems likely. We thank Professor H. Shechter for valuable discussion on this point.

ratio of hydroxy lactone to keto acid is about 3:1 and the ester isolated after 15 min. is 40% $II_n$ and 60% $II_p$. The rate of reaction of the hydroxy lactone form is relatively rapid (compared to route B–C for I) because addition to lactonic carbonyls (in five-membered rings) is in general more rapid than additions to carbonyls in esters.[11]

To summarize, acid II esterifies by routes B, C, and D, and a greater proportion of the esters formed in the 15-min. period involves route B. The 6-methyl group accelerates the rate of $II_p$ formed by route B and also causes the acid II to exist in part in the hydroxy lactone form which is converted into $II_n$ *via* route D. The rate of conversion of $II_p$ to $II_n$ *via* route C is appreciable.

**Esterification of Acid III.**—Since acid III has one methyl group *ortho* to each carbonyl function, one might have expected these steric effects to cancel and that hence the esterification should parallel that of I but at a much slower rate. However, acid III exists largely (93%) in the hydroxy lactone form, whereas I is almost entirely in the keto acid form. Thus esterification of III proceeds mostly by route D, the remainder by route B. Route C (in reverse), which converts $III_n$ to $III_p$, is also involved to a small extent since in an independent 15-min. run $III_n$ was converted into $III_p$ in 13% yield. The over-all rate of esterification of III is lower than that of I as the methyl groups sterically hinder esterification by all routes. That the over-all rate is as high as it is must be due mainly to the fact that esterification by route D is fairly rapid[11] in spite of the added methyl group at position 6.

**Esterification of Acid IV.**—Here esterification is largely by route A, although the 19% of $IV_p$ present shows that route B is significantly involved. Some $IV_n$ is formed *via* route D as the acid IV exists 18% in the hydroxy lactone form. Some $IV_n$ is formed from $IV_p$ *via* route C since in a comparable 15-min. experiment $IV_p$ is converted to $IV_n$ in 17% yield.

**Esterification of Acid V.**—The esterification of V is similar to that of I discussed above. The proportion of $V_n$ to $V_p$ is greater because of the adverse steric effect of the 2′-methyl group on the rate by route B. The methyl groups may also exert a small rate-depressing effect because of polar factors. When treated under the 15-min. conditions, $V_p$ was converted to $V_n$ in 39% yield. Thus, as in the case of I, V is esterified largely by route B and the $V_p$ thus formed is rapidly converted into $V_n$.

**Esterification of Acid VI.**—Acid VI is the other (see acid II) methylated acid which esterifies more rapidly than I. The argument concerning steric acceleration of route B by the 6-methyl group is the same as cited above for II. Since the acid VI is mainly in the keto acid form (80%), only a small amount of normal ester is formed *via* route D. The fact that the over-all rate is less than that for II, but still greater than that for I, means that the 2′-methyl group slows the rate for route B by reducing the concentration of the hemiketal required to enter into the rate-determining cyclization to yield $VI_p$. When subjected to the 15-min. run conditions, $VI_p$ was converted into $VI_n$ in 13% yield. Thus one can conclude that VI esterifies mainly by route B.

(11) For example, the relative rates of acid-catalyzed hydrolysis of δ-valerolactone and ethyl acetate are 357:1: Ph.D. Thesis of C. A. Matuszak, Ohio State University, 1957, p. 39.

**Esterification of Acid VII.**—The esterification of VII is comparable to that of III. The high proportion of $VII_n$ is the result of esterification *via* route D. The fact that an appreciable amount of $VII_p$ is formed shows that even two methyl groups *ortho* to the ketonic function do not eliminate esterification *via* route B.

**Esterification of Acid VIII.**—Esterification is mainly by route A. However, a small amount of esterification *via* route B occurs in spite of two methyl groups *ortho* to the ketonic function. Since $VIII_p$ is relatively rapidly converted into $VIII_n$ (16%) in the 15-min. run, more esterification by route B than that indicated by the composition of the ester formed from VIII (92% $VIII_n$) occurs.

**Esterification of Acid IX.**—This acid probably esterifies entirely by route A. The ester formed is entirely $IX_n$. This result indicates that steric hindrance to addition of methanol to the ketonic carbonyl (start of route B) is greater when two methyl groups in the same ring are *ortho* to the ketonic carbonyl than when the methyl groups are each on a different ring (note that acid VIII esterifies partly by route B).

**Esterification of Acids X and XI.**—The rates for these acids are extremely slow as all routes are sterically hindered. We have no convincing explanation for the fact that acid XI esterifies more rapidly than X. Although both acids appear to be entirely in the keto acid form, the analytical method used (see Experimental part) is not accurate enough to exclude the chance that acid XI exists in the hydroxy lactone form to a greater degree than X and hence could form $XI_n$ more rapidly than X could form $X_n$ by route B. We believe this to be the case as a methyl group at position 3 generally causes that acid to exist more in the hydroxy lactone form than the acid which results from replacement of the 3-methyl group by hydrogen (see Table I; compare acid pairs I and IV, II and III, VI and VII; one exception to this generalization involves acids V and VIII).

**Esterification of Acid XII.**—This acid undoubtedly esterifies almost entirely by route A. The rate is slower than that of acid IX because of the effect of the 3-methyl group.

**General Comments on 15-Min. Esterifications.**—In every pair except one (acids X and XI) the acid containing a 3-methyl group esterifies more slowly than the acid formed by replacing the methyl group with hydrogen, although the reasons for this rate diminution vary from pair to pair (see Table I; note acid pairs I and IV, II and III, V and VIII, VI and VII, IX and XII). Another feature tied up with the 3-methyl group is that in the above same pairs of acids, the acid with the 3-methyl group always forms a greater proportion of the normal ester than pseudo, except in the IX–XII series where essentially only normal esters are formed.

In the experiments on conversion of pseudo esters to normal ester, $I_p$ and $V_p$ are converted comparatively rapidly to $I_n$ and $V_n$ (39% each). In each case this rate is considerably greater than the over-all rate of esterification of free acid. These facts have been mentioned earlier in connection with discussion of the proportion of normal and pseudo esters formed. If one adds an additional methyl group to I in either the 3- or 6-position, the rate of conversion of pseudo to normal

ester is decreased to about the same extent (note $II_p$ to $II_n$, 20%; and $IV_p$ to $IV_n$, 17%). Similarly note $VI_p$ to $VI_n$, 13%; and $VIII_p$ to $VIII_n$, 16%. When there are methyl groups at positions 3 and 6, the rate of conversion of pseudo ester to normal is negligible (see esters $III_p$ and $VII_p$, Table I).

**Interpretation of Equilibrium Data.**—In attempting to account for the composition of the methyl esters at equilibrium the factors described below and illustrated in part in Figure 1 will be used: R, resonance interaction of the ketonic carbonyl with the phenyl ring which does not contain the carbomethoxy function; $R_1$, resonance interaction of the ketonic carbonyl with the phenyl ring which does contain the carbomethoxy function; $R_2$, resonance interaction of the carbonyl of the carbomethoxy function with the attached ring; $R_3$, resonance interaction of the lactonic carbonyl in the pseudo ester form (this interaction should be strong since the carbonyl is perforce virtually coplanar with the phenyl ring); S, the steric effect of a methyl group which tends to decrease resonance interaction of a carbonyl group *ortho* to it; $S_1$, the steric effect of a methyl group adjacent to the ketonic carbonyl which tends to prevent this carbon from becoming tetrahedrally bonded.[12] This effect, when operative, is always to favor the normal ester as only in the pseudo form can the ketonic carbon become $sp^3$.

Using the above effects the proportions of normal and pseudo esters at equilibrium may be rationalized as follows.

**Esters of Acid I (98% N and 2% P).**—The combined influence of factors R, $R_1$, and $R_2$ outweigh factor $R_3$.

**Esters of Acid IV (94% N and 6% P).**—In comparing these results with those for acid I, the slightly greater amount of pseudo ester indicates that effect S on $R_1$ slightly outweighs effect $S_1$.

**Esters of Acid II (63% N and 37% P).**—Here effect S on effect $R_2$ is predominant. In the pseudo form, the steric effect of the methyl group at the 6-position is negligible.[13] Effects R and $R_1$ are relatively little changed from what they are in the case of acid I. The 6-methyl group may assist effect $R_3$ *via* a polar factor.

**Esters of Acid III (15% N and 85% P).**—One must explain the fact that the equilibrium is more favorable to pseudo ester for acid III than for acid II. In ester $II_n$, effects R and $R_1$ operate to favor the normal form, whereas in ester $III_n$, effect S on effect $R_1$ should decrease the importance of effect $R_1$. Thus one should expect more pseudo ester for III than for II. However, effect $S_1$ favors ester $III_n$. One must conclude that the effect of the 3-methyl group is greater on component S than on component $S_1$. Note that in the free acids III exists in the hydroxy lactone form to a greater extent (93%) than does II (75%).

(12) The polar effect of methyl groups is only used occasionally.

(13) Interestingly in the case of 2-benzoyl-1-naphthoic acid, an acid which is analogous to acid II except that it has a fused aromatic ring in place of a methyl group, the equilibrium favors the pseudo ester form completely [see L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936)]. This fact may be explained by assuming that the resonance interaction of the lactonic carbonyl, effect $R_3$, is greater because a naphthalene nucleus is involved rather than a phenyl; and the steric effect of a fused ring is greater than that of a methyl group (effect S). Which of these two effects is mainly responsible can only be determined by further experimentation. One example wherein a fused ring exerts a larger steric effect than a methyl group is provided by the work of J. Packer, J. Vaughan, and E. Wong [*ibid.*, **80**, 905 (1958)].

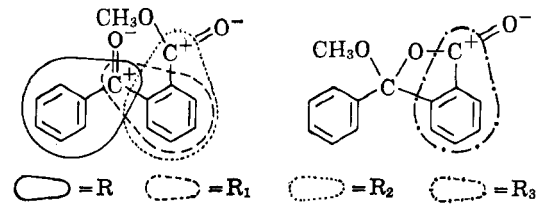



Figure 1.

**Esters of Acid V (100% N).**—As in the case of the esters of I, factors R, $R_1$, and $R_2$ outweigh factor $R_3$. Factor R for V may be decreased because of the S factor but factor $R_3$ may be correspondingly less because of factor $S_1$. Hence the high proportion of normal ester.

**Esters of Acid VIII (100% N).**—The S factor on factors R and $R_1$ tends to reduce the stability of the normal form, whereas the $S_1$ factors of the same methyl groups decrease the stability of the pseudo form. The net result is a preference for the normal form.

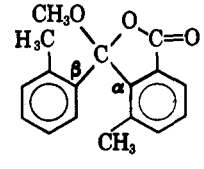
**Esters of Acid VI (93% N and 7% P).**—The S factor on factors R and $R_2$ tends to reduce the stability of the normal form, whereas the $S_1$ factor of only one methyl group reduces the stability of the pseudo form. If one considers the possible favorable effect of the 6-methyl group on the $R_3$ factor, it is surprising that the ratio of $VI_n$ to $VI_p$ is as high as it is. The difference between this ratio for the esters of VI (11.5) compared to that for the esters of II (1.7) must be attributed mainly to the $S_1$ effect of the 2′-methyl group in VI.

**Esters of Acid VII (61% N and 39% P).**—As in the cases of the esters of II and III, one must account for the fact that the equilibrium is more favorable to pseudo ester for acid VII than for acid VI. For VII the S factor on factors R, $R_1$, and $R_2$ acts to reduce the stability of the normal form, whereas the $S_1$ factors of the 2′- and 3-methyl groups reduce the stability of the pseudo form. The stabilization of the pseudo form afforded by any polar effect of the 6-methyl group should be about the same for $VI_p$ and $VII_p$. Since $VII_p$ is favored relative to $VI_p$, apparently the effect of the 3-methyl group is felt more strongly on component S than on $S_1$ (as in the case of acids of II and III).[14] In addition, if one compares the generally lower concentrations of pseudo esters for acids V (0%), VIII (4%), VI (8%), and VII (39%) compared to those for acids I (2%), IV (6%), II (37%), and III (85%), the $S_1$ effect of the 2′-methyl group may be discerned.[15]

**Esters of Acids IX, X, XI, and XII.**—Since in all cases the esters at equilibrium are entirely in the normal form, no comparisons are in order. Apparently the $S_1$ effect of the 2′- and 6-′methyl groups is the dominant factor.

(14) In this connection, it is of interest that acid VII exists in the hydroxy lactone form a larger extent (75%) than does VI (20%). The same effect is apparent in the acids II and III, where III exists in the cyclic form to a larger extent (93%) than does II (74%).

(15) One referee noted that in general the S factor is greater than the $S_1$ factor for the 3-methyl groups but the $S_1$ factor is greater than the S factor for the 2′-methyl group cases. He rationalized this by noting that, in the pseudo ester, the external angle, $\alpha$, is greater than in the normal form and thus effect $S_1$ of the 3-methyl group is decreased relative to the S effect of the 2-methyl group on effect R as in the latter angle $\beta$ remains essentially the same in both normal and pseudo esters.



## Experimental

**Fifteen-Minute Esterification.**—An aqueous standard solution containing 0.005 mole of sodium hydroxide was titrated with freshly prepared methanolic hydrogen chloride solution. The same volume required (8.00 ml. for example) of methanolic HCl was then added to a solution of 0.01 mole of the benzoylbenzoic acid in question in enough absolute methanol to bring the total volume to 25 ml. The same flask was used in each experiment. This solution was placed in a bath at 55.5° (this temperature was maintained by boiling acetone) and held at this temperature for 15 min. The contents were then transferred to a flask containing 6 ml. of 1 *N* aqueous sodium acetate with the aid of a 3-ml. methanol wash. The solvent was then removed in a rotary evaporator, and the product was taken into ether–benzene. After two or three extractions with aqueous sodium bicarbonate (from which extract the unesterified acid was recovered) and a washing with saturated sodium chloride solution, the ether–benzene layer was dried by filtration through a bed of anhydrous magnesium sulfate. The solvents were quantitatively removed under reduced pressure and the amount of ester formed was determined by weighing. The composition of the esters was determined by comparing the ratio of the appropriate methoxy methyl peaks in the n.m.r. spectrum.[6] The $\tau$- values for these groups in methylene chloride are as follows: $I_n$, 6.59; $I_p$, 6.97; $II_n$, 6.52; $II_p$, 6.80; $III_n$, 6.55; $III_p$, 6.96; $IV_n$, 6.76; $IV_p$, 7.02; $V_n$, 6.61; $V_p$, 7.02; $VI_n$, 6.56; $VI_p$, 7.03; $VII_n$, 6.57; $VII_p$, 7.08; $VIII_n$, 6.70; $VIII_p$, 7.07.

The use of sodium acetate for neutralization, rather than potassium carbonate, was adopted after blank experiments with known amounts of normal and pseudo esters. For example, a mixture made up of 39.5% $I_n$ and 60.5% $I_p$ gave analytical figures for 41.5% $I_n$ and 58.5% $I_p$. Considering the lability of $I_p$ in the presence of methanol and the errors inherent in all of the measurements, this gives an idea of the accuracy involved. For some other, less readily rearranged esters, less change occurred during the work-up procedure.

All of the values reported in Table I are the average of at least two determinations, the individual results of which checked to 1–1.5%.

**Equilibrium Values (Column 4, Table I.)**—A solution of 0.01 mole of the *o*-benzoylbenzoic acid in 25 ml. of 0.5 *N* methanolic HCl was held at reflux for 5 hr. Equilibrium was attained in all cases, but those of acids X and XI (see footnotes *i* and *j*, Table I). The proportion of esters formed was determined by n.m.r. analysis as described above.

**Structure of Acids in Methanol.**—The per cent of acid in the keto acid form was determined by comparing the extinction coefficient of the acid in the 325–340-mμ range with that of the corresponding normal methyl ester. We assume that the $\epsilon$ value of the keto acid is the same as that of the normal ester. Because of the errors involved, the values obtained may not be too accurate, but the trend is clearly seen. The values earlier reported[3] were carried out by comparison of extinction coefficients in the 250-mμ region in which both normal and pseudo esters absorb. We believe the present determinations in the 325–340-mμ range (log $\epsilon$ 2.0–2.5), in which there is almost no absorption by the pseudo form, are more valid.

# Benzylidenepyruvic Acids. V. *m*-Nitrobenzylidenepyruvic Acid and Its Enol–Lactone Tautomer*

EMMA DIETZ STECHER,[1] ANITA WALDMAN, AND DIANE FABINY

*Department of Chemistry, Barnard College, New York, New York 10027*

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Acid-catalyzed condensation of *m*-nitrobenzaldehyde with pyruvic acid produces chiefly a stable enol–lactone, 2,4-dihydroxy-4-(*m*-nitrophenyl)crotonic acid $\gamma$-lactone (IV), which is a weak acid, as well as two minor products of multiple condensations. Base-catalyzed condensation forms only *m*-nitrobenzylidenepyruvic acid (I), a strong acid. Reactions of I with bromine and with phenylhydrazine are described, as well as p$K'$ measurements of all acidic compounds.

In a recent publication[2] we reported the preparation of *o*-nitrobenzylidenepyruvic acid and its enol–lactone tautomer. Some differences are noted in the *m*-nitro series. *m*-Nitrobenzaldehyde condenses slowly with pyruvic acid using sodium carbonate as the catalyst in 50% methanol solution, to form yellow sodium *m*-nitrobenzylidenepyruvate.[4] On employing potassium hydroxide in methanol, which is the best method for other members of the series,[3] much decomposition resulted, and, indeed, with *o*-nitrobenzaldehyde, the only product of any base-catalyzed condensation was indigo.

On acidification of sodium *m*-nitro benzylidenepyruvate with hydrochloric acid, a characteristic acid–salt complex[3] often formed; so a reverse procedure of adding the salt solution to warm, dilute mineral acid was used. A more convenient method was that of acidifying in a separatory funnel in the presence of ether and adding ethyl acetate to increase the solubility of the acid product. The acid I was easily converted to its methyl ester II using hydrogen chloride in methanol or diazomethane in ether. The keto acid structure of I was confirmed by its conversion in alkaline hydrogen peroxide solution to known *trans*-*m*-nitrocinnamic acid (III), which with diazomethane gave the known methyl ester of correct melting point. The p$K'$ of the acid I in 50% methanol (2.7)[5] and the rapid hydrolysis rate of the methyl ester[3a] are consistent with the $\alpha$-keto acid and ester structures.

Acid-catalyzed condensation of *o*-nitrobenzaldehyde with 2 equiv. of pyruvic acid at 35° gave the enol–lactone in 60–80% yield.[2] Parallel experiments with *m*-nitrobenzaldehyde resulted in rather poor yields of mixtures difficult to separate. Using either hydrogen chloride or methanesulfonic acid as catalysts, the expected enol–lactone IV crystallized out and could be

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(2) IV: E. D. Stecher and E. Gelblum, *J. Org. Chem.*, **26**, 2693 (1961). For Papers III and II, see ref. 3a and b.

(3) (a) E. D. Stecher, F. Dunn, and E. Gelblum, *J. Am. Chem. Soc.*, **79**, 4748 (1957); (b) E. D. Stecher and A. Clements, *ibid.*, **76**, 503 (1954).

(4) R. Ciusa [*Gazz. chim. ital.*, **49**, 168 (1919)] reported using aqueous sodium carbonate as condensing agent.

(5) The determination of p$K'$ in 50% (v./v.) methanol–0.2 *N* lithium chloride is described in ref. 2a. Present values were also derived from pH titration, but using a recording Titrigraph TTT-1C. Calculations were based on the expression $pK' = pH(obsd.) - \log([X^-]/[HX]) + A\sqrt{I}/(1 + \sqrt{I})$. In the Debye–Hückel term, $A = 0.76$, a constant for 50% (v./v.) methanol solutions, and $I$ is the ionic strength. In most cases this term was equal to 0.02–0.04 p$K$ unit at the midpoint for acid solutions ranging from 0.004–0.0002 *N*. In this way p$K'$ for benzoic acid was found to be 5.18 ± 0.03. We are indebted to Dr. Edward J. King for suggesting this treatment of the data. See his "Acid-Base Equilibria," Pergamon Press, Oxford, 1965, Chapters 1 and 4.