Dioxopyrrolines. LXII.1) Diels–Alder Reaction of 1-Aryl-4- and 5-methoxycarbonyl-1H-pyrrole-2,3-diones with Various 1,3-Dienes

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Two new dioxopyrrolines (1-aryl-4-methoxycarbonyl-1H-pyrrole-2,3-dione 6 and the 5-methoxycarbonyl isomer 8) behaved as good dienophiles to some kind of 1,3-dienes examined. In most cases, the products were explained by the reaction where the largest lobe of HOMO of dienes reacted to the larger LUMO of dienophiles in an expected cis-endo manner. However, in the reactions of 8 with alkylbutadienes, piperylene and isoprene, abnormality in the reaction was observed, which was well explained by taking account of steric factors.

**Key words** dioxopyrrole; Diels–Alder reaction; steric factor; regioselectivity; 1-aryl-4-methoxycarbonyl-1H-pyrrole-2,3-dione; 1-aryl-5-methoxycarbonyl-1H-pyrrole-2,3-dione

1H-Pyrrole-2,3-diones (dioxopyrrolines) are useful synthons in the organic synthesis.2,3) Particularly, the 4,5-dialkoxycarbonyl derivative (1) behaves as a strong dienophile to give hydroindoles.4) The cycloaddition of 1 to 1-substituted butadiene such as 1-methoxy- or 1-sulfenyl-butadiene smoothly occurred in regio- and stereo-selective manners to give 4-substituted hydroindoles in good yields. Although two alkoxycarbonyl groups in 1 are obviously enhancing the dienophile activity of the dioxopyrrole, it is hard to predict the respective contribution of each group to regioselectivity of this cycloaddition reaction. Therefore, we have newly prepared two differently substituted dioxopyrrolines, 4- and 5-methoxycarbonyl derivatives 6 and 8, and examined their cycloaddition reaction to various butadienes hoping to evaluate the contribution of each methoxycarbonyl group in the dienophile on the regioselectivity of treated cycloaddition reaction.

**Results and Discussion**

**Preparation of the Dioxopyrrolines** 4-Methoxycarbonyl and 5-methoxycarbonyl-dioxopyrrolines, 6 and 8, were synthesized from p-anisidine 4 based on the known method, respectively. Oxalation of the enamine 51) prepared from methyl propiolate and 4 with oxalyl chloride gave 6 as reddish purple prisms in a quantitative yield. While oxalation of the condensation product (an equilibrium mixture of imine-enamine tautomers)6) of methyl pyruvate and 4 gave 5-methoxycarbonyl derivative 8 as red prisms. The spectroscopic data [IR, 1H-, 13C-NMR, and high resolution MS (HR-MS)] were compatible to the expected structures, respectively.

**Diels–Alder Reaction of Dioxopyrrolines, 6 and 8**

![Chart 1](chart1.png)
Diels–Alder reaction of 6 with nine kind of butadienes (A to I) were carried out on heating two substrates in toluene at 80 °C for 15 h. In all cases, single product was produced usually in good yield except in the case of isoprene (E) where two regio isomers were produced as discussed below (see Table 1). When the dienes beared an OTMS group (F, I), the products were the expected adducts and/or its desilylated ketones. For them the structure determinations and yield calculations were made after converting the product into single ketones by treatment with acetic acid.

Butadiene (A) and 2,3-dimethylbutadiene (B) gave 9 and 10 in 83% and 92% yield, respectively. 1-Substituted (by alkyl or electron donating group) butadienes (C, D, G, H, I) gave expected endo-adducts (4α-substituted hydroindoles), 11, 12, 16, 17, and 19, respectively.

2-Trimethylsilyloxybutadiene (F) also gave a single adduct 15 (thereof 18) in 72% yield. However, isoprene (E) gave two regio-isomers 13 and 14 in a ratio of 3:1.

5-Methoxycarbonyldioxopyrroline 8 also gave adducts, which were isolated as tautomeric enols. There was a notable difference between 6 and 8 in the reaction of piperylene (C) and isoprene (E). The addition product of 8 to C was a 1:1 mixture of two regio-isomers, 20 and 21, which were separated by chromatography, while isoprene (E) gave a single adduct 23. 1-Methoxybutadiene (D) gave compound 25 in 33% yield after isolation with silica gel chromatography, which is produced from the expected adduct 22 by loss of MeOH followed by aromatization with concomitant cleavage of C–N bond. By the chromatographic isolation of the product using CC-7 (Mallinckrodt, Inc.) column, the adduct 24 was obtained in 23% yield. Treatment of 24 with SiO2 gave 25 in 70% yield.

**Structure Determination of the Product** The spectroscopic data (MS, IR, 1H- and 13C-NMR) of the above isolated compounds from the reaction of 6 and dienes were compatible to the assigned structures, respectively. The regio-chemistry in this cycloaddition and stereochemistry of C-4 substituent were determined with the help of H–H two dimensional (2D) correlated spectroscopy (COSY) and nuclear Overhauser enhancement spectroscopy (NOESY).

Adducts (9—19) gave correlation peaks between ester methyl group and angular H-7a establishing their ring junctures to be cis. For other structure determinations, we will show the procedure by taking 11 as an example. Compound 11 showed clear COSY correlation between H-7a (δ 4.85—4.83, m) and methylene group at δ 2.47 (ddd) and 2.19—2.14 (m) indicating that C-7 position is CH3. The NOESY spectrum showed a correlation between H-4 (geminal to the methyl) and H-7a. Therefore the 4-methyl group must be trans to the ring juncture. Compounds 12, 16, 17, were analyzed in a similar way by the H–H COSY and NOE correlation.

The desilylated ketones 18 and 19 were determined as follows. In addition to the other spectral data (which are com-
patible to the expected structures), H-7a of 18 (δ 5.15, t) showed COSY correlation peak with methylene group at δ 2.80 (dd). This indicated that C-7 is CH₂. The structure of 19 was determined in a similar way where H-7a also exhibited a NOESY correlation with H-4 showing that the stereochemistry of 4-OMe group is α.

The product from the reaction of 6 and isoprene (E) was an oily mixture of two compounds in a ratio of 3 : 1 as shown by the ratio of two methyl signals at δ 1.60 and 1.70 in the 1H-NMR spectrum. Since it was difficult to separate them by column chromatography, the structure of each component was determined without separation. Similar procedures as described above lead to the conclusion that the major product was 6-methyl 13 and the minor product was 5-methyl adduct 14. The H-7a signal (δ 5.05, J = 3.8 Hz) of 13 had a COSY correlation with a broad doublet (J = 3.8 Hz) of H₂ at δ 2.25 which did not show the correlation with the olefinic H at δ 5.61 (m). On the other hand, two H at C-4 in 14 appeared at δ 2.78 and 2.55 as an ABq (J = 15.5 Hz) which did not show the correlation with the olefinic H at δ 5.38 (m).

The enol structure of the products from the cycloaddition of 8 to dienes were indicated by their positive FeCl₃ test, appearance of OH absorption in the IR, and appearance of two new –C= signals (instead of CO, C-3 and C-3a) in the 13C-NMR spectrum.

The regiochemistries of two isomers 20 and 21 from the addition reaction of 8 to piperylene were determined as follows. The compound 20 was reduced with tetra-n-butylammonium borohydride⁹ to the alcohol 26, which showed, in the COSY spectrum, the sequence of H-3 (δ 4.32, dd) to H-3a (δ 2.16, dd) to H-4 (δ 2.60—2.46, m) and to Me (δ 1.19, d), thus confirming the position of the Me group at C-4. The stereochemistry of 4-Me group was revealed to be β (cis to the ring juncture) by the presence of NOE enhancements of H-3a (18.3%) on irradiation of the Me group. Irradiation of H-3 also produced enhancement of H-3a signal (12.9%). The fact implies that the reaction of 8 with piperylene proceeded unexpectedly through exo-stereochemistry. At the same time, the stereochemistry of the newly created hydroxy-group at C-3 was determined as α.

Similarly, reduction of 21 gave the alcohol 27. The NMR analysis gave the sequence of H-3 to H-3a to H₂-4 to H-5 to H-6 to H-7 and to Me, thus the position of methyl group and the stereochemistry of 3α-OH group being established. The difference NOE spectrum of 27, however, did not give clear-cut evidence for the stereochemistry of methyl group at C-7.

On the other hand, reduction of the addition product 23 of isoprene to 8 with potassium borohydride in EtOH under CO₂ gave α-alcohol 28 (66%) and β-alcohol 29 (21%). Treatment of 28 with conc. H₂SO₄ gave the ether 30 in 69% yield. This compound had the same molecular formula (m/z 331) with that before treatment but showed neither OH nor olefinic proton signal in the IR and 1H-NMR spectra, indicating the ether formation. The structure was supported by the 13C-NMR and COSY spectra. Thus, the stereochemistry of 3α-OH group and the position of Me group (at C-5) in 28 were determined.

**Discussion** The LUMO coefficient (LCO) of dioxopyrrolines 6 and 8 calculated by Gaussian 98 Rev. A7,⁸) and the HOMO coefficient (HCO) of piperylene and isoprene in the literature⁹,¹⁰) are shown in Fig. 1. The LCO's indicate that C-5 is more reactive than C-4. But the differences between these dienes are very small (0.001 for C-1 and C-4 in these alkyl-butadienes are very small (0.001 for C and 0.044 for E). This implies that the difference of the reactivity at C-1 and C-4 in these dienes is smaller than that in the other dienes bearing O-functional groups. The disturbance of the rule may be arisen from the steric reasons: obviously addition of isoprene
to 6 is sterically less favorable for C-1 than for C-4. Thus, the reverse product 14, which was initiated by attack of less hindered C-4 (of isoprene) to C-5 (of 6), is accompanied in the reaction of isoprene. In the reaction of piperylene (C) to 6, both the electronic and steric factors play in the same direction to give the single product 11.

Similarly, the steric factor plays an important role in additions of 8 to piperylene and isoprene, where piperylene gave a 1:1 mixture of regio-isomers (20, 21) and isoprene gave a single product (23) with reverse orientation. In compound 8 the difference of LCO between C-4 and C-5 is small (0.141) and the attack to C-5 is obviously more hindered than that to C-4. Thus in the reaction of isoprene, attack of C-1 in the diene to the less hindered C-4 of 8 occurred exclusively to give the reverse oriented product 23. In piperylene, its reactive position (C-4) is less hindered than that of isoprene (C-1). Thus, the addition reaction to 8 takes two paths: one is the attack of C-4 (of C) to C-5 of 8 (electronically more favored) and the other is the attack of C-4 (of C) to C-4 of 8 (sterically more favored). Equal formation of 20 and 21 implies that these two factors play equal role in the reaction of C to 8. Although the reason of the formation of exo-adduct in this case is not clear, it is not exceptional that thermodynamically more stable exo-adduct (β-Me isomer is 0.4 kcal/mol more stable than the α-Me isomer in the dioxo form) is sometimes favored in the Diels–Alder reaction of dioxopyrrolines.11,12)

Conclusion

In conclusion, new dioxopyrrolines 6 and 8 were shown to be good dienophiles in 4+2 cycloaddition reaction. Their LUMO coefficients showed that C-5 had larger values than those of C-4, but the difference is so small in 8 that the steric factor sometimes overcomes the electronic factor. Thus the reaction of 1-O-substituted dienes with 6 gave 4-substituted hydroindoles with expected endo-stereochemistry and 2-O-substituted dienes gave 6-substituted hydroindoles. They are the products where the largest lobe of HOMO of dienes reacted with the largest LUMO (C-5) of dioxopyrrolines. Violations of the rule were observed particularly for the reactions of 1- and 2-methylbutadiene (piperylene and isoprene) in 8, where the steric factors have to be taken into account.

Experimental

Unless otherwise stated, the following procedure was adopted. Melting points were determined on a Yanaco melting point apparatus and uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer, and data are given in cm−1. 1H- and 13C-NMR spectra were taken with a JEOL JNM-EX90 (90 MHz for 1H and 22.5 MHz for 13C) or JEOL JNM-AL300 (300 MHz for 1H and 75 MHz for 13C) or JNM-ec500 (500 MHz for 1H) spectrometer, in CDCl3 solutions with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. MS and HR-MS were taken with a JEOL JMS-D300 and JEOL JMS-HX110A spectrometer and M+ is given in m/z. Elemental analyses were performed with a Yanaco MT-3. TLC was performed on pre-coated Kieselgel 60 F254 plates and spots were monitored by UV (254 nm), then developed by spraying 0.5% Ce(SO4)2–0.5% (NH4)6Mo7O24 in 5% H2SO4 and heating the plates until coloration
took place. Column chromatography was performed on Wakogel C-200 (silica gel). For medium-pressure liquid chromatography, a Kusano CPS-HS-221-1 column (silica gel, 22 mm i.d.×100 mm) was used. All organic extracts were washed with brine, dried over anhydrous MgSO₄, and concentrated to yield the products.

4-Methoxyaniline-1-(4-methoxyphenyl)-1H-pyrrole-2,3-dione (6)
Methyl pyruvate (5.1 g, 50 mmol) and p-anisidine (4.61 mg, 55 mol) was stirred for 1 h at room temperature, then distilled at 5 mmHg to remove excess methyl pyruvate. The residue was dissolved in ether (50 mL) and washed with brine, dried over anhydrous MgSO₄, and concentrated to yield 5 (29.0 g, 72%).

5-Methoxanilonyl-1-(4-methoxyphenyl)-1H-pyrrole-2,3-dione (8)
A mixture of methyl pyruvate (5.1 g, 50 mmol) and p-anisidine (4.61 mg, 55 mol) was stirred for 1 h at room temperature, then distilled at 5 mmHg to remove excess methyl pyruvate. The residue was dissolved in ether (50 mL). The mixture was concentrated to dryness in vacuo. The residue was passed through a short column of SiO₂ with AcOEt-hexane. Concentration of the eluate gave a crude product.

(3aR,7aR)-3a-Methoxyanilonyl-1-(4-methoxyphenyl)-2,3-dioxo-2,3,3a,4,5,6,7,7a-octahydroindole (9)
Brown prisms. mp 134°C (from AcOEt-hexane). IR (KBr): 1770, 1740, 1700, 1510, 1270. 1H-NMR: 7.68, 7.01 (each 2H, d, J=9.9 Hz, Ar-H), 6.03, 5.97, 5.97, 5.95, 5.79, 5.79, 5.78, 5.75 (1H, m), 3.80, 3.80 (each 3H, s, OMe), 2.93 (1H, dd, J=14.6 Hz, H-14), 2.43—2.35 (2H, m), 2.25, 2.25 (1H, d, J=14.6 Hz, CH₃, 2.18—2.12 (1H, s, CH₃), 1.69, 1.54 (each 3H, s, Me). 13C-NMR: 195.8, 168.5, 159.0, 157.2, 128.6, 127.9, 126.1, 124.9×2, 114.8×2, 58.8, 55.3, 53.5, 55.0, 28.3, 26.3. HR-MS: Calcd for C₂₈H₂₇NO₇: 431.1917. Found: 431.1920.

(3aR,7aR)-3a-Methoxyanilonyl-1-(4-methoxyphenyl)-5-methyl-2,3-dioxo-2,3,3a,4,5,6,7,7a-octahydroindole (10)
Yellow prisms. mp 149—152°C (from AcOEt-hexane). IR (KBr): 1770, 1740, 1700, 1510, 1270. 1H-NMR: 7.43, 7.01 (each 2H, d, J=9.9 Hz, Ar-H), 5.05 (1H, t, J=3.6 Hz, H-7a), 3.85, 3.78 (each 3H, s, OMe), 2.64, 2.52 (each 1H, d, J=14.6 Hz, CH₂, 2.24—2.24 (1H, s, CH₃), 1.69, 1.54 (each 3H, s, Me). 13C-NMR: 195.8, 168.5, 159.8, 158.9, 127.4, 125.6, 124.7×2, 114.8×2, 59.5, 55.2, 53.4, 55.1, 34.8, 33.1, 19.0×2. HR-MS: Calcd for C₂₉H₂₉NO₇: 434.1417. Found: 434.1396. Anal. Caled for C₂₉H₂₉NO₇: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.50; H, 6.24; N, 4.04.

(3aR,7aR)-3a-Methoxyanilonyl-1-(4-methoxyphenyl)-4-methyl-2,3-dioxo-2,3,3a,4,5,6,7,7a-octahydroindole (11)
Light yellow prisms. mp 136—140°C (from AcOEt-hexane). IR: 1765, 1760, 1690, 1520. 1H-NMR: 7.37, 6.99 (each 2H, d, J=9.9 Hz, Ar-H), 5.78 (1H, dt, J=8.9, 3.4 Hz, H-5), 5.73—5.69 (1H, m, H-6, 4.85—4.83 (1H, 3H, Me-H, 3.84, 3.81 (each 3H, s, OMe), 2.99—2.93 (1H, m, H-4, 2.47 (1H, dd, J=15.6, 6.7, 1.8 Hz, H-5), 2.19—2.14 (1H, m, H-7), 1.41 (3H, d, J=7.3 Hz, Me). 13C-NMR: 195.1, 169.7, 156.9, 157.7, 128.5, 125.0, 124.9×2, 114.7×2, 60.4, 57.7, 55.5, 53.3, 34.8, 26.1, 14.8. HR-MS: Calcd for C₂₉H₂₉NO₇: 432.1267. Found: 432.1287. Anal. Caled for C₂₉H₂₉NO₇: C, 66.54; H, 6.82; N, 4.25. Found: C, 65.72; H, 5.90; N, 4.26.

(3aR,7aR)-4-Methoxy-3a-methoxyanilonyl-1-(4-methoxyphenyl)-2,3-dioxo-2,3,3a,4,5,6,7,7a-octahydroindole (12)
Yellow light prisms. mp 132—134°C (from AcOEt-hexane). IR (KBr): 1780, 1740, 1710, 1610. 1H-NMR: 7.43, 6.99 (each 2H, d, J=9.0 Hz, Ar-H), 6.29—6.26 (1H, m, H-5), 6.05—6.01 (1H, m, H-6), 4.87 (1H, J=7.0 Hz, H-7a), 4.72 (1H, d, J=4.9 Hz, H-4), 3.84, 3.80, 3.25 (each 3H, s, OMe), 2.53—2.47 (1H, m, H-7), 2.40—2.34 (1H, m, H-7). 13C-NMR: 194.1, 167.8, 158.8, 157.1, 158.9×2, 125.0×2, 114.5×2, 128.5, 76.2, 59.5, 57.2, 55.3, 52.6, 26.9. HR-MS: Calcd for C₁₇H₁₁NO₅: 345.1210. Found: 345.1208. Anal. Caled for C₁₇H₁₁NO₅: C, 66.50; H, 5.55; N, 5.04. Found: C, 62.38; H, 5.61; N, 3.98.

(3aR,7aR)-3a-Methoxyanilonyl-1-(4-methoxyphenyl)-5-methyl-2,3-dioxo-2,3,3a,4,5,6,7,7a-octahydroindole (14)
7H-NMR: 7.61, 7.42 (each 2H, d, J=9.9 Hz, Ar-H), 5.62—5.60 (1H, m, H-5), 5.05 (1H, dd, J=5.8, 3.8 Hz, H-7a), 3.85, 3.79 (each 3H, s, OMe), 2.88 (1H, dd, J=15.0, 6.7 Hz and 2.50 (1H, brd, J=15.0 Hz, H-4), 2.25 (2H, d, J=3.8 Hz, H-7), 1.60 (3H, s, Me) 13C-NMR: 196.1, 166.8, 158.9, 157.2, 138.5, 128.5×2, 114.8×2, 58.9, 55.5, 53.5, 43.1, 28.8, 22.9.

Diel—Aller Reaction of Dioxyproline (6, 8) with Butadienes (General Procedure)
A mixture of dioxyproline and a diene (4 eq mol, see Tables 1 and 2) in dry toluene or benzene was heated at appropriate temperature in a sealed tube with stirring. The reaction mixture was concentrated to dryness in vacuo. The residue was passed through a short column of SiO₂ with AcOEt-hexane. Concentration of the eluate gave a crude product.
114.5±2, 121.9, 70.9, 55.4, 32.9, 43.5, 22.9, 14.9. HR-MS: Calcd for C_{12}H_{17}NO_{3}: 329.1260. Found: 329.1239.

3-Hydroxy-7a-methoxy carbonyl-1-(4-methoxyphenyl)-5-methyl-2-oxo-2,4,7a-tetrahydropyridine (23): Light yellow prisms. mp 206–208 °C (from EtO-O-hexane). IR (KBr): 1740, 1680, 1600, 1500. 1H-NMR: 7.19–6.84 (4H, m, Ar-H), 5.43 (1H, s, CH3), 3.81, 3.65 (each 3H, s, OMe), 3.48–2.09 (4H, m, –CH2–), 1.77 (7H, s, Me). 13C-NMR: 170.4, 167.8, 158.6, 140.9, 131.8, 128.7, 120.1, 127.4±2 (7H, s). 1H-NMR: 114.5±2, 117.7, 66.9, 55.4, 52.8, 33.6, 27.4, 22.7. HR-MS: Calcd for C_{12}H_{17}NO_{3}: 329.1289. Found: 329.1276.

**Diels–Alder Reaction of Diospyrone (8) with 1-Methoxybutadiene**

A solution of 8 (261 mg, 1 mmol) and 1-methoxybutadiene (252 mg, 3 mmol) in dry toluene (10 ml) was heated at 100 °C for 11 h in a sealed tube. The reaction mixture was concentrated to dryness in vacuo and the residue was passed through a column of CC−7 with AcOEt–hexane. Concentration of the eluate gave a crystalline product which was recrystallized from AcOEt–hexane to give 7a-methoxycarbonyl-1-(4-methoxyphenyl)-2,3,7,7a-tetrahydroindole (24, 27 mg, 23%) as yellow prisms, mp 155–157 °C. IR (KBr): 1740 (sh), 1720 (sh), 1690, 1610. 1H-NMR: 7.15 (1H, d, J = 5.0 Hz), 7.10 (2H, d, J = 9.0 Hz), 6.96 (2H, d, J = 9.0 Hz), 6.48–6.30 (2H, m), 3.83 (3H, s), 3.74 (3H, s). 13C-NMR: 192.5, 166.7, 157.9, 141.7, 133.2, 132.7, 127.9, 110.5, 62.3, 55.5, 53.6, 30.7. MS: m/z 313 (M⁺, 16), base peak.

**References and Notes**


