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

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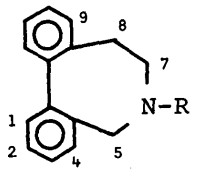
8-Hydroxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines 4b, c and their methoxy and methylenedioxy derivatives 7a—c and 8a—c were prepared by cyclization of *O*-protected 1-phenyl-2-aminoethanols 6b, c, 9a—c and 10a—c with zerovalent nickel, followed by hydrolysis of the resulting *O*-protected azocines 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.

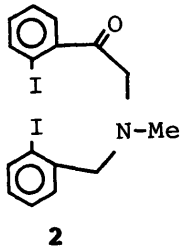
Keywords apogalanthamine analogue; 8-hydroxydibenz[*c*,*e*]azocine; dibenz[*c*,*e*]azocine; halogeno-*N*-benzyl-1-phenyl-2-aminoethanol; biphenyl; cyclization; zerovalent nickel; half-tub conformation; alpha adrenergic blocking agent

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 agents[2] by cyclization reaction of 2-halogeno-*N*-(2-halogenobenzyl)-2-phenylethylamines with zerovalent nickel. Recently, we reported[3] 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



1a-c

	R
a:	Me
b:	H
c:	Et



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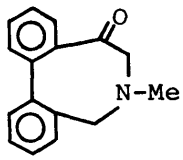

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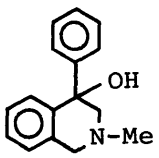

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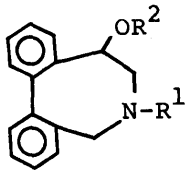
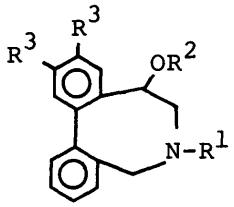
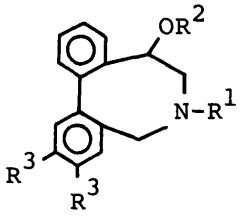


4a-e

	R^1	R^2
a:	Me	H
b:	H	H
c:	Et	H
d:	H	CH_2OMe
e:	Et	Ac

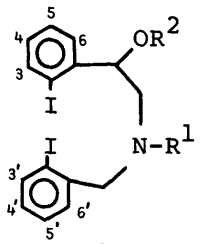


7a-f



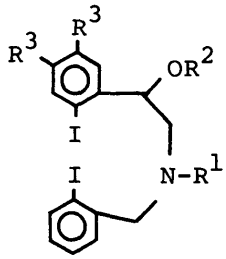
8a-f

	R^1	R^2	R^3
a:	Me	H	OMe
b:	Et	H	OMe
c:	Me	H	OCH_2O
d:	Me	Ac	OMe
e:	Et	Ac	OMe
f:	Me	Ac	OCH_2O

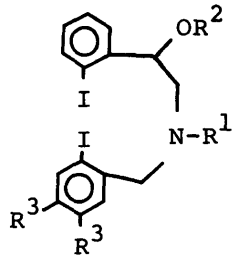


6a-f

	R^1	R^2
a:	Me	Ac
b:	H	CH_2OMe
c:	Et	Ac
d:	H	H
e:	Et	H
f:	Ac	Ac



9a-j



10a-i,k

	R^1	R^2	R^3
a:	Me	Ac	OMe
b:	Et	Ac	OMe
c:	Me	Ac	OCH_2O
d:	Me	H	OMe
e:	Et	H	OMe
f:	Me	H	OCH_2O
g:	H	H	OMe
h:	H	H	OCH_2O
i:	Ac	Ac	OMe
j:	Ac	Ac	OCH_2O
k:	CHO	H	OMe

Chart 1

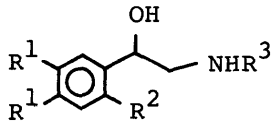
synthesize[4] racemic and optically active **4a** by cyclization of an *N*-benzyl-1-phenyl-2-aminoethanol **6a** with zerovalent nickel. In the course of this series, it was found that the order[6] of the α-adrenolytic activities of the *N*-alkylated azocines **1a**—**c** was Me > Et > H and that the 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 nickel[8] 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 ($NaBH_4$) (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 ($LiAlH_4$) 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 $NaBH_4$ 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 pentoxide[9] 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

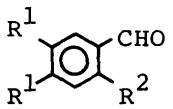
TABLE I. Physical and ^{1}H-NMR Spectral Data for *N*-Benzyl-1-phenyl-2-aminoethanols **9g**, **h** and **10g**, **h**

No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (δ, $CDCl_3$)
9g	90.3	94—96	$C_{17}H_{19}I_2NO_3$	37.87	3.55	2.59	7.79 (1H, dd, 8, 1), 7.12 (1H, s), 7.05 (1H, s), 4.79 (1H, dd, 9, 3.5), 3.85
				(37.96	3.37	2.54)	(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	$C_{16}H_{15}I_2NO_3$	36.73	2.89	2.68	7.80 (1H, d, 8), 7.16 (1H, s), 7.04 (1H, s), 5.92 (2H, s), 4.82 (1H, dd,
				(37.00	2.85	2.45)	9, 3), 3.86 (2H, s), 2.98 (1H, dd, 12, 3), 2.46 (1H, dd, 12, 9)
10g	88.6	94—96	$C_{17}H_{19}I_2NO_3$	37.87	3.55	2.59	7.75 (1H, dd, 8, 2), 7.20 (1H, s), 6.89 (1H, s), 4.92 (1H, dd, 9, 3.5),
				(37.90	3.43	2.32)	3.83 (8H, s), 3.00 (1H, dd, 12.5, 3.5) 2.51 (1H, dd, 12.5, 9)
10h	62.8	144—145	$C_{16}H_{15}I_2NO_3$	36.73	2.89	2.68	7.79 (1H, d, 8), 7.25 (1H, s), 6.90 (1H, s), 5.94 (2H, s), 4.87 (1H, dd,
				(36.87	2.86	2.66)	9, 3), 3.78 (2H, s), 3.02 (1H, dd, 12, 3), 2.51 (1H, dd, 12, 9)



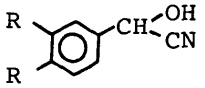
11a-h

	R^1	R^2	R^3
a:	OMe	I	H
b:	OCH_2O	I	H
c:	OMe	H	H
d:	OCH_2O	H	H
e:	OMe	H	CHO
f:	OCH_2O	H	CHO
g:	OMe	I	CHO
h:	OCH_2O	I	CHO



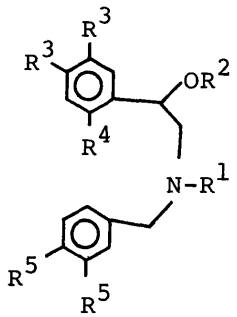
12a-d

	R^1	R^2
a:	OMe	I
b:	OCH_2O	I
c:	OMe	H
d:	OCH_2O	H



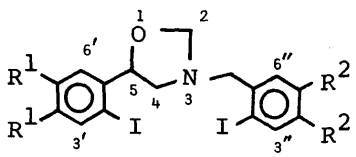
13a,b

	R
a:	OMe
b:	OCH_2O



15a-i

	R^1	R^2	R^3	R^4	R^5
a:	H	CH_2OMe	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_2O	H	H
f:	Me	Ac	OCH_2O	I	H
g:	Me	Ac	H	H	OMe
h:	Et	Ac	H	H	OMe
i:	Me	Ac	H	H	OCH_2O



14a-d

	R^1	R^2
a:	OMe	H
b:	OCH_2O	H
c:	H	OCH_2O
d:	H	H

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 ^{1}H-NMR Spectral Data for 8-Acetoxyazocines **4d, e, 7d—f** and **8d—f**

No.	Formula	MS (*m/z*) (M^+) 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 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 (^{1}H-NMR) spectra (Tables III and V).

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

No.	Formula	MS (*m/z*) (M^+) 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.

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 ^{1}H-NMR Spectral Data for 8-Hydroxyazocines **4b**, **c**, **7a**—**c** and **8a**—**c**

No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (δ, $CDCl_3$)
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	$C_{15}H_{15}NO \cdot C_6H_3N_3O_8$	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	$C_{17}H_{19}NO$	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	$C_{18}H_{21}NO_3$	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	$C_{19}H_{23}NO_3$	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	$C_{17}H_{17}NO_3 \cdot 1/4H_2O$	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	$C_{18}H_{21}NO_3 \cdot 1/2H_2O$	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	$C_{19}H_{23}NO_3 \cdot 1/4H_2O$	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	$C_{17}H_{17}NO_3 \cdot 1/2H_2O$	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 ^{1}H-NMR spectrum was determined as the free base in CD_3OD.

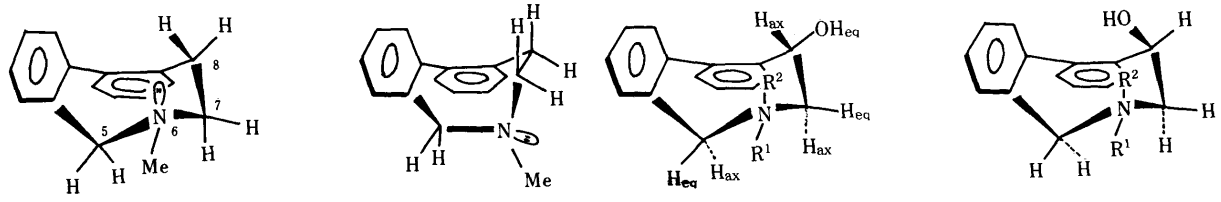


Chart 3

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 ^{1}H-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 field[12] (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 couplings[12] between H_{eq}-7 and H_{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 paper[4] 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. ^{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 values. The plates used for preparative TLC (PLC) were coated with silica gel (Kiesel gel PF_{254} Merck).

1-(3,4-Methylenedioxyphenyl)-2-aminoethanol (11d) A mixture of piperonal (**12d**) (10.0 g) and 2 N $NaHSO_3$ (160 ml) was stirred at 40 °C for 3 h, then a solution of KCN (18.0 g) in H_2O (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%). ^{1}H-NMR: 5.97 (2H, s, OCH_2O), 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 $LiAlH_4$ (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 $C_9H_{11}NO_3 \cdot HCl$: C, 49.66; H, 5.56; N, 6.43. Found: C, 49.63; H, 5.49; N, 6.30. ^{1}H-NMR (free base): 6.88 (1H, s, H-2), 6.76 (2H, s, H-5 and H-6), 5.90 (2H, s, OCH_2O), 4.51 (1H, dd, J=7, 5 Hz, H-β), 2.96—2.62 (2H, m, CH_2NH_2), 2.24 (3H, br s, NH_2 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 $C_{10}H_{15}NO_3 \cdot HCl$: C, 51.40; H, 6.90; N, 5.99. Found: C, 51.17; H, 7.14; N, 5.85. ^{1}H-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×OCH_3), 2.95 (1H, dd, J=13, 4.5 Hz, H-α), 2.73 (1H, dd, J=13, 7 Hz, H-α), 2.13 (3H, br s, NH_2 and OH).

***N*-Formyl-1-(3,4-methylenedioxyphenyl)-2-aminoethanol (11f)** A mixture of the hydrochloride (3.00 g) of **11d**, K_2CO_3 (5.00 g), 3A molecular sieves (5.0 g) and $HCOOC_2H_5$–EtOH (1 : 1) (140 ml) was refluxed for 1.5 h. Work-up in the usual way gave crude crystals. Recrystallization from $CHCl_3$ gave **11f** as colorless cubes (2.40 g, 82.2%), mp 80—82 °C. *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.17; H, 5.18; N, 6.63. ^{1}H-NMR: 8.03 (1H, s, CHO), 6.76 (1H, s, H-2), 5.86 (2H, s, OCH_2O), 4.60 (1H, dd, J=9, 4 Hz, H-β), 3.70—3.10 (2H, m, CH_2-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 $C_{11}H_{15}NO_4$: 225.0998. Found: 225.0980. ^{1}H-NMR: 8.03 (1H, br s, CHO), 6.82 (1H, s, H-2), 6.77 (2H, s, H-5 and H-6), 6.51 (1H, br s, 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, br s, OH).

***N*-Formyl-1-(2-iodo-4,5-methylenedioxyphenyl)-2-aminoethanol (11h)** A solution of iodine (2.96 g) in $CHCl_3$ (140 ml) was added to a mixture of **11f** (2.32 g) and CF_3COOAg (4.89 g) in $CHCl_3$ (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 $C_{10}H_{10}NO_2$I: 334.9657. Found: 334.9677. ^{1}H-NMR: 8.10 (1H, br s, CHO), 7.13 (1H, s, H-3), 7.03 (1H, s, H-6), 6.71 (1H, br s, NH), 5.93 (2H, s, OCH_2O).

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 $C_{11}H_{14}INO_4$: 350.9970. Found: 350.9982. ^{1}H-NMR: 8.14 (1H, br s, CHO), 7.12 (1H, s, H-2), 7.03 (1H, s, H-6), 6.39 (1H, br s, NH), 4.85 (1H, dd, J=7, 3.5 Hz, H-β), 4.07 (1H, s, OH), 3.85 (6H, s, 2×OCH_3), 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 $C_9H_{10}INO_3 \cdot HCl$: C, 31.47; H, 3.23; N, 4.08. Found: C, 31.58; H, 3.02; N, 3.86. ^{1}H-NMR (free base): 7.16 (1H, s, H-3), 7.00 (1H, s, H-6), 5.92 (2H, s, OCH_2O), 4.72 (1H, m, H-β), 2.66 (5H, m, OH, NH_2 and CH_2-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 $C_{10}H_{14}INO_3 \cdot HCl$: C, 33.40; H, 4.20; N, 3.90. Found: C, 33.47; H, 4.40; N, 3.67. ^{1}H-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×OCH_3), 3.15 (1H, dd, J=13, 4 Hz, H-α), 3.04 (3H, br s, OH and NH_2), 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-aminoethanol[4] (1.175 g), 2-iodoveratraldehyde (**12a**) (1.395 g), $NaHCO_3$ (1.12 g) and EtOH (150 ml) was refluxed under N_2 for 3 h. $NaBH_4$ (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 Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, 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 H_3BO_3 (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 $NaBH_4$ (388 mg) was added and the mixture was stirred for 30 min. Acetic acid (4 ml) and H_2O (130 ml) were added. The mixture was concentrated and made basic with NH_4OH. The aqueous solution was extracted with $CHCl_3$. The extract was washed with a saturated solution of NaCl in H_2O, dried and evaporated to give a colorless oil (609 mg). This was subjected to PLC in benzene–$CHCl_3$ (3 : 7). The fraction of *Rf* 0.24—0.50 gave **9d** as an oil (265 mg, 46.9%). HRMS (*m/z*) (M^+): Calcd for $C_{18}H_{21}I_2NO_3$: 552.9612. Found: 552.9574. ^{1}H-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×OCH_3), 3.50 and 3.79 (each 1H, d, J=13.5 Hz, ArCH_2N), 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, NCH_3).

The fraction of *Rf* 0.50—0.60 gave **14a** as an oil (100 mg, 17.7%). HRMS (*m/z*) (M^+): Calcd for $C_{18}H_{19}I_2NO_3$: 550.9456. Found: 550.9421. ^{1}H-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, CH_2-2), 3.90 (3H, s, OCH_3), 3.85 (5H, s, OCH_3 and CH_2-3), 3.67 and 2.69 (each 1H, dd, J=11.5, 7 Hz, CH_2-4).

***N*-(2-Iodo-4,5-dimethoxybenzyl)-*N*-methyl-1-(2-iodophenyl)-2-aminoethanol (10d)** A mixture of **10g** (313 mg), K_2CO_3 (2.674 g), 3A molecular sieves (2.63 g) and HCOOEt–EtOH (1 : 1) (26 ml) was refluxed under N_2 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 $C_{14}H_{19}I_2NO_4$: 566.9408. Found: 566.9455. IR (KBr): 1660 (C=O). ^{1}H-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×OCH_3), 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 B_2H_6 in THF (5 ml) under N_2 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 SiO_2 in benzene–$CHCl_3$ (1 : 1) to give **10d** as an oil (211 mg, 69.3%). HRMS (*m/z*): Calcd for $C_{14}H_{21}I_2NO_3$: 551.9537 (M−1), 553.9690 (M+1). Found: 551.9542 (M−1), 553.9649 (M+1). ^{1}H-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×OCH_3), 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, NCH_3).

***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 $C_{17}H_{17}I_2NO_3$: 536.9299. Found: 536.9273. ^{1}H-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, OCH_2O), 4.92 (1H, dd, J=10, 3 Hz, H-β), 3.47 and 3.68 (each 1H, d, J=14 Hz, ArCH_2N), 2.77 (1H, dd, J=12, 3 Hz, H-α), 2.36 (3H, s, NCH_3), 2.33 (1H, dd, J=12, 10 Hz, H-α). **14c**: Colorless oil (37.6%). HRMS (*m/z*) (M^+): Calcd for $C_{17}H_{15}I_2NO_3$: 534.9142. Found: 534.9141. ^{1}H-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, OCH_2O), 5.10 (1H, dd, J=7, 7 Hz, H-5), 4.56 and 4.65 (each 1H, d, J=5.5 Hz, CH_2-2), 3.67 and 3.83 (each 1H, d, J=14 Hz, ArCH_2N), 3.68 and 2.69 (each 1H, dd, J=12, 7 Hz, CH_2-4).

***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 SiO_2 in benzene–acetone (10 : 1) to give **10a** as a colorless oil (172 mg, 85.9%). HRMS (*m/z*) (M^+): Calcd for $C_{20}H_{23}I_2NO_4$: 594.9719. Found: 594.9704. IR (KBr): 1740 (C=O). ^{1}H-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×OCH_3), 3.72 and 3.44 (each 1H, d, J=14 Hz, ArCH_2N), 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, NCH_3), 2.09 (3H, s, $COCH_3$).

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). ^{1}H-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×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). ^{1}H-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 ^{1}H-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 Rf 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). ^{1}H-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 Rf 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). ^{1}H-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 $C_{19}H_{19}I_2NO_3$: 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). ^{1}H-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). ^{1}H-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×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). ^{1}H-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×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). ^{1}H-NMR: 7.80 (2H, d, J=8 Hz, H-3 and H-3′), 6. 11 (1H, dd, J=6, 6 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). ^{1}H-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, 6 Hz, H-β), 3.83 and 3.80 (each 3H, s, 2×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-iodobenzyl)-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). ^{1}H-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×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 Rf 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. ^{1}H-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, br s, 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 Rf 0.62—0.72 gave **4e** as an oil (155 mg, 77.4%). IR (film): 1740 (C=O) (see Table III for MS and ^{1}H-NMR spectra data). The fraction of Rf 0.89—0.93 gave **15b** as an oil (27 mg, 13.6%). IR (film): 1740 (C=O) (see Table IV for MS and ^{1}H-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 styphnate (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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