Studies on the Imidazo[1,2-*a*]pyridinic System: Synthesis of Pyrido[1′,2′:1,2]imidazo[5,4-*d*][1.3]-benzodiazepines

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3-Nitroso-2-(2-nitrophenyl)imidazo[1,2-*a*]pyridine was converted to its diamino derivative (5) and the open-chain compound 2-*N*(2-pyridyl)benzimidoyl cyanide (6). Compound 5 was condensed with triethyl orthoformate or 2-chlorobenzaldehyde to afford the pyrido[1′,2′:1,2]imidazo[5,4-*d*][1.3]benzodiazepines (7a, b). X-Ray crystallographic analysis confirmed the structure of 7a. The structure of 7b was assigned by two-dimensional nuclear magnetic resonance techniques, ^{1}H–^{1}H and ^{13}C–^{1}H correlation spectroscopy.

Keywords imidazo[1,2-*a*]pyridine; pyrido[1′,2′:1,2]imidazo[5,4-*d*][1.3]benzodiazepines; ^{1}H–^{1}H-COSY; ^{13}C–^{1}H-COSY; X-ray crystallographic analysis; synthesis; structure

Considerable attention has been given in recent years to the synthesis of seven-membered ring compounds. Our particular interest in this area is centered on benzodiazepines. Syntheses of 1,2- and 1,4-benzodiazepines have been well worked out,[1] but 1,3-benzodiazepines have been comparatively less well explored.[2] Recently, a number of reduced 1,3-benzodiazepines were reported to display significant antidepressant-like and antihypertensive properties.[3] Some heterocycles have been incorporated into the benzodiazepinic structure, but no syntheses of 1,3-derivatives fused to the "d" face have been reported. Since Meguro and Kuwata[4] and Hester *et al.*[5] reported that the fusion of a heterocyclic ring to the face of benzodiazepines enhanced the potency and imparted novel biological activity, we have focused our interest on the preparation of 1,3-benzodiazepines. In this work, our syntheses utilize the imidazo[1,2-*a*]pyridinic ring system to form the tetracyclic structures (**7a**, **b**). The synthesis of benzodiazepines (**7a**, **b**) is outlined in Chart 1.

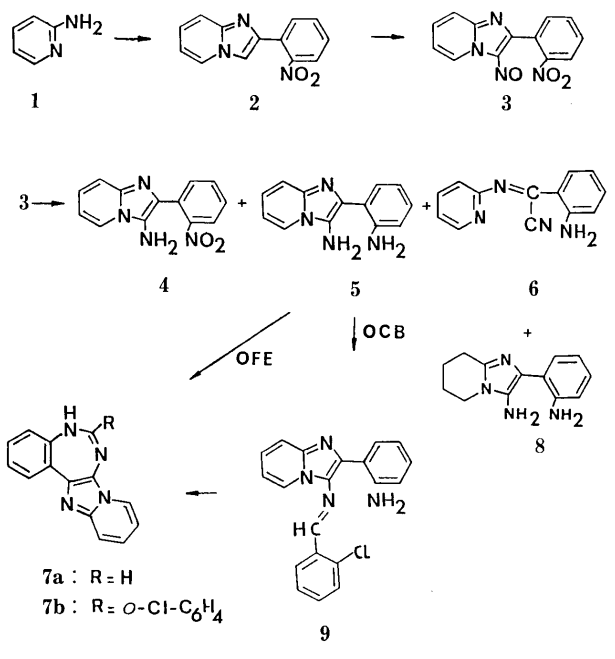


Chart 1

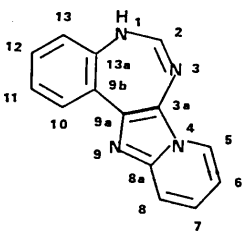
Condensation of 2-aminopyridine with 2-nitrophenacyl bromide yielded (**2**), which, when treated with nitrous acid in a usual manner, gave the corresponding nitroso compound (**3**) in 63% yield. Catalytic hydrogenation of **3** in ethanol containing concentrated hydrochloric acid (100/0.2, v/v) over 5% palladium on carbon at room temperature resulted in a complex mixture of diamines (**5**, **8**), an amine (**4**) and the benzimidoyl cyanide (**6**) in 36, 47, 5 and 12% yields, respectively. With the use of equal weights of catalyst and **3**, the yield of **8** was raised to 82%. Interestingly, in neutral solution, compound **3** or **4** yielded **5** with concomitant formation of **6** in 80/20% yields, respectively.

Structures were assigned to **5**, **6**, **8** and **4** on the basis of nuclear magnetic resonance and mass spectral data. In particular, the nuclear magnetic resonance (NMR) spectrum of **8** contained signals at δ 1.72, 2.65 and 3.41 corresponding to the eight hydrogens of the piperidine nuclei. The ^{13}C-NMR spectral analysis, in $CDCl_3$, led to the required information regarding the structure of the yellow compound (**6**). The quaternary carbon signal at δ 111.05 is typical of the CN carbon. Ring-opening reactions of nitrogen bridgehead compounds have been described,[6] particularly in the case of imidazo[1,2-*a*]pyrimidines and -pyridines.[7]

Cyclization of the diamine (**5**) with triethyl orthoformate, under acid catalysis, gave, after treatment which Na_2CO_3 beside the starting amine (**5**), an unspecified mixture of three compounds and the wanted benzodiazepine (**7a**) as red crystals, in 16% yield.

The 360 MHz ^{1}H-NMR data, obtained in CD_3OD, of **7a** are summarized in Table I; the spectrum was complex. The four signals corresponding to the four protons of the pyridine nuclei were readily identified by the analysis of the observed perturbation in spin-decoupling experiments. Irradiation of the doublet at δ 7.84 caused collapse of the multiplet at δ 6.78 to an expected doublet of doublets. Irradiation of the multiplet at δ 7.10 caused collapse of the signal at δ 7.24 to a singlet and the multiplet at δ 6.78 to a

TABLE I. ^{13}C- and ^{1}H-NMR Spectral Data for **7a**



Carbon or hydrogen	Shifts[a]	J_{C-H}	Shifts[b]	Splitting pattern
2	149.93	196.21	6.11	s
3a	133.37			
5	123.42	187.06	7.84	d
6	114.08	166.17	6.78	m
7	125.76	165.76	7.10	m
8	116.91	168.14	7.24	d
8a	144.14			
9a	131.69			
9b	126.37			
10	127.80	168.98	7.35	d
11	125.59	162.98	6.69	m
12	131.53	161.82	6.82	m
13	119.49	158.20	6.13	d
13a	143.92			

a) Run at 90.55 MHz in CD_3OD. *b*) Run at 360 MHz in CD_3OD.

doublet of doublets. Irradiation of the benzodiazepinic protons at δ 7.35 and δ 6.82 caused collapse of the multiplet at δ 6.69 to a doublet of doublets and the signal at δ 6.13 to a singlet with a simplification (doublet of doublets) at δ 6.70, respectively. The diazepinic proton was identified at δ 6.11 as a singlet. Assignments of pyridinic (H-5—H-8) and benzodiazepinic protons (H-10—H-13) were made initially by using model compounds.[7,8]

Surprisingly, there have been few ^{13}C-NMR studies of 1,4-benzodiazepines[9] and none on the 1,3-compounds. The ^{13}C-NMR spectrum of **7a** in CD_3OD showed the presence of nine C(H) resonances and five quaternary carbons signals (Table I). An unambiguous assignment was carried out, based on selective proton decoupling experiments, decoupled and undecoupled spectra, coupling constant values and comparison with literature data.[10] Irradiating the signals of (H-10), (H-11) or (H-12) caused collapse of the doublets to the expected singlets at δ 127.8 (C-10), 125.59 (C-11) or 131.53 (C-12), and weakly disturbed the signals at δ 116.91 (C-8), 114.08 (C-6) or 125.76 (C-7) corresponding to H-8, H-6 and H-7, respectively. The signal at 123.42 was unequivocally assigned to C-5 (J= 187.0 Hz), being characteristic of C-5 of the imidazo[1,2-*a*]pyridinic ring.[11] Irradiation of the signal at δ 6.11 caused collapse of the doublets to singlets at δ 119.49 and 149.93 (C-13 or C-2). Assignments for C-13 and C-2 were made by using model compounds,[12] and on the bases of the corresponding coupling constant: 152.2 and 196.2 Hz for C-13 and C-2[13] respectively. The resonances for the quaternary carbons (C-3a, C-8a, C-9a, C-9b and C-13a) are consistent with literature data.[11]

The structure of **7a** was confirmed by X-ray analysis. The molecule is flat; a projection of the mean plane of the atoms is given in Fig. 1 (equation of the plane: $0.8393x-0.5170y-0.1681z=0.7922$). The minimum shift is -0.007 (3) Å for

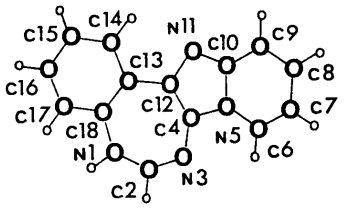


Fig. 1

TABLE II. Bond Distances (Å) and Angles (°) of **7a**

Atom	Bond distance (Å)	Angle (°)
C(2)–N(1)–C(18)	1.344 (4)	133.8 (3)
N(1)–C(2)–N(3)		132.7 (3)
C(2)–N(3)–C(4)	1.287 (5)	120.8 (3)
N(3)–C(4)–N(5)	1.382 (4)	117.7 (3)
N(3)–C(4)–C(12)		136.8 (3)
N(5)–C(4)–C(12)		105.4 (3)
C(4)–N(5)–C(6)	1.374 (4)	129.9 (3)
C(4)–N(5)–C(10)		107.4 (2)
C(6)–N(5)–C(10)	1.381 (4)	122.7 (3)
N(5)–C(6)–C(7)		118.5 (3)
C(6)–C(7)–C(8)	1.354 (5)	120.6 (3)
C(7)–C(8)–C(9)	1.414 (5)	120.9 (3)
C(8)–C(9)–C(10)	1.366 (5)	119.0 (3)
N(5)–C(10)–C(9)	1.388 (4)	118.3 (3)
N(5)–C(10)–N(11)		110.6 (3)
C(9)–C(10)–N(11)	1.410 (5)	131.1 (3)
C(10)–N(11)–C(12)	1.332 (4)	105.5 (3)
C(4)–C(12)–N(11)	1.375 (4)	111.1 (3)
C(4)–C(12)–C(13)		127.2 (3)
N(11)–C(12)–C(13)	1.374 (4)	121.7 (3)
C(12)–C(13)–C(14)	1.464 (4)	118.8 (3)
C(12)–C(13)–C(18)		123.6 (3)
C(14)–C(13)–C(18)	1.397 (4)	117.6 (3)
C(13)–C(14)–C(15)		122.0 (3)
C(14)–C(15)–C(16)	1.389 (5)	119.6 (3)
C(15)–C(16)–C(17)	1.381 (5)	119.5 (3)
C(16)–C(17)–C(18)	1.394 (5)	121.0 (3)
N(1)–C(18)–C(13)	1.427 (4)	125.0 (3)
C(17)–C(18)–N(1)	1.381 (5)	114.7 (3)
C(13)–C(18)–C(17)	1.406 (4)	120.4 (3)

X-Ray numbering.

N (1) and the maximum shift is -0.048 (4) Å for C (16). Bonds lengths and angles are summarized in Table II and the fractional coordinates of the atoms in Table III. Structure factors are available in a supplementary publication (see Experimental).

Condensation of **5** with *o*-chlorobenzaldehyde in benzene at reflux for 16 h provided 3-[(*N*-2-chlorobenzylidene)-amino]-2-imidazo[1,2-*a*]pyridinyl-2,2′-aminobenzene (**9**) in 15% yield and two chromatographically inseparable crystalline products; The ^{1}H-NMR spectrum of **9** revealed one singlet at δ 8.75 and twelve hydrogens as doublets and multiplets, without an N–H group. This structure was confirmed by ^{13}C-NMR; irradiation at δ 8.75 identified the signal due to the doublet centered at δ 152.11 (J= 166 Hz) as a singlet typical of an –HC=N– group. Treatment of the set of inseparable crystalline products in methanol at reflux for 3 h gave the benzodiazepine (**7b**) in 10% yield. Treatment of **5** under acid catalysis in methanol at reflux for 48 h afforded **7b** in 15% yield. The structure (**7b**) was supported by the mass spectrum (MS) (*m/z* 344—346) and ^{1}H- and ^{13}C-NMR spectra (recorded in $CDCl_3$). Assignments of the three sets of proton resonances as

TABLE III. Fractional Atomic Coordinates (x, y and z) of **7a**

Atom	x/a (σ)	y/b (σ)	z/c (σ)	B_{eq}/B_i
N(1)	12411 (7)	2576 (2)	4161 (2)	4.6 (1)
C(2)	10711 (9)	1988 (2)	4018 (2)	4.9 (2)
N(3)	9783 (7)	1506 (2)	4610 (2)	5.0 (1)
C(4)	10557 (8)	1531 (2)	5608 (2)	3.9 (2)
N(5)	9448 (6)	1004 (1)	6199 (2)	3.9 (1)
C(6)	7616 (9)	428 (2)	5956 (3)	5.2 (2)
C(7)	6818 (9)	−19 (2)	6686 (3)	5.5 (2)
C(8)	7879 (9)	96 (2)	7672 (3)	5.2 (2)
C(9)	9720 (8)	662 (2)	7910 (2)	4.6 (2)
C(10)	10530 (8)	1137 (2)	7158 (2)	4.1 (2)
N(11)	12222 (6)	1725 (1)	7191 (2)	4.0 (1)
C(12)	12257 (7)	1966 (2)	6233 (2)	3.7 (1)
C(13)	13886 (7)	2614 (2)	5972 (2)	3.6 (1)
C(14)	15476 (8)	2990 (2)	6717 (2)	4.1 (2)
C(15)	16987 (8)	3620 (2)	6530 (2)	4.7 (2)
C(16)	16986 (9)	3882 (2)	5578 (3)	4.9 (2)
C(17)	15456 (8)	3511 (2)	4819 (2)	4.7 (2)
C(18)	13925 (7)	2888 (2)	5006 (2)	4.0 (2)
H(101)	1265 (8)	287 (2)	354 (2)	6.7
H(102)	1007 (8)	191 (2)	327 (2)	6.2
H(106)	696 (8)	38 (2)	523 (2)	6.2
H(107)	539 (8)	−45 (2)	651 (2)	6.5
H(108)	729 (7)	−25 (2)	823 (2)	6.3
H(109)	1051 (8)	76 (2)	862 (2)	5.9
H(114)	1544 (7)	279 (2)	745 (2)	5.1
H(115)	1812 (8)	388 (2)	709 (2)	5.6
H(116)	1817 (8)	436 (2)	542 (2)	6.6
H(117)	1548 (7)	370 (2)	410 (2)	5.2

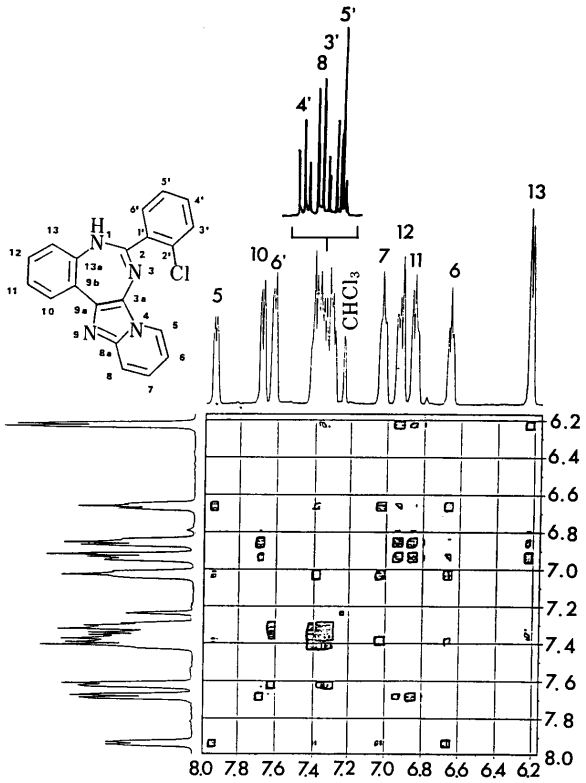


Fig. 2. ^{1}H–^{1}H-COSY Spectra of **7b** in $CDCl_3$

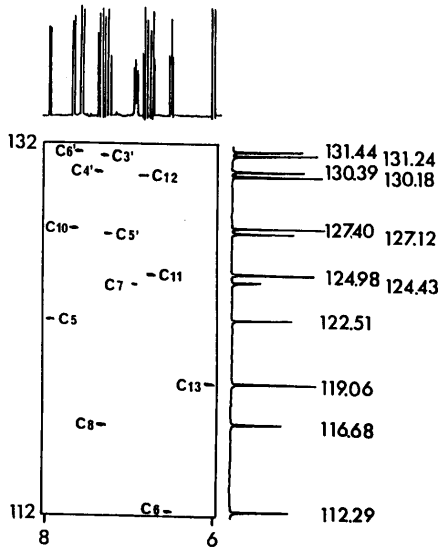


Fig. 3. CH-COSY Spectra of **7b** in $CDCl_3$

phenyl ring, chlorinated ring and pyridine nuclei (12H) were corroborated by homonuclear decoupling experiments. The signal at δ 7.94 (dd) was assignable to H-5, which was interacting with protons H-6, H-7 and H-8 at δ 6.66, 7.02 and 7.36 respectively. The resonance at δ 7.65 (H-10) was split by interactions with H-11 at δ 6.86, H-12 at δ 6.95 and H-13 at δ 6.23. In addition, the signal at δ 7.63 (dd) was interacting with the congested region of the spectrum between 7.30—7.44 ppm (3H) due to the chlorinated ring protons. Finally the mutual couplings of the pyridinic, benzenic and *o*-chlorophenyl ring signals were identified unequivoqually by the off-diagonal signals (cross peaks) in the two-dimensional ^{1}H–^{1}H correlation spectroscopy (COSY)[14] spectrum (Fig. 2). The ^{1}H-NMR data obtained were mainly used to corroborate the ^{13}C-NMR assignments. These assignments are complicated due to the very similar chemical shifts of some carbon resonances. On the basis of the coupled spectra, decoupled spectra and heteronuclear decoupling experiments, in $CDCl_3/D_2O$ (95/5, v/v) the doublets centered at 127.39, 125.06, 130.38 and 119.25 ppm have been assigned to C-10, C-11, C-12 and C-13, respectively. The signals at 122.57, 112.70 and 116.48 ppm were assigned to C-5, C-6 and C-8. The signals at δ 131.38 and 131.44 are attributed to C-4′ and C-6′. However, this method alone does not give crucial assignment information for C-7, C-3′ and C-6′. Complete assignment of all resonances was made unequivocal with the data obtained with the ^{1}H–^{13}C shift correlation spectrum in a COSY experiment,[15] in $CDCl_3$ (Fig. 3). We could identify the C-7 signal at 124.43 and discriminate between C-3′, C-4′, C-5′ and C-6′.

Derivatives with heterocyclic groups annelated to the faces of the diazepinic ring of 1,4-benzodiazepines are of much interest in view of their potential biological activity. We therefore carried out a preliminary biological evaluation of **7b** for central nervous system activity. Further studies of the novel ring system are in progress.

Experimental

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Center, ENSCM, Montpellier. ^{1}H-NMR spectra were recorded on a Varian EM 360 or a Bruker WM 500, WM 360 or MSL 300; ^{13}C-NMR spectra were obtained at 26 °C with proton noise decoupling at 75.470 MHz with a Bruker MSL 300 instrument. Chemical shifts are expressed relative to internal tetramethylsilane in $CDCl_3$ (or CD_3OD) at a concentration of *ca.* 5%. Infrared (IR) spectra were

obtained on a Beckman Acculab 2 spectrometer. MS were recorded on a LKB 2091 spectrometer at 70 eV (source temperature = 180 °C). Compounds were purified by high-performance liquid chromatography (HPLC on a Waters M 590 or JobinYvon apparatus equipped with a preparative alumina column. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin-layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated neutral alumina plates.

2-(2-Nitrophenyl)imidazo[1,2-*a*]pyridine (2) This compound was prepared according to the procedure of Almirante *et al.*[16] in 45% yield. mp 151—153 °C. MS *m/z*: 239. IR (KBr): 1628, 1520, 1360, 748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 1H), 8.01 (d, 1H), 7.80 (s, 1H), 7.74 (d, 1H), 7.65 (t, 1H), 7.63 (d, 1H), 7.44 (t, 1H), 7.21 (t, 1H), 6.81 (t, 1H).

2-(2-Nitrophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (3) This compound was prepared in 64% yield by the general method.[7] mp 175—177 °C. MS *m/z*: 268, 222, 78. ^{1}H-NMR ($CDCl_3$) δ: 9.92 (d, 1H), 8.27 (m, 2H), 8 (m, 4H), 7.5 (m, 1H).

General Procedure for Compounds **4**—**6** and **8** Compound **3** (2.20 g, 8.2 mmol) was slurried in 1 l of ethyl alcohol containing 2 ml of concentrated HCl. The slurry was hydrogenated over 100 mg of 5% palladium on carbon[15] at an initial pressure of 1 bar. The yellow solution was filtered and the filtrate was evaporated to give an oil, which was dissolved in a solution of $EtOH/NH_3$. The solution was the concentrated to give a solid which was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and evaporated *in vacuo*. Chromatography of the residue on a neutral alumina column, eluted with CH_2Cl_2, gave 0.960 g of crude **4**; 46% yield. mp 135—137 °C. MS molecular ion peak at *m/z* 254 with a base peak at *m/z* 78. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (s, 2H), 6.68 (dd, 1H), 7.02 (dd, 1H), 7.56 (m, 6H). Further elution yielded 0.12 g of compound **6**, mp 95—97 °C. MS *m/z*: 222. IR (KBr): 3360, 2225, 1610, 1572, 1530, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.64 (m, 2H), 6.72 (d, 1H), 6.76 (t, 1H), 7.14 (d, 1H), 7.21 (m, 1H), 7.28 (t, 1H), 7.78 (td, 1H), 7.94 (d, 1H), 8.55 (d, 1H). ^{13}C-NMR ($CDCl_3$) δ: 111.05, 114.81, 116.82, 117.42, 122, 132.80, 134.01, 138.10, 143.43, 148.98, 149.90, 159.46. Further elution yielded **5**, 0.20 g, as pale brown plates: mp 131—133 °C. MS molecular ion peak at 224. ^{1}H-NMR ($CDCl_3$) δ: 4.62 (s, 4H), 6.80 (m, 3H), 7.11 (m, 2H), 7.48 (m, 2H), 8.01 (dd, 1H). Further elution with MeOH gave **8** in 12% yield, mp 111—113 °C. MS *m/z*: 228. *Anal.* Calcd for $C_{13}H_{16}N_4$: C, 68.42; H, 7.01; N, 24.56. Found: C, 68.31; H, 6.92; N, 24.33. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.72 (4H, m), 2.65 (2H, m), 3.41 (2H, m), 4.71 (4H, m), 6.82 (4H, m).

2-(2-Aminophenyl)-3-aminoimidazo[1,2-*a*]pyridine (5) Method A: A solution of **3** (2 g, 7.5 mmol) in 1 l of ethyl alcohol was hydrogenated over 50 mg of 5% palladium on carbon. The orange solution was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed (neutral alumina, CH_2Cl_2) to give a small amount of an unidentified red solid (0.15 g). Further elution yielded **6** (0.2 g) and **5** (0.90 g, 54%).

Method B: Compound **5** was prepared according to method A from **4** in 86% yield.

Pyrido[1′,2′:1,2]imidazo[5,4-*d*][1.3]benzodiazepine (7a) A stirred mixture of **5** (free base; 0.650 g, 2.9 mmol), triethyl orthoformate (3.2 g, 21 mmol), and glacial acetic acid (1 ml) was heated for 4 h under reflux, and then concentrated under reduced pressure and partitioned between 5% sodium hydroxide and CH_2Cl_2. The mixture was extracted with CH_2Cl_2 (2 × 100 ml). The extracts were dried and evaporated *in vacuo*. One unidentified compound was isolated in low yield (1%) from the chromatography, and had the following spectra data. ^{1}H-NMR ($CDCl_3$) δ: 6.70 (m, 2H), 7.05 (m, 1H), 7.26 (m, 1H), 7.56 (dd, 1H), 7.74 (m, 1H), 8.28 (dd, 1H), 8.36 (d, 1H). On cooling of the aqueous solution, crystallization occurred to afford **7a** (0.10 g, 16% yield). Recrystallization from CH_3OH afforded **7a** as red crystals; mp 248—250 °C. MS molecular ion peak at 234. *Anal.* Calcd for $C_{14}H_{10}N_4$: C, 71.79; H, 4.27; N, 23.93. Found: C, 71.61; H, 4.36; N, 23.68.

6-(2-Chlorophenyl)pyrido[1′,2:1,2]imidazo[5,4-*d*][1.3]benzodiazepine (7b) Glacial acetic acid (5 ml) was placed in a 250 ml flask under N_2 followed by the dropwise addition of the diamine (**5**) (1.3 g, 5.8 mmol) in 40 ml of CH_3OH. After being stirred for 10 min, the mixture was heated at 40 °C and 2-chlorobenzaldehyde (0.9 g, 7 mmol) in 60 ml of CH_3OH was added dropwise. The reaction mixture was heated under reflux for 3 h. Then, the mixture was cooled, concentrated under reduced pressure, quenched with 10% sodium hydroxide solution and extracted with CH_2Cl_2 (2 × 100 ml). The dried (Na_2SO_4) organic phase was concentrated and the residue was chromatographed over neutral alumina with CH_2Cl_2 as the eluent to give **9** in 15% yield. Recrystallization from CH_3OH afforded **9** as red crystals: mp 185—187 °C. MS *m/z*: 344—346. ^{1}H-NMR ($CDCl_3$) δ: 6.94 (t, 1H), 7.29 (m, 4H), 7.56 (m, 2H), 7.68 (m, 2H), 8.08 (d, 1H), 8.24 (m, 1H), 8.53 (d, 1H), 8.75 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 113.29, 117.49, 123.47, 124.91, 126.30, 127.01, 127.55, 129.44, 129.48, 129.65, 129.93, 129.95, 131.97, 132.32, 133.35, 135.73, 142.91, 149.02, 152.11. Further elution yielded a complex product mixture. A solution of CH_3OH (30 ml) containing 1 g of the mixture was refluxed for 3 h, and then the organic phase was evaporated *in vacuo*. After chromatography on neutral alumina with CH_2Cl_2 as the eluent, **7b** (0.10 g; 10% yield) was obtained as a red solid: mp 249—251 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.57 (m, 1H, N-H), 6.23 (d, 1H), 6.66 (m, 1H), 6.86 (m, 1H), 6.95 (m, 1H), 7.02 (m, 1H), 7.36 (d, 1H), 7.37 (m, 3H), 7.63 (dd, 1H), 7.65 (d, 1H), 7.94 (d, 1H). ^{13}C-NMR ($CDCl_3/D_2O$) δ: 112.70 (170.6), 116.48 (166.9), 119.25 (157.4), 122.57 (187.0), 125.06 (163.1), 125.67, 127.16 (163.7), 127.39 (161.9), 129.36, 130.38 (166.5), 131.38 (163.8), 131.44 (163.4), 131.64, 136.15, 142.34, 142.70, 154.85; ($CDCl_3$) δ 122.51 (C-5), 112.29 (C-6), 124.43 (C-7), 116.68 (C-8), 127.40 (C-10), 124.96 (C-11), 130.16 (C-12), 119.06 (C-13), 130.39 (C-3′), 131.24 (C-4′), 127.12 (C-5′), 131.44 (C-6′), 126.15 (C-9b), 129.41 (C-9a), 131.68 (C-2′), 136.39 (C-3a), 142.39 (C-13a), 143.20 (C-1′), 149.20 (C-8a), 154.62 (C-2).

X-Ray Analysis (7a) Compound **7a** crystallizes in the monoclinic system with $a = 4.197$ (1), $b = 19.155$ (5), $c = 13.508$ (4) Å; $\beta = 91.10$ (3)°; space group $P2^1/c$ with a calculated density of 1.43 g/cm^3 ($Z = 4$). The intensity data were collected on a fully automated Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu$K\alpha$ radiation ($\lambda = 1.54178$ Å) and ω–θ scan ($\omega/\theta = 1$). Of the 1314 unique reflections with $\theta < 60°$ measured in this way, 863 were considered as observed after correction for Lorentz-polarization effects. The structure was solved by direct methods[17] and Fourier technics. The C and N-atoms were located in the best E-map. The fractional coordinates were refined by the block-diagonal least-squares method, with isotropic and anisotropic thermal parameters. H-atoms were derived from difference Fourier synthesis and refined with the other atoms. The final minimum residual was $R = 0.040$ ($R_w = 0.048$, $S = 0.764$). Structure factor tables are available in a Supplementary Publication. Individual bond distances and angles are consistent with accepted values.

Antagonism of Tetrabenazine-Induced Ptosis in Mice The test compound was administered *per os* to male mice weighing 20 to 30 g, in groups of ten. Amitriptyline was also employed with procedural details as previously reported.[18] ED_{50} for **7a**, **b** and amitriptyline: 7.6 (7.0—8.6), 3.1 (2.8—3.5) and 2.2 (1.9—2.7) mg/kg, *p.o.*, respectively.

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