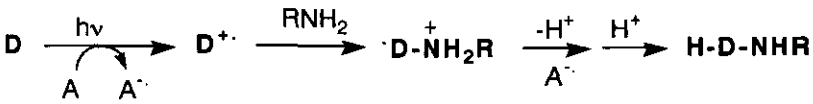
APPLICATION OF PHOTOAMINATION TO SYNTHESIS OF BENZYLISOQUINOLINES, APORPHINS, AND ISOPAVINES

Masahide Yasuda,* Shuichi Hamasuna, Katsuhiko Yamano, Jun-ichi Kubo, and Kensuke Shima

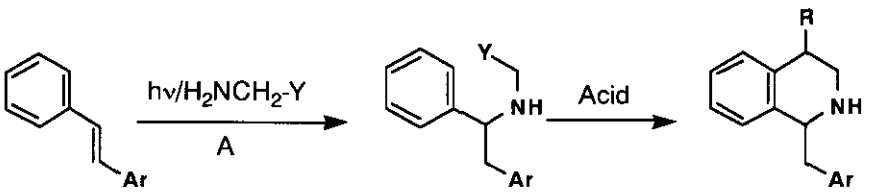
Department of Industrial Chemistry, Faculty of Engineering, Miyazaki University, Gakuen-Kibanadai, Miyazaki 889-21, Japan

Abstract —— The preparation of benzylisoquinolines, isopavines, and aporphines was performed by the photoamination of stilbene, *p*-methoxystilbene, and phenanthrene with amino alcohols, aminoacetal, allylamine in the presence of dicyanobenzene followed by the cyclization with BF_3 or CF_3SO_3H.

A number of synthetic approaches to isoquinolines have been developed for many years.[1] The photochemical reactions have provided useful synthetic tools for heterocyclic construction.[2] We have found a direct photoamination with amines which proceeds *via* nucleophilic addition of an amine to the cation radical of substrate ($D^{+\cdot}$) generated by photochemical electron transfer to electron acceptor (A) as shown in Scheme 1.[3] Since the photoamination is a convenient method to introduce an amino group into electron-rich substrates, our interest in this area is directed toward a synthetic application of the photoamination. In our preliminary communication,[4] we have reported a synthesis of isoquinolines from stilbene derivatives *via* the photoamination (Scheme 2). Here, we extensively applied the photoamination to the synthesis of benzylisoquinolines, isopavines, and aporphines in order to elucidate the synthetic scope and limitation.



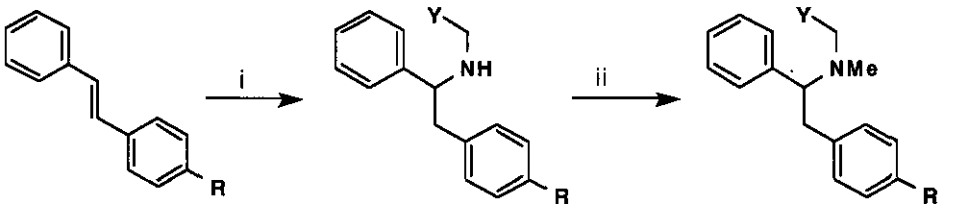
Scheme 1



Scheme 2

The Photoamination with Bifunctional Alkylamines.

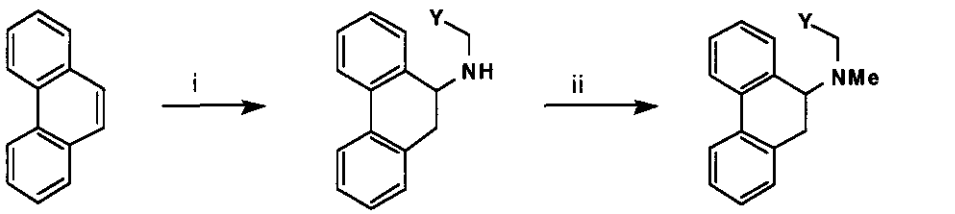
The photoamination of stilbene (**1a**), *p*-methoxystilbene (**1b**), and phenanthrene (**1c**) was performed by the irradiation of an acetonitrile/benzene/water (7:2:1) solution containing **1a-c**, *p*- or *m*-dicyanobenzene (*p*- or *m*-DCNB) and an amine through a Pyrex filter by a high pressure mercury lamp (Scheme 3). *N*-(1,2-Diarylethyl)amino alcohols (**2a-c,f**), *N*-(1,2-diarylethyl)allylamine (**2d, g**), and *N*- (1,2-diarylethyl)aminoacetaldehyde diethyl acetals (**2e, h**) were formed



1a; R= H
1b; R= OMe

2a; Y= CH(OH)Me, R= H
2b; Y= CH(OH)Ph, R= H
2c; Y= CH_2OH, R= H
2d; Y= $CH{=}CH_2$, R= H
2e; Y= $CH(OEt)_2$, R= H
2f; Y= CH(OH)Me, R= OMe
2g; Y= $CH{=}CH_2$, R= OMe
2h; Y= $CH(OEt)_2$, R= OMe

3a; Y= CH(OH)Me, R= H
3b; Y= $CH{=}CH_2$, R=H
3c; Y= $CH(OEt)_2$, R=H
3d; Y= CH(OH)Me, R= OMe
3e; Y= $CH{=}CH_2$, R= OMe
3f; Y= $CH(OEt)_2$, R= OMe



1c

4a; Y= CH(OH)Me
4b; Y= CH(OH)Et
4c; Y= $CH{=}CH_2$

5a; Y= CH(OH)Me
5b; Y= CH(OH)Et
5c; Y= $CH{=}CH_2$

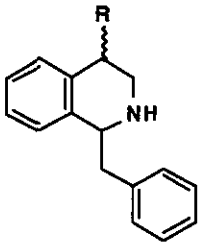
Scheme 3. Reagents: i hν/H_2NCH_2-Y/DCNB, ii HCO_2H/HCHO

from the photoamination of **1a-b** with amino alcohols, allylamine, and aminoacetaldehyde diethyl acetal, respectively. The results were shown in Table 1. Also, *N*-substituted 9-amino-9,10-dihydrophenanthrenes (**4a-c**) were obtained from the photoamination of **1c** with alkylamines. After the photoreaction, DCNB which was used as an electron acceptor was mostly recovered except for a few cases. No photoamination in the absence of DCNB occurred at all. It is noteworthy that the bifunctional alkylamines used as the amination reagent selectively reacted at amino group without the reactions of hydroxy, vinyl and acetal groups. The photoamination of **1b** with the bifunctional alkylamines gave *N*-substituted 1-amino-2-(p-methoxyphenyl)-1-phenylethane accompanying the formation of *N*-substituted 1-amino-1-(p-methoxyphenyl)-1-phenylethane in small amounts (< 14 %). *N*-Methylation of **2a,d-h** and **4a-c** was performed with HCO_2H/ HCHO to give **3a-f** and **5a-c**, respectively.

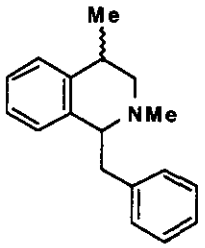
Table 1. Photoamination of **1a-c** with Bifunctional Alkylamines[a)]

run no.	**1**	Y	A[b)]	irradn. time/h	product (yield/%)[c)]	recov. of **1**/%	recov. of DCNB/%
1[d)]	**1a**	CH(OH)Me	*p*-DCNB	8	**2a** (93)	6	98
2[d)]	**1a**	CH(OH)*Ph*	*p*-DCNB	13	**2b** (82)	7	96
3	**1a**	CH_2OH	*p*-DCNB	9	**2c** (97)	0	93
4	**1a**	$CH{=}CH_2$	*p*-DCNB	9	**2d** (46)	8	81
5	**1a**	$CH(OEt)_2$	*p*-DCNB	15	**2e** (86)	1	91
6	**1b**	CH(OH)Me	*p*-DCNB	19	**2f** (82)	4	80
7	**1b**	$CH{=}CH_2$	*p*-DCNB	18	**2g** (48)	16	47
8	**1b**	$CH(OEt)_2$	*p*-DCNB	15	**2h** (73)	7	95
9	**1c**	CH(OH)Me	*p*-DCNB	25	**4a** (90)	3	54
10	**1c**	CH(OH)Et	*p*-DCNB	15	**4b** (87)	10	65
11[e)]	**1c**	$CH{=}CH_2$	*m*-DCNB	12	**4c** (67)	21	35

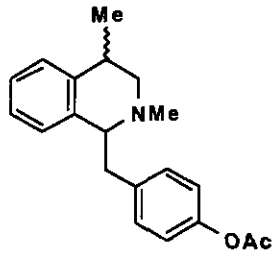
a) For an acetonitrile/benzene/water (7:2:1) solution (100 ml) containing **1** (5 mmol), DCNB (5 mmol), and the amine (25 mmol). b) An electron acceptor. DCNB; dicyanobenzene. c) Isolated yields based on **1** used. d) For an acetonitrile/benzene (8:2) solution. e) For an acetonitrile/water (9:1) solution.



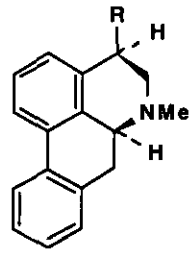
6a; R= Me
6b; R= Ph



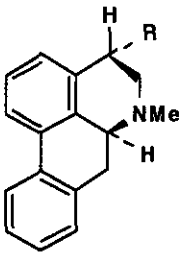
7



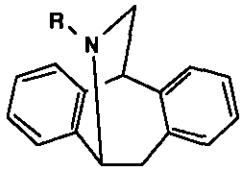
8



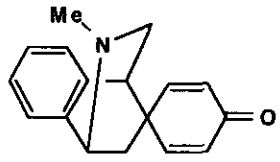
9a; R= Me
9b; R= Et



9a'; R= Me
9b'; R= Et



10a; R= H
10b; R= Me



11

The Cyclization with CF_3SO_3H or BF_3

The *N*-(1,2-diphenylethyl)amino alcohols, **2a-b** and **3a**, were treated with trifluoromethanesulfonic acid (TFSA) to give the 4-substituted 1-benzyl-1,2,3,4-tetrahydroisoquinolines (**6a-b** and **7**), respectively. Also, cyclization of *N*-methyl-*N*-(1,2-diphenylethyl)allylamine (**3b**) occurred with TFSA to give **7** whereas no cyclization of **2d** occurred. Treatment of **3d** and **3e** with TFSA gave *N*-methyl-4-methyl-1-(*p*-acetoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**8**) after acetylation with acetic anhydride. These isoquinolines were obtained as a mixture of diastereomers in the ratios listed in Table 2. Cyclization of *N*-substituted *N*-methyl-9-amino-9,10-dihydrophenanthrenes (**5a-c**) with TFSA gave the corresponding aporphines (**9a**, **9a'**, **9b**, and **9b'**). The structure of **9a** and **9b** can be assigned to be cis isomer since a signal for an aromatic proton in ^1H nmr spectra appeared at higher field by shielding effect of methyl or ethyl group which located in coplanar with aromatic ring, while such a shielding effect of the alkyl group was not observed in the cases of trans isomers (**9a'** and **9b'**). The cyclization of *N*-(2-hydroxyethyl)amino-1,2-diphenylethane (**2c**) with TFSA was not observed.

The cyclization of benzylaminoacetals (**2e** and **3c**) was performed with gaseous BF_3 in dichloro-

Table 2. The Cyclization of the Aminated Compounds with CF_3SO_3H or BF_3

run no	aminated compound	reagent[a]	isoquinoline	yield/%[b]	
1	**2a**	TFSA	**6a**	72	(1:0.4)
2	**2b**	TFSA	**6b**	98	(1:0.3)
3	**3a**	TFSA	**7**	60	(1:0.8)
4	**3b**	TFSA	**7**	94	(1:0.3)
5	**3d**	TFSA	**8**	89	(1:0.7)
6	**3e**	TFSA	**8**	80	(1;0.5)
7	**5a**	TFSA	**9a, 9a'**	41	(1:0.9)
8	**5b**	TFSA	**9b, 9b'**	36	(1:0.8)
9	**5c**	TFSA	**9a, 9a'**	62	(1:0.7)
10	**2e**	BF_3	**10a**	80	
11	**3c**	BF_3	**10b**	89	
12	**3f**	BF_3	**11**	28	

a) TFSA; trifluoromethane sulfonic acid. b) Isolated yields based on the aminated compounds. The values in parenthesis are the diastereomer ratios.

methane to give the isopavines (**10a** and **10b**), respectively. But mineral acids (e.g. HCl, H_2SO_4) and $BF_3{\cdot}OEt_2$ were not effective for the cyclization of these benzylaminoacetals. Moreover, the *treatment of* **3f** *with* BF_3 *gave* **11**, *whereas the reaction of* **2h** *with* BF_3 *gave the intractable* materials.

As has been reported previously,[3b,5] the photoamination of **1a-c** with alkylamines certainly proceeds according to Scheme 1; the cation radical of **1** generated by the photochemical electron transfer to DCNB is nucleophilically attacked by the amine followed by the one-electron reduction of aminated radical by the anion of DCNB to give the final products. We have already elucidated that the photoamination of **1b** and **1c** with ammonia occurred at the benzylic position of unsubstituted phenyl group and at C-9 where the highest positive charge of the cation radicals might develop.[3,5] Thus, the photoamination with alkylamines occurred mainly at the benzylic position of phenyl group of **1b** and at C-9 of **1c**, though the regioselectivity for photoamination of **1b** with the bifunctional alkylamines was slightly lower compared with the case with ammonia, as a consequence from the much higher nucleophilicitiy of the bifunctional alkylamines than ammonia.

Benzylaminoacetals and benzylamino alcohols are known to be the precursors for the preparation of such the isoquinoline compounds as isopavine and benzylisoquinoline alkaloids.[6] The cyclization of *N*-(1,2-diarylethyl)amino alcohols can readily proceed via the carbonium ion generated by TFSA while no cyclization of **2c** occurs since there is no substituent which can stabilize the carbonium ion. The treatment with BF_3 is effective for the cyclization of the *N*-substituted aminoacetals as Vinot has already reported for the cyclization of several aminoacetals.[7]

The convenient method for the preparation of 4-substituted benzylisoquinolines and aporphines has been scarcely reported, though the synthesis of 6,7-substituted aporphines[8] and benzylisoquinolines[9] have been reported. The photoamination, therefore, provides a convenient method for the preparation of the precursors of these isoquinolines.

EXPERIMENTAL

^1H- and ^{13}C-nmr spectra were taken on a Bruker AC-250P spectrometer for chloroform-d_1 solution using tetramethylsilane as internal standard. Mass spectra were taken on a JEOL JMS-D300S spectrometer. Commercially available **1a** and **1c** were used after recrystallization and **1b** was prepared by Wittig reaction of *p*-methoxybenzaldehyde with benzyltriphenylphosphonium chloride. Boron trifluoride gas was supplied from Hashimoto Chemical Co.(Osaka).

Photoamination of 1a-c with Bifunctional Alkylamines - General Procedure

An acetonitrile/water solution containing **1**, DCNB, an alkylamine was bubbled with argon gas and then irradiated by an Eikosha PIH-300 high-pressure mercury lamp through a Pyrex filter under cooling with water. Details of the follow-up process were described in the literature.[3a] Irradiation time, yields of products, recovered yields of the electron acceptor, and conversions of the arenes are listed in Table 1.

N-(2-Hydroxypropyl)amino-1,2-diphenylethane (2a). ^1H Nmr δ 1.00 and 1.01 (d, J= 6.3 Hz, 3H), 2.21 (dd, J= 12.1, 8.8 Hz, 1H), 2.33 (br s, 2H), 2.49 (dd, J= 11.6, 8.9 Hz, 1H), 2.92 (dd, J= 14.2, 11.8 Hz, 2H), 3.52-3.68 (m, 1H), 3.84 (t, J=14.0 Hz, 1H), 7.09-7.33 (m, 10H). ^{13}C Nmr δ 20.0 and 20.4, 44.9 and 45.3, 54.1 and 55.3, 63.9 and 65.4, 65.6 and 66.3, 126.4 and 126.5, 127.0 and 127.1, 127.2, 128.3, 128.4, 128.5, 129.3, 138.7, 143.2 and 143.6. Ms m/z 255 (M^+), 210 (M-CH_3CHOH).

N-(2-Hydroxy-2-phenethyl)amino-1,2-diphenylethane (2b). ^{1}H Nmr δ 2.02-2.46 (br s, 2H), 2.47-2.63 (m, 1H), 2.63-2.82 (m, 1H), 2.94 (dd, J= 8.3, 5.4 Hz, 2H), 3.81 and 3.91 (t, J= 6.9 Hz, 1H), 4.48 and 4.58 (dd, J= 8.3, 3.3 Hz, 1H), 6.87-7.48 (m, 15H). ^{13}C Nmr δ 45.0 and 45.2, 54.6 and 55.3, 63.9 and 65.1, 71.8 and 72.4, 125.7 and 125.8, 126.4 and 126.5, 127.1, 127.3, 127.4, 128.3, 128.4, 128.5, 129.3, 138.6 and 138.7, 142.3 and 142.5, 143.2 and 143.5. Ms m/z 299 (M-H_2O), 226 (M-CH_2Ph).

N-(2-Hydroxyethyl)amino-1,2-diphenylethane (2c). ^{1}H Nmr δ 2.13 (br s, 2H), 2.56 (t, J= 5.2 Hz, 2H), 2.86-3.01 (m, 2H), 3.41-3.57 (m, 2H), 3.86 (dd, J= 7.7, 6.2 Hz, 1H), 7.10-7.34 (m, 10H). ^{13}C Nmr δ 45.1, 48.9, 61.2, 64.5, 126.4, 127.16, 127.24, 128.4, 128.5, 129.3, 138.6, 143.3. Ms m/z 241 (M^+), 196 (M-CH_2CH_2OH).

N-Allylamino-1,2-diphenylethane (2d). ^{1}H Nmr δ 2.28 (br s, 1H), 2.92-3.00 (m, 1H), 2.95 (d, J= 7.0 Hz, 2H), 3.10 (dd, J=8.0, 5.3 Hz, 1H), 3.91 (t, J= 7.1 Hz, 1H), 4.96-5.04 (m, 2H), 5.68-5.94 (m, 1H), 7.09-7.33 (m, 10H). ^{13}C Nmr δ 45.0, 49.8, 63.8, 115.9, 126.3, 127.1, 127.4, 128.4, 128.4, 129.2, 136.4, 138.7, 143.1. Ms m/z 237 (M^+).

N-(2,2-Diethoxyethyl)amino-1,2-diphenylethane (2e). ^{1}H Nmr δ 1.07 (t, J= 6.9 Hz, 3H), 1.09 (t, J= 7.1 Hz, 3H), 1.74 (br s, 1H), 2.46 (dd, J= 12.1, 6.3 Hz, 1H), 2.54 (dd, J= 12.0, 5.2 Hz, 1H), 2.87 (dd, J= 13.1, 8.2 Hz, 1H), 2.95 (dd, J= 13.4, 5.8 Hz, 1H), 3.31-3.42 (m, 2H), 3.46-3.60 (m, 2H), 3.83 (dd, J= 8.2, 5.8 Hz), 4.49 (dd, J= 6.1, 5.1 Hz, 1H), 7.12-7.31 (m, 8H). ^{13}C Nmr δ 15.3, 45.3, 49.8, 61.9 and 62.0, 64.8, 101.8, 126.4, 127.1, 127.3, 128.3, 128.4, 129.3, 138.6, 143.6. Ms m/z 313 (M^+), 268 (M-OEt).

N-(2-Hydroxypropyl)amino-2-p-methoxyphenyl-1-phenylethane (2f). ^{1}H Nmr δ 1.00 (d, J= 6.2 Hz, 3H), 2.15-2.27 (m, 1H), 2.42-2.51 (m, 1H), 2.55 (br s, 2H), 2.86 (d, J= 6.7 Hz, 2H), 3.54-3.67 (m, 1H), 3.73 and 3.74 (s, 3H), 3.76-3.84 (m, 1H), 6.75-6.85 (m, 2H), 6.97-7.03 (m, 2H), 7.21-7.33 (m, 5H). ^{13}C Nmr δ 20.2 and 20.6, 44.1 and 44.3, 54.3 and 55.1, 55.3, 64.1 and 65.5, 65.6 and 66.3, 113.7 and 113.8, 127.1 and 127.1, 128.1 and 128.1, 128.3 and 128.4, 129.2, 130.2 and 130.6, 143.3 and 143.8, 158.1 and 158.2. Ms m/z 299 (M^+), 211.

N-Allylamino-2-p-methoxylphenyl-1-phenylethane (2g). ^{1}H Nmr δ 1.95 (br s, 1H), 2.84-2.97 (m, 3H), 3.05 (dd, J= 14.3, 5.2 Hz, 1H), 3.70 (s, 3H), 3.85 (t, J= 6.5 Hz, 1H), 4.96-5.02 (m, 2H), 5.67-5.82 (m,. 1H), 6.77 (d, J= 8.5 Hz, 2H), 7.01 (d, J= 8.5 Hz, 2H), 7.11-7.29 (m, 5H). ^{13}C Nmr δ 44.1, 49.8, 52.8, 63.9, 113.7, 115.6, 127.0, 127.3, 128.2, 130.1, 130.9, 136.6, 143.4, 158.0.

N-(2,2-Diethoxyethyl)amino-2-p-methoxylphenyl-1-phenylethane (2h) ^{1}H Nmr δ 1.08 (t, J= 7.0 Hz, 3H), 1.09 (t, J= 7.1 Hz, 3H), 1.80 (br s, 1H), 2.42-2.57 (m, 1H), 2.77-2.93 (m, 1H), 3.31-3.58 (m, 4H), 3.77 (s, 3H), 4.50 (t, J= 3.8 Hz, 1H), 6.80 (d, J= 8.6 Hz, 2H), 7.04 (d, J= 8.6 Hz, 2H), 7.11-7.39 (m, 5H). ^{13}C Nmr δ 15.3, 44.4, 49.9, 55.2, 61.9, 62.0, 64.9, 101.8, 113.8, 127.1, 127.3, 128.3, 130.2, 130.8, 143.6, 158.2. Ms m/z 343 (M^+), 211.

N-(2-Hydroxyproppyl)-9-amino-9,10-dihydrophenanthrene (4a). ^{1}H Nmr δ 1.05 and 1.08 (d, J= 6.2 Hz, 3H), 2.19 (br s, 2H), 2.23-2.38 (m, 1H), 2.60 and 2.73 (dd, J=12.0, 3.0 Hz, 1H), 3.06 (dd, J= 8.4, 4.3 Hz, 2H), 3.45-3.51 and 3.68-3.73 (m, 1H), 3.77 (t, J= 5.0 Hz, 1H), 7.15-7.44 (m, 6H), 7.78 (m, 2H). ^{13}C Nmr δ 20.2 and 20.4, 35.2 and 35.4, 53.9 and 54.4, 55.2 and 55.8, 65.2 and 65.8, 123.6, 124.3 and 124.3, 127.4, 127.5, 128.0, 128.3, 128.3, 129.5 and 129.6, 133.2 and 133.3, 133.4 and 133.5, 133.7 and 133.8, 137.4 and 137.6. Ms m/z 253 (M^+), 179.

N-(2-Hydroxybutyl)-9-amino-9,10-dihyrophenanthrene (4b). ^{1}H Nmr δ 0.88 and 0.90 (t, J= 7.2 Hz, 3H), 1.36 (q, J= 7.4 Hz, 2H), 2.22-2.42 (m, 1H), 2.31 (br s, 2H), 2.63 and 2.74 (dd, J= 11.8, 2.9 Hz, 1H), 3.01-3.11 (m, 2H), 3.26-3.28 and 3.43-3.51 (m, 1H), 3.78 (d, J= 4.1 Hz, 1H), 7.24-7.40 (m, 6H), 7.75-7.80 (m, 2H). ^{13}C Nmr δ 9.9, 27.6 and 27.8, 35.1 and 35.5, 52.0 and 52.5, 55.1 and 55.8, 70.5 and 71.0, 123.6, 124.0 and 124.3, 126.4 and 127.3, 127.3 and 127.4, 127.5, 127.9, 128.2 and 128.3, 129.6 and 129.6, 133.2 and 133.3, 133.4 and 133.5, 133.8 and 133.8, 137.4 and 137.7. Ms m/z 267 (M^+), 179.

N-Allyl-9-amino-9,10-dihydrophenanthrene (4c).[3a] ^{13}C Nmr δ 35.4, 49.6, 54.5, 116.0, 123.6, 124.3, 127.2, 127.2, 127.8, 128.0, 128.4, 129.6, 133.2, 133.4, 134.0, 137.0, 137.6.

N-Methylation

To a solution of the aminated compound (4.4 mmol) in 20 ml of dimethylformamide (DMF) was added 0.5 ml of formic acid (88%) and 0.38 ml of formaldehyde (37%) in ice bath, and the solution was heated at reflux temperature for 5 h. The solution was added with 50 ml of aqueous sodium hydroxide (10%) at room temperature and extracted with 150 ml of benzene. The crude material was purified by column chromatography on silica gel (Fuji Devison, BW-300) benzene/ethyl acetate as eluents.

N-(2-Hydroxypropyl)-N-methylamino-1,2-diphenylethane (3a). Yield 77%. ^{1}H Nmr δ 1.00 and 1.06 (d, J= 6.1 Hz, 3H), 2.10-2.37 (m, 2H), 2.13 and 2.24 (s, 3H), 2.95-3.06 (m, 2H), 3.20-3.32 (m, 1H), 3.60-3.73 (m, 1H), 3.83-3.91 (m, 1H), 7.12-7.57 (m, 10H). ^{13}C Nmr δ 19.6 and 19.8,

34.3 and 37.9, 38.3 and 38.7, 60.3 and 62.8, 62.3 and 64.6, 68.6 and 71.1, 126.1 and 126.2, 127.3, 128.0 and 128.1, 128.2 and 128.4, 128.3, 128.8 and 129.0, 138.0 and 138.4, 139.5 and 139.8.

N-Allyl-N-methylamino-1,2-diphenylethane (3b). Yield 82%.^{1}H Nmr δ 2.24 (s, 3H), 2.95-3.16 (m, 2H), 3.15 (dd, J= 13.7, 6.3 Hz, 1H), 3.31 (dd, J= 13.3, 7.9 Hz, 1H), 3.76 (dd, J= 9.3, 5.5 Hz,1H), 5.09-5.16 (m, 2H), 5.75-5.91(m, 1H), 6.98-7.33 (m, 10H). ^{13}C Nmr δ 38.3, 39.1, 57.6, 69.6, 117.2, 125.7, 126.9, 127,8, 127.9, 128.9, 129.3, 136.2, 139.2, 139.6. Ms m/z 241 (M^+).

N-(2,2-Diethoxyethyl)-N-methylamino-1,2-diphenylethane (3c). Yield 98%. ^{1}H Nmr δ 1.15 (t, J= 7.1 Hz, 3H), 1.18 (t ,J= 7.1 Hz, 3H), 2.32 (s, 3H), 2.48 (dd, J= 13.4, 5.2 Hz, 1H), 2.67 (dd, J= 13.6, 5.2 Hz, 1H), 2.98 (dd, J= 13.5, 8.6 Hz, 1H), 3.29 (dd, J= 13.6, 6.2 Hz, 1H), 3.39-3.65 (m, 4H), 3.84 (dd, J= 8.6, 6.2 Hz, 1H), 4.51 (t, J= 5.2 Hz, 1H), 7.04-7.29(m, 10H). ^{13}C Nmr δ 15.3, 38.6, 39.4, 56.8, 61.6, 61.8, 70.5, 101.9, 125.7, 126.9, 127.8, 127.9, 128.8, 129.3, 139.2, 139.9.

N-(2-Hydroxypropyl)-N-methylamino-2-p-methoxyphenyl-1-phenylethane (3d). Yield 80%. ^{1}H Nmr δ 1.03 and 1.05 (d, J= 9.8 Hz, 3H), 2.14 and 2.24 (s, 3H), 2.21-2.37 (m, 2H), 2.92-3.03 (m, 1H), 2.95 (br s, 1H), 3.13-3.25 (m, 1H), 3.71 and 3.72 (s, 3H), 3.76 (d, J= 6.6 Hz, 1H), 3.80-3.88 (m, 1H), 6.75 (d, J= 8.5 Hz, 2H), 6.78 (d, J= 8.4 Hz, 2H), 7.01-7.32 (m, 5H). ^{13}C Nmr δ 19.7 and 19.9, 34.6 and 37.0, 37.5 and 38.8, 55.1, 60.2 and 62.3, 62.9 and 64.4, 69.0 and 71.2, 113.6 and 113.7, 127.3, 128.0 and 128.2, 128.4 and 128.8, 129.8 and 130.0, 131.4 and 131.7, 138.2 and 138.5, 157.9.

N-Allyl-N-Methylamino-2-p-methoxylphenyl-1-phenylethane (3e). Yield 82%. ^{1}H Nmr δ 2.22 (s, 3H), 2.81-3.00 (m, 2H), 3.13 (dd, J= 14.0, 5.6 Hz, 1H), 3.23 (dd, J= 13.9, 5.6 Hz, 1H), 3.60-3.70 (m, 1H), 3.65 (s, 3H), 5.08-5.15 (m, 2H), 5.75-5.91 (m,. 1H), 6.66 (d, J= 8.5 Hz, 2H), 6.88 (d, J= 8.4 Hz, 2H), 7.01-7.32 (m, 5H). ^{13}C Nmr δ 38.2, 38.3, 55.0, 57.6, 69.8, 113.3, 117.1, 126.9, 127.8, 128.8, 130.1, 131.6, 136.2, 139.3, 157.6.

N-(2,2-Diethoxyethyl)-N-methylamino-2-p-methoxyphenyl-1-phenylethane (3f). Yield 69%. ^{1}H Nmr δ 1.16 (d, J= 6.9 Hz, 3H), 1.18 (t, J= 6.9 Hz, 3H), 2.31 (s, 3H), 2.47 (dd, J= 13.4, 5.3 Hz, 1H), 2.66 (dd, J= 13.5, 5.2 Hz, 1H), 2.93 (dd, J= 13.6, 8.8 Hz, 1H), 3.22 (dd, J= 13.7, 6.0 Hz, 1H), 3.40-3.49 (m, 2H), 3.53-3.71 (m, 2H), 3.66 (s, 3H), 4.54 (t, J= 5.2 Hz, 1H), 6.70 (d, J= 8.5 Hz, 2H), 6.96 (d, J= 8.6 Hz, 2H), 7.04-7.35 (m, 5H). ^{13}C Nmr δ 15.3, 37.7, 39.5, 55.1, 56.8, 61.6, 61.7, 70.8, 101.9, 113.3, 126.9, 127.8, 128.6, 130.2, 131.9, 139.3, 157.6. Ms m/z 357 (M^+), 236.

N-(2-Hydroxypropyl)-N-methyl-9-amino-9,10-dihydrophenanthrene (5a). Yield 78%. ^{1}H Nmr δ 1.06 and 1.08 (d, J= 5.0 Hz, 3H), 2.18 and 2.20 (s, 3H), 2.29-2.62 (m, 2H), 2.87 (br s, 1H), 3.00 (dd, J= 15.3, 5.2 Hz, 1H), 3.10 (dd, J= 15.6, 6.6 Hz, 1H), 3.67-3.74 and 3.77-3.81 (m, 1H), 3.91 (t, J= 5.7 Hz, 1H), 7.24-7.48 (m, 6H), 7.78 (m, 2H). ^{13}C Nmr δ 19.9, 30.2, 59.0, 60.7, 61.5, 62.9, 123.5, 123.9, 127.2, 127.6, 127.9, 128.2, 128.5, 128.8, 133.8, 134.9, 135.0, 135.4. Ms m/z 267 (M^+), 179.

N-(2-Hydroxybutyl)-N-methyl-9-amino-9,10-dihydrophenanthrene (5b). Yield 31%. ^{1}H Nmr δ 0.91 and 0.93 (t, J= 7.5 Hz, 3H), 1.31-1.44 (m, 2H), 2.16 and 2.18 (s, 3H), 2.35-2.63 (m, 2H), 2.97 (dd, J= 12.3, 5.2 Hz, 1H), 3.09 (dd, J= 15.9, 7.6 Hz, 1H), 3.20 (br s, 1H), 3.41-3.61 (m, 1H), 3.85 (dd, J= 11.3, 7.3 Hz, 1H), 7.22-7.47 (m, 6H), 7.72-7.80 (m, 2H). ^{13}C Nmr δ 9.9 and 9.9, 27.6, 30.0 and 30.2, 36.4 and 39.0, 59.4 and 60.5, 61.5 and 62.7, 68.1, 123.5, 123.8 and 123.9, 127.1, 127.4 and 127.6, 127.8 and 127.8, 127.9 and 127.9, 128.0 and 128.5, 128.4, 133.8 and 133.8, 134.6 and 134.8, 135.2 and 135.3, 136.0 and 136.4. Ms m/z 281 (M^+), 179.

N-Allyl-N-methyl-9-amino-9,10-dihydrophenanthrene (5c). Yield 78%. ^{1}H Nmr δ 2.21(s, 3H), 2.88-3.09 (m, 3H), 3.26 (dd, J= 13.9, 5.7 Hz, 1H), 3.95 (dd, J= 8.4, 6.4 Hz, 1H), 5.17 (d, J= 10.2 Hz, 1H), 5.20 (d, J= 17.2 Hz, 1H), 5.90-5.96 (m, 1H), 7.13-7.36 (m, 5H), 7.55 (dd, J= 9.9, 2.2 Hz, 1H), 7.72-7.79 (m, 2H). ^{13}C Nmr δ 28.7, 36.5, 55.9, 60.3, 117.1, 123.5, 123.7, 127.0, 127.4, 127.5, 127.5, 127.6, 127.9, 128.4, 133.8, 134.7, 135.6, 136.2. Ms m/z 249 (M^+).

Cyclization with CF_3SO_3H

To the aminated compound (1 mmol) was added 8.8 ml of TFSA, and the solution was heated at 70 °C for 4 h. The solution was quenched with 30 ml of ice in water and extracted with 150 ml of dichloromethane. The crude material was purified by column chromatography on silica gel with benzene/ethyl acetate as eluents. Though the cyclized products were produced as diastereomeric isomers, these isomers could not be separated by column chromatography except a few cases. The isolated yields and diastereomer ratios are listed in Table 2.

1-Benzyl-4-methyl-1,2,3,4-tetrahydroisoquinoline (6a). ^{1}H Nmr δ 1.22 and 1.31 (d, J= 7.0 Hz, 3H), 2.82 (dd, J= 12.3, 7.8 Hz, 1H), 3.01-3.32 (m, 3H), 3.41 (dd, J=12.3, 5.0 Hz, 1H), 4.52-4.62 (m, 1H), 5.39 (br s, 1H), 6.93-7.53 (m, 9H). ^{13}C Nmr δ 19.2 and 19.5, 30.4 and 30.6, 41.0 and 41.4, 45.6 and 47.1, 56.6 and 57.3, 126.4, 126.5, 127.3, 127.5, 127.7, 128.9, 129.6 and 129.7, 132.7 and 133.1, 135.8 and 136.0, 137.7 and 138.1. Ms m/z 237 (M^+), 146 (M-CH_2Ph).

1-Benzyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (6b). ^{1}H Nmr δ 3.24 (m, 2H), 3.45 (dd, J= 14.7, 6.0 Hz, 1H), 3.58 (dd, J= 12.4, 4.8 Hz, 1H), 4.43 (dd, J= 11,4, 4.8 Hz, 1H), 4.45-4.55 and 4.85-4.95 (m, 1H), 4.95 (m, 1H), 6.70-7.43 (m, 14H). ^{13}C Nmr δ 40.4 and 41.0, 41.5 and 41.9, 44.9 and 47.9, 56.1 and 57.6, 125.95, 127.5, 127.8, 128.0, 128.3, 129.1, 129.2, 129.2, 129.5 129.6, 130.3 and 131.1, 133.9 and 134.2, 134.7 and 136.0, 139.7 and 140.0. Ms m/z 299 (M^+), 208 (M-CH_2Ph).

N-Methyl-1-benzyl-4-methyl-1,2,3,4-tetrahydroisoquinoline (7). Major product. ^{1}H Nmr δ 1.23 (d, J= 6.9 Hz, 3H), 2.37 (dd, J= 11.2, 7.9 Hz, 1H), 2.56 (s, 3H), 2.91-2.98 (m, 2H), 3.10 (dd, J= 11.3, 7.1 Hz, 1H), 3.20 (dd, J= 13.9, 6.8 Hz, 1H), 3.93 (t, J= 6.0 Hz, 1H), 6.77 (d, J= 7.7 Hz, 1H), 7.00-7.31 (m, 8H). ^{13}C Nmr δ 19.4 , 32.3, 40.3 , 43.9, 58.1, 66.3, 125.3, 126.0, 126.2, 126.2, 127.2, 128.0, 129.8, 137.1, 139.2, 139.8. Ms m/z 251 (M^+). Minor product. ^{1}H Nmr δ 1.18 (d, J= 6.7 Hz, 3H), 2.55 (s, 3H), 2.85-3.07 (m, 4H), 3.24 (dd, J= 13.8, 5.4 Hz, 1H), 3.87 (t, J= 6.2 Hz, 1H), 6.72 (d, J= 7.7 Hz, 1H), 6.99-7.33 (m, 8H). ^{13}C Nmr δ 19.7, 28.9, 40.9, 42.8, 54.1, 65.5, 125.4, 126.1, 126.6, 127.4, 127.9, 128.0, 129.7, 135.9, 138.7, 139.0. Ms m/z 251 (M^+).

N-Methyl-1-(4-acetoxybenzyl)-4-methyl-1,2,3,4-tetrahydroisoquinoline (8). ^{1}H Nmr δ 1.24 and 1.28 (d, J= 6.9 Hz, 3H), 2.27 and 2.28 (s, 3H), 2.42-2.50 (m, 1H), 2.62 and 2.68 (s, 3H), 2.29-3.03 (m, 2H), 3.20-3.22 (m, 1H), 3.30-3.45 (m, 1H), 4.03 (m, 1H), 6.63-7.26 (m, 8H). ^{13}C Nmr δ 19.1 and 19.4, 21.1, 27.8 and 31.3, 39.7 and 40.5, 42.1 and 43.7, 53.0 and 57.9, 65.4 and 66.3, 121.2 and 121.4, 125.7 and 126.0, 126.3 and 126.9, 127.2 and 127.5, 127.6 and 128.2, 130.7 and 130.8, 132.9 and 135.0, 135.6 and 136.0, 137.1 and 139.2, 149.1 and 149.4, 169.6.

N-Methylaporphines

9a. ^{1}H Nmr δ 1.48 (d, J= 7.1 Hz, 3H), 2.54 (s, 3H), 2.70 (dd, J= 11.4, 4.0 Hz, 1H), 2.80 (d, J= 14.3 Hz, 1H), 2.84 (d, J= 11.3 Hz, 1H), 2.88-2.98 (m, 1H), 3.17 (t, J= 4.3 Hz, 1H), 3.22 (t, J= 4.3 Hz, 1H), 7.11 (d, J= 7.6 Hz, 1H), 7.23-7.31 (m, 4H), 7.57 (d, J= 7.2 Hz, 1H), 7.71 (d, J= 7.4 Hz,1H). ^{13}C Nmr δ 24.0, 33.2, 34.0, 44.5, 59.7, 62.5, 121.8, 123.7, 126.9, 127.3, 127.5, 128.0, 128.4, 133.0, 133.4, 134.4, 135.4, 139.3. Ms m/z 249 (M^+).

9a'. ^{1}H Nmr δ 1.28 (d, J= 6.4 Hz, 3H), 2.26 (t, J= 11.3 Hz, 1H), 2.56 (s, 3H), 2.71 (t, J= 14.0 Hz, 1H), 3.08 (dd, J= 11.6, 5.7 Hz, 1H), 3.17 (dd, J= 14.1, 4.4 Hz, 1H), 3.28 (dd, J= 12.7, 4.5 Hz, 2H), 7.22-7.35 (m, 5H), 7.56 (dd, J= 6.6, 2.2 Hz, 1H), 7.70 (d, J= 7.6 Hz, 1H). ^{13}C Nmr δ 18.4, 32.1, 34.1, 43.6,

61.8, 62.5, 122.1, 123.9, 125.9, 127.2, 127.4, 127.6, 128.3, 133.3, 133.4, 134.5, 135.1, 138.6. Ms m/z 249 (M^+).

9b. ^{1}H Nmr δ 1.04 (t, J= 7.4 Hz, 3H), 1.63-1.76 (m, 1H), 1.82-2.00 (m, 1H), 2.50 (s, 3H), 2.54-2.57 (m, 2H), 2.62 (t, J= 14.9 Hz, 1H), 2.97 (d, J= 10.5 Hz, 1H), 3.09-3.18 (m, 2H), 7.08 (d, J= 7.5 Hz, 1H), 7.18-7.33 (m, 4H), 7.54 (d, J= 7.5 Hz, 1H), 7.70 (d, J= 7.5 Hz, 1H). ^{13}C Nmr δ 12.7, 30.2, 34.1, 40.4, 44.5, 55.7, 62.5, 121.8, 123.7, 126.7, 127.2, 127.5, 128.2, 128.3, 133.3, 133.4, 134.3, 135.5, 138.6. Ms m/z 263 (M^+).

9b'. ^{1}H Nmr δ 0.93 (t, J= 7.4 Hz, 3H), 1.43-1.63 (m, 1H), 1.99-2.08 (m, 1H), 2.38 (t, J= 10.9 Hz, 1H), 2.63 (s, 3H), 2.78 (t, J= 14.0 Hz, 1H), 3.15 -3.27 (m, 3H), 3.42 (dd, J= 13.9, 4.0 Hz, 1H), 7.23-7.35 (m, 5H), 7.56 (d, J= 6.7 Hz, 1H), 7.67 (d, J= 7.8 Hz, 1H). ^{13}C Nmr δ 10.6, 25.9, 33.6, 37.1, 42.9, 58.6, 62.2, 122.3, 124.6, 126.4, 127.5, 127.5, 127.7, 128.5, 132.8, 133.5, 134.3, 134.4, 136.8. Ms m/z 263 (M^+).

Cyclization with BF_3

To a solution of the aminated compound (2 mmol) in 30 ml of dichloromethane was introduced gaseous boron trifluoride at 4 °C for 2 h. The solution was added with 50 ml of aqueous sodium hydroxide (15%) and extracted with 150 ml of dichloromethane. The crude material was purified by column chromatography on silica gel with benzene/ethyl acetate as eluents.

10a. ^{1}H Nmr δ 2.28 (br s, 1H), 3.21 (dd, J= 17.7, 3.3 Hz, 1H), 3.31 (dd, J= 11.5, 4.7 Hz, 1H), 3.49 (dd, J= 17.6, 3.7 Hz, 1H), 3.69 (d, J= 11.3 Hz, 1H), 3.89 (d, J= 3.9 Hz, 1H), 4.33 (t, J= 3.6 Hz, 1H), 7.04-7.25 (m, 8H). ^{13}C Nmr δ 41.3, 46.6, 50.4, 54.8, 124.9, 125.5, 125.9, 126.7, 126.8, 127.2, 127.9, 131.3, 135.1, 139.9, 141.2, 142.7. Ms m/z 221(M^+). The acetamide: mp 204.5-205 °C (from MeOH), Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.48. Found: C, 82.37; H, 6.49; N, 5.48.

10b. ^{1}H Nmr δ 2.50 (s, 3H), 2.93 (dd, J= 10.8, 4.8 Hz, 1H), 2.97 (dd, J= 17.8, 3.4 Hz, 1H), 3.63 (dd, J= 10.7, 1.5 Hz, 1H), 3.67 (dd, J= 18.9, 3.9 Hz, 1H), 3.83 (dd, J= 4.7, 1.3 Hz, 1H), 3.99 (t, J= 3.6 Hz, 1H), 6.92-7.35 (m, 8H). ^{13}C Nmr δ 38.0, 45.1, 46.4, 59.4, 62.7, 125.1, 125.9, 126.1, 126.8, 126.8, 127.5, 127.7, 131.1, 134.7, 137.5, 141.0, 142.0. Ms m/z 235 (M^+), 192 ($M-CH_2NCH_3$), 144 ($M-PhCH_3$).

11. ^{1}H Nmr δ 1.58 (dd, J= 13.6, 2.3 Hz, 1H), 1.83 (dd, J= 10.8, 1.8 Hz, 1H), 2.14 (s, 3H), 2.34 (dd, J= 13.6, 3.3 Hz, 1H), 2.77 (br s, 1H), 3.70-3.80 (m, 2H), 6.04 (dd, J= 10.2, 1.6 Hz, 1H), 6.12 (dd, J= 10.2, 2.8 Hz, 1H), 6.34 (dd, J= 10.2, 1.5 Hz, 1H), 7.11-7.45 (m, 4H), 7.43 (dd, J= 10.2, 2.7 Hz, 1H).

^{13}C Nmr δ 38.5, 39.7, 44.7, 44.9, 53.8, 57.5, 124.5, 125.0, 126.9, 127.2, 127.6, 128.4, 137.1, 139.4, 154.4, 155.9, 185.5. Ms m/z 251 (M^+).

ACKOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan. We are grateful to Hashimoto Chemical Co. Ltd. for providing BF_3 gas. We also thank Ms Kimiko Tanabe for obtaining nmr and ms spectra.

REFERENCES

1. K. Nakanishi, T. Goto, S. Ita, S. Natori, and S. Nozoe, "Natural Products Chemistry," Vol. 2, Academic press, New York, p. 255, 1975; e.g. P. Molina, M. Alajarin and A. Vidal, J. Org. Chem., **1990**, 55, 6140.
2. I. Ninomiya, T. Naito, T. Kiguchi, and O. Miyata, Yuki Gosei Kagaku Kyokaishi, **1990**, 48, 206; G. Dai-Ho and P. S. Mariano, J. Org. Chem., **1987**, 52, 704; B. L. Jensen and K. Chockalingam, J. Heterocyclic Chem., **1986**, 23, 343; R. Beugelmans, J. Chastanet, H. Ginsburg, L. Quinten-Cortes, and G. Rossi, J. Org. Chem., **1985**, 50, 4933; M. Ikeda, K. I. Hirao, N. Numao, and O. Yonemitsu, Tetrahedron, **1977**, 33, 489; K. Maruyama and Y. Kubo, J. Am. Chem. Soc., **1978**, 100, 7772; P. W. Jeffs and J. F. Hansen, J. Am. Chem. Soc., **1967**, 89, 2798; S. M. Kupchan and R. M. Konojia, Tetrahedron Lett., **1966**, 5353.
3. a) M. Yasuda, T. Yamashita, K. Shima, and C. Pac, J. Org. Chem., **1987**, 52, 753. b) M. Yasuda, Y. Matsuzaki, K. Shima, and C. Pac, J. Chem. Soc., Perkin Trans. 2, **1988**, 745.
4. M. Yasuda, J. Kubo, and K. Shima, Heterocycles, **1990**, 31.
5. M. Yasuda, T. Isami, J. Kubo, M. Mizutani, T. Yamashita, and K. Shima, J. Org. Chem., in press.
6. M. J. Bevis, E. J. Forbes, N. N. Naik, and B. C. Uff, Tetrahedron, **1971**, 27, 1253; S. F. Dyke and A. C. Ellis, Tetrahedron, **1971**, 27, 3003; S. F. Dyke, A. C. Ellis, R. G. Kinsman, and A. W. C. White, Tetrahedron, **1974**, 30, 1193; R. Elliott, F. Hewgill, E. McDonald, and P. McKenna, Tetrahedron Lett., **1980**, 21, 4633.
7. N. Vinot and M. R. Quelet, Bull. Soc. Chim. Fr., **1959**, 1164; N. Vinot, Ann. Chim., **1958**, 3, 475.
8. S. M. Kupchan, J. L. Moniot, R. M. Kanojia, and J. B. O'Brien, J. Org. Chem. **1971**, 36, 2413; S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, J. Org. Chem., **1978**, 43, 4076. .
9. S. F. Dyke, A. W. C. White, and D. Hartley, Tetrahedron, **1973**, 29, 857.

Received, 6th January, 1992