Dioxopyrrolines. XLIII.[1] Diels–Alder Reaction of 4,5-Diethoxycarbonyl-1*H*-pyrrole-2,3-dione with Butadienes: Synthesis of Polyfunctionalized Hydroindoles

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A new dioxopyrroline, 4,5-diethoxycarbonyl-1*H*-pyrrole-2,3-dione (3), was proved to be a strong dienophile in the Diels–Alder reaction with various butadienes. This cycloaddition reaction proceeded in a regio- and stereo-selective manner to give the polyfunctionalized hydroindoles (4—8, 10) which may be potential synthetic intermediates of *Erythrina* alkaloids.

Keywords dioxopyrroline; 4,5-diethoxycarbonyl-1*H*-pyrrole-2,3-dione; dienophile; butadiene; 2,3-bis(trimethylsilyloxy)-butadiene; 1-methoxybutadiene; 1-sulfenylbutadiene; 2-trimethylsilyloxy-butadiene; Diels–Alder reaction; hydroindole

The 1*H*-pyrrole-2,3-dione structure (dioxopyrroline) has been demonstrated to be a versatile synthon for a variety of heterocycles.[2] Diels–Alder reaction of a dioxopyrroline with butadiene provided the key step in our total syntheses of *Amaryllidaceae*[3] and *Erythrina* alkaloids.[4] In connection with our continuing studies of dioxopyrroline cycloaddition reactions we have prepared a new dioxopyrroline, 4,5-diethoxycarbonyldioxopyrroline (3), and investigated the Diels–Alder reaction of 3 with butadienes.

The dioxopyrroline (3) was readily synthesized from sodium diethyl oxalacetate (1) in two steps. The salt was treated with ammonium acetate in ethanol to give the enamine (2)[5] in 62% yield. Condensation of 2 with oxalyl chloride in dry ether gave 3 as yellow prisms in 86% yield. In the ultraviolet (UV) spectrum, this showed a characteristic absorption of a dioxopyrroline ring at λ_{max} 384 nm. The yellow crystals readily deteriorated on exposure to moisture (on standing in an open vessel) turning white upon absorption of water. The high electrophilicity of the dioxopyrroline ring[6] is enhanced by the substitution of two electron-attracting COOEt groups. The reactivity of this dioxopyrroline as a dienophile is also expected to be enhanced.

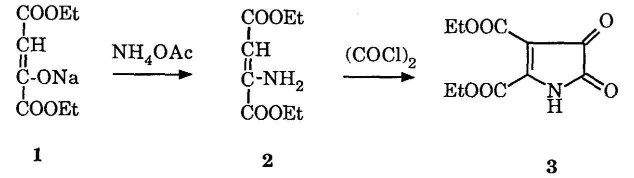

Chart 1

In order to examine its reactivity we carried out Diels–Alder reaction of 3 with various butadienes. Heating of 3 with butadiene in toluene at 120 °C for 2 h gave the adduct (4) in 83% yield. The Diels–Alder reaction with 2,3-bis(trimethylsilyloxy)butadiene took place at 120 °C to give the adduct (5), though in low yield (24%).

The cycloaddition of 3 with 1-substituted butadienes smoothly occurred in a regio- and stereo-selective manner at low temperatures. 1-Methoxybutadiene, on standing at room temperature, gave the adduct (6) in excellent yield (98%), and 1-sulfenylbutadiene, on heating at 85 °C, gave the adduct (7) in good yield (89%).

The Diels–Alder reaction with 2-substituted butadienes also proceeded in a regioselective manner. Thus, isoprene, on heating at 120 °C, gave the adduct (8) in 50% yield and 2-trimethylsilyloxybutadiene, at 160 °C, gave the triketone (10) (54%), in which the expected adduct (9) was desilylated

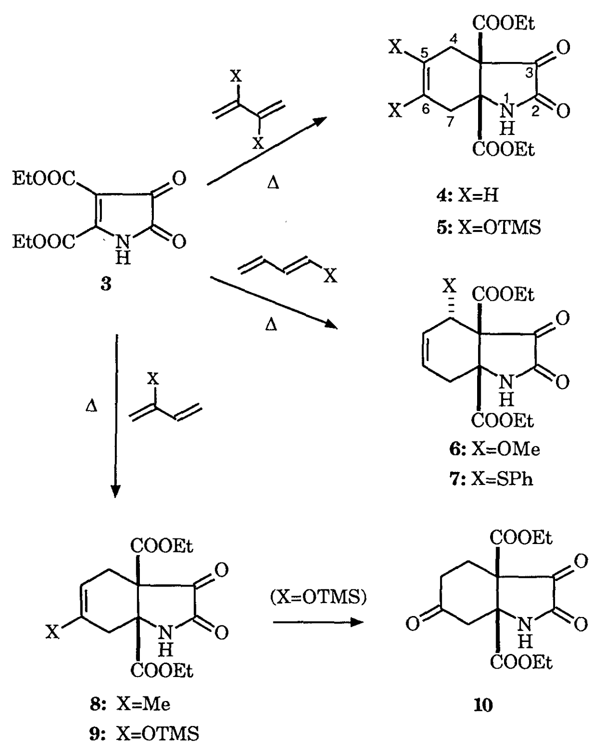

Chart 2

TABLE I. Diels–Alder Reaction of the Dioxopyrroline (3) with Butadienes

Diene[a)]	Solvent	Conditions Temp. (°C)	Time (min)	Product	Yield (%)
A	Toluene	120	240	**4**	82
B	Toluene	120	180	**5**	24
C	Toluene	20	10	**6**	98
D	Benzene	85	60	**7**	89
E	Toluene	120	120	**8**	50
F	Toluene	160	60	**10**	54
G	Toluene	20	5	**11**	82

a) A, butadiene; B, 2,3-bis(trimethylsilyloxy)butadiene; C, 1-methoxy-butadiene; D, 1-sulfenylbutadiene; E, isoprene; F, 2-trimethylsilyloxybutadiene; G, 1-methoxy-3-trimethylsilyloxybutadiene.

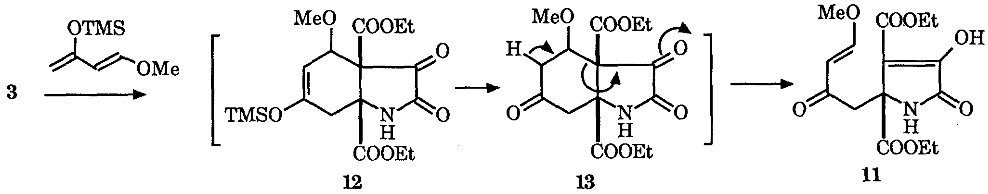

Chart 3

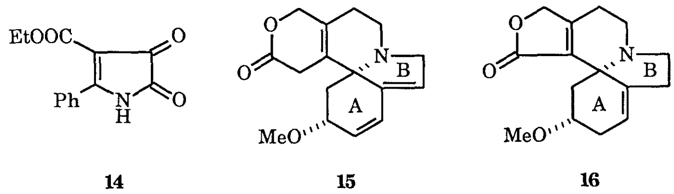

Chart 4

(probably during chromatography).

The reaction of **3** with 1-methoxy-3-trimethylsilyloxybutadiene, an activated butadiene, as expected, occurred rapidly at room temperature. However, the product isolated from the reaction mixture was not the expected hydroindole (**12**) but the pyrrole derivative (**11**). Evidence of the intermediary formation of **12** was obtained when the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of an intact reaction mixture was measured; in addition to the signals due to **11**, it exhibited as a pair of doublets at δ 4.62 and 5.20 attributable to the C_4-methine and C_5-olefinic protons of **12**, respectively. Therefore, formation of **11** can be rationalized in terms of ring cleavage due to the reverse Michael reaction of the intermediary 1,5-diketone (**13**), not the Michael addition of the diene to **3**. This fact, in turn, confirmed the regiochemistry of the Diels–Alder reaction. The results are collected in Table I.

The regio- and stereo-chemistry of the above products were deduced on the basis of the facts described above, and by analogy with the previous results on the Diels–Alder reaction of analogous dioxopyrrolines[4)] as well as generally accepted rules.[7)] The spectral data (see Experimental) of the adducts were consistent with the assigned structures.

The above evidence confirmed that the dioxopyrroline (**3**) has a high dienophilic activity and this reactivity is stronger than that of the 4-ethoxycarbonyl-5-phenyl analog (**14**).[4b)] This is due to the introduction of an additional COOEt group in place of a phenyl group, which enhances the dienophilic activity, as expected. The adducts, polyfunctionalized hydroindoles, possess the skeleton corresponding to the ring A/B of *Erythrina* alkaloids and are thus potential synthetic intermediates particularly for non-aromatic *Erythrina* alkaloids such as β-erythroidine (**15**) and cocculoridine (**16**).

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage melting point apparatus, and are uncorrected. Infrared (IR) spectra were taken in Nujol mulls with a Hitachi 260-10 spectrophotometer and are given in cm^{-1}. UV spectra were measured in dioxane with a Hitachi 200-10 spectrophotometer and are given in λ_{max} nm (ε). ^{1}H-NMR (100 MHz) and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) (25.0 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JEOL FX-100 spectrometer. Chemical shifts are given as δ values (ppm). Thin layer chromatography (TLC) was performed on precoated Silica gel 60 F_{254} plates (Merck). For column chromatography, silica gel (Wako gel C-200) was used.

Diethyl 2-Aminobutenedioate (2) A solution of sodium diethyl oxalacetate (**1**, 158 g, 0.75 mol) and ammonium acetate (116 g, 1.5 mol) in absolute ethanol (700 ml) and acetic acid (43 ml) was refluxed with stirring for 20 min. The mixture was concentrated under reduced pressure and the residue was basified with NH_4OH, then extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and passed through a short column of SiO_2. Concentration of the eluate gave a residue, which was distilled to give **2** as a pale yellow oil, bp 103 °C/2 mmHg (lit.[5)] bp 135—137 °C/16 mmHg), 87 g (62%). IR (neat): 3360, 3340, 1720, 1670, 1610. ^{1}H-NMR: 1.30 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 1.36 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 1.60 (2H, s, NH_2), 4.12 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.32 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 5.51 (1H, s, olefinic H).

2,3-Diethoxycarbonyl-2-pyrroline-4,5-dione (3) A solution of the enamino diester **2** (3.74 g, 0.02 mol) in dry ether (10 ml) was added dropwise to a solution of oxalyl chloride (2.6 ml, 0.03 mol) in dry ether (20 ml) at 40 °C. The mixture was stirred for 20 min, then dioxane (30 ml) was added and the whole was heated at 90 °C for 25 min. Concentration of the mixture at atmospheric pressure gave a crystalline residue, which was crystallized from heptane–Et_2O to give **3** (4.1 g, 86%) as yellow prisms, mp 116—118 °C. IR: 3325, 1800, 1750, 1730, 1695. UV λ_{max} (ε): 384 (2000). ^{1}H-NMR: 1.43 (6H, m, $COOCH_2\underline{CH}_3 \times 2$), 4.38 (4H, m, $COO\underline{CH}_2CH_3 \times 2$), 7.14 (1H, m, NH).

Diels–Alder Reaction of 3 with Butadienes (General Procedure) A solution of **3** and a diene [A, butadiene; B, 2,3-bis(trimethylsilyloxy)-butadiene; C, 1-methoxybutadiene; D, 1-sulfenylbutadiene; E, isoprene; F, 2-trimethylsilyloxybutadiene; G, 1-methoxy-3-trimethylsilyloxybutadiene] in dry toluene or benzene was heated at an appropriate temperature in a sealed tube with stirring. The reaction mixture was concentrated to dryness *in vacuo* and the residue in CH_2Cl_2 was passed through a short column of SiO_2 to give the product.

(3a*R,7a*R**)-3a,7a-Diethoxycarbonyl-6-methyl-2,3-dioxo-2,3,3a,4,7,7a-hexahydroindole (4)** The reaction of **3** (960 mg) and the diene A (5 ml) was carried out in toluene (10 ml) at 120 °C for 4 h to give **4**. Yield, 967 mg (82%), mp 138—140 °C, colorless prisms from hexane–Et_2O. IR: 3175, 3075, 1780, 1740. UV λ_{max} (ε): 254 (3100). ^{1}H-NMR: 1.18 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 1.31 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.50—2.67 (3H, m, 4- or 7-H), 2.91—3.13 (1H, m, 4- or 7-H), 4.17 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.20 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 5.75—6.06 (2H, m, 5- and 6-H), 9.08 (1H, br s, NH). MS *m/z*: M^+ Calcd for $C_{14}H_{17}NO_6$ 295.1056. Found: 295.1094.

(3a*R,7a*R**)-3a,7a-Diethoxycarbonyl-2,3-dioxo-5,6-bis(trimethylsilyloxy)-2,3,3a,4,7,7a-hexahydroindole (5)** The reaction of **3** (1 g) and the diene B (4.6 g) was carried out in toluene (10 ml) at 120 °C for 3 h to give **5**. Yield, 494 mg (24%), mp 112—116 °C, colorless prisms from Et_2O–hexane. IR: 1785, 1740, 1735, 1690. ^{1}H-NMR: 0.00 (9H, s, $OSi(CH_3)_3$), 0.08 (9H, s, $OSi(CH_3)_3$), 1.06 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 1.20 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.17 (1H, J=15 Hz, 4- or 7-H), 2.74 (2H, br s, 4- or 7-H), 2.81 (1H, d, J=15 Hz, 4- or 7-H), 4.06 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.08 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 8.37 (1H, br s, NH). ^{13}C-NMR: 0.0 (q, $2 \times OSi(CH_3)_3$), 13.1 (q, $COOCH_2\underline{C}H_3$), 13.3 (q, $COOCH_2\underline{C}H_3$), 31.9 (t, 4-C), 40.1 (t, 7-C), 60.2 (s, 3a-C), 62.0 (t, $COO\underline{C}H_2CH_3$), 62.2 (t, $COO\underline{C}H_2CH_3$), 65.1 (s, 1a-C), 125.3 (s, 5- or 6-C), 129.6 (s, 5- or 6-C), 158.2 (s, 2-C), 164.8 (s, $\underline{C}OOCH_2CH_3$), 169.7 (s, $\underline{C}OOCH_2CH_3$), 193.8 (s, 3-C). MS *m/z*: M^+ Calcd for $C_{20}H_{33}NO_8Si_2$ 471.1742. Found: 471.1686.

(3a*R,4*S**,7a*R**)-3a,7a-Diethoxycarbonyl-4-methoxy-2,3-dioxo-2,3,3a,4,7,7a-hexahydroindole (6)** The reaction of **3** (100 mg) and the diene C (174 mg) was carried out in toluene at 20 °C for 10 min to give **6**. Yield, 132 mg (98%), mp 122—125 °C, colorless prisms from hexane–Et_2O. IR: 3170, 3090, 1740, 1725. ^{1}H-NMR: 1.24 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 1.27 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 2.78 (2H, m, 7-H), 3.35 (3H, s, OCH_3), 4.16 (2H, q, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 4.20 (2H, q, $J=7$ Hz, $COOCH_2CH_3$), 4.51 (1H, d, $J=2.4$ Hz, 4-H), 6.09 (2H, m, 5- and 6-H). MS *m/z*: M^+ Calcd for $C_{15}H_{19}NO_7$ 325.1162. Found 325.1185.

(3a*R,4*S**,7a*R**)-3a,7a-Diethoxycarbonyl-2,3-dioxo-4-sulfenyl-2,3,3a,4,7,7a-hexahydroindole (7)** The reaction of **3** (100 mg) and the diene D (136 mg) was carried out in benzene (2 ml) at 85 °C for 1 h to give **7**. Yield, 139 mg (89%), mp 151—152 °C colorless prisms from Et_2O–hexane. IR: 3140, 1760, 1730. ^{1}H-NMR: 1.21 (3H, t, $J=7$ Hz, $COOCH_2CH_3$), 1.25 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 2.60 (1H, dd, $J=18$, 5 Hz, 7-H), 3.00 (1H, d with small splittings, $J=18$ Hz, 7-H), 4.02—4.30 (4H, m, $COO\underline{CH}_2CH_3$), 4.35 (1H, d, $J=5$ Hz, 4-H), 6.22—5.72 (2H, m, 5- and 6-H), 7.47—7.25 (5H, m, Ph-H), 8.99 (1H, br s, NH). MS *m/z*: M^+ Calcd for $C_{20}H_{21}NO_6S$ 403.1087. Found: 403.1076.

(3a*R,7a*R**)-3a,7a-Diethoxycarbonyl-6-methyl-2,3-dioxo-2,3,3a,4,7,7a-hexahydroindole (8)** The reaction of **3** (1 g) and isoprene (2 g) was carried out in toluene (4 ml) at 120 °C for 2 h to give **8**. Yield, 643 mg (50%), mp 138—140 °C, colorless prisms from MeOH–Et_2O–hexane. IR: 1780, 1730. UV λ_{max} (ε): 253 (3400). ^{1}H-NMR: 1.17 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 1.30 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 1.69 (3H, s, C–CH_3), 2.28—3.03 (4H, m, 4- and 7-H), 4.16 (2H, q, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 4.19 (2H, t, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 5.62—5.70 (1H, m, 5-H), 8.85—9.42 (1H, br s, NH). ^{13}C-NMR: 13.7 (q, $COOCH_2\underline{C}H_3$), 13.9 (q, $COOCH_2\underline{C}H_3$), 23.1 (q, CH_3), 27.8 (t, 4-C), 40.1 (t, 7-C), 59.9 (s, 3a-C), 62.4 (t, $COO\underline{C}H_2CH_3$), 62.7 (t, $COO\underline{C}H_2CH_3$), 65.2 (s, 7a-C), 121.2 (d, 5-C), 134.2 (s, 6-C), 159.0 (s, 2-C), 166.2 (s, $\underline{C}OOCH_2CH_3$), 170.7 (s, $\underline{C}OOCH_2CH_3$), 195.9 (s, 3-C). MS *m/z*: M^+ Calcd for $C_{15}H_{19}NO_6$ 309.1211. Found: 309.1195.

(3a*R,7a*R**)-3a,7a-Diethoxycarbonyl-2,3,6-trioxo-2,3,3a,4,7,7a-hexahydroindole (10)** The reaction of **3** (600 mg) and the diene F (1.9 g) was carried out in toluene (6 ml) at 160 °C for 1 h to give **10**. Yield, 421 mg (54%), mp 112—115 °C, colorless prisms from Et_2O–hexane. IR: 3200, 1785, 1755, 1730, 1710. UV λ_{max} (ε): 256 (3500). ^{1}H-NMR: 1.21 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 1.28 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 2.32—3.00 (6H, m, 4-, 5- and 7-H), 4.18 (2H, q, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 4.22 (2H, q, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 9.12 (1H, br s, NH). ^{13}C-NMR 13.7 (q, $COOCH_2\underline{C}H_3$), 13.8 (q, $COOCH_2\underline{C}H_3$), 25.0 (t, 4-C), 34.5 (t, 5- or 7-C), 48.2 (t, 5- or 7-C), 57.7 (s, 3a-C), 63.2 (s, 7a-C), 63.5 (t, $COO\underline{C}H_2CH_3$), 63.6 (t, $COO\underline{C}H_2CH_3$), 158.6 (s, 2-C), 165.8 (s, $\underline{C}OOCH_2CH_3$), 169.4 (s, $\underline{C}OOCH_2CH_3$), 194.0 (s, 3-C), 205.0 (s, 6-C).

The Reaction of 3 and 1-Methoxy-3-trimethylsilyloxybutadiene a) The reaction of **3** (100 mg) and the diene F (357 mg) was carried out in toluene (2 ml) at 20 °C for 5 min to give 4,5-diethoxycarbonyl-3-hydroxy-5-(4-methoxybut-3-en-2-one)-1,5-dihydro-2*H*-pyrrole-2-one (**11**). Yield, 126 mg (82%), mp 136—140 °C, colorless prisms from Et_2O–hexane. IR: 3325, 3160, 1730, 1710, 1680, 1655, 1620. UV λ_{max} (ε): 248 (17600). ^{1}H-NMR: 1.21 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 1.37 (3H, t, $J=7$ Hz, $COOCH_2\underline{CH}_3$), 2.49 (1H, d, $J=17$ Hz, 1-H), 3.76 (3H, s, OCH_3), 4.06 (1H, d, $J=17$ Hz, 1-H), 4.15 (2H, q, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 4.36 (2H, q, $J=7$ Hz, $COO\underline{CH}_2CH_3$), 5.63 (1H, d, $J=13$ Hz, 3-H), 7.67 (1H, d, $J=13$ Hz, 4-H), 7.67 (1H, br s, NH). ^{13}C-NMR: 13.4 (q, $COOCH_2\underline{C}H_3$), 14.2 (q, $COOCH_2\underline{C}H_3$), 45.3 (t, 1-C), 57.9 (q, OCH_3), 61.7 (t, $COO\underline{C}H_2CH_3$), 62.4 (t, $COO\underline{C}H_2CH_3$), 62.4 (s, 5-C), 104.9 (d, 3-C), 112.0 (s, 4-C), 156.9 (s, 3-C), 164.0 (d, 4-C), 164.4 (s, 2-C), 164.8 (s, $\underline{C}OOCH_2CH_3$), 168.6 (s, $\underline{C}OOCH_2CH_3$), 196.7 (s, 2-C). MS *m/z*: M^+ Calcd for $C_{15}H_{19}NO_8$ 341.1109. Found: 341.1103.

b) A solution of **3** (52 mg) and the diene G (40 mg) in $CDCl_3$ (1 ml) was allowed to stand at room temperature. The ^{1}H-NMR spectrum of this reaction mixture after 5 min exhibited the signals of **12**. ^{1}H-NMR: 0.25 (9H, s, $OSi(CH_3)_3$), 1.21 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.24 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.78 (2H, s, 7-H), 3.19 (3H, s, OCH_3), 4.16 (4H, m, $CH_2C\underline{H}_3$), 4.62 (1H, d, $J=6$ Hz, 4-H), 5.20 (1H, d, $J=6$ Hz, 5-H), 8.45 (1H, br s, NH).

References and Notes

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