PHOTOINDUCED MOLECULAR TRANSFORMATIONS. PART 147.[1] [2+2] PHOTOADDITION OF PROTECTED 4-HYDROXY-1(2*H*)-ISOQUINOLINONE WITH AN ELECTRON-DEFICIENT ALKENE AND THE FORMATION OF A 3,6-EPOXY-3,4,5,6-TETRAHYDRO-2-BENZAZOCIN-1(2*H*)-ONE *VIA* A β-SCISSION OF CYCLOBUTANOXYL RADICALS GENERATED FROM THE RESULTING PHOTOADDUCT

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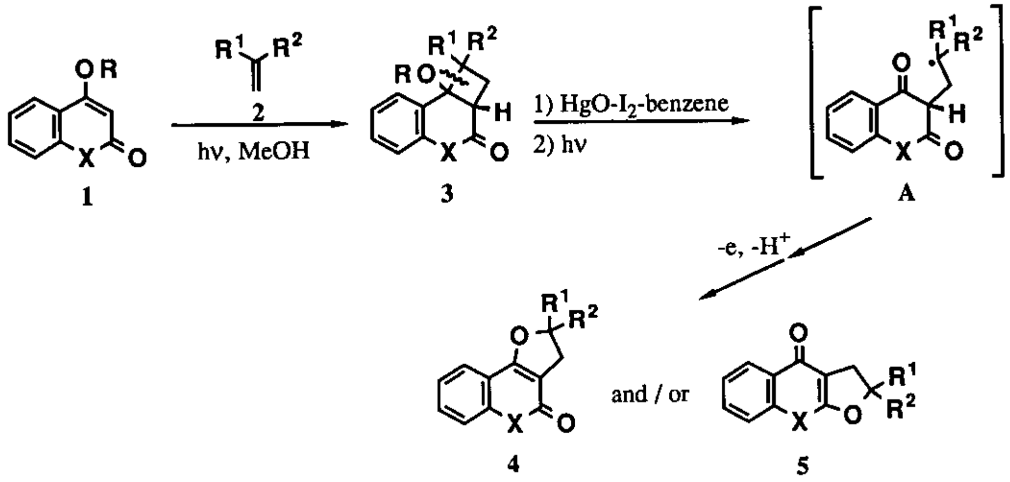
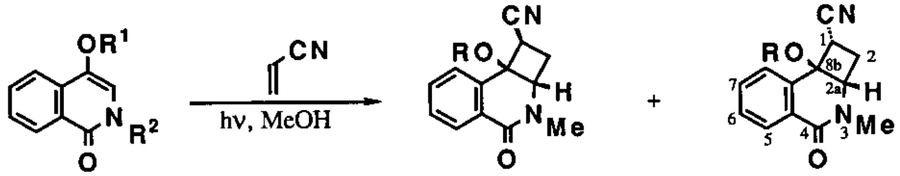
Abstract —The direct irradiation of 4-benzyloxycarbonyloxy-2-methyl-1-(2*H*)-isoquinolinone gave a 1 to 1 ratio of two stereoisomers of [2+2] photoadducts in 97% yield. Removal of the protecting group from the adducts by hydrogenolysis gave the corresponding cyclobutanols, (1α, 2aα, 8bα)-(±)-1-cyano-1,2a,3,8b-tetrahydro-8b-hydroxy-3-methylcyclobut[*c*]-isoquinolin-4(2*H*)-one and its (1α, 2aβ, 8bβ)- isomer in 78 and 67% yields. The photolysis of the hypoiodite generated *in situ* from the (1α, 2aα, 8bα)-(±)-cyclobutanol with mercury(II) oxide - iodine in benzene induced a regioselective β-scission at the ring fusion bond of the cyclobutanoxyl radical to give 5-cyano-3,6-epoxy-3,4,5,6-tetrahydro-6-hydroxy-2-methyl-2-benzazocin-1(2*H*)-one in 76% yield. The cyano substituent and the amide nitrogen play a decisive role in directing the bond to be cleaved.

In previous papers[2] we reported that the (2+2) photoaddition of lactones and lactams having an enolyzed 1,3-dicarbonyl group with alkenes, followed by photolysis of the



R = H or Ac ; R^1, R^2 = H , alkyl , OAc , OMe etc.
X = NMe or O

Scheme 1

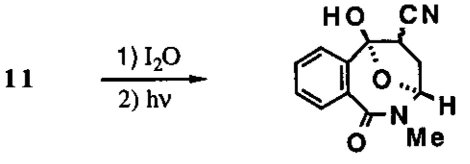


6 R^1 = R^2 = H
7 R^1 = COOCH$_2$C$_6$H$_5$; R^2 = H
8 R^1 = COOCH$_2$C$_6$H$_5$; R^2 = Me

9 R = Cbz
11 R = H

10 R = Cbz
12 R = H

Scheme 2



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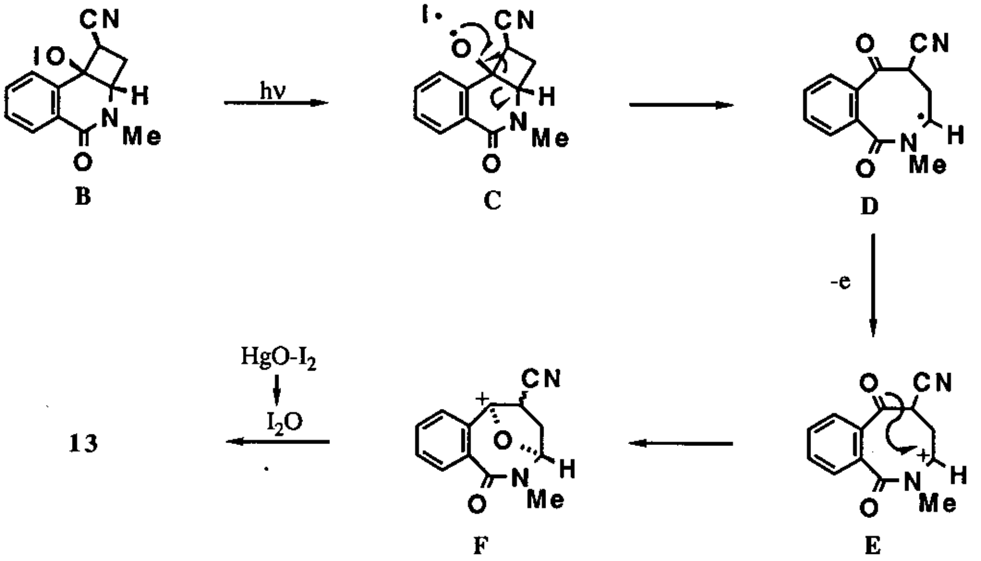
Scheme 3

hypoiodites generated from the resulting cyclobutanols, induced regioselective β-scission of the corresponding cyclobutanoxyl radicals, resulting in a transformation of the cyclobutane rings into furan rings *via* incorporation of the alkoxyl oxygen. For example, photolysis of the hypoiodites derived from the [2+2] photoadducts of 4-hydroxycoumarin (**1** R=H; X = O) or 4-hydroxyquinolin-2(1*H*)-one (**1** R=H; X= NMe) with alkenes (**2**) underwent a regioselective β-scission of their non ring-fusion bond to give furocoumarins (**4**; X = O), furochromones (**5**; X = O), furo[3,2-*c*]quinolin-4(5*H*)-ones (**4**; X = NMe) and furo[2,3-*b*]quinolin-4(9*H*)-ones (**5**; X = NMe), as outlined in Scheme 1.

In continuation of these studies concerning the application of the β-scission of alkoxyl radicals to organic synthesis, we now report on the formation of a new 8-membered lactam (**12**) *via* a selective β-scission of a cylobutanoxyl radical derived from a cyclobutanol (**11**) prepared by the [2+2] photoaddition of a protected 4-hydroxy-1(2*H*)-isoquinolinone (**8**) with an electron-deficient alkene.

A treatment of 4-hydroxy-1(2*H*)-isoquinolinone (**6**)[3] with an excess of benzyloxycarbonyl chloride in pyridine for 1 week at room temperature gave 4-benzyloxycarbonyloxy-1(2*H*)-isoquinolinone (**7**)[4] in 56% yield. *N*-Methylation of the protected isoquinolinone (**7**) with methyl iodide in DMF in the presence of NaH for 45 min at room temperature gave 4-benzyloxycarbonyloxy-2-methyl-1(2*H*)-isoquinolinone (**8**)[5] in 95% yield. Irradiation of the protected *N*-methyl-1(2*H*)-isoquinolinone (**8**) with a large excess of acrylonitrile in methanol under nitrogen with a Pyrex-filtered light generated from a 500-W high-pressure Hg arc lamp for 7.7 h gave two stereoisomers (**9**[6] and **10**[7]) of [2+2] photoadducts in 49 and 48% yields. Removal of the benzyloxycarbonyl group from the isomer **9** by hydrogenolysis in the presence of Pd-C catalyst for 9 min gave the corresponding cyclobutanol (**11**)[8] in 78% yield. Similar hydrogenolysis of stereoisomer (**10**) gave the corresponding cyclobutanol (**12**)[9] in 67% yield. The stereochemistries of these [2+2] photoadducts (**11**) and (**12**) were established to be (1α, 2aα, 8bα)-(±)-8b-1-cyano-8b-hydroxy-1,2a,3,8b-tetrahydro-3-methylcyclobut[*c*]isoquinolin-4(2*H*)-one (**11**) and its (1α, 2aβ, 8bβ)-isomer (**12**) by ^{1}H-nmr spectroscopy including NOE technique: the ^{1}H nmr



Scheme 4

spectrum of cyclobutanol (**12**) exhibited four signals at δ 3.75 (1H, dd, J = 7.92 and 9.57 Hz), 3.32 (1H, dd, J = 8.91 and 11.22 Hz), 2.56 (1H, ddd, J = 7.92. 8.91, and 11.22 Hz) and 1.56 (1H, dt, J = 9.57 and 11.22 Hz). These signals are assignable to 2a-H, 1β-H, 2β-H, and 2α-H on the basis of their chemical shifts and coupling constants. Irradiation of the signal at δ 3.75 enhanced the signal area at δ 3.32 and 2.56. Irradiation of the signal at δ 3.32 enhanced the signal area at δ 3.75 and 2.56. Moreover, irradiation of the signal at δ 1.56 resulted only in an enhancement of the signal at δ 2.56. These NOE results indicated that the protons attached to the carbons 1 and 2a of cyclobutanol (**12**) are *cis* oriented. Thus, the stereochemistries of isomers (**11**) and (**12**) should be (1α, 2aα, 8bα) and (1α, 2aβ, 8bβ), respectively.

Photolysis of the hypoiodite generated *in situ* from the cyclobutanol (**11**) with each 3 equiv. of HgO and I_2 in dichloromethane in a nitrogen atmosphere with a Pyrex-filtered light generated from a 100-W high-pressure Hg arc lamp induced a regioselective β-scission of *the ring-fusion bond* of the corresponding cyclobutanoxyl radical to give a crystalline product (**12**) in 76% yield. An analysis of the structure by spectroscopy indicated that it was 5-cyano-3,6-epoxy-3,4,5,6-tetrahydro-6-hydroxy-2-methyl-2-benzazocin-1(2*H*)-one (**13**).[10,11]

Scheme 4 outlines the pathway leading to lactam (**13**). Thus, a selective β-scission at the ring-fusion bond of the alkoxyl radical **C** generated by the photolysis of the hypoiodite **B** gives a carbon-centered radical **D**. A one-electron oxidation of the carbon-centered radical **D** with metal ion, followed by an intramolecular combination of the resulting cation **E** gives rise to intermediate cation **F**. The reaction of the cation **F** with diiodine oxide gives a new hypoiodite, the hydrolysis of which during a work-up gives lactam (**13**). It is remarkable that the product in this reaction was exclusively those derived from a β-scission of the ring-fusion bond of the cyclobutanoxyl radical **C**, while the products obtained from the cyclobutanoxyl radicals derived from 4-hydroxycoumarin (**1** R = H; X = O) or 4-hydroxyquinolin-2(1*H*)-one (**1** R = H; X = NMe) were exclusively those derived from a β-scission of their *non ring-fusion* bond (Scheme 1). It is apparent here that the cyano group and the lactam nitrogen of the cyclobutanoxyl radical **C** direct the bond to be cleaved; the cyano substituent destabilizes the carbon-centered radical intermediate, such as type **A** (Scheme 1), derived from non ring-fusion bond of cyclobutanol (**11**), while the lactam nitrogen stabilizes the carbon-centered radical **D** derived from the ring-fusion bond. Further work on this radical ring expansion is in progress, and the results will be reported in due course.

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4 **7**: mp 174°C (ethyl acetate).

5 **8**: mp 126°C (hexane-dichloromethane).

6 **9**: mp 212-213°C (dichloromethane-hexane). Ir (Nujol) 2248 (CN), 1750 (BuOCO), and 1647cm^{-1} (MeNCO). Ms *m/z* 363 [(M+1),$^+$ 0.19] and 91 (100%). ^{1}H-Nmr (270 MHz, DMSO) δ 1.99 (1H, dt, *J* 11.9 and 9.6 Hz, exo-2-H), 2.71 (1H, ddd, *J* 11.9, 8.9, and 2.64 Hz, endo-2-H), 3.03 (3H, s, NMe), 3.88 (1H, d, *J* 8.6 Hz, endo-1-H), 4.76 (1H, t, *J* 9.2 Hz, 2a-H), 5.05 (2H, C_6H_5-CH_2COO), 7.3 (5H, m, C_6H_5), 7.6-7.7 (3H, m, 6-, 7-, 8-H), and 8.11 (1H, d, *J* 7.9 Hz, 5-H).

7 **10**: mp 185-186°C (dichloromethane-hexane). Ir (Nujol) 2246 (CN), 1740 (BuOCO), and 1640 cm^{-1} (MeNCO). Ms *m/z* 363 [(M+1),$^+$ 0.1] and 91 (100%). ^{1}H-Nmr (270 MHz, DMSO) δ 1.75 (1H, dt, *J* 10.9 and 9.2 Hz, exo-2-H), 2.84 (1H, dt, J 9.6 and 1.3 Hz, endo-2-H), 4.05 (1H, dd, *J* 10.8 and 9.6 Hz, 1-H), 4.51 (1H, t, *J* 8.9 Hz, 2a-H), 5.05 (2H, *J* 15.8 and 12.2 Hz, $C_6H_5CH_2$COO), 7.29 (5H, m, C_6H_5), 7.65 (2H, m, 6-, 7-H), 7.75 (1H, m, 8-H), and 8.12 (1H, dd, *J* 1.0 and 7.6 Hz, 5-H).

8 **11**: mp 133-133.5°C (dichloromethane-hexane). Ir (Nujol) 3210 (OH), 2248 (CN), and 1634 cm^{-1} (MeNCO).

9 **12**: mp 134-135°C (dichloromethane-hexane). Ir (Nujol) 3216 (OH), 2246 (CN), and 1637 cm^{-1} (MeNCO).

10 **13**: mp 132°C (dichloromethane-hexane). Ir (Nujol) 3298 (OH), 2252 (CN), and 1693 cm^{-1} (MeNCO). Ms *m/z* 244 (M$^+$, 0.27) and 162 [(M - OCHCH_2CHCN)$^+$, 100%). ^{1}H-Nmr (270 MHz, $CDCl_3$) δ 2.55 (1H, dt, *J* 12.5 and 4.3 Hz, 4-H), 2.68 (1H, dd, *J* 12.5 ad 7.9 Hz, 4-H), 3.05 (3H, s, NMe), 4.05 (1H, dd, *J* 12.9 and 7.9 Hz, 5-H), 5.93 (1H, d, *J* 4.3 Hz, 3-H), 7.45-7.60 (3H, m, 7-, 8-, 9-H), and 7.77 (1H, d, *J* 7.26 Hz, 10-H).

11 Satisfactory analytical and spectral results were obtained for all the new compounds described in this paper.

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