REGIO- AND STEREOCHEMISTRY OF THE INTRAMOLECULAR [2+2] PHOTOPRODUCTS

FROM TWO RELATED VINYLOGOUS IMIDES

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Abstract: The regio- and stereochemistry of the intramolecular [2+2] photoproducts from two related vinylogous imides have been determined with the aid of X-ray crystallography; their chemistry and a mechanistic rationale of their formation are presented.

Our desire to exploit the intramolecular [2+2] photocycloaddition of N-allyl vinylogous imides, first reported in detail by Tamura[3] and later investigated by Schell,[4] in the early stages of a synthesis of the taxane diterpene[5] skeleton led us to investigate thoroughly the photochemistry of substances 1. We outline here a complete definition of the regio- and stereochemistry of these photoreactions, some chemistry of the resulting photoproducts, and a mechanistic rationale of their formation.

Imide 1a,[4] available in at least 76% yield by the phase transfer acetylation of the vinylogous amide 2,[4] could be converted to a mixture of the known photoproduct 3a[4] (70% isolated yield) plus 4a (8%) and 5a (13%) by irradiation (Hg arc lamp) of its cyclohexane solution through Pyrex. Similarly, imide 1b, produced in 78% yield by direct interaction of 2 with acetic formic anhydride in THF, led to 3b (60%), 4b (9%), and 5b (15%). No evidence for the formation of C-acetyl isomer 6[4] in the photolysis of scrupulously pure 1a was apparent through careful HPLC comparison of crude reaction mixtures with genuine 6. Likewise, the presence of 7 among the photolysis products of 1b was not detected although less vigorous attempts were made to do so.

The assignment of structures to photoproducts 3b, 4, and 5 was aided by their 360 MHz proton nmr spectra. Thus while 3a exhibited a single resonance for Ha at 2.48δ, 4a showed Ha as a singlet at 2.90δ. Since this proton bears an axial attachment to the six-membered ring in each compound, its chemical shift appears to vary with its exo/endo relationship to the azabicyclo[2.1.1]hexyl substructure.[6] Photoproduct 4a was also characterized by the signals for coupled methylene protons[7] Hb and Hc (Hb=3.25δ,d,J=15 Hz; Hc=1.74δ,d,J=15 Hz) and Hd and He (Hd=3.68δ,d,J=7.5 Hz; He=2.98δ,d,J=7.5 Hz), their respective widely different chemical shifts arising from very different proximities to the amide carbonyl in the first pair and to the cyclohexanone carbonyl in the second. These spatial relationships are a consequence of the ring fusion stereochemistry associated with the cyclohexanone ring and also in the former case the fact that the amide projects its oxygen away form the bridge methylene in the rotamer present. While these data suggested the stereochemistry depicted in 4 for the cyclohexanone ring attach-

ment, a choice between the two possibilities for the cyclohexane ring fusion illustrated in 4 and 8 could not be made. Similar conclusions could reached for 3b (Ha=2.53δ,s) and 4b (Ha=3.04δ,s).

An attempt was made to establish definitively the stereochemistries of 3b and 4 through simple chemical transformations. Exposure of 3a to refluxing methanolic methoxide led slowly (24h) to known enone 9a[4] in good yield (86%). Photoproduct 4a, however, gave a mixture (80%) containing largely the same enone (approximately 60%) contaminated with its cis counterpart but with a greater rate under milder conditions (excess tBuOK/tBuOH, room temperature, 15 min.). As an indicator of stereochemistry, this experiment was ambiguous since epimerization after elimination was clearly taking place. Therefore an X-ray crystallographic analysis was carried out which revealed 4a to be constituted as shown (see ORTEP drawing).[8] In the formyl series, the reduced reactivity toward base-induced elimination associated with 3-type stereochemistry was evidenced in the conversion of 3b to bridgehead imine ketone 10 (up to 76%) by nucleophilic deformylation/fragmentation upon exposure to tBuOK under a variety of conditions. Treatment of 3b with DBN or DBU led to traces of enone 9b at best. Conversion of 10 to known diketone 11[4] (aqueous acid, then Ac$_2$O/pyridine; 43%) confirmed the regiochemistry of 3b. In contrast to the behavior of 3b and analogously to that of 4a, 4b could be rapidly converted to 9b (catalytic tBuOK/tBuOH, room temperature, 15 min.; 49%) containing at most 10% of its cis isomer, thus confirming its regiochemistry. The stereochemical identities of 3b and 4b are assigned by analogy with the firmly established structures of 3a and 4a.

The novel photoproducts 5 were initially thought to incorporate the regiochemistry described above for 3 and 4 and to possess the stereochemistry shown in 12. Such a structure would permit long range W coupling between Ha and Hb. Indeed, Ha for both 5a and 5b resonated as a doublet (5a: Ha=2.95δ,J=10.5 Hz; 5b: Ha=3.07δ,J=10.5 Hz). However, the coupling constant in each case is somewhat larger than those associated with W coupling across bicyclo[2.1.1]hexane systems previously reported.[6a,b] In addition, photoproducts 5 proved to be extremely thermally labile with respect to conversion back to their respective imide precursors, 1a and 1b. Thus while 3b had a half-life of approximately 30h in refluxing mesitylene and 4b showed no reactivity under identical conditions, 5b was converted to 1b in refluxing cyclohexane with a half-life of about 0.5h. These observations suggested that 5 possessed a ring system unrelated to that of 3 and 4 and this was confirmed when X-ray crystallographic analysis of 5a revealed its highly strained azabicyclo[2.2.0]hexane-containing structure (see ORTEP drawing).[8] Clearly, the large splitting of the Ha resonances of 5 is the result of their trans vicinal coupling with Hb.

It is instructive to imagine how currently accepted mechanistic ideas regarding intramolecular enone/olefin [2+2] photoadditions[9] might apply to the formation of photoproducts 3-5. In the pathways to 3 and 4, the so-called "rule of five" suggests collapse of the triplet exciplexes depicted to the respective diradicals. The diradical leading to 3 can adopt a least energy conformation, well suited for bond formation with appropriate stereochemistry. In the case of the diradical leading to 4, the presumed lowest energy reactive conformation (not shown, but possessing the alternative chair conformation for the six-membered ring on the right) would result in photoproduct 8. Perhaps product stability is sufficiently revealed in the transition state that the photoproduct with two trans 6/4 ring fusions is avoided.

a R=COCH₃
b R=CHO

4a

5a
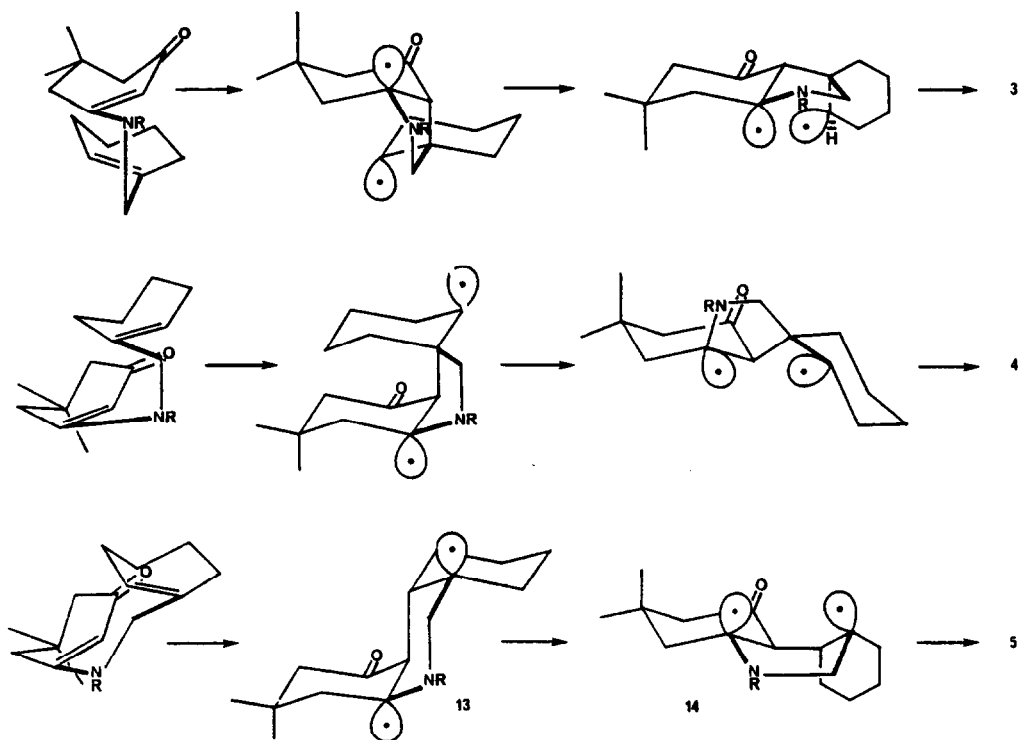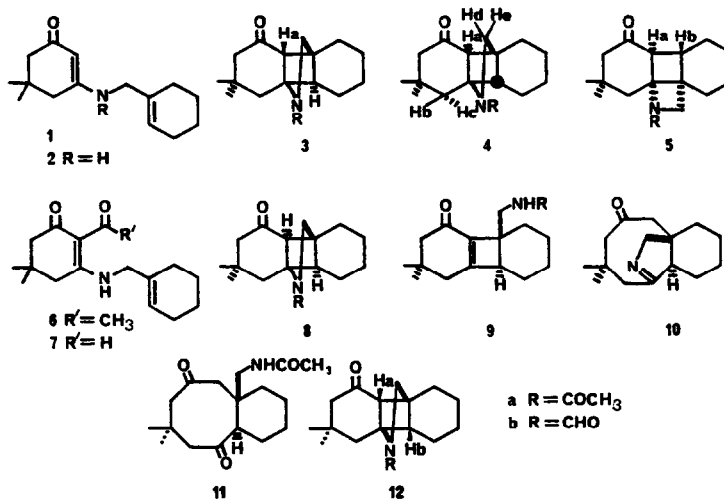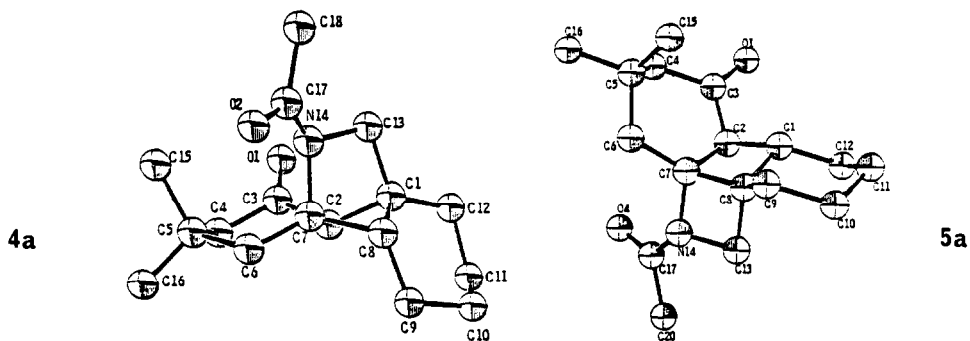
The formation of photoproducts 5 is noteworthy in that intramolecular [2+2] photoaddition of acyl-1,5-hexadiene systems in the so-called "parallel" sense has been observed in only two previous studies.[9c,d,10] Only very recently have the factors involved in this mode of photoreaction been sorted out[9c,d] and indeed this regiochemistry has not been previously observed for photoadditions of N-allyl vinylogous imides. Photoproducts 5 are clearly the result of 1,6 addition of the triplet chromophore to the olefin, initially yielding diradical 13. Again, 14 can adopt a least energy boat conformation suitable for conversion to 5.

Although the above mechanistic outline is simplistic, it can be tested in part by observing the stereochemical fate of substituents, especially on the cyclohexene ring, in this process. This information can then be exploited in the control of stereochemistry _via_ this photoreaction for synthetic purposes. These studies are currently underway.

References and Notes:

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7. Coupled signals were identified through a 2D COSY experiment.

8. Full details of the crystal structure determinations will be disclosed in the full paper.

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