A Simple and Stereoselective Synthesis of 7-Azabicyclo[2.2.1]-heptane-1,2,3,4-tetracarboxylates

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The photoinitiated reaction of 1,1'-bis(methoxycarbonyl)divinylamine with various maleates and fumarates afforded novel 7-azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylates. The spectral investigation of the products showed that the reaction proceeded stereoselectively, retaining the original configuration of the reagents.

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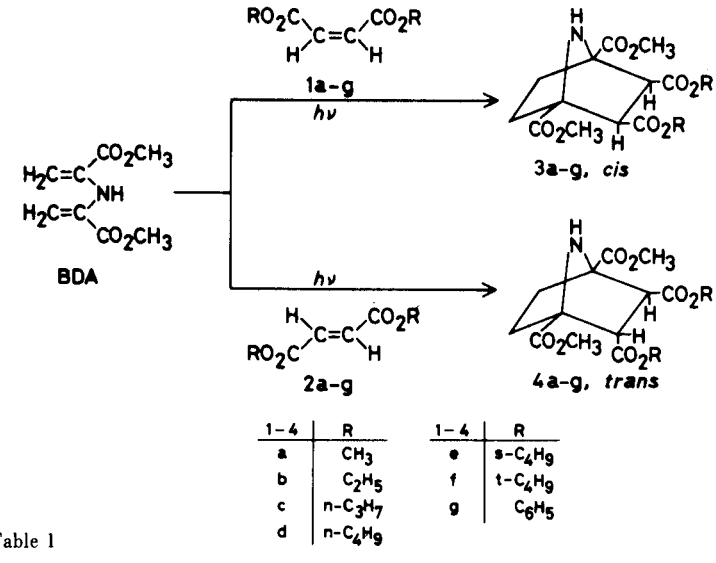
It was previously reported [1] that the photo-initiated electrocyclic reaction of 1,1'-bis(methoxycarbonyl)divinylamine (BDA), a cross-conjugated dienamine, with acetylene dicarboxylates afforded 7-azabicyclo[2.2.1]hept-2-ene-1,2,3,4-tetracarboxylates in a high yield.

In the present paper, we wish to describe similar reactions of BDA with various maleates and fumarates, which yielded the novel compounds, 7-azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylates **3a-g**, **4a-g**. The nmr studies of the products showed that the addition occurred stereoselectively, retaining the original configuration of the reagents (Scheme 1).

Scheme 1



1-4	R
a	CH_3
b	C_2H_5
c	n-C_3H_7
d	n-C_4H_9

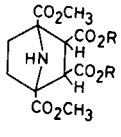
1-4	R
e	s-C_4H_9
f	t-C_4H_9
g	C_6H_5

Results and Discussion.

The structure of the electrocyclized products **3a** and **4a** obtained from BDA with dimethyl maleate **1a** and fumarate **2a**, respectively, were established as follows.

Table 1

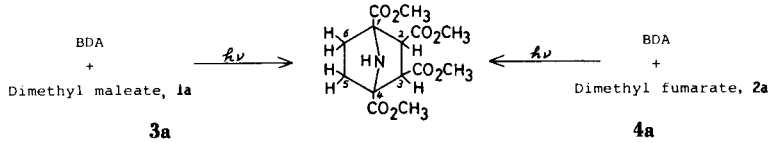
7-Azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylates *cis*-**3a-g** and *trans*-**4a-g**



Compound No.	R	Mp °C	Yield %	Recrystallization solvents	Formula	Analyses Calcd. % C	H	N	Found % C	H	N
3a	CH_3	185-186	84	Acetone	$C_{14}H_{19}NO_8$	51.06	5.77	4.25	51.02	5.79	4.24
3b	C_2H_5	93	65	Acetone	$C_{16}H_{23}NO_8$	53.78	6.44	3.92	53.80	6.54	3.95
3c	n-C_3H_7	108-109	35	Ethyl ether	$C_{18}H_{27}NO_8$	56.10	7.01	3.64	56.25	7.06	3.59
3d	n-C_4H_9	83	28	Ethyl ether-Hexane	$C_{20}H_{31}NO_8$	58.11	7.51	3.39	58.06	7.37	3.47
3e	s-C_4H_9	114-115	25	Ethyl ether-Hexane	$C_{20}H_{31}NO_8$	58.11	7.51	3.39	58.05	7.55	3.26
3f	t-C_4H_9	170	20	Acetone	$C_{20}H_{31}NO_8$	58.11	7.51	3.39	57.99	7.45	3.43
3g	C_6H_5	168	88	Methanol	$C_{24}H_{23}NO_8$	63.58	5.08	3.09	63.69	5.02	3.17
4a	CH_3	99	94	Acetone	$C_{14}H_{19}NO_8$	51.06	5.77	4.25	51.01	5.74	4.21
4b	C_2H_5	syrup	74	—	$C_{16}H_{23}NO_8$	53.78	6.44	3.92	53.72	6.39	3.90
4c	n-C_3H_7	syrup	73	—	$C_{18}H_{27}NO_8$	56.10	7.01	3.64	56.16	6.95	3.67
4d	n-C_4H_9	syrup	70	—	$C_{20}H_{31}NO_8$	58.11	7.51	3.39	58.21	7.54	3.35
4e	s-C_4H_9	syrup	68	—	$C_{20}H_{31}NO_8$	58.11	7.51	3.39	58.01	7.52	3.45
4f	t-C_4H_9	syrup	65	—	$C_{20}H_{31}NO_8$	58.11	7.51	3.39	58.22	7.47	3.40
4g	C_6H_5	116-117	86	Ethyl ether	$C_{24}H_{23}NO_8$	63.58	5.08	3.09	63.65	5.11	3.08

Table 2

Spectroscopic Properties of Compounds **3a** and **4a**



3a **4a**

	3a	**4a**
IR, cm^{-1} (potassium bromide):	3280 (NH), 1740-1710 (C=O)	3280 (NH), 1735-1710 (C=O)
100 MHz ^1H NMR, δ ppm (deuteriochloroform):	1.79-2.10 (4H, m, C-5 and C-6 ring protons), 3.54 (2H, s, C-2 and C-3 ring protons), 3.63 (s, C-2 and C-3 CO_2CH_3), 3.76 (s, C-1 and C-4 CO_2CH_3), } [a]	1.74-2.12 (4H, m, C-5 and C-6 ring protons), 3.22 (1H, br, NH, exchangeable, 3.54 (2H, br, C-2 and C-3 ring protons), 3.70 (s, C-2 or C-3 CO_2CH_3), 3.72 (s, C-2 or C-3 CO_2CH_3), 3.76 (s, C-1 or C-4 CO_2CH_3), 3.80 (s, C-1 or C-4 CO_2CH_3) } [b]
Mass, m/e:	329 (M^+)	329 (M^+)

[a] Since the NH proton overlapped with methyl protons in methyl ester, the signals at δ 3.63 and 3.76 integrate for 13 protons. On deuteration these signals integrate for 12 protons. [b] The signals at δ 3.70, 3.72, 3.76 and 3.80 integrate for 12 protons.

Both the elementary analyses of **3a** and **4a** (Table 1) and the molecular ion peak (m/e = 329) by mass spectral analyses indicated the products to be 1:1-adducts between BDA and the ethylenedicarboxylates **1a** and **2a**. Among the 100 MHz ^1H nmr spectral data (Table 2), signals in the ranges of 1.74-2.12 ppm and 3.54 ppm are consistent with the chemical shifts characteristic of 5,6- and 2,3- ring protons, respectively, for the reported 7-azabicyclo[2.2.1]heptane ring system [2]. In addition, the ir spectra show a NH stretching vibration at 3280 cm^{-1}, which corresponds to that characteristic of the 7-azabicyclo[2.2.1]heptane ring system [3]. These mean that both **3a** and **4a** are tetramethyl 7-azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylate. For methyl protons in the methyl ester in the 100 MHz ^1H nmr, two types of signals were observed in **3a**, whereas four types were observed in **4a** as shown in Table 2, which must suggest the configuration of 2,3-dicarboxylate to be *cis* for **3a** and *trans* for **4a**.

In order to verify the above configuration, 400 MHz ^1H nmr spectra of **3a** and **4a**, illustrated in Figure 1, were next investigated. The nmr spectrum of **3a** shows one singlet at 3.56 ppm assignable to the 2,3-ring protons. A singlet signal would result, since the hydrogens at C-2 and C-3 are chemically equivalent and also there are no long range coupling between the 2,3-ring protons and the 5,6-ring protons or the NH proton. This implies that the hydrogens at C-2 and C-3 must be in an *endo* position, indicating the configuration of 2,3-dicarboxylate of **3a** to be *cis* form.

In contrast to **3a**, the nmr spectrum of **4a** contains one doublet signal (J = 5 Hz) at 3.58 ppm and one doublet of doublet signal (J = 5 Hz, J′ = 2 Hz) at 3.52 ppm, which can be assigned to the 2-*endo*- and 3-*exo*-proton, respec-

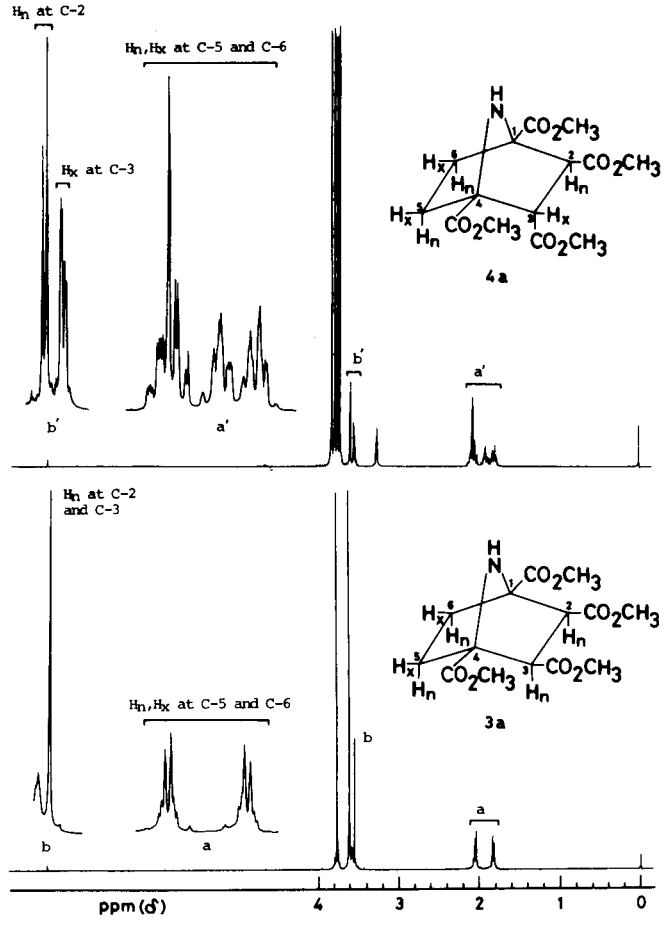
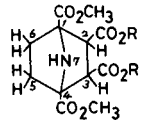


Figure 1. 400 MHz ^1H nmr spectra of 7-azabicyclo[2.2.1]-heptane-1,2,3,4-tetracarboxylate *cis*-**3a** and *trans*-**4a** in deuteriochloroform.

Table 3

100 MHz ^{1}H NMR [a] and IR [b] Spectral Data of 7-Azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylate *cis*-**3b-g** and *trans*-**4b-g**

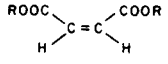


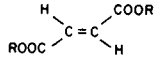
Compound No.	R	NMR, δ ppm H-2 and H-3	H-5 and H-6	H-7 [c]	Methyl protons in Methyl Esters at C-1 and C-4	Protons of R in Esters at C-2 and C-3	IR, cm^{-1} NH	C=O
3b	CH_2CH_3	3.53, s	1.78-2.12, m	3.63, br	3.78, s	1.22, t, 4.07, qa	3270	1735, 1710
3c	$CH_2CH_2CH_3$	3.54, s	1.79-2.11, m	3.15, br	3.77, s	0.92, t, 1.61, sx, 3.98, t	3290	1750-1730
3d	$CH_2(CH_2)_2CH_3$	3.53, s	1.78-2.10, m	[d]	3.76, s	0.92, t, 1.18-1.72, m, 3.98, t	3290	1745-1725
3e	$CH(CH_3)CH_2CH_3$	3.50, s	1.77-2.10, m	3.87, br	3.78, s	0.89, t, 1.18, du, 1.56, qi, 4.73, sx	3290	1755-1725
3f	$C(CH_3)_3$	3.40, s	1.72-2.05, m	3.66, br	3.76, s	1.41, s	3290	1755, 1730
3g	C_6H_5	3.96, s	1.94-2.24, m	[d]	3.80, s	6.88-7.38, m	3260	1755, 1730
4b	CH_2CH_3	3.49, br	1.74-2.12, m	3.11, br	3.74, s, 3.78, s	1.27, t, 4.11, qa	3270	1750-1730 [e]
4c	$CH_2CH_2CH_3$	3.54, br	1.78-2.16, m	3.28, br	3.78, s, 3.82, s	0.95, t, 1.66, sx, 4.05, t	3270	1750-1730 [e]
4d	$CH_2(CH_2)_2CH_3$	3.53, br	1.92-2.21, m	3.27, br	3.76, s, 3.80, s	0.96, t, 1.20-1.78 m, 4.09, t	3280	1750-1725 [e]
4e	$CH(CH_3)CH_2CH_3$	3.50, br	1.82-2.14, m	[d]	3.76, s, 3.79, s	0.90, t, 1.21, du, 1.58, qi, 4.85, sx	3270	1750-1720 [e]
4f	$C(CH_3)_3$	3.41, br	1.78-2.12, m	[d]	3.78, s, 3.81, s	1.44, s	3280	1755-1725 [e]
4g	C_6H_5	3.90, br	2.01-2.27, m	3.42, br	3.79, s, 3.83, s	7.03-7.43, m	3270	1755, 1725

[a] In deuteriochloroform. [b] In potassium bromide unless otherwise noted. [c] Exchangeable with deuterium oxide. [d] NH proton overlapped methyl protons in methyl esters. [e] Neat.

Table 4

Analytical Data of Ethenedicarboxylates **1c-g** and **2c-g**





	R	Formula	Analyses % Calcd./Found C	H
1c	*n*-C_3H_7	$C_{10}H_{16}O_4$	60.00	8.00
	Dipropyl maleate		59.97	7.97
1d	*n*-C_4H_9	$C_{12}H_{20}O_4$	63.16	8.77
	Dibutyl maleate		62.98	8.82
1e	*s*-C_4H_9	$C_{12}H_{20}O_4$	63.16	8.77
	Di-sec-butyl maleate		63.07	8.67
1f	*t*-C_4H_9	$C_{12}H_{20}O_4$	63.16	8.77
	Di-*t*-butyl maleate		63.04	8.79
1g	C_6H_5	$C_{16}H_{12}O_4$	71.64	4.48
	Diphenyl maleate		71.60	4.53

	R	Formula	Analyses % Calcd./Found C	H
2c	*n*-C_3H_7	$C_{10}H_{16}O_4$	60.00	8.00
	Dipropyl fumarate		59.92	7.91
2d	*n*-C_4H_9	$C_{12}H_{20}O_4$	63.16	8.77
	Dibutyl fumarate		63.12	8.87
2e	*s*-C_4H_9	$C_{12}H_{20}O_4$	63.16	8.77
	Di-sec-butyl fumarate		63.08	8.76
2f	*t*-C_4H_9	$C_{12}H_{20}O_4$	63.16	8.77
	Di-*t*-butyl fumarate		63.28	8.86
2g	C_6H_5	$C_{16}H_{12}O_4$	71.64	4.48
	Diphenyl fumarate		71.59	4.59

tively. The splitting in the doublet of doublets arises from coupling of the hydrogen at C-2 with the hydrogen at C-3 (J = 5 Hz) and the *exo* hydrogen at C-3 with the *exo* hydrogen at C-5 (J′ = 2 Hz), respectively. The latter long range coupling constant (J′ = 2 Hz) is in agreement with that reported for bicyclo[2.2.1]heptane ring system [4], and besides its splitting pattern did not disappear on deuteration. Such nmr splitting patterns observed for the hydrogens at C-2 and C-3 confirms the stereochemical assignment indicating the configuration of the 2,3-dicarboxylate of **4a** to be the *trans* form.

As a result of the above structural investigation, it is concluded that the photo-initiated electrocyclic reaction of BDA with maleates and fumarates proceeded stereoselec-

tively, retaining the original configuration of the reagents.

The size of the substituent in the ester groups of the maleates and fumarates seemed to affect the reaction in that the more bulky substituent resulted in the lower yield, particularly in the case of the maleates. The lower reactivity of maleates than fumarates must be caused on the same basis as that of the stereoselective 1,3-dipolar cycloaddition [5].

EXPERIMENTAL

The 100 MHz and the 400 MHz ^{1}H nmr spectra were recorded on Jeol JNP-PS-100 and Jeol FX-400 spectrometers, respectively, using TMS as the internal standard; s = singlet, du = doublet, t = triplet, qa = quartet, qi = quintet, sx = sextet, m = multiplet, br = broad. The ir spectra were taken on a Hitachi EPI-G3 spectrophotometer. Mass spectra were obtained on a Finigan 3300E GC-MS spectrometer. All boiling and melting points were uncorrected.

1,1'-Bis(methoxycarbonyl)divinylamine (BDA).

This compound was prepared by the base catalyzed reaction of methyl β-halo-α-aminopropionate hydrohalide as reported previously [1,6].

Ethenylenedicarboxylate, **1a-g** and **2a-g**.

Dimethyl maleate (**1a**), diethyl maleate (**1b**), dimethyl fumarate (**2a**) and diethyl fumarate (**2b**) were commercially obtained and purified by distillation at reduced pressure or by recrystallization from carbon tetrachloride. Other ethenedicarboxylates, **1c-g** [7] and **2c-g** [7], were prepared by conventional procedures, boiling points, °C/mm Hg [literature, °C/mm Hg]; **1c**, 141/25 ([8], 126/12); **1d**, 154/20 ([8], 147.5/12); **1e**, 145/23 ([9], 130/10); **1f**, mp 67-68°; **1g**, mp 70-70.5° ([10], mp 71-72°); **2c**, 96/3 ([8], 110/5); **2d**, 112/3 ([8], 138.5/8); **2e**, 110/2 ([9], 127/9); **2f**, mp 68.5-69°; **2g**, mp 163-164.5° ([11], mp 160-162°).

Preparation of 7-Azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylate **3a-g** and **4a-g**.

A solution of BDA (0.005 mole) and ethenedicarboxylate (0.02 mole) in carbon tetrachloride (30 ml) was irradiated in a cylindrical Pyrex vessel by a 100 W high pressure mercury lamp under nitrogen atmosphere at 18 ±2°. The reaction was monitored by hplc.

After irradiation for 2-3 hours, the solvent was evaporated *in vacuo*, leaving a solid or syrup residue. The resulting solid was recrystallized from the appropriate solvent, whereas the syrup was purified by elution on slical gel with chloroform. Results are listed in Table 1, ir and 100 MHz ^{1}H nmr data in Tables 2 and 3.

Acknowledgement.

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