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Heterocycles. XI.¹⁾ Synthesis of 2-Amino-6-phenyl-
3,4-dihydro-1,5-benzodiazocines²⁾

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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 $4a \rightleftharpoons 4'a$ and $6 \rightleftharpoons 6'$.

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*-isomers⁹⁾ 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 (CDCl₃), in which the NH₂ protons of the *anti*-isomers appeared at lower magnetic fields ($\delta = ca.$ 6.4–6.8) than those of the *syn*-isomers ($\delta = ca.$ 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. Roskopf, 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₎-CH₃ 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 (CDCl₃) of **4a** showed two multiplets at 2.6–2.8 ppm and 3.3–3.9 ppm due to the –C₍₃₎H₂–C₍₄₎H₂– 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 catalyst¹¹) 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 ₃ N ₃
3e	H	H	H	H	NO ₂	H	H	B	(154–155) ^{f)} 172	95	C ₁₆ H ₁₄ N ₄ O ₂
3f	H	H	H	H	CH ₃ O	H	H	—	oil ^{g)}	—	—
3g	H	H	H	H	Cl	H	Cl	B–H	134–135	84	C ₁₆ H ₁₃ Cl ₂ N ₃
3h^{h)}	H	H	H	H	Cl	H	CH ₃ O	B–H	149–150	42	C ₁₇ H ₁₆ ClN ₃ O
3hⁱ⁾	H	H	H	H	Cl	H	CH ₃ O	E	99–101	35	C ₁₇ H ₁₆ ClN ₃ O
3i	H	H	H	CH ₃ O	CH ₃ O	H	H	A–H	144–146	52 ^{e)}	C ₁₈ H ₁₉ N ₃ O ₂
3j	H	H	CH ₃ O	H	Cl	H	H	E	158–159	82	C ₁₇ H ₁₆ ClN ₃ O
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
3lⁱ⁾	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 ₂ N ₃
3n^{h)}	CH ₃	H	H	H	Cl	H	Cl	A–H	149–150	34	C ₁₇ H ₁₅ Cl ₂ N ₃
3nⁱ⁾	CH ₃	H	H	H	Cl	H	Cl	E–H	113–114	33	C ₁₇ H ₁₅ Cl ₂ N ₃
3o	H	CH ₃	H	CH ₃ O	CH ₃ O	H	H	—	oil ^{g)}	—	—
3p	CH ₃	H	H	CH ₃ O	CH ₃ O	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 ₂ N 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 ($\pm 0.4\%$ 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.			Found		
					C	H	N	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 ₃ N ₃	64.35	4.45	13.24	64.72	4.72	13.09
4e	C-B	242—244	46	C ₁₆ H ₁₄ N ₄ O 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 ₃ O	73.09	6.14	15.04	72.69	6.11	14.73
4g	B	181—183	38	C ₁₆ H ₁₃ Cl ₂ N ₃	60.39	4.12	13.21	60.71	3.90	13.11
4h	M	254—255	60 ^{f)}	C ₁₇ H ₁₆ ClN ₃ O	65.07	5.14	13.39	64.84	4.91	13.12
4i	M	252—254	77	C ₁₈ H ₁₉ N ₃ O ₂	69.88	6.19	13.58	70.05	6.11	13.34
4j	M	216—217	74	C ₁₇ H ₁₆ ClN ₃ O	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 ₂ N 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 ₂ N ₃	61.45	4.55	12.65	61.61	4.48	12.64
4o	A	217—219	32 ^{e)}	C ₁₉ H ₂₁ N ₃ O ₂	70.56	6.55	12.99	70.54	6.50	12.84
4p	M	239—240	53 ^{e)}	C ₁₉ H ₂₁ N ₃ O 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 ₂ N ₃	61.45	4.55	12.65	61.52	4.41	12.53

a) For the substituents (R₁—R₇), 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 conditions¹³⁾ (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 $6 \rightleftharpoons 6'$ 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. 11a).

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) 1H-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 $6 \rightleftharpoons 6'$ and $4a \rightleftharpoons 4'a$ were also found in an alkaline medium. On treatment with sodium deuterioxide (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**).

Experimental¹⁷⁾

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 (CDCl₃) δ : 2.62 (2H, t, $J=6$ Hz, $-\text{CH}_2-$), 3.46 (2H, t, $J=6$ Hz, $-\text{CH}_2-$), 6.58–7.55 (10H, m, arom. H and $-\text{NH}_2$). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450, 3255 ($-\text{NH}_2$), 2240 (CN), 1655 (weak, $>\text{C}=\text{N}-$).

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 (CDCl₃), the NH₂ 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 CDCl₃ 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. NH₄OH–H₂O (200–800 ml) with ice cooling. The precipitate was collected by filtration and washed successively with H₂O, acetone and ether to give colorless crystals (60 g, 85%). Recrystallization from acetone afforded colorless needles, mp 218–220°. NMR (CDCl₃) δ : 2.6–2.8 (2H, m, $-\text{C}_{(3)}\text{H}_2-$), 3.3–3.9 (2H, m, $-\text{C}_{(4)}\text{H}_2-$), 4.66 (2H, b, $-\text{NH}_2$), 6.8–7.7 (8H, m, arom. H). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450, 3150 ($-\text{NH}_2$), 1655 ($>\text{C}=\text{N}-$). MS m/e : 283 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ 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 CDCl₃–DMSO-*d*₆) δ : 2.80–3.36 (2H, m, $-\text{C}_{(3)}\text{H}(\text{CH}_3)$ and $-\text{C}_{(4)}\text{H}(\text{H})$), 3.78 (1H, dd, $J=11$ Hz, 7 Hz, $-\text{C}_{(4)}\text{H}(\text{H})$). 4l (in CDCl₃) δ : 2.36 (1H, dd, $J=16$ Hz, 11 Hz, $-\text{C}_{(3)}\text{H}(\text{H})$), 2.70 (1H, dd, $J=16$ Hz, 6 Hz, $-\text{C}_{(3)}\text{H}(\text{H})$), 3.73 (1H, m, $-\text{C}_{(4)}\text{H}(\text{CH}_3)$).

2-Amino-8-chloro-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocine (13)—NaBH₄ (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 H₂O (300 ml) and extracted with CHCl₃. The extract was washed with H₂O, dried (Na₂SO₄) and concentrated. The crystalline residue was recrystallized from benzene–MeOH to give colorless needles (7.05 g, 70%), mp 194–196°. Anal. Calcd. for C₁₆H₁₆ClN₃: C, 67.24; H, 5.64; N, 14.70. Found: C, 67.46; H, 5.72; N, 14.61. NMR (CDCl₃) δ : *ca.* 1.3 (1H, b, $-\text{NH}-$), 1.8–2.3 (2H, m, two protons of $-\text{CH}_2\text{CH}_2-$), 2.7–3.0 (1H, m, one proton of $-\text{CH}_2\text{CH}_2-$), 3.18–3.4 (1H, m, one proton of $-\text{CH}_2\text{CH}_2-$), 4.57 (1H, s, $-\text{C}_{(6)}\text{H}-$), *ca.* 4.7 (2H, b, $-\text{NH}_2$), 6.7–7.3 (8H, m, arom. H). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3475, 3325, 3125 ($-\text{NH}_2$, $-\text{NH}-$), 1655 ($>\text{C}=\text{N}-$).

2-(2-Aminoethyl)-6-chloro-4-phenylquinazoline (10)—a) A mixture of 1.70 g of 4a, 2.01 g of CH₃NH₂·HCl and 40 ml of MeOH was refluxed for 40 min. After removal of the solvent, the residue was partitioned between 1N NaOH and CHCl₃. The CHCl₃ layer was separated, washed with H₂O, dried (Na₂SO₄) and concentrated to give colorless crystals (1.55 g, 91%). Recrystallization from ether gave pale yellow needles, mp 106–107°. Anal. Calcd. for C₁₆H₁₄ClN₃: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.81; H, 4.96; N, 14.94. NMR (CDCl₃) δ : 1.48 (2H, s, $-\text{NH}_2$), 3.30 (4H, s, $-\text{CH}_2\text{CH}_2-$), 7.5–8.0 (8H, m, arom. H). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400 ($-\text{NH}_2$). UV $\lambda_{\text{max}}^{\text{EtOH}}$ 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 CHCl₃, washed with saturated aq. NaHCO₃ and H₂O, and dried (Na₂SO₄). 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/CD₃OD—A mixture of 135 mg of 6, 0.5 ml of 20% DCl/D₂O and 4.0 ml of CD₃OD was refluxed for 30 min. After removal of the solvent, the residue was partitioned between AcOEt and saturated aq. NaHCO₃. The AcOEt layer was separated, washed with H₂O, dried (Na₂SO₄) 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/CD₃OD—A mixture of 135 mg of 8, 0.5 ml of 20% DCl/D₂O and 4.0 ml of CD₃OD 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/CD₃OD—A mixture of 70 mg of 4a, 0.15 ml of 20% DCl/D₂O and 2.0 ml of CD₃OD was refluxed for 35 min. After removal of the solvent, the residue was partitioned between CHCl₃ and saturated aq. NaHCO₃. The CHCl₃ layer was separated, washed with H₂O, dried (Na₂SO₄) and concentrated. Treatment of the residue with ether gave 16 (35 mg) as pale yellow crystals, mp 104–106°. NMR (CDCl₃) δ : 1.9 (2H, s, $-\text{NH}_2$), 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/CD₃OD—A mixture of 100 mg of 6, 0.12 ml of 40% NaOD/D₂O and 4.0 ml of CD₃OD 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 H₂O, 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/CD₃OD—A mixture of 100 mg of **4a**, 0.06 ml of 40% NaOD/D₂O and 2.0 ml of CD₃OD was refluxed for 40 min. The mixture was treated as described above to give **17** (65 mg) as colorless crystals, mp 228—230°. NMR (CDCl₃) δ : 3.53, 3.86 (each 1H, d, *J*=11 Hz, -C₍₄₎H₂-), 4.7 (2H, b, -NH₂), 6.8—7.7 (8H, m, arom. H). MS *m/e*: 285 (M⁺).

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