

## SUBSTITUENT EFFECTS IN THE REDUCTIVE PHOTOCYCLIZATION OF ENAMIDES

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Abstract-----Variously substituted and hydrogenated lactams (5,6,8,10, 11,15,16,17,20,and 25) were prepared by reductive photocyclization of a variety of enamides (4,7,9,14,19, and 22) which carry either electron-donating or attracting substituents on the benzoyl group of the respective enamide.

Enamides of N-benzoylenamine and N-acryloylenamine types have been shown to undergo ready photocyclization in the presence of sodium borohydride to afford the corresponding hexahydrolactams.<sup>1,2,3,4,5</sup> As an extension of the study on this reductive photocyclization aiming at the evaluation of this reaction as a useful synthetic tool, the present investigation on the effect of substituents on the benzoyl group was undertaken by employing the enamides prepared from 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline and harmalane.

Reductive photocyclization of the enamide (1) bearing an o-methoxy group in the presence of ten molar amount of sodium borohydride in a variety of solvent such as ether, benzene, or acetonitrile, each containing small amount of methanol to dissolve the hydride reagent, yielded the methoxy-migrated lactam (2)<sup>6</sup>(31 %) together with the dehydrolactam (3)(30 %) as in the case of non-oxidative photocyclization.<sup>6,7</sup> This result shows that even under reductive condition, attack of sodium borohydride to a cyclic intermediate is less effective than thermal (1,5)-sigmatropic shift of the methoxy group.<sup>7</sup> On the other hand, the m- and p-methoxy-substituted enamides (4) and (7) afforded two types of the hydrogenated lactams, the one is the lactam (5)<sup>8</sup> with a conjugated diene structure (25 %) and the other the lactams (6)<sup>8</sup>(35 %) and (8)<sup>8</sup>(42 %) with an unconjugated diene structure, upon irradiation under reductive condition.

Previously, we have completed a simple synthesis<sup>2</sup> of alloyohimbone by making a good use of a methoxy group in the enamide prepared from harmalane, in which the substituent was successfully converted into the ketone after photocyclization under reductive condition.

Next, we investigated the effect of electron-attracting substituent on the photocyclization, aiming at a simple synthesis of yohimbine group of alkaloids as an extension of the previous works.<sup>2,9</sup>

Photocyclization of the m-methoxycarbonyl-substituted enamide under reductive condition afforded a mixture of many unstable hydrogenated products which were too unstable to separate. However, when the m-cyano-substituted enamide (9) was irradiated under reductive condition, the products obtained were a mixture of two hydrogenated lactams (10a)<sup>8</sup> (30 %) and (11a)<sup>8</sup> (24 %), which were then dehydrogenated to give the dehydrolactams (12)<sup>8</sup> and (13)<sup>8</sup> respectively. Their regiochemistries were established from their n.m.r. spectra. One of the hydrogenated lactam (10a) thus isolated was proved to have an unconjugated diene structure in addition to the 12-cyano group from its spectral evidences. The other hydrogenated lactam (11a) showed mass spectrum involving a fragment at  $m/z$  338 ( $M^+$ ) and n.m.r. spectrum with peaks at  $\delta$  5.98 and 5.79 due to the presence of two olefinic protons. These spectral evidences firmly established that this product (11a) would be doubly hydrogenated, therefore having the structure including its stereochemistry as shown in the figure.

A similar reductive photocyclization of the same enamide (9) in the presence of sodium borodeuteride afforded two hydrogenated lactams (10b)<sup>8</sup> and (11b)<sup>8</sup>, of which the former (10b) was shown to be deuterated exclusively at the 13a-position and the latter (11b) deuterated both at the 9- and 13a-positions respectively.

Analogously, the m-methoxycarbonyl-substituted enamide (14) was prepared from harmalane and irradiated to afford a mixture of the 16-methoxycarbonyl-substituted lactam (15)<sup>8</sup> with an unconjugated diene structure (17 %) and two 18-methoxycarbonyl-substituted lactams (16)<sup>8</sup> (8 %) and (17)<sup>8</sup> (13 %) both with one double bond but with different stereochemistry with respect to the 18- and 20-positions. The former lactam (15) was heated at 250 °C over palladium on carbon to give the aromatized lactam (18) which was identical with oxygambirtannine.<sup>10</sup>

Reductive photocyclization of the p-methoxycarbonyl-substituted enamide (19) afforded a very unstable lactam (20)<sup>8</sup> with an unconjugated diene structure (50 %) which was readily converted into the dehydrolactam (21)<sup>8</sup> by air oxidation.



Finally, we carried out reductive photocyclization of the 4-methoxy-3-methoxycarbonyl-substituted enamide (22) which was readily prepared from harmalane and the corresponding acid chloride and would be expected to provide an intermediary compound (23) for an efficient synthesis of the alkaloid yohimbine. However, the isolated products were the ring E-aromatized lactam (24)<sup>8</sup> (13 %) and the lactam (25)<sup>8</sup> having one olefinic double bond (26 %), of which the former (24) would be formed by elimination of methanol fragment from the postulated intermediate having a double bond and the latter (25) was readily converted into the former upon treatment with sodium methoxide.

Unexpectedly, this result shows that photocyclization of the enamide (22) occurred regioselectively to the 6-position, thus killing a possibility of yohimbine synthesis by this route.

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