ON THE STRUCTURE OF THE DIELS-ALDER ADDUCTS OBTAINED FROM (E)-3-METHOXYCARBONYLMETHYLENE-2-OXOINDOLINE WITH UNSYMMETRICAL BUTADIENE DERIVATIVES

Kunisuke Okada,* Morihide Kondo, Hideo Tanino, Hisae Kakoi, and Shoji Inoue

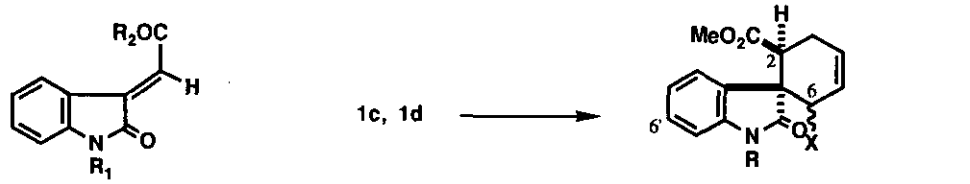
Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468, Japan

Abstruct - The Diels-Alder reaction of (E)-3-methoxycarbonylmethylene-2-oxoindoline with trans- and cis-1,3-pentadienes gave a single product, respectively, in high yield. The structural features of these adducts were elucidated by proton nmr analysis and chemical transformations.

The Diels-Alder reaction of 3-acylmethylene-2-oxoindoline (**1a** or **1b**) has been demonstrated to be one of the facile synthetic methods for spiro-2-oxoindoline derivatives.[1,2] In the previous paper, we reported the structure and stereochemistry of the adducts obtained from (E)-3-methoxycarbonylmethylene-2-oxoindoline (**1c**) and cyclopentadiene.[3] As an extention of this work aimed at the synthesis of naturally occurring spiro-2-oxoindoline derivatives such as surugatoxin (**2**),[4] neosurugatoxin (**3**),[5] and prosurugatoxin (**4**),[6] we examined the synthesis and characterization of the Diels-Alder adducts prepared from **1c** and its derivatives (cross conjugated dienophiles) and unsymmetrical dienes such as trans- and cis-1,3-pentadienes or 1-acetoxy-1,3-butadiene.[7] The structures of the resulting spiro-2-

oxoindoline derivatives are depicted in [A] as shown in Figure 1. The evidences of these results are presented herein.

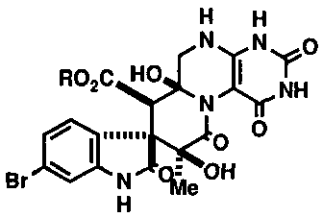
Figure 1



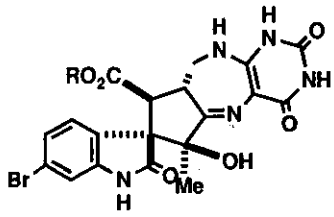
1a: R_1=H, R_2=Me
1b: R_1=Ac, R_2=Ph
1c: R_1=H, R_2=OMe
1d: R_1=CH_2OMe, R_2=OMe

[A]

[R=H, CH_2OMe; X=Me, OAc]



2: R=4-D-*myo*-inositol surugatoxin



3: R=4-(5-*O*-β-D-xylopyranosyl)-D-*myo*-inositol neosurugatoxin

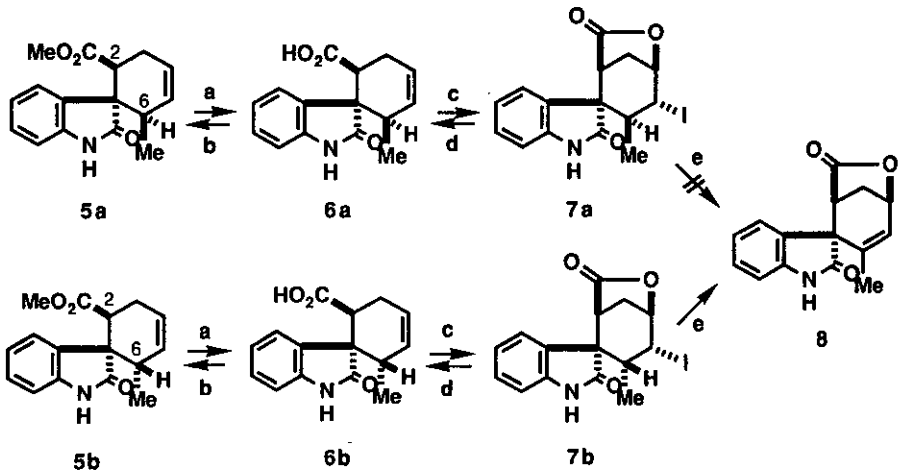
4: R=4-D-*myo*-inositol *prosurugatoxin*

Heating a mixture of (E)-3-methoxycarbonylmethylene-2-oxoindoline (**1c**) and trans-1,3-pentadiene in toluene under reflux for 5 h in a sealed tube gave a single product (**5a**) in 90% yield. Whereas, when cis-1,3-pentadiene was used in this reaction, the C_6 epimer (**5b**) was also obtained as a single product in 90% yield.

Generally, the structure of the Diels-Alder adduct is conducted both by the geometry of the substituents attached to the double bond of the diene and dienophile and also by the orientation of these molecules in transition state. It is well known that the stereochemical feature of the isatinylidene dienophile (**1c**)[8] is illustrated to be E-configuration as shown in Figure 1. Therefore, if maximum overlap of the diene occurs with

the isatinylidene double bond and the methoxycarbonyl group, the structure of the adduct obtained from **1c** and trans-1,3-pentadine is shown as **5a**, and the adduct from **1c** and the cis-isomer is also depicted as the structure (**5b**).

Figure 2



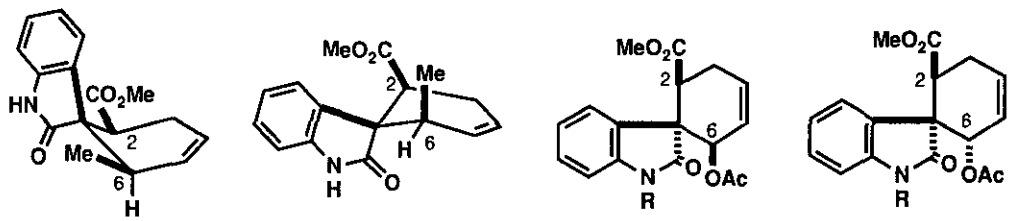
Regiochemistry of the each adduct (**5a**) and (**5b**) was easily determeined from the observed vicinal coupling between C_2 methin and C_3 methylene [3.34 ppm (1H, dd, J_{2-3}=7.1, 10.3 Hz C_2-H) for **5a**; 3.42 ppm (1H, dd, J_{2-3}=7.1, 10.3 Hz; C_2-H) for **5b**] which was confirmed by the decoupling technique. Configurations of the methoxycarbonyl groups at C_2 and the methyl groups at C_6 in **5a** and **5b** were clarified by the following chemical behaviors as shown in Figure 2.

Alkaline hydrolysis of **5a** and **5b** produced the corresponding carboxylic acids (**6a** and **6b**), which were then converted into the iodolactones (**7a**) and (**7b**), respectively, by the usual manner. No epimerization is observed in the above transformations, and the reverse reactions of the resultant lactones (**7a** and **7b**) with Zn/AcOH followed by diazomethane afforded **5a** and **5b** in excellent yields, respectively. Now, it was found that the

iodolactone (**7a**) was completely inactive to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), but another iodolactone (**7b**) was quantitatively transformed into **8** by treatment with DBU in tetrahydrofuran under reflux. In order to account for these chemical behaviors, the structure of **5a** is assigned as a β-methyl isomer, while that of the other product, (**5b**), as a α-methyl isomer.

It is interesting to point out that in the ^{1}*H-nmr spectra of* **5a** and **5b**, notable difference was observed in the chemical shift of the methyl group attached to the cyclohexene ring at C_6, that is, **5a** shows the signal at 0.59 ppm [3H, d, J=7.0 Hz] and **5b** at 1.12 ppm [3H, d, J=7.0 Hz]. This marked difference might depend on the remarkable shielding effect toward the methyl group of **5a**, probably influenced by the 2-oxoindoline chromophore. Accordingly, it was presumed that the more preferable conformation of **5a** is **9** rather than **10** and thus, the depicted conformation (**9**) would also be attributable to the other stereoisomer (**5b**).

Figure 3



9 **10** **11a** **11b**

[R=CH_2OMe]

Similarly, when 1-methoxymethyl-3-methoxycarbonylmethylene-2-oxoindoline (**1d**) was heated with a mixture of trans and cis isomers of 1-acetoxy-1,3-butadiene *in a sealed tube, easily separable two isomeric adducts were* obtained, the structures of which were revealed from the decoupling experiments of vicinal protons between C_2 methine and C_3-methylene in their nmr spectra [3.50 ppm (1H, dd, J_{2-3}=7.0, 11.0 Hz, C_2-H) and 2.65-2.80 ppm (2H, m) for **11a**] and [3.66 ppm (1H, dd, J_{2-3}=7.0, 11.0 Hz, C_2-H) and 2.50-

3.10 (2H, m) for **11b**]. In addition, the stereochemistry of the acetoxyl group at C_6 was assigned by the observation of these chemical shifts at 1.72 ppm for **11a** and at 2.09 ppm for **11b**, as discussed above.

In summary, the Diels-Alder reaction of (E)-3-methoxycarbonylmethylene-2-oxoindoline (**1c**) with trans- or cis-1,3-pentadiene gives a single adduct respectively as shown in the structural features of **5a** and **5b**, in which the methyl group of the terminal substituents of butadiene is obviously located at C_6 position in the spiro-cyclohexene ring. The similar regiospecific reaction was also observed in the Diels-Alder reaction of **1d** with 1-acetoxy-1,3-butadiene. Thus, the structures of these adducts are concluded to be summerized in the formula [**A**]. Now, it is presumed that these Diels-Alder adducts should be useful intermediates for the synthesis of a new class of marine natural products such as surugatoxin, neosurugatoxin, and prosurugatoxin. Recently, the 6'-bromo analogue of **5a** was successfully transformed into a key intermediate having the neosurugatoxin framework.[9] Further exploration of the other applicabilities of these adducts are now in progress.

EXPERIMENTAL

All melting points are uncorrected. Spectra reported herein were recorded on a JASCO IR A-I spectrophotometer, Hitachi M-80 mass spectrometer, and JNM GX-270 nmr spectrometer with Me_4Si as an internal standard. The following abbreviations were used: br=broad, d=doublet, dd=double doublets, m=multiplet, s=singlet, t=triplet. For column chromatography, silica gel (Kanto Chemical, over 100 mesh) was used. Tlc was performed on Kieselgel $60F_{254}$ plates (Art. 5744, Merck).

Diels-Alder adducts (5a) and (5b)

To a suspension of (E)-3-methoxycarbonylmethylene-2-oxoindoline (**1c**) (500 mg, 2.46 mmol) in toluene (50 ml) was added an excess amount of trans-1,3-

pentadiene (4.9 ml, 49.2 mmol) in a sealed tube and the mixture was heated at 120°C for 5 h. After cooling, the reaction mixture was filtered through Hyflo Super-Cel, and the filtrate was concentrated under reduced pressure. The residual syrup was separated with silica gel column chromatography (100 g, AcOEt-hexane=1:2) to give a crystalline adduct (**5a**) (600mg, 90%), mp 220-221°C (from Et_2O); ir(ν, cm^{-1}): 3300-2800 (br), 1735, 1715, 1608 (KBr); ms (m/z): 271(M^+), 256, 239, 203; ^{1}H-nmr ($CDCl_3$) δ: 0.59 (3H, d, J=7.0 Hz), 2.52-2.68 (2H, m), 2.88 (1H, m), 3.34 (1H, dd, J=7.1, 10.3 Hz), 3.43 (3H, s), 5.41 (1H, dd, J=1.7, 10.1 Hz), 5.79 (1H, m), 6.72-7.20 (4H, m), 8.65 (1H, br s). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.79; H, 6.27; N, 5.10. Another isomeric adduct (**5b**) was prepared in 90% yield from **1c** and cis-1,3-pentadiene under the same condition as described above. **5b**: mp 157-158°C (from Et_2O); ir (ν, cm^{-1}): 3190 (br), 1680, 1608 (KBr); ms (m/z): 271 (M^+), 256, 239, 203; ^{1}H-nmr ($CDCl_3$) δ: 1.12 (3H, d, J=7.0 Hz), 2.89-2.97 (3H, m), 3.24 (1H, dd, J=7.1, 10.3 Hz), 3.48 (3H, s), 5.57-5.92 (2H, m), 6.72-7.20 (4H, m), 9.06 (1H, br s). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.63; H, 6.29; N, 5.09.

Iodolactones (7a) and (7b)

Treatment of **5a** (300 mg, 1.11 mmol) with a mixture of 10% aqueous NaOH (2 ml, 5 mmol) and dioxane (2 ml) at 100°C for 15 min gave the corresponding carboxylic acid (**6a**) in almost quantitative yield after a conventional workup. When treated with diazomethane in MeOH, crude **6a** gave the starting ester in about 95% yield, after purified on a silica gel column. Therefore, without purification, **6a** thus obtained was used for the next step. To a solution of **6a** (257 mg, 1.0 mmol) in 2% aqueous $NaHCO_3$ (2 ml) was added an excess amount of 0.1N I_2-KI in a water solution (30 ml, 3 mmol) and the mixture was warmed at 50°C for 1 h to yield a crude **7a** as a precipitate which was collected by filtration, washed with water and air

dried. The crude product (**7a**) was recrystallized from MeOH to give colorless needles (330 mg, 86.2% yield from **6a**), mp 245-246°C; ir (ν, cm^{-1}): 3380-3000 (br), 1795, 1708, 1608 (KBr); ms (m/z): 383 (M^+), 287, 272, 255; ^{1}H-nmr ($CDCl_3$-CD_3OD) δ: 0.73 (3H, d, J=7.0 Hz), 2.30-2.74 (2H, m), 2.84 (1H, dd, J=5.5, 7.0 Hz), 3.14 (1H, dd, J=1.5, 12.8 Hz), 4.24 (1H, dd, J=2.0, 11.0 Hz), 5.34 (1H, m), 6.81-7.35 (4H, m). Anal. Calcd for $C_{15}H_{14}NO_3I$: C, 47.01; H, 3.68; N, 3.66. Found: C, 46.96; H, 3.65; N, 3.37. Under the same procedure, the adduct (**5b**) was also transformed into iodolactone (**7b**) through the corresponding carboxylic acid (**6b**) in 92% yield from **5b**, mp 234-235°C (from MeOH); ir (ν, cm^{-1}): 3400-2900 (br), 1780, 1700, 1608 (KBr); ms (m/z): 383 (M^+), 256, 238, 228, 212; ^{1}H-nmr ($CDCl_3$-CD_3OD) δ: 0.88 (3H, d, J=7.0 Hz), 2.16-2.60 (3H, m), 4.14 (1H, dd, J=1.5, 13.0 Hz), 4.67 (1H, dd, J=3.5, 6.5 Hz), 5.12 (1H, m), 6.78-7.30 (4H, m). Anal. Calcd for $C_{15}H_{14}NO_3I$: C, 47.01; H, 3.68; N, 3.66. Found: C, 47.03; H, 3.61; N, 3.42.

Elimination of hydrogen iodide from 7b with DBU

A solution of **7b** (38.3 mg, 0.10 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 37.4 μl, 0.25 mmol) in THF (1 ml) was heated at 60°C under a nitrogen atmosphere for 5 h. After diluted with CH_2Cl_2 (20 ml), the reaction mixture was washed with 1N HCl, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was crystallized from MeOH to give pure **8** (23.0 mg, 90.2%), mp 246°C (from MeOH); ir (ν, cm^{-1}): 3300-2900 (br), 1775, 1702, 1608 (KBr); ms (m/z): 255 (M^+), 237, 210, 200, 196 ; ^{1}H-nmr ($CDCl_3$-CD_3OD) δ: 1.39 (3H, br s), 2.39 (1H, dd, J=5.0, 11.0 Hz), 2.76 (1H, d, J=5.0 Hz), 3.30 (1H, d, J=11.0 Hz), 4.93 (1H, br t, J=6.0 Hz), 6.38 (1H, br d, J=6.0 Hz), 6.84-7.40 (4H, m). Anal. Calcd for $C_{15}H_{13}NO_6$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.20; H, 5.13; N, 5.23.

Transformation of 7a into 5a

To a solution of **7a** (10 mg, 0.026 mmol) in MeOH (2 ml) were added Zn powder (5 mg, 0.0765 mmol) and AcOH (0.1 ml), and the mixture was stirred for 30 min at room temperature. After diluted with CH_2Cl_2 (5 ml), the mixture was filtered and the collected solid was washed with the mixture of CH_2Cl_2-MeOH (4:1, 5 ml). The combined filtrate and washing were concentrated to dryness. The residue was dissolved in MeOH (2 ml) and treated with diazomethane in ether solution, followed by purification on tlc (CH_2Cl_2-MeOH=100:5) to give **5a** in 90% yield.

Diels-Alder adducts (11a) and (11b)

To a suspension of **1d** (2 g, 0.81 mmol) in toluene (50 ml) was added an excess amount of 1-acetoxy-1,3-butadiene (2 ml, 16.86 mmol) in a sealed tube and the mixture was heated at 120°C for 15 h. After cooling, the reaction mixture was filtered through Hyflo Super-Cel, and the filtrate was concentrated under reduced pressure. The residual syrup was separated on a silica gel column (250 g, AcOEt-hexane=1:5) to give a mixture of two stereoisomeric products, which was separated on a silica gel tlc (AcOEt-hexane=1:4) to give two crystalline adducts (**11a**, 151 mg, 52%) and (**11b**, 107 mg, 37%).

11a: mp 139-140°C (from MeOH); ir (ν, cm^{-1}): 1735, 1715, 1608 (KBr); ms (m/z): 359 (M^+); ^{1}H-nmr ($CDCl_3$) δ: 1.72 (3H, s), 2.65-2.80 (2H, m), 3.38 (3H, s), 3.48 (3H, s), 3.50 (1H, dd, J=7.0, 11.0 Hz), 5.08 (1H, d, J=11.5 Hz), 5.21 (1H, d, J=11.5 Hz), 5.60-5.90 (2H, m), 5.90-6.19 (1H, m), 6.95-7.35 (4H, m). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.16; H, 5.76; N, 3.82.

11b: mp 124-125°C (from MeOH); ir (ν, cm^{-1}): 1735, 1715, 1610 (KBr); ms (m/z): 359 (M^+); ^{1}H-nmr ($CDCl_3$) δ: 2.09 (3H, s), 2.50-3.10 (2H, m), 3.39 (3H, s), 3.52 (3H, s), 3.66 (1H, dd, J=7.0, 11.0 Hz), 5.14 (2H, s), 5.19 (1H, d, J=6.0 Hz), 5.88 (1H, m), 6.30 (1H, m), 6.90-7.42 (4H, m). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.28; H, 5.75;

N, 3.93.

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