[Chem. Pharm. Bull. 33(3)1260—1265(1985)]

Syntheses of Apogalanthamine Analogs as α-Adrenergic Blocking Agents. VIII.[1,2] Syntheses of 4- and 9-Bromo-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines and Their Methylenedioxy Derivatives

MASARU KIHARA, YOSHIYUKI MIYAKE, MORIO IITOMI, and SHIGERU KOBAYASHI*

Faculty of Pharmaceutical Sciences, Tokushima University, 1–78, Sho-machi, Tokushima 770, Japan

(Received June 18, 1984)

The apogalanthamine analogs 4- and 9-bromo-5,6,7,8-tetrahydrodibenz[*c*, *e*]azocines (**5a** and **6a**) and their methylenedioxy derivatives (**5b** and **6b**) were prepared by photolysis of the hydrochlorides of the respective *N*-benzyl-β-phenethylamines (**8a**, **b** and **9a**, **b**) substituted with both iodine and bromine atoms. The dibenz[*c*, *e*]azocines **6a** and **6b** were also obtained by thermal syntheses from the biphenyl compounds **17a** and **17b**, respectively.

Keywords——apogalanthamine analog; tetrahydrodibenz[*c*, *e*]azocine; dibenzazocine; biphenyl derivative; alpha-adrenergic blocking agent; anti-serotonin activity; photolysis; photochemical cyclization

We have synthesized a series of apogalanthamine analogs having a tetrahydrodibenz[*c*, *e*]azocine skeleton, as candidate α-adrenergic blocking agents.[3] Recently we reported that a free phenethylamine moiety in dibenzazocine derivatives such as **1** is important for the adrenolytic activity. On the other hand, the dimethoxybenzylamine moiety of dibenzazocine derivatives such as **2** may be important for the anti-serotonin activity.[4] Furthermore, the α-adrenolytic activity of 4-iodoazocine (**3**), with an iodine atom in benzene ring A, was stronger than that of 9-iodoazocine (**4**), with an iodine atom in benzene ring B,[1] but the anti-serotonin activity of the latter was the stronger.[4] These findings prompted us to synthesize 4- and 9-bromo-5,6,7,8-tetrahydrodibenz[*c*, *e*]azocines (**5a** and **6a**) and their methylenedioxy derivatives **5b** and **6b** to test their pharmacological activities.

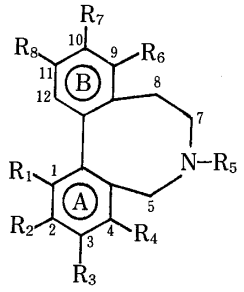
This paper describes the photochemical cyclization of 2-halo-*N*-(2-halobenzyl)-β-phenethylamines to the azocines **5a, b** and **6a, b**, as well as the thermal syntheses of **6a, b**.

Previously, we reported[1] that photolysis of the hydrochloride of 2-iodo-*N*-(2-iodobenzyl)-β-phenethylamine (**7a**) gave 4-iodo- and 9-iododibenzazocines (**3** and **4**). However, we found recently that irradiation of the dibromo compound **7b** did not give the azocine (**5a** and **6a**) under the same conditions as used for the photolysis of **7a**. These findings are consistent with the fact[5] that on photolysis an aryl iodide is more reactive than an aryl bromide. On the basis of this fact, *N*-benzyl-β-phenethylamines having both iodine and bromine atoms (**8a, b** and **9a, b**) were selected as starting materials for preparation of the bromoazocines **5a, b** and **6a, b**, respectively. The amines **7b**, **8a, b** and **9a, b** were prepared from the benzaldehydes **10a**—**c** and β-phenethylamines **11a**—**c** (Tables I and II).

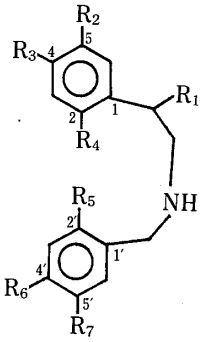
Irradiation of the hydrochloride of **8a** in aqueous solution gave **5a** (6.0% yield, mp 273—277 °C as the picrolonate) along with an unexpected compound[6] and the deiodinated product (**7c**). Similarly, 9-bromoazocine **6a** (mp 236—238 °C as the picrolonate) was obtained in 11.2% yield by photolysis of **9a**. Photolysis of the methylenedioxy compounds **8b** and **9b** gave

the desired products **5b** (oil, 5.0% yield) and **6b** (8.0%, mp 118—121 °C), respectively.

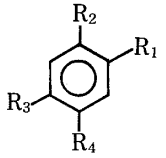
The structures of the dibenzazocines **5a, b** and **6a, b** thus obtained were supported by the physical and spectral data. In the proton nuclear magnetic resonance (^{1}H-NMR) spectra (Table III), AB-type doublets ($J=14$ Hz) in the two regions at δ 3.79—4.26 and 3.04—3.18



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1	H	H	H	H	CH_3	H	H	H
2	OCH_3	OCH_3	H	H	CH_3	H	H	OCH_3
3	H	H	H	I	H	H	H	H
4	H	H	H	H	H	I	H	H
5a	H	H	H	Br	H	H	H	H
5b	H	H	H	Br	H	H	OCH_2O	
6a	H	H	H	H	H	Br	H	H
6b	H	OCH_2O		H	H	Br	H	H
13	H	H	H	H	H	H	H	H
22	H	OCH_2O		H	C_2H_5	Br	H	H
23	H	OCH_2O		H	$COCH_3$	Br	H	H

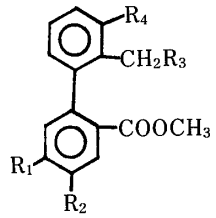


	R_1	R_2	R_3	R_4	R_5	R_6	R_7
7a	H	H	H	I	I	H	H
7b	H	H	H	Br	Br	H	H
7c	H	H	H	H	Br	H	H
7d	H	H	H	Br	H	H	H
8a	H	H	H	I	Br	H	H
8b	H	OCH_2O		I	Br	H	H
9a	H	H	H	Br	I	H	H
9b	H	H	H	Br	I	OCH_2O	
12	OH	H	H	Br	H	H	H

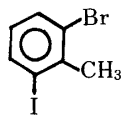


	R_1	R_2	R_3	R_4
10a	CHO	Br	H	H
10b	CHO	I	H	H
10c	CHO	I	OCH_2O	
11a	$CH_2CH_2NH_2$	Br	H	H
11b	$CH_2CH_2NH_2$	I	H	H
11c	$CH_2CH_2NH_2$	I	OCH_2O	

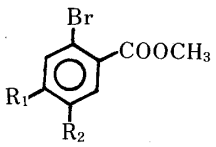
Chart 1



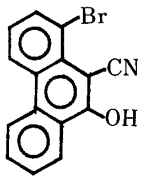
	R_1	R_2	R_3	R_4
14a	H	H	CN	Br
14b	OCH_2O		CN	Br
14c	H	H	CN	H
17a	H	H	H	Br
17b	OCH_2O		H	Br
18a	H	H	Br	Br
18b	OCH_2O		Br	Br



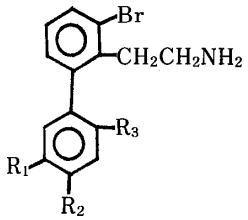
15



16a: $R_1=R_2=H$
16b: R_1, $R_2=OCH_2O$



19



	R_1	R_2	R_3
20a	H	H	CH_2OH
20b	OCH_2O		CH_2OH
21a	H	H	CH_2Br
21b	OCH_2O		CH_2Br

Chart 2

were assigned to C-5 methylene protons[3b] (characteristic of dibenzazocine derivatives). The signals (δ 4.26 and 4.25) of H-5 (lower) in **5a, b** were shifted 0.36 and 0.35 ppm downfield, respectively, compared with that in **13**. These shifts are due to the anisotropic effect of the bromine atoms at C-4 in **5a, b**. The chemical shifts (δ 4.26, 4.25 and 3.93, 3.79) of 5-H (lower) in **5a, b** and **6a, b** were similar to those (δ 4.09 and 3.88) in the iodoazocines **3** and **4**,[1] respectively. In addition to these results, the chemical shifts and coupling patterns of H-3 in **5a, b** and of 10-H in **6a, b** support the indicated structures (Table III).

The structures of the 9-bromoazocines (**6a, b**) were confirmed by direct comparison with authentic **6a, b** prepared by alternative thermal syntheses. These syntheses were achieved by a method which we developed for the synthesis[3d] of the apogalanthamine analog **13**, *via* a cyanomethyl-ester (**14c**). The key intermediates **14a, b** in the routes to **6a, b**, respectively, were prepared as follows. Ullmann condensation of bromotoluene (**15**) with bromobenzoate (**16a** or **16b**) gave the bromobiphenyl (**17a** or **17b**), which was treated with *N*-bromosuccinimide (NBS) to give the bromomethyl-ester (**18a** or **18b**). Cyanation of **18a** or **18b** with potassium cyanide gave **14a** or **14b**, accompanied by the cyclization product **19**[7] in the case of **18a**. Reduction of **14a** with sodium borohydride ($NaBH_4$)[8] and aluminum chloride in diglyme

TABLE I. Synthetic and Physical Data for **7b**, **8a, b** and **9a, b**

Aldehyde (g)	Amine (g)	$NaBH_4$ (mg)	Product as hydrochloride						
				mg (%)[a]	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
10a[b] 1.07	**11a** 0.45	544	**7b**	678 (74.2)	167—169	$C_{15}H_{15}Br_2N \cdot HCl$	44.42 (44.34	3.98 3.84	3.45 3.30)
10a[c] 0.80	**11b** 0.65	786	**8a**	870 (73.3)	162—166	$C_{15}H_{15}BrIN \cdot HCl$	39.80 (40.03	3.56 3.56	3.10 3.02)
10a[c] 0.50	**11c** 0.28	564	**8b**	188 (39.5)	190—195	$C_{16}H_{15}BrINO_2 \cdot HCl$	38.70 (38.90	3.25 3.23	2.82 2.84)
10b[c] 2.30	**11a** 0.91	1710	**9a**	839 (44.5)	171—176	$C_{15}H_{15}BrIN \cdot HCl$	39.80 (40.09	3.56 3.52	3.10 3.28)
10c[c] 2.50	**11a** 2.16	2100	**9b**	3100 (68.9)	160—163	$C_{16}H_{15}BrINO_2 \cdot HCl$	38.70 (38.76	3.25 3.26	2.82 2.67)

a) Yield from the amine (**11**). *b*) See Experimental. *c*) The reaction time was 2 h.

TABLE II. ^{1}H-NMR Spectral Data for the Free Bases of **7b**, **8a, b** and **9a, b** ($CDCl_3$, δ)

	H-3	H-6	H-3′	H-6′	OCH_2O	$ArCH_2N$	$ArCH_2CH_2N$	NH
7b	7.50 (dd, 8, 2)[a]		7.50 (dd, 8, 2)			3.85 (s)	2.91 (s)	1.62 (s)
8a	7.78 (dd, 8, 2)		7.52 (dd, 8, 2)			3.93 (s)	2.95 (s)	1.72 (s)
8b		6.77 (s)	7.59 (dd, 8, 2)		5.92 (s)	3.89 (s)	2.84 (m)	1.74 (s)
9a	7.52 (dd, 8, 2)		7.80 (dd, 8, 2)			3.87 (s)	2.97 (s)	1.77 (s)
9b	7.55 (dd, 8, 2)			6.90 (s)	5.92 (s)	3.76 (s)	2.92 (s)	1.64 (s)

a) The numerical values in parentheses are coupling constants in Hz.

TABLE III. ^{1}H-NMR Spectral Data for 5,6,7,8-Tetrahydrodibenz[*c*, *e*]azocines ($CDCl_3$, δ)

Compd.	Aromatic H								H_2[a)]-5		OCH_2O	NH
	H-1	H-2	H-3	H-4	H-9	H-10	H-11	H-12	Lower	Higher		
5a		7.14 (dd, 8, 8)[b)]	7.62 (dd, 8, 2)						4.26	3.10		2.15 (s)
5b			7.63 (dd, 8, 2)		6.72 (s)			6.76 (s)	4.25	3.14	6.01 (s)	2.40 (br s)
6a						7.60 (dd, 8, 2)	7.07 (dd, 8, 8)		3.93	3.18		2.29 (s)
6b	6.71 (s)			6.84 (s)		7.62 (dd, 8, 2)	7.10 (dd, 8, 8)		3.79	3.04	5.98 (s)	2.02 (br s)
13[c)]	7.30 (m) (7.40—7.20)								3.90	3.14		1.76 (br s)

a) Signals of H_2-5 were AB-type doublets having a coupling constant of 14 Hz. *b*) Numerical values in parentheses are coupling constants in Hz. *c*) Ref. 3*d*.

gave the desired azocine (**6a**) (4.4% yield) and an amino-alcohol (**20a**) (64.3% yield). Bromination of **20a** with phosphorus tribromide followed by cyclization with ethanolic potassium hydroxide gave **6a** in 52.1% yield. Similar reduction of **14b** gave **6b** (14.5% yield) and the amino-alcohol **20b** (6.3% yield). Similarly, compound **20b** was brominated and cyclized to give an *N*-ethylated azocine (**22**), which seemed to have been formed by *N*-ethylation of the cyclization product **6b** during these treatments. The structure of this unexpected compound (**22**) was confirmed by direct comparison with authentic **22** prepared by acetylation of **6b** followed by reduction of the product (**23**) with lithium aluminum hydride.

The azocines **6a, b** obtained by photolysis of **9a, b** were identical with those prepared by thermal synthesis from **14a, b**, respectively.

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi model EPI-G2 for infrared (IR) spectra, a JEOL model JMS-D 300 for mass spectra (MS), and a JEOL model JNM-PS-100 for ^{1}H-NMR spectra, with tetramethylsilane (TMS) as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; m, multiplet; br s, broad singlet. Irradiation was carried out with a RIKO UVL-400H apparatus. The plates used for preparative thin-layer chromatography (PLC) were coated with silica gel (Kieselgel, PF_{254}, Merck). The product in each fraction obtained by PLC was eluted with $CHCl_3$–MeOH (1 : 1).

2-Iodo-4,5-methylenedioxy-*N*-(2-bromobenzyl)-β-phenethylamine (8b)——A mixture of 500 mg of **10a** and 278 mg of **11c**[3c)] was heated in a sealed tube at 110 °C for 2 h. The reaction mixture was taken up in 20 ml of $CHCl_3$–EtOH (3 : 2), then 564 mg of $NaBH_4$ was gradually added with stirring at room temperature for 3 h. The solvent was evaporated off *in vacuo*. The residue was taken up in 5 ml of H_2O and the solution was extracted with $CHCl_3$. The extract was mixed with 15% HCl and the $CHCl_3$ layer was concentrated to give the hydrochloride (188 mg, 39.5%) of **8b** as colorless needles (from acetone–MeOH), mp 190—195 °C.

The β-phenethylamines **7b**, **8a** and **9a, b** were prepared in the same way as **8b** (Tables I and II).

Photolyses of the Hydrochlorides of 2-Halo-*N*-(2-halobenzyl)-β-phenethylamines (8a, b and 9a, b)——i) Photolysis of **8a**: A solution of the hydrochloride (300 mg) of **8a** in H_2O (500 ml) was irradiated under N_2 with stirring at room temperature for 10 h. The reaction mixture was adjusted to pH 10 with Na_2CO_3 and extracted with $CHCl_3$. The extract was concentrated to give an oil (224.3 mg), which was subjected to PLC on SiO_2 in $CHCl_3$–MeOH (7 : 1). Fraction I (*Rf* 0.52—0.62) gave **5a** as an oil (11.5 mg, 6.0%), which was crystallized as its picrolonate (from $CHCl_3$–MeOH), mp 273—277 °C. *Anal.* Calcd for $C_{25}H_{22}BrN_5O_5 \cdot H_2O$: C, 52.65; H, 4.24; N, 12.28. Found: C, 52.77; H, 3.84; N, 12.04. Fraction II (*Rf* 0.62—0.67) gave an oily product (3.8 mg).[6)] Fraction III (*Rf* 0.78—0.87) afforded

an oil (41.4 mg, 16.3%) of **7c**. ^{1}H-NMR ($CDCl_3$) δ: 7.50 (1H, dd, J=8, 2 Hz, C-3′–H), 3.90 (2H, s, N–C$\underline{H}_2$–Ar), 2.90 (4H, m, N–C$\underline{H}_2$C$\underline{H}_2$–Ar), 1.79 (1H, s, NH). This oil was converted to its hydrochloride, mp 146—151 °C. *Anal.* Calcd for $C_{15}H_{16}BrN \cdot HCl \cdot 1/4H_2O$: C, 54.39; H, 5.32; N, 4.23. Found: C, 54.47; H, 5.60; N, 4.34. **8a** (77.6 mg, 22.7%) was recovered as an oil from fraction IV (*Rf* 0.87—0.92).

ii) Photolysis of **8b**: Similar treatment of the hydrochloride (190 mg) of **8b** in H_2O (420 ml) for 1.5 h gave **5b** (4.0 mg, 5.0%) and **8b** (26.2 mg, 15.2%). MS *m/z* (oil of **5b**): Calcd for $C_{16}H_{14}NO_2$: 331.0206 (M^+), 333.0186 (M^++2). Found: 331.0171 (M^+), 333.0148 (M^++2).

iii) Photolysis of **9a**: Similar treatment of the hydrochloride (300 mg) of **9a** in H_2O (500 ml) for 10 h gave **6a** (21.5 mg, 11.2%), the ethanolamine (**12**) (13.1 mg, 6.5%), **7d** (4.2 mg, 2.2%) and **9a** (76.3 mg, 27.7%). The oil **6a** was crystallized as its picrolonate, mp 236—238 °C (from $CHCl_3$–MeOH). *Anal.* Calcd for $C_{25}H_{22}BrN_5O_5$: C, 54.36; H, 4.01; N, 12.68. Found: C, 54.16; H, 4.07; N, 12.42. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O), 1520, 1330 (NO_2). Compound **12** had mp 66—69 °C (from ether). *Anal.* Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57. Found: C, 59.08; H, 5.27; N, 4.29. ^{1}H-NMR ($CDCl_3$) δ: 7.58 (1H, dd, J=8, 2 Hz, C-3–H), 5.06 (1H, dd, J=8, 4 Hz, –CH$\diagdown^{O}$), 3.12 (1H, dd, J=12, 4 Hz, CH(OH)–CH$\diagdown^{H}_{N}$), 2.64 (1H, dd, J=12, 8 Hz, –CH(OH)–C$\underline{H}\diagdown^{H}_{N}$), 3.88 (2H, br s, N–C$\underline{H}_2$–Ar), 2.79 (2H, br s, NH and OH). ^{1}H-NMR ($CDCl_3$) δ (**7d**): 7.47 (1H, dd, J=8, 2 Hz, C-3–H), 3.82 (2H, br s, N–C$\underline{H}_2$–Ar), 2.98 (4H, m, N–C$\underline{H}_2$C$\underline{H}_2$–Ar), 2.09 (1H, s, NH).

iv) Photolysis of **9b**: Similar treatment of the hydrochloride (304 mg) of **9b** in H_2O (500 ml) for 70 min gave **6b** (12.4 mg, 8.1%), mp 118—121 °C (from benzene). *Anal.* Calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; N, 4.22. Found: C, 57.45; H, 4.36; N, 4.30.

Methyl 3′-Bromo-2′-methyl-2-biphenylcarboxylates (17a, b)——i) Synthesis of **17a**: A mixture of 1.002 g of **15**,[9,10] 1.463 g of **16a** and 5.4 g of copper powder was heated in a sealed tube at 200 °C for 4 h. Work-up in the usual way[3b] gave a brown oil, which was subjected to PLC on SiO_2 in benzene. Fraction I (*Rf* 0.80—0.87) gave 3,3′-dibromo-2,2′-dimethylbiphenyl (oil, 52.8 mg, 9.2%). ^{1}H-NMR ($CDCl_3$) δ: 7.58 (2H, dd, J=8, 2 Hz, C-4– and C-4′–H), 2.12 (6H, s, CH_3 × 2). Fraction II (*Rf* 0.55—0.67) afforded **17a** (319 mg, 30.9%), mp 61—62 °C (from petr. ether). *Anal.* Calcd for $C_{15}H_{13}BrO_2$: C, 58.74; H, 4.32. Found: C, 59.03; H, 4.29. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.97 (1H, dd, J=8, 2 Hz, C-3–H), 3.60 (3H, s, $COOCH_3$), 2.12 (3H, s, Ar–C$\underline{H}_3$). Fraction III (*Rf* 0.36—0.54) gave 2′-methyl-2,2″-bis(methoxycarbonyl)-1,1′: 3′,1″-terphenyl (32.8 mg, 2.8%), mp 92—94.5 °C (from petr. ether). *Anal.* Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.53; H, 5.48. IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.94 and 7.96 (each 1H, dd, J=8, 2 Hz, C-3– and C-3″–H), 3.64 and 3.70 (each 3H, s, $COOCH_3$ × 2). Fraction IV (*Rf* 0.14—0.29) gave dimethyl diphenate (328 mg, 36.4%), mp 70—71 °C (from petr. ether) (lit.[3b] mp 71—72 °C).

ii) Synthesis of **17b**: Similar treatment of a mixture of **15** (1.0 g), **16b** (1.13 g) and copper powder (2.46 g) gave two products, one of which was **17b** (377.4 mg, 31.8%), mp 116—119.5 °C (from ether). *Anal.* Calcd for $C_{16}H_{13}BrO_4$: C, 55.04; H, 3.75. Found: C, 54.88; H, 3.68. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.56 (1H, m, C-4′–H), 7.47 (1H, s, C-3–H), 6.59 (1H, s, C-6–H), 6.04 (2H, s, OCH_2O), 3.55 (3H, s, $COOCH_3$), 2.12 (3H, s, Ar–C$\underline{H}_3$). The other product was dimethyl 4,5 : 4′,5′-bismethylenedioxydiphenate (160 mg, 20.3%), mp 153—155 °C (from ether). *Anal.* Calcd for $C_{18}H_{14}O_2$: C, 60.34; H, 3.94. Found: C, 60.30; H, 3.96. IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.45 (2H, s, C-3– and C-3′–H), 6.56 (2H, s, C-6– and C-6′–H), 6.02 (4H, s, OCH_2O × 2), 3.60 (6H, s, $COOCH_3$ × 2).

Methyl 3′-Bromo-2′-bromomethyl-2-biphenylcarboxylates (18a, b)——i) Synthesis of **18a**: A mixture of **17a** (102.2 mg), NBS (71 mg) and benzoyl peroxide (10 mg) in CCl_4 (6 ml) was heated under reflux for 7 h. The reaction mixture was filtered and the filtrate was washed with 5% $Na_2S_2O_3$, dried and evaporated to give **18a** (74.9 mg, 58.2%), mp 88.5—90 °C (from ether). *Anal.* Calcd for $C_{15}H_{12}Br_2O_2$: C, 46.91; H, 3.15. Found: C, 46.70; H, 3.30. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 8.04 (1H, dd, J=8, 2 Hz, C-3–H), 4.17 and 4.44 (each 1H, d, J= 10 Hz, AB-type of CH_2Br), 3.59 (3H, s, $COOCH_3$).

ii) Synthesis of **18b**: Similar treatment of **17b** (1.4 g), NBS (856 mg) and benzoyl peroxide (10 mg) in CCl_4 (20 ml) gave **18b** (684 mg, 39.7%), mp 150—153 °C (from ether). *Anal.* Calcd for $C_{16}H_{12}Br_2O_4$: C, 44.80; H, 2.83. Found: C, 45.05; H, 2.90. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.57 (1H, dd, J=8, 2 Hz, C-4′–H), 7.48 (1H, s, C-3–H), 6.78 (1H, s, C-6–H), 6.08 (2H, s, OCH_2O), 4.25 and 4.49 (each 1H, d, J=10 Hz, AB-type of CH_2Br), 3.58 (3H, s, $COOCH_3$).

Methyl 3′-Bromo-2′-cyanomethyl-2-biphenylcarboxylates (14a, b)——i) Synthesis of **14a**: A solution of **18a** (1.041 g) in dimethylsulfoxide (DMSO) (30 ml) was added to a solution of KCN (196.5 mg) in DMSO (13 ml) with stirring at room temperature for 10 min. Work-up in the usual way gave an oil, which was subjected to PLC on SiO_2 in benzene. Fraction I (*Rf* 0.15—0.37) gave **14a** (327 mg, 41.6%), mp 91.5—93 °C (from ether). *Anal.* Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.06; H, 3.47; N, 4.21. IR ν_{max}^{KBr} cm^{-1}: 2260 (CN), 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 8.04 (1H, dd, J=8, 2 Hz, C-3–H), 3.36 and 3.66 (each 1H, d, J=16 Hz, AB-type of CH_2CN), 3.61 (3H, s, $COOCH_3$). Fraction II (*Rf* 0.48—0.60) afforded **18a** (171.8 mg, 16.8%), mp 85—86 °C. Fraction III (*Rf* 0.00—0.08) gave **19** (168.9 mg, 20.9%), mp 245—246 °C (from MeOH). *Anal.* Calcd for $C_{15}H_8BrNO$: C, 60.42; H,

2.70; N, 4.70. Found: C, 60.17; H, 2.36; N, 4.52. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 2230 (C≡N). ^{1}H-NMR (DMSO-d_6) δ: 8.96 (2H, dd, J=8, 2 Hz, C-4– and C-5–H), 8.50 (1H, dd, J=8, 2 Hz, C-7–H), 7.52 (1H, dd, J=8, 8 Hz, C-6–H), 12.6—11.4 (1H, br s, OH).

ii) Synthesis of **14b**: Similar treatment of **18b** (676.5 mg) with KCN (123.4 mg) in DMSO (30 ml) gave **14b** (190 mg, 32.1%), mp 120—122 °C (from ether). *Anal.* Calcd for $C_{17}H_{12}BrNO_4$: C, 54.57; H, 3.23; N, 3.74. Found: C, 54.63; H, 3.42; N, 3.83. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.58 (1H, dd, J=8, 2 Hz, C-4′–H), 7.48 (1H, s, C-3–H), 6.64 (1H, s, C-6–H), 6.06 (2H, s, OCH_2O), 3.44 and 3.66 (each 1H, d, J=16 Hz, AB-type of CH_2CN), 3.56 (3H, s, $COOCH_3$).

9-Bromo-5,6,7,8-tetrahydrodibenz[*c*, *e*]azocine (6a)——i) From Cyanomethyl-ester (**14a**): A solution of **14a** (220 mg) in anhydrous diglyme (4 ml) was mixed with a solution of $NaBH_4$ (88 mg) in anhydrous diglyme (2.5 ml) and a solution of $AlCl_3$ (312 mg) in anhydrous diglyme (1.2 ml). The mixture was stirred at room temperature for 3.5 h, then heated at 80—94 °C for 1 h. Work-up in the usual way gave an oil, which was subjected to PLC on SiO_2 in $CHCl_3$–MeOH (6:1). Fraction I (*Rf* 0.27—0.55) gave **20a** (131 mg, 64.3%), mp 104—106.5 °C (from ether). *Anal.* Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.80; H, 5.66; N, 4.31. IR ν_{max}^{KBr} cm^{-1}: 3340, 3210 (NH_2), 2300—3500 (br OH). ^{1}H-NMR ($CDCl_3$) δ: 7.54 (1H, m, C-4′–H), 4.28 and 4.45 (each 1H, d, J=12 Hz, AB-type of CH_2OH), 2.80 (4H, m, N–C$\underline{H}_2$C$\underline{H}_2$–Ar), 1.94 (3H, br s, OH and NH_2). Fraction II (*Rf* 0.66—0.69) gave an oil (8.4 mg, 4.4%) of **6a**, which was crystallized as its picrolonate, mp 241—245 °C (dec.) (from MeOH). *Anal.* Calcd for $C_{25}H_{22}N_5O_5$: C, 54.36; H, 4.01; N, 12.68. Found: C, 54.07; H, 3.83; N, 12.63.

ii) From **20a**: A solution of **20a** (25.5 mg) in benzene (3 ml) was mixed with PBr_3 (0.3 ml), allowed to stand at room temperature overnight and then heated at 45 °C for 1 h. Then 50% KOH (4 ml) and EtOH (14 ml) were added and the mixture was refluxed for 2 h. Work-up in the usual way gave **6a** as an oil (12.5 mg, 52.1%), which was converted to its picrolonate, mp 236—238 °C (dec.) (from MeOH). The picrolonates prepared in i) and ii) were found to be identical upon direct comparison.

Reduction of 14b with $NaBH_4$ and $AlCl_3$ in Diglyme——The crude product obtained from **14b** (150 mg), $NaBH_4$ (49 mg), $AlCl_3$ (182 mg) and diglyme (6.1 ml) in the same manner as described for **6a** was subjected to PLC on SiO_2 in $CHCl_3$–MeOH (10:1). Fraction I (*Rf* 0.36—0.48) gave **6b** (19.3 mg, 14.5%), mp 123—124 °C (from ether). *Anal.* Calcd for $C_{16}H_{14}BrNO_2$: C, 57.58; H, 4.25; N, 4.22. Found: C, 57.66; H, 4.15; N, 3.93. IR ν_{max}^{KBr} cm^{-1}: 3230 (NH). Fraction II (*Rf* 0.06—0.13) gave a yellow oil (8.8 mg, 6.3%) of **20b**. ^{1}H-NMR ($CDCl_3$) δ: 7.60 (1H, m, C-4′–H), 6.45 (1H, s, C-6–H), 5.98 (2H, s, OCH_2O), 4.14 and 4.36 (each 1H, d, J=12 Hz, AB-type of CH_2OH), 2.30 (3H, br s, NH_2 and OH).

***N*-Ethyl-9-bromo-2,3-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*, *e*]azocine (22)**——i) From **23**: The azocine **6b** (15.6 mg) was treated with acetyl chloride (55.3 mg), NaOH (37.6 mg), H_2O (0.6 ml) and benzene (0.5 ml) in the usual way to give **23** (6.9 mg), mp 162—164 °C (from petr. ether–benzene). *Anal.* Calcd for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 58.03; H, 4.34; N, 3.73. ^{1}H-NMR ($CDCl_3$) δ: 7.62 (1H, dd, J=8, 2 Hz, C-10–H), 7.42 (1H, s, C-4–H), 6.73 (1H, s, C-1–H), 6.00 and 5.98 (each 1H, d, J=2 Hz, AB-type of OCH_2O), 5.28 and 3.03 (each 1H, d, J=14 Hz, AB-type of C-5 H_2), 2.14 (3H, s, $COCH_3$). Treatment of **23** (8.5 mg) with $LiAlH_4$ (5 mg) in dry ether in the usual way gave an oil (6 mg) of **22**. MS *m/z*: 360 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, dd, J=8, 2 Hz, C-10–H), 6.86 (1H, s, C-4–H), 6.71 (1H, s, C-1–H), 5.97 (2H, m, OCH_2O), 3.53 and 2.77 (each 1H, d, J=14 Hz, AB-type of C-5 H_2), 1.24 (3H, t, J=6 Hz, N–$CH_2C\underline{H}_3$).

ii) From **20b**: Compound **22** (1.9 mg) was also prepared from **20b** (7.6 mg), PBr_3 (0.1 ml), 50% KOH (1 ml) and EtOH (3 ml) by the same procedure as described for **6a** (ii). The products obtained by methods (i) and (ii) were identical on the basis of a ^{1}H-NMR comparison.

References and Notes

1) Part VII: S. Kobayashi, M. Kihara, and T. Shingu, *Yakugaku Zasshi*, **100**, 302 (1980).
2) This forms Part XXIII of "Studies on the Syntheses of Benzoheterocyclic Compounds." Part XXII: ref. 1.
3) *a*) S. Kobayashi, M. Kihara, K. Yamasaki, Y. Ishida, and K. Watanabe, *Chem. Pharm. Bull.*, **23**, 3036 (1975); *b*) S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, and H. Matsumoto, *ibid.*, **25**, 3312 (1977); *c*) M. Kihara and S. Kobayashi, *ibid.*, **26**, 155 (1978); *d*) S. Kobayashi, M. Kihara, and S. Mineo, *ibid.*, **26**, 635 (1978); *e*) S. Kobayashi, M. Kihara, and Y. Nakauchi, *Yakugaku Zasshi*, **98**, 161 (1978); *f*) S. Kobayashi, M. Kihara, and H. Matsumoto, *ibid.*, **98**, 863 (1978).
4) Y. Ishida, K. Sadamune, S. Kobayashi, and M. Kihara, *J. Pharmacobio-Dyn.*, **6**, 391 (1983).
5) *a*) N. Kharasch, R. K. Sharma, and H. B. Lewis, *Chem. Commun.*, **1966**, 418; *b*) N. Kharasch, *Intra-Sci. Chem. Rep.*, **3**, 203 (1969).
6) S. Kobayashi, M. Kihara, and Y. Miyake, *Heterocycles*, **23**, 159 (1958).
7) S. Kobayashi, K. Kitamura, A. Miura, M. Fukuda, and M. Kihara, *Chem. Pharm. Bull.*, **20**, 694 (1972).
8) *a*) H. C. Brown and B. C. S. Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955); *b*) *Idem, ibid.*, **78**, 2582 (1956).
9) G. Lock, *Chem. Ber.*, **68**, 1505 (1935).
10) J. B. Cohen and J. Miller, *J. Chem. Soc.*, **85**, 1622 (1904).