α,β-Unsaturated Carboxylic Acid Derivatives. XVI. Synthesis and Configuration of Diels-Alder Adducts from Ethyl 3-Nitro-2-alkenoate and 1,3-Butadiene[1]

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The Diels-Alder reaction of individual (*E*)- and (*Z*)-isomers of ethyl 3-nitroacrylate and 3-nitrocrotonate with 1,3-butadiene, 1-acetoxy- or 1,4-diacetoxy-1,3-butadiene was conducted to give ethyl 6-nitro-3-cyclohexene-, 5-acetoxy-, and 2,5-diacetoxy-6-nitro-3-cyclohexene-carboxylates, respectively. The stereochemistry of the cycloaddition products has been elucidated by analysis of the NMR spectrum.

In previous papers, the Diels-Alder reaction of cyclopentadiene with ethyl (*E*)- and (*Z*)-3-nitrocrotonate (**6**) or ethyl (*Z*)-3-nitrocinnamate and subsequent reduction of the resulting (2+2)- and (2+4)-nitro adducts with aluminum–amalgam (Al–Hg) were carried out to give unique tricyclic isoxazolidione derivatives.[1,2]

In order to synthesize desirable starting materials for antibiotics oryzoxymycin[3] and related compounds[4,5] having a 6-amino-5-hydroxy-1,3-cyclohexadiene-1-carboxylate structure, here, the cycloaddition reaction of ethyl (*E*)-3-nitroacrylate (**1**) or **6** has been extended to 1,3-butadiene, 1-acetoxy- and 1,4-diacetoxy-1,3-butadienes. The conformational determination of all the new (2+4)-nitro adducts has been established on the basis of the spectral data.

Results and Discussion

*Reaction of **1** with 1,3-Butadiene.* According to the method of Shechter[6] and Shin,[7,8] compound **1** was prepared stereoselectively from the reaction of ethyl 2-chloro-3-nitropropanoate with sodium acetate. Thermal and photochemical isomerization of **1** to its (*Z*)-isomer failed. However, the structure of **1** was determined to be the (*E*)-isomer from the coupling constant between C-1 and C-6 protons and the spectral properties of the cycloaddition products.

Heating a solution of (***E***)-**1** and 1,3-butadiene in chloroform in an autoclave at 80—100 °C under 2—3 atmospheres for *ca.* 40 h gave a cycloaddition product of a colorless oil (**2**) in *ca.* 80% yield. The reaction of **1** with 1-acetoxy-1,3-butadiene in benzene at room temperature for 72 h afforded an analogous nitro adduct (**3**) as colorless crystals in a 57.4% yield. Similarly, the reaction of **1** with 1,4-diacetoxy-1,3-butadiene[9] under reflux for 5.5 h gave only the nitro adduct (**5**) quantitatively as colorless crystals. The reaction conditions and yields for **2** and **3** are listed in Tables 1 and 2.

From the NMR spectral and TLC analyses, it was found that each reaction proceeded stereospecifically to give a homogeneous product. The structural assignment of **2**, **3**, and **5** was based on their NMR spectral data as well as the satisfactory elemental analysis. The chemical shifts and the coupling constants are given in Table 4. The structure of **3**, being either (A) or (B) as illustrated in Fig. 1, was confirmed chemically to be (A) as shown in Scheme 1. The reduction

Table 1. Cycloaddition of **1** with 1,3-butadiene

Reaction condition[a]				
Temp (°C)	Pressure (atm)	Time (h)	Molar ratio diene/**1**	Yield of **2** (%)
80	2—3	40	1.5	80.8
r. t[b]	1	100[c]	1.5	0
100	2—3	37	1.5	80.1
80	2—3	40	1.2	59.7
150	2—3	35	1.5	61.2
120	12—15	35	1.5	63.4

a) In chloroform. b) Room temperature. c) With stirring.

Table 2. Cycloaddition of **1** with 1-acetoxy-1,3-butadiene

Reaction conditions					
Temp (°C)	Pressure (atm)	Time (h)	Solvent	Molar ratio diene/**1**	Yield of **3** (%)
r. t[a]	1	72[b]	benzene	1.2	57.4
90—100	2—3	7	chloroform	1.2	47.3
reflux	1	6	toluene	1.2	21.2

a) Room temperature. b) With stirring.

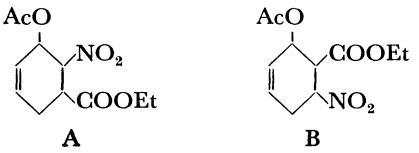
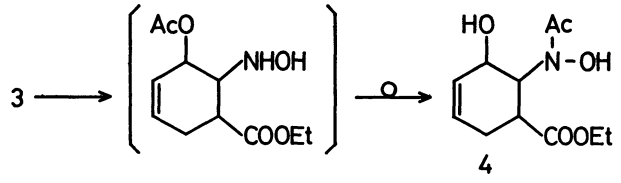


Fig. 1.



Scheme 1.

of **3** with Al–Hg gave the corresponding hydroxyamino derivative, in which *O*-acetyl 1,4-shift to nitrogen occurred to give ethyl 6-*N*-acetylhydroxyamino-5-hydroxy-3-cyclohexene-1-carboxylate (**4**). The migration product gave satisfactory elemental analysis and turned deep violet with ferric chloride in methanol, indicating the presence of a hydroxamic acid structure.

Furthermore, the conformational assignment of **2**, **3**, and **5** was studied. In the spectrum of **2**, the signals at δ 3.24 ($J_{1,6}=J_{1,2a}=11.0$ Hz, $J_{1,2e}=6.0$ Hz) and 4.88 ($J_{5a,6}=10.0$ Hz, $J_{5e,6}=6.0$ Hz) appearing as two sextets are attributable to the two protons at C-1 and C-6 positions, respectively. The similar signals at δ 3.43 and 4.90 in the spectrum of **3** exhibit a sextet ($J_{1,6}=J_{1,2a}=11.8$ Hz) and a quartet ($J_{5e,6}=3.9$ Hz), respectively, which have been assigned as axial hydrogens. From the relatively large J value (11.8 Hz), the dihedral angle between C-1 and C-6 or C-2a protons has been deduced to be near to 180°. The orientation of C-5 (δ 5.76, $J_{5e,6}=7.0$ Hz) and C-6 positions of **3** have been established by a spin-spin decoupling method, since the irradiation of C-6 proton collapsed C-5 proton at δ 5.76 to a doublet ($J_{4,5}=4.0$ Hz). The large J value of C-2 ($J_{2a,2e}=18.0$ Hz) is in agreement with the quasi-axial and quasi-equatorial protons at allyl positions on shikimic acid ($J_{2a,2e}=18.5$ Hz).[10] The signals of **5** at δ 3.49 and 5.04 and the coupling constant ($J_{1,6}=12.0$ Hz) between C-1 and C-6 protons are remarkably identical with those of **3**, but the J value between C-1 and C-2 protons exhibits 9.2 Hz as a broad doublet. Moreover, the chemical shift and coupling constant of the C-5 proton (δ 5.86, $J_{5e,6}=6.0$ Hz) of **5** was also remarkably similar to that of C-5 proton of **3**. Accordingly, the orientation of the C-2 proton has been assigned as quasi-axial and, therefore, that of the C-2 acetoxyl group as quasi-equatorial. The above results are further confirmed by the irradiation of the signal at δ 5.64 due to the C-2 proton collapsing to a quartet ($J_{1,2e}=9.2$ Hz) of methine proton to a doublet ($J_{1,6}=12.0$ Hz).

From the above facts, the structures of the three (2+4)-nitro adducts have been unambiguously assigned to be ethyl *t*-6-nitro-3-cyclohexene-*r*-1-carboxylate (**2**), ethyl *t*-5-acetoxy-*t*-6-nitro- (**3**) and *t*-2, *t*-5-diacetoxy-*t*-6-nitro-3-cyclohexene-*r*-1-carboxylates (**5**), respectively, all of which have half-chair conformations. The physical constants and IR spectral data of **2**, **3**, and **5** are summarized in Table 3.

*Reaction of **6** with 1,3-Butadienes.* The reaction of (***E***)-**6** with 1,3-butadiene in chloroform in a sealed tube at 100 °C for 35 h gave only a kind of syrup (**7**) in 66.6% yield. Similarly, the reaction of (***E***)-**6** with 1-acetoxy-1,3-butadiene for 25 h gave a syrup, containing two diastereomers (**8** and **9**) in poor yield. Similarly, the reaction of (***Z***)-**6**[8] with 1,3-butadiene gave a syrup (**10**) in 20.0% yield together with **7** in 22.9% yield, whereas the reaction of (***Z***)-**6** with 1-acetoxy-1,3-butadiene gave crystals (**11**) in poor yield along with a mixture of **8** and **9**. This indicates that (***Z***)-**6** is partially isomerized by heating[8] to (***E***)-**6**, which undergoes the cycloaddition to give **8** and **9**.

The structures and conformations of **7**—**10** and **11** have also been elucidated from their spectroscopic data and elemental analyses (see Tables 3 and 4).

The NMR spectra of **7** and **10** showed the C-1 proton signals at δ 3.49 ($J_{1,2a}=10.0$ Hz, $J_{1,2e}=7.0$ Hz) and 3.40 ($J_{1,2a}=5.5$ Hz, $J_{1,2e}=2.5$ Hz) as a quartet. Furthermore, from the comparison of the NMR spectral data of **7** and **10** with that of **2** and **3**, the conformations of **7** and **10** were inferred to be ethyl *c*-6-methyl-*t*-6-nitro- and *t*-6-methyl-*c*-6-nitro-3-cyclohexene-*r*-1-carboxylates. Although the mixture of **8** and **9** could not be separated, both signals at δ 3.57 ($J_{1,2a}=11.5$ Hz,) $J_{1,2e}=6.3$ Hz) and 3.26 ($J_{1,2a}=11.3$ Hz, $J_{1,2e}=6.3$ Hz) as a quartet have been clearly assigned to be an axial protons of C-1 position. However, the coupling constant ($J_{4,5}=10.0$ Hz) of **8** was remarkably different from that of **9** ($J_{4,5}=4.8$ Hz), suggesting that the orientation of the 3-acetoxyl group of **8** was quasi-axial whereas that of **9** was quasi-equatorial. The different NMR spectral pattern of **11** ($J_{1,2e}=6.3$ Hz, $J_{1,2a}=8.8$ Hz) contrasted to that of **8** and **9** and of the

Table 3. Physical data and IR spectra of ethyl 6-nitro-3-cyclohexene-1-carboxylates

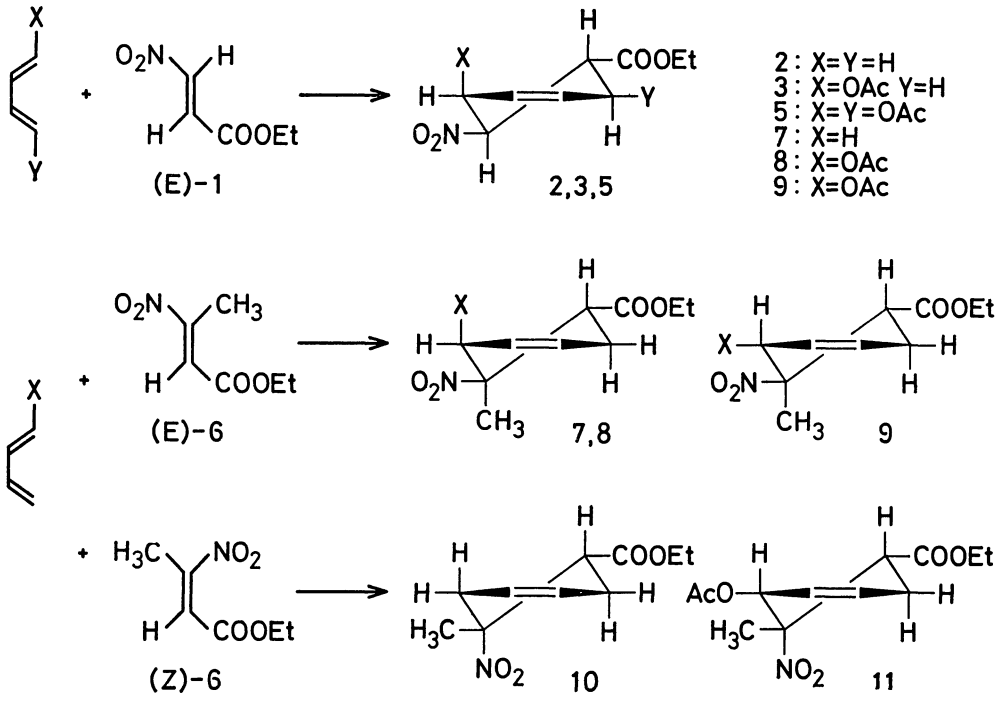
Compound No.	Yield (%)	Bp °C/mmHg (Mp °C)	Formula	Found, %			Calcd, %			IR spectrum, cm^{-1} in KBr		
				C	H	N	C	H	N	COOEt	C=C	NO_2
2	80.8	86—88/0.5	$C_9H_{13}NO_4$	54.77	6.72	6.92	54.26	6.58	7.03	1740,	1660,	1555, 1380
3	57.4	(75—76)	$C_{11}H_{15}NO_6$	51.65	5.92	5.44	51.36	5.88	5.45	1755, 1735[a]	1660,	1565, 1380
5	91.3	(119—120)	$C_{13}H_{17}NO_8$	49.76	5.50	4.47	49.52	5.44	4.44	1745, 1740, 1735[b]	1650,	1560, 1380
7	66.6 (22.9)[c]	85—88/0.55	$C_{10}H_{15}NO_4$	55.94	7.23	6.86	56.32	7.09	6.57	1740,	1660,	1550, 1390
8	10.0	125—129/0.5[e]	$C_{12}H_{17}NO_6$	53.01	6.28	5.30	53.13	6.32	5.16	1760,	1660,	1550, 1370
9	6.2 (8.3)[d]											
10	20.0	93—95/0.7	$C_{10}H_{15}NO_4$	56.03	7.01	6.80	56.32	7.09	6.57	1740,	1660,	1550, 1390
11	6.2	(85—86)	$C_{12}H_{17}NO_6$	53.77	6.51	5.23	53.13	6.32	5.16	1760, 1740[a]	1660,	1550, 1380

a) Band of 5-acetoxyl group. b) Bands of 2,5-diacetoxyl groups. c) By-products from (***Z***)-**6** and 1,3-butadiene. d) By-products from (***Z***)-**6** and 1-acetoxy-1,3-butadiene. e) Boiling point of a mixture of **8** and **9**.

Table 4. Chemical shifts (δ) and coupling constants (Hz) of the Diels-Alder adducts

Compound No.	H^1	H^{2a}	H^{2e}	H^3	H^4	H^{5a}	H^{5e}	H^6	6-CH_3	$OCOCH_3$
2	3.24(dt) $J_{1,2a}=11.0$ $J_{1,6}=11.0$	4.2—6.0(m) $J_{1,2e}=6.0$		5.70(m)		4.2—6.0(m)		4.88(dt) $J_{5a,6}=10.0$ $J_{5e,6}=6.0$	—	—
3	3.43(dt) $J_{1,2a}=11.8$ $J_{1,6}=11.8$	2.24(dd) $J_{2a,2e}=18.0$ $J_{1,2a}=11.8$	2.76(bd)	5.94(m) $J_{2e,3}=3.0$		—	5.76(dd) $J_{4,5e}=7.0$ $J_{5e,6}=3.9$	4.90(dd) $J_{5e,6}=3.9$ $J_{1,6}=11.8$	—	2.00(s)
5	3.49(dd) $J_{1,2a}=9.2$ $J_{1,6}=12.0$	5.64(d) $J_{1,2a}=9.2$	—	6.13(m)		—	5.86(m) $J_{4,5e}=6.0$	5.04(dd) $J_{5e,6}=4.2$ $J_{1,6}=12.0$	—	2.04(s) 2.14(s)
7	3.47(dd) $J_{1,2a}=10.0$ $J_{1,2e}=7.0$	2.22(d) $J_{2a,2e}=19.5$	2.61(m) $J_{1,2e}=7.0$	5.68(m)		2.46(d) $J_{5a,5e}=14.8$	2.80(m)	—	1.69(s)	—
8	3.57(dd) $J_{1,2a}=11.5$ $J_{1,2e}=6.3$	2.25(d) $J_{2a,2e}=18.8$	2.76(m) $J_{1,2e}=6.3$	5.98(m)		—	5.52(d) $J_{4,5e}=10.0$	—	1.84(s)	1.95(s)
9	3.26(dd) $J_{1,2a}=11.3$ $J_{1,2e}=6.3$	2.25(d) $J_{2a,2e}=18.8$	2.76(m) $J_{1,2e}=6.3$	5.85(m)		5.35(d) $J_{4,5a}=4.8$	—	—	1.68(s)	2.05(s)
10	3.40(dd) $J_{1,2a}=5.5$ $J_{1,2e}=2.5$	2.0—3.4(m) $J_{1,2e}=2.5$		5.67(m)		2.0—3.4(m)		—	1.65(s)	—
11	3.17(dd) $J_{1,2a}=8.1$ $J_{1,2e}=6.3$	2.44(bd) $J_{2a,2e}=18.0$	2.85(bd) $J_{1,2e}=6.3$	5.54(m)	6.00(m)	5.58(m)	—	—	1.65(s)	2.08(s)

Measured in $CDCl_3$.



Scheme 2.

cis-addition principle, indicates the structure of **11** to be ethyl *t*-5-acetoxy-*t*-6-methyl-*c*-6-nitro-3-cyclohexene-*r*-1-carboxylate.

Experimental

All boiling and melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 Spectrometer. The NMR spectra were measured with a JNM-PS-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd), using tetramethylsilane as an internal standard.

Preparation of ***1*** *and* ***6***. A solution of ethyl acrylate (70 g, 0.7 mol) and nitrosyl chloride (90 g, 1.36 mol) in $CHCl_3$ (500 ml) was allowed to stand at room temperature for 2 weeks. After the usual work up, 63.4 g (50.1%) of ethyl 2-chloro-3-nitropropionate, bp 64—68 °C/1 mmHg was ob-

tained. Subsequently, to a mixture of AcONa (100 g, 1.2 mol) in ether (300 ml) was added the prepared propionate (100 g, 0.55 mol) at room temperature. After stirring for 24 h, the excess AcONa and the precipitated NaCl were filtered off and the ether filtrate concentrated. The residue was distilled under reduced pressure to give **1** as a pale yellow oil, bp 95—98 °C/21 mmHg, yield 71.3 g (89.5%). IR (KBr): 1740 (ester), 1650 (C=C), 1555 and 1360 (NO_2) cm^{-1}. NMR ($CDCl_3$): δ 7.09 and 7.73 (2H, d, $J_{2,3}$=13.5 Hz, 2, 3-H).

The (*E*)- and (*Z*)-isomer of **6** were prepared by the method previously reported.[7,8]

Preparation of ***2***. *Typical Procedure*: To a solution of 1,3-butadiene (22.7 g, 0.42 mol) in dry $CHCl_3$ (50 ml) was added **1** (40 g, 10.2 mol) at room temperature. The resulting solution was heated in an autoclave at 80 °C under 2—3 atmospheres for 40 h. After removal of $CHCl_3$, the residue was distilled under reduced pressure to give **2** as a colorless oil.

Preparation of ***3***. *Typical Procedure*: To a solution of 1-acetoxy-1,3-butadiene (34 g, 0.34 mol) in dry benzene (200 ml) was added **1** (40 g, 0.28 mol), with stirring, at room temperature. After stirring for 72 h, the mixture was evaporated under reduced pressure to give a syrup. The syrup was dissolved in a solution of EtOH (50 ml) and petroleum ether (20 ml). After standing in the refrigerator for 1—2 days, the crystals separated out, were collected and washed once with petroleum ether. Recrystallization from EtOH gave **3** as colorless needles.

Reduction of ***3***. A solution of **3** (7 g, 27.2 mmol) in ether (20 ml) was added dropwise to a suspension of Al-Hg (made from Al (5 g) and $HgCl_2$ (5 g)) in ether (200 ml) with vigorous stirring at room temperature. After a few minutes, the ether began to reflux, the state being maintained by addition of a few drops of water at 20-min intervals. After addition was complete, stirring was continued for 6 h. The mixture was extracted several times with ether and the combined extracts evaporated to a crude syrup (4.8 g) which gradually solidified to give crystals. Recrystallization from $CHCl_3$ gave colorless needles to be ethyl *t*-6-*N*-acetyl-hydroxyamino-*t*-5-hydroxy-3-cyclohexene-*r*-1-carboxylate (**4**), yield 2.1 g (32%) mp 148—150 °C. IR (KBr): 3220 (OH), 1740 (ester), 1655 (C=C), 1630 (amide) cm^{-1}. NMR (DMSO-d_6): δ 1.97 (3H, s, CH_3), 2.31 (1H, dd, $J_{2a,2e}$=15.5 Hz, 2a-H), 2.49 (1H, dq, 2e-H), 3.13 (1H, dt, $J_{1,6}$=12.0 Hz, $J_{1,2e}$=5.5 Hz, $J_{1,2a}$=12.0 Hz, 1-H), 4.09 (1H, m, 5-H), 4.44 (1H, dd, $J_{5,6}$=8.0 Hz, $J_{1,6}$=12.0 Hz, 6-H), 5.73 (2H, d, 3, 4-H), 4.93 and 8.96 (2H, s and bs, OH).

Found: C, 54.38; H, 7.03; N, 5.87%. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76%.

Preparation of ***5***. A solution of 1,4-diacetoxy-1,3-butadiene (1.0 g, 5.9 mmol) and **1** (1.0 g, 6.9 mmol) in dry benzene (30 ml) was refluxed for 5.5 h and then evaporated under reduced pressure to give **5** as colorless prisms after recrystallization from EtOH.

Preparation of ***7***. A solution of (***E***)-**6** (5.0 g, 31 mmol) and 1,3-butadiene (2.0 g, 37 mmol) in dry $CHCl_3$ (30 ml) was heated in a sealed tube at 100 °C for 35 h. After removal of $CHCl_3$, the syrup was distilled under reduced pressure to give **7** as a colorless oil.

Preparation of ***8*** *and* ***9***. In the same manner, the reaction of (***E***)-**6** (4.0 g, 25 mmol) with 1-acetoxy-1,3-butadiene (3.4 g, 30 mmol) in $CHCl_3$ (30 ml) for 25 h gave a mixture of **8** and **9** as a colorless oil.

Preparation of ***10***. Similarly, the reaction of (***Z***)-**6** (5.0 g, 25 mmol) with 1-acetoxy-1,3-butadiene (2.0 g, 37 mmol in $CHCl_3$ (80 ml) for 35 h gave a mixture of **7** and **10** (6:5), which on distillation afforded **10** (20.0%).

Preparation of ***11***. A solution of (***Z***)-**6** (4.0 g, 25 mmol) and 1-acetoxy-1,3-butadiene (3.4 g, 30 mmol) in dry $CHCl_3$ (50 ml) was stirred overnight at room temperature. After removal of $CHCl_3$, the residual syrup was chromatographed on a silica gel column (benzene) to give two fractions. After removal of benzene under reduced pressure, the first fraction gave **11** as colorless crystals and the second one gave a mixture of **8** and **9** as a colorless oil.

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