Reinvestigation for the Synthesis of 1,2-Isoindolo-1,(2*H*),3,4-tetrahydro-*β*-carboline

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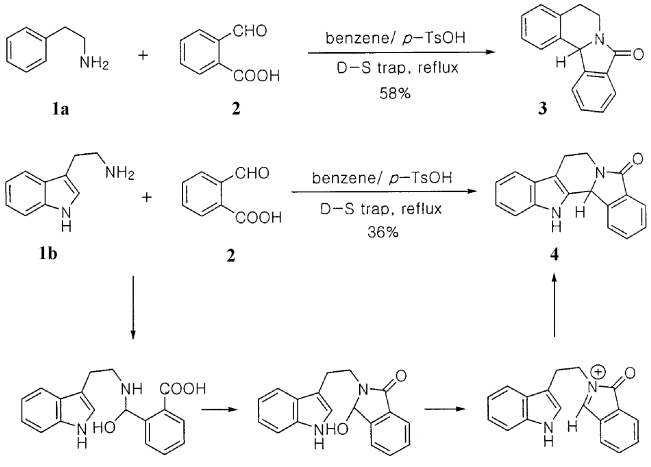
Received January 18, 2000

Tricyclic or tetracyclic lactam derivatives have been known to possess many interesting biological activities.[1] These include Nuevamine, *β*-carbolines, and various tricyclic lactam derivatives. Some of them show potent NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) activity.[1a,1b] Mertenes *et al.* have reported that some 9b-aryl-2,3-dihydrothiazolo[2,3-*a*]isoindole-5(9b*H*)-one derivatives show anti-HIV-1 activity. These new class of NNRTIs adopt a butterfly-like conformation and, like nevirapine, bind to a site on the reverse transcriptase enzyme.[1a,1b]

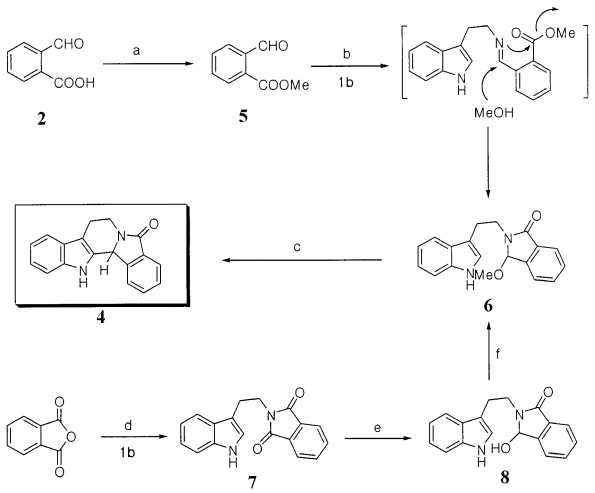
Our interest was focused on the structural modification of the reported NNRTIs to improve biological activity. There are many reported methods for the synthesis of polycyclic lactams.[2] Especially, the synthesis of 1,2-isoindolo-1,(2*H*), 3,4-tetrahydro-*β*-carboline structure, reported quite recently by Heaney *et al.*,[3] attracts our attention. However, the method requires multi-step reaction sequence and expensive reagents, and thus more efficient synthetic procedure was needed in order to obtain sufficient amounts of sample and examine its biological activities.

In these contexts we examined the model study using the reaction of *β*-arylethylamines such as phenethylamine (**1a**) and tryptamine (**1b**) with 2-formylbenzoic acid (**2**) as shown in Scheme 1.

The reaction of **1a** and **2** in benzene in the presence of *p*-toluenesulfonic acid using Dean-Stark trap gave the corresponding tetracyclic lactam derivative **3** in 58% isolated yield.[4] The structure was identified by the comparison of its melting point and ^{1}H and ^{13}C NMR spectra with those of the reported.[2d,4] The reaction of **1b** and **2** afforded pentacyclic lactam derivative **4** in 36% isolated yield.[5] The plausible mechanism for the formation of **4** is depicted in Scheme 1. However, to our surprise, the spectroscopic data (^{1}H and ^{13}C NMR) and its melting point of **4** was different with those of the reported.[3] Thus, we prepared **4** according to the Heaney's procedure[3] with slight modification as shown in Scheme 2.[4]



Scheme 1



Reaction conditions : a. CH_3I, DBU, acetonitrile, rt, 20 h, 83%, b. $MgSO_4$, methanol, reflux, 24 h, 15%, c. $Sc(OTf)_3$ (10 mol%), methylene chloride, rt, 20 h, 54%, d. acetic acid, reflux, 15 h, 91%, e. $NaBH_4$, methanol−dichloromethane, rt, 4 h, 92%, f. NaH, CH_3I, tetrahydrofuran, rt, 20 h, 55%

Scheme 2

The reaction of methyl 2-formylbenzoate **5** and **1b** in methanol gave the methoxy derivative **6** in low yield. In an alternate method, the reaction of phthalic anhydride and **1b** in acetic acid gave the cyclic imide **7**. We could obtain **6** from **7**

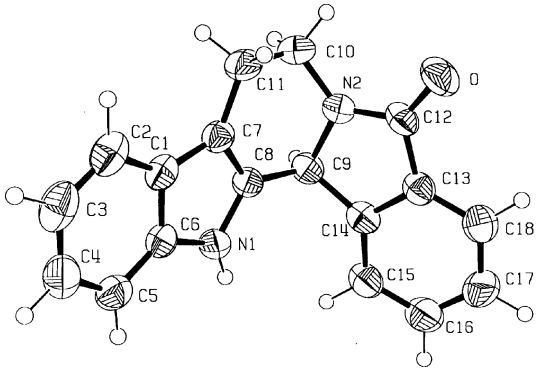


Figure 1. ORTEP drawing of 1,2-isoindolo-1,(2H),3,4-tetrahydro-*β*-carboline (**4**).

Table 1. Summary of Crystal Data

Crystal data	
$C_{18}H_{14}N_2O$	D=1.341 (calc.) gcm^{-3}
Mw=1097.25 amu	Mo-Kα Radiation
Monoclinic	λ = 0.7107 Å
$P2_{1/n}$	Cell parameters from 25 reflections
a=12.780 (5) Å	2=15°-40°
b=7.408 (4) Å	μ = 0.08 mm^{-1}
c=14.794 (9) Å	T=293 (2) K
β = 104.11 (6)°	0.2 × 0.2 × 0.7 mm
V=1358.48 (3) Å^3	colorless
Z=4	
Data collection	
Enraf-Nonius CAD-4 Diffractometer	θ_{max} = 25°
$\omega/2\theta$ Scan type	$h = 0 \rightarrow 15$
Absorption correction: none	$k = 0 \rightarrow 8$
	$l = -17 \rightarrow 17$
2382 independent reflections	3 standard reflection monitored every one hour
1125 observed reflections [I > 2σ(I)]	intensity variation: none
Refinements	
Refinement on F^2	
R(F)=0.049	$\Delta\rho_{max}$= 0.22 eÅ^{-3}
wR(F^2)=0.112	$\Delta\rho_{min}$= –0.28 eÅ^{-3}
S=1.051	Extinction correction: none
1125 reflections	Atomic scattering factors from *International Tables for Crystallography* (1974, Vol. IV, Table 2.2B)
246 parameters	
Calculated weights w=1/[σ^2(F_o^2)+(0.0700P)^2+0.00P] where P=(F_o^2+2F_c^2)/3	

by reduction followed by methylation. As Heaney reported, we could obtain **4** from **6** by using scandium triflate in 54% isolated yield. However, the obtained compound **4** was identical with ours in Scheme 1 in all respects. Thus we prepared some crystals suitable for X-ray analysis after much effort in order to obtain unequivocal evidence of the structure of **4**. The ORTEP drawing was shown in Figure 1 and the crystal data are summarized in Table 1.[6]

From the various spectroscopic data, melting point, and X-ray crystal structure we could conclude that the Heaney's data of the compound **4** might be miswritten, especially in its mp, ^{1}H NMR, and ^{13}C NMR data.[3]

Acknowledgment. This work was supported by the Ministry of Education of Korea (BK-21 Project).

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4. Selected spectral data of **3** and **5**-**8**. **3**: white solid; mp 114-116 °C (lit.[2d] 115-117 °C); ^{1}H NMR ($CDCl_3$) δ 2.76-3.05 (m, 2H), 3.37-3.47 (m, 1H), 4.31-4.40 (m, 1H), 5.60 (s, 1H), 7.09-7.82 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 29.37, 38.15, 50.08, 123.42, 123.80, 125.16, 126.65, 127.39, 128.43, 129.25, 131.46, 132.77, 134.28, 134.74, 144.15, 167.90. **5**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 7.64-8.00 (m, 4H), 10.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.78, 128.45, 130.39, 132.01, 132.40, 132.95, 137.03, 166.75, 192.08. **6**: white solid; mp 149-150 °C (lit.[3] 153-155 °C); ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 3H), 3.14-3.21 (m, 2H), 3.49-3.65 (m, 1H), 4.11-4.21 (m, 1H), 5.77 (s, 1H), 7.10 (s, 1H), 7.12-7.86 (m, 8H), 8.05 (brs, NH); ^{13}C NMR ($CDCl_3$) δ 22.89, 38.84, 48.26, 85.53, 110.14, 111.83, 117.73, 118.42, 120.89, 121.07, 122.38 (2C by ^{1}H-^{13}C COSY), 126.35, 128.90, 130.93, 132.16, 135.25, 139.41, 166.81. **7**: white solid; mp 161-162 °C (lit.[7] 164 °C); IR (KBr) 3384, 2945, 2858, 1770, 1703, 1398 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.16 (t, J = 7.8 Hz, 2H), 4.01 (t, J = 7.8 Hz, 2H), 7.09-7.86 (m, 9H), 8.01 (brs, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 24.88, 38.90, 111.52, 112.82, 119.29, 119.92, 122.43, 122.54, 123.61, 127.78, 132.57, 134.30, 136.59, 168.82. **8**: white solid; mp 166-168 °C (lit.[8] 166-168 °C); ^{1}H NMR (DMSO-d_6) δ 2.95-3.10 (m, 2H), 3.40-3.60 (m, 1H), 3.80-4.00 (m, 1H), 5.82 (s, 1H), 7.17 (s, 1H), 6.96-7.70 (m, 8H), 10.83 (s, 1H); ^{13}C NMR (CD_3OD) δ 25.65, 41.92, 83.63, 112.64, 113.45, 119.70, 120.05, 122.78, 123.85, 124.08, 124.90, 129.10, 131.05, 133.32, 133.81, 138.55, 146.64, 169.80.
5. Physicochemical data of compound **4**. DEPT results were inserted in ^{13}C NMR data. white needles; mp 212-214 °C (EtOAc); IR (KBr) 1670, 3259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84-3.05 (m, 2H), 3.36-3.47 (m, 1H), 4.84-4.92 (m, 1H), 5.84 (s, 1H), 7.08-7.91 (m, 8H), 8.35 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.64 (CH_2), 38.15 (CH_2), 56.98 (CH), 109.57 (C), 111.04 (CH), 118.69 (CH), 120.10 (CH), 122.05 (CH), 122.64 (CH), 124.51 (CH), 126.79 (C), 128.89 (CH), 130.02 (C), 131.85 (CH), 132.59 (C), 136.53 (C), 142.84 (C), 168.08 (C=O); EIMS (70 eV) *m/z* (rel intensity) 77 (9), 109 (25), 217 (17), 245 (37), 273 (87), 274 (M^+, 100); FAB-Mass 275 (M^++1), 549 ($2M^+$+1).
6. All of the crystal data, data collection and refinements of **4** are summarized in Table 1. The structure was solved by direct method and refined by the full-matrix least-squares using the program SHELXL-97 (Sheldrick, G. M.; SHELXL-97: Program for the Solution Refinement of Crystal Structures. University of Gottingen, Germany, 1997).
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