POLYCYCLIC N-HETERO COMPOUNDS. XXI. SYNTHESIS OF NOVEL RING SYSTEM, 4H-IMIDAZO[1',2':1,6]PYRIMIDO[5,4-d][1]BENZAZEPINE AS B-HOMO-6,11,13,15-TETRAAZASTEROIDAL ANALOGUE

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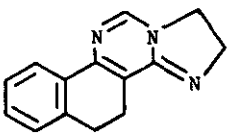
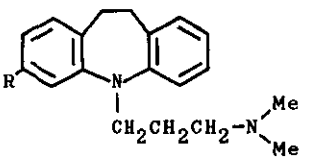
Abstract - A synthesis of 4H-imidazo[1',2':1,6]pyrimido-[5,4-d][1]benzazepine (XIIIa) having a novel ring system is described. Methyl anthranilate (IVa) was converted to 4-(2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]-benzazepine (XIa) in several steps and XIa was cyclized to XIIIa. A synthesis of 8-chloro derivative of XIIIa is also described.

1,2,4,5-Tetrahydrobenz[h]imidazo[1,2-c]quinazoline (I), which was synthesized in our laboratory[1], exhibited an antidepressive activity and a moderate toxicity in mice[2]. So we were interested in carrying out the chemical modification of compound I in the hope that a more effective but non-toxic azasteroidal antidepressant could be found and the introduction of the benzazepine moiety of imipramine (IIa), which is one of the iminodibenzyl derivatives and a typical tricyclic antidepressant, to the AB ring moiety of compound I was intended to perform.



I

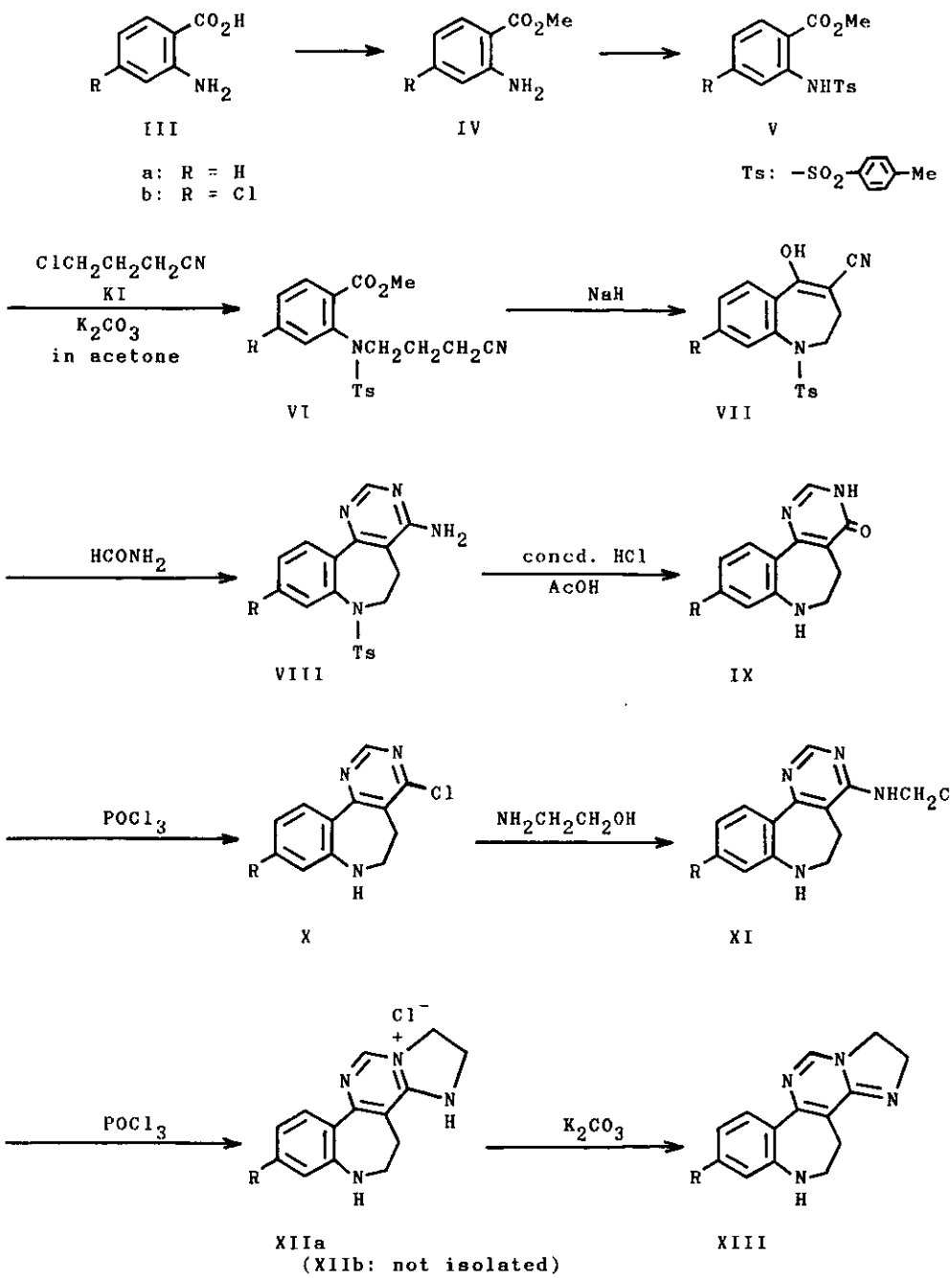


IIa: R = H
b: R = Cl

The present paper deals with the synthesis of B-homo-6,11,13,15-tetraaza-steroidal compounds having a novel ring system, namely 1,2,5,6-tetrahydro-4H-imidazo[1',2':1,6]pyrimido[5,4-d][1]benzazepines (XIII).

The synthetic route is shown in scheme 1. Methyl N-tosylanthranilate (Va) was prepared by the method of Proctor et al.[3] from methyl anthranilate (IVa) and tosyl chloride in dry pyridine. The introduction of the 3-cyanopropyl group to the imino nitrogen of Va was carried out using the technique of Proctor et al.[3] In our case, 4-chlorobutyronitrile was used instead of ethyl 4-bromobutyrate used by Proctor et al.[3] and methyl N-(3-cyanopropyl)-N-tosylanthranilate (VIa) was obtained. The ir spectrum of VIa showed C≡N band at 2250 cm^{-1} and disappearance of N-H band which was observed at 3126 cm^{-1} in that of Va. In the manner described by McCall et al.[4], Dieckmann cyclization of VIa with sodium hydride in dimethylformamide afforded 5-hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-carbonitrile (VIIa). Proctor et al.[5] already obtained VIIa from 5-oxo-1-tosyl-2,3,4,5-tetrahydro-1H-1-benzazepine in three steps. In our case, VIIa could be obtained more easily in high yield.

Heating of VIIa with formamide under ammonia stream at 150-160°C afforded 4-amino-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (VIIIa) as pale gray prisms. Nmr spectrum of VIIIa in acetic acid-d_4 showed one proton singlet at 8.31 ppm attributable to a newly produced pyrimidine ring proton at 2-position. Hydrolysis of 4-amino group of VIIIa to hydroxyl one was performed with hydrochloric acid-acetic acid. In this step, N-tosyl group was simultaneously hydrolyzed and 6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepin-4(3H)-one (IXa) was obtained as pale greenish yellow prisms. The presence of carbonyl group was demonstrated by the measurement of the ir spectrum of IXa, that is, the absorption was strongly appeared at 1620 cm^{-1}. Transformation of IXa to 4-chloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (Xa) was performed by heating with phosphoryl chloride. Treatment of Xa with ethanolamine gave 4-(2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (XIa) in high yield. Cyclization of XIa with phosphoryl chloride afforded 1,2,5,6-tetrahydro-4H-imidazo[1',2':1,6]pyrimido[5,4-d][1]benzazepinium chloride (XIIa) as monohydrate. Treatment of XIIa with potassium hydroxide gave a final product, 1,2,5,6-tetrahydro-4H-imidazo[1',2':1,6]-pyrimido[5,4-d][1]benzazepine (XIIIa). On pmr spectrum, the absorption of the pyrimidine ring proton at 2-position of XIa appeared at 8.38 ppm,


CO2H
NH2
R
III
a: R = H
b: R = Cl
CO2Me
NH2
IV
NHTs
V
Ts: −SO2−Me
ClCH2CH2CH2CN
KI
K2CO3
in acetone
NCH2CH2CH2CN
Ts
VI
NaH
OH
CN
VII
HCONH2
NH2
VIII
concd. HCl
AcOH
NH
O
IX
POCl3
Cl
X
NH2CH2CH2OH
NHCH2CH2OH
XI
Cl−
+
XIIa
(XIIb: not isolated)
K2CO3
XIII

Scheme 1

however, the absorption of the corresponding proton at 12-position of XIIIa was shifted to higher field (7.79 ppm) owing to the decrease of the aromatic character of the pyrimidine ring.

As the next starting material, 4-chloroanthranilic acid (IIIb) was chosen by the reason of its easy to obtain commercially and the interest for the examination of the bioactivity of the final product, 8-chloro-1,2,5,6-tetrahydro-4H-imidazo[1',2':1,6]pyrimido[5,4-d][1]benzazepine (XIIIb), which has a chloro group at a similar position to that of the benzazepine moiety of chlomipramine (IIb), which is one of the tricyclic antidepressants of iminodibenzyl type. By the technique of Atkinson et al.[6], methyl 4-chloroanthranilate (IVb) was prepared from IIIb and IVb was derived to methyl 4-chloro-N-tosylanthranilate (Vb) according to the method of Gupta et al.[7] Vb could be converted to XIIIb similarly as described in the preparation of XIIIa from Va although 8-chloro-1,2,5,6-tetrahydro-4H-imidazo[1',2':1,6]-pyrimido[5,4-d][1]benzazepinium chloride (XIIb) was not isolated.

The screening test for antidepressive activity of above compounds and further study of this series are in progress.

EXPERIMENTAL

Mps were recorded on a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer in KBr pellet. The nmr spectra were measured on a Hitachi R-22FTS-A FT-NMR spectrometer (90Hz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard. The mass spectra were taken with a Shimadzu LKB-9000 instrument at 70eV. The uv spectra were taken on a Hitachi ESP-2 spectrophotometer in ethanol.

The procedures from VIb to XIIIb were carried out with almost similar manner to those from VIa to XIIIa, unless otherwise noted.

Methyl N-(3-Cyanopropyl)-N-tosylanthranilate (VIa)

A mixture of 240 g (786 mmole) of Va, 84.1 g (788 mmole) of 4-chlorobutyro-

nitrile, 296 g (2.13 mole) of anhydrous potassium carbonate, and 38.7 g (231 mmole) of potassium iodide in 870 ml of dry acetone was refluxed for 7 days. After cooling, the reaction mixture was poured into 2.5 L of ice-water. The precipitated white crystals were filtered, washed with water, and recrystallized from ethyl acetate-petroleum ether to give 277 g (95%) of VIa as colorless plates, mp 102.5-103.5°C; ir: ν max 2250, 1733, 1347, 1159 cm^{-1}; nmr ($CDCl_3$): δ 1.94 (quin, J = 7 Hz, $C\underline{H}_2$-CH_2-CN, 2H), 2.43 (s, CH_3 of Ts, 3H), 2.64 (t, J = 7 Hz, CH_2-CN, 2H), 3.67 (m, N-CH_2, 2H), 3.86 (s, CO_2CH_3, 3H), 6.87 (m, H-3, 1H), 7.38 (m, H-4, 5, and Ar-H of Ts, 6H), 7.87 (m, H-6, 1H); ms: parent peak (372) was not observed. Ms: m/z 217 (M - Ts, 65%), 185 (M - Ts - MeOH, 100).

Anal. Calcd. for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C,60.90, H, 5.39, N, 7.34.

5-Hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-carbonitrile (VIIa)

To a solution of 301 g (0.81 mole) of VIa in 1.5 L of dry dimethylformamide, was cautiously added a suspension of 123 g of sodium hydride (60% dispersion) in a mixture of 2.3 ml of dry methanol and 100 ml of dry dimethylformamide with stirring under nitrogen stream and cooling in an ice bath. After the addition was complete, the reaction mixture was poured into 3 L of diluted hydrochloric acid (ca. 8%) with stirring and the mixture was stirred for 2.5 h under cooling in an ice bath. The precipitated pale gray crystals were filtered, washed with water and recrystallized from ethanol to afford 241 g (88%) of VIIa as pale gray plates, mp 154-155°C (lit.[5a] mp 152-154°C).

4-Amino-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (VIIIa)

A mixture of 240 g (0.73 mole) of VIIa and 750 ml of formamide was heated at 150-160°C for 23 h with stirring under ammonia stream. The reaction mixture was allowed to stand overnight in a refrigerator and the precipitated crystals were filtered, washed with 100 ml of methanol and recrystallized from pyridine to give 215 g (83%) of VIIIa as pale gray prisms, mp 284-285°C; ir: ν max 3435, 3335, 3230, 1328, 1150 cm^{-1}; nmr (acetic acid-d_4): δ 2.33 (s, CH_3, 3H), 2.60 (t, J = 7 Hz, H-5, 2H), 4.32 (t, J = 7 Hz, H-6, 2H), 6.95-7.67

(m, H-8, 9, 10, 11, and Ar-H of Ts, 8H), 8.31 (s, H-2, 1H); ms: m/z 366 (M^+, 53%), 211 (M^+ - Ts, 100); uv: λ max 236 nm (log ε 4.21), 293 (3.34), 329 (shoulder).

Anal. Calcd. for $C_{19}H_{20}N_2O_4S$: C, 62.28; H, 4.95; N, 15.29. Found: C, 62.26; H, 4.83; N, 15.32.

6,7-Dihydro-5H-pyrimido[5,4-d][1]benzazepin-4(3H)-one (IXa)

A mixture of 215 g (0.59 mole) of VIIIa, 1 L of concd. hydrochloric acid, and 1 L of acetic acid was refluxed for 27 h. Further 700 ml of concd. hydrochloric acid was added to the reaction mixture and it was refluxed for more 43 h. The resulting solution was evaporated to dryness. The residue was dissolved in as small amount of water as possible and the solution was neutrallized with sodium carbonate. The mixture was allowed to stand for 3 h in an ice bath. The precipitated yellow crystals were filtered, washed with water, and recrystallized from ethanol to give 118 g (94%) of IXa as pale greenish yellow prisms, mp 231-232°C; ir: ν max 3335, 1620 cm^{-1}; nmr (DMSO-d_6): δ 2.78 (t, J = 5 Hz, H-5, 2H), 3.47(t, J = 5 Hz, H-6, 2H), 6.30, 12.30 (each br, exchanged with D_2O, H-7, H-3, each 1H), 6.70 (m, H-8 and 10, 2H), 7.13 (td, $J_{9,8}$,$J_{9,10}$ = 8 Hz, $J_{9,11}$ = 2 Hz, H-9, 1H), 8.00 (dd, $J_{10,11}$ = 8 Hz, $J_{9,11}$ = 2 Hz, H-11, 1H), 8.08 (s, H-2, 1H); ms: m/z 213 (M^+, 100%); uv: λ max 235 nm (log ε 4.38), 259 (shoulder), 286 (3.71), 296 (3.70), 309 (shoulder), 376 (3.49).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.54; H, 5.27; N, 19.43.

4-Chloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (Xa)

A mixture of 47.8 g (0.22 mole) of IXa, 100 ml of ethanol-free dry chloroform, and 200 ml (2.2 mole) of phosphoryl chloride was refluxed for 30 min. The reaction mixture was evaporated to dryness and 2 L of ice-water was poured at once to the residue. A sodium carbonate solution was added to the mixture to make alkali with stirring, followed by cooling in an ice bath for 30 min. The precipitated yellow crystals were filtered and recrystallized from benzene to afford 49.2 g (95%) of Xa as yellow prisms, mp 161-162°C; ir: ν max

3290 cm^{-1}; nmr ($CDCl_3$): δ 3.17 (t, J = 5 Hz, H-5, 2H), 3.43 (br, exchanged with D_2O, H-7, 1H), 3.80 (t, J = 5 Hz, H-6, 2H), 6.77 (d, $J_{8,9}$ = 7.5 Hz, H-8, 1H), 6.97 (t, J = 7.5 Hz, H-10, 1H), 7.30 (t, J = 7.5 Hz, H-9, 1H), 8.06 (d, $J_{11,10}$ = 7.5 Hz, H-11, 1H), 8.90 (s, H-2, 1H); ms: m/z 233 (M^+ + 2, 31%), 232 (M^+ + 2 - H, 50), 231 (M^+, 98), 230 (M^+ - H, 100); uv: λ max 242 nm (log ε 4.26), 262 (4.05), 280 (3.89), 390 (3.69).

Anal. Calcd. for $C_{12}H_{10}ClN_3$: C, 62.21; H, 4.35; N, 18.21. Found: C, 62.13; H, 4.31; N, 18.03.

4-(2-Hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (XIa)

A mixture of 10.0 g (43 mmole) of Xa and 20.0 ml (331 mmole) of ethanolamine was heated at 60-70°C for 2 h with stirring. The reaction mixture was evaporated to dryness in vacuo and 100 ml of 10% sodium carbonate solution was added to the residue. The precipitated crystals were filtered, washed with cold water, and recrystallized from water to give 10.7 g (97%) of XIa as pale yellow needles, mp 149-150°C; ir: ν max 3405, 3365, 3260 cm^{-1}; nmr (DMSO-d_6): δ 2.71 (t, J = 5 Hz, H-5, 2H), 3.53 (m, H-6 and N-CH_2CH_2-O, 6H), 4.71, 5.86, 6.91 (each br, exchanged with D_2O, 2 x NH and OH, each 1H), 6.73 (t, J = 8 Hz, H-10, 1H), 6.78 (d, $J_{8,9}$ = 8 Hz, H-8, 1H), 7.13 (td, $J_{8,9}$, $J_{9,10}$ = 8 Hz, $J_{9,11}$ = 2 Hz, H-9, 1H), 7.94 (dd, $J_{10,11}$ = 8 Hz, $J_{9,11}$ = 2 Hz, H-11, 1H), 8.38 (s, H-2, 1H); ms: m/z 256 (M^+, 100%), 239 (M^+ - OH, 83), 225 (M^+ - CH_2OH, 60), 211 (M^+ - CH_2CH_2OH, 49); uv: λ max 235 nm (log ε 4.65), 249 (shoulder), 268 (shoulder), 300 (3.93), 308 (shoulder), 345 (shoulder).

Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.71; H, 6.25; N, 21.70.

1,2,5,6-Tetrahydro-4H-imidazo[1',2':1,6]pyrimido[5,4-d][1]benzazepinium chloride (XIIa, as monohydrate)

A mixture of 10.6 g (41 mmole) of XIa and 60 ml (0.67 mole) of phosphoryl chloride was refluxed for 6 h. The reaction mixture was evaporated to dryness in vacuo. The residue was recrystallized from water to afford 10.7 g (89%) of XIIa as yellow needles, mp 278-281°C (dec.); ir: ν max 3390, 1620 cm^{-1}; nmr (DMSO-d_6): δ 2.83 (t, J = 4 Hz, H-4, 2H), 3.47 (t, J = 4 Hz, H-5,

2H), 4.00, 6.70 (each br, exchanged with D_2O, 2 x NH, each 1H), 3.91 (m, H-2, 2H), 4.49 (m, H-1, 2H), 6.66 (td, $J_{8,9}$,$J_{9,10}$ = 8 Hz, $J_{7,9}$ = 1.5 Hz, H-9, 1H), 6.81 (dd, $J_{7,8}$ = 8 Hz, $J_{7,9}$ = 1.5 Hz, H-7, 1H), 7.17 (td, $J_{7,8}$,$J_{8,9}$ = 8 Hz, $J_{8,10}$ = 1.5 Hz, H-8, 1H), 8.07 (dd, $J_{9,10}$ = 8 Hz, $J_{8,10}$ = 1.5 Hz, H-10, 1H), 8.51 (s, H-12, 1H); ms: parent peak (274) was not observed. Ms: m/z 238 (M - HCl, 98%), 237 (M - HCl - H, 40), 223 (M - HCl - H - CH_2, 100); uv: λ max 241 nm (log ε 4.39), 268 (shoulder), 289 (shoulder), 308 (shoulder), 322 (shoulder), 335 (shoulder), 364 (shoulder), 392 (3.50).

Anal. Calcd. for $C_{14}H_{15}ClN_4.H_2O$: C, 57.44; H, 5.85; N, 19.14. Found: C, 57.71; H, 5.77; N, 19.19.

1,2,5,6-Tetrahydro-4H-imidazo[1',2':1,6]pyrimido[5,4-d][1]benzazepine (XIIIa)

To a solution of XIIa in water was cautiously added a potassium hydroxide solution to make alkali and the mixture was allowed to stand for 2 h. The precipitated crystals were filtered and recrystallized from benzene to afford XIIIa quantitatively as pale yellow needles, mp 219-219.5°C; ir: ν max 3290 cm^{-1}; nmr ($CDCl_3$): δ 2.81 (t, J = 5.5 Hz, H-4, 2H), 3.70 (t, J = 5.5 Hz, H-5, 2H), 3.90 (br, exchanged with D_2O, H-6, 1H), 4.06 (br s, H-1 and 2, 4H), 6.67 (dd, $J_{7,8}$ = 8 Hz, $J_{7,9}$ = 1.5 Hz, H-7, 1H), 6.87 (td, $J_{8,9}$,$J_{9,10}$ = 8 Hz, $J_{7,9}$ = 1.5 Hz, H-9, 1H), 7.18 (td, $J_{7,8}$,$J_{8,9}$ = 8 Hz, $J_{8,10}$ = 2 Hz, H-8, 1H), 7.79 (s, H-12, 1H), 7.97 (dd, $J_{9,10}$ = 8 Hz, $J_{8,10}$ = 2 Hz, H-10, 1H); ms: m/z 238 (M^+, 97%), 237 (M^+ - H, 37), 223 (M^+ - CH_3, 100); uv: λ max 242 nm (log ε 4.54), 268 (4.25), 289 (shoulder), 325 (shoulder), 339 (shoulder), 358 (3.75), 386 (shoulder).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.65; H, 5.91; N, 23.38.

Methyl 4-Chloro-N-(3-cyanopropyl)-N-tosylanthranilate (VIb)

Recrystallization of VIb from methanol gave colorless plates (95%), mp 85-86.5°C; ir: ν max 2240, 1722, 1343, 1152 cm^{-1}; nmr ($CDCl_3$): δ 1.94 (quin, J = 7 Hz, CH_2-CH_2-CN, 2H), 2.44 (s, CH_3 of Ts, 3H), 2.64 (t, J = 7 Hz, CH_2-CN, 2H), 3.68 (m, N-CH_2, 2H), 3.85 (s, CO_2CH_3, 3H), 6.84 (d, $J_{3,5}$ = 2 Hz, H-3, 1H), 7.34 (m, H-5 and Ar-H of Ts, 5H), 7.85 (d, $J_{6,5}$ = 8 Hz, H-6, 1H); ms: parent

peak (406) was not observed. Ms: m/z 251 (M - Ts, 62%), 219 (M - Ts - CH_3OH, 100).

Anal. Calcd. for $C_{19}H_{19}ClN_2O_4S$: C, 56.09; H, 4.71; N, 6.88. Found: C, 55.99; H, 4.69; N, 6.84.

8-Chloro-5-hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-carbonitrile (VIIb)

Recrystallization of VIIb from ethanol gave pale gray prisms (85%), mp 162-164°C; ir: ν max 3130, 2210, 1338, 1152 cm^{-1}; nmr (DMSO-d_6): δ 2.12 (t, J = 6 Hz, H-3, 2H), 2.40 (s, CH_3, 3H), 3.97 (t, J = 6 Hz, H-2, 2H), 7.50 (m, Ar-H, 7H), 11.0 (br, exchanged with D_2O, OH, 1H); ms: m/z 376 (M^+ + 2, 4%), 374 (M^+, 12), 208 (M^+ - 166, 100).

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3S$: C, 57.68; H, 4.03; N, 7.47. Found: C, 57.54; H, 3.96; N, 7.19.

4-Amino-9-chloro-7-tosyl-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (VIIIb)

Recrystallization of VIIIb from acetonitrile gave pale gray needles (73%), mp 244-247°C; ir: ν max 3370, 3165, 1340, 1155 cm^{-1}; nmr (DMSO-d_6): δ 2.32 (s, CH_3, 3H), 2.50 (t, J = 6 Hz, H-5, 2H), 4.14 (t, J = 6 Hz, H-6, 2H), 6.73 (br, exchanged with D_2O, NH_2, 2H), 7.37 (m, H-8, 10, and 11 and Ar-H of Ts, 7H), 8.07 (s, H-2, 1H); ms: m/z 402 (M^+ + 2, 20%), 400 (M^+, 64), 247 (402 - Ts, 36), 245 (M^+ - Ts, 100); uv: λ max 241 nm (log ε 4.33), 268 (shoulder), 294 (3.42), 300 (shoulder).

Anal. Calcd. for $C_{19}H_{17}ClN_4O_2S$: C, 56.93; H, 4.27; N, 13.98. Found: C, 56.92; H, 4.07; N, 14.04.

9-Chloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepin-4(3H)-one (IXb)

Recrystallization of IXb from acetone gave pale greenish yellow prisms (79%), mp 264-267°C; ir: ν max 3280, 1620 cm^{-1}; nmr (DMSO-d_6): δ 2.80 (t, J = 4.5 Hz, H-5, 2H), 3.45 (t, J = 4.5 Hz, H-6, 2H), 6.50 (br, exchanged with D_2O, H-7, 1H), 6.64 (dd, $J_{10,11}$ = 9 Hz, $J_{8,10}$ = 2 Hz, H-10, 1H), 6.82 (d, $J_{8,10}$ = 2 Hz, H-8, 1H), 8.04 (d, $J_{10,11}$ = 9 Hz, H-11, 1H), 8.07 (s, H-2, 1H); ms: m/z 249 (M^+ + 2, 32%), 247 (M^+, 100); uv: λ max 237 nm (log ε 4.40), 258 (shoulder),

284 (3.77), 296 (3.72), 309 (shoulder), 374 (3.66).
Anal. Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07; N, 16.97. Found: C, 57.94; H, 4.00; N, 16.78.

4,9-Dichloro-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (Xb)

A mixture of 30 g (0.12 mole) of IXb and 100 ml of phosphoryl chloride was refluxed for 15 min. Similar treatment was carried out as described in the preparation of Xa. Recrystallization of Xb from benzene-cyclohexane gave 29 g (90%) of yellow prisms, mp 203-205°C; ir: ν max 3320 cm^{-1}; nmr ($CDCl_3$): δ 3.19 (t, J = 6 Hz, H-5, 2H), 3.76 (t, J = 6 Hz, H-6, 2H), 4.30 (br, exchanged with D_2O, H-7, 1H), 6.71 (d, $J_{8,10}$ = 2 Hz, H-8, 1H), 6.89 (dd, $J_{10,11}$ = 9 Hz, $J_{8,10}$ = 2 Hz, H-10, 1H), 8.05 (d, $J_{10,11}$ = 9 Hz, H-11, 1H), 8.86 (s, H-2, 1H); ms: m/z 269 (M^+ + 4, 12%), 267 (M^+ + 2, 66), 265 (M^+, 100); uv: λ max 221 nm (shoulder), 245 (log ε 4.31), 264 (4.06), 288 (3.88), 385 (3.77).
Anal. Calcd. for $C_{12}H_9Cl_2N_3$: C, 54.16; H, 3.41; N, 15.79. Found: C, 54.46; H, 3.33; N, 15.70.

9-Chloro-4-(2-hydroxyethylamino)-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepine (XIb)

A mixture of 12.0 g (45.2 mmole) of Xb and 25.0 ml (414 mmole) of ethanolamine was heated at 80°C for 45 min with stirring. Similar treatment was carried out as described in the preparation of XIa. Recrystallization of XIb from dioxane gave 12.6 g (96%) of pale yellow prisms, mp 183.5-184.5°C; ir: ν max 3440, 3320, 3170 cm^{-1}; nmr (DMSO-d_6): δ 2.74 (t, J = 5.5 Hz, H-5, 2H), 3.53 (m, H-6 and CH_2CH_2-O, 6H), 4.71, 6.30, 6.96 (each br, exchanged with D_2O, 2 x NH and OH, each 1H), 6.71 (dd, $J_{10,11}$ = 8.5 Hz, $J_{10,8}$ = 2.5 Hz, H-10, 1H), 6.85 (d, $J_{8,10}$ = 2.5 Hz, H-8, 1H), 7.99 (d, $J_{10,11}$ = 8.5 Hz, H-11, 1H), 8.37 (s, H-2, 1H); ms: m/z 292 (M^+ + 2, 31%), 290 (M^+, 100), 275 (292 - OH, 40), 273 (M^+ - OH, 77), 261 (292 - CH_2OH, 24), 259 (M^+ - CH_2OH, 66); uv: λ max 239 nm (log ε 4.54), 259 (shoulder), 303 (3.67), 310 (shoulder), 348 (3.57).
Anal. Calcd. for $C_{14}H_{15}ClN_4O$: C, 57.83; H, 5.20; N, 19.27. Found: C, 57.85; H, 5.24; N, 19.30.

8-Chloro-1,2,5,6-tetrahydro-4H-imidazo[1',2':1,6]pyrimido[5,4-d][1]benzazepine (XIIIb)

A mixture of 11.0 g (37.9 mmole) of XIb and 55 ml (0.16 mole) of phosphoryl chloride was refluxed for 3 h with stirring. The reaction mixture was evaporated to dryness in vacuo and 50 ml of hot water was added to dissolve the residue. The solution was basified with potassium hydroxide. The precipitated crystals were filtered and recrystallized from ethyl acetate to give 9.1 g (88%) of XIIIb as pale greenish yellow needles, mp 242-243°C; ir: ν max 3240 cm^{-1}; nmr ($CDCl_3$): δ 2.85 (t, J = 5 Hz, H-4, 2H), 3.69 (t, J = 5 Hz, H-5, 2H), 4.07 (s, H-1 and 2, 4H), 4.23 (br, exchanged with D_2O, H-6, 1H), 6.66 (d, $J_{7,9}$ = 2.5 Hz, H-7, 1H), 6.83 (dd, $J_{9,10}$ = 9 Hz, $J_{7,9}$ = 2.5 Hz, H-9, 1H), 7.80 (s, H-12, 1H), 7.97 (d, $J_{9,10}$ = 9 Hz, H-10, 1H); ms: m/z 274 (M^+ + 2, 32%), 272 (M^+, 100); uv: λ max 245 nm (log ε 4.57), 268 (shoulder), 274 (4.22), 289 (shoulder), 325 (shoulder), 338 (shoulder), 357 (3.78), 376 (shoulder). Anal. Calcd. for $C_{14}H_{13}ClN_4$: C, 61.65; H, 4.80; N, 20.54. Found: C, 61.89; H, 4.71; N, 20.49.

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