DEGRADATIONS OF 1-METHYL-3-BENZENESULFONYLOXYALLOXAZINE BY NUCLEOPHILIC REAGENTS

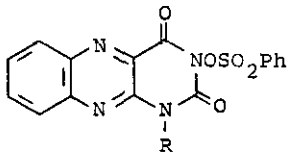
James M. Hamby and Ludwig Bauer*

Department of Medicinal Chemistry, College of Pharmacy, University of Illinois at Chicago, P.O. Box 6998, Chicago, IL 60680, U.S.A.

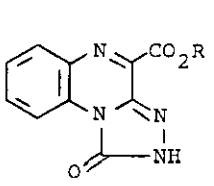
Dedicated to Professor Gilbert Stork on his 65th Birthday

Abstract - Degradation of 1-methyl-3-benzenesulfonyloxyalloxazine by nucleophilic reagents produced derivatives of 2-hydrazino-3-quinoxalinecarboxylic acid and anhydro-1-hydroxy-3-methyl-s-triazolo-[4,3-a]quinoxalinium hydroxide.

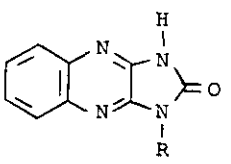
Reactions of benzenesulfonyloxyalloxazine (**1**) with sodium hydroxide, alcohols and amines have yielded derivatives of either s-triazolo[4,3-a]quinoxaline-1(2H)-one-4-carboxylic acid (**3**) or imidazolo [4,5-b] quinoxaline, (**4**).[1,2] We report now some interesting and unexpected reactions of 1-methyl-3-benzenesulfonyloxyalloxazine (**2**) with the same nucleophilic reagents.[3]



1, R = H
2, R = CH_3



3



4

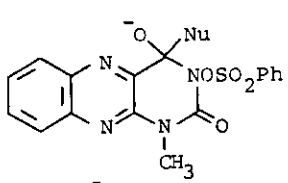
It had been reported that **1** reacted with warm sodium hydroxide to furnish the acid **3** (R = H).[1] This conversion is accomplished even better by aqueous triethylamine (15 min, 25 °C, 100%).[2] Although this acid was quite stable at room temperature, it was decarboxylated upon heating above 80 °C. It was therefore surprising to discover that a fast reaction of **2** with 5% sodium hydroxide (90 °C, 5 min) yielded 2-hydroxy-3-quinoxalinecarboxylic acid (**12**, X = CO_2H, 48%). Yet, hot aqueous triethylamine (100 °C, 2 h) transformed **2** to the known[4] mesoionic triazoloquinoxaline **10** (X = H, 73%). From these reactions of **3** in basic media, we had expected to isolate the homologous acid (presented by **9**, Nu = OH, or **10**, X = CO_2H). Apparently, this acid decarboxylated already at room temperature, since all efforts to isolate the acid failed.

The reactions of **1** or **2** with alcohols, in the presence of triethylamine, proved to be quite analogous. For example, the reaction of **1** in boiling methanol and triethylamine yielded the ester **3** (R = OCH_3, 98%),[1] while under these conditions **2** afforded the ester **9** (Nu = OCH_3, 96%). The reactions of **2** with ethanol, 1- and 2-

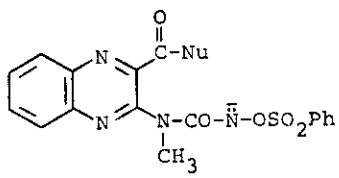
propanol were investigated. There was obtained a series of esters (**9**, Nu = OR) in very good yields (ethyl, 94%; n-propyl, 94%; isopropyl, 50%). As the size of the attacking alcohol increased, the yield of the ester decreased. For example, with t-butyl alcohol, this reaction failed.

Small and excellent nucleophiles, like methylamine and hydrazine, reacted quickly with **2** at room temperature to provide amides **9** (Nu = $NHCH_3$ and $NHNH_2$, respectively). However, this kind of reaction is not always that clean and frequently mixtures of products were obtained, as will be evident from the examples cited below.

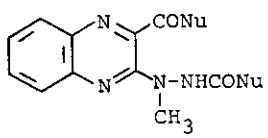
The majority of the initial reaction by alcohols and amines can be explained as follows. Nucleophilic attack on the highly electrophilic C-4 carbonyl group of **2** forms the tetrahedral intermediate, **5**. Collapse of this intermediate, with ring opening, generates the acid, or an acid derivative, and the anion of an O-sulfonyl hydroxamic acid, **6**. This anion would be expected to undergo an almost spontaneous Lossen rearrangement to form an isocyanate,[5,6] in this instance, **7**. The isocyanate can either add an equivalent of the nucleophilic reagent (HNu) to form a carbamic acid derivative **8** (**Route a**), or cyclize with the neighboring quinoxaline nitrogen to furnish the mesoionic triazolone **9** (**Route b**). Competition between **Routes a** and **b** explains the mixture of products isolated in some of these reactions.



5

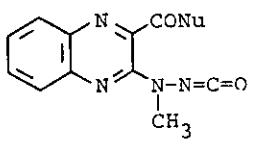


6



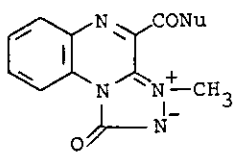
8

Route a



7

Route b

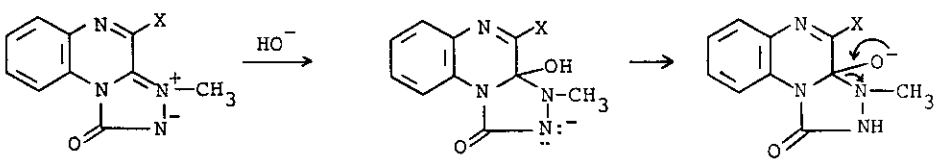


9

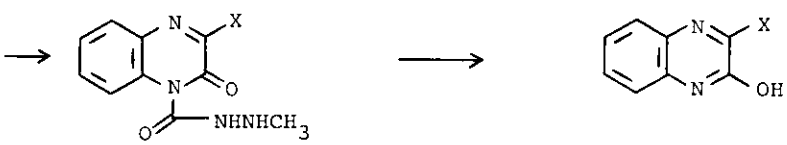
Frequently, relatively small changes in reaction conditions provided a mixture of products. For example, the reaction of **2** with methanol and sodium methoxide (0-5 ^{o}C, 5 min), yielded the urethane ester, **8** (Nu = OCH_3, 11%), the ester, **9** (Nu = OCH_3, 21%) and the parent mesoionic compound, **10** (X = H, 17%). The formation of **8** and **9** is explained in terms of the mechanisms postulated for these degradations from **7** via either **Route a** or **Route b**, respectively. The isolation of **10** (X = H) is more difficult to rationalize. Although the temperature was kept low for the reaction and the work-up, some of the ester (**9**, Nu = OCH_3) could have hydrolyzed to the unstable acid (**9**, Nu = OH), which would then account for the isolation of **10** (X = H).

From the reaction of **2** with two equivalents of piperidine in boiling methylene chloride (1.5 h) there was isolated the mesoionic amide, **9** [Nu = $N(CH_2)_5$, 32%], the amide semicarbazide, **8** [Nu = $N(CH_2)_5$, 8%] and 3-hydroxyalloxazine[1] (52%). While the formation of compounds of type **8** and **9** can be explained via **Routes b** and **a**, respectively, the isolation of 3-hydroxyalloxazine was unexpected. It is suggested that the latter arises after the relatively bulky piperidine attacks the electrophilic sulfur atom of the sulfonate group of **2**. During such a nucleophilic displacement, a sulfonamide is formed and the anion of 3-hydroxyalloxazine becomes the leaving group. Apparently, such a reaction can predominate when the steric volume of the attacking nucleophile inhibits attack of Nu: at C-4 of **2** to form **5**.[7]

The initial degradation of **2** to **12** (X = CO_2H) by sodium hydroxide requires some explanation. In view of related reactions by small nucleophiles, it is reasonable to assume that hydroxide ion converts **2** quickly via **Route b** to the sodium salt of the unknown acid, namely **9** (Nu = O^- Na^+). It is suggested that a further degradation takes place in this basic medium, when hydroxide ion attacks the mesoionic system of **9** to form the tetrahedral intermediate, **11** (X = CO_2^- Na^+). Collapse of **11** to the semicarbazide, **11a**, and hydrolysis of the latter leads to 2-hydroxy-3-quinoxalinecarboxylic acid **12** (X = CO_2H).



10 **11**



11a **12**

It was shown that the mesoionic system of **9** was very susceptible to base-catalyzed hydrolysis. Indeed, the parent (**10**, X = H) was hydrolyzed by aqueous sodium hydroxide to 2-hydroxyquinoxaline (**12**, X = H). Similarly, the methyl ester (**9**, Nu = OCH_3) also underwent base-catalyzed hydrolysis to yield 2-hydroxy-3-quinoxalinecarboxylic acid (**12**, X = CO_2H).

However, the mesoionic system of **9** was stable to acid. Upon boiling with hydrochloric acid, the hydrazide (**9**, Nu = $NHNH_2$, or **10**, X = $CONHNH_2$) was converted quantitatively to the parent compound **10** (X = H). This observation substantiates the assumption that the acid (**10**, X = CO_2H) which should have been formed from the hydrazide decarboxylates readily.

These and related reactions are being investigated further.

REFERENCES

1. K.-Y. Tserng and L. Bauer, J. Heterocycl. Chem., **1974**, 11, 163.
2. J. M. Hamby and L. Bauer, Presented at the 186th American Chemical Society National Meeting, Washington, DC, ORGN Abstr. 255 August 28, 1983.
3. J. M. Hamby and L. Bauer, Presented at the 188th American Chemical Society National Meeting, Philadelphia, PA, ORGN Abstr. 235, August 26, 1984.
4. K. T. Potts, S. K. Roy, S. W. Schneller, and R. M. Huseby, J. Org. Chem., **1968**, 33, 2559.
5. C.D. Hurd and L. Bauer, J. Am. Chem. Soc., **1954**, 76, 2791.
6. L. Bauer and O. Exner, Angew. Chem., Int. Ed. Engl., **1974**, 13, 376.
7. For examples of such a displacement, see K.-Y. Tserng and L. Bauer, J. Org. Chem., **1973**, 38, 3498.

Received, 10th March, 1986