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An N^{15} Tracer Study of the Transformations of Acetophenone 2,6-Xylylhydrazone under the Conditions of the Fischer Indole Synthesis[1]

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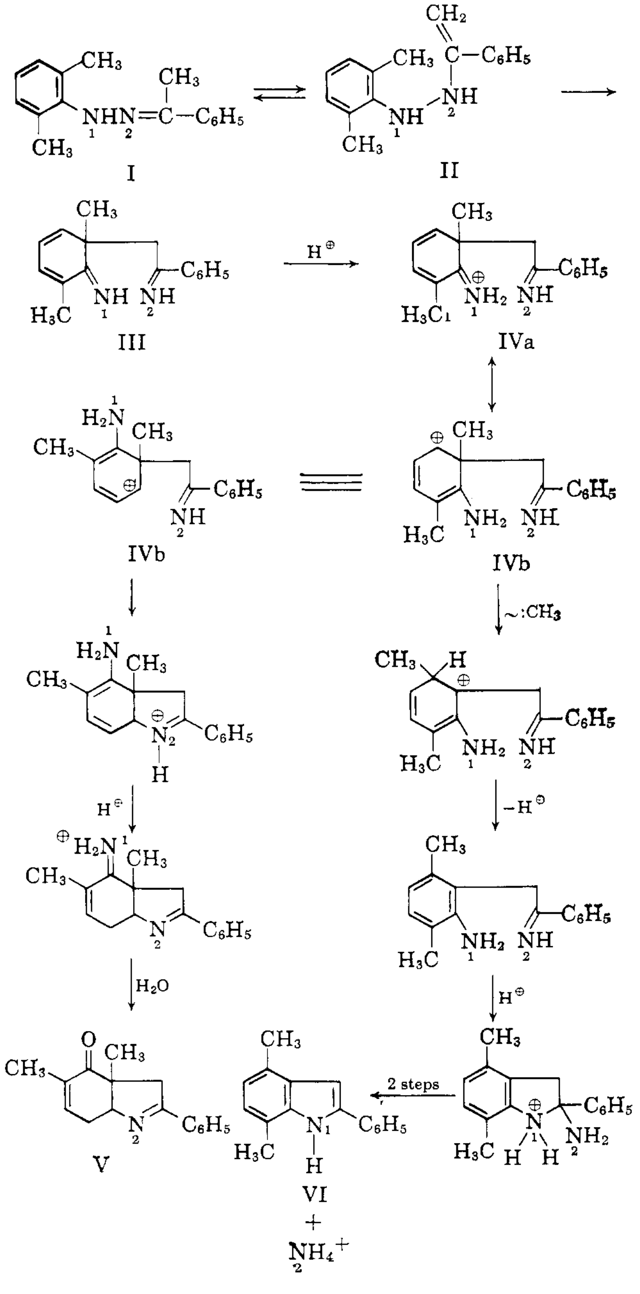
RECEIVED JULY 13, 1964

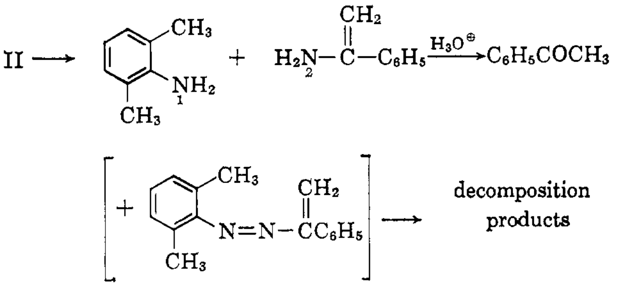
Acetophenone 2,6-xylylhydrazone-N^{15}-2 (I), treated under previously described conditions, afforded 2-phenyl-4,7-dimethylindole (VI) that contained little labeled nitrogen, 2-phenyl-3a,5-dimethyl-3a,4,7,7a-tetrahydro[3H]-pseudoindolone-4 (V) that contained nitrogen with the full complement of N^{15}, and 2,6-xylidine that was unlabeled. These observations show: (1) that no appreciable N^{15} appears at N-1 of 2,6-xylylhydrazine as a result of its preparation from 2,6-xylidine and sodium nitrite-N^{15}, and, therefore, that (2) the proposed mechanism, in which V and VI are shown arising from a common intermediate IV, receives substantial support.

A nonaromatic intermediate IV is the critical species previously postulated to account for the formation of both 2-phenyl-4,7-dimethylindole (VI)[3] and 2-phenyl-3a,5-dimethyl-3a,4,7,7a-tetrahydro[3H]pseudoindolone-4 (V)[4] from acetophenone 2,6-xylylhydrazone (I). The proposed mechanism, expressed in Chart I, requires that the nitrogen atom 1 in the original arylhydrazone (I) be retained in the indole VI, as it is in the formation of indoles from *ortho*-unsubstituted arylhydrazones,[5] but that the nitrogen atom 2 be retained in V. The experiments described in this paper were designed to test the validity of the proposed mechanism by labeling nitrogen atom 2 with excess N^{15} and then searching the products for this isotope.

CHART I



2,6-Xylylhydrazine-N^{15}-2 was prepared by diazotizing 2,6-xylidine with sodium nitrite enriched in N^{15} to the extent of about 5.2 atom % and then reducing the diazonium salt.[4] That excess N^{15} was substantially absent from nitrogen atom 1 of the hydrazine was shown by isolating 2,6-xylidine from the reaction mixture in which V and VI were formed from I and showing that only trace amounts of excess N^{15} was present in it (Table I). (Both 2,6-xylidine and acetophenone are always formed from this reaction, and it seems likely that they and analogous by-products from other Fischer reactions are formed from II and its analogs by a process similar in character to the disproportionation of hydrazobenzenes to anilines and the corresponding azo compounds.) Thus, although Insole and Lewis[6] observed a small degree of incursion of N^{15} into the N-1 position of diazotized aniline during its solvolysis, no such exchange was observed in more than trace amounts during diazotization of 2,6-xylidine and reduction of the diazonium salt under the conditions imposed.



2,6-Xylylhydrazine-N^{15}-2 was converted to I, the latter was subjected to the conditions of the Fischer reaction, and the products were isolated and purified as previously described.[4] Nitrogen in each product was converted to nitrogen gas by quantitative Dumas com-

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[1] This investigation was supported in part by National Science Foundation Grants No. NSF-G11396 and GP-1948.

[2] Submitted by A. J. Magistro in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology.

[3] R. B. Carlin, W. O. Henley, Jr., and D. P. Carlson, *J. Am. Chem. Soc.*, **79**, 5712 (1957).

[4] R. B. Carlin and D. P. Carlson, *ibid.*, **81**, 4673 (1959).

[5] C. F. H. Allen and C. V. Wilson, *ibid.*, **65**, 611 (1943).

[6] J. M. Insole and E. S. Lewis, *ibid.*, **85**, 122 (1963).

bustion, and the gas was subjected to mass spectrographic analysis. The results appear in Table I.

TABLE I

N^{15} ENRICHMENT IN PRODUCTS OF THE FISCHER REACTION OF ACETOPHENONE 2,6-XYLYLHYDRAZONE

Compound	Atom % Calcd.	N^{15} enrichment[a] Found
2,6-Xylylhydrazine HCl	2.56	2.56[b]
2,6-Xylidine (N-acetyl deriv.)	0.00	0.06
2-Phenyl-3a,5-dimethyl-3a,4,7,7a-tetrahydro[3H]pseudoindolone-4 (V)	5.12	5.10 ± 0.05[c]
2-Phenyl-4,7-dimethylindole (VI) picrate	0.00	1.00[d]

[a] Corrected for normal N^{15} isotopic abundance, 0.37%. [b] Taken as standard for other calculated values in column. Thus, assuming N-1 to contain no excess N^{15}, the enrichment at N-2 must be twice 2.56% or 5.12%. [c] Average of three determinations. [d] Four times the net N^{15} enrichment (0.25%) observed in nitrogen gas evolved, since three of every four nitrogen atoms must come from unenriched picric acid.

The data of Table I fully support the postulated mechanism (Chart I). Evidently the ketone V retains N-2 of the hydrazone I; the N^{15} enrichment found in V is undiluted. The presence of N^{15} in the indole VI probably indicates contamination of our sample by V, rather than incorporation of N^{15} into VI. The difficulties attending efforts to free VI from V may be appreciated by taking into account the facts that: (1) VI and V were isolated in 3 and 25% yields, respectively; especially when the reaction is carried out on a relatively small scale, VI is difficult to isolate and purify; (2) V and VI form a crystalline 1:1 molecular compound[4]; and (3) the indole VI from these reactions could be obtained in crystalline form only as its picrate, but V also forms a crystalline picrate of at least equal stability. Acid extraction removes most of V from effectively neutral VI, but eradication of the last traces of V by this method appears to be asymptotic in nature. For example, an indole picrate sample after preliminary purification gave nitrogen gas showing 0.52% net N^{15} enrichment. When the indole was regenerated from this picrate, extracted with acid, and reconverted to picrate, the new sample showed 0.25% net enrichment (Table I). Acid extraction therefore reduced but did not eliminate the source of enrichment. Repeated acid extractions doubtless would have further reduced the N^{15} found in VI, but the quantity of material available was insufficient for further definitive experiments. Nevertheless, the evidence at hand suggests that VI itself probably contains no excess N^{15} and that the figure opposite VI in the "Found" column of Table I probably represents an artifact.

However, even if the 1.00% enriched N^{15} in VI is accepted as a correct figure, more than 80% of the nitrogen in VI must have been derived from N-1 of the hydrazone I. This observation agrees with those made earlier by Allen and Wilson[5] on indoles formed from *ortho*-unsubstituted phenylhydrazones.

Experimental

2,6-Xylylhydrazine-N^{15}-2.—Sodium nitrite enriched to the extent of about 5.2 atom % in N^{15} was prepared by adding 3.24 g. containing 0.2 g. of N^{15} (30% enriched[7]) to 13 g. of enriched sodium nitrite. A mixture of 25 g. of 2,6-xylidine in 52 ml. of concentrated hydrochloric acid and 25 ml. of water was treated with a solution of the enriched sodium nitrite in 25 ml. of water. The diazotization and reduction of the diazonium salt to 2,6-xylylhydrazine hydrochloride was carried out in 71% yield in accordance with procedures previously described.[4] Recrystallized hydrazine hydrochloride, m.p. 210–211°, was subjected to mass spectral analysis. The atom per cent enrichment thus determined, 2.56%, was taken as half the value of the enrichment; therefore 5.12% was actually introduced into the 2-nitrogen atom of 2,6-xylylhydrazine by the sodium nitrite-N^{15}.

Action of Zinc Chloride in Nitrobenzene on Acetophenone 2,6-Xylylhydrazone (I).—A solution of 24.4 g. of acetophenone 2,6-xylylhydrazone-N^{15}-2[4] in 80 ml. of nitrobenzene was treated with 40 g. of zinc chloride, and the reaction was carried out and products were isolated in accordance with previously published procedures.[4] 2-Phenyl-3a,5-dimethyl-3a,4,7,7a-tetrahydro[3H]-pseudoindolone-4 (V) was isolated in 25% yield as large, light yellow crystals, m.p. 86–95°. Three recrystallizations from ether afforded large white crystals, m.p. 92–101°, undepressed in a sample mixed with an authentic specimen.[4] The infrared spectra of the two samples were also identical. The recrystallized material was submitted to mass spectral analysis.

2-Phenyl-4,7-dimethylindole (VI) was isolated in 3% yield as a red oil, b.p. 143–144° (1 μ). It was converted by ethanolic picric acid to its maroon picrate, m.p. 168–170°, after recrystallization from ethanol. Mixture melting point determinations and comparison of infrared absorption spectra with those of previously prepared specimens[4] showed the picrate to be identical with the substance obtained formerly. The recrystallized picrate was submitted to mass spectral analysis; then a sample was converted back to the indole by treatment with base, the indole extracted with 5% aqueous hydrochloric acid, and the picrate was regenerated by treatment with ethanolic picric acid. The new sample gave the mass spectral analysis listed in Table I.

2,6-Xylidine, recovered from the reaction mixture in 14% yield as a reddish oil, was converted to its crystalline N-acetyl derivative, white needles, m.p. 176–178°, by means of acetic anhydride in benzene solution. The N-acetyl derivative, after recrystallization from ethanol, was submitted for mass spectral analysis.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.04; N, 8.58. Found: C, 73.51; H, 7.97; N, 8.41.

Determination of N^{15} Enrichment.—All analyses were performed by means of a Consolidated Electrodynamics mass spectrometer, Model 21-103C, equipped with a standard gas inlet and a Microtek heated inlet.[8] The atom percentage enrichment in N^{15} in 2,6-xylylhydrazine and ketone V was qualitatively measured by comparing the parent ion and the parent plus one ion peaks of enriched and unenriched samples placed in the heated inlet.

Quantitative determination of the extent of N^{15} enrichment was performed by mass spectral analysis of the nitrogen gas obtained from analytical specimens of the respective compounds by means of the micro-Dumas[9] method. The apparatus was modified only by mounting an evacuated bulb at the top of the gas buret so that the collected gas could be transferred from the buret to the bulb without being contaminated by air. The atom percentage enrichment in N^{15} was calculated from the mass spectra by standard means.[10] In accordance with previous experience, no effort was made to use the m/e 30 peak in the analyses of samples containing 5% or less N^{15} enrichment; only the 29 peak was employed. Values obtained by mass spectral analysis were corrected for natural isotopic abundance of N^{15} and for traces of residual air in the evacuated bulb. The corrected values appear in Table I.

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(7) Volk Laboratory, Chicago, Ill.

(8) Mr. S. Wrbican carried out the analyses.

(9) *Cf.* J. Grant, "Quantitative Organic Microanalysis," 4th Ed., The Blakiston Co., Philadelphia, Pa., 1946, p. 63.

(10) G. P. Barnard, "Modern Mass Spectrometry," Institute of Physics, London, 1953, p. 262.