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TAUTOMERIZATION OF 3a,7a-DIHYDROINDOLE-2,3,3a,4-TETRACARBOXYLATE

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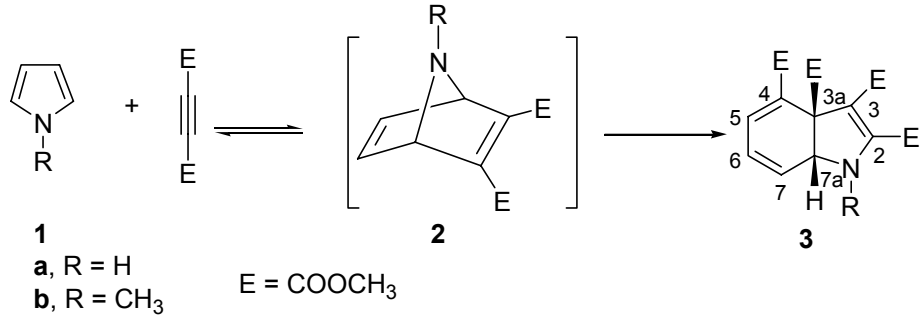
Abstract- Tetramethyl 3a,7a-dihydroindole-2,3,3a,4-tetracarboxylate which is a 1:2 adduct of pyrrole with dimethyl acetylenedicarboxylate dissolved in various solvents underwent tautomerization to 3a,7a-dihydroindolenine esters. Acid or base externally added to the pure solvents promotes the isomerization.

INTRODUCTION

Pyrrole (**1a**) and 1-methylpyrrole (**1b**) show striking differences in reactivities as a diene in Diels-Alder reaction.[1] For example, **1b** undergoes the cycloaddition with dimethyl acetylenedicarboxylate (DMAD) upon reflux in ether for 24 h giving an 1:2 adduct **3b** in 78% yield.[2]



1
a, R = H
b, R = CH_3

2

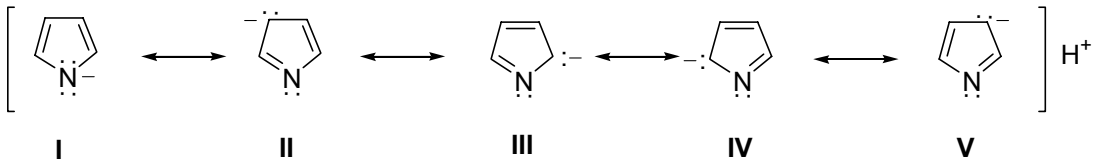
E = $COOCH_3$

3

An intermediate (**2b**) which is a 1:1 adduct between **1b** and DMAD is considered to be formed initially. But **1a** gives **3a** in less than 6% yield after reflux for 4 days.[3]

Apparently, hyperconjugation of pyrrole enhances the resonance contribution as shown **I-V**, diminishing the diene character of the pyrrole ring. Therefore, the formation of a 1:1 adduct (**2a**) in equilibrium should be unfavorable. On the other hand, a hyperconjugation contribution is unlikely in the *N*-methyl

analog (**1b**). The reactivity of the diene should be increased by the electron donating methyl group. In addition, the interaction between the hydrogen atoms of C_α-H and *N*-CH_3 in **1b** should be decreased as the 7-azanorbornadiene intermediate (**2b**) forms because the hybridization of C_α is changing from sp^2 in **1b** to sp^3 in **2b**.

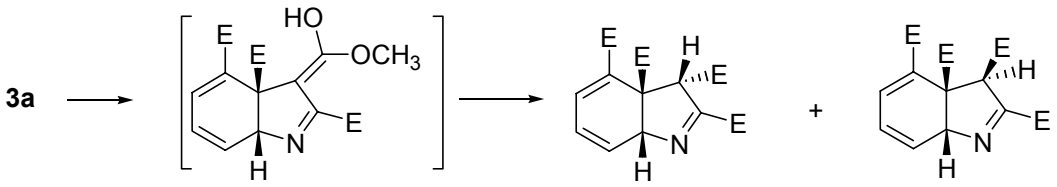


I **II** **III** **IV** **V**

As we continue the study on the chemistry of the 1:2 adducts (**3a** and (**3b**) in order to explore their possible conversion to indole derivatives we have found that the N-H compound (**3a**) underwent enamine-imine tautomerization. Althought there are a number of reports related to the tautomerism involving hydroxypyrroles and aminopyrroles it is rare to find such phenomenon with a dihydropyrrole derivative.[4] In this paper we report a versatile transformation of **3a** through tautomerization under various conditions.

RESULTS AND DISCUSSION

At first we attempted to recrystallize the 1:2 adduct (**3a**) from methanol but were only able to recover about 50% of **3a** in analytically pure state. The filtrate after removal of the pure **3a** was found to be a mixture of **3a** and **4** in 1:4 molar ratio by NMR spectrometry. The mixture was chromatographed using a column of silica gel to isolate **4** in pure state.



VI **4** **5**

The yield of **4** from **3a** was about 35%. When the filtrate after recovery of **4** was left for 7 days at room temperature and then evaporated to dryness, a mixture of **4** and **5** was resulted. Compound (**5**) was also isolated by column chromatography in about 5% yield.

The structures of **4** and **5** are imines which are the direct results of the tautomerization of the enamine (**3a**). The structures of the imines (**4**) and (**5**) were established by spectroscopic methods. IR spectra of **4** and **5** show no peak corresponding to the N-H group. Both ^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOR spectroscopy were employed for correct assignment of each peak. The HETCOR spectrum of **4** shows correlation of a

doublet at δ 4.75 (J = 1.60 Hz) with a peak at 63.95 ppm. The ^{13}C resonance at 63.95 ppm should be a definite evidence of an sp^3-hybridized carbon. The other sp^3-hybridized carbon atoms are 3a-C and 7a-C which appear at 56.88 and 74.84 ppm, respectively. The latter shows a correlation with a doublet of doublets at δ 5.29. ^{1}H and ^{13}C NMR spectral data are listed in Tables 1 and 2, respectively.

It is conceivable that the conjugation of the lone pair electrons of N atom through 2-C—3-C and C—O double bonds may result in an enol form like **VI**. Then the tautomerization of the enol form should give **4** preferably because the ester groups at 3-$COOCH_3$ and 3a-$COOCH_3$ groups are *trans* each other. Compound (**4**) was the sole product when the tautomerization was carried out at room temperature.

The stereochemistry of **4** was conformed by ^{1}H-^{1}H COSY spectroscopy of **4** as shown in Figure 1.

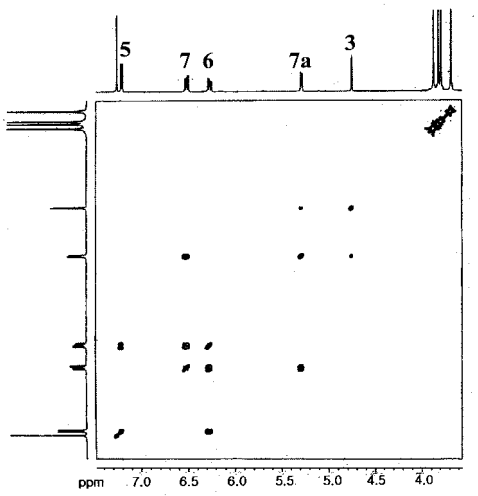


Figure 1. ^{1}H-^{1}H COSY spectrum of **4**.

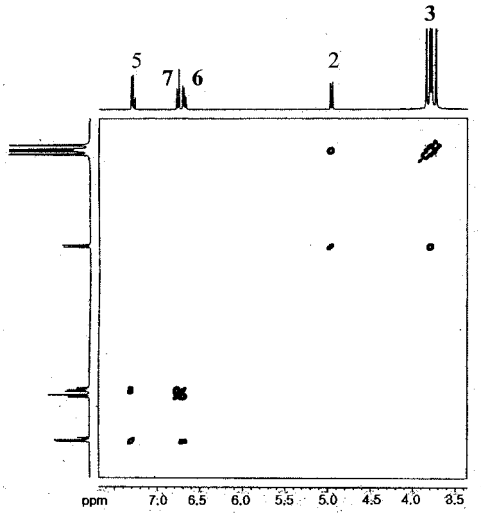


Figure 2. ^{1}H-^{1}H COSY spectrum of **6**.

Correlation between 3-H and 7a-H is clearly shown, which is an indication of the presence of a long-range coupling of these protons. The magnitude of the coupling constant of 1.6 Hz should be the result of *cis* orientation of the two protons.[5] On the other hand, there was no coupling between 3-H and 7a-H of **5** (spectrum not shown), indicating the protons are in *trans* arrangement. Figure 1 also shows an allylic coupling between 6-H and 7a-H.

It is also notable that the order of the appearance of the resonances corresponding to 5-, 6-, and 7-H that are bonded to sp^2-hybridized carbon atoms is changed from **3a** to **4** and **5** in Table 1. The order from the down-field is 5-H > 6-H > 7-H for **3a**, but 5-H > 7-H > 6-H for **4** and **5**. It is remarkable that the 7-H signal shifts to down field by 0.83 ppm as the enamine (**3a**) tautomerizes to the imine (**4**). The shift may be caused by the shielding of the 7-H of **3a** by the lone pair electrons on the sp^3-hybridized N atom as shown in **VII**. Such electronic influences would be diminished as the hybridization of the N atom changes from sp^3 to sp^2. If the inductive effect of the N atom is responsible for such down field shift, the

effect should be much greater on 7a-H than on 7-H. The signal of 7a-H is shifted merely by 0.19 ppm. Therefore, it may be ruled out that the change in the inductive effect upon the change in hybridization of N atom is not the cause of the significant down-field shift of 7-H in **3a**

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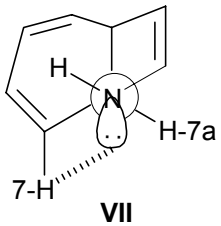


VII

Table 1. ^{1}H NMR Chemical Shift Values (δ) of the Tetraesters in Chloroform-*d* (*J* in Hz)

Position	**3a**[a]	**4**	**5**	**6**	**7**
2-$COOCH_3$	3.67 s[b]	3.87 s[b]	3.92 s[b]	3.80 s[b]	3.81 s[b]
2-H ($J_{2,3}$)				4.97 d (9.6)	5.29 d (5.7)
3-$COOCH_3$	3.76 s[b]	3.68 s[b]	3.56 s[b]	3.73 s[b]	3.68 s[b]
3-H ($J_{3,2}$)		4.75 d[c]	5.03 s	3.80 d (9.6)	4.58 d (5.8)
3a-$COOCH_3$	3.80 s[b]	3.79 s[b]	3.73 s[b]	3.68 s[b]	3.53 s[b]
4-$COOCH_3$	3.85 s[b]	3.82 s[b]	3.78 s[b]	3.79 s[b]	3.79 s[b]
5-H ($J_{5,6}$)	7.05 d (6.0)	7.22 d (6.1)	7.13 d (6.0)	7.30 d (6.0)	7.25 d (6.0)
6-H	6.15 ddd	6.28 ddd	6.07 ddd	6.71 dd	6.71 dd
($J_{6,5}$; $J_{6,7}$; $J_{6,7a}$)	(6.0; 9.7; 1.6)	(6.1; 9.5; 0.8)	(6.0; 9.8; 3.0)	(6.3; 9.7)	(6.1; 9.5)
7-H	5.69 dd	6.52 dd	6.18 dd	6.77 d	6.85 d
($J_{7,6}$; $J_{7,7a}$)	(9.7; 3.0)	(9.5; 5.7)	(9.8; 3.1)	(9.7; -)	(9.5; -)
7a-H ($J_{7a,7}$)	5.10 t (3.0)	5.29 dd (5.7)	5.49 t (3.0)	-	-
	$J_{7a,NH}$ = 2.3	*c*	$J_{7a,6}$ = 3.0		

[a] A doublet corresponding to N-H appears at δ 4.19 with $J_{NH,7a}$ = 2.3 Hz. [b] Singlet corresponding to OCH_3 of the ester group and the assignment is uncertain. [c] $J_{3,7a}$ = 1.6 Hz.

Table 2. ^{13}C NMR Chemical Shift Values (ppm) of the Tetraesters in Chloroform-*d*

Position	**3a**	**4**	**5**	**6**	**7**
2-C	146.99	161.61	161.41	75.50	74.34
2-$COOCH_3$	51.53	53.26	53.22	52.87	52.62
3-C	109.33	63.95	63.58	57.19	58.23
3-$COOCH_3$	52.03	52.95	52.48	52.45	53.16
3a-C	57.53	56.88	54.46	64.08	65.77
3a-$COOCH_3$	53.28	52.19	53.46	53.43	52.21
4-C	125.73	126.21	125.75	133.00	132.61
4-$COOCH_3$	52.88	53.17	52.16	52.17	52.12
5-C	131.85	133.75	132.88	132.69	133.55
6-C	123.40	123.60	120.87	133.94	133.69
7-C	129.16	128.58	128.87	127.15	127.69
7a-C	65.13	74.84	78.47	167.83	166.72
C=O	162.44	163.05	164.59	164.74	164.90
	164.30	165.89	165.98	170.22	169.94
	166.20	168.40	168.26	170.51	169.96
	174.52	170.77	173.75	172.20	170.56

Compound (**5**) is a diastereomer of **4**. Two ester groups at 3-C and 3a-C of **5** are *cis*. Because the five-membered ring and the six-membered ring are *cis*-fused, the 3- $COOCH_3$ group and 7a-H are also *cis*. This is confirmed by the most down-field shift of 7a-H signal of **5** (δ 5.49) compared to **4** (δ 5.29) and **3a** (δ 5.10). Unlike to the down-field shift of 7a-H the signals of 5-, 6-, and 7-H of **5** are shifted to up-field when they are compaired to those of **4**.

The tautomerization of **3a** to **4** was investigated in various solvents and the results are listed in Table 3.

The isomerization of **3a** to **4** took place significantly when a commercial chloroform-*d* was used. About two thirds of **3a** changed to **4** in 24 h and complete conversion was apparent after 48 h. But the

isomerization was quite slow when the purified chloroform-*d* (treated with solid NaOH and then distilled prior to use) was used, shown only 40% of **3a** was converted to **4** after 48 h.

When a solution of **3a** in methanol-d_4 was monitored by an NMR spectrometer, the ratio of **3a** to **4** was about 1:1 after 24 h and not changed significantly after 7 days, indicating that the equilibrium was reached in 24 h. The equilibrium was achieved most rapidly in DMSO-d_6 in one hour with a ratio of 4:1, and then the composition did not change after 7 days.

Acetonitrile-d_3 also induced the tautomerization but the rate of such process seemed to be quite slow. The ratio of **3a** to **4** was changing even after 7 days. The tautomerization did not take place in benzene-d_6 and in acetone-d_6.

Table 3. Ratios of **3a** and **4** in Various Solvents Determined by NMR Spectroscopy

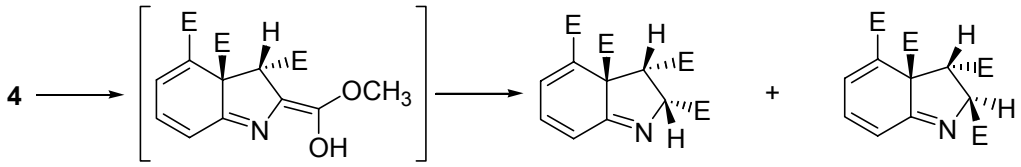
Time	$CDCl_3$	$CDCl_3$[a]	CD_3OD	CD_3SOCD_3	CD_3CN	CD_3COCD_3	C_6D_6
0 h	100/0	100/0	100/0	100/0	100/0	100/0	100/0
1 h	99/1	100/0	88/12	80/20	90/10	100/0	100/0
2 h	84/16	100/0	75/25	80/20	87/13	100/0	100/0
3	82/18	100/0	77/23	80/20	83/17	100/0	100/0
6 h	77/23	100/0	73/27	80/20	78/22	100/0	100/0
12 h	67/33	93/7	64/36	80/20	74/26	100/0	100/0
24 h	32/68	80/20	52/48	80/20	72/28	100/0	100/0
48 h	0/100	60/40	47/53	80/20	71/29	100/0	100/0
7 days	[b]	20/70[c]	43/57	80/20	61/39	100/0	100/0

[a] Chloroform-*d* was treated with solid sodium hydroxide and then distilled prior to use.

[b] 3:2 mixture of **4** and **5**. [c] A 2:7:1 mixture of **3a**, **4**, and **5**.

The effect of acid and base on the tautomerization of **3a** was also examined by monitoring the NMR spectrum. The tautomerization of **3a** to **4** proceeded slowly in chloroform-*d* in the presence of 1 mole percent of acetic acid and completed after 24 h. On the other hand, the presence of 1 mole percent of NaOH facilitated the tautomerization and formation of both tautomers **4** and **5** resulted in 1 h in approximately 1:1 ratio with only trace of the starting material remaining.

Compound (**4**) undergoes further isomerization to form **6** and **7** in about 1:1 ratio upon reflux in methanol for 24 h.



Although the mechanism for the transformation of **4** to **6** and **7** is not clear, an intermediate **VIII** and subsequent enol-keto tautomerization may be involved in the process. The mixture was separated by column chromatography to afford **6** and **7** in pure form whose structures were determined by spectroscopic methods. The stereochemistry of **6** and **7** was determined by the coupling constant of 2-H and 3-H as shown in Figure 2. They are *cis* in **6** with a coupling constant of 9.6 Hz. On the other hand, **7** showed a coupling constant of 5.7 Hz, indicating a *trans* arrangement.

The stereochemistry at 2-C of **6** and **7** was determined from the chemical shift of 3-H. At first it was difficult to locate the signal corresponding to 3-H of **6** because it was overlapped with the singlets of the four $COOCH_3$ groups at δ 3.68-3.80. ^{1}H-^{1}H COSY spectrum in Figure 2 clearly shows the correlation of the peaks at δ 3.80 with a doublet at δ 4.97 (J = 9.6 Hz). Being trans to the 2-$COOCH_3$ group, the 3-H should be out of the diamagnetic anisotropic effect of the carbonyl group at 2-C, resulting in a significant up field shift (δ 3.80). On the other hand, the proton at 3-C and 2-$COOCH_3$ group are *cis* in **7** in which case the anisotropic effect should cause a down field shift. The signal appears at δ 4.58 as a doublet with J = 5.8 Hz. Because the ester groups are *trans*, the protons and the ester groups are *cis*, leading to a significant down field shift of both the 2-H and 3-H signals.

We examined the potential isomerization of the imine (**4**) to the starting enamine (**3a**) under various conditions, but such a transformation did not take place. Also, the reverse process of **6** or **7** to **4** or **5** did not take place upon reflux in methanol.

The compounds (**6**) and (**7**) may be useful as chiral auxiliaries after a conversion to the corresponding carboxylic acid or hydroxylmethyl groups because of the unique arrangement of the ester groups.

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX-400 FT NMR spectrometer in the Central Lab of Kangwon National University at 400 MHz for ^{1}H and 100 MHz for ^{13}C and were referenced to tetramethylsilane. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. MS spectra were obtained using a Micromass Autospec M363 in the Central Lab of Kangwon National University. The ionization

conditions were at 60 °C and 70 eV. Elemental analysis was performed by the Central Lab of Kangwon National University.

Pyrrole and dimethyl acetylenedicarboxylate (DMAD) were obtained as the commercial products and were distilled prior to use. The deuteriated solvents are all commercial products which were used as delivered.

Reaction of pyrrole (1a) with DMAD. A solution of pyrrole (**1a**, 1.0 mL, 0.014 mol) and DMAD (3.8 mL, 0.031 mol) in ether (50 mL) was heated at reflux for 7 days. White solid was collected by filtration and dried under vacuum to give **3a** (0.25 g, 20%, mp 160-165 °C, lit.,[3] 162-165 °C). The filtrate was mostly the starting materials as confirmed by NMR spectroscopy. The solid was dissolved in methanol (10 mL) by heating to boiling. The hot solution was filtered once and cooled slowly to result precipitation. The solid was collected by filtration and dried under vacuum to give the pure form of **3a** (0.11 g, 44% recovery, mp 163-163.5 °C, lit.,[3] 162-165 °C). The filtrate was warmed gently, and ether was added just enough to result cloudiness. Upon keeping the solution in a refrigerator for 2 days pale yellow solid formed, which was collected by filtration and dried. The solid was recrystallized from methanol to give **4** (0.08 g, 33%, mp 110-111 °C): IR (KBr) cm^{-1} 1744s, 1729s, 1643w, 1437m, 1324m, 1267s, 1193s, 1136s, 1090m; LRMS, *m/z* (%) 351 (9, M^+), 320 (47), 261 (65), 260 (100, M^+ - CH_3OCO – CH_3OH), 248 (54), 228 (87), 216 (63); HRMS calcd for $C_{16}H_{17}NO_8$ 351.0954. Found 351.0957. Anal. Calcd for $C_{16}H_{17}NO_8$ (351.29): C, 54.71; H, 4.87; N, 3.99. Found: C, 54.75; H, 4.88; N, 3.95.

The filtrate after separating **4** was chromatographed on a column of silica gel eluting with ethyl acetate-hexane to give **4**, **5**, **6**, and **7** in the order of elution. The total yield of **4** was 35%. Compound (**5**) was recrystallized from methanol to give a colorless prism (0.02 g, 4%, mp 117-118 °C): IR (KBr) cm^{-1} 1736s, 1725s, 1437m, 1285ms, 1230ms, 1198ms, 1118m; ; LRMS, *m/z* (%) 351 (1, M^+), 320 (8), 261 (19), 260 (100, M^+ - CH_3OCO – CH_3OH), 248 (24), 228 (44), 216 (22); HRMS calcd for $C_{16}H_{17}NO_8$ 351.0954. Found 351.0953. Anal. Calcd for $C_{16}H_{17}NO_8$ (351.29): C, 54.71; H, 4.87; N, 3.99. Found: C, 54.70; H, 4.85; N, 3.90.

Compound (**6**) was recrystallized from methanol to give a colorless prism (0.03 g, 5%, mp 138-139 °C): IR (KBr) cm^{-1} 1743s, 1704s, 1636w, 1436m, 1364m, 1270s, 1243s, 1205s; LRMS, *m/z* (%) 351 (3, M^+), 320 (5), 261 (27), 260 (100, M^+ - CH_3OCO – CH_3OH), 248 (92), 228 (13), 216 (75); HRMS calcd for $C_{16}H_{17}NO_8$ 351.0954. Found 351.0967. Anal. Calcd for $C_{16}H_{17}NO_8$ (351.29): C, 54.71; H, 4.87; N, 3.99. Found: C, 54.81; H, 4.90; N, 3.89.

Compound (**7**) was recrystallized from methanol to give a colorless solid (0.01 g, 2%, mp 70-72 °C): IR (KBr) cm^{-1} 1730s, 1640w, 1436m, 1335m, 1276s, 1212s, 1060m; LRMS, *m/z* (%) 351 (39, M^+), 320 (5), 261 (25), 260 (100, M^+ - CH_3OCO – CH_3OH), 248 (67), 228 (12), 216 (47); HRMS calcd for $C_{16}H_{17}NO_8$ 351.0954. Found 351.0960. Anal. Calcd for $C_{16}H_{17}NO_8$ (351.29): C, 54.71; H, 4.87; N, 3.99. Found: C,

54.72; H, 4.92; N, 3.91.

Tautomerization of **4** to **6** and **7**. A solution of the indolenine (**4**) (0.10 g) in methanol (5 mL) was heated at reflux for 2 h. After evaporation of the solvent, the residue was examined by NMR spectroscopy to find a presence of **6** and **7** in about 1:1 molar ratio. The mixture was separated by column chromatography (silica gel) using ethyl acetate-hexane (9:1 by volume).

ACKNOWLEDGEMENT

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