SYNTHESIS OF A NEW AZACYCLAZINE, INDOLIZINO[3,4,5,6-cde]QUINOXALINE[1]

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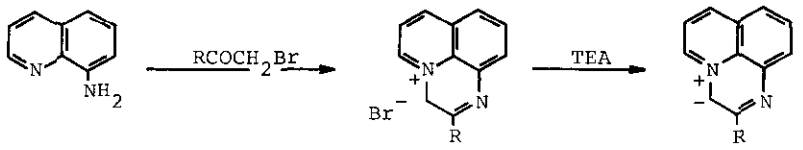
Abstract —— A new peripheral azomethine ylid 1,3-dipole, anhydro 3H-pyrido[1,2,3-de]quinoxalin-4-ium hydroxide, was generated from the pyridoquinoxalinium bromide and reacted with dimethyl acetylenedicarboxylate giving the indolizino[3,4,5,6-cde]quinoxaline in quantitative yield. With electron-deficient olefins such as diethyl fumarate and N-benzylmaleimide, the corresponding [4+2] cycloadducts were formed, which were then dehydrogenated with p-chloranil into the similar heterocycles in fair yields.

It is well known that cycloaddition reaction of indolizine to electron-poor acetylene under dehydrogenating conditions is a simple and convenient preparative method of cyclazine. Thus, some cycl[3.2.2]azines[2] and their aza analogs[3] have been synthesized by the reactions of indolizines and azaindolizines, respectively. If a 1,3-dipole is developed on the periphery of heterocycle with a ring junction nitrogen atom, this heterocycle may be employed as a starting material for cyclazine synthesis. However no attempt to prove this possibility has been seen in the literature probably because an idea of peripheral 1,3-dipole is not familiar. Here in this communication, a new synthetic way into cyclazine derivatives is reported with the reaction of anhydro 2-substituted 3H-pyrido[1,2,3-de]quinoxalin-4-ium hydroxide (2) with electron-deficient acetylene and olefin.

An equivalent amount of 8-aminoquinoline was warmed in methanol with bromoacetone and ω-bromoacetophenone for half an hour to yield, after evaporation of the solvent, red crystals of 2-methyl- (1a) (mp 346-348°C) and 2-phenyl-3H-pyrido[1,2,3-de]-quinoxalin-4-ium bromide (1b) (mp 276-279°C), respectively. These salts 1 showed no vibrational absorption for NH in the ir spectra. They are soluble in water, methanol, and ethanol and were purified by recrystallization from ethanol-acetone mixture.

When methanolic solution of the salts 1 was treated with excess triethylamine, color of the reaction mixture turned deep violet indicating the formation of the ylid, anhydro 2-methyl (or 2-phenyl) -3H-pyrido[1,2,3-de]quinoxalin-4-ium hydroxide (2). The color gradually faded on exposure of the solution to the air. Attempts to isolate the ylids 2 were unsuccessful.

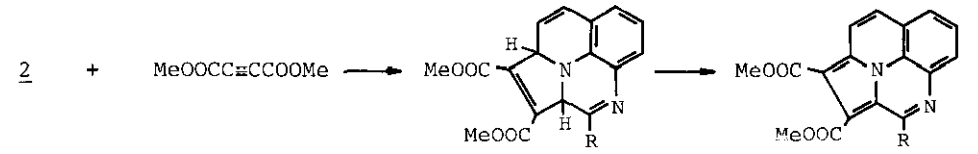


1a: R=Me
1b: R=Ph

2a: R=Me
2b: R=Ph

A methanolic solution of 1a and dimethyl acetylenedicarboxylate was treated with excess triethylamine at room temperature. All volatile materials were removed by evaporation in vacuo and the solid residue obtained was washed with water giving orange-colored prisms of 4a (mp 202-202.5°C) in quantitative yield. The product 4a has two carbonyl stretching vibration at 1730 and 1700 cm^{-1} in its ir spectrum. No signals for methine hydrogens were revealed in the nmr spectrum showing a fully conjugated structure of the product. The mass spectrum also gave a parent ion peak at m/e 322 for the dehydrogenated cycloadduct 4a. The reaction involves a cycloaddition reaction of an azomethine ylid 1,3-dipole in 2a to the acetylene forming the initial [4+2] cycloadduct 3a which was then easily dehydrogenated even at room temperature into the isolated product 4a.

The similar reaction of phenyl substituted salt 1b afforded the dehydrogenated cycloadduct 4b (mp 276-278°C) also in quantitative yield.

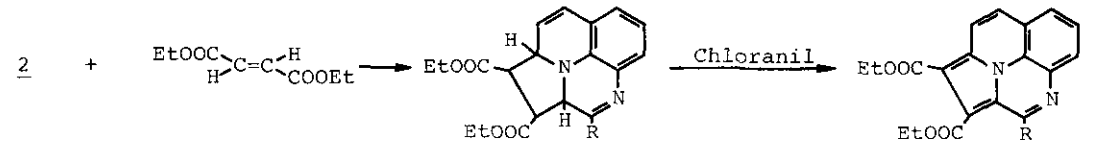


3a: R=Me
3b: R=Ph

4a: R=Me
4b: R=Ph

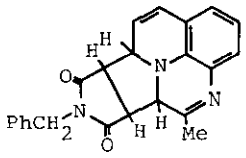
On the other hand, the reactions of 2 with diethyl fumarate in methanol gave the mixture of two stereoisomers, both of which were found to be the [4+2] cycloadducts on the basis of the nmr spectra and the results of the following dehydrogenation

with p-chloranil. Thus, 3-methyl- (6a) (mp 139-142°C) and 3-phenyl-1,2-bis(ethoxycarbonyl)indolizino[3,4,5,6-cde]quinoxaline (6b) (mp 196-198°C) were obtained in fair yields.



5a: R=Me
5b: R=Ph

6a: R=Me
6b: R=Ph



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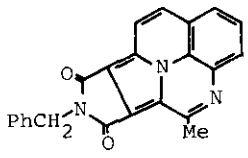

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N-Benzylmaleimide reacted with 2a to give the single [4+2] cycloadduct 7 (mp 160.5-162°C) in quantitative yield, which was identified as an endo cycloadduct as discussed in the another publication[4]. The endo cycloadduct 7 was also easily dehydrogenated with p-chloranil affording 8 (mp 276-279°C).

Table. Dehydrogenated Cycloadducts 4, 6, and 8.

Compounds	Mp (°C)	Yield (%)	$\nu_{C=O}$ (cm^{-1})	M^+ (m/e)
4a	202-202.5	100[a)]	1730, 1700	322
4b	276-278	100[a)]	1735, 1700	384
6a	139-142	30[a)]	1715, 1700	350
6b	196-198	55[a)]	1730, 1700	412
8	276-279	95[b)]	1750, 1695	365

Yield based on a) 1 and b) 7.

It has been found that the cycloaddition reactions of 2 to electron-deficient acetylenes and olefins in the absence or presence of p-chloranil are useful synthetic methods for the indolizino[3,4,5,6-cde]quinoxalines. A wide applicability

of the above reactions is under investigation by using other acetylenes and olefins. The results will be shown in near future.

REFERENCES

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