1,3-Dipolar Addition of Nitrile Oxides to 3a,4-Dihydro-1-isoindolinones[1)]

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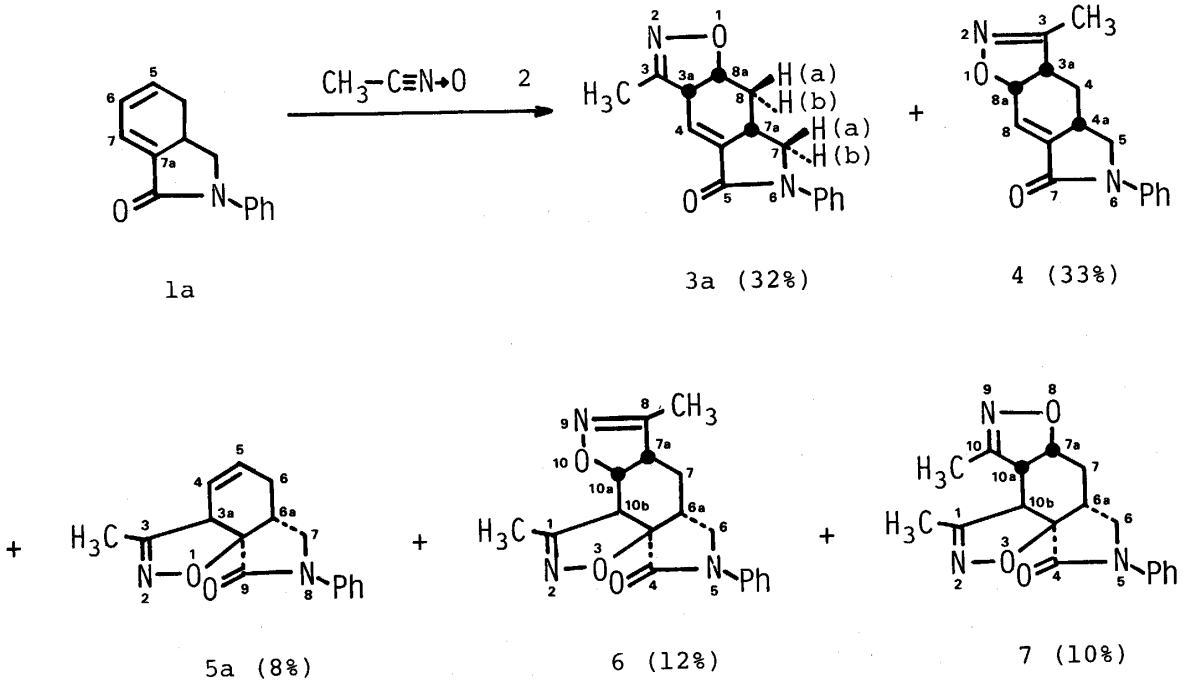
Abstract

1,3-Dipolar addition of acetonitrile oxide to 2-phenyl-3a,4-dihydro-1-isoindolinone was carried out in a stereoselective but regiorandam manner. However, the introduction of substituent, *e. g.*, methyl group, at the 4-position of the 1*H*-isoindol-1-one system turned out to improve regioselectivity of the addition. The regio- and stereoselective isoxazoline synthesis was also accomplished in the reaction with other nitrile oxides. The transformation of the isoxazoline ring was also examined.

Introduction

In the previous paper,[1)] we described the selctive introduction of functional groups into 1*H*-isoindol-1-one system, which was made of the epoxidation of 3a,4-dihydro-1-isoindolinones and successive ring opening reaction of the resultant oxiranes. Therein, the fused lactam ring of the dihydro-1-isoindolinones controlled the stereochemistry of the epoxidation and the successive ring opening reaction.

Recently, selective isoxazoline ring formation *via* 1,3-dipolar addition of nitrile oxide



Scheme 1

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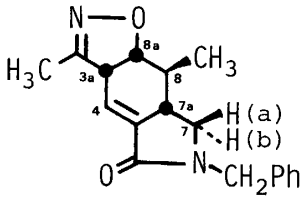
to olefin followed by transformation of the heterocyclic ring provided an efficient means for selective functionalization.[2] In the present paper, we wish to describe the problems in applying this strategy to the 3a,4-dihydro-1-isoindolinone system, especially lies at the stage of nitrile oxide cycloaddition.

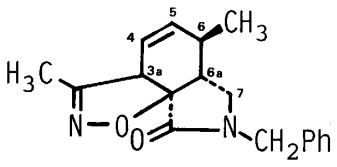
Results and Discussion

Reaction of 2-phenyl-3a,4-dihydro-1-isoindolinone (1a) and 3 molar equiv. of acetonitrile oxide (2), generated by Mukaiyama-Hoshino method,[3] gave three regioisomeric 1 : 1 adducts 3a, 4, and 5a and two 1 : 2 adducts 6 and 7 (Scheme 1). Therein, the 1,3-dipolar addition of 2 to 1a was carried out with less regioselectivity. However, the configuration between the resulting isoxazoline ring and lactam one of 3a or 4 was *syn* and, therefore, the addition of 2 onto the 5-6 bond of 1a was performed stereoselectively. The structures of these products were confirmed on the basis of the spectral data as delineated later.

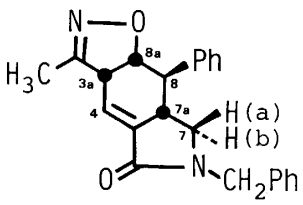
To improve the regioselectivity of cycloaddition, the reaction of 4-substituted 1-isoindolinones was surveyed. Nitrile oxide 2 was allowed to react with 2-benzyl-4-methyl-3a,4-dihydro-1-isoindolinone (1b) to afford 3b and 5b in 75 and 14% yields, respectively. On the other hand, the reaction of 2 with 2-benzyl-4-phenyl derivative 1c underwent sluggishly to give 3c (30%) and an unseparable mixture of two 1 : 1 adducts (total 10%) together with the unreacted 1c (48%).



3b

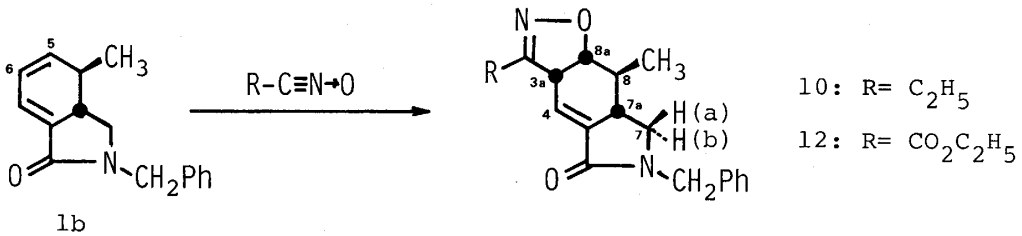


5b



3c

The structural confirmation of the products was accomplished as follows: for 3b the results of proton nuclear Overhauser effect difference spectroscopy (^{1}H-NOEDS) measurement revealed the configurations among 7a-, 8-, and 8a-H to be *trans* and *trans* (Fig. 1). On the other hand, its long-range coupling constant (J = 1.5 Hz) between 3a- and 7a-H confirmed a *cis* configuration of these two protons (Table 1). The *cis* ralationship between 4a- and 8a-H of 4 was confirmed also by its long-range coupling constant (J = 1.8 Hz).



1b

10: R= C_2H_5

12: R= $CO_2C_2H_5$

A ralatively high regioselectivity was attained in the reaction with 1b, so further reaction of other nitrile oxides with 1b was examined. The reaction of 1b with propionitrle oxide (8) and (ethoxycarbonyl)formonitrile oxide (9) gave the expected adducts 10 and 12 in 82 and 75% yields, respectively. Regioisomer 11 was also detectable in ^{1}H NMR spectrum of reaction mixture as a minor product (below 5%) in the former case and, unfortunately, it could not be isolated by a usual working up.

As mentioned above, the addition of nitrile oxides onto 1b occurred stereo- and regioselectively to give 3a,5,7,7a,8,8a-hexahydro-6*H*-isoindolo[5,6-*d*]isoxazole derivatives.

The lactam ring of 1 caused an excellent *syn*-directing effect in the epoxidation with MCPBA[1] and, therefore, a similar effect is conceivable in the present reaction. On one hand, as a possible explaination for the regioselective addition of nitrile oxides to 1b, we propose the electronic features[4] of diene systems of 1 as well as the steric influence.

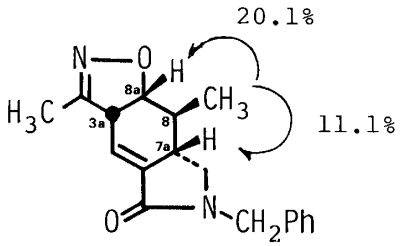
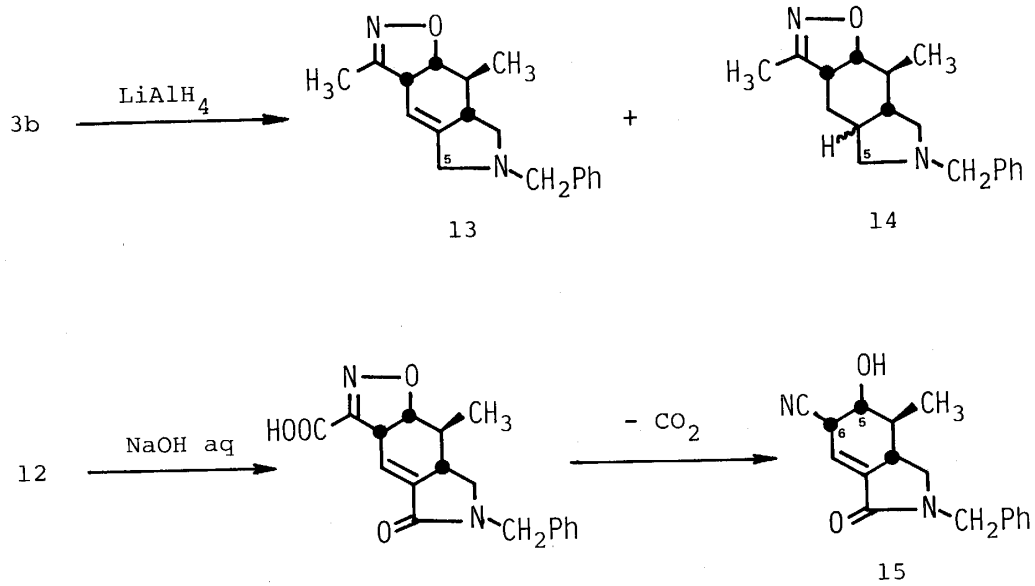


Fig. 1 ^{1}H-NOEDS Results for 3b.
% : Enhancement of signal area.

A few chemical conversions were examined in order to introduce functional groups into 1*H*-isoindol-1-one system. Similarly to the Jäger's method,[5] 3a was treated with 1.3 molar equiv. of lithium aluminiumhydride ($LiAlH_4$) in THF afforded 13 and 14, in which the reduction of the lactam ring was performed. The alkaline hydrolysis of 12 followed by decarboxylation gave the expected α-cyano alcohol 15 in 40% yield (Scheme 2).



Scheme 2

In conclusion, the 1,3-dipolar addition of nitrile oxides to 3a,4-dihydro-1-isoindolinones was carried out regio- and stereoselectively to afford 6*H*-isoindolo[5,6-*d*]isoxazole derivatives. The chemical conversions of the isoxazoline ring indicates a novel synthetic method for polyfunctionalized 1*H*-isoindol-1-one system. Other chemical transformation of the isoxazoline ring of these products are now under progress, and the results will be reported elsewhere.

Experimental[6]

Reaction of 1 with 2. Typical Procedure: To a mixture of **1a** (4.73 mmol) and phenyl isocyanate (28.4 mmol) in benzene (20 mL) nitromethane (14.1 mmol) in benzene (10 mL) containing a few drops of triethylamine was added at room temperature. After the completion of addition, the reaction mixture was stirred for additional 20 h. The resultant *N,N'*-diphenylurea was filtered off and the filtrate was evaporated to dryness. The residue was subjected to a column chromatography over silica gel to give **5a** (chloroform), **3a** (chloroform-ethyl acetate: 4/1), **6**,**4** (chloroform-ethyl acetate: 2/1), and **7**(ethyl acetate).

3a: Colorless needles (ethanol); mp 242-245°C; IR(KBr)cm^{-1}: 1660-1630 (CO and C=N); MS *m/z*: 268(M^+). Found: C, 71.35; H, 6.01; N, 10.25%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

4: Colorless needles (ethanol); mp 208-210°C; IR(KBr)cm^{-1}: 1660-1620(CO and C=N), ^1H NMR($CDCl_3$)δ=1.79 (1H,dt, 4-H,$J_{gem}=J_{4-4a}$=13.7 and J_{3a-4}=5.1 Hz), 1.98 (3H, s, CH_3), 2.44 (1H,ddd, 4-H, J_{gem}=13.7, $J_{=3a-4}$=2.4, and J_{4-4a}=5,4 Hz), 2.72 (1H,m, 4a-H),3.51(1H,dd, 5-H, J_{gem}=9.6 and J_{5-4a}=7.8Hz),3.60(1H, ddd,3a-H,J_{3a-4}=2.4, J_{3a-4}= 5.1, and J_{3a-8a}=9.5Hz), 3.98 (1H, t, 5-H, $J_{gem}=J_{4a-5}$=9.5Hz), 5.24 (1H, ddd, 8a-H, J_{3a-8a}= 9.5,J_{8-8a}=4.4, and J_{4a-8}=1.8Hz), 6.58 (1H, dd,8-H, J_{4a-8}=3.2 and J_{8-8a}=4.8Hz), and 7.1 (5H, m, phenyl); MS *m/z*: 268(M^+). Found: C, 71.73; H, 6.04; N, 10.35%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

5a: Colorless needles (ethanol); mp 170-172°C; IR(KBr)cm^{-1}: 1660-1620 (CO and C=N); ^1H NMR($CDCl_3$)δ=2.09 (3H, s, CH_3), 2.1-2.5 (3H, overlapped with each other, 6-and 6a-H), 3.77 (1H, m, 3a-H), 3.8-4.0 (2H, m, 7-H), 5.77 (1H, br d, 4-H, J_{4-5}=8.5Hz), 6.05 (1H, m, 5-H), and 7.3-7.7 (5H, m, phenyl); MS *m/z*: 268(M^+). Found: C, 71.74; H, 5.99; N, 10.39%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

6: Colorless needles (ethanol); mp 170-171°C; IR(KBr)cm^{-1}: 1680-1660 (CO and C=N); ^1H NMR($CDCl_3$)δ=1.43 (1H, dt, 7-H, $J_{gem}=J_{6a-7}$=14.8 and J_{7-7a}=9.6Hz), 1.75 (1H, dd, 7-H, J_{gem}=14.8 and J_{6a-7}=4.5 Hz), 2.05, 2.12 (3H each, 2s, CH_3), 2.37 (1H, dd, 6a-H, J_{6-6a}=6.8, J_{6a-7}=4.5, and J_{6a-7}=14.8 Hz), 3.24 (1H, br t, 7a-H, $J_{7-7a}=J_{7a-10a}$= 9.6Hz), 3.46 (1H, d, 6-H, J_{gem}=10.8 Hz), 3.67 (1H, d, 10b-H, $J_{10a-10b}$=4.6Hz), 4.33 (1H, dd, 6-H, J_{gem}=10.8 and J_{6-6a}=6.8 Hz), 4.95 (1H, dd, 10a-H, $J_{10a-10b}$=4.6 and J_{7a-10a}=9.6 Hz), and 7.1-7.7 (5H, m, phenyl); ^{13}C NMR($CDCl_3$) δ=11.7, 12.1 (CH_3), 25.6 (7-C), 30.7 (6a-C), 46.8 (7a-C), 50.7, 52.4 (6- and 10b-C), 75.7 (10a-C), 88.3 (3a-C), 120.0, 125.5, 129.2, 139.1 (Ph-C), 154.8, 158.4 (1- and 8-C), 170.3 (4-C); MS *m/z*: 325(M^+). Found: C, 66.44; H, 5.91; N, 12.89%. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.9%.

Adduct **7** could not be obtained as a pure from from the mixture with*N,N'*-diphenylurea. However, the structure was confirmed to be 1,10-dimethyl-5-phenyl-4,5,6,6a,7,7a,10a,10b-octahydroisoxazolo[5',4' : 3a,4]isoindolo[5,6-*d*]isoxazol-4-one from

the following data : MS*m / z* : 325(M^+) ; ^{1}H NMR($CDCl_3$)δ = 1.06(1H,m,7-H),2.00,2.03 (3H each, 2s, CH_3), 2.42 (1H, m, 7-H), 3.6-4.0 (4H, overlapped with each other, 6-, 6a, and 10b-H), 4.65 (1H, dd, 10a-H, J_{7a-10a}=9.8 and $J_{10a-10b}$=1.2 Hz), and 7.0-7.7 (5H, m, phenyl).

3b : Colorless needles (ethanol) ; mp 176-177°C ; IR(KBr)cm^{-1} : 1670-1640 (CO and C=N) ; MS *m/z* : 296(M^+). Found : C, 72.98 ; H, 6.70 ; N, 9.59%. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95 ; H, 6.80 ; N, 9.45%.

Adduct **5b** could not be obtained as a pure torm from the mixture with and, however, its structure was confirmed by the following ^{1}H NMR spectral data : δ=1.05 (3H, d, CH_3, J=7.0 Hz), 2.0 (3H, s, CH_3), 1.8-2.0 (2H, overlapped with each other, 6- and 6a-H), 2.90 (1H, dd, 7-H, J_{gem}=7.0 and J_{6-6a}=1.6 Hz), 3.59 (1H, dd, 7-H, J_{gem}=7.0 and J_{6-6a}=3.8 Hz), 3.96 (1H, m, 3a-H), 4.52 (2H, s, -CH_2-Ph), 5.6-5.8 (2H, overlapped with each other, 4- and 5-H), and 7.1-7.4 (5H, m, phenyl).

3c : Colorless prisms (ethanol) ; mp 248-250°C ; IR(KBr)cm^{-1} : 1660-1620 (CO and C=N) ; MS *m/z* : 358(M^+). Found : C, 76.97 ; H, 6.24 ; N, 7.81%. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07 ; H, 6.19 ; N, 7.82%.

10 : Colorless prisms (ethanol) ; mp 111-113°C ; IR(KBr)cm^{-1} : 1670-1640 (CO and C=N) ; MS *m/z* : 310(M^+). Found : C, 73.68 ; H, 7.20 ; N, 8.93%. Calcd for $C_{19}H_{22}N_2O_2$: C,73.52 ; H, 7.14 ; N, 9.03%.

Adduct **11** was assigned to be 8-benzyl-3-ethoxycarbonyl-6-methyl-3a,6,6a,7,8,9-hexahydroisoindolo[4,3a-*d*]isoxazole, same type of product as **5**, from the following ^{1}H NMR spectral data : δ=1.05 (3H, d, CH_3, J=7 Hz), 2.00 (3H, s, CH_3), 1.8-2.0 (2H, overlapped with each other, 6- and 6a-H), 2.90 (1H, dd, 7-H, J_{gem}=7.8 and J_{6a-7}=1.6 Hz), 3.59 (1H, dd, 7-H, J_{gem}=7.8 and J_{6a-7}=4.1 Hz), 3.96 (1H, br s, 3a-H), 4.52 (2H, s, -CH_2-Ph), and 7.1-7.4 (5H, m, phenyl).

Reaction of 1b with 9. To a benzene solution (20 mL) of ethyl chloro (hydroxyimino)-acetate[2e] (2.09 mmol) and **2c** (4.18 mmol), triethylamine (2.09 mmol) in benzene (10 mL) was added dropwise for 5h. The resultant triethylamine hydrochloride was filtered off and the filtrate was concentrated under a reduced pressure. The residue was subjected to column chromatography on silica gel to give **12** as chloroform-ethyl acetate (3/1) eluent.

Table 1. ^{1}H NMR Spectral Date for 3a,6,7,7a,8,8a-Hexahydro-5*H*-isoindolo[5,6-*d*]isoxazol-5-ones **3**, **10**, and **12** in $CDCl_3$: δ

Compd	3a-H	4-H	7-H(a)	7-H(b)	7a-H	8-H(a)	8-H(b)	8a-H	Others
3a	3.88	6.65	4.08	3.60	3.02	2.62	1.52	4.94	2.05(Me)
	m	dd	t	dd	m	ddd	ddd	dt	7.1-7.7(Ph)
	J (Hz) : 3a-4=5.8, 3a-7a=1.0, 3a-8a=8.8, 4-7a=3.2, 7(a)-7(b)=7(a)-7a=9.8, 7(b)-7a=7.8, 7a-8(a)=5.4, 7a-8(b)=11.7, 8(a)-8(b)=13.7, 8(a)-8a=8(b)-8a=2.6								
3b	3.82	6.51	3.48	2.94	3.67		1.63	4.63	1.16, 2.02(Me)
	m	dd	t	dd	m		m	dd	4.46, 4.65 (-CH_2-Ph)
	J (Hz) : 3a-4=5.1, 3a-7a=1.5, 3a-8a=9.2, 4-7a=3.4,								7.2-7.4(Ph)

	7(a)−7(b)=7(a)−7a=9.8, 7(b)−7a=7.7, 7a−8=10.5, 8−8a=2.4, 8−Me=7.0							
3c	3.95	6.60	3.31	2.85	3.40	2.77	4.83	2.05 (Me)
	m	dd	t	dd	m	dd	dd	4.37, 4.64 ($-CH_2-Ph$)
	J (Hz) : 3a−4=4.8, 3a−7a=1.0, 3a−8a=8.8, 4−7a=3.8, 7(a)−7(b)=7(a)−7a=9.8, 7(b)−7a=6.6, 7a−8=11.2, 8−8a=2.4							
10	3.90	6.48	3.48	2.94	2.67	1.62	4.61	1.17, 1.23 (Me)
	m	dd	t	dd	m	m	dd	2.38 ($-CH_2-$)
	J (Hz) : 3a−4=4.8, 3a−7a=1.0 3a−8a=8.8, 4−7a,=3.4, 7(a)−7(b)=7(a)−7(a)=9.7, 7(b)−7a=7.8, 7a−8=11.4, 8−8a=2.6, 8−Me=7.2							4.46, 4.67 ($-CH_2-Ph$) 7.2−7.4 (Ph)
12	4.2−4.3	6.61	3.48	2.95	2.62	1.71	4.86	1.20, 1.38 (Me)
	m[a]	dd	t	dd	m	m	dd	4.2−4.3[a] ($-CH_2-$)
	J (Hz) : 3a−4=4.8, 3a−8a=9.4, 4−7a=3.4, 7(a)−7(b)=7(a)−7a=9.6, 7(b)−7a=7.8, 7a−8=10.5, 8−8a=2.4, 8−Me=7.2							4.42, 4.63 ($-CH_2-Ph$) 7.1−7.4 (Ph)

a) Overlapped with each other.

12 : Colorless oil ; IR(Neat)cm^{-1} : 1720-1650 (CO and C=N) ; MS *m/z* : 354(M^+). Found : *m/z* 354.1567. Calcd for $C_{22}H_{22}N_2O_2$: M, 354.1577.

The ^1H NMR spectral data for **3**, **10**, and **12** are summarized in Table 1.

Reduction of 3b with $LiAlH_4$ To a stirred solution of **3b** (300 mg, 1.01 mmol) in THF (10 mL), 1.3 molar equiv. of $LiAlH_4$ was added bit by bit at room temperature. After the completion of addition, the reaction mixture was heated at reflux for 3 h. The excess $LiAlH_4$ was destroyed with ethyl acetate and the solvent evaporated *in vacuo*. The residue was poured into water and extracted with chloroform. The chloroform was evaporated to give a residue, which was subjected to column chromatography on silica gel to afford **13** (42%) and **14** (43%) as chloroform-ethyl acetate eluent.

13 : Colorless needles (hexane-benzene) ; mp 99-100°C ; ^1H NMR($CDCl_3$) δ=1.16(3H, d, CH_3, *J*=7Hz), 1.6(1H, m, 8-H), 1.91(3H, s, CH_3), 2.0-2.2(2H, m), 2.52(1H, m, 7a-H), 3.0(1H, dd, 7-H), 3.20(1H, t, 7-H), 3.4-3.9(3H, m, -CH_2-Ph and 5-H), 4.56(1H, dd, 8a-H, *J*=8 and 2 Hz), 5.38(1H, m, 4-H), and 7.3(5H, s, phenyl) ; MS *m/z* : 282(M^+). Found : C, 76.72 ; H, 7.92 ; N, 9.72%. Calcd for $C_{18}H_{22}N_2O$: C, 76.56 ; H, 7.85 ; N, 9.22%.

14 ; Pale yellow oil ; IR(Neat)cm^{-1} : 1680 (C=N) ; ^1H NMR ($CDCl_3$) δ=1.04 (3H, d, CH_3, *J*=7Hz), 1.5-1.8(3H, m), 1.88(3H, s, CH_3), 1.9-2.2(4H, m), 2.9-3.0(2H, m), 3.4(1H, m), 3.6(2H, s, -CH_2-Ph), 4.60(1H, dd, 8a-H, *J*=8 and 2 Hz), and 7.2-7.4(5H, m, phenyl) ; MS *m/z* : 284(M^+). Found : *m/z* 284.1919. Calcd for $C_{18}H_{24}N_2O$: M, 284.1889.

Alkaline hydrolysis of 12 followed by decarboxylation. A solution of **12** (400 mg, 1.13 mmol) in ethanol-10% aqueous sodium hydroxide (10 mL-20 mL) was stirred at room temperature for 30 min. The reaction mixture was cooled in ice bath and made neutral

with conc. hydrochloric acid. The resultant carboxylic acid was filtered off and dried. This was pyrolyzed at 169 °C untill evalution of gas for 5 min. The reaction mixture was subjected to column chromatography on silica gel to give **15** (40%) as ethyl acetate eluent.

15 : Colorless prisms (ethanol) ; IR(KBr)cm^{-1} : 3340(OH), 2240(CN), and 1660(CO) ; ^1H NMR($CDCl_3$) $\delta=1.17$ (3H,d,CH_3, $J=7Hz$), 2.7-3.1 (1H,m, 4-H), 2.7-3.1 (2H, m, 3a-H and OH), 3.26 (2H, m, 3-H), 3.44 (1H, m, 6-H), 4.53 (2H, s, -CH_2-Ph), 4.62 (1H, m, 5H), 6. 47 (1H, br, 7-H), and 7.2-7.4 (5H, m, phenyl) ; MS m/z : 282(M^+).

Acknowledgement

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References

1) Cycloaddition Reaction of 2-Pyrones and Related Compounds. Part VI. Part V of this series : M. Noguchi, M. Yoshioka, S. Kakimoto, and S. Kajigaeshi, Bull. Chem. Soc. Jpn., **60**, 3261 (1987).
2) a) P. A. Wase and H. R. Hinney, J. Am. Chem. Soc., **101**, 1319 (1979) ; b) M. Asaoka, M, Abe, T. Mukuta, and H. Takei, Chem. Lett., **1982**, 215 ; c) D. P. Curran, J. Am. Chem. Soc., **105**, 5826 (1983) ; d) D. P, Curran, S. A. Scanga, and C. J. Fenk, J. Org. Chem., **49**, 3474 (1984) ; e) A. P. Kozikowski and M. Adamczyk, *ibid*., **48**, 366 (1983) ; f) A. P. Kozikowski and P.-u. Park, J. Am. Chem. Soc., 107, 1763 (1985).
3) T. Mukaiyama and T. Hoshino, J. Am. Chem. Soc., **82**, 5339 (1960).
4) For instance, the difference of chemical shifts between 5-and 6-H of 1b was larger than that of 1a.[1]
5) V. Jäger and H. Grund, Angew. Chem., Int. Ed. Engl., **15**, 50 (1976) : V. Jäger, H. Grund, and W. Schwab, *ibid*., **18**, 78 (1979).
6) The general experimental procedures were the same as in Part V.[1]