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STEREOCHEMISTRY OF THE REACTION OF AMMONIA WITH DIETHYL BROMOFUMARATE AND DIETHYL BROMOMALEATE[1]

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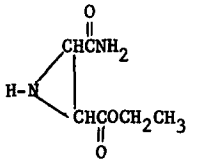
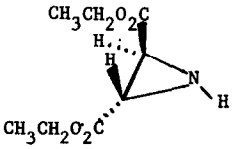
Very few reactions of ammonia with α-bromo-α,β-unsaturated and α,β-dibromo carboxylic acid esters have been recorded. The stereochemistry of reactions of such esters has been unknown. An old report[3] indicates that diethyl dibromosuccinate and ethanolic ammonia yield aziridine I.

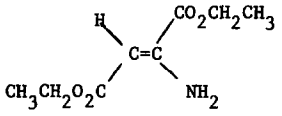
We have reinvestigated the reaction of ammonia with diethyl meso- and dl-dibromosuccinate, diethyl bromofumarate and diethyl bromomaleate. Each of the four esters gave the same two products, identified as aziridine II and enamine III. Undoubtedly some amides were formed, but in minor amounts, and none were isolated. Cis/trans isomers of II were expected but apparently



I



II



III

the steric requirements of the transition state of the cis form prevent its creation and the more stable enamine III is formed. It is generally agreed that the first step in the reaction of an α,β-dibromo carbonyl compound with ammonia and amines is dehydrohalogenation to a vinylic bromide.[4,5] Scheme 1 shows the probable reaction sequence in our work. The composition of the mixture of erythro and threo esters cannot be determined since the components collapse immediately into aziridine II and enamine III. The threo form can react by two routes: intramolecular displacement of bromide ion to yield the cis aziridine, or trans elimination of hydrogen bromide give the trans enamine. Conversely the erythro form can produce the trans aziridine or the cis enamine. The formation of only trans aziridine II and trans enamine III indicates that the erythro ester reacts with intramolecular displacement of bromide to yield trans II and no cis enamine, and the threo isomer by trans elimination of hydrogen bromide yields trans III and no cis aziridine. The formation of an enol intermediate seems necessary because the cis and trans vinylic bromides give the same products in about the same ratio. Cromwell[4] has postulated this type of intermediate in the formation of cis and trans ethylen-

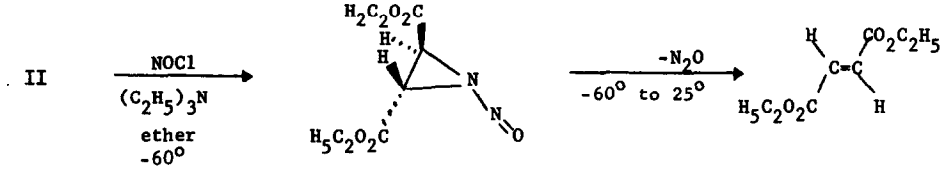
NH3
threo
erythro
II
+
III

imine ketones. Experimental evidence[6] suggests there is a most favored conformation of the enol resulting from 1,4-addition of an amine and that relative sizes and interactions of groups in the intermediate α-bromo-β-amino ketone can explain cis/trans product ratios. Apparently in our case steric hindrance in the transition state leading to the cis aziridine causes the reaction species to take the most favored conformation to form trans III.

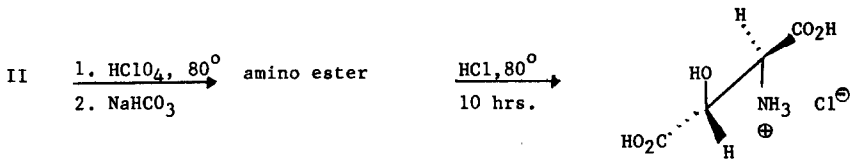
IR analysis of III indicates strong intramolecular hydrogen bonding between an ester carbonyl group and the amine protons, typical of such compounds.[7] The NMR spectrum of III in $CDCl_3$ shows peaks due to non-equivalent ethyl groups. A singlet at δ 5.45 (vinyl proton) and a broad signal at δ 6.59 (amine protons) are observed. Enamine III resisted all acylation attempts.

Aziridine II was identified on the basis of chemical behavior, analytical data, IR and NMR analysis. The IR spectrum showed a single band at 3280 $cm.^{-1}$ (sec. amine). The NMR spectrum of II showed peaks due to equivalent ethyl groups and singlets at δ 1.85 (amine proton) and δ 2.84 (ring protons). Spectroscopic evidence alone was insufficient to indicate stereochemistry of the aziridine since we had obtained only one isomer. The assumption that II was trans owing to steric requirements could not be justified since trans-1-substituted-2,3-dibenzylaziridines are epimerized readily by sodium ethoxide to the corresponding cis compounds.[8] With II and ethanolic sodium ethoxide, no reaction occurred under conditions similar to those reported.

N-Unsubstituted aziridines with nitrosyl chloride at low temperatures yield the N-nitroso derivatives, which lose N_2O stereospecifically to yield alkenes of the same stereochemistry as the aziridines.[9] Treatment of II with nitrosyl chloride and triethylamine in ether at -60° gave only diethyl fumarate, indicating that II has the trans structure.



Many cleavages of aziridines with dilute acid to yield vicinal amino alcohols are known.[10] This reaction proceeds with inversion and is highly stereospecific.[10b] Treatment of II with dilute perchloric acid and subsequent acid hydrolysis gave a compound identical in IR spectrum to authentic DL-erythro-β-hydroxyaspartic acid hydrochloride.



Thus II has the trans structure. Steric requirements are probably sufficient in the transition state leading to the cis isomer of II to prevent its formation. Only the aziridines and enamines corresponding to II and III were obtained by treatment of dimethyl and di-n-propyl bromofumarate and dimethyl bromomaleate with ammonia in the corresponding alcohol. Aziridine II could be N-acylated in good yield with carboxylic acid chlorides and triethylamine. Crystalline products were obtained with 2,4-dichlorophenylacetyl chloride and p-nitrobenzoyl chloride.

When II was heated at 125° for 1.5 hours, it was converted almost quantitatively to III, which evidently has the greater stability.

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These are just a few of the many examples.