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On the Mechanism of the Wolff Aromatization Reaction[1]

A large number of examples of ketoximes which do not undergo the expected Beckmann transformation under acid conditions have been reported[2]. Of particular interest have been the reactions of various tetralone and cyclohexenone oximes which under a variety of acid conditions aromatize to naphthylamines and anilines[3,4]. As the amount of data has increased concerning the mechanism of the conversion of an oxime to an amide, considerable knowledge concerning the structural characteristics of molecules undergoing this rearrangement has been elucidated. In turn, the application of these principles to such anomalous processes as the Wolff aromatization should be expected to more clearly assist in the formulation of a working hypothesis for the mechanism of this reaction. In this paper, the knowledge of the various parameters governing the aromatization process are interpreted in light of the present knowledge available concerning the Beckmann rearrangement[2] and other anomalous oxime reactions including the oxime cleavage process[5] and the Neber reaction[6,7].

Characteristic of the Wolff aromatization reaction is the presence of an unsaturated linkage or a carbon atom capable of ready carbanion formation in a position α to the oximino group. Such systems generally under rather mild conditions such as acetic acid-acetic anhydride-hydrogen chloride mixtures or aqueous hydrogen chloride aromatize rather than undergo carbon-nitrogen rearrangement. It has also been shown that under more strenuous acid conditions, direct rearrangement apparently occurs to give as the reaction product, the amide (lactam) expected from Beckmann rearrangement[8]. It has been the attempt of previous investigators to attempt to classify the rearrangement into distinct categories[2,9], rather than to apply sound structural modifications of the basic reaction mechanism to interpret these data.

Examining the rearrangement of a ketoxime from a mechanistic viewpoint one might logically consider the reaction as initiated by protonation or esterification of the oxime hydroxyl, weakening the N-O bond sufficiently to allow loss of the hydroxyl, leaving an electron-deficient nitrogen. In the normal rearrangement, this process proceeds with the simultaneous migration of the α-carbon *trans* to the oxime hydroxyl. The azacyclopropene transition state may be stabilized by the substitutent groups or may immediately collapse to products.

In the case of the Neber rearrangement, the formation of a carbanion fragment at the α-carbon, activated by both the adjacent phenyl ring and the oximino group, an analogous azacyclopropene intermediate has been shown to most accurately describe the transformation to an α-

[1] This work was supported by Grant No. B-3628 from the Department of Health, Education and Welfare, Public Health Service.

[2] For a general review of the Beckmann rearrangement see: L. G. Donaruma and W. Z. Heldt, Org. Reactions *11*, 1 (1960).

[3] (a) F. W. Semmler, Ber. dtsch. chem. Ges. *25*, 3352 (1892). – (b) L. Wolff, M. Gabler, and F. Heyl, Liebigs Ann. *322*, 351 (1902). – (c) A. A. Kotz and T. Grethe, J. prakt. Chem. *80*, 500 (1902). – (d) P. A. Berry, A. K. MacBeth, and T. B. Swanson, J. chem. Soc. *1937*, 986. – (e) H. E. Zaugg, M. Freifelder, and B. W. Horrom, J. org. Chem. *15*, 1197 (1950). – (f) R. G. Cooke and A. K. Macbeth, J. chem. Soc. *1957*, 1593.

[4] For a recent discussion of the mechanism see: M. W. Bhatt, Exper. *13*, 70 (1957).

[5] For review of oxime cleavage processes see: R. K. Hill, J. org. Chem. *27*, 29 (1962) and references therein.

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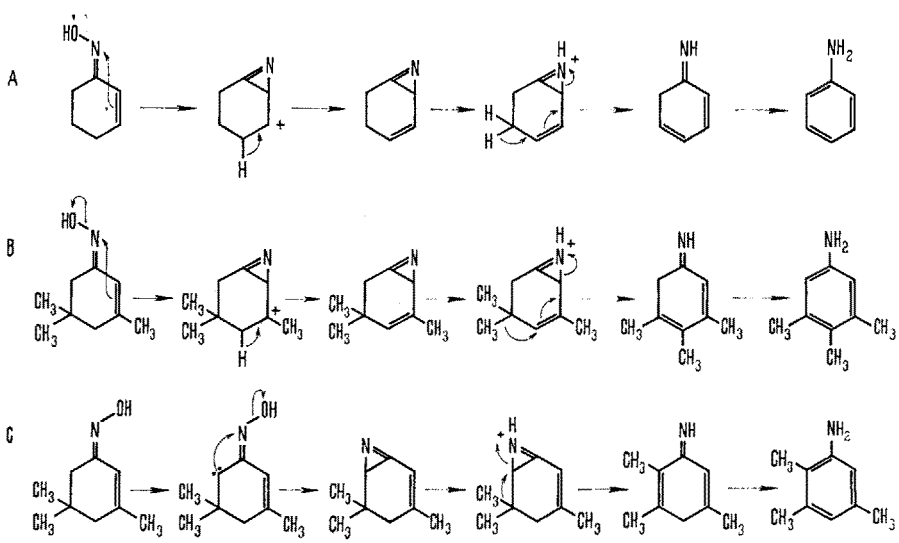
[7] For a recent discussion of the mechanism see: D. J. Cram and M. J. Hatch, J. Amer. chem. Soc. *75*, 33, 38 (1953).

[8] For example see: E. C. Horning, V. L. Stromberg, and H. A. Lloyd, J. Amer. chem. Soc. *74*, 5153 (1952).

[9] A. H. Blatt, Chem. Rev. *12*, 215 (1933).



aminoketone[7]. Applying a similar line of reasoning to the aromatization process, the reaction may be visualized as proceeding through a similar intermediate with the double bond participating in place of the migrating group. The subsequent steps in the aromatization process are best described as the simultaneous ejection of a proton, followed by collapse of the azacyclopropene intermediate through the attack of the reagents on the unsaturated reaction intermediate to yield a cyclohexadienone-imine as the initial reaction product. Tautomerization to the aromatic amine analog in each case adequately describes the final step in the aromatization process. The applicability to a system bearing geminal dimethyl groups through concurrent methyl migrations is apparent in the Figure, equation B. Further, this process should be dependent as in all Beckmann type rearrangements upon the configuration of the departing oxime-hydroxyl group. Competing with this mechanism in the case of oximes capable of isomerization will be participation of the α-carbanion in those cases in which its formation is possible (Figure, equation C).

Utilizing this mechanism, the aromatization of certain 2-tetralone[3e] can be described and as well the formation of amino-thiophenes[10] and dehydrogenation of 2-benzyl-1-tetralone[11] by partial oxime aromatization. The details of each of these processes can accurately be predicted on the basis of a mechanism of this type. The dependency of the process upon the catalyst and solvent system adds additional support to a mechanism in which multidirectional collapse of the transition state controlled by the solvent catalyst environment most adequately describes the aromatization process. The mechanism presented here also has the advantage that it describes the reaction in terms of the closely related and in some cases competing Beckmann processes.

Zusammenfassung. Es wird ein Mechanismus für die sauer-catalysierende Aromatisierung der Oxime (Wolff-Aromatisierung) vorgeschlagen, der es erlaubt, z.B. die Beckmann-Umlagerungsprozesse und Fragmentierungen entsprechend den heutigen Erkenntnissen aufzufassen. Die einschlägige moderne Literatur wird im Sinn dieser neuen Beziehungen interpretiert.

R. T. CONLEY

Department of Chemistry, Seton Hall University, South Orange (New Jersey, U.S.A.), May 9, 1962.

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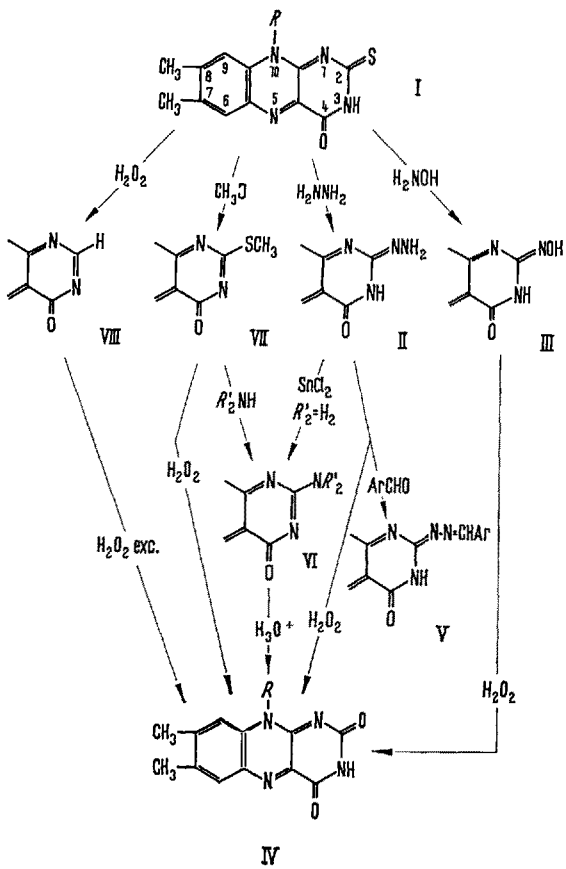
Neue funktionelle Derivate des Riboflavins: Substitutionsreaktionen am Isoalloxazin-Kern

Im Rahmen unserer Studien zur Koordinationschemie der Flavocoenzyme[1,2] benötigten wir Derivate des Isoalloxazins mit abgewandelten Substituenten im Pyrimidin-Teilkern. Im Gegensatz zu der Mannigfaltigkeit bekannter Derivate dieses Typs in den verwandten Reihen der Pteridine und Purine sind seit unserer ersten Synthese[3] des 2-Thiolumiflavins und des 2-Lumiflavimins in jüngster Zeit nur noch die analogen Ribitylderivate 2-Thioriboflavin[4] und 2-Riboflavimin[5] beschrieben worden.



Ausgehend von 2-Thioisoalloxazinen I ($R = CH_3$ bzw. R = Ribityl) konnten wir eine grössere Zahl der gesuchten Derivate auf folgenden Wegen erhalten:

1. Die sehr reaktiven Thione I geben mit Hydrazin und Hydroxylamin in wasserfreiem Milieu (Dimethylformamid) direkt die Flavohydrazone II und die Flavoxime III. Beide Verbindungstypen sind nur in kationischer Form gegen O_2 und H_2O stabil, mit Peroxiden reagieren sie besonders leicht unter Rückbildung der unsubstituierten Flavine IV. Die Hydrazone II lassen sich weiter stabilisieren als unsymmetrische Azine V.

2. Die Thione I reagieren nur unbefriedigend mit anderen wasserfreien Basen zu den Aminen VI, lassen sich aber leicht (ohne Basenkatalyse!) alkylieren zu den S-Alkylderivaten VII, welche wir früher irrtümlich als N(3)-Alkylisomere angesehen haben[6] und welche nun leicht mit wasserfreien Basen zu den gewünschten Aminen VI reagieren. Die Grundkörper VI, $R' = H$, erhält man jedoch noch einfacher durch Reduktion der Hydrazone II mit $SnCl_2$.

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