

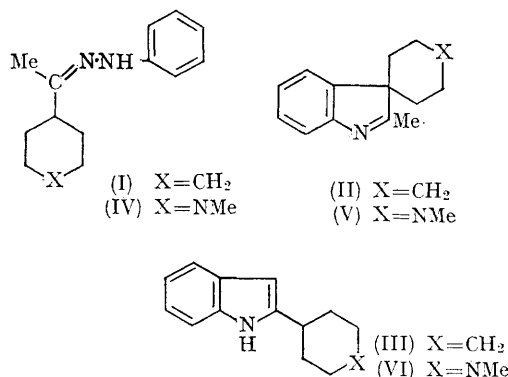
On the Direction of Cyclization of Unsymmetrical Ketone Phenylhydrazones in the Fischer Indole Synthesis

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THE Fischer indole synthesis with methyl *s*-alkyl ketone phenylhydrazones has been stated to lead exclusively to the corresponding 3*H*-indoles. The direction of the ring closure was presumedly determined by the greater stability of the enol-like tautomer having the larger number of substituents. Many examples of this generalization have been reported.¹ The ease of reaction of such compounds was difficult to reconcile with the resistance of 1-methyl-4-piperidyl phenyl ketone phenylhydrazone to undergoing the Fischer synthesis.² Furthermore, in 1938, cyclohexyl methyl ketone phenylhydrazone (I) was reported to undergo a simple conversion into the spiro-3*H*-indole (II) on heating with acetic acid,³ in agreement with the generalizations,¹ while in 1941 the Fischer synthesis with (I) under unspecified conditions was reported to give a poor yield of 2-cyclohexylindole (III).⁴ These results suggested that some further parameter than the degree of substitution must be important in determining the direction of the cyclization in the Fischer reaction with such compounds. To obtain information on this point the Fischer indole synthesis with cyclohexyl methyl

and methyl 1-methyl-4-piperidyl ketone phenylhydrazones (I and IV) were investigated.



The Fischer indole synthesis with (I) or (IV) catalyzed by polyphosphoric acid (PPA) gave primarily the corresponding 2-substituted indoles, (III) or (VI), (See Table) contrary to what would

have been predicted.¹ The structural assignments were based on i.r., u.v., and n.m.r. spectral data as well as comparison of melting points with those reported for (III) and (VI) prepared by unequivocal routes. The reported melting points were 103—105°⁴ for (III) and 182°⁵ or 183—187°⁶

considering the principles of $A^{1,2}$ strain as elaborated with enamines of cyclohexane derivatives.⁷ This relationship is most useful in correlating the relative yields of 1-substituted-1,2,3,4-tetrahydrocarbazoles and 4a-substituted-2,3,4,4a-tetrahydro-4aH-carbazoles from the Fischer synthesis with 2-

TABLE

Variation of yields with catalyst in the Fischer reaction

Phenylhydrazone	Product	PPA %	Acetic acid %	Zinc chloride %
(I)	(II)	5.2	73	67
	(III)	80	—	—
(IV)	(V)	2.3	4.9	91 ^a
	(VI)	64 ^a		

All yields were estimated by gas-chromatographic analysis except "a" which are yields based on isolated product.

for (VI) and were quite close to those of the products of the Fischer reaction with (I) (102—103°) and (IV) (184—185°). Small amounts of the isomeric 3H-indoles (II) and (V) were detected in the product mixture using gas-chromatographic analysis.

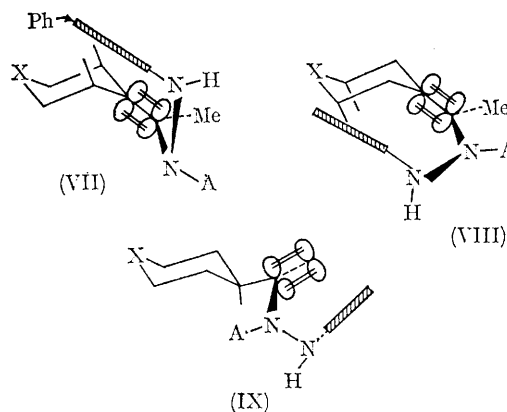
Using zinc chloride as the acidic catalyst, (I) and (IV) gave products containing only 3H-indoles (II) and (V). Acetic acid appeared to cause reaction to give only the 3H-indoles; however the yield of (V) was not very large.

These data (See Table) can be rationalized if the direction of cyclization is considered relative to the stabilities of the transition states leading to the two products. For the formation of the 3H-indole the transition state requires the approach of the phenyl ring to the π -lobes of the double bond. Models show that approach from one side is hindered by the 2- and 6-axial hydrogens (VII) and from the other side by the 3- and 5-axial hydrogens (VIII). Thus with a small acid "A", such as a proton from PPA, transition states derived from either (VII) or (VIII), leading to 3H-indole, are less stable than the transition state to the indole derived from the isomeric tautomer (IX).

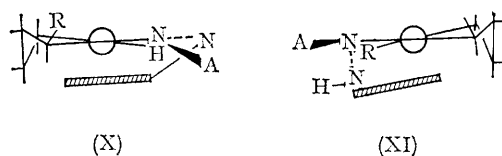
With a large acid such as zinc chloride the steric interaction of "A" with the cyclohexane ring in tautomer (IX) and the stabilization of multiple substitution of the double bond overcome the steric interference to approach by path (VII). Thus 3H-indoles are formed. The acetic acid probably functions not as a proton acid but by acylation. Thus "A" would be an acyl group and present large steric requirements as does zinc chloride.

The relative stabilities of the transition states from (VII), (VIII), and (IX) can be estimated by

substituted-cyclohexanone phenylhydrazones.⁸ The reaction *via* the transition state from enamine (X) is favoured in a reaction using a small acid as catalyst or by thermal rearrangement. A large



acid or acetic acid again would introduce unfavourable steric interactions with the substituent



in tautomer (X) and would favour reaction by a transition state from (XI).

Thus the generalizations relating the direction of cyclization of phenylhydrazones of unsymmetrical

ketones must include consideration of steric interactions of the $A^{1,2}$ type.

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