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Unusual Photochemical Behavior of 5-Amino-*endo*-Dicyclopentadien-3-ones

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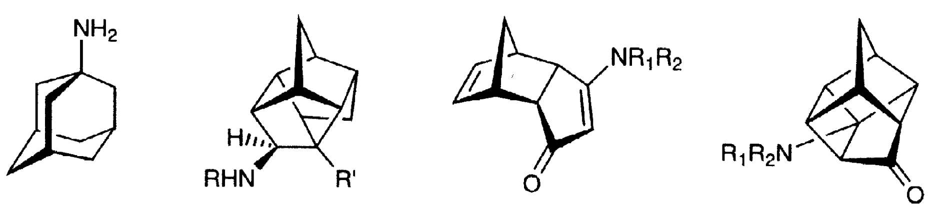
Abstract: Irradiation of 5-amino-substituted *endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones 3 did not lead to the anticipated [π^2 + π^2]-photocyclization to afford bridgehead 1,3-bishomocubyl amines 4. Instead an unexpected photoreduction of the norbornene C_8-C_9 double bond was observed, which based on D-labelling studies involves a photo-electron transfer process. The desired [π^2 + π^2]-photo-cyclization furnishing 4-amido-substituted 1,3-bishomocubanones 7 could however be effected by N-acylation of the amino function in 3.

Amino-substituted polycyclic compounds are of particular interest as they generally exhibit interesting biological activity either as such or when contained in larger structures *e.g.* proteins. Illustrative examples are 1-amino-adamantane 1[1] and amino-trishomocubanes 2[2] which show antiviral and anti-Parkinson activity. The presence of the polycyclic moiety not only leads to an increased lipophilicity of these amines but also precludes their rapid inactivation by oxidative enzymes.[3] Recently, we reported an efficient and



1 2 3 4

enantioselective synthesis of *endo*-5-amino-tricyclo[5.2.1.0^{2,6}]decadienones 3.[4] These *endo*-tricyclic enaminones should be suitable precursors for bridgehead substituted 1,3-bishomocubyl amines 4 because generally *endo*-tricyclodecadienones readily undergo intramolecular [π^2+π^2]-photocyclization to give the 1,3-bishomocubyl cage system.[5] This facile cage formation originates from the close spatial proximity and parallel alignment of the carbon-carbon double bonds

Initial irradiation experiments, using a high pressure mercury vapor immersion lamp with a pyrex filter, were performed with 5-cyclohexylamino- 3a, 5-benzylamino- 3b and 5-morpholino-*endo*-tri-cyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one 3c dissolved in either methanol or acetonitrile (Scheme 1). Unexpectedly, these tricyclic enaminones were quite photostable. Monitoring the reaction using gas

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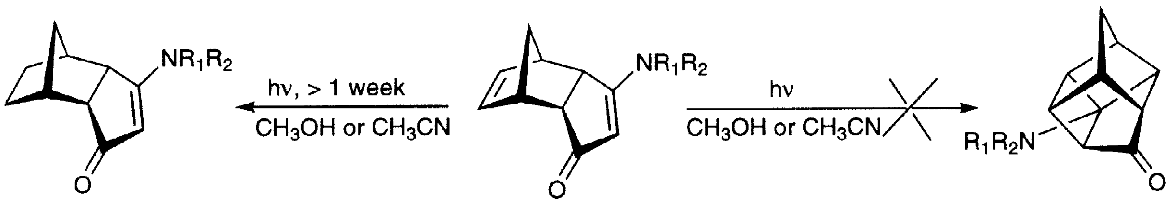
chromatography revealed that only a very slow and non-selective reaction was taking place leading to incomplete conversion of the starting enaminones even after irradiating for more than one week. This result contrasts sharply with the general [π^2+π^2]-photocyclization of the *endo*-tricyclodecadienone system which is usually complete within a few hours. For all enaminones **3a**-**c** complete conversion was only achieved after irradiation for 9 to 14 days leading to rather complex mixtures, all containing one major component. Flash column chromatography resulted in the isolation of the principal product in pure form, in about 25-28% yield. Its spectral data definitely excluded the formation of cage structure **4**, but strongly suggested structures **5a**-**c** for the photo-products, which are the result of reduction of the C_8-C_9 olefinic bond in **3a**-**c**. Unambiguous proof of this assignment was provided by an X-ray diffraction analysis of **5b**.[6]



5a,b,c (25-28%) | **3a** R_1= H; R_2= cyclohexyl | **4**

3b R_1= H; R_2= benzyl (Bn)

3c R_1= R_2= -$(CH_2)_2O(CH_2)_2$- (morpholino)

Scheme 1

The observation that the anticipated [π^2+π^2]-photocyclization of tricyclic enaminones **3** to afford 1,3-bishomocubyl amines **4** does not take place at all, but instead leads to appreciable photoreduction of the olefinic moiety is quite remarkable. This is particularly so, because several examples of successful [π^2+π^2]-photocyclizations of β-enaminones have been reported.[7] However, the efficiency of such cyclizations appears to be strongly dependent on the molecular structure of the enaminone.[7] In none of these studies photoreduction of the alkene moiety was ever observed.

In order to shed light on the mechanism of this unprecedented photoreduction of enaminones **3**, the irradiation of **3c** was repeated in deuterated methanol (CD_3OD) to establish the origin of the newly introduced C_8-C_9 hydrogens in the photoproducts **5**. Again, reduction was observed with the same efficiency as in unlabelled methanol but, most surprisingly, the obtained product **5c** did not contain any deuterium as was unequivocally shown by both NMR- and mass spectral analysis (MS/EI and HRMS). This result excludes any interference of the solvent in this photoreduction process. As there are no other hydrogen sources available, it must be concluded that starting tricyclic enaminone **3** itself supplies the necessary hydrogens in this reduction process. This conclusion was further confirmed by conducting the same experiments at different concentrations of **3c**. At a four times higher concentration of **3c** a considerable rate enhancement (4-5 times faster) was observed with identical product composition. This is agreement with a more efficient intermolecular hydrogen transfer at higher concentrations of **3c**. In addition, the observed low efficiency both in time and yield (less than 25%) for this reduction process, and the relatively large amounts of deteriorated material isolated also points to a complicated intermolecular process which requires at least a second molecule of enaminone for the photoreduction to occur. All experiments described above strongly suggest a photo-electron transfer (PET) process *via* an excimer involving the amino-nitrogen atom of one substrate molecule as the electron donor and the norbornene double bond of another substrate molecule as the acceptor.

Any other process would allow the solvent to interfere. More detailed studies will be necessary to explain this peculiar photoreduction process.

The failure of the enaminones <u>3</u> to undergo intramolecular [π^2+π^2]-cyclo-addition may be attributed to extensive n-π-interaction of the amine N-electrons with the enone moiety which may effect the nature of the enaminone excited state in such a way that photocyclization, although geometrically quite favorable, is completely blocked therefore allowing the competing photoreduction of the norbornene double bond in <u>3</u> to occur. The occurrence of extensive electron n-π-delocalization in enaminones <u>3</u> is convincingly demonstrated by an X-ray diffraction study on the related methyl benzyl enaminone **<u>3d</u>** (R_1= H; R_2= $CH(CH_3)Ph$; Fig. 1).[8] The C_3-C_4 (1.413[3] Å) bond in **<u>3d</u>** is considerably shorter and the C_4-C_5 (1.370[2] Å) significantly longer than observed for the corresponding C_3-C_4 (1.465[2]Å) and C_4-C_5 (1.320[2]Å) bond lengths in *endo*-tricyclo[5.2.1.0^{2,6}]decadienones containing an unsubstituted enone system.[9] Such a n-π-delocalization is expected to be less pronounced if the electrons on nitrogen are less available either by protonation or by introducing an electron withdrawing group at the amino nitrogen atom. In order to test this hypothesis the cycloaddition reactions of enaminones <u>3</u> were repeated in the presence of hydrogen chloride. However, under these conditions no cycloaddition was observed.

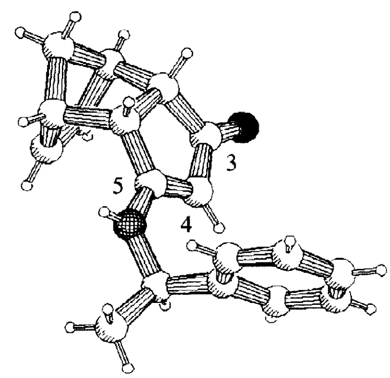
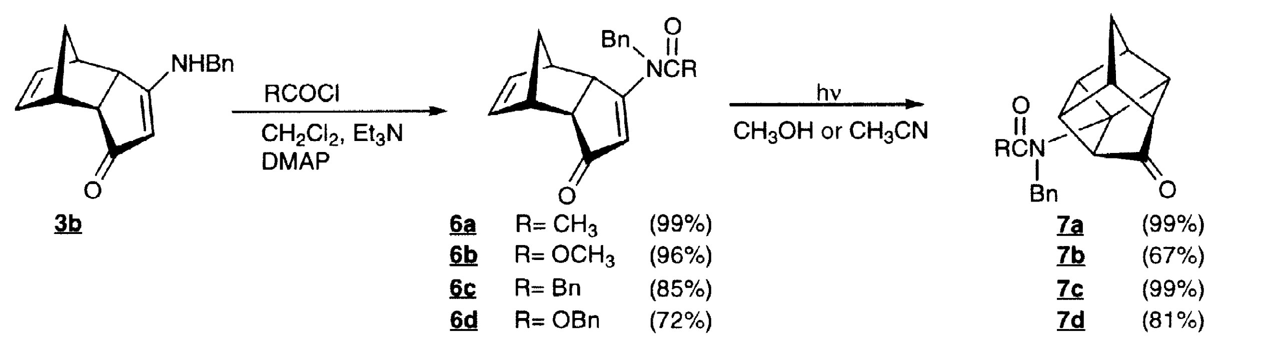


Figure 1. Crystal structure of methylbenzyl enaminone <u>3d</u>

A completely different and most rewarding result was obtained when *N*-acylated enaminone **<u>6a</u>**, synthesized in quantitative yield from **<u>3b</u>** by treatment with acetyl chloride in the presence of DMAP/Et_3N,



Scheme 2

was subjected to irradiation in methanol (Scheme 2). After only 4 h complete conversion was achieved to give 5-amido-substituted 1,3-bishomocubanone <u>7a</u> in quantitative yield. Similarly good results were obtained for some other N-acylated enaminones <u>6</u>. These results clearly demonstrate the presumed influence of n-π-electron delocalization involving the amino nitrogen atom on the photochemistry of these tricyclic enaminones. Although the effect is usually not as dramatic as observed above for tricyclic enaminones <u>3</u>, the positive influence of *N*-acylation on the efficiency of [π^2+π^2]-cyclizations of enaminones has been reported earlier.[10]

In conclusion, we have found that 5-amino-*endo*-tricyclodecadienones <u>3</u> show unusual photochemical behavior. In contrast to *endo*-tricyclodecadienones which generally undergo intramolecular cyclization to 1,3-bishomocubanones in excellent yields, no such photocyclization to <u>4</u> was observed at all for <u>3</u>. Instead a remarkable and unprecedented photoreduction to <u>5</u> was observed involving at least two molecules of enaminones participating in a photo-electron transfer process. Quite remarkably, smooth photocycloaddition could be accomplished by irradiation of the *N*-acetylated derivatives of the 5-amino-*endo*-tricyclodecadienones showing the dramatic effect of acylation on the ability to undergo cage closure reactions. The bridgehead substituted 1,3-bishomocubyl amides 7 produced are interesting compounds from a pharmaceutical point of view and also offer promising prospects for the synthesis of amino substituted triquinone type structures.[11]

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