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Photochemical Rearrangement of Oxaziridines and Nitrones in the Hexahydroindole Series: A Convenient Synthetic Route to 1-Azabicyclo[5.2.0]nonan-2-ones as Novel RGD Mimetics

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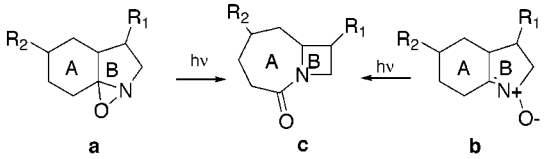
ABSTRACT



Photolysis of oxaziridines a or nitrones b provides a convenient synthetic route to fused bicyclic lactams c adequately substituted on both cycles A and B as scaffolds for mimicking conformationally constrained *β*-turn peptides as in the tripeptide RGD signaling motif of fibronectin.

Attempts to mimic *β*-turn topologies of signaling peptide motifs, as is the case of the Arg-Gly-Asp (RGD) tripeptide in a variety of extracellular matrix proteins, have converged toward the synthesis of constrained non-peptide molecules, several of them including a seven-membered benzodiazepine scaffold.[1,2] The conformational adaptability of a seven-membered ring certainly contributes to the ability of such benzodiazepine-type compounds to interact efficiently with different cell adhesion receptors (integrins), as does the occurrence of guanidinium and carboxylate groups that mimic the Arg and Asp side chains of RGD, respectively.[3]

We investigate here the possibility of synthesizing fused bicyclic lactams **c** (with cycle A being a seven-membered ring and cycle B being a four-membered ring) as non-peptide scaffolds mimicking a peptidyl *β*-turn topology. The 1-azabicyclo[5.2.0]nonan-2-one bicyclic skeleton is not common and has been synthesized rarely.[4] Methods have been

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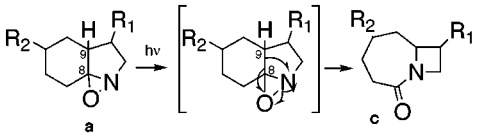
described,[4b−d] but the synthetic routes are not straightforward and usually result in poor yields.

A possible route to the synthesis of such lactams **c** with a bridgehead nitrogen atom is offered by the photolysis of an oxaziridine **a** or conversely of the corresponding nitrone **b**, which leads to oxaziridine **a** as an intermediate,[5] taking into account the mechanistic aspects of such a well-established photochemical rearrangement.[6]

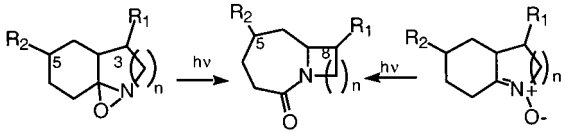
The originality of such a photochemical reaction with oxaziridines **a** resides in the rearrangement of both cycles A (ring expansion) and B (ring contraction) to yield the lactam **c** (Scheme 1). To our knowledge, such a photochemical rearrangement has only been reported on two occasions, although in poor yield[7a,b] (for a recent review on oxaziridine rearrangement chemistry, see 7c).

Scheme 1. Intracyclic Oxaziridine−Lactam Photorearrangement (A-Cycle Expansion, B-Cycle Contraction after Homolytic Cleavage of the N−O Bond)



Here we investigated the case of oxaziridines **a** with a six-membered ring A and a five-membered ring B (hexahydroindole series) differently substituted (Table 1). Since the photochemical reaction involves a restricted set of atoms (namely, N, O, C_8 and C_9; Scheme 1), substituents on both rings A and B can be present without interfering with the course of the rearrangement. As shown in Scheme 2, oxaziridine **3** (prepared from *cis* hexahydroindole[8] **1** via imine **2**) upon UV irradiation[9] afforded the expected 1-azabicyclo[5.2.0]nonan-2-one **4** in 48% yield (Table 1). It is known that the oxaziridine−lactam photorearrangement is a rather complex reaction,[6b] and this could explain the moderate lactam yields (Table 1).

Table 1. Photorearrangement of Hexahydroindole ($n = 1$) or Octahydroquinoline ($n = 2$) Oxaziridines and Nitrones

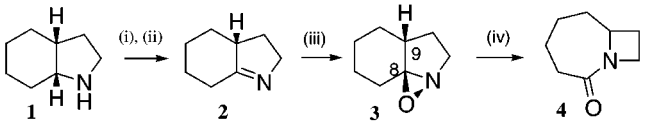


a : 3, 6, 8 **c : 4, 7, 9, 12, 14** **b :10, 11, 13**

compd[a]	*n*	R_2	R_1	lactam	yield[b]
		Oxaziridines			
3	1	H	H	**4**	48
6	1	Ph-O-*m*Ph-CH_2O-CO	$(CH_2)_2CO_2Et$	**7**	50
8	1	$PhCH_2$-OCO-$NH(CH_2)_3$-NHCO	$(CH_2)_2CO_2Et$	**9**	45
		Nitrones			
10	1	H	H	**4**	40
11	2	H	H	**12**	20
13	2	CH_3CO-O	CO_2Et	**14**	20

[a] Photolysis conditions were as follows: a solution of 0.6 mmol of nitrone or oxaziridine in 125 mL of CH_3CN was irradiated for 18 h by using a water-cooled quartz reactor (18 °C) and a Heraeus TQ 150 Z3 lamp. The reaction mixture was flushed with a stream of dry nitrogen to remove dissolved oxygen. [b] Yields of isolated pure products. All new compounds gave spectral and analytical data that are consistent with the assigned structures.

Scheme 2. Photochemical Synthesis of the Fused Bicyclic Lactam **4** (All Racemic Compounds)



$\Delta^{1(8)}$Hexahydroindole **2** was obtained in 77% yield from *cis* hexahydroindole **1** upon treatment of the latter with *N*-chlorosuccinimide[10] (NCS), followed by dehydrochlorination using potassium superoxide in the presence of crown ether [18,6].[11a] This procedure[11b] significantly improves the synthesis of imine **2**.[12] Oxidation of **2** with *m*-chloroperbenzoic acid (*m*CPBA) at 0 °C[13] resulted in a highly stereoselective reaction thus leading to a single oxaziridine **3**.[14] In the absence of any firm proof for determining the stereochemistry of **3** by NMR in solution or by X-ray crystallography (oily compound that produced no crystals), **3** was converted into the corresponding *N*-methyl oxaziridinium salt **5**, according to a previously reported protocol,[15] X-ray analysis of which revealed its structure:[16] both C_8−O and the C_9−H bonds adopt a relative *cis* configuration at

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(9) Alicyclic fused oxaziridines are known to display an n → s* type transition in the 225 nm region, which could be responsible of their photosensitivity upon irradiation in the 250 nm region. See ref 6b.

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(13) Bohé,L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.

(14) (a) The oxaziridine **3** is characterized by a single ^{13}C NMR peak at 90.9 ppm for the tetrasubstituted C_8 carbon ($CDCl_3$). (b) Yield of isolated pure product.

(15) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, *49*, 423.

the A/B junction (Figure 1). With **3** being a highly constrained structure, its nitrogen atom cannot invert, and the methyl in **5** takes the place of the nitrogen lone pair in **3**.

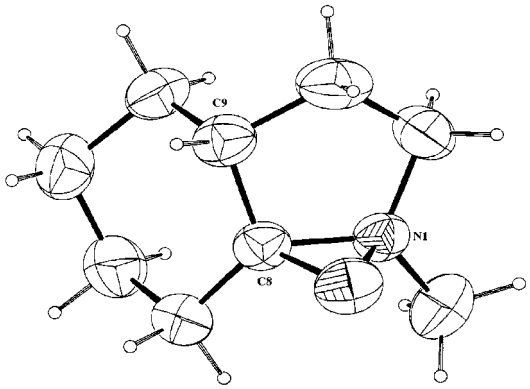


Figure 1. ORTEP diagram for **5** (*N*-methyl-1,8-oxido-hexahydroindole tetrafluoroborate). Ellipsoids are drawn at the 50% probability level. One of the enantiomeric forms of **5** is given here.

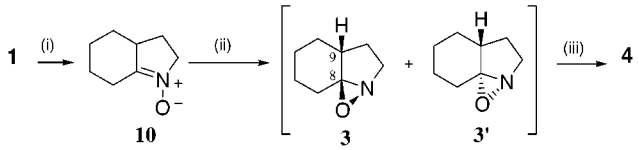
The observed selectivity of the oxidation of **2** can be explained by the favored *exo* approach of the peracid due to the roof-type conformational effect for the curved bicyclic imine **2**. The alternative *endo* approach appears disfavored because of steric interactions on the concave face of the molecule**.** On the basis of kinetic data,[20] oxidation of an imine by a peracid to yield an oxaziridine appears as a two-step process with the intermediate formation of an α-amino-peracid ester (such an intermediate, however, has not been identified so far). Both steps likely have their own stereochemical characteristics. Thus the highly stereoselective formation of **3** from **2** would require a more detailed understanding of the stereochemical features at the level of each of both steps.

The fused bicyclic lactam **4** itself was synthesized from an α-substituted cyclohexanone and involved the final formation of the azetidine ring in 46% yield as previously reported.[4c] Our photochemical approach, however, is likely to be more versatile when substituted 1-azabicyclo[5.2.0]-nonan-2-ones are targeted (Table 1).

After the successful synthesis of the 1-azabicyclo[5.2.0]-nonan-2-one **4**, we extended our approach to prepare 5,8-disubstituted 1-azabicyclo[5.2.0]nonan-2-ones **7** and **9** (n = 1; Table 1), as precursors of more complex disubstituted lactams **c** (work in progress). As expected, the photorearrangement of oxaziridines **6** and **8** was not influenced by disubstitution at positions 3 and 5 in the hexahydroindole motif.

Similarly, we investigated the synthesis of 1-azabicyclo-[5.3.0]decan-2-ones by photorearrangement of the corresponding oxaziridines (Table 1). All our attempts, however, were hampered by the poor yields and the instability[21] of the corresponding imines starting from the octahydroquinoline precursors. We thus selected another synthetic approach involving the photolysis of a nitrone, which produces an oxaziridine intermediate[5] before the rearrangement to the expected lactam. As shown in Table 1, both bicyclic fused lactams **12** and **14** were obtained through photolysis of nitrones **11** and **13**, although in poor yield. To establish the equivalence of both synthetic routes, i.e., photolysis of an oxaziridine versus photolysis of the corresponding nitrone, we investigated the synthesis of **4** by photolyzing nitrone **10** (Scheme 3).

Scheme 3. Two-Step Photoisomerization of Nitrone **10** into Lactam **4**



N-Oxydo $\Delta^{1(8)}$hexahydroindole **10** was prepared by direct oxidation of *cis* octahydrindole[8] **1** with hydrogen peroxide using the Murahashi's catalyst.[22a] $Na_2WO_4 \cdot H_2O$ gave the highest yield of 38%.[22b] This method is superior to another reported[23] synthesis of nitrone **10** (yield ca. 12%). UV irradiation of **10** for 18 h (see Table 1 for photolysis conditions) gave the lactam **4** in 40% yield. If the UV irradiation was interrupted after 1 h, a mixture of two diastereoisomeric oxaziridines **3** and **3′** (ratio 1:1) was obtained on the basis of ^{13}C NMR evidence. Carbone C_8 gives rise to two distinct ^{13}C resonances in the 85−90 ppm region.

The lack of stereoselectivity during nitrone−oxaziridine photoisomerization has been observed with a steroidal

(16) Crystal data for **5**: $C_9H_{16}NOBF_4$, M_r = 241.03, monoclinic, space group $P2_1/c$ with a = 7.786(2), b = 13.897(5), c = 11.027(3) Å, β = 108.00(2)°, volume = 1134.7(6) Å^3, Z = 4, ρ/calc = 1.411 g/cm^3, F(000) = 504. Colorless single crystal (0.35 × 0.30 × 0.27 mm^3). θ range for data collection: 2.4−27.5° by an ω-scan using a Huber 4-circle X-ray diffractometer at room temperature with the graphite monochromatized Mo Kα radiation (λ = 0.71069 Å). A total of 4931 reflections were integrated and retained of which 2603 were unique (⟨redundancy⟩ = 1.9, R_{int} = 2.78%, R_{sig} = 3.98%). Of the unique reflections, 1539 were observed with $I > 2\sigma(I)$. Solution was achieved utilizing direct methods followed by least squares refinement with anisotropic displacement parameters for the non-hydrogen atoms. Conventional refinement indices are R_1 = 0.0779 for the 1539 observed reflections and wR_2 = 0.2568 for all data. The structure was solved using SHELXS-97 and refined with SHELXL-97. To our knowledge only one oxaziridium tetrafluoroborate structure has been reported[17] so far with two main characteristic features: the N−O bond (1.46 Å) is significantly shorter and the valence angle OCN (60.7°) is significantly smaller than in the oxaziridines (1.51−1.55 Å and 63.5−64.7°, respectively.[6c,18,19] We note that our oxaziridinium **5** corresponds to an N−O bond length of 1.464 ± 0.003 Å and a valence angle OCN of (60.7 ± 0.2)°. Schematically viewed the three-membered ring in an oxaziridinium is closer to an equilateral triangle than the corresponding oxaziridine ring.

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(22) (a) Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736. Murahashi, S. I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383. (b) The isomeric nitrone, *N*-oxydo Δ1(2) hexahydroindole was also obtained as a minor compound (19% yield).

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nitrone,[6b] but this is far from being a general feature.[6b,19] The observation that photolysis of pure diastereoisomeric oxaziridine **3** (racemic mixture) gives **4** with a yield of ca. 48% whereas the 1:1 mixture of diastereoisomers **3** and **3′** also gives **4** with a similar yield (ca. 40%) suggests that the photorearrangement of oxaziridines **3** and **3′** into lactam **4** is not dependent on the stereochemistry of the oxaziridine ring itself. It needs to be established, however, whether the *trans* oxaziridine **3′** does yield **4** rather than being selectively converted into products that were not identified in this work. Similarly, intermediate oxaziridines are likely to be formed upon photolysis of nitrones **11** and **13** in the octahydroquinoline series (not given here). These nitrones were obtained from the corresponding octahydroquinoline compounds through H_2O_2 oxidation in the presence of Murahashi's catalyst. We note in Table 1 that the yields of the corresponding 1-azabicyclo[5.3.0]decan-2-ones are significantly lower (ca. 20%) than those observed in the hexahydroindole series.

In closing, the photolysis of oxaziridines **a** or nitrones **b** (Table 1) appears to be an appropriate and novel synthetic route to bicyclic fused lactams **c**. We have finally obtained a 5,8-disustituted 1-azabicyclo[5.2.0] nona-2-one **15** (**9** → **15**; $R_2 = NH_2C(=NH)NH(CH_2)_3NHCO$; $R_1 = (CH_2)_2CO_2H$) in which position 8 is substituted by a carboxylate group and position 5 by an Arg-like side chain with a guanidinium group. This compound **15**[24] (isolated as racemic mixtures of two different diastereoisomers) displays an efficient antagonist activity toward the fibronectin−integrin $\alpha_5\beta_1$ interactions[25] comparable, in the case of one of both diastereoisomers, to that of a noncyclic RGD peptide competitor (in preparation) using an in vitro assay recently reported,[26] in which both protein components are recombinant miniaturized versions of the native proteins. These results suggest that the photochemical rearrangement of complex oxaziridines (or nitrones) in the hexahydroindole series is a convenient synthetic route toward non-peptide compounds mimicking the β-turn topology of the RGD signal in fibronectin.[27]

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