[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

1,3-Shifts. V. The Intermolecular Nature of Some 1,3-Shifts

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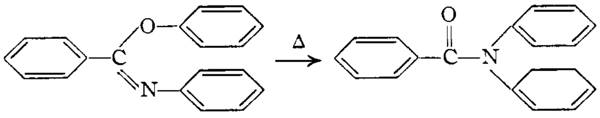
RECEIVED JANUARY 16, 1957

It has been found that the rearrangements of α-methoxystyrene to propiophenone, of methyl benzoate with oxygen-to-oxygen migration of the methyl group, of methyl N-phenylformimidate to N-methylformanilide and of 2-methoxypyridine to N-methylpyridone are all intermolecular. The reactions were studied using a C^{13}-labeled methyl group as the tracer, and analyzing for the mixed reaction product with a mass spectrometer. The mechanisms of the reactions are discussed.

Introduction

We have shown previously that the thermal rearrangement of phenyl N-phenylbenzimidate (I) to N-phenylbenzanilide is intramolecular,[1] whereas the corresponding rearrangement of an alkyl N-phenylbenzimidate or an alkyl styryl ether is probably a free radical chain reaction.[2] In order to obtain further evidence on this matter, we have examined four reactions in order to determine whether they are inter- or intramolecular. The examples chosen were the rearrangements of α-methoxystyrene (II), methyl benzoate (III), methyl N-phenylformimidate (IV) and α-methoxypyridine (V). The reactions were studied in a manner which permitted the use of a mass spectrometer's unique ability to sort molecular species on a mass basis.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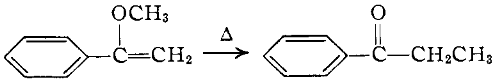
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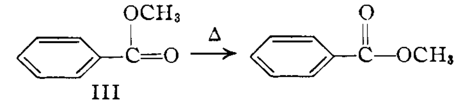
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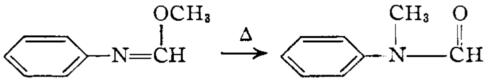
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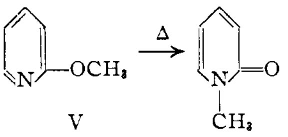
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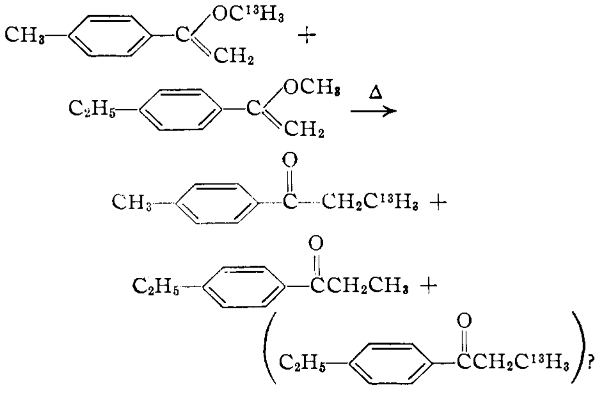
Results

The most common method of determining whether a reaction is inter- or intramolecular involves carrying out the reaction using a mixture of two similar compounds which undergo the reaction, and analyzing the product for a mixed compound which would arise from an intermolecular reaction. For a satisfactory determination of this type, three factors must be considered. First, the two compounds must react at very similar rates. Second, the migrating groups must have essentially equal reactivity toward either of the two reactants. Third, it should be possible to quantitatively isolate any mixed products which might be formed.

In the rearrangement of α-alkoxystyrenes, the rates of reaction will be essentially the same if the two compounds are substituted in the *p*-position with methyl and ethyl groups, respectively, since the σ-values for these groups are very close.[3] Ordinarily, it would be difficult to separate the mixed product if two such similar groups were used, since all of the products would have very similar properties. However, the use of a mass spectrometer obviates this difficulty if the reactants can be separated from the products, or if the reaction is carried to completion, since it can quantitatively separate the products on a mass basis. One may use essentially the same migrating group in both compounds if one contains an ordinary methyl group and the other contains a C^{13}-labeled methyl group. The only difference would be due to the C^{13} isotope effect which would be negligible in this case. If the lower molecular weight reactant is labeled, one may analyze for a mixed compound in the product by examining the mass spectrum of the product and determining if a new peak appears at a mass number one higher than that of the higher molecular weight reactant. In this way, one can quantitatively determine the amount of mixed product without resorting to long, tedious separation procedures.



The alkyl styryl ethers were prepared by treating the appropriately substituted styrene with methanol or methanol-C^{13}, mercuric oxide and iodine, followed by dehydrohalogenation of the intermediate iodoether. The rate of rearrangement of each of the two alkoxystyrenes was determined using the infrared spectrum, and in each case somewhat more than half-reaction was noted after heating for four hours at 220°. The C^{13} content of the α-methoxy-*p*-methylstyrene was determined by com-

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[1] K. B. Wiberg and B. I. Rowland, THIS JOURNAL, **77**, 2205 (1955).

[2] K. B. Wiberg and B. I. Rowland, *ibid.*, **77**, 1159 (1955).

[3] H. H. Jaffé, *Chem. Revs.*, **53**, 222 (1953).

paring its mass spectrum with that of an unlabeled sample,[4] both spectra being obtained at a low ionizing potential in order to minimize cracking (Table I).

TABLE I

MASS SPECTRA FOR VINYL ETHER REARRANGEMENT

Reactant α-Methoxy-p-methylstyrene, ionizing potential 7.0 v.			Product p-Ethylpropiophenone, ionizing potential 14 v.		
Mass	Labeled	Unlabeled[a]	Mass	Labeled	Unlabeled[a]
147	0.0	0.0	161	18.4	12.3
148	100.0	100.0	162	100.0	100.0
149	40.4	12.5	163	23.9	13.8
% C^{13}	28.8	11.1		20.0	12.3
Excess C^{13}	17.7	0.0		7.9	0.0

[a] Containing the natural abundance of C^{13}.

A mixture of equal amounts of labeled α-methoxy-p-methylstyrene and ordinary α-methoxy-p-ethylstyrene was heated to 250° for a time corresponding to several half-lives. The mass spectrum of the product, and of unlabeled p-ethylpropiophenone was determined, allowing a calculation of the amount of C^{13} in the p-ethylpropiophenone from the reaction. Starting with α-methoxy-C^{13}-p-methylstyrene containing 17.7% excess C^{13} over normal abundance, the p-ethylpropiophenone was found to contain 7.9% excess C^{13}. For an intermolecular reaction, if the rates were equal, this product should contain 8.9% excess C^{13} since it can be equally distributed between the two mixed products. The good agreement between the observed and calculated values indicates the reaction to be intermolecular.

In the rearrangement of methyl benzoate, the requirement for equal rates of rearrangement for the two reactants is of little consequence so long as the rates are comparable, since the products and reactants are identical, and the rearrangement can be observed only by using O^{18} labeling.[5] Methyl-C^{13} benzoate was mixed with methyl p-toluate and the mixture was heated to 410° for a time corresponding to about three half-lives for the methyl benzoate rearrangement.

The mass spectra of the methyl-C^{13} benzoate and the product were compared with that of methyl benzoate and methyl toluate giving the data in Table II. Starting with methyl-C^{13} benzoate having 17.9% excess C^{13}, the product methyl toluate had 8.7% excess C^{13} indicating the rearrangement to be intermolecular.

TABLE II

MASS SPECTRA FOR METHYL BENZOATE REARRANGEMENT

Reactant Methyl benzoate, ionizing potential 10 v.			Product Methyl p-toluate, ionizing potential 10 v.		
Mass	Labeled	Unlabeled[a]	Mass	Labeled	Unlabeled[a]
135	1.5	1.5	149	0.0	0.5
136	100.0	100.0	150	100.0	100.0
137	36.3	9.4	151	22.8	10.7
% C^{13}	26.7	8.6		18.6	9.7
Excess C^{13}	17.9	0.0		8.7	0.0

[a] Containing the natural abundance of C^{13}.

The product of the rearrangement of methyl N-phenylbenzimidate is of too high molecular weight for a mass spectrometric analysis. Its hydrolysis product is also not desirable since it contains a readily exchangeable hydrogen, and the mass spectrometer had previously been used for the analysis of methanol-d and contained some exchangeable deuteriums adsorbed on its walls. Consequently, the corresponding methyl N-phenylformimidates[6] were used.

Methyl-C^{13} N-(p-tolyl)-formimidate was prepared by treating the silver salt of p-methylformanilide[7] with methyl-C^{13} iodide. Methyl N-(p-ethylphenyl)-formimidate was prepared by the same method, and a mixture of the two esters was rearranged at 300° for four hours. It had been found that either of the esters was about three-quarters decomposed (as indicated by the infrared spectrum) under these conditions. The products were separated from the reactants, and then reduced with lithium aluminum hydride to the N,N-dimethylanilines. This was necessary since the formanilides had too low a vapor pressure to be analyzed directly with the mass spectrometer. The data are given in Table III.

TABLE III

MASS SPECTRA FOR N-PHENYLFORMIMIDATE ESTER REARRANGEMENT

Ionizing potential = 10 v.

Mass	Labeled	Unlabeled[a]
148	1.7	0.8
149	100.0	100.0
150	22.8	12.4
% C^{13}	18.6	11.0
Excess C^{13}	7.5	0.0

[a] Containing the normal abundance of C^{13}.

The methyl-C^{13} N-(p-tolyl)-formimidate was assumed to have the C^{13} content of the alcohol from which it was prepared, 17.8% excess C^{13}. The product N,N-dimethyl-p-ethylaniline was found to contain 7.5% excess C^{13} indicating the rearrangement to be intermolecular.

The rearrangement of α-methoxypyridine to N-methylpyridone was found to proceed in essentially quantitative yield in contrast to previous reports.[8] α-Methoxy-C^{13}-4-methylpyridine was prepared by the reaction of 2-bromo-4-methylpyridine with methoxide-C^{13} ion. The α-methoxy-4-ethylpyridine was prepared in a corresponding manner, and a mixture of the methoxypyridines was heated

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[4] In this and subsequent compounds, the unlabeled material was found to have a C^{13} content very close (±0.2%) to the expected amount (1.1% times the number of carbons). The precision of the results determined from duplicate spectra was also about ±0.2% in the observed values.

The C^{13} content was determined by dividing the (p + 1) peak by the sum of the parent and (p + 1) peaks. In the cases in which cracking was found, this was corrected for by subtracting the product of the intensities of the (p + 1) and (p − 1) peaks divided by 100 from the parent peak before calculating the C^{13} content. Since the observed C^{13} content of the unlabeled compounds was very close to the expected amount, the excess C^{13} in the labeled compounds was taken as the observed C^{13} content less that expected in the unlabeled compound.

In the case of methyl benzoate and methyl toluate, it was shown that the C^{13} found in the product did not arise from an exchange process occurring in the mass spectrometer since the observed C^{13} content of methyl toluate mixed with an equal amount of methyl benzoate having 17.9% excess C^{13} was identical with that of pure methyl toluate.

(5) K. B. Wiberg, THIS JOURNAL, **75**, 2665 (1953).

(6) W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1471 (1900).

(7) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924).

(8) H. Meyer, *Monatsh.*, **28**, 47 (1907).

to 200° for 14 hours. It had been found that the two methoxypyridines rearranged at essentially the same rate (as indicated by the infrared spectra) and that this length of time gave almost complete reaction. The N-methylpyridones obtained as the product were reduced to the N-methylpiperidones before being analyzed since the latter gave more satisfactory mass spectra. The spectra of the products and the reduced reactants are given in Table IV.

TABLE IV

MASS SPECTRA FOR METHOXYPYRIDINE REARRANGEMENT

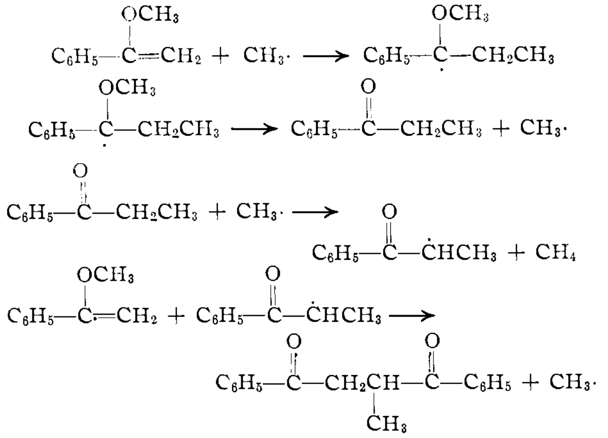
Reactant α-Methoxy-4-methylpyridine, ionizing potential 7.5 v.			Product N-Methyl-4-ethyl-2-piperidone, ionizing potential 35 v.		
Mass	Labeled	Unlabeled[a]	Mass	Labeled	Unlabeled[a]
126	25.2	26.4	144	20.5	22.8
127	100.0	100.0	145	100.0	100.0
128	30.9	8.4	146	20.4	9.6
% C^{13}	24.8	7.8		17.6	8.9
Excess C^{13}	17.1	0.0		8.8	0.0

[a] Containing the normal abundance of C^{13}.

Starting with α-methoxy-4-methylpyridine containing 17.1% excess C^{13}, the product N-methyl-4-ethyl-2-piperidone was found to contain 8.8% excess C^{13} indicating the reaction to be intermolecular.

Discussion

The relationship of the above results to the mechanisms of the reactions may now be considered. In the vinyl ether rearrangement, it is known that the migrating group, if optically active, is racemized during the reaction.[2] The rearrangement of α-neopentoxystyrene led to the formation of a ketone without skeletal rearrangement of the migrating group.[2] These data, coupled with the observation of an intermolecular path for the reaction, demonstrate that the migrating group is free at some time during the rearrangement and strongly suggest that it exists as a free radical. These conclusions are further substantiated by the observation that the reaction can be initiated by free radicals[2] and by the nature of the by-products of the reaction (1,2-dibenzoylpropane and methane).[9] The available data are well accommodated by the chain-propagating steps shown. The nature of the initiation and



$$C_6H_5-\overset{OCH_3}{\overset{|}{C}}=CH_2 + CH_3\cdot \longrightarrow C_6H_5-\underset{\cdot}{\overset{OCH_3}{\overset{|}{C}}}-CH_2CH_3$$

$$C_6H_5-\underset{\cdot}{\overset{OCH_3}{\overset{|}{C}}}-CH_2CH_3 \longrightarrow C_6H_5-\overset{O}{\overset{\|}{C}}-CH_2CH_3 + CH_3\cdot$$

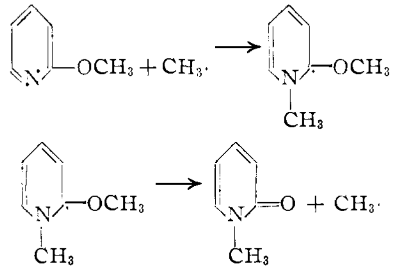
$$C_6H_5-\overset{O}{\overset{\|}{C}}-CH_2CH_3 + CH_3\cdot \longrightarrow C_6H_5-\overset{O}{\overset{\|}{C}}-\dot{C}HCH_3 + CH_4$$

$$C_6H_5-\overset{OCH_3}{\overset{|}{C}}=CH_2 + C_6H_5-\overset{O}{\overset{\|}{C}}-\dot{C}HCH_3 \longrightarrow C_6H_5-\overset{O}{\overset{\|}{C}}-CH_2\underset{\underset{CH_3}{|}}{CH}-\overset{O}{\overset{\|}{C}}-C_6H_5 + CH_3\cdot$$

termination steps are not known, although the former possibly involves the decomposition of a hydroperoxide formed by the autoöxidation of the vinyl ether. The kinetics of the rearrangement of α-benzyloxystyrene, a case which gives essentially no by-products, is now being studied.

In contrast to the rearrangement of phenyl N-phenylbenzimidate,[1] the rearrangement of methyl N-phenylformimidate was found to be intermolecular. The yield of rearranged product is quite low (about 40% from the unsubstituted compound and about 20% from the *p*-ethyl or *p*-methyl substituted compounds) and a principal by-product is N,N′-diphenylformamidine.[10] There are no available data on which to base a mechanistic hypothesis for this reaction, although it is possible that it may be similar in nature to the vinyl ether rearrangement. The reason for the difference between the phenyl migration and the alkyl migration has been discussed already.[1]

The rearrangement of 2-methoxypyridine to 2-pyridone also has been found to be intermolecular. This fact, coupled with the observations that the reaction may be catalyzed by benzoyl peroxide and that old samples of 2-methoxypyridine rearrange at a much faster rate than fresh samples (probably due to hydroperoxide formation), suggest that this is also a free radical chain reaction. In contrast to the previously mentioned reactions, this one leads to a nearly quantitative yield of rearranged product with a negligible amount of side reaction. If the radical chain mechanism is correct, it would appear that the attack of a methyl radical on a hydrogen is much less favorable than the attack on nitrogen, in contrast to the vinyl ether rearrangement.



The rearrangement of methyl benzoate, although found to be intermolecular, may be different from the previously discussed rearrangements. A rather high temperature (400°) is required for this reaction, whereas the others proceed at 250° or below. This may indicate a change in mechanism, or may be a consequence of the fact that only the ester cannot form hydroperoxides which may be chain initiators. In the case of methyl toluate, no gas formation was noted, whereas if methyl radicals were formed as an intermediate one might expect that a certain proportion of them would react with the methyl group attached to the ring to give methane and *p*-carbomethoxybenzyl radicals. It is somewhat unlikely that a methylcarbanion or carbonium ion was formed in the reaction.

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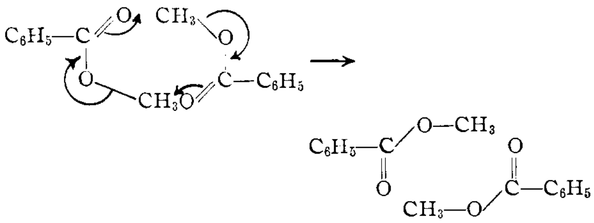
[9] E. H. MacDougall, W. M. Lauer and M. A. Spielman, THIS JOURNAL, **55**, 4089 (1933); W. M. Lauer and M. A. Spielman, *ibid.*, **55**, 4923 (1933); M. A. Spielman and C. W. Mortenson, *ibid.*, **61**, 666 (1939); **62**, 1609 (1940).

[10] W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1471 (1900), reported that the rearrangement of methyl N-phenylformimidate gave 65% of N-methylformanilide and considerable diphenylformamidine.

This suggests that the mechanism could involve the formation of an eight-membered cyclic activating complex. This is of course speculation, and a knowledge of the rate law for the reaction would be required before any mechanism for the reaction could be accepted.



Acknowledgment.—We wish to acknowledge the invaluable assistance of Mr. B. J. Nist in obtaining the mass spectra. The work was supported by the Office of Ordnance Research, U. S. Army, and assistance in purchasing certain equipment for the mass spectrometer was given by the Atomic Energy Commission.

Experimental[11]

Methanol-C^{13}.—Methanol-C^{13} was prepared by the lithium aluminum hydride reduction of carbon-C^{13} dioxide using essentially the same procedure as described by Nystrom, Hanko and Brown for the reduction of carbon-C^{14} dioxide.[12] On a tenth-mole scale, 85% of the theoretical amount of methanol was obtained.

Methyl-C^{13} Iodide.—Methanol-C^{13} was converted to the iodide by the procedure previously described for the conversion of methanol-C^{14} to the iodide.[12] On a 0.03-mole scale, 90% of the theoretical amount of methyl-C^{13} iodide was obtained.

α-Methoxy-*p*-ethylstyrene.—To a mixture of 16.3 g. (0.075 mole) of mercuric oxide, 25.0 g. of methanol and 36.5 g. (0.15 mole) of iodine in a glass stoppered bottle cooled in an ice-bath was added, with shaking, 20.0 g. (0.15 mole) of *p*-ethylstyrene (b.p. 74–76° at 15 mm., $n^{25}D$ 1.5364)[13] in 50 ml. of pentane. The bottle was sealed, placed in an ice-bath and shaken for four hours. The reaction mixture was filtered and the precipitated mercuric iodide was washed twice with 10-ml. portions of pentane. The combined pentane solutions were washed with sodium bisulfite solution to remove excess iodine, and then washed with water and dried over anhydrous potassium carbonate.

The pentane was removed under reduced pressure and the residue was treated with a solution of 16.8 g. (0.30 mole) of potassium hydroxide in 78 ml. of 95% ethanol. The reaction mixture was heated to reflux for three hours, and then cooled and filtered; 30 ml. of water was added and the solution was extracted three times with 30-ml. portions of pentane. The combined pentane extracts were dried over potassium carbonate. Distillation gave 13.3 g. (51%) of α-methoxy-*p*-ethylstyrene, b.p. 110° at 12 mm., $n^{25}D$ 1.5334, d^{25} 0.965.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.2; H, 8.6.

α-Methoxy-C^{13}-*p*-methylstyrene.—The unlabeled material was prepared by the above procedure substituting *p*-methylstyrene (b.p. 65° at 20 mm., $n^{25}D$ 1.5364) for *p*-ethylstyrene. The methoxy-*p*-methylstyrene had b.p. 94° at 10 mm., $n^{25}D$ 1.5397, d^{25} 0.977, and was obtained in 60% of the theoretical amount.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.0; H, 8.2. Found: C, 80.8; H, 8.4.

To a mixture of 3.5 g. (0.016 mole) of mercuric oxide, 1.0 g. (0.031 mole) of methanol-C^{13} and 7.9 g. (0.062 g. atom) of iodine in a glass stoppered bottle cooled in an ice-bath was added with shaking, 3.7 g. (0.031 mole) of *p*-methylstyrene in 6 ml. of freshly distilled ether. The bottle was sealed with paraffin, and placed in an ice-bath and shaken for four hours. The solution was filtered and the precipitated mercuric iodide was washed with a few ml. of ether. The ether solution was washed with sodium bisulfite solution, water and then dried over anhydrous potassium carbonate.

The ether was removed under reduced pressure and the residue was treated with a solution of 3.5 g. (0.063 mole) of potassium hydroxide dissolved in 16 ml. of 95% ethanol. The mixture was warmed briefly on a steam-bath, and then allowed to stand overnight. The solution was filtered and diluted with 20 ml. of water followed by extraction with three 10-ml. portions of pentane. The pentane extracts were dried over potassium carbonate and distilled giving 2.13 g. (46%) of α-methoxy-C^{13}-*p*-methylstyrene, b.p. 93–94° at 10 mm., $n^{25}D$ 1.5370.

Rearrangement of α-Methoxystyrene.—α-Methoxy-*p*-methylstyrene was found to be slightly less than one-half decomposed (as indicated by the infrared spectrum) after heating for four hours at 220°.

α-Methoxy-*p*-ethylstyrene was found to be slightly less than one-half decomposed after heating for four hours at 220°. In one case the product, *p*-ethylpropiophenone, was isolated (60%), b.p. 112–114° at 10 mm. The oxime had m.p. 57–58° and the 2,4-dinitrophenylhydrazone had m.p. 167° and showed no depression on admixture with an authentic sample.[14]

A mixture of 1.0 g. of α-methoxy-C^{13}-*p*-ethylstyrene and 1.0 g. of α-methoxy-*p*-ethylstyrene was heated in a sealed tube for 2 hours and 45 minutes at 250°. The reaction mixture was distilled, collecting the fraction having b.p. 112–114° at 10 mm. (largely *p*-ethylpropiophenone). This material was analyzed for its C^{13} content giving the data shown in Table I.

***p*-Ethylformanilide.**—To 50 ml. of 90% formic acid was added 25 g. (0.21 mole) of *p*-ethylaniline (b.p. 94–95° at 11 mm., $n^{25}D$ 1.5524)[15] which had been purified *via* the *p*-toluenesulfonamide. The mixture was heated for one hour on a steam-bath. The liquid was poured onto cracked ice and separated and distilled giving 28 g. (96%) of *p*-ethylformanilide, b.p. 132–134° at 0.8 mm., m.p. 42.5–44.2°.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.4; H, 7.4; N, 9.4. Found: C, 72.1; H, 7.4; N, 9.1.

Silver Salt of *p*-Ethylformanilide.—To a filtered solution of 28 g. of *p*-ethylformanilide and 29 g. of silver nitrate in 250 ml. of 50% ethanol was added slowly with stirring at 0°, a solution of 4.9 g. of sodium dissolved in 25 ml. of ethanol. The precipitate was washed by decantation, filtered and dried in a vacuum oven at 85–90°. The dark brown material was ground to a powder and dried over phosphorus pentoxide in an evacuated desiccator. The yield was quantitative.

Methyl N-(*p*-Ethylphenyl)-formimidate.—To 30 g. (0.12 mole) of the silver salt of *p*-ethylformanilide was added 10 ml. (0.16 mole) of methyl iodide and sufficient anhydrous ether to make a paste. The reaction mixture was allowed to stand for one week. The silver iodide was filtered and washed twice with 20-ml. portions of pentane. The combined extracts were concentrated and the residue was distilled giving 10.9 g. (56%) of methyl N-(*p*-ethylphenyl)-formimidate, b.p. 106° at 13 mm., $n^{25}D$ 1.5288.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.5; H, 8.0. Found: C, 73.6; H, 8.2.

Methyl-C^{13} N-(*p*-Tolyl)-formimidate.—This compound was prepared by the procedure previously described for the unlabeled compound[16] except that methyl-C^{13} iodide was used instead of methyl iodide. The compound had b.p. 92–93° at 10 mm., $n^{25}D$ 1.5335, and was obtained in 56% of the theoretical amount.

Rearrangement of Methyl N-Phenylformimidates.—Both methyl N-(*p*-tolyl)-formimidate and methyl N-(*p*-ethylphenyl)-formimidate were found to be about three-quarters decomposed (as indicated by the infrared spectrum)

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[11] All melting points are corrected; boiling points are not corrected. The mass spectra were obtained using a Consolidated Engineering Corp. model 21-103 mass spectrometer. The analyses were obtained by B. J. Nist.

[12] R. F. Nystrom, W. H. Hanko and W. G. Brown, THIS JOURNAL, **70**, 411 (1948).

[13] D. Mowry, M. Renoll and W. F. Huber, *ibid.*, **68**, 1105 (1946).

[14] O. Klages, *Ber.*, **32**, 1558 (1899), reported m.p. 58–59° for the oxime.

[15] W. C. Davies and E. L. Hulbert, *J. Soc. Chem. Ind.*, **57**, 394T (1938).

[16] M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924).

after heating to 300° for four hours. In each case, the amide was obtained in about 20% yield, whereas the unsubstituted compound gave the amide in approximately 40% yield.

A mixture of 1.25 g. of methyl-C^{13} N-(*p*-tolyl)-formimidate and 1.25 g. of methyl N-(*p*-ethylphenyl)-formimidate was heated in a sealed evacuated tube for four hours at 300°. The reaction mixture was distilled and the fraction having b.p. 132–140° at 10 mm. (largely N-methyl-*p*-ethylformanilide) was collected (0.24 g.). This material was not sufficiently volatile for mass spectrometric analysis, and thus it was treated with 50 mg. of lithium aluminum hydride dissolved in 8 ml. of anhydrous ether and the solution was heated to reflux for three hours. Water was added, and the ether solution was separated and concentrated to a small volume. The solution was distilled in a micro still at 10 mm. with a bath temperature of 135–140° giving 0.05 ml. of N,N-dimethyl-*p*-ethylaniline. The infrared spectrum of this material was identical with that of an authentic sample of N,N-dimethyl-*p*-ethylaniline.[15] The C^{13} content was determined giving the data in Table II.

Methyl-C^{13} Benzoate.—To 0.75 ml. (0.0185 mole) of methanol-C^{13} dissolved in 3.1 g. (0.039 mole) of pyridine was added 2.5 ml. (0.02 mole) of benzoyl chloride, and the resulting mixture was shaken for one-half hour. The reaction mixture was poured into 10 ml. of water and extracted three times with 5-ml. portions of ether. The ether extracts were washed with dilute hydrochloric acid and with water. After drying over potassium carbonate, distillation gave 1.32 g. (53%) of methyl-C^{13} benzoate, b.p. 198–199°, $n^{25}D$ 1.5131.

Rearrangement of Methyl Benzoate.—A mixture of 1.0 g. of methyl-C^{13} benzoate and 1.0 g. of methyl *p*-toluate was heated in an evacuated sealed tube at 410–412° for six hours. The reaction mixture was distilled, and the fraction having b.p. 215–217° (mainly methyl toluate) was collected and analyzed for its C^{13} content. The data are given in Table II.

2-Methoxy-4-ethylpyridine.—A mixture of 99 g. (0.93 mole) of 4-ethylpyridine, 42.5 g. (1.09 moles) of sodium amide and 210 ml. of xylene was heated to reflux for 11 hours. The solution was cooled in an ice-bath and cautiously treated with water, followed by concentrated hydrochloric acid. The aqueous layer was separated and made basic by the addition of potassium hydroxide. The amine was extracted with ether, and isolated by distillation giving 42 g. (37%) 2-amino-4-ethylpyridine, b.p. 140–148° at 20 mm., m.p. 64–66°.[17]

To 210 ml. (1.86 moles) of 48% hydrobromic acid was added 40 g. (0.33 mole) of 2-amino-4-ethylpyridine. The solution was cooled to 0° and 64 ml. (1.25 moles) of bromine was added with stirring. A solution of 73 g. (1.16 moles) of sodium nitrite in 100 ml. of water was then added over a period of 90 minutes, maintaining the temperature between 5–10°. After an additional 30 minutes, a solution of 160 g. (4.0 moles) of sodium hydroxide in 150 ml. of water was added with cooling. The amine was extracted with ether, and the ether solution was dried over potassium hydroxide and distilled giving 41.7 g. (62%) of 2-bromo-4-ethylpyridine, b.p. 124–125° at 28 mm., $n^{25}D$ 1.5511, d^{25} 1.425.

Anal. Calcd. for C_7H_8NBr: C, 45.2; H, 4.3. Found: C, 45.1; H, 4.5.

A solution of 20 g. (0.097 mole) of 2-bromo-4-ethylpyridine and 8.1 g. (0.150 mole) of sodium methoxide in 120 ml. of *t*-butyl alcohol was heated to reflux for 6 hours. Most of the *t*-butyl alcohol was then removed by distillation. The solution was filtered and the precipitate of sodium bromide was washed with ether. The combined filtrates were distilled giving 10 g. (75%) of 2-methoxy-4-ethylpyridine, b.p. 66–67° at 9.5 mm., $n^{26}D$ 1.4970, d^{25} 1.001.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.0; H, 8.1; neut. equiv., 137. Found: C, 70.1; H, 8.3; neut. equiv., 139.

2-Methoxy-4-methylpyridine.—2-Bromo-4-methylpyridine was prepared by the procedure described above, substituting 2-amino-4-methylpyridine for 2-amino-4-ethylpyridine. The conversion to the methoxypyridine was effected in the same manner as above, and 2-methoxy-4-methylpyridine (65%), b.p. 67° at 21 mm., $n^{25}D$ 1.5021 was obtained. The 2-methoxy-C^{13}-4-methylpyridine was obtained in the same manner.

Anal. Calcd. for C_7H_9NO: C, 68.3; H, 7.4. Found: C, 68.1; H, 7.5.

Rearrangement of Methoxypyridines.—Both 2-methoxy-4-methylpyridine and 2-methoxy-4-ethylpyridine were found to be one-third rearranged (as indicated by the infrared spectrum) after heating at 210° for 4.5 hours in a sealed tube. The rearrangement of 1.0 g. 2-methoxy-4-methylpyridine at 210° for 20 hours gave 0.9 g. of N-methyl-4-methylpyridone, m.p. 56–59°; hydrochloride, m.p. 169–171°; picrate, m.p. 167–168°.[18]

The rearrangement of 1.2 g. of 2-methoxy-4-ethylpyridine at 210° for 20 hours gave 0.98 g. of N-methyl-4-ethyl-2-pyridone, b.p. 152° at 14 mm., $n^{25}D$ 1.5462; hydrochloride, m.p. 129–130°; neut. equiv. calcd. 174; found 175; picrate, m.p. 132.5–133.0°.

Anal. Calcd. for $C_{14}H_{14}N_4O_8$: C, 45.9; H, 3.9. Found: C, 46.2; H, 4.2.

The rearrangement of a mixture of 0.6 g. of 2-methoxy-C^{13}-4-methylpyridine and 0.6 g. of 2-methoxy-4-ethylpyridine was effected at 200° for 14 hours. Since the pyridones did not give good mass spectra, the crude product was reduced with platinum and hydrogen in dilute aqueous hydrochloric acid solution giving the corresponding piperidones.[19] The fraction (0.3 g.) having b.p. 115–118° at 13 mm. (largely N-methyl-4-ethyl-2-piperidone, b.p. 117–121° at 12 mm., $n^{25}D$ 1.4755) was collected and analyzed for its C^{13} content, giving the data in Table IV.

Peroxide Catalysis of 2-Methoxy-4-methylpyridine Rearrangement.—A mixture of 0.5 g. (4.06 mmoles) of 2-methoxy-4-methylpyridine and 22.6 mg. (0.1 mmole) of benzoyl peroxide was heated to 165° for 22.5 hours giving an essentially quantitative yield of N-methyl-4-methylpyridone, m.p. 54.5–57.5°, and which did not depress the m.p. of an authentic sample on admixture. In the absence of benzoyl peroxide, less than one-quarter of complete rearrangement was observed.

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[17] German Patent 398,204 (*Chem. Zent.*, **95, II,** 1409 (1924)) reported b.p. 134–139° at 14 mm., m.p. 68–69°.

[18] R. Adams and A. W. Schrecker, THIS JOURNAL, **71,** 1186 (1949), reported m.p. 59°; hydrochloride, m.p. 173–174°; picrate, m.p. 168–169°.

[19] The procedure was essentially that described by T. B. Grave, *ibid.*, **46,** 1470 (1924).