

formation of the O---H bonds. It appears to the authors that more than 50% of the *o*-bromophenol molecules in dioxane have the *trans*-configuration, compared to about 12% in carbon tetrachloride.

Summary

A comparison of the observed electric moments of *o*-fluoroanisole, *o*-chloroanisole, *o*-bromoanisole and *o*-chlorophenetole in benzene solution with values calculated for various configurations reveals that the double bond character of the ring-to-oxygen bond is sufficient to lock these molecules in a *trans*-configuration.

The moments obtained for *o*-fluorophenol, *o*-chlorophenol and *o*-bromophenol in carbon tetrachloride show that between 85 and 90% of these molecules have the hydroxyl group in the *cis*-position, due to intramolecular hydrogen bonding. The large moments of these compounds in dioxane have been interpreted as indicating that dioxane forms hydrogen bonds with the *trans*-molecules and thus brings about a shift in the *cis-trans* equilibrium. The order of bond strength in the substituted phenols is revealed to be H---F > H---Cl > H---Br.

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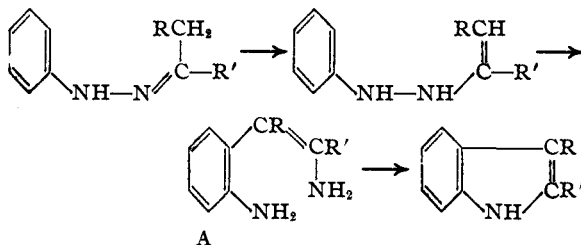
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The Use of N¹⁵ as a Tracer Element in Chemical Reactions. The Mechanism of the Fischer Indole Synthesis

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The mechanism of the Fischer indole synthesis has been the subject of much speculation. As the various proposed mechanisms have been well summarized recently elsewhere,¹ it is unnecessary to give them here. The Robinson representation² has been generally accepted as the most probable. This involves an *o*-benzidine type rearrangement prior to ring closure.



The method of elimination of the ammonia has not been explained by any of the proposed mechanisms, but it has been generally accepted that it is the nitrogen atom farthest removed from the aromatic ring that is eliminated; this conclusion was based upon the observation that *N*-alkylindoles are produced when *as*-*N*-alkylphenylhydrazones are submitted to the Fischer reaction.^{3,4} With the advent of heavy nitrogen, it has become possible to devise a series of reactions using it as a tracer element, and to obtain con-

firmation of this conclusion. Also, the opportunity has been taken to interpret the mechanism of the reaction in a slightly different way.

2-Phenylindole was used in the work described in this paper, being prepared by steps from benzamide N¹⁵. The N¹⁵ was introduced into benzamide by treating benzoyl chloride with ammonium hydroxide containing N¹⁵. The benzamide was degraded to aniline N¹⁵ by the Hofmann method; the N¹⁵ is thus attached to the ring in the aniline. Conversion of this to the hydrazine by the customary procedure gives a molecule in which the N¹⁵ is in the *alpha*-position, adjacent to the ring, but the ordinary nitrogen, introduced by nitrous acid, is in the *beta*-position. The acetophenone phenylhydrazone was then prepared, and used in the Fischer synthesis, giving 2-phenylindole; the latter should still contain the N¹⁵, and analysis showed that such was, indeed, the case. Thus, the N¹⁵ has remained attached to the *Ar* ring throughout all the reactions. Conversely, the ordinary nitrogen has been eliminated; but the ordinary nitrogen is that farthest from the ring. Its elimination thus confirms the conclusions drawn from the use of *as*-alkylphenylhydrazones.

Our view of the mechanism is the same as the Robinsons' as far as the elimination of ammonia, which they represent as either a removal as such from both ends of a chain that are close together in space (A), or by a prior hydrolysis to hydroxyl,

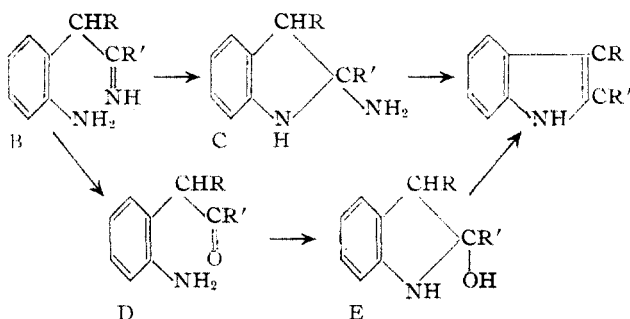
(1) Van Order and Lindwall, *Chem. Rev.*, **30**, 80 (1942).

(2) Robinson and Robinson, *J. Chem. Soc.*, **113**, 639 (1918); *ibid.*, 827 (1924).

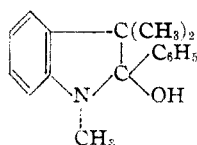
(3) Fischer and Hess, *Ber.*, **17**, 559 (1884).

(4) Degen, *Ann.*, **226**, 151 (1886).

and loss of water. However, it seems to us that the usual addition-elimination mechanism is to be preferred. The imine B is a tautomeric form of A; the —NH_2 group of B enters into a 1,2-addition reaction with the >C=N— to form C, from which ammonia is at once eliminated.



The existence of either the imine B or unsaturated amine A is entirely possible in the Fischer synthesis, for, although ketimines and unsaturated amines are characterized by ease of hydrolysis, examples are known that are relatively stable in acid media.^{5,6,7} If one prefers to regard the imino group as being hydrolyzed to a carbonyl group as in D, then the 1,2-addition product is to be represented by E. This hydrolysis of imino to keto group mechanism (B-D), prior to the addition, would appear to be favored by Jenisch's report,⁸ that the phenylmethylhydrazine of isopropyl phenyl ketone gave 2-hydroxy-1,3,3-trimethyl-2-phenylindoline in the Fischer synthesis.



(5) Conrad and Zart, *Ber.*, **39**, 2282 (1905).

(6) Mohr, *J. prakt. Chem.*, **79**, 16 (1909).

(7) Kohler and Richtmyer, *THIS JOURNAL*, **50**, 3092 (1928).

(8) Jenisch, *Monatsh.*, **27**, 1223 (1906).

This mechanism is equally applicable to the formation of oxindoles from acid hydrazides, and to Piloty's synthesis of pyrroles from ketazines.⁹

Experimental

The only trouble encountered in the various steps of the synthesis of 2-phenylindole (N^{15}) was in the Hofmann degradation. Since no details were found, the following procedure was used. To a cold solution of 85 g. of bromine in an excess of sodium hydroxide was added 62 g. of benzamide (N^{15}).¹⁰ The mixture was heated for one hour on the steam-bath, and then at its boiling point for two hours. It was then submitted to a steam distillation. The aniline was separated, the aqueous layer being extracted once with ether. The total amine was then converted into phenylhydrazine hydrochloride by the usual procedures: the over-all yield was 12%.

The phenylhydrazine hydrochloride and 2-phenylindole were analyzed for N^{15} by David W. Stewart, of these Laboratories, using a mass spectrometer of the Nier type.¹¹ The per cent. N^{15} of the total nitrogen found in the phenylhydrazine hydrochloride was $3.92 \pm 0.03\%$, and in the 2-phenylindole, $7.06 \pm 0.06\%$. The original ammonia used in the preparation contained 7.28% N^{15} . That is, all the nitrogen in the indole is essentially that in the ammonia, whereas only half that in the hydrazine corresponds to the starting material. This agrees with the chemical fact—the second nitrogen of the hydrazine was introduced by ordinary sodium nitrite.

Summary

An example of the use of N^{15} as a tracer element for determining the course of a chemical reaction has been given.

A mechanism for the last step in the Fischer indole synthesis, the elimination of ammonia, has been proposed.

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(9) Piloty, *Ber.*, **43**, 497 (1910).

(10) The ammonia from 105 g. of ammonium nitrate (7.25% N^{15}) was collected in water to form a 15% solution. This was converted to benzamide N^{15} by treatment with benzoyl chloride, in a yield of 78% (the ammonium chloride N^{15} is, of course, saved for recovery of the N^{15}H_3).

(11) Nier, *Rev. Sci. Instr.*, **11**, 212 (1940).