A Study of Intramolecular Diels-Alder Reactions of Allylamino Dienenitriles

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The intramolecular Diels-Alder reactions of 2-allylanilino 3,5-heptadienenitriles (**3**) produced equimolar amounts of perhydroisoindoles **4** and **5**, the structures of which were determined by spectral methods, but also by X-ray diffraction of **4a**.

INTRODUCTION

Intramolecular Diels-Alder reactions have been effectively used in the synthesis of bridged and fused polycyclic compounds, which include many natural products. The control of regio- and stereochemistry in these reactions has been the central issue of several reviews.¹⁻⁴ We here describe the results with regard to the intramolecular Diels-Alder reactions of 2-allylanilino 3,5-heptadienenitriles (**3**).

RESULTS AND DISCUSSION

According to the Strecker's procedure, condensation of the commercially available 2,4-hexadienal (**1**) with *N*-allylaniline and potassium cyanide in the presence of an acid catalyst afforded a high yield of 2-allylanilino-3*E*,5*E*-heptadienenitrile **3a**.⁵ The analogous trienes **3b** and **3c** were similarly prepared in 87% and 84% yields, respectively. The triene **3a** underwent intramolecular Diels-Alder reactions in refluxing benzene to give two perhydroisoindoles **4a** and **5a** in the ratio 1:1 (Scheme I). Both **4a** and **5a** are crystalline compounds. The stereo-structure of **4a** was rigorously established to be 1*β*-cyano-*N*-phenyl-5*β*-methyl-1*α*,3,4,5*α*,8*α*,9*β*-hexahydroisoindole by an X-ray diffraction (Fig. 1). From mechanistic considerations (Scheme II) and detailed analysis of the NMR data (Tables 1 and 2), we assign the structure of **5a** to the *cis* isomer, 1*α*-cyano-*N*-phenyl-5*β*-methyl-1*β*,3,4,5*α*,8*α*,9*α*-hexahydroisoindole. In agreement with the assigned structure, the *endo* H-1 of **5a** appears up field, δ 4.09, than that of **4a** (at δ 4.47), whereas the *exo* H-8 of **5a** appears down field, δ 3.21, than that of **4a** (at δ 2.53). For a similar reason, the two C-4

protons of **4a** have the same chemical shift at δ 1.80, but those of **5a** split into two resonances at δ 0.98 and 1.71.

Scheme I

Fig. 1. ORTEP drawing of **4a**.

Dedicated to Professor Yau-Tang Lin (林耀堂) on the occasion of his eightieth birthday.

Table 1. ^1H NMR Spectral Data of Compounds 4a-5c (δ , 300 MHz, CDCl_3 , TMS)

H-	4a	4b	4c	5a	5b	5c
1	4.47	4.45	4.50	4.09	4.04	4.17
3	3.00 / 3.53	3.02 / 3.51	3.11 / 3.35	3.25 / 3.75	3.51 / 3.66	3.49 (2 H)
4	1.80 (2 H)	2.02		0.98 / 1.71	1.05	
5	2.53	2.43	2.00	2.48	1.85	2.01
6	5.80	5.85	5.77	5.76	5.72	5.56
7	5.88	5.85	5.84	5.88	5.86	5.68
8	2.53	2.62	2.67	3.21	3.25	3.24
9	2.31	2.15	2.28	2.24	2.14	2.46
2', 6'	6.64	6.66	6.63	6.67	6.69	6.64
3', 5'	7.27	7.28	7.27	7.26	7.29	7.27
4'	6.79	6.80	6.78	6.82	6.82	6.78
Me-4		0.98	0.93 / 1.01		1.01	0.86 / 1.04
Me-5	1.11	1.04	1.03	0.97	1.03	1.05

The crystal data of compound 4a are as followings: $\text{C}_{16}\text{H}_{18}\text{N}_2$ crystallized in orthorhombic space group Pbca , cell parameters $a = 9.186(2)$, $b = 24.925(7)$, $c = 12.003(4)$ Å, $V = 2748(1)$ Å³, $Z = 4$. The intensity data were collected on a CAD-4 diffractometer using monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.7107$ Å) up to $2\theta = 44^\circ$. A total number of 1979 reflections was measured. Among them 927 reflections were considered to be observed [$I > 3\sigma(I)$] and were used in the full matrix least squares refinement. The structure was solved by a direct method with MULTAN program. The atomic parameters were obtained by minimizing the quantity $\sum w_i(F_o - F_c)^2$. The final agreement indices are $R = 0.055$, $wR = 0.036$, $S = 2.29$. The molecular structure is shown here with 50% probability of the thermal ellipsoids. The atomic parameters are given in Table 3. Selected bond distances and angles are given in

Table 4.

The intramolecular cycloadditions of 3b and 3c were also completed after refluxing for 24 h in benzene to give equimolar amounts of the trans perhydroisindoles (4b,c) and the cis isomers (5b,c). The C-4 methyl group of 5b is assigned as the α -face because of the great shielding effect on the adjacent 5 α proton, which shows at δ 1.85 as compared to the normal position of H-5 (δ 2.48) in 5a. The signal at particularly high field (δ 1.05) of 4 β -H in the cis perhydroisindole 5b supports the above assignment. On the other hand, compound 4b has two methyl groups on the same β -face with both H-4 and H-5 appearing at normal NMR fields.

By comparison with the report of Gschwend and Lee on the intramolecular Diels-Alder reactions of pentadienylacrylamides,⁶ it seems that the allylamines 3 under-

Table 2. ^{13}C NMR Spectral Data of Compounds 4a-5c (δ , 75 MHz, CDCl_3)

carbon-	4a	4b	4c	5a	5b	5c
1	52.4	52.7	52.6	54.1	54.4	52.6
3	51.6	50.2	47.2	55.1	52.3	46.3
4	30.2	34.8	32.8	29.9	35.0	32.8
5	31.6	35.4	42.6	33.9	36.3	42.6
6	111.8	111.7	111.7	113.0	113.0	112.5
7	117.8	117.7	117.8	118.3	118.3	118.1
8	46.1	47.2	44.0	44.2	44.7	43.9
9	36.6	41.2	43.0	35.7	42.3	43.0
1'	146.2	145.4	145.5	145.5	145.5	145.0
2', 6'	121.5	120.7	119.8	122.9	122.2	122.1
3', 5'	137.3	138.4	138.2	137.1	136.7	138.2
4'	129.5	129.4	129.4	129.3	129.2	129.4
Me-4		16.1	21.9, 25.6		19.9	22.3, 25.6
Me-5	21.9	15.2	16.8	21.3	17.9	17.0
CN	117.5	117.4	117.5	119.0	118.9	117.8

Table 3. Atomic Fractional Coordinates of Compound 4a. $B_{eq}(\text{\AA}^2) = 1/3(4\pi^2 \sum_{ij} u_{ij} a_i^* a_j^* a_i a_j)$

Atom	x	y	z	Beq	Atom	x	y	z	Beq
N1	0.8972(4)	0.0521(1)	0.1141(3)	5.0(2)	H21	0.9912	0.0719	0.2773	6.3
C2	1.0149(6)	0.0724(2)	0.1857(4)	5.1(3)	H22	1.1199	0.0495	0.1788	6.3
C3	1.0345(5)	0.1295(2)	0.1423(4)	4.2(3)	H3	0.9484	0.1547	0.1782	6.3
C4	1.1782(5)	0.1592(2)	0.1561(4)	5.9(3)	H41	1.2093	0.1612	0.2457	6.3
C5	1.1659(6)	0.2153(2)	0.1049(4)	6.4(3)	H42	1.2668	0.1356	0.1162	6.3
C6	1.0728(6)	0.2169(2)	0.0017(4)	6.2(3)	H5	1.2796	0.2303	0.0819	6.3
C7	0.9964(6)	0.1764(2)	-0.0391(4)	5.2(3)	H6	1.0576	0.2572	-0.0382	6.3
C8	1.0021(5)	0.1232(2)	0.0177(4)	4.1(3)	H7	0.9241	0.1829	-0.1131	6.3
C9	0.8702(5)	0.0859(2)	0.0184(4)	4.3(3)	H8	1.0985	0.1008	-0.0185	6.3
C11	0.8277(5)	0.0034(2)	0.1297(4)	4.2(3)	H9	0.8691	0.0605	-0.0618	6.3
C12	0.8726(5)	-0.0306(2)	0.2158(4)	4.9(3)	H12	0.9609	-0.0163	0.2754	6.3
C13	0.8037(6)	-0.0796(2)	0.2309(4)	5.7(3)	H13	0.8434	-0.1080	0.2983	6.3
C14	0.6935(6)	-0.0957(2)	0.1620(4)	6.2(3)	H14	0.6343	-0.1338	0.1781	6.3
C15	0.6483(5)	-0.0623(2)	0.0769(4)	5.5(3)	H15	0.5606	-0.0769	0.0161	6.3
C16	0.7144(5)	-0.0126(2)	0.0602(4)	4.7(3)	H16	0.6738	0.0151	-0.0107	6.3
C20	0.7310(6)	0.1165(2)	0.0321(4)	4.6(3)	H221	0.9893	0.2504	0.1913	6.3
N21	0.6258(5)	0.1400(2)	0.0431(3)	6.8(3)	H222	1.1365	0.2972	0.1733	6.3
C22	1.1114(7)	0.2563(2)	0.1917(4)	9.8(4)	H223	1.1508	0.2469	0.2758	6.3

went cycloadditions as efficiently as those acrylates. The methyl substituents on the allylic moiety caused no substantial deceleration in the intramolecular Diels-Alder reactions. It is considered that the trans cycloadducts 4a-c were

obtained from the *endo* transition states whereas the cis cycloadducts 5a-c were derived from the *exo* transition states as depicted in Scheme II. Thus, intramolecular cycloadditions of 3 exert a certain degree of stereochemical control to create up to five contiguous chiral centers.⁶⁷ The specific cis relationship between the cyano group and C-9 proton in either adduct 4 or 5 may be accounted by these transition states; otherwise the C-1 epimers (not formed) may have the cyano group either interacting with the adjacent C-8 proton or positioned on an energetically unfavorable *endo* face. Transformation of 1-cyano isindoles (4 or 5) into the corresponding isindolones can conceivably be achieved by a base-catalyzed auto-oxidation.⁸⁹ Thus, the present study is also applicable to the synthesis of

Table 4. Selected Bond Lengths (Å) and Angles (°) of Compound 4a

Bond Length			
N(1)-C(2)	1.471(6)	C(7)-C(8)	1.493(6)
N(1)-C(9)	1.447(5)	C(8)-C(9)	1.527(7)
N(1)-C(11)	1.385(6)	C(9)-C(20)	1.499(7)
C(2)-C(3)	1.526(6)	C(11)-C(12)	1.398(6)
C(3)-C(4)	1.522(7)	C(11)-C(16)	1.392(6)
C(3)-C(8)	1.533(6)	C(12)-C(13)	1.389(6)
C(4)-C(5)	1.533(7)	C(13)-C(14)	1.368(7)
C(5)-C(6)	1.506(7)	C(14)-C(15)	1.382(7)
C(5)-C(22)	1.543(7)	C(15)-C(16)	1.394(6)
C(6)-C(7)	1.323(7)	C(20)-N(21)	1.137(6)
Bond Angle			
C(2)-N(1)-C(9)	112.9(3)	C(3)-C(8)-C(9)	102.3(3)
C(2)-N(1)-C(11)	124.2(3)	C(7)-C(8)-C(9)	121.0(4)
C(9)-N(1)-C(11)	122.6(4)	N(1)-C(9)-C(8)	102.8(4)
N(1)-C(2)-C(3)	102.0(3)	N(1)-C(9)-C(20)	110.8(4)
C(2)-C(3)-C(4)	121.2(4)	C(8)-C(9)-C(20)	111.6(3)
C(2)-C(3)-C(8)	102.3(3)	N(1)-C(11)-C(12)	119.7(4)
C(4)-C(3)-C(8)	109.0(4)	N(1)-C(11)-C(16)	121.0(4)
C(3)-C(4)-C(5)	109.6(4)	C(12)-C(11)-C(16)	119.3(4)
C(4)-C(5)-C(6)	113.3(4)	C(11)-C(12)-C(13)	119.7(4)
C(4)-C(5)-C(22)	110.9(4)	C(12)-C(13)-C(14)	121.1(4)
C(6)-C(5)-C(22)	110.8(4)	C(13)-C(14)-C(15)	119.5(4)
C(5)-C(6)-C(7)	125.9(4)	C(14)-C(15)-C(16)	120.8(4)
C(6)-C(7)-C(8)	119.3(4)	C(11)-C(16)-C(15)	119.6(4)
C(3)-C(8)-C(7)	111.2(4)	C(9)-C(20)-N(21)	179.5(5)

Scheme II

cytochalasin alkaloids which comprise the nucleus skeleton of isoindolones.^{10,11}

EXPERIMENTAL SECTION

Melting points were measured on a Yanaco micro melting point apparatus, and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer 240c elemental analyzer. Infrared spectra were measured on a Perkin-Elmer 985 infrared spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Varian EM-90 or a Bruker AM-300 WB spectrometer. Mass spectra were recorded on a Finnigan TSQ 46c spectrometer operating at an ionizing voltage 70 eV.

Preparation of

2-(N-allylbenzenamino)-3,5-heptadienenitriles (3)

Allylaniline (1.06 g, 8 mmol) was added at 0°C to a mixture of 2*E*,4*E*-hexadienal (0.77 g, 8 mmol) and 1.34 mL of 6 M HCl. The mixture was stirred for 40 min, KCN (0.7 g, 10 mmol) was added, and the solution was stirred for an additional 2 h until the yellow organic phase separated from the aqueous phase. The aqueous phase was extracted with EtOAc. The combined organic phase was dried (Na₂SO₄), concentrated, and purified by chromatography to give 1.64 g (86%) of 2-(*N*-allylbenzenamino)-3*E*,5*E*-heptadienenitrile 3a. By a similar procedure, 2-[*N*-(but-2-en-1-yl)benzenamino]-3*E*,5*E*-heptadienenitrile 3b and 2-[*N*-(3-methylbut-2-en-1-yl)benzenamino]-3*E*,5*E*-heptadienenitrile 3c were prepared in 87% and 84% yields, respectively. 3a: oil; IR (neat) 2232 cm⁻¹ (CN absorption); ¹H NMR (CDCl₃) 1.66 (3 H, *d*, *J* = 7 Hz), 3.75 (2 H), 5.04-5.18 (3 H), 5.40 (1 H, *dd*, *J* = 15, 5 Hz), 5.66-5.79 (2 H), 5.96 (1 H, *dd*, *J* = 15, 10 Hz), 6.45 (1 H, *dd*, *J* = 17, 10 Hz), 6.82 (3 H, *d*, *J* = 8 Hz), 7.17 (2 H, *t*, *J* = 8 Hz); [M]⁺ at *m/z* 238 (55%) and base peak at *m/z* 77. 3b: oil; IR (neat) 2232 cm⁻¹; ¹H NMR (CCl₄) 1.66 (3 H, *d*, *J* = 6 Hz), 1.72 (3 H, *d*, *J* = 6 Hz), 3.76 (2 H), 5.01 (1 H, *m*), 5.42-5.66 (3 H), 5.66-5.96 (2 H), 6.40-6.62 (1 H, *m*), 6.82 (3 H, *d*, *J* = 8 Hz), 7.17 (2 H, *t*, *J* = 8 Hz); [M]⁺ at *m/z* 252 (25%) and base peak at *m/z* 77; 3c: oil; IR (neat) 2230 cm⁻¹; ¹H NMR (CCl₄) 1.64-1.68 (9 H), 3.78 (2 H, *d*, *J* = 7 Hz), 5.03-5.15 (2 H), 5.42-5.56 (1 H), 5.86-6.03 (1 H), 6.53-6.67 (2 H), 6.83 (3 H, *d*, *J* = 8 Hz), 7.19 (2 H, *t*, *J* = 8 Hz); [M]⁺ at *m/z* 266 (3%) and base peak at *m/z* 93.

General procedure for intramolecular Diels-Alder reactions of compounds 3

A solution of allylanilino dienenitrile 3a (238 mg, 1 mmol) in 5 mL benzene was heated under reflux for 24 h under an atmosphere of nitrogen. The solution was cooled and concentrated *in vacuo*. The residue was subjected to chromatography on a silica gel column with elution of 1% EtOAc-hexane to give two crystalline compounds 4a (95 mg) and 5a (95 mg) in 86% total yield. By the similar procedure, 3b yielded 89 % of the cycloaddition products 4b and 5b (1:1); and 3c yielded 84 % of 4c and 5c (1:1). The ¹H and ¹³C NMR data of 4 and 5 are listed in Tables 1 and 2. 4a: mp 135-136°C; IR (KBr); 2233 cm⁻¹ (CN group); [M]⁺ at *m/z* 238 (base peak). 4b: mp 137-138°C; IR (KBr) 2229 cm⁻¹; [M]⁺ at *m/z* 252 (base peak); Exact mass C₁₇H₂₀N₂ requires 252.1626, found 252.1624. 4c: mp 139-140°C; IR (KBr) 2226 cm⁻¹; [M]⁺ at *m/z* 266 (70%) and base peak at *m/z* 144; Exact mass C₁₈H₂₂N₂ requires 266.1783, found 266.1795. 5a: mp 83-84°C; IR (KBr) 2233 cm⁻¹; [M]⁺ at *m/z* 238 (base peak), Anal. C, H, N. 5b: mp 84-85°C; IR (KBr) 2233 cm⁻¹; [M]⁺ at *m/z* 252 (base peak). 5c: mp 85-86°C; IR (KBr) 2225 cm⁻¹; [M]⁺ at *m/z* 266 (55%) and base peak at *m/z* 144.

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Key Words-

Amino nitriles; Trienes; Intramolecular Diels-Alder reaction; Regiochemistry; Stereochemistry; Perhydroisoindoles; X-ray diffraction.

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