Syntheses of Apogalanthamine Analogues as α-Adrenergic Blocking Agents. XIII.[1] Syntheses of Phenolic 8-Hydroxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines

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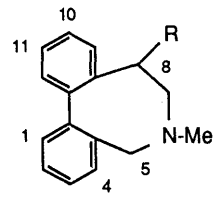
10,11-Diphenolic 8-hydroxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine 3, having a partial structure of adrenaline, was prepared by demethylation of the dimethoxyazocine 12 with boron tribromide. The related monophenolic 8-hydroxyazocines 4 and 5 were prepared by cyclization of the dihalogeno-β-phenylethanolamines 6c and 7c with zerovalent nickel, followed by hydrolysis and debenzylation of the *O*-protected dibenz[*c*,*e*]azocines 13 and 14, respectively.

Keywords apogalanthamine analogue; 8-hydroxydibenz[*c*,*e*]azocine; phenolic dibenz[*c*,*e*]azocine; *N*-benzyl-β-phenylethanolamine; cyclization; zerovalent nickel; debenzylation; demethylation; alpha adrenergic blocking agent

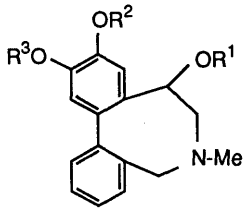
As a part of our synthetic studies of apogalanthamine analogues as α-adrenergic blocking agents, we have described a convenient synthesis of 6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**1**)[2] with α_1-selective adrenergic blocking activity.[3] In the previous paper, we reported the syntheses of racemic and optically active 8-hydroxy-6-methylazocine **2**[4] and its methoxy and methylenedioxy derivatives,[1] which were found to have α-adrenergic blocking activities.[5] In view of these results, 10,11-diphenolic 8-hydroxyazocine **3** having a partial structure of adrenaline[6] is of interest from a pharmacological point of view.

This paper describes syntheses of the azocine **3** and the related monophenolic compounds, 8,11-dihydroxy-10-methoxy-and 8,10-dihydroxy-11-methoxyazocines **4** and **5**, for testing of their pharmacological activities (Chart 1).

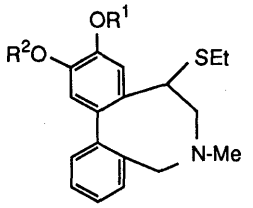
For the syntheses of the monophenolic azocines **4** and **5**, dihalogeno-*N*-benzyl-β-phenylethanolamines **6a** and **7a** were selected as key intermediates, in which the phenolic hydroxy group is protected by a benzyl group. Compounds **6a** and **7a** were prepared by condensation of the β-phenylethanolamines **8a** and **8b** with the benzaldehydes **9a** and **9b**, respectively, followed by reduction with sodium borohydride ($NaBH_4$). The ethanolamine **8a** was prepared by reduction of the the cyanohydrin **10a** of the benzaldehyde **9c** with diborane (B_2H_6). The ethanolamine **8b** was obtained from the cyanohydrin **10b** as follows. Lithium aluminum hydride ($LiAlH_4$) reduction of **10b** gave the



1: R=H
2: R=OH

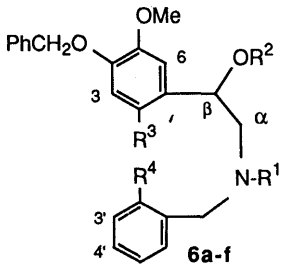


	R^1	R^2	R^3
3 :	H	H	H
4 :	H	Me	H
5 :	H	H	Me
12 :	H	Me	Me
13 :	Ac	Me	CH_2Ph
14 :	Ac	CH_2Ph	Me
15 :	Ac	H	Me
17 :	H	Me	CH_2Ph
18 :	H	CH_2Ph	Me
20 :	Ac	Ac	Ac

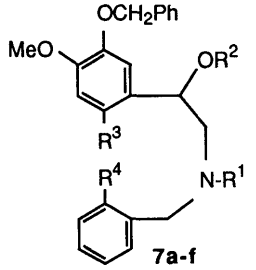


16: R^1=H, R^2=Me
19: R^1=Me, R^2=H

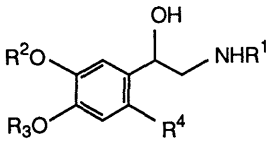
Chart 1



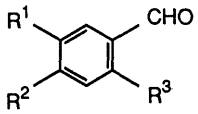
	R^1	R^2	R^3	R^4
a :	H	H	Br	Br
b :	Me	H	Br	Br
c :	Me	Ac	Br	Br
d :	Me	Ac	Br	H
e :	Me	Ac	H	H
f :	Ac	Ac	Br	Br



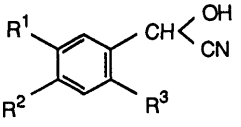
	R^1	R^2	R^3	R^4
a :	H	H	I	I
b :	Me	H	I	I
c :	Me	Ac	I	I
d :	Me	Ac	I	H
e :	Me	Ac	H	H
f :	Ac	Ac	I	I



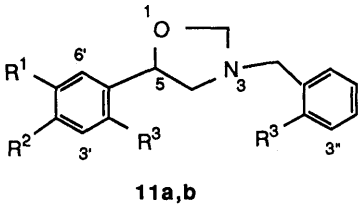
	R^1	R^2	R^3	R^4
a :	H	Me	CH_2Ph	Br
b :	H	CH_2Ph	Me	I
c :	H	CH_2Ph	Me	H
d :	CHO	CH_2Ph	Me	H
e :	CHO	CH_2Ph	Me	I



	R^1	R^2	R^3
a :	H	H	Br
b :	H	H	I
c :	OMe	OCH_2Ph	Br



	R^1	R^2	R^3
a :	OMe	OCH_2Ph	Br
b :	OCH_2Ph	OMe	H



	R^1	R^2	R^3
a :	OMe	OCH_2Ph	Br
b :	OCH_2Ph	OMe	I

Chart 2

ethanolamine **8c**, which was *N*-formylated with ethyl formate to afford the amide **8d**. Then, iodination of **8d** with iodine and silver trifluoroacetate (CF_3COOAg) gave the iodide **8e** and hydrolysis of **8e** afforded the ethanolamine **8b** (Chart 2).

The key intermediates **6a** and **7a** thus obtained were treated with formalin and $NaBH_4$ to give the *N*-methyl compounds **6b** and **7b** along with the oxazolidine derivatives **11a** and **11b**. The benzylic hydroxy group in **6b** and **7b** was acetylated with acetic anhydride and pyridine to afford the acetates **6c** and **7c**. In the previous paper, a stoichiometric amount of zerovalent nickel[7] was used for cyclization of dihalogeno-β-phenethylamines to the dibenz[*c*,*e*]azocines **1**,[2] **2**,[4] and **12**.[1] Similarly, the ethanolamines **6c** and **7c** were treated with zerovalent nickel generated *in situ* to give the *O*-protected dibenzazocines **13** (5.6%) and **14** (29.2%) along with the dehalogenated *N*-benzyl-β-phenylethanolamines **6d** and **6e**, and **7d** and **7e**, respectively. In order to remove the benzyl group in **14**, compound **14** was treated with aluminum chloride–ethanethiol[8] to give a mixture of debenzylated 8-acetoxyazocine **15** and 8-ethylthioazocine **16**, which could not easily be separated. Thus, the 8-acetoxyazocines **13** and **14** were hydrolyzed with 7% ethanolic potassium carbonate to give the 8-hydroxyazocines **17** and **18**, quantitatively. Finally, **17** and **18** were debenzylated with aluminum chloride–ethanethiol to give the phenolic 8-hydroxyazocines **4** and **5** in 44.8 and 31.5% yields, respectively. In these debenzylation reactions, nucleophilic substitution products, 8-ethylthioazocines **19** and **16**, were also obtained.

The structures of the phenolic azocines **4** and **5**, and **16** and **19** were determined by analysis of their high-resolution mass spectra (HR-MS) and proton nuclear magnetic resonance (^{1}H-NMR) spectra. The ^{1}H-NMR spectra of **4**, **5**, **16** and **19** showed characteristic AB-type doublets (C-5) and ABX-type coupling patterns (C-7 and C-8; see Experimental) similar to those of the 8-hydroxyazocines **2**[4] and **12**.[1]

On the other hand, the diphenolic 8-hydroxyazocine **3** was obtained by demethylation of the dimethoxyazocine **12**, reported in the previous paper,[1] with boron tribromide[9] in 46% yield. The ^{1}H-NMR spectrum of **3** showed the broad doublets (J = 14 Hz) of the C-5 methylene protons at δ 4.24 and 3.54, and the singlet due to the *N*-methyl protons at δ 2.87, which were at lower field than the corresponding signals in **4** and **5**. These findings suggest the presence of a zwitterionic form in **3**. Furthermore, the structure of the azocine **3** was confirmed by acetylation of **3** to give the triacetate **20**.

The pharmacological activities of the phenolic 8-hydroxyazocines **3**, **4** and **5** will be reported elsewhere.

Experimental

All melting points are given as uncorrected values. Infrared (IR) spectra were taken with a Hitachi IR-215 spectrometer and are given in cm^{-1}. HR-MS were determined with a JEOL JMS-D 300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer in $CDCl_3$ unless otherwise indicated, with tetramethylsilane as a standard, and are given in δ. The plates used for preparative thin layer chromatography (PLC) were coated with silica gel (Kiesel gel PF_{254} Merck).

β-(4-Benzyloxy-2-bromo-5-methoxyphenyl)ethanolamine (8a) A solution of $NaHSO_3$ (3.9 g) in H_2O (8 ml) was added to a solution of **9c** (6.0 g) in MeOH (110 ml) at 55 °C and the mixture was stirred at room temperature for 4 h. The resulting precipitates were filtered off, washed with MeOH and suspended in H_2O (45 ml). To this suspension, a solution of KCN (2.5 g) H_2O (20 ml) was added, and the mixture was stirred at room temperature for 20 min, then extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give an oil (8 g). This crude product was taken up in $CHCl_3$ (30 ml) and MeOH (40 ml), and a solution of $NaHSO_3$ (6.6 g) in H_2O (15 ml) was added. The mixture was stirred for 30 min. Work-up in the usual way gave the cyanohydrin **10a** as a crude oil (1.6 g). ^{1}H-NMR: 7.15 (1H, s, H-6), 7.02 (1H, s, H-3), 5.68 (1H, br s, ArC$\underline{H}$), 5.05 (2H, s, ArC$\underline{H}_2$O), 3.58 (3H, s, OCH_3).

A solution of the crude cyanohydrin **10a** (1.6 g) in dry tetrahydrofuran (THF) (10 ml) was added by syringe to 1.0 M diborane in THF (22.0 ml). The mixture was refluxed under N_2 for 2 h and then allowed to stand overnight. EtOH (6.5 ml) was added, and the reaction mixture was saturated with dry HCl under ice-cooling. The resulting precipitates were filtered off and recrystallized from MeOH to give the hydrochloride of **8a** as colorless needles (1.2 g, 16.5%), mp 204—206 °C (dec.). ^{1}H-NMR (free base): 7.08 (1H, s, H-6), 6.98 (1H, s, H-3), 5.05 (2H, s, ArC$\underline{H}_2$O), 4.82 (1H, dd, J = 7,4 Hz, H-β), 3.81 (3H, s, OCH_3), 3.10—2.30 (5H, m, OH, NH_2 and CH_2-α). *Anal.* Calcd for $C_{16}H_{18}BrNO_3 \cdot HCl$: C, 49.42; H, 4.89; N, 3.60. Found: C, 49.34; H, 4.94; N, 3.45.

β-(3-Benzyloxy-4-methoxyphenyl)ethanolamine (8c) 3-Benzyloxy-4-methoxybenzaldehyde (12.4 g) was treated with $NaHSO_3$ (10.6 g) and KCN (7.7 g) in the same way as **9c** to give a mixture (8.2 g) of the starting material and the cyanohidrin **10b** (1 : 1), the structure of which was supported by the ^{1}H-NMR spectrum: 7.42 (1H, d, J = 8 Hz, H-5), 7.23 (1H, s, H-2), 6.93 (1H, d, J = 8 Hz, H-5), 5.28 (1H, s, ArC$\underline{H}$), 5.05 (2H, s, ArC$\underline{H}_2$O), 3.80 (3H, s, OCH_3).

A solution of the crude cyanohydrin **10b** (8.2 g) in dry THF (25 ml) was added dropwise to a suspension of $LiAlH_4$ (2.7 g) in dry THF (70 ml) under stirring. The mixture was stirred at room temperature for 6 h. Work-up in the usual way gave **8c** as an oil (4.13 g, 29.5%). ^{1}H-NMR: 6.90 (1H, s, H-2), 6.83 (2H, s, H-5 and H-6), 5.08 (2H, s, ArC$\underline{H}_2$O), 4.60 (1H, dd, J = 9, 5 Hz, H-β), 3.82 (3H, s, OCH_3), 2.90 (4H, m, CH_2-α and NH_2).

The compound **8c** was used for *N*-formylation without a further purification.

β-(5-Benzyloxy-2-iodo-4-methoxyphenyl)ethanolamine (8b) A mixture of **8c** (4.9 g), K_2CO_3 (5.8 g), and 3A molecular sieves (5.8 g) in ethyl formate–EtOH (1 : 1) (60 ml) was refluxed under N_2 for 3 h. Work-up in the usual way gave an oil (4.0 g). This crude product was purified by flash chromatography on SiO_2 in $CHCl_3$–MeOH (20 : 1) to afford **8d** as an oil (2.9 g, 54.1%). IR (KBr): 3375 (OH), 1660 (C=O). ^{1}H-NMR: 7.97 (1H, s, CHO), 6.92 (1H, s, H-2), 6.83 (2H, s, H-5 and H-6), 6.27 (1H, br s, NH), 5.11 (2H, s, ArC$\underline{H}_2$O), 4.60 (1H, dd, J = 8, 4 Hz, H-β), 3.83 (3H, s, OCH_3), 3.51 (1H, dd, J = 14, 4 Hz, H-α), 3.15 (1H, dd, J = 14, 8 Hz, H-α). HR-MS (m/z) (M^+): Calcd for $C_{17}H_{19}NO_4$: 301.1314. Found: 301.1340.

A solution of I_2 (2.80 g) in $CHCl_3$ (25 ml) was added dropwise to a suspension of **8d** (2.78 g) and CF_3COOAg (3.20 g) in $CHCl_3$ (80 ml) during 1 h. The mixture was stirred for 1 h and filtered. The filtrate was washed with a saturated solution of $Na_2S_2O_3$ in H_2O, 5% NaOH and H_2O, successively. The $CHCl_3$ solution was dried and evaporated to give **8e** as an oil (3.13 g, 79.5%). ^{1}H-NMR: 7.94 (1H, s, CHO), 7.14 (1H, s, H-3), 7.06 (1H, s, H-6), 6.09 (1H, br s, NH), 5.07 (2H, s, ArC$\underline{H}_2$O), 4.81 (1H, dd, J = 7, 3 Hz, H-β), 3.78 (3H, s, OCH_3), 3.56 (1H, dd, J = 15, 3 Hz, H-α), 3.19 (1H, dd, J = 15, 7 Hz, H-α). HR-MS (m/z) (M^+): Calcd for $C_{17}H_{18}INO_4$: 427.0283. Found: 427.0291.

A solution of **8e** (3.1 g) in concentrated HCl–MeOH (1 : 9) (40 ml) was stirred at room temperature for 7.5 h. The resulting precipitates were filtered off and washed with ether. Recrystallization from MeOH gave the hydrochloride of **8b** as colorless needles (2.3 g, 72.5%), mp 211—212 °C. IR (KBr) (free base): 3350, 3285 (NH_2). ^{1}H-NMR (free base): 7.15 (1H, s, H-3), 7.03 (1H, s, H-6), 5.07 (2H, s, ArC$\underline{H}_2$O), 4.60 (1H, br s, H-β), 3.78 (3H, s, OCH_3), 3.00—1.80 (5H, br, NH_2, CH_2-α and OH). *Anal.* Calcd for $C_{16}H_{18}INO_3 \cdot HCl$: C, 44.09; H, 4.36; N, 3.21. Found: C, 44.29; H, 4.32; N, 2.95.

β-(4-Benzyloxy-2-bromo-5-methoxyphenyl)-*N*-(2-bromobenzyl)ethanolamine (6a) A mixture of the hydrochloride (1.4 g) of **8a**, **9a** (0.90 g), and $NaHCO_3$ (1.3 g) in EtOH (70 ml) was refluxed under N_2 for 2 h. The reaction mixture was cooled and $NaBH_4$ (460 mg) was added. The mixture was refluxed for 2 h and filtered. The filtrate was evaporated and the residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give crude crystals. Recrystallization from MeOH afforded **6a** as colorless needles (1.70 g, 92.5%), mp 109—110 °C. ^{1}H-NMR: 7.51 (1H, dd, J = 7, 2Hz, H-3′), 7.10 (1H, s, H-6), 6.96 (1H, s, H-3), 5.04 (2H, s, ArC$\underline{H}_2$O), 4.97 (1H, dd, J = 9, 3 Hz, H-β), 3.90 (2H, s, ArC$\underline{H}_2$N), 3.82 (3H, s, OCH_3), 3.40 (2H, br s, NH and OH), 2.97 (1H, dd,

$J=12$, 3 Hz, H-α), 2.55 (1H, dd, $J=12$, 9 Hz, H-α). *Anal.* Calcd for $C_{23}H_{23}Br_2NO_3$: C, 52.98; H, 4.41; N, 2.69. Found: C, 52.79; H, 4.41; N, 2.69.

The ethanolamine **7a** was prepared from **8b** and **9b** in the same way as **6a**.

β-(5-Benzyloxy-2-iodo-4-methoxyphenyl)-*N*-(2-iodobenzyl)ethanolamine (7a) Colorless needles (from $CHCl_3$, 80.8%), mp 133—134 °C. ^{1}H-NMR: 7.80 (1H, dd, $J=8$, 1 Hz, H-3′), 7.19 (1H, s, H-3), 7.14 (1H, s, H-6), 5.09 (2H, s, $ArC\underline{H}_2O$), 4.78 (1H, dd, $J=9$, 3 Hz, H-β), 3.84 (5H, s, $ArC\underline{H}_2N$ and OCH_3), 2.91 (1H, dd, $J=12$, 9 Hz, H-α), 2.41 (1H, dd, $J=12$, 3 Hz, H-α). *Anal.* Calcd for $C_{23}H_{23}I_2NO_3$: C, 44.88; H, 3.74; N, 2.28. Found: C, 44.80; H, 3.59; N, 2.01.

β-(4-Benzyloxy-2-bromo-5-methoxyphenyl)-*N*-(2-bromobenzyl)-*N*-methylethanolamine (6b) A solution of formalin (1 ml) and H_3BO_3 (96 mg) in MeOH (10 ml) was added to a solution of **6a** (110 mg) in MeOH (10 ml). The mixture was stirred for 5 min. $NaBH_4$ (73 mg) was added and the mixture was stirred for 1 h. Acetic acid (1 ml) and H_2O (25 ml) were added, and the reaction mixture was concentrated and made basic with NH_4OH. The aqueous solution was extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give an oil (113 mg). This was subjected to PLC in benzene–$CHCl_3$ (1 : 20). The fraction of *Rf* 0.09—0.22 gave **6b** as an oil (44 mg, 38.8%). ^{1}H-NMR: 7.55 (1H, dd, $J=8$, 2 Hz, H-3′), 7.12 (1H, s, H-6), 6.99 (1H, s, H-3), 5.05 (2H, s, $ArC\underline{H}_2O$), 4.98 (1H, dd, $J=8$, 3 Hz, H-β), 3.84 (3H, s, OCH_3), 3.51 (1H, br s, OH), 2.78 (1H, dd, $J=12$, 3Hz, H-α), 2.37 (1H, dd, $J=12$, 8 Hz, H-α), 2.34 (3H, s, NCH_3). HR-MS (*m/z*): Calcd for $C_{24}H_{25}Br_3NO_3$: 533.0200 (M^+), 535.0179 (M+2), 537.0161 (M+4). Found: 533.0163 (M^+), 535.0156 (M+2), 537.0126 (M+4).

The fraction of *Rf* 0.25–0.36 gave **11a** as an oil (45 mg, 40.3%). ^{1}H-NMR: 7.54 (1H, dd, $J=8$, 2 Hz, H-3′′), 7.18 (1H, s, H-6′), 7.01 (1H, s, H-3′), 5.20 (1H, dd, $J=7$, 7 Hz, H-5), 5.06 (2H, s, $ArC\underline{H}_2O$), 4.66 and 4.56 (each, 1H, d, $J=5$ Hz, CH_2-2), 3.88 (3H, s, OCH_3), 3.84 (2H, s, $ArC\underline{H}_2N$), 3.63 and 2.75 (each 1H, dd, $J=12$, 7 Hz, CH_2-4). HR-MS (*m/z*) (M+2): Calcd for $C_{24}H_{23}Br_2NO_3$: 533.0027. Found: 533.0060.

β-(5-Benzyloxy-2-iodo-4-methoxyphenyl)-*N*-(2-iodobenzyl)-*N*-methylethanolamine (7b) The ethanolamine **7b** was prepared from **7a** with the oxazolidine **11b** in the same way as **6b**.

7b: Pale brown oil (45.1%). ^{1}H-NMR: 7.86 (1H, dd, $J=8$, 1 Hz, H-3′′), 7.12 (1H, s, H-6′), 5.07 (2H, s, $ArC\underline{H}_2O$), 4.83 (1H, dd, $J=10$, 3 Hz, H-β), 3.81 (3H, s, OCH_3), 3.73 and 3.51 (each 1H, d, $J=14$ Hz, $ArC\underline{H}_2N$), 3.44 (1H, br s, OH), 2.68 (1H, dd, $J=12$, 3 Hz, H-α), 2.33 (3H, s, NCH_3), 2.27 (1H, dd, $J=12$, 10 Hz, H-α). HR-MS (*m/z*) ($M-H_2O$): Calcd for $C_{24}H_{23}I_2NO_2$: 610.9822. Found: 610. 9833.

11b: Pale yellow oil (36.1%). ^{1}H-NMR: 7.79 (1H, dd, $J=8$, 2 Hz, H-3′′), 7.15 (1H, s, H-6′), 5.18 (2H, s, $ArC\underline{H}_2O$), 5.05 (1H, dd, $J=7$, 7 Hz, H-5), 4.58 (2H, s, CH_2-2), 3.84 (3H, s, OCH_3), 3.80 (2H, s, $ArC\underline{H}_2N$), 3.59 and 2.63 (each 1H, dd, $J=12$, 7 Hz, CH_2-4). HR-MS (*m/z*) (M^+): Calcd for $C_{24}H_{23}I_2NO_3$: 626.9771. Found: 626.9776.

***O*-Acetyl-β-(4-benzyloxy-2-bromo-5-methoxyphenyl)-*N*-(2-bromobenzyl)-*N*-methylethanolamine (6c)** A mixture (669 mg) of **6b** and **11a** prepared from **6a** (578 mg) in the same way as above was dissolved in acetic anhydride (20 ml) and pyridine (20 ml). The mixture was stirred at room temperature for 18 h and concentrated *in vacuo*. The residue (1.0 g) was subjected to flash chromatography on SiO_2 in benzene–ether (6 : 1) to give two fractions. The first fraction gave **6c** as a pale yellow oil (446 mg, 69.7% from **6a**). IR (film): 1740 (C=O). ^{1}H-NMR: 7.49 (1H, dd, $J=7.5$, 2 Hz, H-3′), 7.01 (1H, s, H-3), 6.81 (1H, s, H-6), 6.25 (1H, dd, $J=8$, 5 Hz, H-β), 5.06 (2H, s, $ArC\underline{H}_2O$), 3.79 (3H, s, OCH_3), 3.76 and 3.58 (each 1H, d, $J=14$ Hz, $ArC\underline{H}_2N$), 2.82 (1H, dd, $J=10$, 8 Hz, H-α), 2.78 (1H, dd, $J=10$, 5 Hz, H-α), 2.40 (3H, s, NCH_3), 2.08 (3H, s, $OCOCH_3$). HR-MS (*m/z*): Calcd for $C_{26}H_{27}Br_2NO_4$: 575.0306 (M^+), 577.0285 (M+2). Found: 575.0261 (M^+), 577.0253 (M+2).

The second fraction gave the diacetate **6f** as a pale yellow oil (221 mg, 32.9% from **6a**). IR (film): 1740, 1645 (C=O). ^{1}H-NMR: 7.57 (1H, dd, $J=7.5$, 2 Hz, H-3′), 7.01 (1H, s, H-3), 6.84 (1H, s, H-6), 6.20 (1H, dd, $J=8$, 5 Hz, H-β), 5.06 (2H, s, $ArC\underline{H}_2O$), 3.87 (5H, s, OCH_3 and $ArC\underline{H}_2N$), 3.53 (1H, dd, $J=11$, 8 Hz, H-α), 3.41 (1H, dd, $J=11$, 5 Hz, H-α), 2.27 and 2.03 (3H, each s, $NCOCH_3$), 2.09 (3H, s, $OCOCH_3$). HR-MS (*m/z*): Calcd for $C_{27}H_{27}Br_2NO_5$: 603.0254 (M^+), 605.0234 (M+2), 607.0214 (M+4). Found: 603. 0247 (M^+), 605.0192 (M+2), 607.0179 (M+4).

***O*-Acetyl-β-(5-benzyloxy-2-iodo-4-methoxyphenyl)-*N*-(2-iodobenzyl)-*N*-methylethanolamine (7c)** The ethanolamine **7a** was *N*-methylated and the resulting mixture of **7b** and **11b** was acetylated without separation in the same way as **6a** to give the monoacetate **7c** and the diacetate **7f**.

7c: Pale yellow oil (46% from **7a**). IR (film): 1735 (C=O). ^{1}H-NMR: 7.79 (1H, dd, $J=8$, 1 Hz, H-3′), 6.73 (1H, s, H-6), 6.00 (1H, dd, $J=8$, 5 Hz, H-β), 5.09 (2H, s, $ArC\underline{H}_2O$), 3.84 (3H, s, OCH_3), 3.69 and 3.50 (each 1H, d, $J=14$ Hz, $ArC\underline{H}_2N$), 2.76 (1H, dd, $J=12$, 5 Hz, H-α), 2.60 (1H, dd, $J=12$, 8 Hz, H-α), 2.40 (3H, s, NCH_3), 1.94 (3H, s, $OCOCH_3$). HR-MS (*m/z*) ($M-CH_3COOH$): Calcd for $C_{24}H_{23}I_2NO_2$: 610.9819. Found: 610. 9806.

7f: Pale yellow oil (39.6% from **7a**). IR (film): 1740, 1650 (C=O). ^{1}H-NMR: 7.82 (1H, dd, $J=8.2$ Hz, H-3′), 6.77 (1H, s, H-6), 5.97 (1H, dd, $J=9$, 5 Hz, H-β), 5.17 (2H, s, $ArC\underline{H}_2O$), 3.84 (5H, s, OCH_3 and $ArC\underline{H}_2N$), 3.42 (1H, dd, $J=13$, 5 Hz, H-α), 3.20 (1H, dd, $J=13$, 9 Hz, H-α), 2.22 and 1.92 (3H, each s, $NCOCH_3$), 1.97 (3H, s, $OCOCH_3$). HR-MS (*m/z*) (M^+): Calcd for $C_{27}H_{27}I_2NO_5$: 698.9980. Found: 698.9969.

8-Acetoxy-11-benzyloxy-10-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz-[*c*,*e*]azocine (13) Ph_3P (1.0 g, 3.81 mmol), $(Ph_3P)_2NiCl_2$ (1.3 g, 1.99 mmol), Zn powder (133 mg, 2.03 mmol), and KI (339 mg, 2.04 mmol) were placed in a two-necked flask. The flask was evacuated and filled with N_2. Dry, oxygen-free dimethylformamide (DMF) (13 ml) was added by syringe. The mixture was stirred at 55 °C for 30 min. A solution of **6c** (512 mg, 0.89 mmol) in dry, oxygen-free DMF (2.0 ml) was added and the reaction mixture was stirred at 55 °C for 10 h. Then, 2% HCl (45 ml) was added and the aqueous layer was washed with ether. The aqueous layer was made basic with Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give an oil (558 mg). This crude product was subjected to flash chromatography on SiO_2 in acetone–benzene (1 : 10). The first fraction gave the debrominated product **6d** as a pale yellow oil (107 mg, 24.3%). ^{1}H-NMR: 7.36 (5H, br s, $C_6\underline{H}_5CH_2O$), 7.23 (5H, s, $C_6\underline{H}_5CH_2N$), 7.01 (1H, s, H-3), 6.77 (1H, s, H-6), 6.25 (1H, dd, $J=7.5$, 5 Hz, H-β), 5.02 (2H, s, $ArC\underline{H}_2O$), 3.78 (3H, s, OCH_3), 3.66 and 3.45 (each 1H, d, $J=13$ Hz, $ArC\underline{H}_2N$), 2.76 (1H, dd, $J=13.5$, 5 Hz, H-α), 2.34 (3H, s, NCH_3), 2.10 (3H, s, $OCOCH_3$). HR-MS (*m/z*): Calcd for $C_{26}H_{28}BrNO_4$: 497.1201 (M^+), 499.1199 (M+2). Found: 497.1156 (M^+), 499.1164 (M+2).

The second fraction gave a crude oil (111 mg), which was further purified by PLC in acetone–benzene (1 : 10) to afford **6e** as a pale yellow oil (83 mg, 22.2%). ^{1}H-NMR: 6.77 (3H, s, H-2, H-5 and H-6), 5.89 (1H, dd, $J=8$, 5 Hz, H-β), 5.09 (2H, s, $ArC\underline{H}_2O$), 3.81 (3H, s, OCH_3), 3.53 (2H, s, $ArC\underline{H}_2N$), 2.84 (1H, dd, $J=13.5$, 8 Hz, H-α), 2.60 (1H, dd, $J=13.5$, 5Hz, H-α), 2.28 (3H, s, NCH_3), 2.06 (3H, s, $OCOCH_3$). HR-MS (*m/z*) (M^+): Calcd for $C_{26}H_{29}NO_4$: 419.2094. Found: 419.2083.

The third fraction gave a crude oil (123 mg). This was further purified by PLC in acetone–benzene (1 : 5) to afford the azocine **13** as a pale yellow oil (21 mg, 5.6%). ^{1}H-NMR: 7.01 (1H, s, H-9), 6.78 (1H, s, H-12), 5.31 (1H, dd, $J=8$, 2 Hz, H-8), 5.09 (2H, s, $ArC\underline{H}_2O$), 3.90 (3H, s, OCH_3), 3.66 and 3.21 (each 1H, d, $J=14$ Hz, CH_2-5), 2.97 (2H, m, CH_2-7), 2.46 (3H, s, NCH_3), 2.03 (3H, s, $OCOCH_3$). HR-MS (*m/z*) (M^+): Calcd for $C_{26}H_{27}NO_4$: 417.1940. Found: 417.1941.

8-Acetoxy-10-benzyloxy-11-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz-[*c*,*e*]azocine (14) The acetate **7c** (293 mg) was treated with zerovalent nickel in the same way as **6c** to give a crude product (301 mg). This was subjected to PLC in acetone–benzene (1 : 5). The fraction of *Rf* 0.26—0.30 gave the azocine **14** as a white powder (53 mg, 29.2%). ^{1}H-NMR: 6.97 (1H, s, H-9), 6.77 (1H, s, H-12), 5.34 (1H, dd, $J=7$, 2 Hz, H-8), 5.27 and 5.18 (each 1H, d, $J=7$ Hz, $ArC\underline{H}_2O$), 3.88 (3H, s, OCH_3), 3.68 and 3.22 (each 1H, d, $J=14$ Hz, CH_2-5), 2.94 (2H, m, CH_2-7), 2.47 (3H, s, NCH_3), 1.87 (3H, s, $OCOCH_3$). HR-MS (*m/z*) (M^+): Calcd for $C_{26}H_{27}NO_4$: 417.1937. Found: 417.1922.

The fraction of *Rf* 0.55—0.58 gave **7e** as an oil (61.7 mg, 33.8%). ^{1}H-NMR: 6.84 (3H, s, H-2, H-5 and H-6), 5.84 (1H, dd, $J=8$, 5 Hz, H-β), 5.11 (2H, s, $ArC\underline{H}_2O$), 3.86 (3H, s, OCH_3), 3.53 (2H, s, $ArC\underline{H}_2N$), 2.80 (1H, dd, $J=13.5$, 8 Hz, H-α), 2.51 (1H, dd, $J=13.5$, 5 Hz, H-α), 2.25 (3H, s, NCH_3), 2.01 (3H, s, $OCOCH_3$). HR-MS (*m/z*) (M^+): Calcd for $C_{26}H_{29}NO_4$: 419.2095. Found: 419.2095.

The fraction of *Rf* 0.64—0.67 gave **7d** as an oil (12.4 mg, 5.2%). ^{1}H-NMR: 7.33 (5H, s, $C_6\underline{H}_5CH_2O$), 7.24 (5H, s, $C_6\underline{H}_5CH_2N$), 7.19 (1H, s, H-3), 6.73 (1H, s, H-6), 6.02 (1H, dd, $J=8$, 5 Hz, H-β), 5.06 (2H, s, $ArC\underline{H}_2O$), 3.84 (3H, s, OCH_3), 3.67 and 3.44 (each 1H, d, $J=14$ Hz, $ArC\underline{H}_2N$), 2.66 (1H, dd, $J=14$, 8 Hz, H-α), 2.48 (1H, dd, $J=14$, 5 Hz, H-α), 2.33 (3H, s, NCH_3), 1.97 (3H, s, $OCOCH_3$). HR-MS (*m/z*) ($M-CH_3COOH$): Calcd for $C_{24}H_{24}INO_2$: 485.0854. Found: 485.0875.

11-Benzyloxy-8-hydroxy-10-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz-[*c*,*e*]azocine (17) A mixture of **13** (61 mg) in EtOH (4 ml) and 7% K_2CO_3 (4 ml) was stirred at room temperature for 24 h. H_2O (40 ml) was added and the mixture was concentrated. The aqueous layer was extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give **17** as an oil (53 mg, quantitative yield). ^{1}H-NMR: 7.21 (1H, s, H-9), 6.76

(1H, s, H-12), 5.11 (2H, s, $ArC\underline{H}_2O$), 4.31 (1H, dd, J=9, 2 Hz, H-8), 3.92 (3H, s, OCH_3), 3.51 and 3.05 (each 1H, d, J=14 Hz, CH_2-5), 3.01 (1H, dd, J=12, 2 Hz, H-7), 2.66 (1H, dd, J=12, 9 Hz, H-7), 2.40 (3H, s, NCH_3). HR-MS (m/z) (M^+): Calcd for $C_{24}H_{25}NO_3$: 375.1832. Found: 375.1832.

10-Benzyloxy-8-hydroxy-11-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (18) The acetate **14** (33 mg) was treated with 7% K_2CO_3 (2 ml) and EtOH (2 ml) in the same way as **13** to give **18** as an oil (30 mg, quantitative yield). ^{1}H-NMR: 7.20 (1H, s, H-9), 6.72 (1H, s, H-12), 5.19 (2H, s, $ArC\underline{H}_2O$), 4.29 (1H, dd, J=9, 3 Hz, H-8), 3.86 (3H, s, OCH_3), 3.50 and 3.03 (each 1H, d, J=14 Hz, CH_2-5), 2.97 (1H, dd, J=13, 3 Hz, H-7, 2.58 (1H, dd, J=13, 9 Hz, H-7), 2.40 (3H, s, NCH_3), 2.35 (1H, br s, OH). HR-MS (m/z) (M^+): Calcd for $C_{24}H_{25}NO_3$: 375.1832. Found: 375.1807.

8,11-Dihydroxy-10-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (4) A solution of **17** (29 mg) in dry CH_2Cl_2 (1 ml) was added to a solution of $AlCl_3$ (73 mg), dry EtSH (4 ml) in dry CH_2Cl_2 (20 ml) under N_2 with stirring at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into 2% HCl (20 ml). The aqueous layer was made basic (pH 8) with NH_4OH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and evaporated to give an oil (14.2 mg). This was subjected to PLC in $CHCl_3$–MeOH (10 : 1). The fraction of Rf 0.14—0.24 gave **4** as a white powder (10 mg, 44.8%), mp 144—145 °C. ^{1}H-NMR [$CDCl_3$–CD_3OD (1 : 1)]: 7.18 (1H, s, H-9), 6.72 (1H, s, H-12), 4.33 (1H, dd, J=9, 2 Hz, H-8), 3.93 (3H, s, OCH_3), 3.54 and 3.09 (each 1H, d, J=14 Hz, CH_2-5), 3.05 (1H, dd, J=11, 2 Hz, H-7), 2.67 (1H, dd, J=11, 9 Hz, H-7), 2.45 (3H, s, NCH_3). HR-MS (m/z) (M^+): Calcd for $C_{17}H_{19}NO_3$: 285.1365. Found: 285.1366.

The fraction of Rf 0.52—0.60 gave **19** as an oil (1.7 mg, 6.6%). ^{1}H-NMR: 7.28 (1H, s, H-9), 6.79 (1H, s, H-12), 3.94 (3H, s, OCH_3), 3.81 (1H, dd, J=9, 2 Hz, H-8), 3.62 and 3.20 (each 1H, d, J=14 Hz, CH_2-5), 3.07 (1H, dd, J=13, 2 Hz, H-7), 2.81 (1H, dd, J=13, 9 Hz, H-7), 2.44 (3H, s, NCH_3), 2.19 (2H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 0.93 (3H, t, J=7 Hz, $SCH_2C\underline{H}_3$). HR-MS (m/z) (M^+): Calcd for $C_{19}H_{23}NO_2S$: 329.1450. Found: 329.1483.

8,10-Dihydroxy-11-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (5) The benzyloxy derivative **18** (28 mg) was treated with $AlCl_3$ (64 mg) and EtSH (4 ml) in CH_2Cl_2 (21 ml) in the same way as **17**. The crude product (8.3 mg) was subjected to PLC in $CHCl_3$–MeOH (10 : 1). The fraction of Rf 0.08—0.27 gave **5** as a white powder (6.8 mg, 31.5%), mp 163—168 °C. ^{1}H-NMR [$CDCl_3$–CD_3OD (1 : 1)]: 7.18 (1H, s, H-9), 6.74 (1H, s, H-12), 3.89 (3H, s, OCH_3), 3.60 and 3.15 (each 1H, d, J=14 Hz, CH_2-5), 3.07 (1H, dd, J=12, 2 Hz, H-7), 2.69 (1H, dd, J=12, 9 Hz, H-7), 2.49 (3H, s, NCH_3). HR-MS (m/z) (M^+): Calcd for $C_{17}H_{19}NO_3$: 285.1362. Found: 285.1324.

The fraction of Rf 0.41—0.49 gave **16** as an oil (1.9 mg, 7.6%). ^{1}H-NMR: 7.30 (1H, s, H-9), 6.69 (1H, s, H-12), 3.86 (3H, s, OCH_3), 3.78 (1H, dd, J=9, 2 Hz, H-8), 3.62 and 3.21 (each 1H, d, J=14 Hz, CH_2-5), 3.03 (1H, dd, J=13, 2 Hz, H-7), 2.81 (1H, dd, J=13, 9 Hz, H-7), 2.43 (3H, s, NCH_3), 2.18 (2H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 0.92 (3H, t, J=7 Hz, $SCH_2C\underline{H}_3$). HR-MS (m/z) (M^+): Calcd for $C_{19}H_{23}NO_2S$: 329.1446. Found: 329.1401.

6-Methyl-8,10,11-trihydroxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (3) A solution of BBr_3 (491 mg) in dry CH_2Cl_2 (1 ml) was added to a solution of **12** (41 mg) in dry CH_2Cl_2 (6 ml) under stirring at −60 °C. The mixture was allowed to warm to room temperature under stirring during 1 h. The reaction mixture was poured into ice-water (10 ml). The aqueous layer was separated, made basic (pH 8) with NH_4OH and extracted with ethyl acetate. The extract was washed with a saturated solution of NaCl in H_2O, dried and evaporated to give **3** as a white powder (16.9 mg, 46.0%), mp 226—230 °C. ^{1}H-NMR [$CDCl_3$–CD_3OD (1 : 1)]: 4.80 (1H, m, H-8), 4.27 and 3.54 (each 1H, d, J=14 Hz, CH_2-5), 2.87 (3H, s, NCH_3). FAB-MS (m/z): 272 (M+1).

6-Methyl-8,10,11-triacetoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (20) A solution of **3** (5.5 mg) in acetic anhydride (0.4 ml) and pyridine (0.4 ml) was stirred at room temperature for 22 h. The mixture was concentrated *in vacuo* to give **20** as an oil (4.8 mg, 60.0%). ^{1}H-NMR: 7.21 (1H, s, H-12), 5.42 (1H, dd, J=7, 3 Hz, H-8), 3.78 and 3.34 (each 1H, d, J=14 Hz, CH_2-5), 3.08 (2H, m, CH_2-7), 2.50 (3H, s, NCH_3), 2.32 and 2.28 (each 3H, s, 2 × $ArOCOCH_3$), 2.04 (3H, s, $OCOCH_3$). HR-MS (m/z) (M^+): Calcd for $C_{22}H_{23}NO_6$: 397.1524. Found. 397.1509.

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