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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*

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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; α -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.

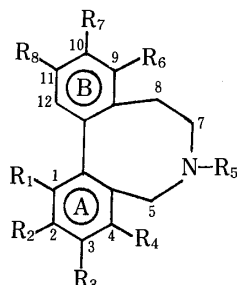
This paper describes the photochemical cyclization of 2-halo-*N*-(2-halobenzyl)- β -phenethylamines to the azocines **5a, b** and **6a, b**, as well as the thermal syntheses of **6a, b**.

Previously, we reported¹⁾ 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 fact⁵⁾ 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).

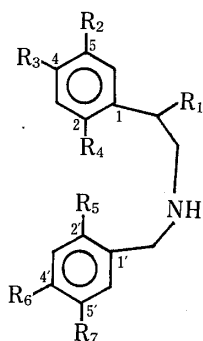
Irradiation of the hydrochloride of **8a** in aqueous solution gave **5a** (6.0% yield, mp 273—277°C as the picrolonate) along with an unexpected compound⁶⁾ and the deiiodinated product (**7c**). Similarly, 9-bromoazocine **6a** (mp 236—238°C as the picrolonate) was obtained in 11.2% yield by photolysis 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.

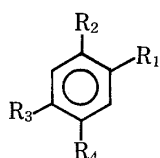
The structures of the dibenzazocines **5a, b** and **6a, b** thus obtained were supported by the physical and spectral data. In the proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra (Table III), AB-type doublets ($J=14\text{ Hz}$) in the two regions at $\delta\ 3.79\text{--}4.26$ and $3.04\text{--}3.18$



	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 ₂ O	
6a	H	H	H	H	H	Br	H	H
6b	H	OCH ₂ O	H	H	H	Br	H	H
13	H	H	H	H	H	H	H	H
22	H	OCH ₂ O	H	C ₂ H ₅	Br	H	H	H
23	H	OCH ₂ O	H	COCH ₃	Br	H	H	H

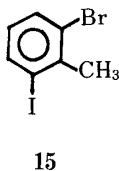
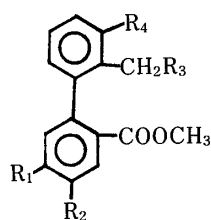


	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇
7a	H	H	H	I	I	H	H
7b	H	H	H	Br	Br	H	H
7c	H	H	H	H	Br	H	H
7d	H	H	H	Br	H	H	H
8a	H	H	H	I	Br	H	H
8b	H	OCH ₂ O	I	Br	H	H	H
9a	H	H	H	Br	I	H	H
9b	H	H	H	Br	I	OCH ₂ O	H
12	OH	H	H	Br	H	H	H

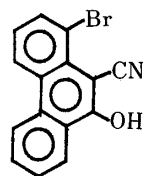


	R ₁	R ₂	R ₃	R ₄
10a	CHO	Br	H	H
10b	CHO	I	H	H
10c	CHO	I	OCH ₂ O	
11a	CH ₂ CH ₂ NH ₂	Br	H	H
11b	CH ₂ CH ₂ NH ₂	I	H	H
11c	CH ₂ CH ₂ NH ₂	I	OCH ₂ O	

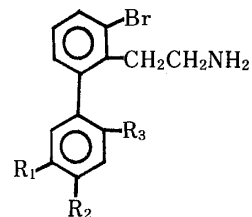
Chart 1



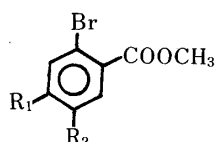
15



19



	R ₁	R ₂	R ₃	R ₄
14a	H	H	CN	Br
14b	OCH ₂ O	CN	Br	
14c	H	H	CN	H
17a	H	H	H	Br
17b	OCH ₂ O	H	Br	
18a	H	H	Br	Br
18b	OCH ₂ O	Br	Br	



16a: R₁=R₂=H
16b: R₁, R₂=OCH₂O

	R ₁	R ₂	R ₃
20a	H	H	CH ₂ OH
20b	OCH ₂ O	CH ₂ OH	
21a	H	H	CH ₂ Br
21b	OCH ₂ O	CH ₂ Br	

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)	mg (%) ^{a)}	mp (°C)	Formula	Product as hydrochloride		
						Analysis (%)		
						Calcd (Found)		
						C	H	N
10a ^{b)} 1.07	11a 0.45	544	7b 678 (74.2)	167—169	$\text{C}_{15}\text{H}_{15}\text{Br}_2\text{N} \cdot \text{HCl}$	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	$\text{C}_{15}\text{H}_{15}\text{BrIN} \cdot \text{HCl}$	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	$\text{C}_{16}\text{H}_{15}\text{BrINO}_2 \cdot \text{HCl}$	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	$\text{C}_{15}\text{H}_{15}\text{BrIN} \cdot \text{HCl}$	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	$\text{C}_{16}\text{H}_{15}\text{BrINO}_2 \cdot \text{HCl}$	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. ^1H -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	$\text{ArCH}_2\text{CH}_2\text{N}$	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. $^1\text{H-NMR}$ Spectral Data for 5,6,7,8-Tetrahydrodibenz[*c, e*]azocines (CDCl_3 , δ)

Compd.	Aromatic H								$\text{H}_2^{a)-5}$		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. 3d.

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 $^1\text{H-NMR}$ 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 $\text{C}_{25}\text{H}_{22}\text{BrN}_5\text{O}_5 \cdot \text{H}_2\text{O}$: 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**. $^1\text{H-NMR}$ (CDCl_3) δ : 7.50 (1H, dd, $J=8$, 2 Hz, C-3'-H), 3.90 (2H, s, $\text{N-CH}_2\text{-Ar}$), 2.90 (4H, m, $\text{N-CH}_2\text{CH}_2\text{-Ar}$), 1.79 (1H, s, NH). This oil was converted to its hydrochloride, mp 146–151 °C. *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{BrN}\cdot\text{HCl}\cdot 1/4\text{H}_2\text{O}$: 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 (R_f 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 $\text{C}_{16}\text{H}_{14}\text{NO}_2$: 331.0206 (M^+), 333.0186 ($\text{M}^+ + 2$). Found: 331.0171 (M^+), 333.0148 ($\text{M}^+ + 2$).

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 ethanolinamine (**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 picolonate, mp 236–238 °C (from $\text{CHCl}_3\text{-MeOH}$). *Anal.* Calcd for $\text{C}_{25}\text{H}_{22}\text{BrN}_5\text{O}_5$: C, 54.36; H, 4.01; N, 12.68. Found: C, 54.16; H, 4.07; N, 12.42. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1640 (C=O), 1520, 1330 (NO_2). Compound **12** had mp 66–69 °C (from ether). *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{BrNO}$: C, 58.84; H, 5.27; N, 4.57. Found: C, 59.08; H, 5.27; N, 4.29. $^1\text{H-NMR}$ (CDCl_3) δ : 7.58 (1H, dd, $J=8$, 2 Hz, C-3-H), 5.06 (1H, dd, $J=8$, 4 Hz, $-\text{CH} \begin{smallmatrix} \text{O} \\ \diagup \end{smallmatrix}$), 3.12 (1H, dd, $J=12$, 4 Hz, $\text{CH}(\text{OH})-\text{CH} \begin{smallmatrix} \text{H} \\ \diagdown \end{smallmatrix} \text{N}$), 2.64 (1H, dd, $J=12$, 8 Hz, $-\text{CH}(\text{OH})-\text{CH} \begin{smallmatrix} \text{H} \\ \diagdown \end{smallmatrix} \text{N}$), 3.88 (2H, br s, $\text{N-CH}_2\text{-Ar}$), 2.79 (2H, br s, NH and OH). $^1\text{H-NMR}$ (CDCl_3) δ (**7d**): 7.47 (1H, dd, $J=8$, 2 Hz, C-3-H), 3.82 (2H, br s, $\text{N-CH}_2\text{-Ar}$), 2.98 (4H, m, $\text{N-CH}_2\text{CH}_2\text{-Ar}$), 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 $\text{C}_{16}\text{H}_{14}\text{BrNO}_2$: 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 (R_f 0.80–0.87) gave 3,3'-dibromo-2,2'-dimethylbiphenyl (oil, 52.8 mg, 9.2%). $^1\text{H-NMR}$ (CDCl_3) δ : 7.58 (2H, dd, $J=8$, 2 Hz, C-4- and C-4'-H), 2.12 (6H, s, $\text{CH}_3 \times 2$). Fraction II (R_f 0.55–0.67) afforded **17a** (319 mg, 30.9%), mp 61–62 °C (from petr. ether). *Anal.* Calcd for $\text{C}_{15}\text{H}_{13}\text{BrO}_2$: C, 58.74; H, 4.32. Found: C, 59.03; H, 4.29. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1730 (C=O). $^1\text{H-NMR}$ (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-CH_3). Fraction III (R_f 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 $\text{C}_{23}\text{H}_{20}\text{O}_4$: C, 76.65; H, 5.59. Found: C, 76.53; H, 5.48. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1725 (C=O). $^1\text{H-NMR}$ (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, $\text{COOCH}_3 \times 2$). Fraction IV (R_f 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 $\text{C}_{16}\text{H}_{13}\text{BrO}_4$: C, 55.04; H, 3.75. Found: C, 54.88; H, 3.68. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1720 (C=O). $^1\text{H-NMR}$ (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-CH_3). The other product was dimethyl 4,5:4',5'-bismethylenedioxydiphenate (160 mg, 20.3%), mp 153–155 °C (from ether). *Anal.* Calcd for $\text{C}_{18}\text{H}_{14}\text{O}_2$: C, 60.34; H, 3.94. Found: C, 60.30; H, 3.96. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1705 (C=O). $^1\text{H-NMR}$ (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, $\text{OCH}_2\text{O} \times 2$), 3.60 (6H, s, $\text{COOCH}_3 \times 2$).

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% $\text{Na}_2\text{S}_2\text{O}_3$, dried and evaporated to give **18a** (74.9 mg, 58.2%), mp 88.5–90 °C (from ether). *Anal.* Calcd for $\text{C}_{15}\text{H}_{12}\text{Br}_2\text{O}_2$: C, 46.91; H, 3.15. Found: C, 46.70; H, 3.30. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1720 (C=O). $^1\text{H-NMR}$ (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 $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{O}_4$: C, 44.80; H, 2.83. Found: C, 45.05; H, 2.90. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1720 (C=O). $^1\text{H-NMR}$ (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 (R_f 0.15–0.37) gave **14a** (327 mg, 41.6%), mp 91.5–93 °C (from ether). *Anal.* Calcd for $\text{C}_{16}\text{H}_{12}\text{BrNO}_2$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.06; H, 3.47; N, 4.21. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2260 (CN), 1730 (C=O). $^1\text{H-NMR}$ (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 (R_f 0.48–0.60) afforded **18a** (171.8 mg, 16.8%), mp 85–86 °C. Fraction III (R_f 0.00–0.08) gave **19** (168.9 mg, 20.9%), mp 245–246 °C (from MeOH). *Anal.* Calcd for $\text{C}_{15}\text{H}_8\text{BrNO}$: C, 60.42; H,

2.70; N, 4.70. Found: C, 60.17; H, 2.36; N, 4.52. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300 (OH), 2230 ($\text{C}\equiv\text{N}$). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) 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, brs, 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 $\text{C}_{17}\text{H}_{12}\text{BrNO}_4$: C, 54.57; H, 3.23; N, 3.74. Found: C, 54.63; H, 3.42; N, 3.83. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2250 (CN), 1720 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (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 (R_f 0.27—0.55) gave **20a** (131 mg, 64.3%), mp 104—106.5 °C (from ether). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{BrNO}$: C, 58.84; H, 5.27; N, 4.57. Found: C, 58.80; H, 5.66; N, 4.31. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3340, 3210 (NH_2), 2300—3500 (br OH). $^1\text{H-NMR}$ (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, $\text{N-CH}_2\text{CH}_2\text{-Ar}$), 1.94 (3H, brs, OH and NH_2). Fraction II (R_f 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 $\text{C}_{25}\text{H}_{22}\text{N}_5\text{O}_5$: 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 (R_f 0.36—0.48) gave **6b** (19.3 mg, 14.5%), mp 123—124 °C (from ether). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{BrNO}_2$: C, 57.58; H, 4.25; N, 4.22. Found: C, 57.66; H, 4.15; N, 3.93. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3230 (NH). Fraction II (R_f 0.06—0.13) gave a yellow oil (8.8 mg, 6.3%) of **20b**. $^1\text{H-NMR}$ (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, brs, 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 $\text{C}_{18}\text{H}_{16}\text{BrNO}_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 58.03; H, 4.34; N, 3.73. $^1\text{H-NMR}$ (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^+). $^1\text{H-NMR}$ (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, $\text{N-CH}_2\text{CH}_3$).

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 $^1\text{H-NMR}$ 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).