Photoisomerization of 3*H*-Azepines

Robert A. Odum and Bernard Schmall*,[3]

Department of Chemistry, Brooklyn College of The City University of New York, Brooklyn, NY 11210, U.S.A.

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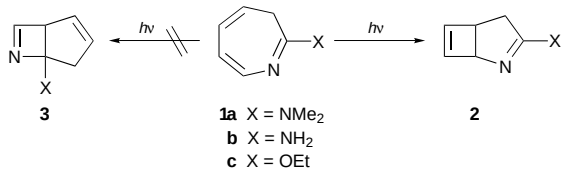
Photoelectrocyclization of 3*H*-azepines substituted in the 2-position with ethoxy, amino, and dimethylamino groups yielded 3-substituted 2-azabicyclo[3.2.0]hepta-2,6-dienes as the only major volatile products, in all cases.

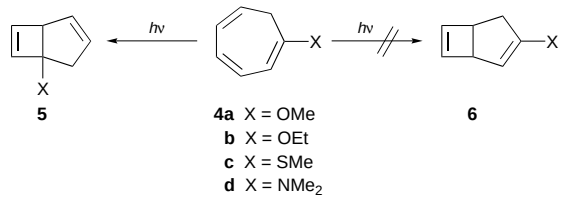
An active area of photochemical research has been concerned with the photoisomerization reactions of conjugated double bonds and with the application of orbital symmetry theory for such processes. Photoelectrocyclization reactions have been observed for symmetrical cyclohepta-1,3,5-trienes and 1-azacyclohepta-2,4,6-trienes (1*H*-azepines). In all cases, only one electrocyclization product could be formed by a symmetry-allowed disrotatory closure. At least two different concerted bicyclic photoproducts are possible with unsymmetrical cyclohepta-1,3,5-trienes and 1*H*-azepines. However, a number of compounds have exhibited stereoselectivity in the formation of the bicyclic isomers. We have been interested in the photochemistry of 1-azacyclohepta-1,4,6-trienes (3*H*-azepines). 3*H*-Azepine itself is unstable. A number of 2-substituted 3*H*-azepines were known when our investigation was initiated.[27,28,33] We were particularly interested in the photochemistry of 2-dimethylamino-3*H*-azepine,[28] 2-amino-3*H*-azepine[27] and 2-ethoxy-3*H*-azepine. Our studies showed that these compounds underwent selective photoelectrocyclization to 3-substituted 2-azabicyclo[3.2.0]hepta-2,6-dienes. Since our work was completed, further syntheses of 2-substituted 3*H*-azepines have been reported. Surprisingly, there has been only one additional example on the photoelectrocyclization of 2-substituted 3*H*-azepines to the 3-substituted azabicyclo[3.2.0]heptadiene. 2-Diethylamino-3*H*-azepine was isomerized to 3-diethylamino-2-azabicyclo[3.2.0]hepta-2,6-diene in agreement with the selectivity exhibited by 2-dimethylamino-3*H*-azepine (**1a**). Concise reviews on the photochemistry of azepines have appeared. Although a preliminary account of our work has been given,[55] full details of the syntheses have not been reported. Direct irradiation of dilute pentane solutions of 2-dimethylamino-3*H*-azepine (**1a**), 2-amino-3*H*-azepine (**1b**) and 2-ethoxy-3*H*-azepine (**1c**) with medium-pressure mercury lamps gave the corresponding 3-substituted 2-azabicyclo[3.2.0]hepta-2,6-dienes **2**.[55] Product yields were determined by GC analysis and were based on reactant consumed. Highest yields were obtained when pentane was employed as solvent and the azepines were irradiated at wavelengths corresponding to their maximum absorptions in the ultraviolet. Reaction solutions were purged of oxygen prior to irradiation. Irradiation of **1a–c** gave **2a–c** in 70, 50 and 60% yields, respectively. Although there were some uncharacterized products formed in the reactions, they do not alter the basic observation of selectivity in the photoisomerization of the 3*H*-azepines **1a–c** to **2a–c** because the minor compounds were formed in very small amounts.[3] On the basis of elemental and spectroscopic (UV, IR, ^{1}H NMR) evidence compounds **2a–c** can be unequivocally assigned to the photoproducts of the 3*H*-azepines **1**. The structural assignments for compounds **2a–c** are supported by chemical transformations (Scheme 4).

Although photoelectrocyclization reactions of the unsymmetrical 3*H*-azepine system can lead to the corresponding 5-substituted 6-azabicyclo[3.2.0]hepta-2,6-dienes **3** by orbital symmetry-allowed disrotatory processes, selectivity in the photoisomerization of the 3*H*-azepines **1** was observed, and the only major products were the 3-substituted 2-azabicyclo-[3.2.0]hepta-2,6-dienes **2** (Scheme 1).

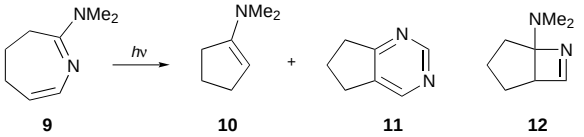
Conrotatory closure leading to azanorcaradiene structures should be sterically unfavourable. Sigmatropic rearrange-



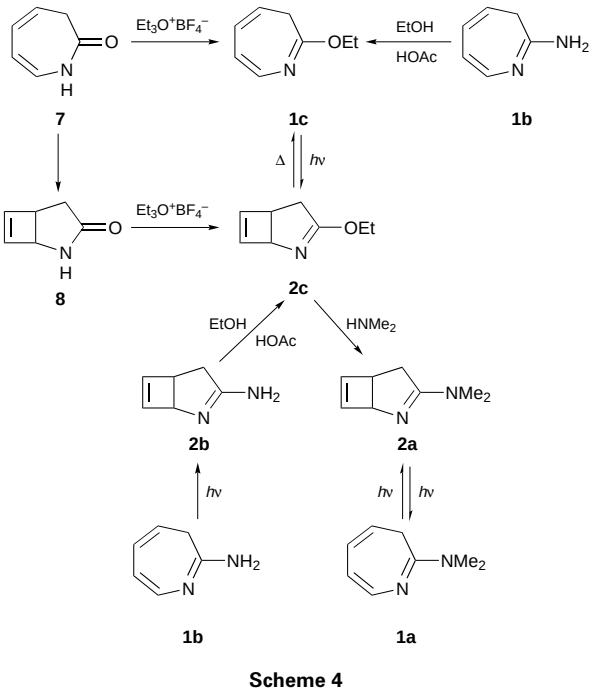
Scheme 1



Scheme 2



Scheme 3



Scheme 4

*To receive any correspondence. *Current Address:* National Institutes of Health, PET Department, Building 10, Room 1C-401, Bethesda, MD 20892. E-mail: Schmall@nmdhst.cc.nih.gov.

ment products should be unimportant since the 3*H*-azepine structure is the more stable tautomer.[27] The selectivity of the 3*H*-azepines is different from that observed in the photoisomerization reactions of cyclohepta-1,3,5-trienes **4** (Scheme 2) with electron-donating substituents in the 1-position of the seven-membered ring. These unsymmetrical cycloheptatrienes have been observed to photoisomerize selectively to 5-substituted bicyclo[3.2.0]hepta-2,6-dienes **5** in direct contrast to the mode of reaction of the 3*H*-azepines **1**, their heterocyclic analogues. A few percent of the 3-substituted bicyclo[3.2.0]hepta-2,6-dienes **6** may have escaped detection, and in fact, in the case of the dimethylamino isomer **4d**, about 3% of **6d** was observed. Photoelectrocyclization reactions of 3*H*-azepines **1** should be disrotatory processes, but the reasons for their observed selectivity are unknown. We have made the simple suggestion[55] that in order to avoid the loss of resonance energy the preferred pathway for the amidine or imidate ester systems is that leading to the corresponding 3-substituted 2-azabicyclo-[3.2.0]hepta-2,6-dienes **2**. The direction of the photo-ring closure of unsymmetrical cycloheptatrienes to bicyclo-[3.2.0]heptadienes may be controlled by the electronic nature of the substituent and the charge distribution in the excited state. However, this concept is not useful for the electrocyclization reactions of 3*H*-azepines. A reactivity index that predicts the site selectivity in the photocyclization of cycloheptatrienes has been derived by considering the energy change in the excited state. However, site selectivity predictions are inconsistent with experimental observations in unsymmetrical 1*H*-azepine systems, and have not been applied to the 3*H*-azepine system. Electrostatic considerations and extended Huckel calculations have been used to allow a choice between two symmetry-allowed pathways in the photochemical ring closure of 1-substituted cycloheptatrienes to bicyclo[3.2.0]heptadienes. However, arguments based on the direction of polarization of the excited state of the 3*H*-azepines leads to consideration of two extreme dipolar states. Unlike the case of 1-methoxycycloheptatriene, both states are stabilized. Therefore, the formation of both **2** and **3** may be expected from photolysis of **1**. In agreement with our simple explanation, the failure to observe the formation of **3** may be due to the preferential excitation to the dipolar state in which the resonance stabilized amidine and imidate ester functions are maintained.

Another simple explanation is that formation of 5-substituted 6-azabicyclo[3.2.0]hepta-2,6-dienes **3** involves a 1-azetine structure which may be potentially unstable. However, 1-azetine itself has been prepared and thermally transformed to 2-azabutadiene. The thermal ring opening of 1-azetine to 2-azabutadiene has been predicted by molecular orbital theory to proceed along a pathway similar to that for hydrocarbon analogues. The simple HMO method predicts that introduction of nitrogen atoms into butadiene and hexatriene should not cause any important perturbation in the course of electrocyclic reactions. Thus, 2-azabutadiene should react conrotatorily in a thermal reaction and disrotatorily upon photochemical excitation. Similar conclusions may also be drawn from a detailed all valence-electron calculation of the CNDO/2 or extended Huckel type. Although a number of 1-azetines have been reported in non-photolytic reactions, they have been observed only as intermediates or unstable products in light-induced electrocyclization reactions. Thus, 1-azetines have been prepared by irradiation of a dihydro-3*H*-azepine to an unstable azetine structure which was not isolated, and is the postulated intermediate **12** in the irradiation of 2-dimethylamino-4,5-dihydro-3*H*-azepine (**9**) to an eneamine **10** and pyrimidine **11** (Scheme 3).[75] In these reactions, however, an alternative electrocyclization reaction path did not exist and the formation of the 1-azetine structure demonstrates that without this alternative reaction path the loss of amidine resonance energy does occur. Therefore, although a 1-azetine structure may potentially be formed, albeit photochemically unstable, the observed selectivity in the photoisomerization of the 3*H*-azepines **1** may be due to preservation of amidine or imidate ester resonance energy.

The full paper gives complete synthetic and spectroscopic details on the photoisomerization reactions of the 3*H*-azepines **1**, which have not been previously reported. In addition, this paper reports an unexpected transformation of an amidine to an imidate ester which was observed during this investigation. In order to obtain pure 2-ethoxy-3*H*-azepine **1c** for photochemical studies, the possibility of transforming amidines into imidate esters was investigated. Whereas there was ample precedent for the alcoholysis of imidate esters, the isolation of an imidate ester from the reaction of an amidine with an alcohol was unknown. The conversion of **1b** and **2b** to the corresponding imidate esters **1c** and **2c** in absolute ethanol was effected in the presence of a catalytic amount of glacial acetic acid.

The possibility that orbital symmetry considerations could rationalize the direction of closure of the 3*H*-azepines **1** and unsymmetrical cyclohepta-1,3,5-trienes **4** is given elsewhere,[3] where the concept is developed that, 'given an orbital symmetry scheme', orbital symmetry considerations can account for the direction of closure of unsymmetrical seven-membered ring systems without invoking steric or charge distribution arguments.

Techniques used: UV, IR, ^{1}H NMR, GC, polarimetry

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