Tetrahedron Letters No.54 pp.4745-4748, 1969. Pergamon Press. Printed in Great Britain.

CYCLIZATION REACTIONS OF AN ALLENIC OXOQUINAZOLINE[x]

Conny Bogentoft, Örjan Ericsson, Pål Stenberg and Bengt Danielsson

Department of Organic Chemistry, Farmaceutiska Fakulteten, Box 6804, S-113 86 Stockholm

(Received in the U K 21st October 1969; accepted for publication 25th October 1969)

Attempts to reduce the carbonyl group of 3-propargyl-3,4-dihydro-4-oxoquinazoline (I) with $LiAlH_4$ only afforded the allene II [cf. (1)]. When I was reacted with sodium in ethanol, the same rearrangement took place and the allene II, together with some other products, was isolated from the reaction mixture. It was found that the allene underwent a series of reactions (II → III → IV; II → VII) which are discussed below and summarized in the chart. It is the purpose of the present report to describe the course of these transformations.

3-Propadienyl-3,4-dihydro-4-oxoquinazoline (II) was obtained in 50 % yield by refluxing I with 0.2 equiv. of sodium in absolute ethanol for 5 min. The product separated upon cooling and two additional compounds (III, VII) remained in the filtrate, as indicated by TLC; M.p. 130-131°C. Mol. wt. 184 (MS). NMR ($CDCl_3$): τ 4.35 (2H, doublet, J=6.4 cps), indicating a terminal allene; spectrum featureless at higher field. Although it is a terminal allene, II does not show any prominent IR-absorption in the 1920-2000 cm^{-1} range, only a weak band at 1955 cm^{-1} (KBr) being observed. Hydrogenation of II (Pd/C) afforded 3-propyl-3,4-dihydro-4-oxoquinazoline (X) [spectroscopic comparison with authentic specimen (2)]. Reduction of II with $NaBH_4$ yielded 3-propadienyl-1,2,3,4-tetrahydro-4-oxoquinazoline (XI), which had no IR-absorption at 1920-2000 cm^{-1}. The NMR and mass spectra of XI were in agreement with the proposed structure.

2-(2-Formamidophenyl)-5-methyloxazole (III) was prepared by heating the above-mentioned reaction mixture (I → II) for 2 hr, 96 % ethanol being used instead of absolute alcohol. Compound III was also formed from II as indicated in the chart. - M.p. 74-75°C. Mol. wt. 202 (MS). NMR ($CDCl_3$): τ 7.68 (3H, singlet, methyl). The base peak (174) of the mass spectrum corresponds to a loss of 28 (CO) from the molecular ion, which has been observed in other

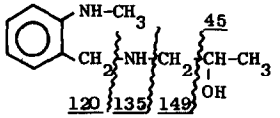
---

[x] Studies on the medicinal chemistry of oxoquinazolines V. Paper IV: Bogentoft, C., Kronberg, L. and Danielsson, B. Acta Pharm. Suecica 6, 489 (1969).

formamides (3). From 174 and down, the mass spectra of III and IV are very similar.

2-(2-Aminophenyl)-5-methyloxazole (IV) was prepared by acid or alkaline hydrolysis of III. - M.p. (·HCl) 207-208°C. Mol. wt. 174 (MS). The compound was deaminated by diazotization and hydrolysis with hypophosphorous acid to yield 5-methyl-2-phenyloxazole (V) which was identified by spectroscopic comparison with a specimen prepared by cyclization of N-propargylbenzamide according to (4).

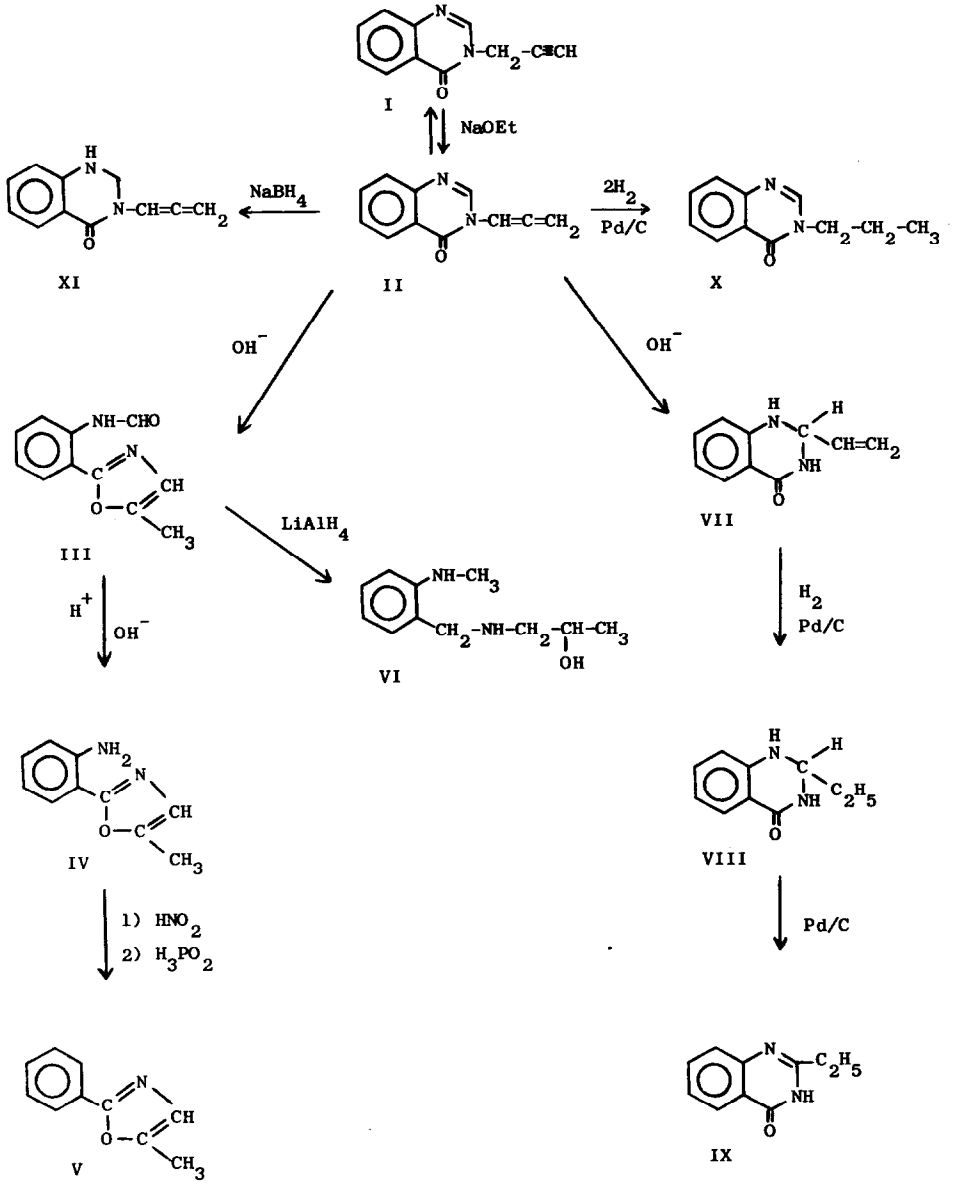
On reduction with $LiAlH_4$ for 30 hr, compound III afforded N-(2-hydroxypropyl)-N-(2-methylaminobenzyl)amine (VI). - M.p. (oxalate) 164-166°C. Mol. wt. 194 (MS). NMR ($CDCl_3$): τ 8.98 (3H, doublet, J=6 cps, indicating CH-CH_3), τ 7.30 (3H, singlet, NH-CH_3), τ 6.40 (2H, singlet, benzylic protons). MS: prominent peaks at m/e 194 (M^+), 149, 135, 121, 120 (base peak), 118, 91, 45. Some of these peaks are accounted for as follows:



2-Vinyl-1,2,3,4-tetrahydro-4-oxoquinazoline (VII), as mentioned, was formed as a by-product in the reaction I → II. It was prepared in 20 % yield by refluxing I with 1 equiv. of potassium hydroxide in 96 % ethanol for 1.5 hr and was also formed if II was used as starting material. - M.p. 151-152°C. Mol. wt. 174 (MS). Hydrogenation (Pd/C) at atmospheric pressure for 30 min. afforded 2-ethyl-1,2,3,4-tetrahydro-4-oxoquinazoline (VIII), the structure of which was proved by comparison (IR) with a specimen prepared by an unambiguous method (5). When the reaction over Pd/C was prolonged to 60 hr, dehydrogenation to 2-ethyl-3,4-dihydro-4-oxoquinazoline (IX) had occurred; IX was identified by comparison with an authentic sample.

Elementary analyses of all the new compounds were in good agreement with the calculated values.

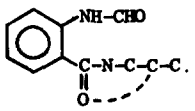
Discussion of the results. - Since I and II are isomers, and since the IR spectrum of II did not indicate categorically the occurrence of a terminal allene group, the possible rearrangement of the side-chain of I to an N-(1-propynyl) group was contemplated. However, this structure was ruled out on account of the NMR-spectrum, which did not show any methyl signals, but strongly supported an allene structure. Since the allene XI entirely lacks IR absorption in the 1920-2000 cm^{-1} range, we feel that due caution should be exercized in rejecting allene structures on IR spectroscopic evidence alone.



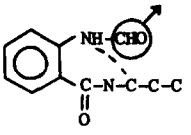
Reactions of 3-propadienyl-3,4-dihydro-4-oxoquinazoline

The formation of 4-methyloxazoles from N-propargyl compounds has been reported earlier (4), although these investigators used acid catalysts. In connection with the $LiAlH_4$ reduction of III to the carbinol VI, it may be mentioned that similar reactions have been performed with sodium in ethanol (6).

Although the reaction mechanism has not been investigated, it seems reasonable to suppose that in the reactions II → III and II → VII a common open-chain intermediate governs the reaction. This hypothetical intermediate, which could be postulated to have the skeletal structure XII, may undergo ring-closure in two different ways:



XII → III



XII → VII

It should be noted that the carbon atom C-2 of the original quinazoline II is lost as a formyl group in the reaction XII → VII.

A full report, including a discussion of the mass spectra, will be published elsewhere.

References

1. Jacobs, R. and Wilcox, R. J. Am. Chem. Soc. 86, 2240 (1964).

2. Hanford, W., Liang, P. and Adams, R. Ibid. 56, 2780 (1934).

3. Unpublished results from this Department.

4. Schulte, K., Reisch, J. and Sommer, M. Arch. Pharm. 299, 107 (1966).

5. Böhme, H. and Böing, H. Ibid. 293, 1011 (1960).

6. Fischer, E. Ber. 29, 205 (1896).