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A NEW OCTAHYDROQUINOXALINE SYSTEM VIA THE INTRAMOLECULAR ADDITION OF A SECONDARY AMINE TO AN ISOLATED TRIPLE BOND. A NOVEL HETEROCYCLIZATION REACTION.

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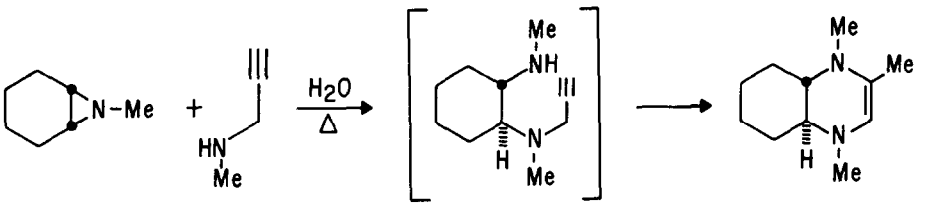
In the course of our search for biologically active agents, we discovered a novel heterocyclization reaction. We wish to report details of the reaction and then comment on possible mechanisms implicated in the cyclization.

When an aqueous solution of 7-methyl-7-azabicyclo[4.1.0]heptane (1) and 2 eq of N-methylpropargylamine (2) was heated at reflux temperature overnight with a trace of ammonium chloride,[2] the expected N,N'-dimethyl-N-2-propynyl-1,2-cyclohexanediamine 3 was not obtained. Instead, 1,4,4aβ,5,6,7,8,8aα-octahydro-1,2,4-trimethylquinoxaline (4) was isolated as a pale yellow oil in 50% yield, after fractional distillation (BP 68-71°, 0.3 mm) of the crude reaction mixture.



1 2 3 4

The air sensitive oil was assigned structure 4 on the basis of 1) IR, NMR and mass spectroscopic evidence summarized below, and 2) characterization of a chemical derivative.

From elemental analysis and mass spectrum compound 4 was assigned molecular formula $C_{11}H_{20}N_2$. The mass spectrum displayed ions [P^+: 180 (100); $P^+ - 124$: 56 (45) and $P^+ - 138$: 42 (28)] corresponding to parent, $MeN \equiv CMe$ and $MeN \equiv CH$, respectively. The last two ions suggested an unsymmetrical 1,4-enediamine.

Further evidence for a 1,4-enediamine was detected in the IR in which indicated carbon-carbon double bond stretching at 1675, 1655 and 1565 cm^{-1}. Similar stretching patterns are recorded for enamines.

The NMR spectrum of compound 4 (Table 1) also indicated a vinylproton at δ 4.98 ppm, which corresponds in chemical shift to enamine-type vinyl proton. Furthermore, a vinylmethyl

was seen at δ 1.70 ppm in D_6DMSO which was split into doublet (J = 1 Hz) apparently through long range coupling with the vinylproton of compound 4.

Additional proof of structure for enediamine 4 was provided by characterization of a chemical derivative. Thus 4 was treated with one equivalent of para-trifluoromethylbenzoyl chloride in a solution of tetrahydrofuran and triethylamine at room temperature overnight. Upon workup 1,4,4aβ,5,6,7,8aα-octahydro-1,3,4-trimethylquinoxalin-2-yl-α,α,α-trifluoro-p-tolylketone 5 (mp 123-124°) was obtained in 50% yield after crystallization from diethylether.

Structure 5 was assigned on the basis of IR, UV, NMR and mass spectroscopic evidence summarized below.

From elemental analysis and mass spectrum compound 5 was assigned molecular formula $C_{18}H_{23}F_3N_2O$. The mass spectrum exhibited ions [P^+: 352 (100); P^+ -179: 173 (26) and P^+ -296: 56 (69)] corresponding to parent, $O \equiv \overset{\oplus}{C}$- p$\emptyset CF_3$ and $MeN \equiv \overset{\oplus}{C}Me$. The last two ions are consistent with the p-trifluoromethylbenzoyl addend located on C-2 in structure 5.

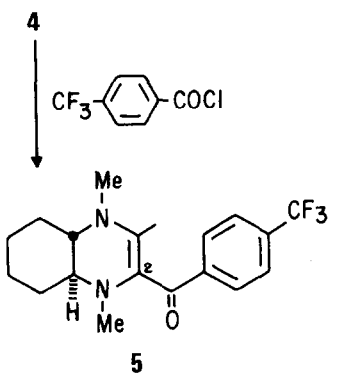
The IR of compound 5 displayed carbonyl absorption at 1620 cm^{-1} and the UV indicated extended conjugation with absorptions at 282 nm (ε 8,150), 335 (3,750) and 390 (9,700) in ethanol.

Comparison of the NMR spectra of 5 (Table 1) and 4 showed that all the protons of 4, except for the vinylproton, were present in 5.

Table 1 NMR Spectral Data [a]

	Compound 4	Compound 5
	δ ppm	δ
Aromatic	-	7.73
Vinylmethine	4.98	-
N-methyls	2.46 and 2.38	2.99 and 2.34
N-methines	2.5 to 2.7	2.5 to 2.7
Vinylmethyl	1.71	1.98
Ring methylene	1.1 to 2.4	1.1 to 1.9

[a] Spectra were observed at 60 and 100 MHz in d-chloroform solution



5

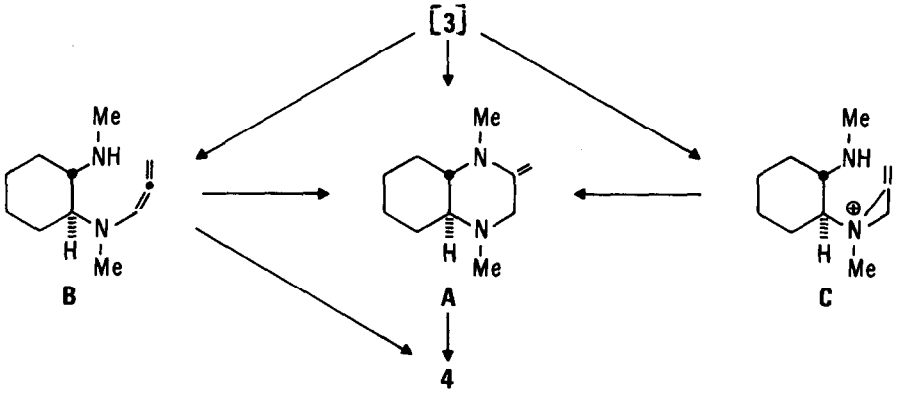
A search for structural precedents of compound 4 showed that although many aromatic quinoxalines are known,[3] saturated quinoxalines are few in number.[4] In fact, we were able to find only one previous synthesis of an octahydroquinoxaline.[5] In this case, 2-chlorocyclohexanone was condensed with N,N'-dimethylethylenediamine to give 1,2,3,4,5,6,7,8-octahydro-1,4-dimethylquinoxaline.

Therefore, as far as we were able to determine, compound 4 represents a new octahydroquinoxaline system.[6]

The possible mechanism for the formation of 4 deserves a comment. As an initial intermediate, diamine 3 seemed reasonable because the syntheses of analogous trans 1,2-alkyldiamines from secondary amines and aziridines are known.[7] However, the transformation 3 ⟶ 4 would be the result of an unusual intramolecular addition of a secondary amine to an isolated triple bond.

A review of the literature showed that nucleophilic additions of primary and secondary amines to activated triple bonds can be very facile.[8] On the other hand, the usual conditions for adding alkylamines to unactivated alkynes (following Reppe) involve elevated temperatures, pressures and a catalyst such as zinc, mercuric acetate or thallium acetate.[9] We found a few reports in which amines added noncatalytically to triple bonds, but these cases were not good analogies for the transformation 3 ⟶ 4 since the reported acetylenes are in conjugation with olefins or other acetylenes.[10]

A precedent for the nucleophilic addition of a secondary amine to an isolated acetylene appeared recently.[11] By analogy, 3 could give (via direct addition due to proximity effects) intermediate A, which then would rearrange to 4 (Scheme 1).



Another mechanism could involve intermediate B (Scheme 1). Ample evidence was located for base induced prototropic rearrangements of propargylamines to allenylamines[12], and addition of amines to activated allenes[13,14]. It should be emphasized, however, that the conversion 3 ⟶ 4 occurs under very mild conditions.

A third possible intermediate is the aziridinium ion C (Scheme 1).[15] However, little precedent for neighboring group participation in propargylamines was found to support the formation of C.

In summary, the new octahydroquinoxaline system 4 was synthesized by a novel heterocyclization reaction. Whether intermediate A, B, or C, or another intermediate is involved in the formation of 4 remains to be determined.

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