[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

The Mechanistic Fate of Carbonyl Oxygen in the Rearrangement of 2-Anilino-1-phenyl-1-propanone[1]

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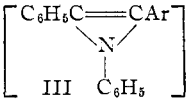
The rearrangement of 2-anilino-1-phenyl-1-propanone (I) to give 1-anilino-1-phenyl-2-propanone (II) is reversibly catalyzed by mild acids. Mechanisms which have been proposed to explain this rearrangement include nucleophilic ring opening of intermediates of the ethylene oxide or ethylene imine type as well as carbonyl addition–elimination processes. Results in 95% ethanol made up with water containing 1.2 atom per cent. excess O-18 using aniline hydrobromide and pyridine hydrobromide as catalysts clearly indicate that there is no important oxygen exchange directly associated with the rearrangement. Therefore, any mechanism that is proposed must specifically provide for *intramolecular* migration of the carbonyl oxygen.

The synthesis of indoles from α-haloketones *via* α-arylaminoketones usually gives not the product that would be expected from direct cyclization of the α-arylaminoketone, but one which differs from it by having the expected 3-substituent in the 2-position.[4–7] The discovery that certain α-amino ketones readily rearrange[8–10] suggested that such rearrangements might precede most of the reactions leading to the 2-substituted indoles.

Several different mechanisms have been proposed for the rearrangements of α-arylaminoketones. In some cases only intermediates have been suggested.

Cowper and Stevens[11] proposed that III is the intermediate involved when the rearrangement occurs without amine exchange in the presence of a

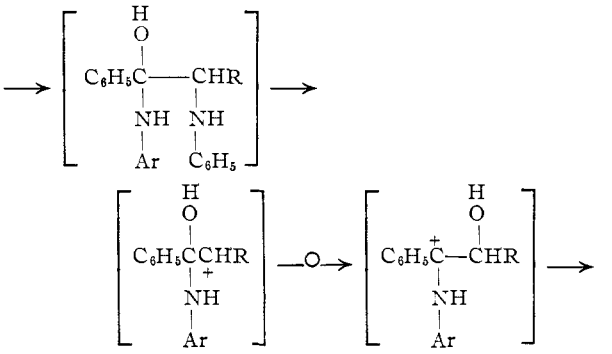


III

tertiary amine salt as catalyst. This structure was based upon the presumed demonstration of intramolecular migration of the amine function and the observation that an N-alkylarylaminoketone will not rearrange. No suggestions were offered as to how III would be formed or react to give the product.

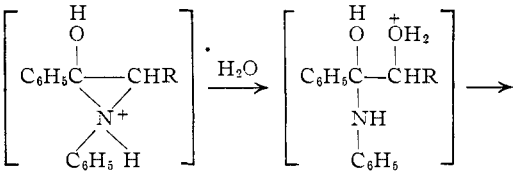
Brown and Mann[10] had rejected the intermediate III proposed by Cowper and Stevens[11] on the grounds of stereochemical improbability and proposed an addition–elimination–migration scheme as shown.

This scheme does not provide for amine exchange without rearrangement or catalysis by secondary and tertiary amine salts without amine exchange. Furthermore, Brown and Mann did not offer any specific suggestion as to how the hydroxyl migration occurs, although it apparently is expected to be intramolecular.



Whether Cowper and Stevens' competitive experiment[11] really demonstrates the intramolecular migration of the nitrogen function is doubtful. Nevertheless we were attracted to their proposed intermediate III because it appeared to offer the most convenient experimental test.

An internal ring-closure addition to give the intermediate IV followed by hydrolytic ring-opening



IV

would be more plausible than the proposal of Cowper and Stevens. The expected unfavorable steric hindrance in the ring-closure step could explain the failure[11] of N-alkylarylamino ketones to rearrange.

If the actual rearrangement involved either intermediate III or IV, the original carbonyl oxygen would be lost and the new carbonyl oxygen in the rearranged product would come from water in the solvent. If the solvent was prepared with water enriched in O-18, the carbonyl group in the rearranged product should have an O-18 content comparable to the enriched solvent. We were of course concerned about carbonyl oxygen exchange without rearrangement and hoped that this factor would not obscure the results.

Discussion of Results

We studied the rearrangement of 2-anilino-1-phenyl-1-propanone (I) to give 1-anilino-1-phenyl-

(1) The Mechanism of the Möhlau-Bischler Indole Synthesis. I.

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(3) This paper is based upon work reported in the dissertation submitted by Mr. Seefeld to the Graduate School of Wayne University in partial fulfillment of the requirements for the degree of Master of Science. It was presented before the Organic Division of the American Chemical Society, Atlantic City, N. J., September 18, 1956.

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(5) A. Bischler, *ibid.*, **25**, 2860 (1892).

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(9) S. N. McGeoch and T. S. Stevens, *J. Chem. Soc.*, 1032 (1935).

(10) F. Brown and F. G. Mann, *ibid.*, 847, 858 (1948).

(11) R. M. Cowper and T. S. Stevens, *ibid.*, 1041 (1947).

2-propanone (II) in 95% ethanol made up with water containing 1.2 atom-per cent. excess O-18. Reactions were carried out at the reflux temperature using aniline hydrobromide (V) and pyridine hydrobromide (VI) as catalysts. The rearrangement product (II) also was prepared and its rearrangement to I was similarly studied. The results are summarized in Table I.

Table I

Summary of Results from Tracer Experiments

	Reaction	Yield of isolated product,[a] g.		Atom-per cent. excess O-18 in isolated products[b]	
(a)	I, no catalyst, 10.5 hr.	..	..	0.02	..
(b)	I + V, 8.5 hours	0.55	1.09	.68	0.36
(c)	I + VI, 20 hours	1.13	0.38	.84	.16
(d)	II + V, 4 hours	0.14	1.25	.39	.16
(e)	II + VI, 12 hours	..	..	..	.26

[a] Each experiment was begun with 2.25 g. (0.01 mole) of I or II with 1.74 g. (0.01 mole) of V or 2.00 g. (0.01 mole) of VI. [b] The maximum atom-per cent. excess O-18 assuming complete equilibration between carbonyl oxygen and solvent water would have been 0.95.

Reaction a indicates that oxygen exchange in the absence of catalyst is very slow and that any rearrangement under the same conditions must be insignificant.

Reaction e indicates either that the reverse rearrangement is so much slower with pyridine hydrobromide (VI) than with aniline hydrobromide (V) that significant reaction did not occur in the time allowed or, alternatively, that the position of equilibrium may be so much further toward the product II that reverse rearrangement cannot be detected. The first conclusion may be correct since conversion of I to II is much slower with VI than with V.

Since the unrearranged starting compounds in reactions b, c, and d are all significantly enriched in O-18, there is exchange of oxygen between the carbonyl group and solvent exclusive of any rearrangement.

The fact that the rearranged compound II from reactions b and c contains less O-18 than the recovered starting compound I clearly indicates that there is no important oxygen exchange directly associated with the rearrangement of I to II.

Since the rearranged compound I from reaction d contains more O-18 than the recovered starting compound II, one might be tempted to conclude that significant oxygen exchange is directly associated with the reverse rearrangement of II to I. However, the rearranged compound I from reaction d contains considerably less O-18 than the unrearranged compound I from reaction b and c and much less than the maximum O-18 expected for complete exchange with the solvent. There is thus no important oxygen exchange directly associated with the rearrangement of II to I.

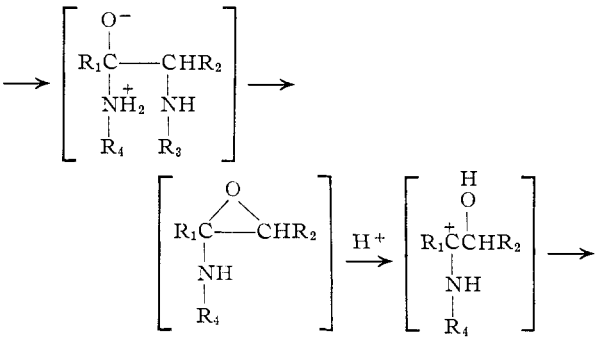
The results of reactions b, c and d indicate that oxygen exchange without rearrangement occurs more rapidly with I than it does with II.

It is clear that there is no important oxygen exchange directly associated with the rearrangement in either direction. Although oxygen exchange does occur without rearrangement, the amounts of excess O-18 in each case for the rearranged compound (I or II) should be corrected for that portion which is formed from starting compound which was exchanged before it rearranged.

Thus neither III nor IV can be an intermediate. Any reaction mechanism that is proposed must provide for intramolecular migration of the carbonyl oxygen.

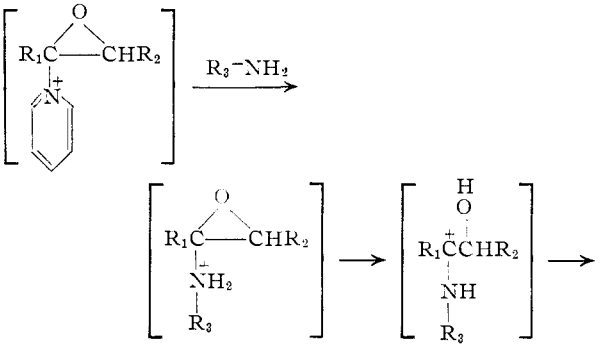
The catalytic superiority of aniline hydrobromide (V) over pyridine hydrobromide (VI), the observation that amine exchange does occur when primary amine salts are used as catalysts, and the established requirement of intramolecular oxygen migration have led us to propose a new scheme for consideration and test (Scheme A).[12]

Scheme A



When the catalyst is a tertiary amine salt, a slightly different intermediate sequence would be expected (Scheme A[1]).

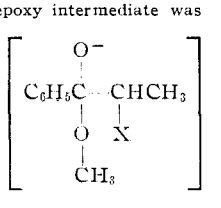
Scheme A[1]



Schemes A and A[1] assign a role to the amine moiety of the catalyst for which significant differences would be expected. The modified sequence provides adequately for rearrangement without amine exchange (in the broad sense). It is of course not possible to choose or suggest the exact details for the hydrogen transfer steps. However, schemes A and A[1] seem to offer sufficient advantages over other proposals to warrant provisional adoption.

The mechanistic fate of the amine function ac-

(12) The model for the formation of the epoxy intermediate was provided by the observations that 1,2-epoxy-1-methoxy-1-phenylpropanone is obtained from 2-bromo- or 2-chloro-1-phenyl-1-propanone [T. I. Temnikova and E. M. Kropacheva, *Zhur. Obshchei Khim.*, **19**, 1917 (1949); C. L. Stevens, W. Malik and R. Pratt, This Journal, **72**, 4758 (1950)]. This reaction is considered to involve carbonyl addition to give the intermediate which gives the epoxide by ring-closure displacement of the halogen.



companying rearrangements which occur with and without amine exchange is now being studied.

Experimental Part[13]

α-Bromoketones.—2-Bromo-1-phenyl-1-propanone and 1-bromo-1-phenyl-2-propanone were prepared by bromination of the corresponding ketones in glacial acetic acid.

2-Anilino-1-phenyl-1-propanone (I) was prepared in 80% yield by the procedure of Julian, *et al.*,[14] as pale yellow prisms, m.p. 100–102° (lit.[14] 100–102°).

1-Anilino-1-phenyl-2-propanone (II) was prepared in 68% yield by modification of procedure of Verkade and Janetsky[7]; white needles, m.p. 90–91.5° (lit. 89–92°,[7] 90.5–91.5°[14]).

Amine hydrobromides were prepared by passing anhydrous hydrogen bromide into an ether solution of the amine. The precipitated amine hydrobromide was separated by filtration, washed with cold ether and recrystallized from 95% ethanol: **aniline hydrobromide (V)**, white prisms, m.p. 283° with decomposition (lit.[15] 286°); ***p*-chloroaniline hydrobromide**, white plates, m.p. 243–245°; **pyridine hydrobromide (VI)** white hygroscopic powder, m.p. 216–217° (lit.[16] 213°).

Rearrangement of 2-Anilino-1-phenyl-1-propanone.—A solution of 2-anilino-1-phenyl-1-propanone (6.75 g., 0.03 mole) and aniline hydrobromide (5.22 g., 0.03 mole) in 75 ml. of 95% ethanol was refluxed for two hours. The solution was chilled and poured into 200 ml. of ice-water. The precipitate was separated by filtration and dried. Fractional crystallization from 95% ethanol yielded 0.75 g. of yellow crystals, m.p. 99–102°, and 0.31 g. of white crystals, m.p. 89–91°. These did not depress the melting points of 2-anilino-1-phenyl-1-propanone and 1-anilino-1-phenyl-2-propanone, respectively.

Rearrangement using pyridine hydrobromide was much slower. A solution of 2-anilino-1-phenyl-1-propanone (2.25 g., 0.01 mole) and pyridine hydrobromide (2.00 g., 0.012 mole) in 25 ml. of 95% ethanol was refluxed for 20 hours. The product was isolated and fractionally crystallized as above to give 1.13 g. of 2-anilino-1-phenyl-1-propanone and 0.38 g. of 1-anilino-1-phenyl-2-propanone.

Rearrangement of 1-Anilino-1-phenyl-2-propanone.—A solution of 1-anilino-1-phenyl-2-propane (2.25 g., 0.01 mole) and aniline hydrobromide (1.74 g., 0.01 mole) in 25 ml. of 95% ethanol was refluxed for two hours. The solution was chilled and poured into 50 ml. of ice-water. The precipitate was separated by filtration and dried. Fractional crystallization from 95% ethanol yielded 0.14 g. of 2-anilino-1-phenyl-1-propanone and 1.25 g. of 1-anilino-1-phenyl-2-propanone.

Reaction times up to 24 hours failed to produce any rearranged product using pyridine hydrobromide.

Rearrangement with Amine Exchange.—A solution of 2-anilino-1-phenyl-1-propanone (2.25 g., 0.01 mole) and *p*-chloroaniline hydrobromide (1.64 g., 0.008 mole) in 25 ml. of 95% ethanol was refluxed for 8 hours. The solution was chilled and poured into 300 ml. of ice-water. The precipitate was separated by filtration and dried. Recrystallization from 95% ethanol yielded only one product, 1-(4-chloroanilino)-1-phenyl-2-propanone, white needles, m.p. 129–131°.

Anal. Calcd. for $C_{15}H_{14}NOCl$: Cl, 13.65. Found: Cl, 14.19.

Visible Spectra.—Pyridine hydrobromide (0.03 molar) in 95% ethanol does not absorb in the visible region of the spectrum. 2-Anilino-1-phenyl-1-propanone (0.03 molar) in 95% ethanol does not absorb at wave lengths above 475 mμ. Its yellow color is due to a broad absorption region which begins at 475 mμ and increases as the wave length decreases extending into the ultraviolet region. 1-Anilino-1-phenyl-2-propanone (0.03 molar) in 95% ethanol does not absorb at wave lengths above 375 mμ. It has a broad absorption region which begins at 375 mμ and increases as the wave length decreases into the ultraviolet region. The absorption at 380 mμ provides an elegant and sensitive means for determining the amount of 2-anilino-1-phenyl-1-propanone in a solution which also contains pyridine hydrobromide and 1-anilino-1-phenyl-2-propanone.

Great care must be taken to exclude oxygen, however, since 1-anilino-1-phenyl-2-propanone is oxidized very easily to give highly colored products.

Tracer Experiments.—The labeled solvent was prepared by dilution of 5.00 g. of water (1.4 atom per cent. O-18, Stuart Oxygen Co., San Francisco, Calif.) to 100.0 ml. with absolute ethanol.

Except in the first experiment without catalyst, a solution of α-anilinoketone (2.25 g., 0.01 mole) and amine hydrobromide (1.74 g., 0.01 mole, of aniline hydrobromide or 2.00 g., 0.012 mole, of pyridine hydrobromide) was prepared in 25 ml. of labeled solvent. After refluxing under nitrogen, the solution was poured into ice-water. The precipitate was separated by filtration and dried. The isomers were separated by fractional crystallization from 95% ethanol.

From each experiment, the separate isomers were analyzed according to Doering's modification[17] of the Untersaucher method of oxygen analysis of organic compounds.[18] The method consists essentially of pyrolyzing the compound, passing the gases through carbon black at 1120° to convert all the oxygen to carbon monoxide, and oxidation of the carbon monoxide to carbon dioxide by passing it through iodine pentoxide at room temperature. The carbon dioxide is passed through a drying agent and condensed in a U-tube with liquid nitrogen. The U-tube is fitted with stopcocks and $ inner joint so that it can be directly attached to the mass spectrometer.

The mass spectrometric analyses are given in Table I.[19]

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DETROIT, MICH.

(13) All melting points are uncorrected. We are indebted to Mrs. Delores Phillips for assistance with the spectrophotometric analyses and to Miss Mary Keen for microanalyses.

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(18) A. Steyermark, "Quantitative Organic Microanalysis," The Blakiston Co., New York, N. Y., 1951, Chapter 14.

(19) We wish to express special appreciation to Dr. Oliver H. Gaebler of the Department of Biochemistry, Edsel B. Ford Institute for Medical Research, Detroit, Mich., for the mass spectrometric analyses.