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Heterocycles. XI.[1] Synthesis of 2-Amino-6-phenyl-3,4-dihydro-1,5-benzodiazocines[2]

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2-Amino-6-phenyl-3,4-dihydro-1,5-benzodiazocine derivatives (**4**) were synthesized by cyclization of 3-(2-amino-α-phenylbenzylideneamino)propionitriles (**3**). The reactivity of the diazocine (**4a**) was different from that of the structurally similar diazepine (**6**). Reaction of **4a** with methylamine hydrochloride or with methanolic hydrogen chloride did not give the diazocine (**9** or **11**) but afforded the aminoethylquinazoline (**10**). The ultraviolet spectra indicated that the conjugation systems of **4a** and **6** are different. Deuterium exchange reactions of **4a** and **6** confirmed the presence of the equilibria **4a**⇌**4'a** and **6**⇌**6'**.

Keywords——1,5-benzodiazocines; 1,4-benzodiazepines; amidine; quinazoline; acid-catalyzed cyclization; deuterium exchange experiment

In connection with 1,4-benzodiazepine chemistry, considerable attention has been directed toward eight-membered ring systems such as 1,4,5-benzotriazocine[1,4] and 1,5-benzodiazocine.[5] This paper deals with a facile synthesis of new 2-amino-3,4-dihydro-1,5-benzodiazocine derivatives (**4**),[6,7] and reports their chemical and pharmacological properties.

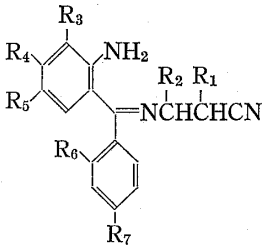
Synthesis of **4** was achieved by an extension of the method which we developed for the synthesis of 2-amino-1,4-benzodiazepines (**6**)[8] (Chart 1). 3-(2-Amino-α-phenylbenzylideneamino)propionitriles (**3**) were prepared by an exchange reaction of the 2-aminobenzophenone Schiff bases (**1**) with the 3-aminopropionitriles (**2**) in the presence of acetic acid (Table I). Some of the geometrical isomers of **3** (*i.e.*, **3h** and **3h'**; **3l** and **3l'**; **3n** and **3n'**) could easily be separated. Cyclization of **3** to **4**, however, was performed using the crude isomeric mixture since the *syn*- and *anti*-isomers[9] of **3** were both expected to cyclize to **4**, as in the case of the cyclization of the benzylideneaminoacetonitriles (**5**) to **6**.[8] Assignment of the stereochemistry of the separated isomers of **3** was based on the nuclear magnetic resonance (NMR) spectrum ($CDCl_3$), in which the NH_2 protons of the *anti*-isomers appeared at lower magnetic fields (δ=*ca.* 6.4—6.8) than those of the *syn*-isomers (δ=*ca.* 3.6) owing to intramolecular hydrogen bonding.[8]

1) Part X: H. Natsugari, K. Meguro, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **27**, 2084 (1979).
2) A part of this work was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
4) K. Meguro and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2375 (1973).
5) *a*) M.E. Derieg, R.M. Schweininger, and R.I. Fryer, *J. Org. Chem.*, **34**, 179 (1969); *b*) M. Denzer and H. Ott, *ibid.*, **34**, 183 (1969); *c*) M. Steinmann and J.G. Topliss, *J. Pharm. Sci.*, **58**, 830 (1969); *d*) H. Liepmann, W. Milkowski, and H. Zeugner, *Eur. J. Med. Chem., Chimica Therapeutics*, **11**, 501 (1976); *e*) E. Finner, F. Rosskopf, and W. Milkowski, *ibid.*, **11**, 512 (1976); *f*) D.D.S.A. Pharmaceutical Ltd., Japan Patent Application, 69041 (1975), 71239 (1976).
6) H. Natsugari, K. Meguro, and Y. Kuwada, Japan Patent Application, 77313 (1970).
7) An independent synthesis of the $N_{(1)}$–CH_3 analog of **4** was reported in a patent (Cassela Farbwerke Mainkur AG. DT-2024472 (1970)).
8) K. Meguro, H. Tawada, and Y. Kuwada, *Yakugaku Zasshi*, **93**, 1253 (1973).
9) With respect to the amino-substituted phenyl group (see ref. 8).

Reaction of **3** with dry hydrogen chloride in methanol afforded 2-amino-6-phenyl-3,4-dihydro-1,5-benzodiazocines (**4**)[10] (Chart 1, Table II). Compounds **4** did not show an infrared (IR) absorption band due to a nitrile group. The NMR spectrum ($CDCl_3$) of **4a** showed two multiplets at 2.6—2.8 ppm and 3.3—3.9 ppm due to the $-C_{(3)}H_2-C_{(4)}H_2-$ group, while the ethylene protons of **3a** appeared at 2.62 and 3.46 ppm as two triplets.

The amidine moiety of **4** was expected to have reactivity similar to that of **6**, which afforded the 2-(substituted)amino-1,4-benzodiazepines (**7**) by reaction with amines in the presence of an acid catalyst[11] and the 1,4-benzodiazepin-2-one (**8**) by acid hydrolysis (or

TABLE I. 2-(2-Amino-α-phenylbenzylideneamino)propionitriles (**3**)



Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Recrystn.[a] solvent	mp[b] (°C)	Yield[c] (%)	Formula[d]
3a	H	H	H	H	Cl	H	H	B-H	130—135	95	$C_{16}H_{14}ClN_3$
3b	H	H	H	H	H	H	H	B-H	96—105	91	$C_{16}H_{15}N_3$
3c	H	H	H	H	CH_3	H	H	B-H	111—113	79	$C_{17}H_{17}N_3$
3d	H	H	H	H	CF_3	H	H	E-H	125—127	76[e]	$C_{17}H_{14}F_3N_3$
3e	H	H	H	H	NO_2	H	H	B	(154—155)[f] 172	95	$C_{16}H_{14}N_4O_2$
3f	H	H	H	H	CH_3O	H	H	—	oil[g]	—	—
3g	H	H	H	H	Cl	H	Cl	B-H	134—135	84	$C_{16}H_{13}Cl_2N_3$
3h[h]	H	H	H	H	Cl	H	CH_3O	B-H	149—150	42	$C_{17}H_{16}ClN_3O$
3h'[i]	H	H	H	H	Cl	H	CH_3O	E	99—101	35	$C_{17}H_{16}ClN_3O$
3i	H	H	H	CH_3O	CH_3O	H	H	A-H	144—146	52[e]	$C_{18}H_{19}N_3O_2$
3j	H	H	CH_3O	H	Cl	H	H	E	158—159	82	$C_{17}H_{16}ClN_3O$
3k	CH_3	H	H	H	Cl	H	H	A-H	138—140	89	$C_{17}H_{16}ClN_3$
3l[h]	H	CH_3	H	H	Cl	H	H	M-D	193—195	53	$C_{17}H_{16}ClN_3$
3l'[i]	H	CH_3	H	H	Cl	H	H	A-H	135—138	35	$C_{17}H_{16}ClN_3$
3m	H	CH_3	H	H	Cl	H	Cl	A-H	159—160	28	$C_{17}H_{15}Cl_2N_3$
3n[h]	CH_3	H	H	H	Cl	H	Cl	A-H	149—150	34	$C_{17}H_{15}Cl_2N_3$
3n'[i]	CH_3	H	H	H	Cl	H	Cl	E-H	113—114	33	$C_{17}H_{15}Cl_2N_3$
3o	H	CH_3	H	CH_3O	CH_3O	H	H	—	oil[g]	—	—
3p	CH_3	H	H	CH_3O	CH_3O	H	H	—	oil[g]	—	—
3q	H	CH_3	H	H	CH_3	H	H	A-H	150—151	38[e]	$C_{18}H_{19}N_3$
3r	CH_3	H	H	H	CH_3	H	H	A-H	110—111	84[e]	$C_{18}H_{19}N_3$
3s[j]	CH_3	H	H	H	Cl	Cl	H	A-H	120—121	71	$C_{17}H_{15}Cl_2N_3$

a) B, benzene; H, hexane; E, diethyl ether; A, acetone; M, methanol; D, dichloromethane.
b) Analytical samples; uncorrected.
c) Calculated for crude material including isomeric mixtures.
d) Satisfactory elementary analyses (±0.4% for C, H, N) were obtained for crystalline compounds listed herein.
e) Based on the corresponding 2-aminobenzophenone.
f) Sinter.
g) Used in the subsequent reaction without purification.
h) *Anti*-form (see "Experimental").
i) *Syn*-form (see "Experimental").
j) The exchange reaction was carried out in ethanol for 82 hr.

10) The 2-amino structure is taken in this paper to include possible tautomerism between 2-amino and 2-imino forms with respect to the amidine moiety.
11) *a*) K. Meguro, H. Natsugari, H. Tawada, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2366 (1973); *b*) K. Meguro and Y. Kuwada, *ibid.*, **21**, 2375 (1973).

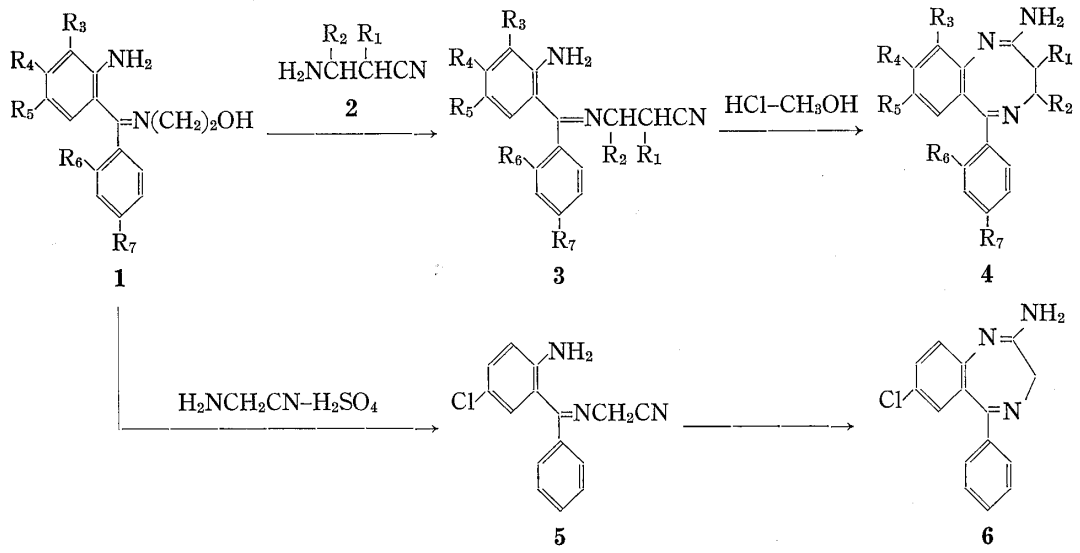
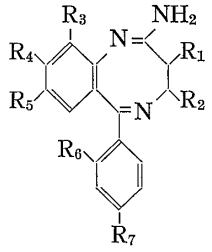


Chart 1

TABLE II. 2-Amino-3,4-dihydro-6-phenyl-1,5-benzodiazocines (4)



Compd.[a] No.	Recrystn.[b] solvent	mp[c] (°C)	Yield[d] (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4a	A	218—220	85	$C_{16}H_{14}ClN_3$	67.72	4.97	14.81	67.52	4.92	15.19
4b	A	186—187	60	$C_{16}H_{15}N_3$	77.08	6.06	16.86	77.23	5.94	17.06
4c	D-H	185—186	70	$C_{17}H_{17}N_3$	77.53	6.51	15.96	77.34	6.32	15.65
4d	B	213—214	74	$C_{17}H_{14}F_3N_3$	64.35	4.45	13.24	64.72	4.72	13.09
4e	C-B	242—244	46	$C_{16}H_{14}N_4O_2$	65.29	4.80	19.04	64.99	4.76	19.00
4f	M-C	225—228	47[e]	$C_{17}H_{17}N_3O$	73.09	6.14	15.04	72.69	6.11	14.73
4g	B	181—183	38	$C_{16}H_{13}Cl_2N_3$	60.39	4.12	13.21	60.71	3.90	13.11
4h	M	254—255	60[f]	$C_{17}H_{16}ClN_3O$	65.07	5.14	13.39	64.84	4.91	13.12
4i	M	252—254	77	$C_{18}H_{19}N_3O_2$	69.88	6.19	13.58	70.05	6.11	13.34
4j	M	216—217	74	$C_{17}H_{16}ClN_3O$	65.07	5.14	13.39	64.91	5.20	13.37
4k	A-H	218—220	80	$C_{17}H_{16}ClN_3$	68.56	5.41	14.11	68.69	5.33	14.02
4l	A-H	182—184	66[f]	$C_{17}H_{16}ClN_3$	68.56	5.41	14.11	68.53	5.39	14.09
4m	A-H	213—215	25	$C_{17}H_{15}Cl_2N_3$	61.45	4.55	12.65	61.59	4.63	12.68
4n	A-H	215—217	82[f]	$C_{17}H_{15}Cl_2N_3$	61.45	4.55	12.65	61.61	4.48	12.64
4o	A	217—219	32[e]	$C_{19}H_{21}N_3O_2$	70.56	6.55	12.99	70.54	6.50	12.84
4p	M	239—240	53[e]	$C_{19}H_{21}N_3O_2$	70.56	6.55	12.99	70.46	6.71	12.90
4q	A-H	179—181	40	$C_{18}H_{19}N_3$	77.94	6.91	15.15	78.00	6.78	14.85
4r	A	215—217	69	$C_{18}H_{19}N_3$	77.94	6.91	15.15	78.06	6.62	15.37
4s	A	265—267	29	$C_{17}H_{15}Cl_2N_3$	61.45	4.55	12.65	61.52	4.41	12.53

a) For the substituents (R_1—R_7), see Table I.
b) A, acetone; B, benzene; D, dichloromethane; H, hexane; C, chloroform; M, methanol.
c) Uncorrected.
d) A crude isomeric mixture of **3** was used for the cyclization.
e) Based on the corresponding 2-amino benzophenone.
f) A mixture of *syn* and *anti* (1:1) isomers was used for this cyclization.

methanolysis).[8] However, reaction of **4a** with methylamine hydrochloride or with methanolic hydrogen chloride did not give the diazocine (**9** or **11**) but afforded the 2-(2-aminoethyl)quinazoline (**10**). The formation of **10** can be explained in terms of the intermediate formation of **12** through easy cleavage of the azomethine bond ($N_{(5)}=C_{(6)}$) of **4a** followed by re-cyclization to the six-membered ring.[12]

On the other hand, reduction of **4a** with sodium borohydride in methanol at room temperature afforded the 3,4,5,6-tetrahydro-1,5-benzodiazocine (**13**), while the azomethine bond ($N_{(4)}=C_{(5)}$) of **6** was not reduced under the same conditions[13] (Chart 2).

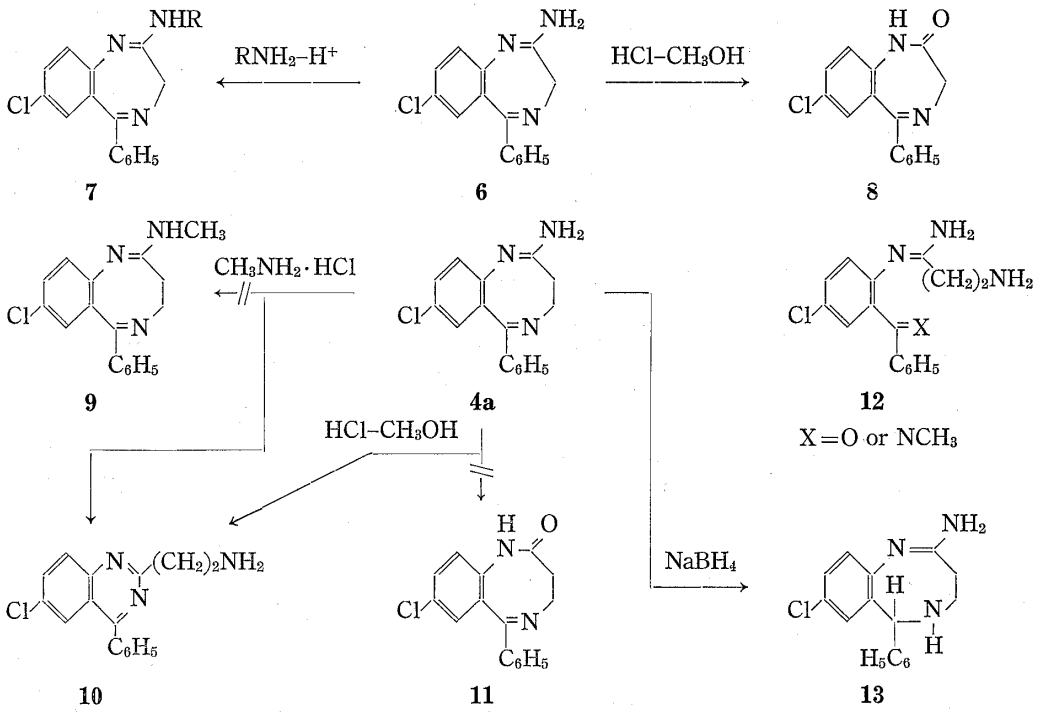


Chart 2

These marked differences of reactivity between **4a** and **6** may be due to different susceptibilities of their azomethine moieties to nucleophilic attack.

Inspection of molecular models of **4a** and **6** revealed that the diazocine ring is more distorted than the diazepine ring, suggesting that the azomethine bond of **4a** could not be conjugated with the fused benzene ring, while such conjugation might be present in **6**. In fact, the ultraviolet (UV) spectrum (EtOH) of **4a** showed an absorption maximum at 248 nm (ε 16400), while that of **6** showed absorption maxima at 228 nm (ε 22300) and 338 nm (ε 2650). The longer wave-length absorption (338 nm) of **6** may be attributed to conjugation of the azomethine bond with the fused benzene ring.[14] The higher stability of the azomethine bond of **6** may be explained in terms of this conjugation effect.

Moreover, the azomethine bond of **6** may be more stabilized by the contribution of a possible equilibrium **6**⇌**6′**[15] in which another conjugation is introduced. The presence of

12) Another mechanism including nucleophilic $C_{(6)}$-attack by the 2-amino group prior to cleavage of the azomethine bond cannot be ruled out.

13) Treatment of **6** with lithium aluminum hydride affords the 4,5-dihydro compound (see ref. 11*a*).

14) A similar suggestion has been made for the *syn*- and *anti*-isomers of 2-amino-5-chlorobenzophenone Schiff bases; S.C. Bell, G.L. Conklin, and S.J. Childress, *J. Org. Chem.*, **29**, 2368 (1964).

15) 1*H*-Forms of 1,4-benzodiazepines such as **6′** are known in the literature; *a*) R.I. Fryer, J.V. Earley, and L.H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967); *b*) D.L. Coffen, J.P. DeNoble, E.L. Evance, G.F. Field, R.I. Fryer, D.A. Katonak, B.J. Mandel, L.H. Sternbach, and W.J. Zally, *ibid.*, **39**, 167 (1974); *c*) R.I. Fryer, D.L. Coffen, J.V. Earley, and A. Walser, *J. Heterocyclic Chem.*, **10**, 473 (1973); *d*) R.I. Fryer, J.V. Earley and J.F. Blount, *J. Org. Chem.*, **42**, 2212 (1977).

6′ during acid solvolysis was confirmed by deuterium exchange reactions. When **6** was heated in methanol-d_4 (CD_3OD) in the presence of deuterium chloride (DCl), the 1,4-benzodiazepin-2-one-d_2 (**14**) with a deuterium content of 87% was obtained. Treatment of **8** under the same conditions afforded **14** with a lower deuterium content (50%). These results indicate that deuterium exchange in the former reaction took place mainly prior to solvolysis of the amino group of **6**, plausibly *via* **6′**. For comparison, **4a** was treated with DCl in CD_3OD, and quinazoline-d_2 (**16**) with a rather low deuterium content (50%) only at the α-methylene position of the aminoethyl residue was obtained. This result suggests the possibility of a contribution of the tautomeric form **4′a**. However, the tautomerism might have little effect in increasing the stability of the azomethine bond of **4a**, since new conjugation is not introduced in the diazocine ring.

The equilibria **6**⇌**6′** and **4a**⇌**4′a** were also found in an alkaline medium. On treatment with sodium deuteroxide (NaOD) in CD_3OD, **6** and **4a** gave the dideuterio compounds **15** and **17**, respectively (Chart 3).

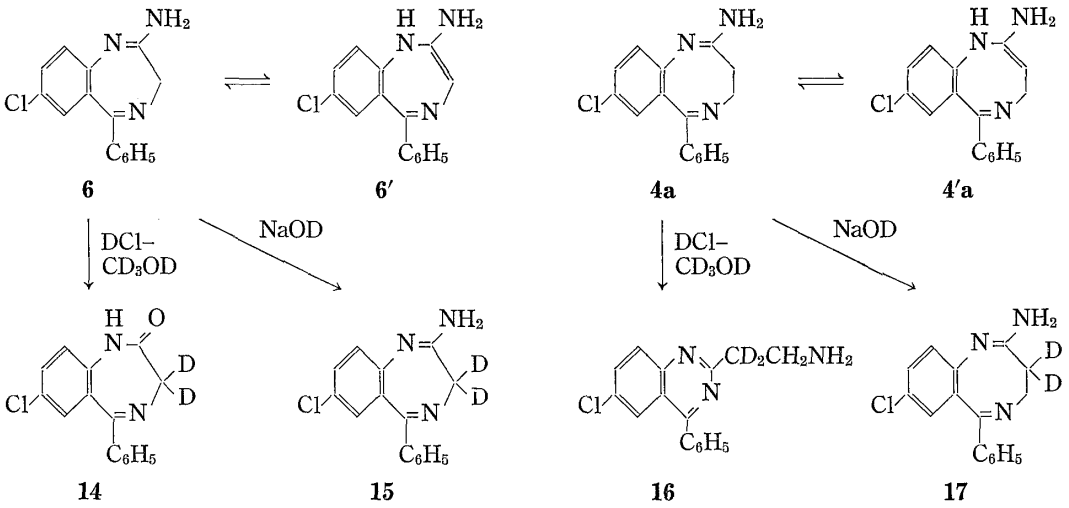


Chart 3

On preliminary screening tests,[16] these benzodiazocines (**4**) exhibited diuretic, analgesic and anti-inflammatory activities, and some (*e.g.* **4k**, **4l**) showed stimulative activity on the central nervous system, rather than sedative activity which is a typical feature of benzodiazepines (**6**).

Experimental[17]

3-(2-Amino-5-chloro-α-phenylbenzylideneamino)propionitrile (**3a**)——A mixture of 27.4 g (0.1 mol) of 2-(2-amino-5-chloro-α-phenylbenzylideneamino)ethanol,[8] 21.0 g (0.3 mol) of 3-aminopropionitrile, 18 ml (0.3 mol) of AcOH and 500 ml of MeOH was refluxed for 1 hr. After removal of the solvent, the residue was dissolved in $CHCl_3$, washed with H_2O and dried (Na_2SO_4). Removal of the solvent followed by treatment with hexane gave pale yellow crystals (27.0 g, 95%), mp 102 (sinter)—125° (melt). This crude material, which was presumed to be a mixture of *syn*- and *anti*-isomers, was used in the subsequent cyclization. A

16) Biological activity was examined in this Division.

17) All melting points were determined with a Yanagimoto micro melting point apparatus (a hot-stage type) and are uncorrected. IR spectra were measured on a Hitachi 215 spectrophotometer, NMR spectra on a Varian T-60 (60 MHz), a Varian A-60 (60 MHz) or a Varian HA-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard, UV spectra on a Perkin Elmer 450 spectrophotometer, and mass spectra (MS) on a Hitachi RMS-4 single-focussing mass spectrometer with a direct sample inlet system. The following abbreviations are used; s=singlet, t=triplet, dd=doublet of doublets, m=multiplet and b=broad. Removal of solvents was performed on a rotary evaporator under water aspirator pressure.

part of this crude material was recrystallized from benzene–hexane to give colorless flakes, mp 130—135°. NMR ($CDCl_3$) δ: 2.62 (2H, t, J=6 Hz, $-CH_2-$), 3.46 (2H, t, J=6 Hz, $-CH_2-$), 6.58—7.55 (10H, m, arom. H and $-NH_2$). IR ν_{max}^{KBr} cm^{-1}: 3450, 3255 ($-NH_2$), 2240 (CN), 1655 (weak, >C=N–).

Other 3-(2-amino-α-phenylbenzylideneamino)propionitriles (**3b**—**3s**, Table I) were similarly prepared from the corresponding **1** and **2**.

In the case of **3h**–**3h′**, **3l**–**3l′** and **3n**–**3n′**, the crude material was separated into the isomers by fractional recrystallization. In the NMR spectrum ($CDCl_3$), the NH_2 protons appeared as follows (δ); **3h** (*anti*), *ca.* 6.4; **3h′** (*syn*), *ca.* 3.6; **3l′** (*syn*), *ca.* 3.6; **3n** (*anti*), *ca.* 6.8; **3n′** (*syn*), *ca.* 3.6. NMR measurement of **3l** in $CDCl_3$ was not possible due to its insolubility.

2-Amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine (4a)——A stirred and ice-cooled suspension of 70 g of **3a** in 420 ml of MeOH was treated with dry hydrogen chloride (*ca.* 60 g) until the mixture became clear. The mixture was allowed to stand at room temperature for 3.5 hr, concentrated to *ca.* half the original volume and poured into conc. NH_4OH–H_2O (200—800 ml) with ice cooling. The precipitate was collected by filtration and washed successively with H_2O, acetone and ether to give colorless crystals (60 g, 85%). Recrystallization from acetone afforded colorless needles, mp 218—220°. NMR ($CDCl_3$) δ: 2.6—2.8 (2H, m, $-C_{(3)}H_2-$), 3.3—3.9 (2H, m, $-C_{(4)}H_2-$), 4.66 (2H, b, $-NH_2$), 6.8—7.7 (8H, m, arom. H). IR ν_{max}^{KBr} cm^{-1}: 3450, 3150 ($-NH_2$), 1655 (>C=N–). MS *m/e*: 283 (M^+). UV λ_{max}^{EtOH} nm (ε): 248 (16400).

Other 2-amino-3,4-dihydro-6-phenyl-1,5-benzodiazocines (**4b**—**4s**, Table II) were similarly prepared from the corresponding **3**. The NMR spectra of **4b**—**4s** also showed complex patterns due to $C_{(3)}$ and $C_{(4)}$ protons. Typical examples are seen in the spectra of **4k** and **4l**: **4k** (in $CDCl_3$–DMSO-d_6) δ: 2.80—3.36 (2H, m, $-C_{(3)}\underline{H}(CH_3)$ and $-C_{(4)}\underline{H}(H)$), 3.78 (1H, dd, J=11 Hz, 7 Hz, $-C_{(4)}\underline{H}(H)$). **4l** (in $CDCl_3$) δ: 2.36 (1H, dd, J=16 Hz, 11 Hz, $-C_{(3)}\underline{H}(H)$), 2.70 (1H, dd, J=16 Hz, 6 Hz, $-C_{(3)}\underline{H}(H)$), 3.73 (1H, m, $-C_{(4)}\underline{H}(CH_3)$).

2-Amino-8-chloro-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocine (13)——$NaBH_4$ (5.32 g) was added portionwise with stirring to a suspension of 10 g of **4a** in 250 ml of MeOH. After stirring for 2 hr at room temperature, the mixture was diluted with H_2O (300 ml) and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and concentrated. The crystalline residue was recrystallized from benzene–MeOH to give colorless needles (7.05 g, 70%), mp 194—196°. *Anal.* Calcd. for $C_{16}H_{16}ClN_3$: C, 67.24; H, 5.64; N, 14.70. Found: C, 67.46; H, 5.72; N, 14.61. NMR ($CDCl_3$) δ: *ca.* 1.3 (1H, b, –NH–), 1.8—2.3 (2H, m, two protons of $-CH_2CH_2-$), 2.7—3.0 (1H, m, one proton of $-CH_2CH_2-$), 3.18—3.4 (1H, m, one proton of $-CH_2CH_2-$), 4.57 (1H, s, $-C_{(6)}H-$), *ca.* 4.7 (2H, b, $-NH_2$), 6.7—7.3 (8H, m, arom. H). IR ν_{max}^{KBr} cm^{-1}: 3475, 3325, 3125 ($-NH_2$, –NH–), 1655 (>C=N–).

2-(2-Aminoethyl)-6-chloro-4-phenylquinazoline (10)——a) A mixture of 1.70 g of **4a**, 2.01 g of CH_3NH_2·HCl and 40 ml of MeOH was refluxed for 40 min. After removal of the solvent, the residue was partitioned between 1 N NaOH and $CHCl_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4) and concentrated to give colorless crystals (1.55 g, 91%). Recrystallization from ether gave pale yellow needles, mp 106—107°. *Anal.* Calcd. for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.81; H, 4.96; N, 14.94. NMR ($CDCl_3$) δ: 1.48 (2H, s, $-NH_2$), 3.30 (4H, s, $-CH_2CH_2-$), 7.5—8.0 (8H, m, arom. H). IR ν_{max}^{KBr} cm^{-1}: 3400 ($-NH_2$). UV λ_{max}^{EtOH} nm (ε): 230.5 (46700), 263 (8200), 327.5 (5900). Ninhydrin (+). MS *m/e*: 283 (M^+), 254 (M^+-29).

b) A mixture of 284 mg of **4a** and 2 ml of 10% (w/v) methanolic hydrogen chloride in 8 ml of MeOH was refluxed for 2.5 hr. After removal of the solvent, the residue was dissolved in $CHCl_3$, washed with saturated aq. $NaHCO_3$ and H_2O, and dried (Na_2SO_4). The solvent was removed and the residue was treated with ether to give pale yellow crystals (150 mg, 53%), mp 105—108°. The IR spectrum was identical with that of the compound obtained by method a).

Reaction of 6 with DCl/CD_3OD——A mixture of 135 mg of **6**, 0.5 ml of 20% DCl/D_2O and 4.0 ml of CD_3OD was refluxed for 30 min. After removal of the solvent, the residue was partitioned between AcOEt and saturated aq. $NaHCO_3$. The AcOEt layer was separated, washed with H_2O, dried (Na_2SO_4) and concentrated. Treatment of the residue with ether gave **14** (40 mg) as pale yellow crystals, mp 215—217° (dec.). MS *m/e*: 272 (M^+). NMR spectrometric analysis indicated that the deuterium content at the $C_{(3)}$-methylene was 87%.

Deuterium Exchange Reaction of 8 with DCl/CD_3OD——A mixture of 135 mg of **8**, 0.5 ml of 20% DCl/D_2O and 4.0 ml of CD_3OD was refluxed for 30 min. The mixture was treated as described above to give **14** (55 mg) as pale yellow crystals, mp 217—218° (dec.). MS *m/e*: 272 (M^+). NMR spectrometric analysis indicated that the deuterium content at the $C_{(3)}$-methylene was 50%.

Reaction of 4a with DCl/CD_3OD——A mixture of 70 mg of **4a**, 0.15 ml of 20% DCl/D_2O and 2.0 ml of CD_3OD was refluxed for 35 min. After removal of the solvent, the residue was partitioned between $CHCl_3$ and saturated aq. $NaHCO_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4) and concentrated. Treatment of the residue with ether gave **16** (35 mg) as pale yellow crystals, mp 104—106°. NMR ($CDCl_3$) δ: 1.9 (2H, s, $-NH_2$), 3.3 (3H, s, undeuterated ethylene), 7.5—8.0 (8H, m, arom. H). MS *m/e*: 285 (M^+), 256 (M^+-29).

Deuterium Exchange Reaction of 6 with NaOD/CD_3OD——A mixture of 100 mg of **6**, 0.12 ml of 40% NaOD/D_2O and 4.0 ml of CD_3OD was refluxed for 40 min. The solvent was removed and water was added to the residue. The pale yellow crystals which separated were collected by filtration and washed successively

with H_2O, acetone and ether to give **15** (75 mg), mp 245—247° (dec.). The NMR (DMSO-d_6) spectrum showed no signal of methylene protons. MS *m/e*: 271 (M^+).

Deuterium Exchange Reaction of 4a with NaOD/CD_3OD——A mixture of 100 mg of **4a**, 0.06 ml of 40% NaOD/D_2O and 2.0 ml of CD_3OD was refluxed for 40 min. The mixture was treated as described above to give **17** (65 mg) as colorless crystals, mp 228—230°. NMR ($CDCl_3$) δ: 3.53, 3.86 (each 1H, d, J=11 Hz, $-C_{(4)}H_2-$), 4.7 (2H, b, $-NH_2$), 6.8—7.7 (8H, m, arom. H). MS *m/e*: 285 (M^+).

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