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ON THE REACTION OF PHENYLGLYOXAL WITH 2-AMINOPYRIDINE

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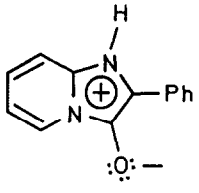
SUMMARY: A structure of 2-phenyl-1H-imidazo[1,2-a]pyridinium-3-olate (1) has been assigned to the product of the title reaction instead of the previously reported one. In solution, 1 undergoes photo-oxidation related to that occurring in Cypridina luciferine.

Goto et al.[1] assigned the structure of 2-phenylimidazo[1,2-a]pyridin-3-ol (2) to the product, with correct analytical and spectroscopic data, resulting from the reaction between phenylglyoxal and 2-aminopyridine. Later, Deady and Stanborough[2] reported the synthesis of 2 and of some derivatives by reaction of phenacyl bromides with 2-aminopyridine 1-oxide. On the other hand, structures related to 2 are biologically active with both Oplophorus and Cypridina luciferase showing that a pyrazine structure is not essential for biological activity with the latter[3].

In the course of a systematic study on the reactions of α-dicarbonyl compounds with heterocyclic amines, we have isolated a compound from the reaction between phenylglyoxal and 2-aminopyridine whose spectroscopic and



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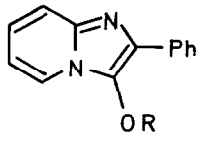


2 R = H

3 R = Me

analytical data do not conform with structure 2. The condensation was carried out by stirring at room temperature equimolar amounts of phenylglyoxal hydrate and 2-aminopyridine in benzene. After 48 h an almost quantitative yield of a yellow raw material was obtained. Treatment of this with boiling ethanol

separated an orange solid (35%). By cooling of the mother liquors a crystalline yellow solid (55%) was obtained[4]. As deduced from u.v., ^{1}H n.m.r., and mass spectra both the orange and the yellow products have the same structure. Analysis of the orange product gave the formula $C_{13}H_{10}N_2O$ in agreement with structures 1 and 2. Data for the yellow compound corresponded to a dihydrate of the same compound[5]. It is this yellow compound which corresponds to the one previously reported by other authors. On the basis of u.v. data the meso-ionic bicyclic structure 1 should be assigned to both products. Thus, the u.v. spectrum in methanol of the orange compound was compared (Figure) with that of the O-methyl derivative 3[6], a spectral model for the hydroxy tautomer 2. This comparison

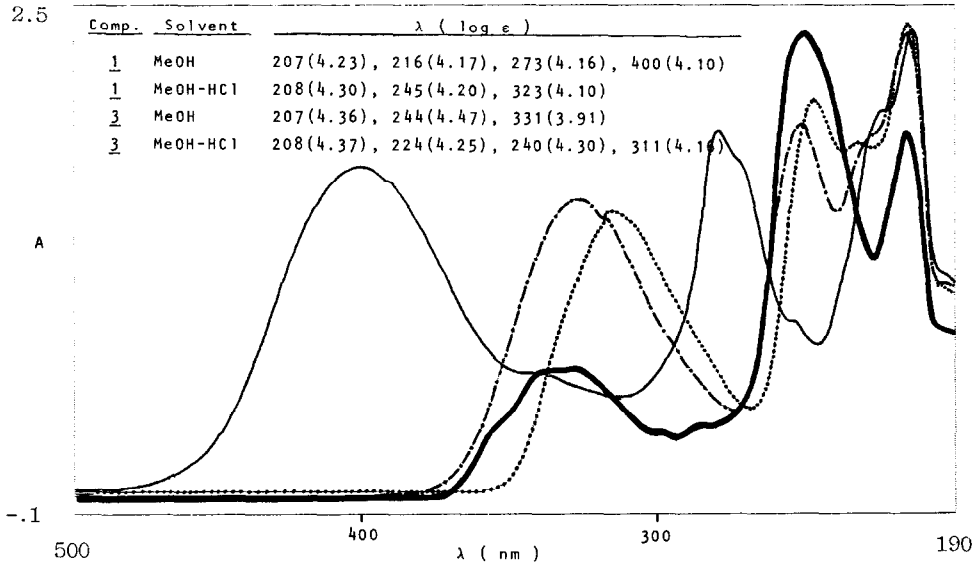
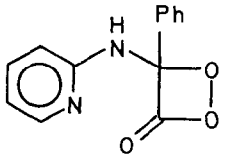


Figure.- U.v. spectra of compounds 1 in MeOH (——) and in MeOH-HCl (–·–·–), and 3 in MeOH (▬▬) and in MeOH-HCl (·····).

showed that the compound is not in the hydroxy form and should have the meso-ionic structure. Furthermore, when a drop of concentrated HCl was added to the solution of 1 in methanol, its colour faded quickly out and the u.v. spectrum of the resulting solution became rather similar to that of compound 3 in acidic medium. Thus, in neutral solution (fluorescent greenish-yellow) the chromophore of compound 1 is different from that in acidic solution (nearly colourless).

Furthermore, it has been observed that solutions of 1 in methanol, N,N-dimethylformamide and other solvents are stable only in the absence of visible light or when total exclusion of air is secured. Thus, when a methanol solution

of 1 is exposed to air and sunlight, photo-oxidation takes place yielding a mixture of products. From this mixture N-(2-pyridyl)-benzamide (major product, 45%), methyl phenylglyoxalate and 2-aminopyridine were isolated and characterized[7]. Formation of these products can be accounted for through the intermediate dioxetanone 4, in a process similar to that proposed for oxidation in Cypridina luciferine and related structures[8].



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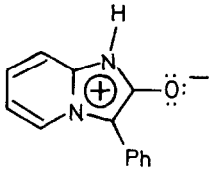

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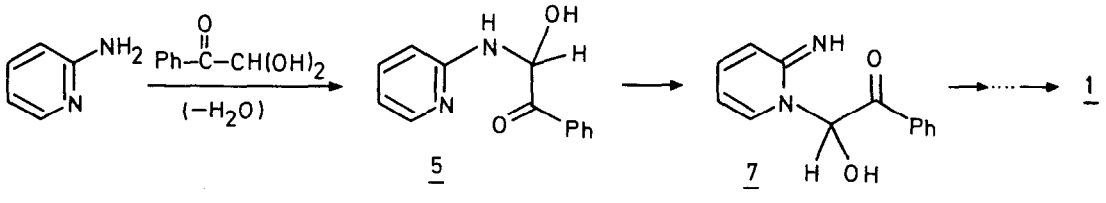
Finally, isolation and characterization of the intermediate carbinolamine 5[9] and identification of the final structure as 1 (which has been synthesized by an independent route[2] allowing so to discard the regioisomer 6) allow us to propose tentatively the mechanism in the Scheme for the reaction between phenylglyoxal and 2-aminopyridine. The key-step in the whole process is the rearrangement of intermediate 5 to the pyridinone imine 7, which would be favoured by the strong nucleophilicity of the ring nitrogen atom and the electrophilicity of the carbinolaminic carbon atom. This rearrangement could be related to some isomerization equilibria of the Chapman type[10]. The high nucleophilicity of the ring nitrogen atom should be a determinant factor since other carbinolamines similar to 5 derived from 2-aminopyrazine and 2-aminopyrimidine cyclize to the corresponding compounds related to 1 only in the presence of $BF_3.Et_2O$. This catalyst should presumably favour isomerization by enhancing the electrophilic character of the carbinolaminic carbon atom[11]. It



5 7

Scheme

is also well known that intermediates related to 7 cyclize easily but those related to the aminopyridine 5 cyclize only with difficulty[12].

The study of all these processes and the extension to other heteroaromatic amines, including aminodiazines and aminoazoles is now in progress.

REFERENCES AND NOTES

1. S. Inoue, S. Sugiura, H. Kakoi, and T. Goto, Tetrahedron Lett., 1609 (1969).

2. L. W. Deady and M. S. Stanborough, J. Heterocyclic Chem., 16, 187 (1979).

3. I. Yamaguchi, Biochem. J., 151, 9 (1975).

4. Both products melt with decomposition above 230°C.

5. Variable temperature mass spectra and thermogravimetric analysis afforded similar conclusions. These products are easily interconvertible by addition and elimination of water (azeotropic distillation with benzene or heating in vacuo).

6. Obtained according to A. J. Guildford, M. A. Tometzki, and R. W. Turner, Synthesis, 987 (1983).

7. Exposure to direct sunlight for 15 h. Column chromatography allowed the separation of five products, two of which are not yet characterized. With 30% aqueous NaOH in the presence of air a similar reaction occurs yielding N-(2-pyridyl)-benzamide (67%), 2-aminopyridine and phenylglyoxilic acid, the latter isolated as benzoic acid.

8. See, for instance: (a) T. Goto, S. Inoue, and S. Sugiura, Tetrahedron Lett., 3873 (1968); (b) T. Goto, H. Iio, S. Inoue, and H. Kakoi, ibid., 2321 (1974).

9. This compound was isolated in 80% yield from the reaction mixture forming 1 after 15 min as a white solid decomposing above 80°C. It also decomposes slowly at room temperature but can be maintained unaltered below -20°C. I.r. (KBr): 3400-2500 (OH), 3330 (sharp, NH), and 1680 (C=O). By $LiAlH_4$ reduction 1-phenyl-2-N-(2-pyridyl)-aminoethanol was obtained. Furthermore, compound 5 was independently converted into 1.

10. T. S. Stevens and W. E. Watts, "Selected Molecular Rearrangements", Van Nostrand Reinhold, New York, p.67 (1973).

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12. A. J. Elliot, H. Guzik, and R. Soler, J. Heterocyclic Chem., 19, 1437 (1982).

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