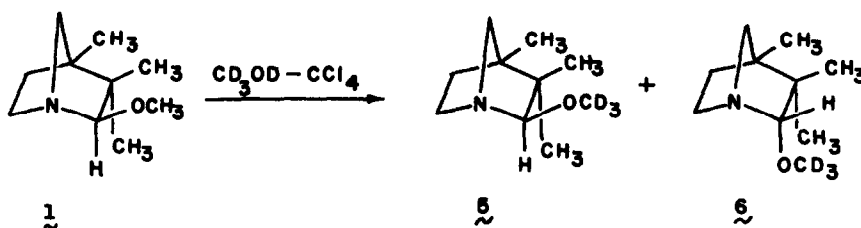


Table 1. Epimerization of 1 (0.01M) at 130°

<u>Solvent System</u>	<u>Time (hr)</u>	<u>%₂/₁</u>
CH ₃ OH	72	0.00
CH ₃ OH-0.001M HCl	72	0.01
CH ₃ OH-0.010M HCl	72	0.22
CH ₃ OH-0.100M HCl	72	0.32
CH ₃ OH-0.100M HCl	144	0.75
CH ₃ OH-CCl ₄ (1:1)	72	1.50
CH ₃ OH-CCl ₄ -NaOCH ₃	72	1.44
CH ₃ OH-CHCl ₃	72	1.08

was not a simple acid-catalyzed process.

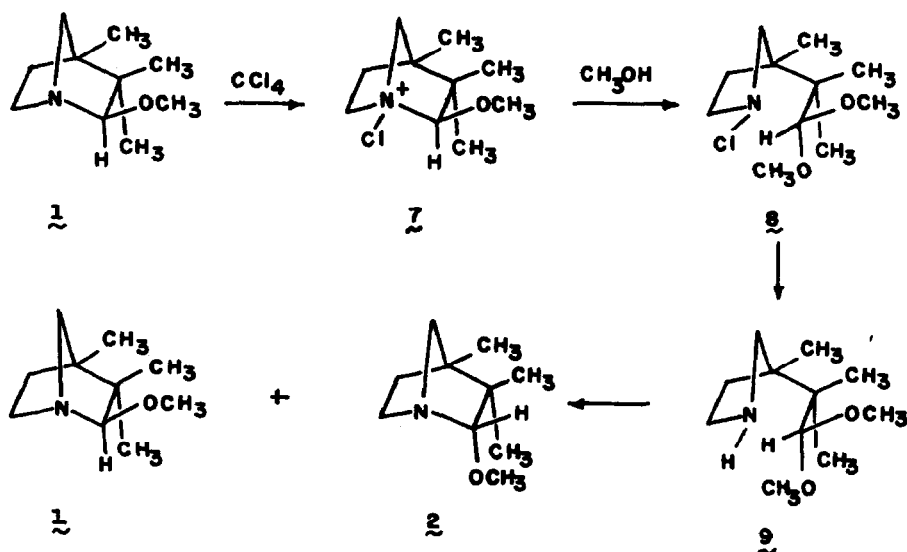
The effectiveness of carbon tetrachloride and chloroform initially suggested that a



free radical process might be involved. However, addition of benzoylperoxide or azobisisobutyronitrile (up to 10 equivalents) failed to accelerate the epimerization at 130° or to promote any epimerization at 80° in methanol-carbon tetrachloride. Additional evidence against a free radical process was obtained when the reaction was carried out in methanol-d₄. In the presence of the labelled methanol, only the methoxyl group was exchanged. No exchange of the proton at the 2-position could be detected. After ca. 5% epimerization, approximately 15% of the methoxyl groups had been exchanged. When the exo/endo ratio became 46/54, only 20% of the non-labelled methoxyl groups remained.

Mechanistically, we prefer a process in which the first step involves nucleophilic attack on carbon tetrachloride to displace a trichloromethyl anion, in a manner similar

to that discussed by Heublein^{3a} for the reaction of aliphatic amines with carbon tetrachloride. The trichloromethyl anion would be expected to be protonated by the methanol to yield chloroform⁶ which can be isolated from the reactions. Cleavage of the N-chlorinated ammonium salt, 7, and addition of methanol would then yield 8. N-Chloropyrrolidine was instantaneously converted to pyrrolidine under the reaction conditions.⁷ Thus, 8 would be expected to yield 9. When an independently synthesized sample of 9^b was exposed



to the reaction conditions, it was immediately converted to a mixture of 1 and 2. Thus, the tentative mechanistic scheme shown above is consistent with all of the known facts connected with this epimerization.

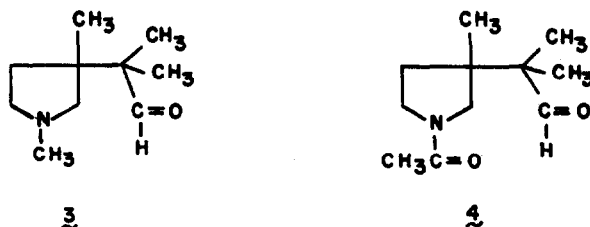
Acknowledgement. We are indebted to the National Cancer Institute of the Public Health Service for a grant which supported this investigation.

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5. In addition to the formation of 2 from 1, small amounts of 3 were slowly produced. The structure of 2 was established on the basis of extensive spectroscopic evidence,



via its conversion back to 1, and through the conversion of both 1 and 2 into 4 on reaction with acetic anhydride.

6. In the methanol-chloroform epimerization, methylene chloride was isolated as a by-product.
7. This transformation could involve either a homolytic cleavage of the N-Cl bond, followed by hydrogen abstraction from methanol, or a heterolytic cleavage of the N-Cl bond to yield a singlet nitrenium ion, which would be expected to spin invert to a triplet nitrenium ion.⁸ This triplet nitrenium would also be expected to abstract hydrogen from methanol. In either instance, formaldehyde should be formed. This formaldehyde was isolated in the form of its dimethyl acetal, dimethoxymethane.
8. P.G. Gassman and R.L. Cryberg, *J. Amer. Chem. Soc.*, 91, 5176 (1969).
9. The details of this synthesis will be presented in a full paper on this subject.