A NEW SYNTHESIS OF QUINUCLIDINIUM DERIVATIVES

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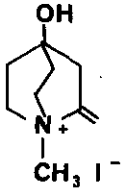
Abstract - Six membered rings including at the positions 1 and 4 a basic nitrogen and a propargylic chain undergo cyclization by intramolecular nucleophilic attack of nitrogen on triple bond. Quinuclidiniums are isolated as iodides. The reaction is investigated in the field of *piperidine*, *piperazine*, and tropane derivatives.

The biological properties of quinuclidine derivatives gave rise to a number of studies in recent years, interest being focused on the field of cholinergic, ganglion-blocking, and antihistaminic activities [1,2]. Methods of synthesis for quinuclidines have been reviewed [1]. Most of them proceed by intramolecular alkylation or acylation of 4-substituted piperidines [1,3]; attack of a carbanion on a conjugated double bond was reported [4] while acetylenic cyclization does not seem to have been attempted.

We present in this report a new synthetic route to the methylene quinuclidinium 1, its pluricyclic derivative 3, and the aza analog 2.



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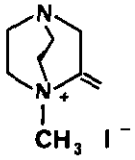

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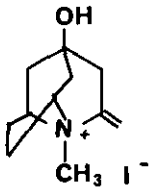

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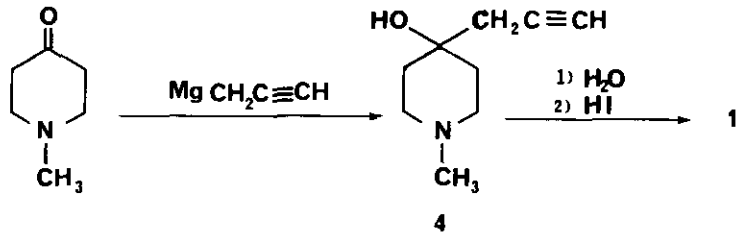
The reaction of propargylmagnesium bromide [5] with N-methyl-4-oxopiperidine leads to the alcohol 4, which cyclizes by heating in the presence of water and methanol (50/50) to a quaternary ammonium hydroxide [6]. Neutralization using hydriodic acid leads to the iodide 1.



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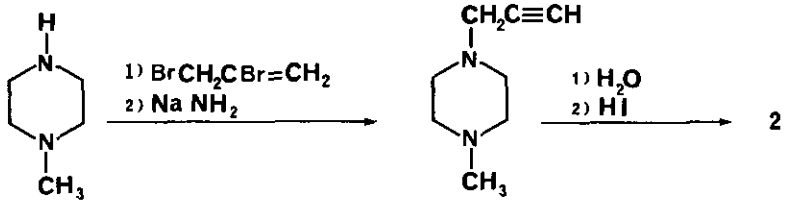
The propargylation of N-methyl-piperazine (alkylation by 2,3-dibromopropene followed by dehydrohalogenation) leads to compound 5 [7], which cyclizes in a similar way to the azaquinuclidinium 2.



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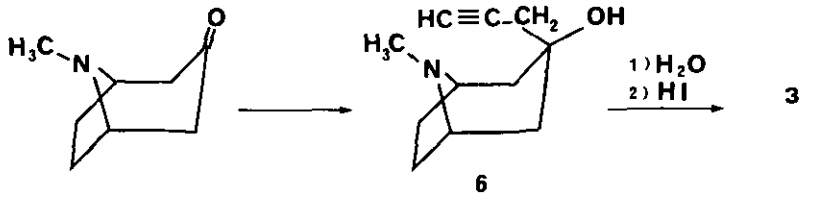
Compound 3 has been prepared by propargylation of tropanone [5] : the intermediate alcohol 6, used without further purification, is cyclized to 3 by heating in methanol-water (50/50) solution.



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Physical and spectral data of the compounds thus obtained are given in Table 1. The main feature of all these compounds (1 to 6) is their high hydrophilicity, which makes it difficult to extract and purify the reaction products and sometimes lowers yields.

Table 1. Physical and spectral data for compounds 1 to 6.

Product No	Yield %	mp or bp °C	Analysis	C	H	N	^{1}H-NMR, Solvent(*) δ ppm
1	53	>260	Calc.	38.45	5.73	4.98	1.93 (m,4H); 2.72 (m,2H); 3.17 (s,3H); 3.4 to 4.1 (m,4H); 5.3 (m,1H); 5.48 (s,1H); 5.5 (m,1H).
			Found	38.5	5.6	5.1	
			$C_9H_{16}INO$				
2	64	190	Calc.	36.12	5.68	10.53	2.30 (s,2H); 3.4 (m,4H); 3.46 (s,3H); 3.8 (m,4H); 5.55 (m, 1H); 5.80 (m,1H).
			Found	36.2	5.7	10.7	
			$C_8H_{15}IN_2$				
3	24	>260	Calc.	43.0	5.86	4.56	1.6 to 2.8 (m,10H); 3.10 (s, 3H); 4.2 (m,2H); 5.5 (m,1H); 5.72 (s,1H); 5.8 (m,1H).
			Found	43.1	5.8	4.5	
			$C_{11}H_{18}INO$				
4	20	94	Calc.	70.59	9.80	9.15	1.72 (t,4H); 2.12 (t,1H); 2.34 (s,3H); 2.2 to 2.8 (m,7H).
			Found	70.8	9.6	9.1	
			$C_9H_{15}NO$				
5	50	101/12	crude product				2.26 (s,3H); 2.5 (m,7H); 3.28 (d,2H).
6	20	125/18	crude product				1.7 to 2.3 (m,12H); 2.34 (s, 3H); 3.17 (m,2H).

(*) 1 and 3, in DMSO-d_6; 2, in D_2O; 4, 5, and 6, in $CDCl_3$

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