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QUINOXALINE MONO-N-OXIDE DERIVATIVES: A FACILE ELIMINATION

Makhluf J. Haddadin and Costas H. Issidorides

Department of Chemistry

American University, Beirut, Lebanon

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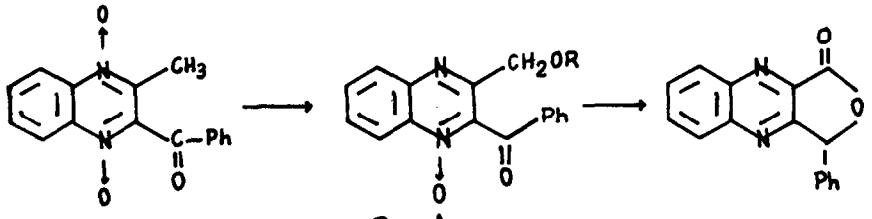
To supplement earlier work on the acylative rearrangement of quinoxaline-di-N-oxides[1], we examined the reaction of acetic anhydride-acetic acid with 2-methyl-3-benzoylquinoxaline-di-N-oxide (1) and found that the product of this reaction undergoes a remarkable transformation under conditions of basic hydrolysis.

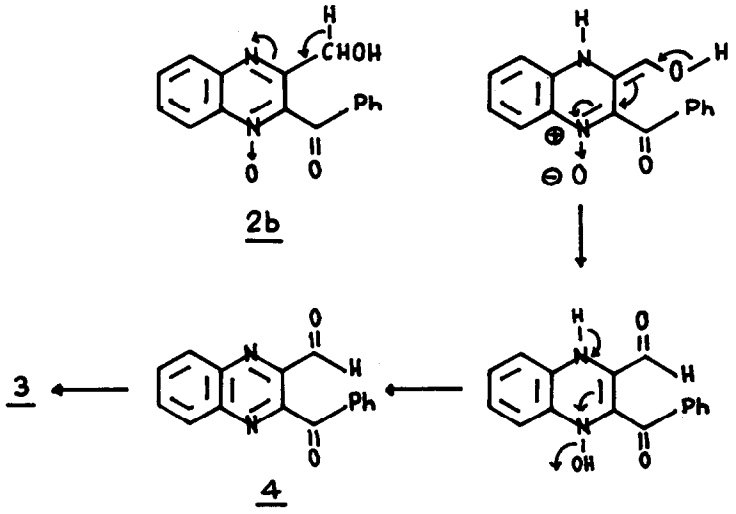
Treatment of 1 with acetic anhydride-acetic acid gave 2-benzoyl-3-acetoxymethylquinoxaline-1-oxide (2a) in good yield. Product 2a underwent normal hydrolysis in 5% alcoholic potassium hydroxide at room temperature to give the expected alcohol 2b. When carried out at reflux temperature, however, this hydrolysis took an unexpected course to give, after acidification, the five-membered lactone 3. Since the hydrolysis at room temperature of 2a to 2b was faster than the conversion of 2a into 3, it is evident that 2b is the species responsible for the formation of the lactone from 2a.



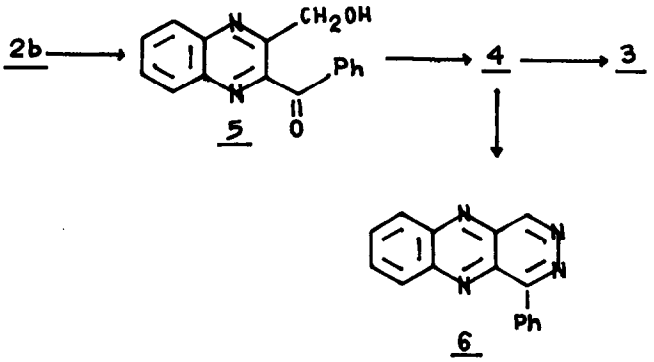
1 2 3

We believe that the transformation of 2b to 3 proceeds by two successive tautomeric shifts and a 1,4-elimination step to the fully aromatic keto-aldehyde 4 (Scheme 1). The observed product (3) is postulated to arise from an intramolecular Cannizzaro reaction of the keto-aldehyde.

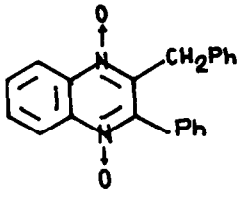
Scheme 1



Supporting evidence for the intermediacy of 2-benzoyl-quinoxaline-5-carboxaldehyde (4) was obtained by an independent synthesis of this compound from 2b by reduction to 5 with sodium dithionite, followed by oxidation to the desired product with manganese dioxide in chloroform. The independently synthesized intermediate (4) was readily converted into lactone 3 by treatment with 5% methanolic potassium hydroxide at reflux temperature, followed by acidification. The evidently high reactivity of the keto-aldehyde (4) is revealed not only by the ease with which it undergoes the Cannizzaro reaction but also by the ease with which it condenses with hydrazine to give a derivative (6) of the hitherto unknown heterocyclic system pyridazino [4,5-b] quinoxaline.



To obtain further supporting evidence for the intermediacy of 4 in the mechanism outlined in Scheme 1, we searched for another substrate that would give rise to an isolable carbonyl compound via steps analogous to those postulated for the conversion of 2a to 4. This expectation was realized with 2-benzyl-3-phenylquinoxaline-di-N-oxide (7) as the starting material. Acylative rearrangement of this product gave 2-phenyl-3α-acetoxybenzylquinoxaline-1-oxide (8a), which, on hydrolysis with 5% methanolic potassium hydroxide at room temperature, yielded the expected alcohol (8b). Treatment of either 8a or 8b with 5% methanolic potassium hydroxide at reflux temperature gave the sought after ketone (9), identical in all respects with an authentic sample of 2-benzoyl-3-phenylquinoxaline.



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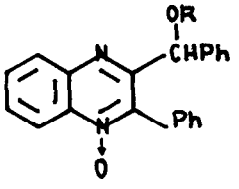
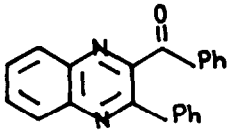


8 a R=Ac
b R=H



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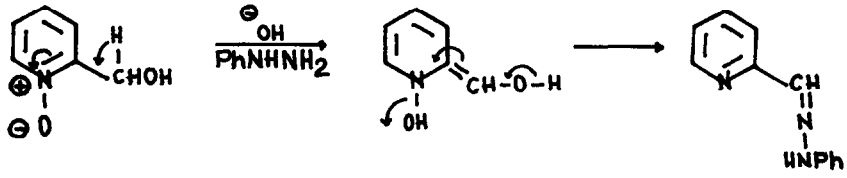
The elimination reactions described above (2b ⟶ 4, 8 ⟶ 9) can be also effected under acid catalysis.

While this work was in progress, Chilton and Butler[2] reported the isolation of pyridine carboxaldehyde phenylhydrazones from the reaction of 2-and 4-hydroxymethylpyridine N-oxides with base in the presence of phenylhydrazine. 3-Hydroxymethylpyridine-N-oxide failed to undergo this reaction presumably because, in this case, a prototropic shift from the side chain is not possible owing to lack of a driving force. Although compounds 2b and 8b of the present work are partially related to 3-hydroxymethylpyridine-N-oxide, they can accomodate such a tautomeric shift via the nitrogen atom at position 4 (Scheme 1).[3, 4]



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References

1. M.J. Haddadin and A. Salameh, J. Org. Chem., 33, 2127 (1968).
2. W.S. Chilton and A.K. Butler, J. Org. Chem., 32, 1270 (1967).
3. After this work was completed G. Tennant, J. Chem. Soc. (C), 2658 (1967), reported that 1, 2, 4-benzotriazine 1-N-oxide derivatives are converted into 1, 2, 4-benzotriazines under acid or base catalysis.
4. All new compounds gave correct elemental analysis and their structures were confirmed by spectroscopic data (I.R. and N.M.R.).