

Syntheses of Apogalanthamine Analogues as α -Adrenergic Blocking Agents. XII.¹⁾ Syntheses and Stereochemistry of Methoxy and Methyleneedioxy Derivatives of 8-Hydroxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocines

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8-Hydroxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocines **4b, c** and their methoxy and methyleneedioxy derivatives **7a-c** and **8a-c** were prepared by cyclization of *O*-protected 1-phenyl-2-aminoethanols **6b, c**, **9a-c** and **10a-c** with zerovalent nickel, followed by hydrolysis of the resulting *O*-protected azocines **4d, e**, **7d-f** and **8d-f**, respectively. The half-tub conformation of the tetrahydroazocine ring of these 8-hydroxydibenz[*c,e*]azocines and the quasi-equatorial configuration of the 8-hydroxy group were supported by the proton nuclear magnetic resonance spectra.

Keywords apogalanthamine analogue; 8-hydroxydibenz[*c,e*]azocine; dibenz[*c,e*]azocine; halogeno-*N*-benzyl-1-phenyl-2-aminoethanol; biphenyl; cyclization; zerovalent nickel; half-tub conformation; alpha adrenergic blocking agent

In the previous paper,¹⁾ we have reported the syntheses of apogalanthamine analogues, 6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (**1a**) and its methoxy derivatives, as α_1 -adrenergic blocking agents²⁾ by cyclization reaction of 2-halogeno-*N*-(2-halogenobenzyl)-2-phenylethylamines with zerovalent nickel. Recently, we reported³⁾ that the

reaction of *N*-(2-iodobenzyl)-*N*-methyl-2-iodophenacylamine (**2**) with zerovalent nickel did not give the expected carbonyl compound **3** as a precursor of an 8-hydroxyazocine **4a**, which was of interest from the pharmacological point of view,⁴⁾ but gave a tetrahydroisoquinolin-4-ol **5**, a new potentiator of noradrenaline.⁵⁾ However, we could

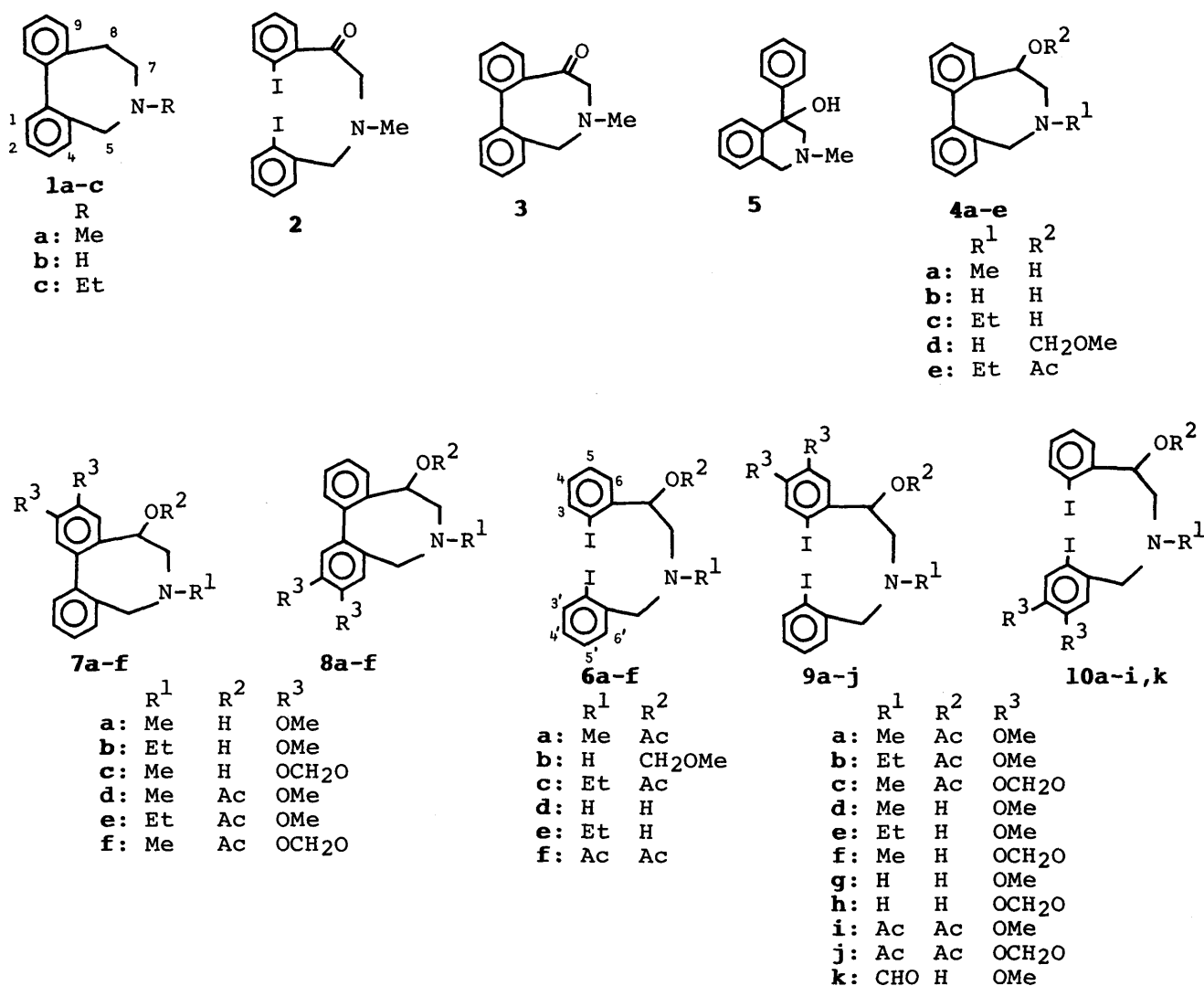


Chart 1

synthesize⁴⁾ racemic and optically active **4a** by cyclization of an *N*-benzyl-1-phenyl-2-aminoethanol **6a** with zerovalent nickel. In the course of this series, it was found that the order⁶⁾ of the α -adrenolytic activities of the *N*-alkylated azocines **1a—c** was Me > Et > H and that the potency of the α -adrenolytic or anti-serotonin activity in the azocine **1a** was greatly affected^{6,7)} by the introduction of substituents such as methoxy and methylenedioxy groups on the benzene ring. These findings prompted us to synthesize a secondary amine **4b** and its *N*-ethyl derivative **4c**, and their methoxy and methylenedioxy derivatives to test their pharmacological activities. This paper describes the syntheses of the 8-hydroxyazocines **4b, c, 7a—c** and **8a—c** by cyclization of the *O*-protected 1-phenyl-2-aminoethanols **6b, c, 9a—c** and **10a—c** with zerovalent nickel⁸⁾ followed by deprotection of the resulting azocines **4d, e, 7d—f** and **8d—f** (Chart 1).

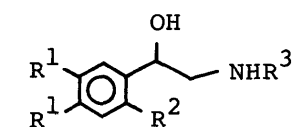
The key intermediates, *N*-(2-iodobenzyl)-1-(2-iodophenyl)-2-aminoethanols **9g, h** and **10g, h**, for the syntheses of the 8-hydroxyazocines **7a—c** and **8a—c** were prepared by condensation of 1-(2-iodophenyl)-2-aminoethanols **11a, b** and 2-iodobenzaldehydes **12a, b** followed by reduction of

the resulting Schiff's bases with sodium borohydride (NaBH₄) (Table I). The compounds **11a, b** were prepared from veratraldehyde (**12c**) and piperonal (**12d**) as follows (Chart 2). The 2-aminoethanols **11c, d** obtained by lithium aluminium hydride (LiAlH₄) reduction of the cyanohydrins **13a, b** of **12c, d** were treated with ethyl formate to give the amides **11e, f**. These compounds **11e, f** were iodinated to give the amides **11g, h**, which were hydrolyzed to give **11a, b**. The compounds **9g, h** and **10h** were treated with formalin and NaBH₄ to give the *N*-methyl derivatives **9d, f** and **10f** along with the oxazolidine derivatives **14a—c**. The *N*-methyl derivative **10d** was obtained from **10g** via an *N*-formyl compound **10k**. Then, the compounds **9d, f** and **10d, f** were acetylated to the acetates **9a, c** and **10a, c**. The *N*-ethylated acetates **6c, 9b** and **10b** were prepared by reduction of the diacetyl derivatives **6f, 9i** and **10i** of **6d, 9g** and **10g** with diborane. The 2-aminoethanol **6d** was treated with methylal and phosphorus pentoxide⁹⁾ to give the methoxymethyl derivative **6b**.

The *O*-protected compounds **6b, c, 9a—c** and **10a—c** thus obtained were treated with stoichiometric amounts of zerovalent nickel generated *in situ*¹⁰⁾ and potassium iodide

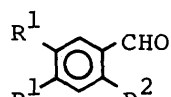
TABLE I. Physical and ¹H-NMR Spectral Data for *N*-Benzyl-1-phenyl-2-aminoethanols **9g, h** and **10g, h**

No.	Yield (%)	mp (°C)	Formula	Analysis (%)			¹ H-NMR (δ , CDCl ₃)
				Calcd	Found	N	
9g	90.3	94—96	C ₁₇ H ₁₉ I ₂ NO ₃	37.87 (37.96)	3.55 3.37	2.59 2.54	7.79 (1H, dd, 8, 1), 7.12 (1H, s), 7.05 (1H, s), 4.79 (1H, dd, 9, 3.5), 3.85 (3H, s), 3.82 (3H, s), 2.76 (1H, dd, 12.5, 3.5), 2.42 (1H, dd, 12.5, 9)
9h	57.1	143—145	C ₁₆ H ₁₅ I ₂ NO ₃	36.73 (37.00)	2.89 2.85	2.68 2.45	7.80 (1H, d, 8), 7.16 (1H, s), 7.04 (1H, s), 5.92 (2H, s), 4.82 (1H, dd, 9, 3), 3.86 (2H, s), 2.98 (1H, dd, 12, 3), 2.46 (1H, dd, 12, 9)
10g	88.6	94—96	C ₁₇ H ₁₉ I ₂ NO ₃	37.87 (37.90)	3.55 3.43	2.59 2.32	7.75 (1H, dd, 8, 2), 7.20 (1H, s), 6.89 (1H, s), 4.92 (1H, dd, 9, 3.5), 3.83 (8H, s), 3.00 (1H, dd, 12.5, 3.5) 2.51 (1H, dd, 12.5, 9)
10h	62.8	144—145	C ₁₆ H ₁₅ I ₂ NO ₃	36.73 (36.87)	2.89 2.86	2.68 2.66	7.79 (1H, d, 8), 7.25 (1H, s), 6.90 (1H, s), 5.94 (2H, s), 4.87 (1H, dd, 9, 3), 3.78 (2H, s), 3.02 (1H, dd, 12, 3), 2.51 (1H, dd, 12, 9)



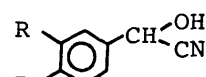
11a-h

	R ¹	R ²	R ³
a:	OMe	I	H
b:	OCH ₂ O	I	H
c:	OMe	H	H
d:	OCH ₂ O	H	H
e:	OMe	H	CHO
f:	OCH ₂ O	H	CHO
g:	OMe	I	CHO
h:	OCH ₂ O	I	CHO



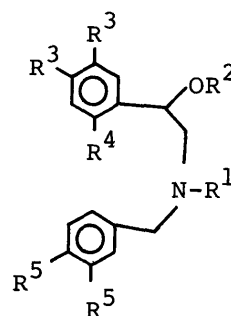
12a-d

	R ¹	R ²
a:	OMe	I
b:	OCH ₂ O	I
c:	OMe	H
d:	OCH ₂ O	H

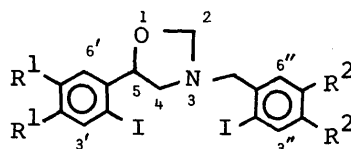


13a,b

	R
a:	OMe
b:	OCH ₂ O



15a-i



14a-d

	R ¹	R ²
a:	OMe	H
b:	OCH ₂ O	H
c:	H	OCH ₂ O
d:	H	H

	R ¹	R ²	R ³	R ⁴	R ⁵
a:	H	CH ₂ OMe	H	H	H
b:	Et	Ac	H	H	H
c:	Me	Ac	OMe	H	H
d:	Et	Ac	OMe	H	H
e:	Me	Ac	OCH ₂ O	H	H
f:	Me	Ac	OCH ₂ O	I	H
g:	Me	Ac	H	H	OMe
h:	Et	Ac	H	H	OMe
i:	Me	Ac	H	H	OCH ₂ O

Chart 2

TABLE II. Syntheses^{a)} of 8-Acetoxyazocines **4d**, **e**, **7d—f** and **8d—f** Using Zerovalent Nickel

Starting material No.	8-Acetoxyazocine No.	Yield (%)	By-product ^{b)} No.	Yield (%)
6b	4d	43.4	15a	23.6
6c	4e	77.4	15b	13.6
9a	7d	57.4	15c	18.3
9b	7e	57.1	15d	21.5
9c	7f	27.2	15e	15.3
			15f	9.7
10a	8d	53.4	15g	35.4
10b	8e	48.4	15h	40.0
10c	8f	36.1	15i	43.6

a) Reaction conditions were as given in Experimental. b) Oily material.

TABLE III. Mass and ¹H-NMR Spectral Data for 8-Acetoxyazocines **4d**, **e**, **7d—f** and **8d—f**

No.	Formula	MS (<i>m/z</i>) (<i>M</i> ⁺) Calcd (Found)	¹ H-NMR (δ , CDCl ₃)
4d	C ₁₇ H ₁₉ NO ₂	269.1414 (269.1414)	4.50 and 4.38 (each 1H, d, 7), 4.31 (1H, dd, 9.5, 2.5), 3.95 and 3.18 (each 1H, d, 14.5), 3.51 (1H, brs), 3.42 (1H, dd, 13, 2.5), 3.22 (3H, s), 2.89 (1H, dd, 13, 9.5)
4e	C ₁₉ H ₂₁ NO ₂	295.1570 (295.1548)	5.38 (1H, dd, 9, 1.5), 3.75 and 3.20 (each 1H, d, 14), 3.27 (1H, dd, 12.5, 1.5), 2.86 (1H, dd, 12.5, 9), 2.63 (2H, q, 7), 2.02 (3H, s), 1.16 (3H, t, 7)
7d	C ₂₀ H ₂₃ NO ₄	341.1624 (341.1612)	7.07 (1H, s), 6.81 (1H, s), 5.40 (1H, dd, 8, 2.5), 3.97 (3H, s), 3.90 (3H, s), 3.73 and 3.29 (each 1H, d, 14), 3.14 (1H, dd, 14, 2.5), 2.95 (1H, dd, 14, 8), 2.51 (3H, s), 2.06 (3H, s)
7e	C ₂₁ H ₂₅ NO ₄	355.1781 (355.1773)	7.01 (1H, s), 6.75 (1H, s), 5.34 (1H, dd, 9, 1), 3.96 (3H, s), 3.89 (3H, s), 3.79 and 3.12 (each 1H, d, 14), 3.25 (1H, dd, 12.5, 1), 2.86 (1H, dd, 12.5, 9), 2.78 (2H, q, 7), 2.05 (3H, s), 1.19 (3H, t, 7)
7f	C ₁₉ H ₁₉ NO ₄	325.1311 (325.1295)	6.96 (1H, s), 6.72 (1H, s), 5.96 (2H, s), 5.32 (1H, dd, 8, 3), 3.72 and 3.26 (each 1H, d, 14), 3.00 (1H, dd, 14, 3), 2.92 (1H, dd, 14, 8), 2.46 (3H, s), 2.01 (3H, s)
8d	C ₂₀ H ₂₃ NO ₄	341.1624 (341.1622)	6.90 (1H, s), 6.87 (1H, s), 5.51 (1H, dd, 9, 1.5), 3.96 (3H, s), 3.92 (3H, s), 3.63 and 3.14 (each 1H, d, 14), 3.19 (1H, dd, 13, 1.5), 2.91 (1H, dd, 13, 9), 2.52 (3H, s), 2.05 (3H, s)
8e	C ₂₁ H ₂₅ NO ₄	355.1781 (355.1773)	6.86 (1H, s), 6.84 (1H, s), 5.47 (1H, dd, 9, 1), 3.93 (3H, s), 3.88 (3H, s), 3.63 and 3.08 (each 1H, d, 14), 3.22 (1H, dd, 13, 1), 2.84 (1H, dd, 13, 9), 2.77 (2H, q, 7), 2.04 (3H, s), 1.19 (3H, t, 7)
8f	C ₁₉ H ₁₉ NO ₄	325.1311 (325.1299)	6.80 (1H, s), 6.78 (1H, s), 5.95 (2H, s), 5.43 (1H, dd, 9, 2), 3.54 and 3.08 (each 1H, d, 14), 3.11 (1H, dd, 13, 2), 2.90 (1H, dd, 13, 9), 2.48 (3H, s), 2.02 (3H, s)

(KI) to give the 8-acetoxyazocines **4d**, **e**, **7d—f** and **8d—f** as oily products in yields of 40—70% except for those of the methylenedioxy compounds **7f** and **8f**, as shown in Table

TABLE IV. Mass and ¹H-NMR Spectral Data for Deiodinated By-products **15a—i**

No.	Formula	MS (<i>m/z</i>) (<i>M</i> ⁺) Calcd (Found)	¹ H-NMR (δ , CDCl ₃)
15a	C ₁₇ H ₂₁ NO ₂	271.1573 (271.1593)	4.83 (1H, dd, 8.5, 4.5), 4.58 (2H, s), 3.89 (2H, s), 3.35 (3H, s), 3.00 (1H, dd, 12.5, 8.5), 2.80 (1H, dd, 12.5, 4.5)
15b	C ₁₉ H ₂₃ NO ₂	297.1727 (297.1682)	5.90 (1H, dd, 8, 5), 3.63 (2H, s), 2.92 (1H, dd, 14, 8), 2.67 (1H, dd, 14, 5), 2.57 (2H, q, 7), 2.06 (3H, s), 1.10 (3H, t, 7)
15c	C ₂₀ H ₂₅ NO ₄	343.1784 (343.1789)	6.81 (2H, s), 6.76 (1H, s), 5.89 (1H, dd, 8, 5.5), 3.86 (6H, s), 3.54 (2H, s), 2.77 (1H, dd, 12, 5.5), 2.46 (1H, dd, 12, 8), 2.28 (3H, s), 2.06 (3H, s)
15d	C ₂₁ H ₂₆ NO ₄	356.1862 ^{a)} (356.1893)	6.80 (2H, s), 6.74 (1H, brs), 5.90 (1H, dd, 8, 6), 3.85 (3H, s), 3.83 (3H, s), 3.63 (2H, s), 2.39—2.87 (4H, m), 2.04 (3H, s), 1.00 (3H, t, 7)
15e	C ₁₉ H ₂₁ NO ₄	327.1467 (327.1439)	6.74 (3H, s), 5.90 (2H, s), 5.84 (1H, dd, 8, 5), 3.58 (2H, s), 2.84 (1H, dd, 14, 8), 2.54 (1H, dd, 14, 5), 2.28 (3H, s), 2.06 (3H, s)
15f	C ₁₉ H ₂₀ INO ₄	453.0436 (453.0394)	7.16 (1H, s), 6.76 (1H, s), 6.08 (1H, dd, 8, 5), 5.92 (2H, s), 3.70 and 3.46 (each 1H, d, 13), 2.56 (1H, dd, 14, 8), 2.38 (1H, dd, 14, 5), 2.36 (3H, s), 2.08 (3H, s)
15g	C ₂₀ H ₃₅ NO ₄	342.1705 ^{a)} (342.1706)	6.80 (1H, s), 6.74 (2H, s), 5.95 (1H, dd, 8, 5), 3.81 (3H, s), 3.84 (3H, s), 3.48 (2H, s), 2.77 (1H, dd, 12.5, 5), 2.58 (1H, dd, 12.5, 8), 2.28 (3H, s), 2.07 (3H, s)
15h	C ₂₁ H ₂₇ NO ₄	357.1940 (357.1973)	6.81 (1H, s), 6.75 (2H, s), 5.92 (1H, dd, 8, 6), 3.86 (3H, s), 3.83 (3H, s), 3.59 (2H, s), 2.95 (1H, dd, 14, 8), 2.70 (1H, dd, 14, 6), 2.56 (2H, q, 7), 2.08 (3H, s), 1.00 (3H, t, 7)
15i	C ₁₉ H ₂₁ NO ₄	327.1471 (327.1516)	6.70 (1H, s), 6.66 (2H, s), 5.92 (1H, dd, 8, 5), 5.87 (2H, s), 3.52 and 3.36 (each 1H, d, 13), 2.87 (1H, dd, 13, 8), 2.55 (1H, dd, 13, 5), 2.27 (3H, s), 2.05 (3H, s)

a) Fragment of *M* - 1.

II. In these cyclization reactions, the deiodinated by-products **15a—i** were obtained in yields of 10—40% (Table IV). Finally, the 8-acetoxyazocines **4e**, **7d—f** and **8d—f** were hydrolyzed with 7% aqueous potassium carbonate-ethanol to afford the 8-hydroxyazocines **4c**, **7a—c** and **8a—c** in yields of 60—80%, respectively. Hydrolysis of the methoxymethyl derivative **4d** with 5% HCl gave the secondary amine **4b** as an oil, which was crystallized as a styphnate. The structures of the 8-methoxymethyl-, 8-acetoxy- and 8-hydroxyazocines thus obtained were determined from their physical data, high-resolution mass spectra (HRMS) and proton nuclear magnetic resonance (¹H-NMR) spectra (Tables III and V).

The stereochemistry of the 8-hydroxyazocines is interesting in relation to their binding ability with α -adrenoceptors.⁷⁾ We considered that the tetrahydroazocine ring of the racemic 8-hydroxyazocines such as **4a—c**, **7a—c** and **8a—c**, has half-tub conformations C and its enantiomer, and that

TABLE V. Physical and ^1H -NMR Spectral Data for 8-Hydroxyazocines **4b**, **c**, **7a**—**c** and **8a**—**c**

No.	Yield (%)	mp (°C)	Formula	Analysis (%)			^1H -NMR (δ , CDCl_3)
				Calcd	(Found)		
				C	H	N	
4a ^{a)}							7.68 (1H, dd, 8, 2), 4.35 (1H, dd, 9, 1), 3.50 (1H, d, 14), 3.01 (1H, d, 14), 3.01 (1H, m, 12, 1), 2.66 (1H, dd, 12, 9), 2.49 (1H, brs), 2.41 (3H, s)
4b ^{b)}	75.4	218.5—220	$\text{C}_{15}\text{H}_{15}\text{NO}$ $\cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_8$	53.62 (53.47)	3.86 (3.62)	11.91 (11.65)	7.66 (1H, d, 8), 4.27 (1H, dd, 9, 1.5), 3.97 and 3.15 (each 1H, d, 14), 3.73 (1H, dd, 13, 9), 2.96 (1H, dd, 13, 1.5)
4c	80.0	129.5—130	$\text{C}_{17}\text{H}_{19}\text{NO}$	80.66 (80.46)	7.57 (7.63)	5.43 (5.37)	7.68 (1H, d, 8), 4.38 (1H, dd, 9, 1), 3.59 (1H, d, 14), 2.86 (1H, d, 14), 3.13 (1H, m, 12, 1), 2.63 (1H, s), 2.63 (1H, dd, 12, 9), 2.56 (2H, q, 7), 1.15 (3H, t, 7)
7a	50.8	137—141	$\text{C}_{18}\text{H}_{21}\text{NO}_3$	72.22 (72.06)	7.07 (7.11)	4.68 (4.40)	7.21 (1H, s), 6.72 (1H, s), 4.40 (1H, dd, 9, 1.5), 3.95 (3H, s), 3.89 (3H, s), 3.58 and 3.11 (each 1H, d, 13.5), 3.06 (1H, dd, 12, 1.5), 2.70 (1H, dd, 12, 9), 2.69 (1H, s), 2.46 (3H, s)
7b	57.9	105—109	$\text{C}_{19}\text{H}_{23}\text{NO}_3$	MS (m/z) (M^+): 313.1679 (Found: 313.1694)			7.20 (1H, s), 6.71 (1H, s), 4.33 (1H, dd, 9, 1), 3.92 (3H, s), 3.87 (3H, s), 3.61 and 2.89 (each 1H, d, 13.5), 3.10 (1H, dd, 12, 1), 2.61 (1H, dd, 12, 9), 2.65 (2H, q, 7), 1.16 (3H, t, 7)
7c	79.8	135—139	$\text{C}_{17}\text{H}_{17}\text{NO}_3$ $\cdot 1/4 \text{H}_2\text{O}$	71.03 (71.24)	6.13 (5.96)	4.87 (4.70)	7.14 (1H, s), 6.68 (1H, s), 5.96 (2H, s), 4.34 (1H, dd, 9, 1.5), 3.54 and 3.08 (each 1H, d, 14), 3.02 (1H, dd, 12, 1.5), 2.64 (1H, dd, 12, 9), 2.48 (1H, brs), 2.44 (3H, s)
8a	69.1	198—199.5	$\text{C}_{18}\text{H}_{21}\text{NO}_3$ $\cdot 1/2 \text{H}_2\text{O}$	70.11 (70.40)	7.19 (6.97)	4.54 (4.36)	7.68 (1H, d, 8), 6.79 (1H, s), 6.67 (1H, s), 4.19 (1H, dd, 9, 1), 3.91 (3H, s), 3.73 (3H, s), 3.44 and 2.93 (each 1H, d, 14), 2.94 (1H, dd, 12, 1), 2.67 (1H, dd, 12, 9), 2.42 (3H, s)
8b	60.2	178—180	$\text{C}_{19}\text{H}_{23}\text{NO}_3$ $\cdot 1/4 \text{H}_2\text{O}$	71.79 (71.91)	7.45 (7.56)	4.41 (4.16)	7.68 (1H, d, 8), 6.78 (1H, s), 6.72 (1H, s), 4.34 (1H, dd, 9.5, 1), 3.92 (3H, s), 3.80 (3H, s), 3.52 and 2.78 (each 1H, d, 13.5), 3.11 (1H, dd, 11.5, 1), 2.60 (1H, dd, 11.5, 9.5), 2.60 (2H, q, 7), 1.19 (3H, t, 7)
8c	65.0	189.5—190	$\text{C}_{17}\text{H}_{17}\text{NO}_3$ $\cdot 1/2 \text{H}_2\text{O}$	69.84 (69.56)	6.21 (5.95)	4.79 (4.68)	8.15 (1H, d, 8), 6.90 (1H, s), 6.76 (1H, s), 5.88 and 5.93 (each 1H, d, 1.5), 4.88 (1H, dd, 9, 2), 3.50 and 3.07 (each 1H, d, 13), 3.48 (1H, dd, 12, 2), 2.96 (1H, dd, 12, 9), 2.43 (3H, s)

a) Ref. 4. b) This compound was crystallized as a styphnate and the ^1H -NMR spectrum was determined as the free base in CD_3OD .

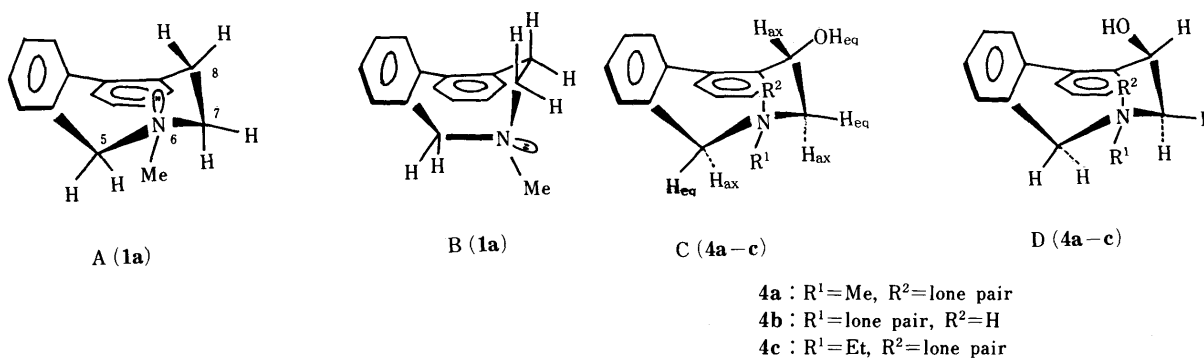


Chart 3

the 8-hydroxy groups took a quasi-equatorial position (Chart 3). As reported in the previous paper,¹¹⁾ we determined that the conformation of the dibenz[*c,e*]azocine **1a** was a half-tub conformation A, but not a tub conformation B. Similarly, the half-tub conformations C, D and their enantiomers for the tetrahydroazocine ring were suggested by the following ^1H -NMR spectral data of the 8-hydroxyazocines: i) the signals of the quasi-equatorial protons (δ 3.50 and 3.59) and quasi-axial protons (δ 3.01 and 2.86) at C-5 in **4a**⁴⁾ and **4c**, respectively, were at higher field¹²⁾ (0.47 and 0.38 ppm, and 0.14 and 0.29 ppm) than those of the corresponding protons (δ 3.97 and 3.15) in **4b**; ii) long-range couplings¹²⁾ between $\text{H}_{\text{eq}}-7$ and $\text{H}_{\text{eq}}-5$ in **4a** and **4c** (W-rule) were observed.¹³⁾

The configuration of the 8-hydroxy group in these half-tub conformations C, D and their enantiomers was concluded to be quasi-equatorial for the following reasons. i) The dihedral angles between H-7 and H-8 were calculated to be 145—155° and 67—75° from the coupling constants

(9.0—9.5 Hz and 1.0—1.5 Hz) according to the Karplus formula and analogous formulas.¹⁴⁾ This means that the 8-hydroxy group was located at a quasi-equatorial position, as shown in C and its enantiomer, but not at a quasi-axial position in D and its enantiomer. ii) The quasi-equatorial 8-hydroxy group in C seemed to have less steric hindrance than the quasi-axial one in D.

On the basis of the above results, (8*S*)- and (8*R*)-hydroxy-6-methylazocines *S*-**4a** and *R*-**4a** in the previous paper⁴⁾ were assigned as C and its enantiomer, respectively.

The α -adrenergic blocking activities of the 8-hydroxyazocines **4a**—**c**, **7a**—**c** and **8a**—**c** 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} . HRMS were determined with a JEOL JMS-D 300 spectrometer. ^1H -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 values. The plates used for preparative TLC (PLC) were coated with silica gel (Kiesel gel PF₂₅₄ Merck).

1-(3,4-Methylenedioxyphenyl)-2-aminoethanol (11d) A mixture of piperonal (12d) (10.0 g) and 2 N NaHSO₃ (160 ml) was stirred at 40 °C for 3 h, then a solution of KCN (18.0 g) in H₂O (40 ml) was added, and the mixture was stirred under ice-cooling for 15 min. Work-up in the usual way gave a cyanohydrin 13b as an oil (6.67 g, 56.6%). ¹H-NMR: 5.97 (2H, s, OCH₂O), 5.37 (1H, s, H- β), 3.37 (1H, s, OH). A solution of 13b (3.77 g) in dry tetrahydrofuran (THF) (90 ml) was treated with LiAlH₄ (4.40 g) and the mixture was stirred at room temperature for 6 h. Work-up in the usual way gave an oil (3.97 g), which was converted to the hydrochloride of 11d as colorless needles (2.06 g, 44.4%), mp 180–182 °C (from MeOH–acetone). *Anal.* Calcd for C₉H₁₁NO₃·HCl: C, 49.66; H, 5.56; N, 6.43. Found: C, 49.63; H, 5.49; N, 6.30. ¹H-NMR (free base): 6.88 (1H, s, H-2), 6.76 (2H, s, H-5 and H-6), 5.90 (2H, s, OCH₂O), 4.51 (1H, dd, *J* = 7, 5 Hz, H- β), 2.96–2.62 (2H, m, CH₂NH₂), 2.24 (3H, brs, NH₂ and OH).

The 2-aminoethanol 11c was prepared from 12c in the same way as 11d.

1-(3,4-Dimethoxyphenyl)-2-aminoethanol (11c) The hydrochloride of 11c was recrystallized from MeOH–acetone as colorless cubes, mp 163–165 °C (lit.¹⁵) mp 166–166.5 °C). *Anal.* Calcd for C₁₀H₁₃NO₃·HCl: C, 51.40; H, 6.90; N, 5.99. Found: C, 51.17; H, 7.14; N, 5.85. ¹H-NMR (free base): 6.87 (1H, s, H-2), 6.80 (2H, s, H-5 and H-6), 4.53 (1H, dd, *J* = 7, 4.5 Hz, H- β), 3.86 (6H, s, 2 × OCH₃), 2.95 (1H, dd, *J* = 13, 4.5 Hz, H- α), 2.73 (1H, dd, *J* = 13, 7 Hz, H- α), 2.13 (3H, brs, NH₂ and OH).

N-Formyl-1-(3,4-methylenedioxyphenyl)-2-aminoethanol (11f) A mixture of the hydrochloride of 11d, K₂CO₃ (5.00 g), 3A molecular sieves (5.0 g) and HCOOC₂H₅–EtOH (1 : 1) (140 ml) was refluxed for 1.5 h. Work-up in the usual way gave crude crystals. Recrystallization from CHCl₃ gave 11f as colorless cubes (2.40 g, 82.2%), mp 80–82 °C. *Anal.* Calcd for C₁₀H₁₁NO₄: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.17; H, 5.18; N, 6.63. ¹H-NMR: 8.03 (1H, s, CHO), 6.76 (1H, s, H-2), 5.86 (2H, s, OCH₂O), 4.60 (1H, dd, *J* = 9, 4 Hz, H- β), 3.70–3.10 (2H, m, CH₂- α).

The amide 11e was prepared from 11c in the same way as 11f.

N-Formyl-1-(3,4-dimethoxyphenyl)-2-aminoethanol (11e) Colorless oil (97.4%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₁H₁₅NO₄: 225.0998. Found: 225.0980. ¹H-NMR: 8.03 (1H, brs, CHO), 6.82 (1H, s, H-2), 6.77 (2H, s, H-5 and H-6), 6.51 (1H, brs, NH), 4.68 (1H, dd, *J* = 8, 4 Hz, H- β), 3.27 (1H, dd, *J* = 13.5, 8 Hz, H- α), 3.50 (1H, brs, OH).

N-Formyl-1-(2-iodo-4,5-methylenedioxyphenyl)-2-aminoethanol (11h) A solution of iodine (2.96 g) in CHCl₃ (140 ml) was added to a mixture of 11f (2.32 g) and CF₃COOAg (4.89 g) in CHCl₃ (115 ml). The mixture was stirred at room temperature for 1 h. Work-up in the usual way gave 11h as an oil (2.14 g, 57.8%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₀H₁₀NO₂: 334.9657. Found: 334.9677. ¹H-NMR: 8.10 (1H, brs, CHO), 7.13 (1H, s, H-3), 7.03 (1H, s, H-6), 6.71 (1H, brs, NH), 5.93 (2H, s, OCH₂O).

The amide 11g was prepared from 11e in the same way as 11h.

N-Formyl-1-(2-iodo-4,5-dimethoxyphenyl)-2-aminoethanol (11g) Colorless oil (73.4%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₁H₁₄INO₄: 350.9970. Found: 350.9982. ¹H-NMR: 8.14 (1H, brs, CHO), 7.12 (1H, s, H-2), 7.03 (1H, s, H-6), 6.39 (1H, brs, NH), 4.85 (1H, dd, *J* = 7, 3.5 Hz, H- β), 4.07 (1H, s, OH), 3.85 (6H, s, 2 × OCH₃), 3.45 (1H, dd, *J* = 12, 3.5 Hz, H- α), 3.39 (1H, dd, *J* = 12, 7 Hz, H- α).

1-(2-Iodo-4,5-methylenedioxyphenyl)-2-aminoethanol (11b) A solution of 11h (2.03 g) in MeOH–concentrated HCl (9 : 1) (25 ml) was stirred at room temperature for 5 h. The precipitate formed was filtered off. Recrystallization from MeOH gave the hydrochloride of 11b as colorless needles (1.10 g, 53.1%), mp 221–224 °C. *Anal.* Calcd for C₉H₁₀INO₃·HCl: C, 31.47; H, 3.23; N, 4.08. Found: C, 31.58; H, 3.02; N, 3.86. ¹H-NMR (free base): 7.16 (1H, s, H-3), 7.00 (1H, s, H-6), 5.92 (2H, s, OCH₂O), 4.72 (1H, m, H- β), 2.66 (5H, m, OH, NH₂ and CH₂- α).

The ethanolamine 11a was prepared from 11g in the same way as 11b.

1-(2-Iodo-4,5-dimethoxyphenyl)-2-aminoethanol (11a) The hydrochloride of 11a was recrystallized from MeOH as colorless cubes (64.1%), mp 225–227 °C. *Anal.* Calcd for C₁₀H₁₄INO₃·HCl: C, 33.40; H, 4.20; N, 3.90. Found: C, 33.47; H, 4.40; N, 3.67. ¹H-NMR (free base): 7.29 (1H, s, H-3), 7.22 (1H, s, H-6), 5.00 (1H, dd, *J* = 9, 4 Hz, H- β), 3.85 and 3.80 (each 3H, s, 2 × OCH₃), 3.15 (1H, dd, *J* = 13, 4 Hz, H- α), 3.04 (3H, brs, OH and NH₂), 2.80 (1H, dd, *J* = 13, 9 Hz, H- α).

N-(2-Iodo-4,5-dimethoxybenzyl)-1-(2-iodophenyl)-2-aminoethanol (10g) A mixture of 1-(2-iodophenyl)-2-aminoethanol⁴⁾ (1.175 g), 2-iodoveraldehyde (12a) (1.395 g), NaHCO₃ (1.12 g) and EtOH (150 ml) was refluxed under N₂ for 3 h. NaBH₄ (0.8 g) was added under ice-cooling and the mixture was refluxed for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. Then, 5% HCl (700 ml) was added and the

solution was washed with ether. The aqueous solution was made basic with Na₂CO₃ and extracted with CHCl₃. The extract was washed with H₂O, dried and evaporated to give crude crystals. Recrystallization from EtOH gave 10g as colorless cubes (1.873 g, 88.6%), mp 94–96 °C (Table I).

The ethanolamines 9g, h and 10h were prepared in the same way as 10g, respectively (Table I).

N-(2-Iodobenzyl)-N-methyl-1-(2-iodo-4,5-dimethoxyphenyl)-2-aminoethanol (9d) A solution of H₃BO₃ (445 mg) and formalin (4 ml) in MeOH (40 ml) was added to a solution of 9g (551 mg) in MeOH (40 ml). The mixture was stirred at room temperature for 5 min, then NaBH₄ (388 mg) was added and the mixture was stirred for 30 min. Acetic acid (4 ml) and H₂O (130 ml) were added. The mixture was concentrated and made basic with NH₄OH. The aqueous solution was extracted with CHCl₃. The extract was washed with a saturated solution of NaCl in H₂O, dried and evaporated to give a colorless oil (609 mg). This was subjected to PLC in benzene–CHCl₃ (3 : 7). The fraction of *R_f* 0.24–0.50 gave 9d as an oil (265 mg, 46.9%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₈H₂₁I₂NO₃: 552.9612. Found: 552.9574. ¹H-NMR: 7.85 (1H, d, *J* = 8 Hz, H-3'), 7.15 (1H, s, H-3), 7.04 (1H, s, H-6), 4.87 (1H, dd, *J* = 10, 3 Hz, H- β), 3.84 (6H, s, 2 × OCH₃), 3.50 and 3.79 (each 1H, d, *J* = 13.5 Hz, ArCH₂N), 2.74 (1H, dd, *J* = 12.5, 3 Hz, H- α), 2.31 (1H, dd, *J* = 12.5, 10 Hz, H- α), 2.37 (3H, s, NCH₃).

The fraction of *R_f* 0.50–0.60 gave 14a as an oil (100 mg, 17.7%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₈H₁₉I₂NO₃: 550.9456. Found: 550.9421. ¹H-NMR: 7.81 (1H, d, *J* = 8 Hz, H-3'), 5.07 (1H, t, *J* = 7 Hz, H-5), 4.73 and 4.56 (each 1H, d, *J* = 5.5 Hz, CH₂-2), 3.90 (3H, s, OCH₃), 3.85 (5H, s, OCH₃ and CH₂-3), 3.67 and 2.69 (each 1H, dd, *J* = 11.5, 7 Hz, CH₂-4).

N-(2-Iodo-4,5-dimethoxybenzyl)-N-methyl-1-(2-iodophenyl)-2-aminoethanol (10d) A mixture of 10g (313 mg), K₂CO₃ (2.674 g), 3A molecular sieves (2.63 g) and HCOOEt–EtOH (1 : 1) (26 ml) was refluxed under N₂ for 3 h. Work-up in the usual way gave an *N*-formyl compound 10k as an oil (320 mg, 97.3%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₄H₁₉I₂NO₄: 566.9408. Found: 566.9455. IR (KBr): 1660 (C=O). ¹H-NMR: 8.35 and 8.28 (1H, each s, CHO), 7.71 (1H, d, *J* = 8 Hz, H-3), 7.18 (1H, s, H-3'), 6.71 (1H, s, H-6'), 5.05 (1H, dd, *J* = 7, 3.5 Hz, H- β), 3.83 (6H, s, 2 × OCH₃), 3.52 (1H, dd, *J* = 15, 7 Hz, H- α), 3.28 (1H, dd, *J* = 15, 3.5 Hz, H- α).

A solution of 10k (312 mg) in dry THF (5 ml) was added to a solution of 1.0 M B₂H₆ in THF (5 ml) under N₂ with ice-cooling. The mixture was refluxed for 1 h. Work-up in the usual way gave a colorless oil (330 mg). This was purified by flash chromatography on SiO₂ in benzene–CHCl₃ (1 : 1) to give 10d as an oil (211 mg, 69.3%). HRMS (*m/z*): Calcd for C₁₄H₂₁I₂NO₃: 551.9537 (*M*–1), 553.9690 (*M*+1). Found: 551.9542 (*M*–1), 553.9649 (*M*+1). ¹H-NMR: 7.76 (1H, d, *J* = 8 Hz, H-3), 7.25 (1H, s, H-3'), 6.84 (1H, s, H-6'), 4.95 (1H, dd, *J* = 10.5, 3.5 Hz, H- β), 3.87 (6H, s, 2 × OCH₃), 2.95 (1H, dd, *J* = 12, 3.5 Hz, H- α), 2.31 (1H, dd, *J* = 12, 10.5 Hz, H- α), 2.38 (3H, s, NCH₃).

N-(2-Iodo-4,5-methylenedioxybenzyl)-N-methyl-1-(2-iodophenyl)-2-aminoethanol (10f) This compound 10f was prepared from 10h along with 14c in the same way as 9d. 10f: Colorless oil (57.1%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₇H₁₇I₂NO₃: 536.9299. Found: 536.9273. ¹H-NMR: 7.77 (1H, d, *J* = 8 Hz, H-3), 7.56 (1H, d, *J* = 8 Hz, H-6), 7.35 (1H, dd, *J* = 8, 8 Hz, H-5), 7.28 (1H, s, H-3'), 6.85 (1H, s, H-6'), 5.95 (2H, s, OCH₂O), 4.92 (1H, dd, *J* = 10, 3 Hz, H- β), 3.47 and 3.68 (each 1H, d, *J* = 14 Hz, ArCH₂N), 2.77 (1H, dd, *J* = 12, 3 Hz, H- α), 2.36 (3H, s, NCH₃), 2.33 (1H, dd, *J* = 12, 10 Hz, H- α). 14c: Colorless oil (37.6%). HRMS (*m/z*) (*M*⁺): Calcd for C₁₇H₁₅I₂NO₃: 534.9142. Found: 534.9141. ¹H-NMR: 7.78 (1H, d, *J* = 8 Hz, H-3'), 7.57 (1H, d, *J* = 8 Hz, H-6'), 7.24 (1H, s, H-3'), 7.01 (1H, s, H-6'), 5.93 (2H, s, OCH₂O), 5.10 (1H, dd, *J* = 7, 7 Hz, H-5), 4.56 and 4.65 (each 1H, d, *J* = 5.5 Hz, CH₂-2), 3.67 and 3.83 (each 1H, d, *J* = 14 Hz, ArCH₂N), 3.68 and 2.69 (each 1H, dd, *J* = 12, 7 Hz, CH₂-4).

O-Acetyl-N-(2-iodo-4,5-dimethoxybenzyl)-N-methyl-1-(2-iodophenyl)-2-aminoethanol (10a) A solution of 10d (186 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was stirred for 2 d. Evaporation of the solvent gave an oil (186 mg). This was purified by flash chromatography on SiO₂ in benzene–acetone (10 : 1) to give 10a as a colorless oil (172 mg, 85.9%). HRMS (*m/z*) (*M*⁺): Calcd for C₂₀H₂₃I₂NO₄: 594.9719. Found: 594.9704. IR (KBr): 1740 (C=O). ¹H-NMR: 7.77 (1H, d, *J* = 8 Hz, H-3), 7.15 (1H, s, H-3'), 6.92 (1H, s, H-6'), 6.08 (1H, dd, *J* = 7, 5.5 Hz, H- β), 3.85 (6H, s, 2 × OCH₃), 3.72 and 3.44 (each 1H, d, *J* = 14 Hz, ArCH₂N), 2.84 (1H, dd, *J* = 11.5, 5.5 Hz, H- α), 2.66 (1H, dd, *J* = 11.5, 7 Hz, H- α), 2.41 (3H, s, NCH₃), 2.09 (3H, s, COCH₃).

The acetates 9a and 10c were prepared from 9d and 10f in the same way as 10a, respectively.

O-Acetyl-N-(2-iodobenzyl)-N-methyl-1-(2-iodo-4,5-dimethoxyphenyl)-2-aminoethanol (9a) Colorless oil (63.7%). HRMS (*m/z*) (*M*⁺): Calcd for

$C_{20}H_{23}I_2NO_4$: 594.9717. Found: 594.9681. IR (film): 1735 (C=O). 1H -NMR: 7.64 (1H, dd, $J=7, 2$ Hz, H-3'), 7.17 (1H, s, H-3), 6.73 (1H, s, H-6), 6.08 (1H, dd, $J=7.5, 5.5$ Hz, H- β), 3.82 and 3.80 (each 3H, s, $2 \times OCH_3$), 3.80 and 3.56 (each 1H, d, $J=14$ Hz, $ArCH_2N$), 2.83 (1H, dd, $J=10.5, 7.5$ Hz, H- α), 2.64 (1H, dd, $J=10.5, 5.5$ Hz, H- α), 2.43 (3H, s, NCH_3), 2.09 (3H, s, $COCH_3$).

O-Acetyl-N-(2-iodo-4,5-methylenedioxybenzyl)-N-methyl-1-(2-iodophenyl)-2-aminoethanol (10c) Colorless oil (86.2%). HRMS (m/z): Calcd for $C_{19}H_{19}I_2NO_4$: 577.9330 (M-1), 579.9486 (M+1). Found: 577.9371 (M-1), 579.9502 (M+1). 1H -NMR: 7.79 (1H, d, $J=8$ Hz, H-3), 7.20 (1H, s, H-3'), 6.92 (1H, s, H-6'), 6.12 (1H, dd, $J=8, 5$ Hz, H- β), 5.91 (2H, s, OCH_2O), 3.61 and 3.44 (each 1H, d, $J=14$ Hz, $ArCH_2N$), 2.77 (1H, dd, $J=14, 8$ Hz, H- α), 2.62 (1H, dd, $J=14, 5$ Hz, H- α), 2.42 (3H, s, NCH_3), 2.10 (3H, s, $COCH_3$).

O-Acetyl-N-(2-iodobenzyl)-N-methyl-1-(2-iodo-4,5-methylenedioxyphenyl)-2-aminoethanol (9c) The 2-aminoethanol **9h** (300 mg) was treated with H_3BO_3 (248 mg), formalin (2.3 ml) and $NaBH_4$ (220 mg) in the same way as **9g** to give a mixture (oil, 347 mg) of **9f** and **14b**, whose structures were deduced from the 1H -NMR spectrum. This mixture was dissolved in pyridine (14 ml) and acetic anhydride (14 ml) and stirred for 2 d. Work-up in the usual way gave an oil (485 mg), which was subjected to PLC in benzene-ether (6:4). The fraction of R_f 0.73–0.85 gave **9c** as colorless needles (169 mg, 55.1%), mp 136–138 °C. HRMS (m/z) (M-AcOH): Calcd for $C_{19}H_{19}I_2NO_4$: 518.9825. Found: 518.9815. IR (KBr): 1730 (C=O). 1H -NMR: 7.98 (1H, d, $J=8$ Hz, H-3'), 7.16 (1H, s, H-3), 6.74 (1H, s, H-6), 6.08 (1H, dd, $J=8, 5$ Hz, H- β), 5.92 (2H, s, OCH_2O), 3.72 and 3.52 (each 1H, d, $J=14$ Hz, $ArCH_2N$), 2.78 (1H, dd, $J=14, 8$ Hz, H- α), 2.60 (1H, dd, $J=14, 5$ Hz, H- α), 2.44 (3H, s, NCH_3), 2.08 (3H, s, $COCH_3$). The fraction of R_f 0.27–0.37 gave **9j** as an oil (115 mg, 34.6%). HRMS (m/z) (M^+): Calcd for $C_{20}H_{19}I_2NO_6$: 622.9348. Found: 622.9305. IR (film): 1745, 1660 (C=O). 1H -NMR: 7.82 (1H, m, H-3'), 7.17 (1H, s, H-3), 6.92 and 6.82 (1H, each s, H-6), 6.10 (1H, dd, $J=9, 5$ Hz, H- β), 5.94 (2H, s, OCH_2O), 4.84 and 4.52 (each 1H, d, $J=16$ Hz, $ArCH_2N$), 3.94 (1H, dd, $J=14, 9$ Hz, H- α), 3.32 (1H, dd, $J=14, 5$ Hz, H- α), 2.32 and 2.02 (3H, each s, $NCOCH_3$), 2.06 (3H, s, $OCOCH_3$).

N,O-Diacetyl-N-(2-iodobenzyl)-1-(2-iodophenyl)-2-aminoethanol (6f) A solution of **6d** (871 mg) in pyridine (20 ml) and acetic anhydride (20 ml) was stirred at room temperature for 2 d. Work-up in the usual way gave crude crystals. Recrystallization from MeOH gave **6f** as colorless cubes (784 mg, 76.6%), mp 101.5–103 °C. Anal. Calcd for $C_{19}H_{19}I_2NO_5$: C, 40.54; H, 3.40; N, 2.49. Found: C, 40.79; H, 3.55; N, 2.26. IR (KBr): 1750, 1660 (C=O). 1H -NMR: 7.82 (2H, d, $J=8$ Hz, H-3 and H-3'), 6.20 (1H, dd, $J=9, 4$ Hz, H- β), 4.88 and 4.56 (1H, d, $J=16$ Hz, $ArCH_2N$), 4.03 (1H, dd, $J=14, 9$ Hz, H- α), 3.37 (1H, dd, $J=14, 4$ Hz, H- α), 2.29 and 2.02 (3H, each s, $NCOCH_3$), 2.10 (3H, s, $OCOCH_3$).

The acetates **9i** and **10i** were prepared from **9g** and **10g** in the same way as **6f**, respectively.

N,O-Diacetyl-N-(2-iodobenzyl)- β -(2-iodo-4,5-dimethoxyphenyl)-2-aminoethanol (9i) Pale brown oil (80.8%). HRMS (m/z) (M^+): Calcd for $C_{21}H_{23}I_2NO_5$: 622.9667. Found: 622.9645. IR (film): 1745, 1650 (C=O). 1H -NMR: 7.90 (1H, m, H-3'), 7.17 (1H, s, H-3), 6.91 and 6.80 (1H, each s, H-6), 6.15 (1H, dd, $J=9, 4$ Hz, H- β), 4.72 and 4.39 (each 1H, d, $J=12$ Hz, $ArCH_2N$), 4.04 (1H, dd, $J=14, 9$ Hz, H- α), 3.87 and 3.83 (each 3H, s, $2 \times OCH_3$), 3.29 (1H, dd, $J=14, 4$ Hz, H- α), 2.29 and 2.05 (3H, each s, $NCOCH_3$), 2.09 (3H, s, $OCOCH_3$).

N,O-Diacetyl-N-(2-iodo-4,5-dimethoxybenzyl)-1-(2-iodophenyl)-2-aminoethanol (10i) Pale yellow oil (95.9%). HRMS (m/z) (M^+): Calcd for $C_{21}H_{23}I_2NO_5$: 623.9748. Found: 623.9779. IR (KBr): 1740, 1650 (C=O). 1H -NMR: 7.81 (1H, d, $J=8$ Hz, H-3), 7.26 (1H, s, H-3'), 6.86 and 6.46 (1H, each s, H-6'), 6.14 (1H, dd, $J=7.5, 4$ Hz, H- β), 4.51 and 4.87 (each 1H, d, $J=14$ Hz, $ArCH_2N$), 4.00 (1H, dd, $J=13.5, 7.5$ Hz, H- α), 3.43 (1H, dd, $J=13.5, 4$ Hz, H- α), 3.85 and 3.80 (each 3H, s, $2 \times OCH_3$), 2.27 and 2.06 (3H, each s, $NCOCH_3$), 2.12 and 2.09 (3H, each s, $OCOCH_3$).

O-Acetyl-N-ethyl-N-(2-iodobenzyl)-1-(2-iodophenyl)-2-aminoethanol (6c) A solution of **6f** (331 mg) in dry THF (2 ml) was added dropwise to a solution of 1 M B_2H_6 in THF (4 ml) under N_2 with ice-cooling over a period of 10 min. The mixture was refluxed for 1 h. Work-up in the usual way gave an oil (295 mg). A solution of this oil in pyridine (12 ml) and acetic anhydride (12 ml) was stirred for 2 d. Work-up in the usual way gave **6c** as an oil (203 mg, 62.8%). HRMS (m/z) (M-1): Calcd for $C_{19}H_{21}I_2NO_2$: 547.9584. Found: 547.9538. IR (film): 1740 (C=O). 1H -NMR: 7.80 (2H, d, $J=8$ Hz, H-3 and H-3'), 6.11 (1H, dd, $J=6, 4$ Hz, H- β), 3.84 and 3.63 (each 1H, d, $J=14$ Hz, $ArCH_2N$), 2.85–2.62 (4H, m, CH_2 - α and CH_2CH_3), 2.04 (3H, s, $OCOCH_3$), 1.08 (3H, t, $J=7$ Hz, CH_2CH_3).

The *N*-ethyl compounds **9b** and **10b** were prepared from **9i** and **10i** in the same way as **6c**, respectively.

O-Acetyl-N-ethyl-N-(2-iodobenzyl)-1-(2-iodo-4,5-dimethoxyphenyl)-2-aminoethanol (9b) Pale brown oil (67.7%). HRMS (m/z) (M^+): Calcd for $C_{21}H_{25}I_2NO_4$: 608.9877. Found: 608.9879. IR (film): 1735 (C=O). 1H -NMR: 7.77 (1H, d, $J=8$ Hz, H-3'), 7.29 (1H, s, H-3), 6.73 (1H, s, H-6), 6.05 (1H, dd, $J=6, 4$ Hz, H- β), 3.83 and 3.80 (each 3H, s, $2 \times OCH_3$), 3.73 (2H, s, $ArCH_2N$), 2.87–2.41 (4H, m, CH_2 - α and CH_2CH_3), 2.06 (3H, s, $COCH_3$), 1.17 (3H, t, $J=7$ Hz, CH_2CH_3).

O-Acetyl-N-ethyl-N-(2-iodo-4,5-dimethoxybenzyl)-1-(2-iodophenyl)-2-aminoethanol (10b) Pale yellow oil (41.8%). HRMS (m/z) (M^+): Calcd for $C_{21}H_{25}I_2NO_4$: 608.9874. Found: 608.9833. IR (film): 1740 (C=O). 1H -NMR: 7.81 (1H, d, $J=8$ Hz, H-3), 7.20 (1H, s, H-3'), 7.04 (1H, s, H-6'), 6.16 (1H, dd, $J=6.5, 6.5$ Hz, H- β), 3.85 (6H, s, $2 \times OCH_3$), 3.83 and 3.55 (each 1H, d, $J=14.5$ Hz, $ArCH_2N$), 2.87–2.45 (4H, m, CH_2 - α and CH_2CH_3), 2.05 (3H, s, $COCH_3$), 1.05 (3H, t, $J=7$ Hz, CH_2CH_3).

N-(2-Iodobenzyl)-O-methoxymethyl-1-(2-iodophenyl)-2-aminoethanol (6b) P_2O_5 (3.5 g) was gradually added to a mixture of **6d**⁴⁾ (868 mg), methylal (15 ml), and P_2O_5 (1.5 g) in $CHCl_3$ (25 ml) under stirring at room temperature for 45 min. The mixture was poured into a saturated solution (150 ml) of Na_2CO_3 in H_2O under ice-cooling and extracted with $CHCl_3$. The extract was washed with a saturated solution of NaCl in H_2O , dried and evaporated to give an oil (852 mg). This was subjected to PLC in benzene-ether (6:4). The fraction of R_f 0.82–0.93 gave **6b** as a pale yellow oil (520 mg, 54.8%). HRMS (m/z) (M+1): Calcd for $C_{17}H_{19}I_2NO_2$: 523.9587. Found: 523.9619. 1H -NMR: 7.72 (2H, d, $J=8$ Hz, H-3 and H-3'), 4.99 (1H, t, $J=6$ Hz, H- β), 4.58 (2H, s, OCH_2O), 3.83 (2H, s, $ArCH_2N$), 3.50 (3H, s, OCH_3), 2.80 (2H, d, $J=6$ Hz, CH_2 - α), 2.17 (1H, brs, NH).

8-O-Acetoxy-6-ethyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (4e) Ph_3P (3.41 mmol), $(Ph_3P)_2NiCl_2$ (1116 mg, 1.71 mmol), Zn powder (112 mg, 1.70 mmol) and KI (288 mg, 1.73 mmol) were placed in a two-necked flask. The flask was evacuated and filled with N_2 . Dry, oxygen-free dimethylformamide (DMF) (17 ml) was added through a syringe. The mixture was stirred at 55 °C for 30 min. A solution of **6c** (440 mg, 0.80 mmol) in dry DMF (1.7 ml) was added, and the mixture was stirred at 55 °C for 10 h. Then, 2% HCl (80 ml) was added. The aqueous layer was washed with ether and made basic with Na_2CO_3 . The aqueous layer was extracted with $CHCl_3$. The extract was washed with H_2O , dried and evaporated to give an oil (319 mg). This was subjected to PLC in benzene-ether (1:9). The fraction of R_f 0.62–0.72 gave **4e** as an oil (155 mg, 77.4%). IR (film): 1740 (C=O) (see Table III for MS and 1H -NMR spectra data). The fraction of R_f 0.89–0.93 gave **15b** as an oil (27 mg, 13.6%). IR (film): 1740 (C=O) (see Table IV for MS and 1H -NMR spectral data).

The 8-*O*-protected azocines **4d**, **7d**–**f** and **8d**–**f** were prepared from **6b**, **9a**–**c** and **10a**–**c** in the same way as **4e**, respectively (Tables II–IV).

8-Hydroxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (4b) A solution of **4d** (43 mg) in 5% HCl (15 ml) was heated at 50 °C for 5 min. The solution was made basic with Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with a saturated solution of NaCl in H_2O , dried and evaporated to give an oil (39 mg). This was crystallized as a stypnate (62 mg, 75.4%) of **4b**, which was recrystallized from acetone-ether to afford yellow needles, mp 218.5–220 °C (dec.) (Table V).

8-Hydroxy-6-ethyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (4c) A mixture of **4e** (47 mg) and 7% K_2CO_3 -EtOH (1:1) (10 ml) was stirred at room temperature for 9 h. H_2O (50 ml) was added and the solvent was evaporated off *in vacuo*. The aqueous layer was extracted with $CHCl_3$. The extract was washed with a saturated solution of NaCl in H_2O , dried and concentrated to give a white solid (54 mg). Recrystallization from $CHCl_3$ gave **4c** as colorless needles (46 mg, 80%), mp 129.5–133 °C (Table V).

The 8-hydroxyazocines **7a**–**c** and **8a**–**c** were prepared from **7d**–**f** and **8d**–**f** in the same way as **4c**, respectively (Table V).

References and Notes

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