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DIELS-ALDER REACTION OF 3-METHOXYCARBONYLMETHYLENE-2-OXOINDOLINE DERIVATIVES WITH UNSYMMETRICAL BUTADIENES

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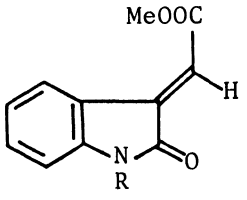
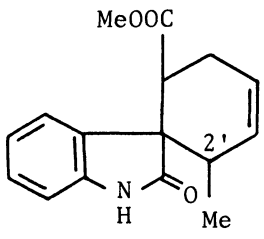
Diels-Alder reaction of 3-methoxycarbonylmethylene-2-oxoindoline derivatives (1a and 1b) with unsymmetrical butadienes (1,3-pentadiene and 1-acetoxy-1,3-butadiene) gave two stereoisomeric adducts (11) as the respective reaction products in high yields.

As a part of our synthetic works on naturally occurring spiro-2-oxoindoline derivatives such as surugatoxin,[1] we examined the detailed Diels-Alder reaction of 3-methoxycarbonylmethylene-2-oxoindoline derivatives with some unsymmetrical dienes. This paper deals with the structures and stereochemistry of the adducts obtained from 3-methoxycarbonylmethylene-2-oxoindoline derivatives[2] (1a and 1b) and 1,3-pentadiene and 1-acetoxy-1,3-butadiene.

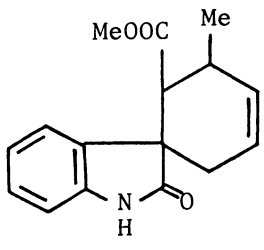
Heating a mixture of 3-methoxycarbonylmethylene-2-oxoindoline (1a) and 1,3-pentadiene [a cis and trans mixture in a ratio of about 1:1.5] in toluene under reflux for 5 h gave two isomeric adducts [$C_{16}H_{17}NO_3$ (m/e 271(M^+)); (2):mp 220-221°C; (3):mp 158°C] in a ratio of about 1:1 in 90% yields. The structures of both adducts (2) and (3) were concluded to be (A) rather than (B) by their ^1H NMR studies,[3] but the stereochemical definitions of the methyl group at C-2' still remain to be clarified.



(1a):R=H
(1b):R=CH_2OMe

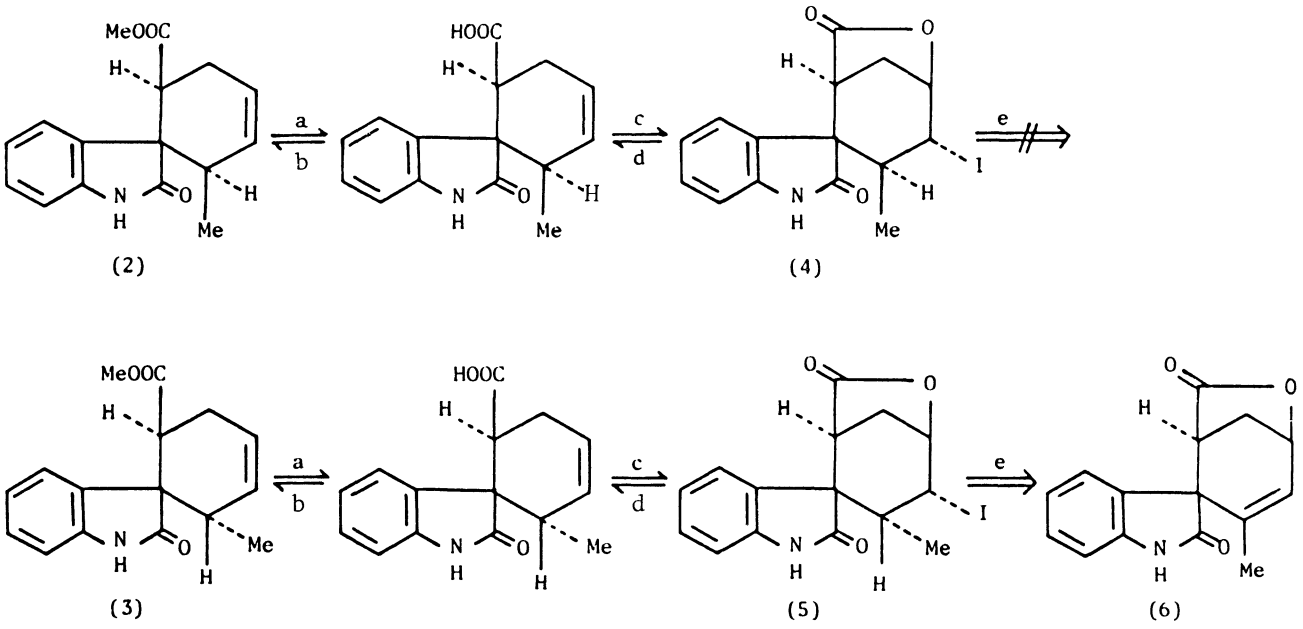


(A)



(B)

To establish the configuration of the methyl group in (A), the following chemical reactions were carried out as shown in Fig. 1. Iodolactone (4)[4] [mp 235-236°C, $C_{15}H_{14}NO_3I$ (m/e 383(M^+)), ν(KBr) 1780 cm^{-1}] derived from the adduct (2) was completely inactive to DBU,[5] but another iodolactone (5)[4] [mp 245-246°C, $C_{15}H_{14}NO_3I$ (m/e 383(M^+)), ν(KBr) 1795 cm^{-1}] obtained from (3) was quantitatively transformed to (6) [mp 246°C, $C_{15}H_{13}NO_3$ (m/e 255(M^+)), ν(KBr) 1775 cm^{-1}, δ($CDCl_3$) 1.39(3H, s), 2.39 (1H, d.d, J_1=11Hz, J_2=5Hz), 2.76(1H, d, J=5Hz), 3.32(1H, d, J=11Hz), 4.93(1H, br.t, J=6Hz), 6.37(1H, br.d, J=6Hz)] by treatment with DBU in THF under reflux. In order to account for these chemical behaviors, the structure of the product (2) is assigned to be the β-methyl isomer, while that of the other product (3) to be the α-methyl isomer.

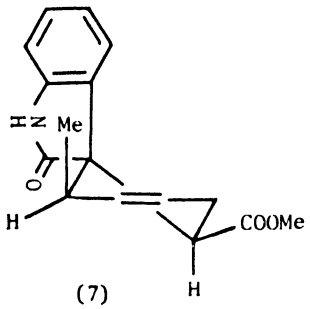


[a:10% KOH, b:CH_2N_2, c:I_2-KI, d:Zn-AcOH, e:DBU]

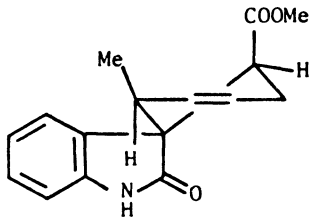
Fig. 1.

It is interesting to point out that in the ^1H NMR spectra of (2) and (3), notable difference was observed in the chemical shift of the methyl group attached to the cyclohexene ring, that is, the product (2) shows the signal at 0.59 ppm [3H, d, J=7Hz] and the product (3) at 1.12 ppm [3H, d, J=7Hz]. This marked difference might depend on the remarkable shielding effect toward the methyl group of (2), probably influenced by the 2-oxoindoline chromophore.[6]

Accordingly, we presumed that the most probable conformation of (2) to be (7) rather than (8) and thus, the depicted conformation would also be attributable to the product (3).

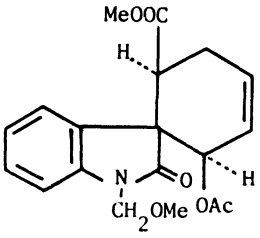


(7)

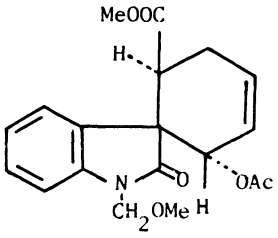


(8)

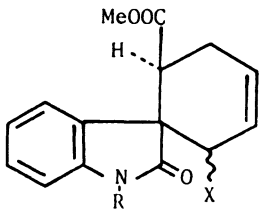
The similar phenomenon was also observed in the chemical shift of the acetoxy groups of the adducts (9)[7] [mp 139-140°C, $C_{19}H_{21}NO_6$ (m/e 359(M^+)), $\delta(CDCl_3)$ 1.72 (3H, s; -OCO$\underline{CH_3}$), 52% yield] and (10)[8] [mp 124-125°C, $C_{19}H_{21}NO_6$ (m/e 359(M^+)), $\delta(CDCl_3)$ 2.09(3H, s; -OCO$\underline{CH_3}$), 37% yield] obtained from 1-methoxymethyl-3-methoxycarbonylmethylene-2-oxoindoline (1b) and 1-acetoxy-1,3-butadiene.[9]



(9)



(10)



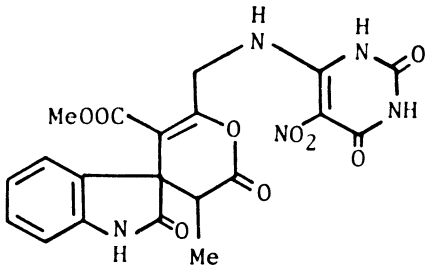
(11)

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

On conclusion, the Diels-Alder reaction of 3-methoxycarbonylmethylene-2-oxoindoline derivatives with unsymmetrical butadienes gives two stereoisomeric products as summerized in the formula (11). Since a high yield synthesis of spiro-2-oxoindoline derivatives is now become available, further transformations to surugatoxin derivatives from these adducts are now in progress.[10]

REFERENCES AND NOTES

1. T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Narita, Tetrahedron Lett., 2545 (1972) and references cited therein.
2. R. L. Autrey, and F. C. Tahk, Tetrahedron, 23, 901 (1967).
3. The structure (B) was neglected by the following reasons:
   1) The methine signals (-$\underline{\text{CH}}$-COOMe) of (2) and (3) were quartet [(2): 3.34 ppm (1H, q, J_1=10Hz, J_2=7Hz), (3): 3.24 ppm (1H, q, J_1=10Hz, J_2=7Hz)].
   2) No changes in the shape of the above methine signals were observed by the irradiation at the frequency of the allylic methine signals (CH_3-$\underline{\text{CH}}$-CH=CH-) of (2) and (3).
4. Elemental analysis and NMR spectra including decoupling data are also satisfied with the structures depicted in (4) and (5), respectively.
5. 1,5-Diazabicyclo[5,4,0]undec-5-ene.
6. A similar difference in the chemical shift of the methyl groups in dihydro-derivatives of (2) and (3) was also observed; 2H-(2): 0.50 ppm (3H, d, J=7Hz), 2H-(3): 0.71 ppm (3H, d, J=7Hz).
7. $\delta(CDCl_3)$ 1.72(3H, s), 2.72(2H, m), 3.37(3H, s), 3.47(3H, s), 3.53(1H, m), 5.13 (2H, ABq, J=11Hz), 5.73(1H, br.d, J=11Hz), 5.88(1H, br.s), 6.05(1H, br.d, J=11Hz).
8. $\delta(CDCl_3)$ 2.09(3H, s), 2.40-3.02(2H, m), 3.38(3H, s), 3.52(3H, s), 3.69(1H, q, J_1=11Hz, J_2=6Hz), 5.13(2H, s), 5.19(1H, d, J=5Hz), 5.83(1H, m), 6.30(1H, m).
9. A solution of (1b) and an excess amount of 1-acetoxy-1,3-butadiene in toluene was refluxed for 15 h.
10. For example, the adducts (2) and (3) have already been transformed to the enol-lactone derivative (12), synthesis of which was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, April 3, 1978 (Okayama): K. Okada, M. Kondo, K. Hashizume, and S. Inoue, Abstract, 3w11-16.



(12)

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