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Syntheses of Apogalanthamine Analogs as α-Adrenergic Blocking Agents[1]

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The apogalanthamine analogs, 10,11-methylenedioxy-, 10,11-dimethoxy-, and 11,12-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines (**2**, **5**, and **7**, respectively) and their N-substituted derivatives (**1**, **3**, **4**, **6**, **8**, and **9**) as α-adrenergic blocking agents, and the related compounds, 2,3-dimethoxy-, 2,3-methylenedioxy-, and 11-methoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines (**10**, **11**, and **12**, respectively) were synthesized by intramolecular cyclization of the corresponding amino-alcohols (**30a**—**f**) *via* the corresponding bromo-amines (**16a**—**f**). The preparation of the nitrovinyl compounds (**19a**—**f**) as startnig materials for the amino-alcohols was investigated.

The conformation of these azocines was discussed in relation to nuclear magnetic resonance spectral data.

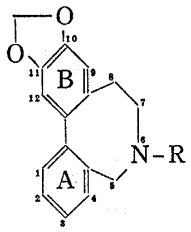
Keywords——apogalanthamine analog; α-adrenergic blocking agent; 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine; intramolecular cyclization; biphenylcarboxylate; styphnate; Ullmann reaction

Recently we reported the synthesis[3] of the 6-(β-bromoethyl) derivative (**1**) of 10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**2**) having an apogalanthamine skeleton, and the results on the irreversible α-adrenergic blocking activity[4] of **1** on rat aorta strips. In contrast, **2** and its 6-alkylated derivatives (**3** and **4**), 10,11-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**5**) and its 6-methylated derivative (**6**), 11,12-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**7**) and its 6-alkylated derivatives (**8** and **9**) showed reversible α-adrenolytic action.[5]

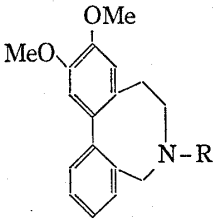
This paper reports the syntheses of the apogalanthamine analogs **2**—**9** having pharmacological activities, and of the related compounds, 2,3-dimethoxy-,2,3-methylenedioxy-, and 11-methoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**10**, **11**, and **12**, respectively).

Previously we reported the synthesis of the apogalanthamine derivatives **13**[6] and **14**.[7] The apogalanthamine skeleton of the latter compound was formed by two different procedures: (i) intermolecular cyclization of the dibromide (**15a**) with methylamine and (ii) intramolecular cyclization of the bromo-amine (**16h**) in the presence of a base. The yield of the cyclic amine (N-demethylated compound of **14**) prepared from **16h** by procedure (ii) was better than that of **14** obtained from **15a** by procedure (i). Furthermore, since an attempt to cyclize the dibromide (**15b**)[8] to the azocine (**17**) by procedure (i) was unsuccessful, attempts were made to prepare the azocines (**2**,**5**,**7**, and **10**—**12**) from the bromo-amines (**16a**—**f**) by procedure (ii).

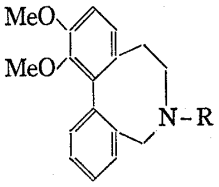
1) This forms Part XVI of "Studies on the Syntheses of Benzohetrocyclic Compounds" by Kobayashi, Part XV: S. Kobayashi, and M. Kihara, *Yakugaku Zasshi*, **97**, 901 (1977).
2) Location: *1-78, Sho-machi, Tokushima, 770, Japan.*
3) S. Kobayashi, M. Kihara, K. Yamasaki, Y. Ishida, and K. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **23**, 3036 (1975).
4) Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, *Jpn. J. Pharmacol.*, **26**, 607 (1976).
5) Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, *Chem. Pharm. Bull.* (Tokyo), **25**, 1851 (1977).
6) S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, **1957**, 638.
7) J. Koizumi, S. Kobayashi, and S. Uyeo, *Chem. Pharm. Bull.* (Tokyo), **12**, 696 (1964).
8) The preparation of this new compound will be reported elsewhere.



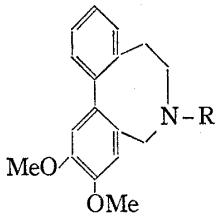
1: R=CH_2CH_2Br
2: R=H
3: R=Me
4: R=Et
36: R=CH_2CH_2Cl
37: R=CH_2CH_2OH



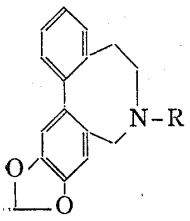
5: R=H
6: R=Me
31: R=Et



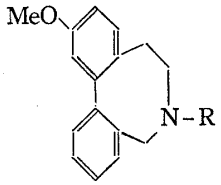
7: R=H
8: R=Me
9: R=Et



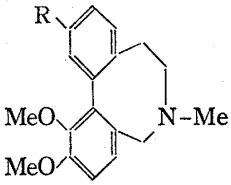
10: R=H
17: R=Me
33: R=CHO



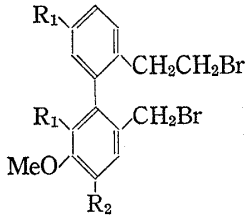
11: R=H
32: R=Et



12: R=H

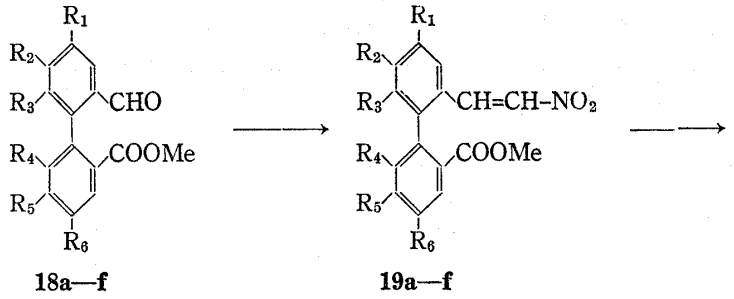


13: R=H
14: R=OMe

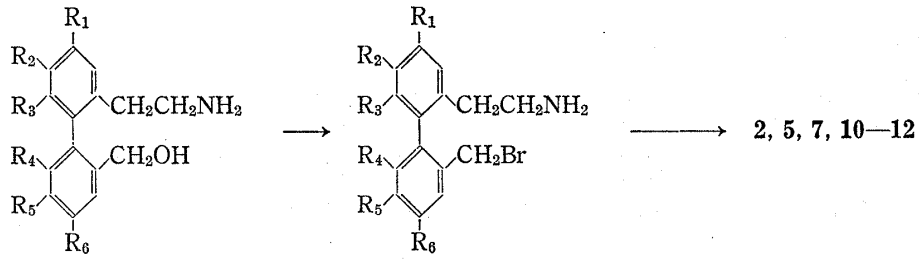


15a: R_1=OMe, R_2=H
15b: R_1=H, R_2=OMe

Chart 1



18a—f **19a—f**



30a—f **16a—h** **2, 5, 7, 10—12**

a : R_1,R_2=OCH_2O, R_3=R_4=R_5=R_6=H
b : R_1=R_2=OMe, R_3=R_4=R_5=R_6=H
c : R_2=OMe, R_1=R_3=R_4=R_5=R_6=H
d : R_1=R_2=R_3=R_4=H, R_5=R_6=OMe
e : R_1=R_2=R_3=R_4=H, R_5,R_6=OCH_2O
f : R_2=R_3=OMe, R_1=R_4=R_5=R_6=H
g : R_1=R_2=R_3=R_6=H, R_4=R_5=OMe
h : R_1=R_3=R_6=H, R_2=R_4=R_5=OMe

Chart 2

The bromo-amines were prepared as follows. The methyl 2′-formyl-2-biphenylcarboxylate derivatives (**18a—f**), obtained by Ullmann condensation of the corresponding *o*-halogenobenzoate and *o*-halogenobenzaldehyde derivatives, were selected as the key intermediates. The striking characteristic of the syntheses of these azocines was the good conversion (67—92%

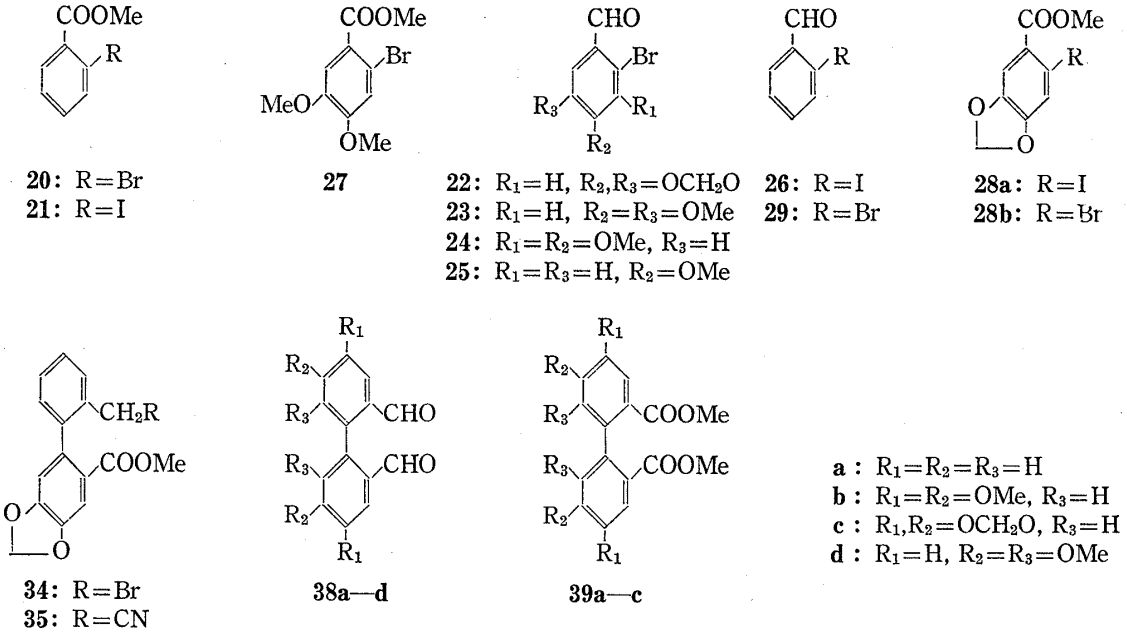


Chart 3

yields) of **18a—e** to the nitrovinyl compounds (**19a—e**) *via* the Schiff's bases of **18a—e**. Reduction of **19a—f** with lithium aluminum hydride (LAH) followed by bromination gave the bromo-amines (**16a—f**).

Methyl 2′-Formyl-2-biphenylcarboxylate Derivatives (18a—f)

The biphenyl compounds, **18a**,[9] **18b**,[10] and **18f**[10] were prepared by Ullmann condensation of methyl 2-halogenobenzoate (**20** or **21**) with 6-bromopiperonal (**22**), and 6-bromo- and 2-bromo-veratraldehydes (**23** and **24**), respectively, as shown in Table I. The yield of **18a**

Table I. Syntheses of Methyl 2′-Formyl-2-biphenylcarboxylates (**18a—f**) by Ullmann Condensation[a]

Starting material: Aldehyde g (m mol)	Starting material: Ester g (m mol)	Cu g (m mol)	Reaction temp. (°C)	Product: Monoester g (%)	Dialdehyde g (%)	Diester g (%)
22 4.8 (21.0)	**20** 3.5 (16.3)	9.0 (142)	210	**18a**[b] 1.30 (28.1)	**38c**[c] 0.39 (12.4)	**39a** 1.19 (54.1)
23 11.0 (44.9)	**21** 18.5 (70.6)	13.0 (205)	205	**18b** 1.59 (11.8)	**38b**[c] 2.08 (28.1)	**39a** 1.91 (20.0)
25 3.0 (13.9)	**20** 15.0 (69.7)	16.2 (255)	200	**18c** 1.40 (37.1)		**39a** 4.0 (42.4)
26 5.37 (23.1)	**27** 4.0 (14.5)	12.24 (193)	200	**18d** 1.69 (38.7)	**38a**[c] 1.26 (51.7)	**39b**[d] 1.01 (35.7)
26 2.28 (9.8)	**28a** 1.5 (4.9)	3.0 (47.2)	195	**18e** 0.21 (15.3)	**38a**[c] 0.58 (56.3)	**39c**[e] 0.18 (20.4)
24 16.92 (69.0)	**21** 22.77 (86.9)	56.0 (881)	170	**18f** 5.71 (27.5)	**38d**[c] 3.22 (28.2)	**39a** 1.99 (16.8)

a) The reaction time was 4 hr in every case.
b) See ref. 9.
c) See ref. 17.
d) K. Freudenberg and C.L. Chen, *Chem. Ber.*, **100**, 3638 (1967).
e) See ref. 10.

9) S. Kobayashi, M. Kihara, T. Hashimoto, and T. Shingu, *Chem. Pharm. Bull.* (Tokyo), **24**, 716 (1976).
10) S. Kobayashi, S. Mineo, M. Kihara, and S. Tagashira, *Chem. Pharm. Bull.* (Tokyo), **24**, 2191 (1976).

seemed to be better on condensation of **22** with **20** than on reaction[11] of **22** with **21**. Compound **18c** was obtained in good yield by the reaction of 2-bromo-4-methoxybenzaldehyde (**25**) with **20**, but no **18c** was obtained by the reaction of **25** with **21**. Compounds **18d**[10] and **18e**[10] were prepared by condensation of 2-iodobenzaldehyde (**26**) with methyl 6-bromoveratrate (**27**) and with methyl 6-iodopiperonylate (**28a**), respectively. Attempts to prepare **18e** by the reaction of 2-bromobenzaldehyde (**29**) with methyl 6-bromopiperonylate (**28b**) or **28a** and by the reaction of **26** with **28b** were unsuccessful.

Table II. Methyl 2′-Formyl-2 biphenylcarboxylates (**18a—f**)

Compd.	Appearance (recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
18a[a]	Prisms (ether)	102—103.5	$C_{16}H_{12}O_5$	67.60	4.26	67.85	4.54
18b	Cubes (benzene)	120.5—121.5	$C_{17}H_{16}O_5$	67.99	5.37	67.99	5.42
18c	Needles (pet. ether)	98—100	$C_{16}H_{14}O_4$	71.10	5.22	70.95	5.16
18d	Prisms (ether)	107.5—108	$C_{17}H_{16}O_5$	67.99	5.37	68.21	5.66
18e	Prisms (ether)	88—88.5	$C_{16}H_{12}O_5$	67.60	4.26	67.69	4.18
18f	Prisms (ether)	91—93	$C_{17}H_{16}O_5$	67.99	5.37	68.37	5.24

a) See ref. 9.

Table III. NMR and IR Spectra of Methyl 2′-Formyl-2-biphenylcarboxylates (**18a—f**)

Compd.	NMR (in $CDCl_3$, δ) Aromatic H	CHO	$COOCH_3$	OCH_3	IR ν_{max}^{KBr} cm^{-1} OCH_2O	CHO	$COOCH_3$
18a	8.10 (1H, m, C-3) 7.51 (1H, s, C-3′) 7.36 (1H, m, C-6) 6.73 (1H, s, C-6′)	9.66	3.68		6.12	1670	1720
18b	8.00 (1H, m, C-3) 7.51 (1H, s, C-3′) 7.00 (1H, s, C-6′)	9.62	3.65	3.99 (C-4′) 3.93 (C-5′)		1680	1720
18c	7.98 (1H, d, 9,[a] C-3) 7.30 (1H, q, 8,2, C-6) 6.98 (1H, q, 9,2, C-4′) 6.72 (1H, d, 2, C-6′)	9.68	3.59	3.82		1680	1720
18d	7.98 (1H, q, 6,2, C-3′) 7.60 (1H, s, C-3) 7.24 (1H, q, 6,2, C-6′) 6.71 (1H, s, C-6)	9.82	3.56	3.96 (C-4) 3.87 (C-5)		1690,	1710 (sh,[b] 1720)
18e	7.96 (1H, q, 6,2, C-3′) 6.69 (1H, s, C-6)	9.85	3.55		6.08	1690	1720
18f	7.80 (1H, d, 8, C-3′) 7.05 (1H, d, 8, C-4′)	9.51	3.65	3.96 (C-5′) 3.50 (C-6′)		1670	1720

a) The numerical values in parentheses are coupling constants as Hz values.
b) The abbreviation, sh, means a shoulder.

11) T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, **1956**, 4749.

The biphenyl compounds were identified by the physical and spectral data on them in Tables II and III. The infrared (IR) spectra of **18a—f** showed carbonyl absorptions for the ester groups at 1720 cm^{-1}, and for the formyl groups in the *p*-position to the methoxyl or methylenedioxy group at 1670—1680 cm^{-1}, and for other formyl groups at 1690 cm^{-1}. In the nuclear magnetic resonance (NMR) spectra, the signals of the formyl protons in **18a—c** and **18f** are *ca.* 0.2 ppm further upfield than those of the protons in **18d** and **18e**. This is due to the diamagnetic effect of the methoxy or methylenedioxy group, as reported previously.[9] From studies on nuclear magnetic double resonance (NMDR), the signals of the methoxy protons in **18b**, **18d**, and **18f** were assigned as shown in Table III.

Table IV. Syntheses of Methyl 2′-(2-Nitrovinyl)-2-biphenylcarboxylates (**19a—f**)

Startnig material mg	Procedure (i) $MeNH_2 \cdot HCl$ mg	(i) Na_2CO_3 mg	(i) MeOH ml	(i) Benzene ml	(i) $MeNO_2$ ml	(ii) $AcONH_4$ mg	(ii) AcOH ml	(ii) $MeNO_2$ ml	(iii) *n*-$BuNH_2$ ml	(iii) AcOH ml	(iii) $MeNO_2$ ml	Product mg (%)
18a												**19a**
1800									4.32	1.55	16.74	1919(92.7)
18b												**19b**
50	5	5	2.5	0.5	0.15							46(80.4)
60									0.14	0.05	0.27	47(68.5)
18c												**19c**
50	5.4	5.9	3.7		0.1							8(13.8)
50						52.3	1.34	0.1				1(1.7)
100									0.54	0.13	0.11	78(67.4)
18d												**19d**
25	20	24	5.7	0.25	0.075							6(21.0)
55						70	1.8	0.13				20(31.8)
420									0.92	0.32	3.82	422(88.0)
18e												**19e**
62.3									0.90	0.15	1.86	49(68.0)
18f												**19f**
50	4.5	5.5	2.5	0.5	0.15							34.5(60.3)
561						1206	18	2				374(58.4)
199									0.96	0.17	1.76	76(33.3)

Table V. Methyl 2′-(2-Nitrovinyl)-2-biphenylcarboxylates (**19a—f**)

Compd.	Appearance (recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
19a	Yellow prisms (methanol)	167—170	$C_{17}H_{13}NO_6$	62.38	4.00	4.28	62.10	3.94	4.57
19b	Yellow prisms (methanol)	149—151	$C_{18}H_{17}NO_6$	62.97	4.99	4.08	63.09	4.86	3.88
19c	Yellow prisms (methanol)	112—113	$C_{17}H_{15}NO_5$	65.17	4.82	4.47	64.93	4.74	4.36
19d	Yellow cubes (methanol)	160—161.5	$C_{18}H_{17}NO_6$	62.97	4.99	4.08	62.76	4.92	3.82
19e	Yellow needles (benzene)	131—133.5	$C_{17}H_{13}NO_6$	62.38	4.00	4.28	62.67	4.05	4.32
19f	Yellow needles (methanol)	127—128.5	$C_{18}H_{17}NO_6 \cdot 1/2H_2O$	61.90	5.15	3.98	62.17	4.96	4.11

Methyl 2′-(2-Nitrovinyl)-2-biphenylcarboxylate Derivatives (19a—f)

The nitrovinyl compounds (**19c, 19d,** and **19f**) were prepared from aldehydes **18c, 18d,** and **18f,** respectively, by three procedures: (i) treatment of the aldehydes with nitromethane at room temperature in the presence of methylamine, (ii) heating the aldehydes with nitromethane using ammonium acetate and acetic acid as condensing agents, and (iii) heating the aldehydes with *n*-butylamine, followed by treatment of the resultant Schiff's bases with nitromethane and acetic acid (see Table IV). The yield of **19f** obtained by procedure (i)

Table VI. NMR and IR Spectra of Methyl 2′-(2-Nitrovinyl)-2-biphenylcarboxylates (**19a—f**)

Compd.	NMR (in $CDCl_3$, δ)						IR ν_{max}^{KBr} mc^{-1}	
	Aromatic H	CH=CH–NO_2[a]	CH=CH–NO_2[a]	$COOCH_3$	OCH_3	OCH_2O	C=C	$COOCH_3$
19a	7.11 (1H, s, C-3′) 6.74 (1H, s, C-6′)	7.37	7.67	3.69		6.10	1610	1720
19b	8.03 (1H, m, C-3) 7.04 (1H, s, C-3′) 6.73 (1H, s, C-6′)	7.33	7.72	3.65	3.97 (C-4′) 3.89 (C-5′)		1620	1720
19c	8.04 (1H, m, C-3) 6.94 (1H, q, 10,2,[b] C-4′) 6.72 (1H, d, 2, C-6′)	7.28	7.68	3.60	3.80		1620	1720
19d	6.62 (1H, s, C-6)	7.38	7.74	3.54	3.94 (C-4) 3.82 (C-5)		1630	1720
19e	6.62 (1H, s, C-6)	7.37	7.77	3.61		6.12	1630	1720
19f	7.47 (1H, d, 9, C-3′) 7.03 (1H, d, 9, C-4′)	7.22	7.63	3.67	3.92 (C-5′) 3.49 (C-6′)		1620	1720

a) Each vinyl proton is a doublet having a coupling constant of 14 Hz.
b) The numerical values in parentheses are coupling constants as Hz values.

Table VII. Syntheses of Dibenz[*c*,*e*]azocines from Nitrovinyl Compounds (**19a—f**)

Compd. mg		Reduction: $LiAlH_4$ g	Ether ml	Amino-alcohol	mg	Bromination[a]: PBr_3 ml	Benzene ml	Cyclization: 50% KOH ml	EtOH ml	Product	mg (%)[b]	By-product	mg (%)[b]
19a	500	5	530	**30a**	370	4.0	20	60	200	**2**	125 (32.3)	**4**	23 (5.3)
19b	300	4	330	**30b**	218	1.8	6	24	160	**5**	71 (30.2)	**31**	Trace
19c	600	6.18	420	**30c**	418	4.2	25	100	600	**12**	58 (12.7)		
19d	422	5	300	**30d**	343	1.9	6	30	200	**10-N**[c]	111.9 (22.7)		
	900	10	290	**30d**	447	2.5	6	65	200	**10-N**[c]	176 (17.1)	**33**	43 (5.4)
19e	55.9	0.5	50	**30e**	28	0.4	2	10	35	**11-N**[c]	19.2 (29.9)		
				30e[d]	67.7	1.0	5	21[e]	28	**11-N**[c]	11.3 (12.0)	**32-A**[c]	52.9 (38.3)
19f	220	2	80	**30f**	156	2.0	4	30	104	**7-N**[c]	60 (23.9)	**9-A**[c]	28.5 (8.2)

a) The product of this step was not isolated in a pure state, but used directly as the starting material for the next reaction.
b) Overall yield based on the nitrovinyl compound, except in the case of **30e**.[d]
c) N and A indicate neutral and acidic styphnates, respectively.
d) This compound was used as the starting material.
e) 25% KOH solution.

varied from 0 to 60.3%, possibly because the reaction conditions were difficult to control. A similar variable yield (0—80%) was obtained in the synthesis of **19b** by the same procedure. On the other hand, procedure (iii) was better than procedure (ii) for preparing **19c—d**, as shown in Table IV. Therefore, **19a**, **19b**, and **19e** were synthesized by procedure (iii) in good yield. Procedure (ii) seemed to be better than the others for preparing sterically hindered biphenyl compounds, such as **19f**, since similar compounds, such as methyl 5,6-dimethoxy- and 5′,5,6-trimethoxy-2′-(2-nitrovinyl)-2-biphenylcarboxylate (**19g**[6] and **19h**[7]) were prepared by this procedure in 59.2 and 51.5% yield, respectively.

These nitrovinyl compounds were characterized by their physical and spectral data given in Tables V and VI. The IR spectra of all these compounds showed absorptions for

Table VIII. Dibenz[*c*,*e*]azocines

Compd.	Appearance (recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
1	Needles (ether)	227—230	$C_{18}H_{18}BrNO_2 \cdot H_2O$	57.15 (57.44)	5.33 (5.63)	3.70 (3.40)
2	Cubes (ether)	98.5—100	$C_{16}H_{15}NO_2$	75.87 (75.64)	5.97 (6.00)	5.53 (5.37)
3-A[a]	Prisms (acetone)	216.5—217.5 (dec.)	$C_{17}H_{17}NO_2 \cdot C_6H_3N_3O_8$	53.91 (53.87)	3.93 (3.97)	10.93 (10.72)
4	Needles (ether)	78.5—81.5	$C_{18}H_{19}NO_2$	76.87 (76.85)	6.81 (6.95)	4.98 (4.85)
5	Cubes (ether)	119—123	$C_{17}H_{19}NO_2$	75.81 (76.12)	7·11 (7.10)	5.20 (5.09)
5-N[a]	Needles (methanol)	193—197	$C_{17}H_{19}NO_2 \cdot 1/2C_6H_3N_3O_8 \cdot H_2O$	58.60 (58.32)	5.53 (5.33)	8.54 (8.27)
6	Needles (petr.ether)	72—73	$C_{18}H_{21}NO_2$	76.29 (76.20)	7.47 (7.52)	4.94 (4.73)
7-A	Needles (acetone)	186—188	$C_{17}H_{19}NO_2 \cdot C_6H_3N_3O_8$	53.70 (53.84)	4.31 (4.28)	10.89 (10.58)
7-N	Needles (acetone)	199—201	$C_{17}H_{19}NO_2 \cdot 1/2C_6H_3N_3O_8 \cdot 1/2H_2O$	59.92 (60.23)	5.41 (5.43)	8.74 (8.35)
9-A	Needles (acetone)	192—193	$C_{19}H_{23}NO_2 \cdot C_6H_3N_3O_8$	55.35 (55.30)	4.83 (5.01)	10.33 (10.04)
10-A	Cubes (acetone)	196—198	$C_{17}H_{19}NO_2 \cdot C_6H_3N_3O_8$	53.70 (53.72)	4.31 (4.29)	10.89 (10.60)
10-N	Plates (ether)	222—224 (dec.)	$C_{17}H_{19}NO_2 \cdot 1/2C_6H_3N_3O_8 \cdot 1/2H_2O$	59.92 (59.63)	5.41 (5.20)	8.74 (8.41)
11-N	Cubes (methanol)	217.5—219.5 (dec.)	$C_{16}H_{15}NO_2 \cdot 1/2C_6H_3N_3O_8 \cdot 1/4H_2O$	60.00 (59.95)	4.51 (4.50)	9.21 (8.93)
12	Needles (petr.ether)	58.5—60.5	$C_{16}H_{17}NO$	80.30 (80.03)	7.16 (7.20)	5.85 (5.54)
12-A[a]	Needles (ether)	202—209	$C_{16}H_{17}NO \cdot C_6H_3N_3O_8 \cdot H_2O$	52.59 (52.89)	4.41 (4.14)	11.15 (10.96)
12-N[a]	Prisms (acetone)	219—223	$C_{16}H_{17}NO \cdot 1/2C_6H_3N_3O_8$	63.06 (62.78)	5.15 (5.12)	9.67 (9.38)
17-A	Prisms (acetone)	223—226.5 (dec.)	$C_{18}H_{21}NO_2 \cdot C_6H_3N_3O_8$	54.54 (54.63)	4.85 (4.56)	10.60 (10.32)
31-A	Cubes (acetone)	215—218	$C_{19}H_{23}NO_2 \cdot C_6H_3N_3O_8$	55.35 (55.20)	4.83 (4.81)	10.33 (10.12)
32-A	Cubes (acetone)	174.5—177.5	$C_{18}H_{19}NO_2 \cdot C_6H_3N_3O_8$	54.75 (54.65)	4.21 (4.21)	10.64 (10.67)
33	Needles (methanol)	179—182	$C_{18}H_{19}NO_3$	72.70 (72.41)	6.44 (6.46)	4.71 (4.43)
36	Prisms (acetone)	199—201	$C_{18}H_{18}ClNO_2 \cdot HCl$	61.37 (61.46)	5.44 (5.35)	3.98 (3.99)
37	Needles (methanol)	101—103	$C_{18}H_{19}NO_3 \cdot 1/2H_2O$	70.57 (70.83)	6.58 (6.35)	4.57 (4.67)

a) **A** and **N** indicate the acidic and neutral styphnates of azocines, respectively.

the carbonyl group at 1720 cm^{-1} and for the double bond at 1610—1630 cm^{-1} (see Table VI). The pair of doublets at δ 7.70±0.07 and 7.30±0.08, having a coupling constant of 14 Hz, was due to the nitrovinyl protons. These NMR spectra indicate that these compounds are *trans* forms.

5,6,7,8-Tetrahydrodibenz[*c*,*e*]azocine Derivatives (2,5,7, and 10—12)

Reduction of the nitrovinyl compounds (**19a—f**) with LAH gave the 2-aminoethyl-2′-hydroxymethylbiphenyl derivatives (**30a—f**) in quantitative yield. Treatment of these amines (**30a—f**) with phosphorus tribromide and then heating the resulting bromides (**16a—f**) with ethanolic potassium hydroxide gave the 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine derivatives (**2**,**5**,**7**, and **10—12**) in 10—30% yield based on the nitrovinyl compounds, as shown in Table VII. The structures of these azocines were established by the physical and spectral data on them given in Table VIII and IX.

Table IX. Chemical Shifts[a] of the Free Bases of Dibenz[*c*,*e*]azocines (in $CDCl_3$, δ)

Compd.	Aromatic H					C-5 H_2[b]		OCH_2O	OCH_3					N–R
	C-1	C-4	C-9	C-10	C-12	Lower	Higher		C-2	C-3	C-10	C-11	C-12	
1			6.67		6.73	3.64	3.18	5.95						
2			6.68		6.74	3.88	3.17	5.95						1.49 (1H, s, NH)
3			6.70		6.76	3.58[c]	3.14[c]	5.96						2.46 (3H, s, NCH_3)
4			6.69		6.76	3.62	2.91	5.95						1.19 (3H, t, 7, $N-CH_2C\underline{H}_3$)[d]
5			6.74		6.82	3.95	3.22				3.93	3.88		2.00 (1H, s, NH)
6			6.73		6.80	3.63	3.16				3.95	3.90		2.49 (3H, s, NCH_3)
7			6.91	6.91		3.85	3.21					3.86	3.42	1.79 (1H, s, NH)
8			6.90	6.90		3.55[c]	3.13[c]					3.87	3.44	2.44 (3H, s, NCH_3)
9			6.92	6.92		3.62	2.95					3.86	3.45	1.19 (3H, t, 7, $NCH_2C\underline{H}_3$)[d]
10	6.82	6.85				3.88	3.13		3.91	3.96				1.69 (1H, s, NH)
11	6.76	6.80				3.81	3.07	5.96						1.96 (1H, s, NH)
12			7.10 (d,8)[d]	6.84 (q,8,3)[d]	6.80 (d,3)[d]	3.84	3.18					3.76		1.76 (1H, s, NH)
17	6.79	6.89				3.50	3.04		3.87	3.94				2.48 (3H, s, NCH_3)
31			6.74		6.81	3.69	2.99				3.92	3.87		1.24 (3H, t, 7, $NCH_2C\underline{H}_3$)
32	6.72	6.83				3.52	2.88	5.97[e] 5.93[e]						1.20 (3H, t, 7, $NCH_2C\underline{H}_3$)
33	6.78					5.06	3.10		3.86	3.92				8.35 and 8.10 (1H, each s, NCHO)
37			6.70		6.75	3.66	3.20	5.96						

a) Signals are for singlets except for those combined with parentheses and for those of C-5 H_2.
b) The signals of C-5 H_2 are for AB type doublets having a coupling constant of 14 Hz.
c) These AB type doublets have a coupling constant of 13 Hz.
d) The numerical values in parentheses are coupling constants as Hz values.
e) This signal is an AB type doublet (J=1.5 Hz).

An alternative synthesis of **5** was heating **30b** with hydrochloric acid, as in the synthesis[12] of the phenanthridon derivative from ismine. However, since the yield of compound

12) R.J. Highet, *J. Org. Chem.*, **26**, 4767 (1961).

5 was only 10.6%, based on **30b**, other amino-alcohols (**30a** and **30c—f**) were not treated by this procedure.

Of these azocines, the oily bases **7**, **10**, and **11** were characterized as their crystalline neutral or acidic or as both styphnates. From the work of Zingaro,[13] we found that the IR spectra of neutral styphnates differed from those of acidic ones in having no absorption bands at frequencies above 1600 cm^{-1}, while those of acidic styphnates had a well defined absorption band at 1630—1640 cm^{-1} (see Table X). On cyclization of **16a**, **16b**, **16e**, and **16f** to the

Table X. IR Spectra of the Acidic and Neutral Styphnates of Dibenz[*c*,*e*]azocines (ν_{max}^{KBr} cm^{-1})

Compd.	Acidic styphnate			Neutral styphnate		
3	1635 (vs)[a]	1585 (s)	1530 (s)			
5	1635 (vs)	1585 (vs)		1600 (vs)	1555 (s)	1510 (s)
7	1635 (vs)	1580 (vs)	1535 (vs)	1600 (sh)	1580 (vs)	1560 (sh)
9	1635 (vs)	1580 (vs)	1540 (s)			
10	1640 (vs)	1590 (vs)	1530 (vs)	1600 (vs)	1580 (vs)	1520 (vs)
11	1635 (vs)	1585 (vs)		1600 (vs)	1580 (s)	
12	1635 (vs)	1600 (s)	1535 (s)	1610 (s)	1580 (vs)	
17	1640 (vs)	1570 (s)	1530 (s)	1600 (sh)	1585 (vs)	1515 (s)
31	1635 (vs)	1580 (s)	1540 (s)			
32	1625 (vs)	1575 (vs)	1530 (s)			

a) The abbreviations used are as follows: vs, very strong; s, strong; sh, shoulder.

azocines (**2**, **5**, **11**, and **7**, respectively), N-ethylated azocines (**4**, **31**, **32**, and **9**, respectively) were obtained as by-products. These compounds were identified by elementary analyses of the free bases or their styphnates and by their NMR spectra. They seemed to be formed by ethylation of the azocines (**2**, **5**, **11**, and **7**) with ethyl bromide formed by the action of phosphorus tribromide on ethanol.

In the case of the cyclization of **16d** to **10**, an unexpected by-product, mp 179—182°, $C_{18}H_{19}NO_3$, was concluded to be N-formylated **10** (**33**)[14] from IR[ν_{max}^{KBr} 1660 cm^{-1} (C=O of amide)] and NMR [δ 8.35 and 8.10 (3/13 and 10/13 H, respectively, each s, *cis-trans* forms of N–CH=O)][15] spectral data (see Table IX).

To confirm this conclusion, **33** was reduced with LAH and the resulting product (**17**) was characterized as its acidic styphnate. Direct comparison showed that the styphnate was identical with that of an authentic sample of **17** prepared by Eschweiler–Clarke methylation of **10**.

An alternative synthesis of **30e** was also used since it was somewhat troublesome to prepare **28a** from piperonal: namely treatment of methyl 2′-bromomethyl-4,5-methylenedioxy-2-biphenylcarboxylate (**34**) with potassium cyanide in dimethyl sulfoxide (DMSO) and reduction of the resulting nitrile (**35**) with LAH afforded **30e** in 22.9% yield (from **34**).

N-Substituted Derivatives of Azocines

The N-methylated azocines **6**, **8**, and **17** were prepared by Eschweiler–Clarke methylation of **5**, **7**, and **10**, respectively. Compound **3** was obtained by treatment of **2** with formalin and sodium borohydride.

N-Ethylated azocines (**4**, **9**, **31**, and **32**) were obtained as by-products during cyclization of the corresponding bromo-amines, as described above.

13) R.A. Zingaro, *J. Am. Chem. Soc.*, **76**, 816 (1954).
14) The mechanism of formation of **33** in unknown.
15) M.T. Rogers and L.A. LaPlanche, *J. Phys. Chem.*, **69**, 3648 (1965).

The N-(β-halogenoethyl)-azocines **1** and **36** were prepared as follows: treatment of **2** with ethylene chlorohydrin in the presence of triethylamine gave the amino-ethanol (**37**), which was brominated with phosphorus tribromide to give the β-bromoethyl compound (**1**).[3] Treatment of the hydrochloride of **37** with thionyl chloride gave the hydrochloride of **36**.

NMR Spectra of 5,6,7,8-Tetrahydrodibenz[*c*,*e*]azocines

In the NMR spectra of the seventeen derivatives of dibenz[*c*,*e*]azocines prepared in this study, the diastereotopic hydrogens at C-5 appeared as AB type doublets[3] having a geminal coupling constant of *ca.* 14 Hz. The assignments of aromatic benzylic methylene (C-5), and methoxyl protons in the azocines, **2**,**5**,**6**,**10**, and **17** were verified by NMDR studies; on the basis of these data the corresponding signals in other azocines were assigned as shown in Table IX.

The signals (δ 3.88±0.07) of C-5-H (lower) in secondary amines, **2**,**5**,**7**,**10**,**11**, and **12** are *ca.* 0.73 ppm further downfield than those (δ 3.15±0.07) of C-5-H (higher). This means that the azocine ring exists predominantly in one conformation at room temperature, and that inversion of the system by partial rotation of the skewed biphenyl is hindered,[16] and that the C-5-H (lower) is deshielded by the ring A, while the C-5-H (higher) is placed in a position to be shielded by the ring B.

This conclusion is supported by the fact that the signals of the methylenedioxy protons in **32** appeared at δ 5.96 and 5.94 as a pair of AB type doublets having a coupling constant of 1.5 Hz. These results can be explained with molecular models, assuming that these azocines adopt a distorted half-tub conformation as reported by Jeffs, *et al.*[16]

The signals of C-12-OCH_3 in **7**, **8**, and **9** are 0.4—0.5 ppm further upfield than those of C-11-OCH_3 in these compounds and than those of C-10- or C-11-OCH_3 in other azocines having methoxyl groups, because of shielding by the ring A.

The chemical shifts of the methylene protons at C-5 in **11** are 0.07—0.1 ppm further upfield than those of the same protons in **2**. This is due to the diamagnetic effect of the methylenedioxy group in ring A, as reported previously.[9] A similar effect explains why the signals of the methylene protons at C-5 in **10**, **17**, and **32** are at higher field than those of the same protons in **5**, **6**, and **4**, respectively.

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi EPI-G2 model for IR spectra, a Hitachi RMU-6E model for mass spectra, and a JEOL JNM-PS-100 or a Hitachi R-22 model for NMR spectra with TMS as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Methyl 4′,5′-Dimethoxy-2′-formyl-2-biphenylcarboxylate (18b)——A mixture of **21** (18.5 g), **23** (11 g), and copper powder (13 g) was heated in a sealed tube at 205° for 4 hr. The reaction mixture was extracted with $CHCl_3$ and the solvent was evaporated off. The residue gave 2.08 g (28.1%, mp 189—208°) of ether-insoluble material and 5.97 g (mp 87—95°) of ether-soluble material; **38b**,[17] mp 207—210.5°, was obtained by recrystallization of the ether-insoluble material from $CHCl_3$. The ether-soluble material was applied to an Al_2O_3 column (60 g). Elution with petr. ether and evaporation of the solvent gave **39a** (1.91 g, 20.0%) as white plates, mp 71—72° (from ether). Further elution with benzene and evaporation of the benzene afforded 1.59 g (11.8%, from **23**) of **18b** as cubes, mp 120.5—121.5° (from ether) (see Tables I, II, and III). Compounds **18a**,**c**—**f** were prepared similarly, as shown in Table I.

Methyl 5′,6′-Dimethoxy-2′-(2-nitrovinyl)-2-biphenylcarboxylate (19f)——Procedure (i): A mixture of Na_2CO_3 (5.5 mg), CH_3NH_2–HCl (4.5 mg), and MeOH (1.5 ml) was filtered and the filtrate was added to a solution of **18f** (50 mg) and CH_3NO_2 (0.15 ml) in benzene (0.5 ml) and MeOH (1 ml). The reaction mixture was allowed to stand at room temperature for 60.5 hr. Then the solvent was evaporated off and the residue was triturated with MeOH to give **19f** (34.5 mg, 60.3%) as yellow needles, mp 127—128.5° (from MeOH).

16) P.W. Jeffs, J.F. Hansen, and G.A. Brine, *J. Org. Chem.*, **40**, 2883, (1975).
17) S. Kobayashi, F. Senoo, M. Kihara, K. Sakata, and M. Miura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1262 (1971).

Procedure (ii): A mixture of **18f** (561 mg) and $AcONH_4$ (1.206 g), AcOH (18 ml), and CH_3NO_2 (2 ml) was heated in a sealed tube at 98° for 4 hr. The reaction mixture was extracted with benzene–MeOH and the solvent was evaporated off from the extract. The residue was extracted with benzene. The extract was washed with 2% NH_4OH and then H_2O, dried, and evaporated to give **19f** (374 mg, 58.4%), mp 125—127°.

Procedure (iii): A mixture of **18f** (199 mg) and *n*-butylamine (0.96 ml) was heated in a sealed tube at 130° for 80 min. The reaction mixture was extracted with benzene and the extract was evaporated to give an oil (240 mg). A mixture of the oil (240 mg), CH_3NO_2 (1.76 ml), and AcOH (0.17 ml) was allowed to stand at room temperature for 19 hr. Then the mixture was concentrated *in vacuo*, and the residue was triturated with MeOH–petr.ether to give yellow needles of **19f** (76 mg, 33.3%), mp 127—128.5° (from MeOH) (see Tables IV, V, and VI).

On direct comparison the products obtained by procedures (ii) and (iii) were identical with a sample of **19f** prepared by procedure (i).

The nitrovinyl compounds **18a—e** were prepared similarly, as shown in Table IV.

10,11-Methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**2**)——A solution of **19a** (500 mg) in dry ether (500 ml) was added dropwise to a suspension of $LiAlH_4$ (5 g) in dry ether (30 ml) with stirring for 20 min. The mixture was refluxed for 5 hr. Excess $LiAlH_4$ was decomposed with ether (100 ml) and H_2O (50 ml), and the ethereal solution was extracted with 10% HCl (120 ml). The aqueous extract was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to give **30a** (370 mg) as an oil. A mixture of **30a** (370 mg), PBr_3 (4 ml), and benzene (20 ml) was stirred at room temperature overnight and then heated at 45° for 1 hr. The solution was mixed with EtOH (200 ml) and then 50% KOH (60 ml) and refluxed for 2 hr. The solvent was evaporated off *in vacuo*, and the residue was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated to a pale brown oil. The oil was triturated with ether to give white cubes of **2** (102 mg), mp 98.5—100° (from ether) (see Tables VIII and IX). Mass spectrum *m/e*: 253 (M^+).

The ethereal solution (110 mg) separated from **2** was submitted to preparative thin-layer chromatography (TLC) using Al_2O_3 [benzene–acetone (4: 1)]. Elution of the material of *Rf* 0—0.54 with $CHCl_3$ gave an additional crop of **2** (23 mg, total 125 mg, 32.3%). Elution of the material of *Rf* 0.72—1.0 with $CHCl_3$ gave an oil (23 mg, 5.3%), which was triturated with ether to give white needles of **4**, mp 78.5—81.5° (from ether). Mass spectrum *m/e*: 281 (M^+).

The azocines, **5**, **7**, **10**, **11**, and **12** were prepared similarly, as shown in Table VII.

Generally, the neutral styphnate of an azocine was obtained by addition of an equivalent amount of styphnic acid in ether to a solution of the azocine in ether, whereas the acidic styphnate of an azocine was prepared by treating a solution of neutral styphnate in acetone with excess styphnic acid.

Alternative Synthesis of 5——An alternative synthesis of **5** was as follows: **30b** (89 mg) was heated with 6N-HCl (5 ml) at 95° for 30 min; the solution was worked up in the usual way, and the crude neutral styphnate of **5** obtained was recrystallized from MeOH to give 31 mg (10.6% based on **30b**) of yellow needles, mp 193—197°.

Isolation of the By-product (**33**)——The nitrovinyl compound (**19d**) (900 mg) was treated as shown in Table VII in the same manner as for **2**. The crude azocine (301 mg) thus obtained was dissolved in ether, and the solution was extracted with 8% HCl. The extract gave 176 mg of the neutral styphnate of **10**, mp 222—224° (dec.). The ether layer separated from the 8% HCl layer gave the neutral by-product (43 mg, mp 174—178°), which was recrystallized from MeOH to afford **33** as white needles, mp 179—182°.

6-Methyl-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**3**)——A solution of **2** (28 mg) in MeOH (1.5 ml) was added to a solution of boric acid (30 mg) and formalin (0.3 ml) in MeOH (1 ml) and stirred at room temperature for 5 min. Then $NaBH_4$ (86 mg) was gradually added to the mixture with stirring for 30 min. The solution was mixed with AcOH (0.3 ml) and H_2O (10 ml) and worked up in the usual way to give a colorless oil (29 mg) which was converted to the acidic styphnate (31 mg, 54.8%) of **3**, mp 216.5—217.5° (dec.) (from acetone) (see Tables VIII, IX, and X). NMR (DMSO-d_6) δ: 8.64 (1H, s, aromatic H of styphnic acid). 7.80 (1H, m, C-1-H), 7.07 (1H, s, C-12-H), 6.89 (1H, s, C-9-H), 6.09 and 6.05 (each 1H, d, J=2 Hz, AB type of OCH_2O), 4.30 and 3.72 (each 1H, d, J=13 Hz, AB type of C-5 H_2), 2.96 (3H, d, N-CH_3).

10,11-Dimethoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**6**)——A mixture of **5** (40 mg), HCOOH (0.15 ml), and formalin (0.15 ml) was heated in a sealed tube at 100° for 15 hr. The crude product (25 mg) obtained by working up in the usual way was recrystallized from petr. ether to give white needles of **6** (15 mg, 35.6%), mp 72—73°.

2,3-Dimethoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (**17**)——(i) From **10**: A mixture of **10** (35 mg), formalin (0.89 ml), HCOOH (1.14 ml), and H_2O (0.36 ml) was heated in a sealed tube at 140° for 5 hr. The mixture was worked up in the usual way to give the neutral styphnate (37 mg) of **17** (mp 194—197°), which was converted to its acidic styphnate [mp 223—226.5° (dec.)].

(ii) From **33**: The crude product (**17**), prepared by treatment of **33** (27 mg) in dry tetrahydrofuran (THF) (9 ml) with $LiAlH_4$ (500 mg) in the usual way, was characterized as its acidic styphnate (18.3 mg, 38%), mp 220—224° (dec.). The acidic styphnate of **17** obtained by method (ii) was identical with the sample prepared from **10** by method (i).

11,12-Dimethoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (8)——A mixture of **7** (7 mg), HCOOH (0.15 ml), and formalin (0.15 ml) was heated in a sealed tube at 100° for 7.5 hr. Working up in the usual was gave 4 mg of **8** as a colorless oil (see Table IX), which was crystallized as its picrate (3 mg), mp 175—177°. NMR ($CDCl_3$) δ: 8.90 (2H, s, aromatic H of picric acid), 7.03 (2H, s, C-9-H and C-10-H), 3.91 (3H, s, C-11-OCH_3).

6-(β-Hydroxyethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (37)——A mixture of **2** (76 mg), ethylene chlorohydrin (65 mg), and Et_3N (101 mg) was heated at 65° for 2 hr. Then ethylene chlorohydrin (67 mg) and Et_3N (200 mg) was added and the mixture was heated at 70° for 9.5 hr. The crude product (**37**) obtained by work-up in the usual way was recrystallized from MeOH to give white needles (49 mg, 55.1%), mp 101—103° (see Tables VIII and IX).

6-(β-Bromoethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (1)——A mixture of **37** (32 mg), PBr_3 (0.3 ml), and dry benzene (2 ml) was allowed to stand at room temperature overnight and then heated at 50° for 1.5 hr. The solvent was evaporated off, the residue was dissolved in H_2O, made alkaline with 50% NaOH, and extracted with ether. The extract was washed with H_2O, dried, and concentrated to give **1** (21 mg, 53.8%) as white needles, mp 227—230°.

6-(β-Chloroethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (36)——A mixture of the hydrochloride [derived from **37** (27 mg) and conc. HCl (2 drops)], $CHCl_3$ (3 ml), and $SOCl_2$ (0.2 ml) was refluxed for 2.5 hr. Evaporation of the solvent gave the hydrochloride of **36** (15 mg, 46.9%), mp 199—201° (from acetone).

2′-(2-Aminoethyl)-2-hydroxymethyl-4,5-methylenedioxybiphenyl (30e)——An alternative synthesis of **30e** was as follows: a mixture of **34** (2.4 g),[12] KCN (456 mg), and DMSO (46 ml) was stirred at room temperature for 23 min, and then made acidic with conc. HCl. The reaction mixture was extracted with ether, and the extract was washed with H_2O, dried, and evaporated. The residue gave white prisms of **35** (921 mg, 45.4%), mp 111—113° (from ether). *Anal.* Calcd. for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.85; H, 4.57; N, 4.50. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN), 1720 ($COOCH_3$). NMR ($CDCl_3$) δ: 6.65 (1H, s, C-3-H), 6.10 (2H, s, OCH_2O), 3.62 (3H, s, $COOCH_3$), 3.50 (2H, s, CH_2CN).

A mixture of $AlCl_3$ (177 mg) and dry ether (15 ml) was added to a suspension of $LiAlH_4$ (53 mg) in dry ether (5 ml). The mixture was stirred at room temperature for 10 min and then a solution of **35** (160 mg) in dry ether (12 ml) was added drop-wise and the mixture was stirred at room temperature for 1 hr. Excess $LiAlH_4$ was decomposed with H_2O and 6.3% H_2SO_4 (15 ml), and the mixture was worked up in the usual way to give white prisms of **30e** (74.5 mg, 50.4%), mp 123—125° (from ether). This compound was identified by the following spectral data. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 3300 (NH_2). NMR ($CDCl_3$) δ: 7.00 (1H, s, C-3-H), 6.54 (1H, s, C-6-H), 5.98 (2H, s, OCH_2O), 4.34 and 5.83 (each 1H, d, J=12 Hz, AB type of CH_2OH), 3.20—2.52 (4H, m, $C\underline{H}_2C\underline{H}_2N$), 2.28 (3H, s, $N\underline{H}_2$ and $O\underline{H}$).

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