Polycyclic *N*-Hetero Compounds. XLII: Convenient Syntheses of 6,7-Dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine as a Novel Polyheterocyclic Ring System and Its 4-Substituted Derivatives

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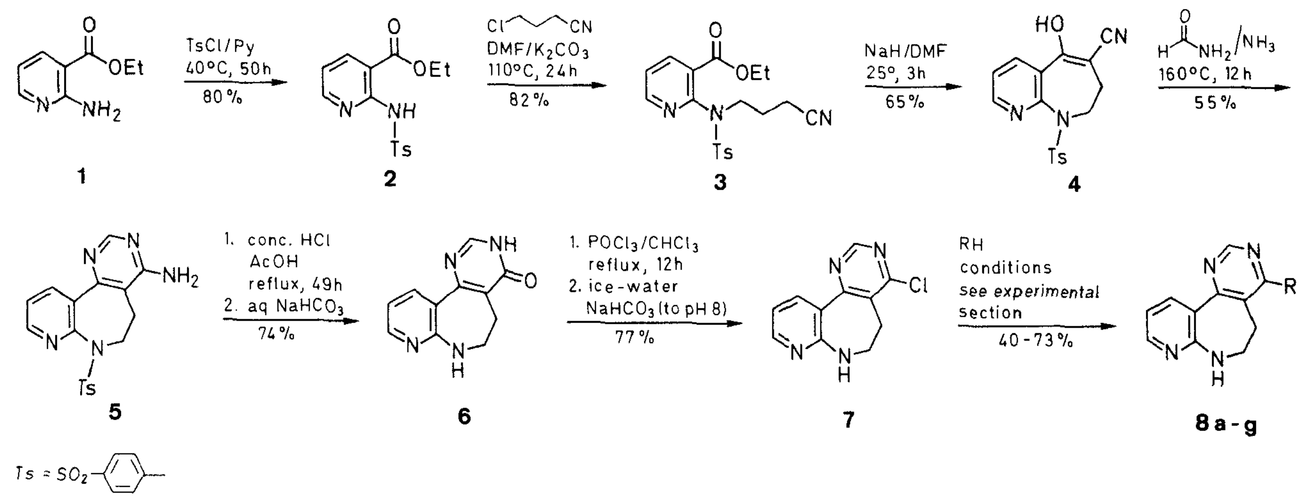
A convenient synthetic route for the syntheses of 6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine and its 4-substituted derivatives starting from ethyl 2-aminopyridine-3-carboxylate is described as the fist example of the unknown ring system. A new class of anti-platelet aggregation activity for them against collagene-induced aggregation of rabbit blood platelet in vitro was found.

Since the discovery or potential inhibitory activity against collagene-induced aggregation of rabbit blood platelet in 4-alkylamino-5,6-dihydrobenzo[*h*]quinazolines,[1] there has been a growing interest in such polyheterocyclic compounds which might have potential anti-platelet aggregation activity. We have recently designed to prepare the compounds with new ring systems and actually discovered that activity in the polyheterocyclic compounds such as 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines,[2] 5,6-dihydro-4*H*-benzo[3,4]-cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidines,[3] 1,2,4,5-tetrahydro[1]benzothiepino[5,4-*e*]imidazo[1,2-*c*]pyrimidines,[4] 5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidines,[4] 1,2,4,5-tetrahydro[1]benzoxepino[4,5-*e*]imidazo[1,2-*c*]-pyrimidines,[5] 5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidines,[5] and 1,2,5,6-tetrahydro-4*H*-imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1]benzazepines.[6] We report herein an efficient methodology for the preparation of the hitherto unknown ring system, 6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (**10**) and its 4-substituted derivatives **8a–g**, in a simple synthetic route.

The sequential synthetic methods are shown in Scheme **1**. The starting material, ethyl 2-(tosylamino)pyridine-3-carboxylate (**2**), was prepared by the tosylation of ethyl 2-aminopyridine-3-carboxylate (**1**) with tosyl chloride in dry pyridine. The IR spectrum of **2** showed the characteristic SO_2 bands at ν_{as} = 1335 and ν_s = 1160 cm^{-1}. The introduction of the 3-cyanopropyl group to the imino nitrogene of **2** was achieved by prolonged heating **2** with 4-chlorobutyronitrile in the presence of potassium carbonate in dry dimethylformamide to afford ethyl 2-[tosyl(3-cyanopropyl)amino]pyridine-3-carboxylate (**3**) which showed the characteristic C≡N band at ν = 2250 cm^{-1} in the IR spectrum. The key intermediate, 5-hydroxy-9-tosyl-8,9-dihydro-7*H*-pyrido[2,3-*b*]azepine-6-carbonitrile (**4**), was prepared by the Dieckmann-type cyclization of **3** with sodium hydride as a base in dimethylformamide. The structure of **4** having a 7-membered ring was verified by satisfactory analytical and spectral data. In particular, the IR spectrum in potassium bromide showed the β-oxonitrile structure indicated by the characteristic C=O band at ν = 1692 cm^{-1} and C≡N band at ν = 2240 cm^{-1}. The ^{1}H-NMR spectrum can be used to distinguish clearly between the two forms. Namely, the spectrum in DMSO-d_6 showed the β-hydroxynitrile structure indicated by the presence of the broad singlet signal of one proton at δ = 11.35 which was attributable to the OH at the 5-position. Whereas the spectrum in $CDCl_3$ showed the β-oxonitrile structure indicated by the presence of the double doublet signal of one proton at δ = 4.50 which was attributable to the proton at the 6-position and by the absence of the broad singlet signal of OH in the β-hydroxynitrile form.

Compound **4** thus obtained was then successfully cyclized by the reaction with formamide under ammonia stream at 160 °C to produce an additional pyrimidine ring on the azepine skeleton. The structure of the tricyclic compound, 4-amino-7-tosyl-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (**5**), was confirmed by satisfactory analytical and spectral data. Especially, the characteristic NH_2 bands at ν_{as} = 3370, ν_s = 3360, and δ = 1665 cm^{-1} in the IR spectrum and one proton singlet signal at δ = 8.37 attributable to the proton at the 2-position on the newly born pyrimidine ring in the ^{1}H-NMR (DMSO-d_6) spectrum were observed. Hydrolysis of the 4-amino and *N*-tosyl group of **5** to afford 6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepin-4(3*H*)-one (**6**) was effected by prolonged heating **5** with a mixture of concentrated hydrochloric acid and glacial acetic acid. Compound **6** exhibited NH and C=O absorptions in the IR spectrum at ν = 3240, 3050 and 1674 cm^{-1}, respectively, and demonstrated one proton singlet signal at δ = 12.41 attributable to the NH on the pyrimidine ring in the ^{1}H-NMR (DMSO-d_6) spectrum. Refluxing **6** with phosphoryl chloride in chloroform gave the corresponding 4-chloro derivative **7** in 77% yield. The 4-substituted 6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepines **8a–g** were easily prepared by the treatment of **7** with an appropriate alkylamine or alcohol. These structures were confirmed by elemental analyses, IR spectra, FAB mass spectrometry, and ^{1}H-NMR spectroscopy as shown in the experimental section.

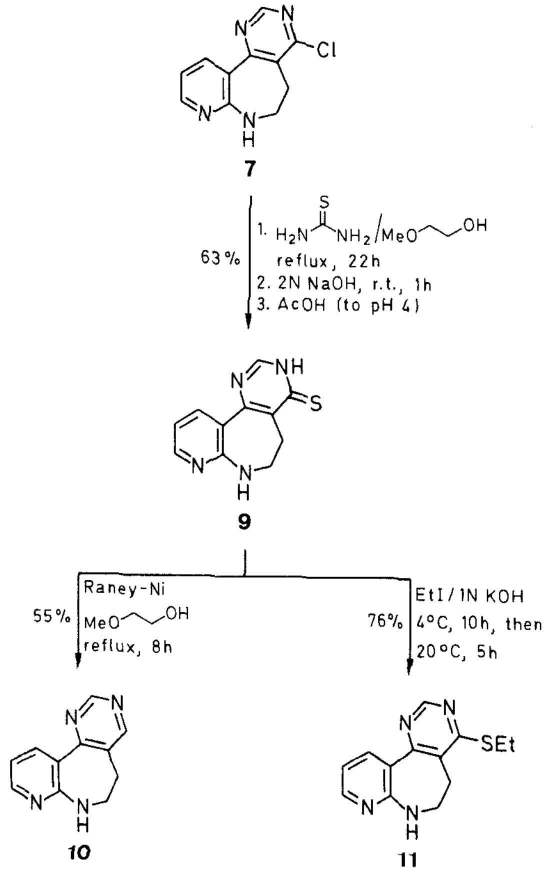
While the unsubstituted compound, 6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (**10**), was prepared by desulfurization of 6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepin-4(3*H*)-thione (**9**) using Raney-nickel catalyst. The requisite precursor **9** was synthesized by the thiation of the 4-chloro derivative **7**, that is, heating **7** under reflux with thiourea in 2-methoxyethanol followed by treatment with 2N sodium hydroxide gave the 4-thione derivative **9**. Then, boiling a mixture of **9** with an excess of Raney-nickel in 2-methoxyethanol afforded the unsubstituted compound **10** in 55% yield. The structure of **10** was verified by the disappearance of the characteristic NH and C=S bands due to the thiolactam of **9** at ν = 3140 and 1228 cm^{-1}, respectively, in the IR spectrum, and by the appearance of the one proton singlet signal at δ = 8.41 attributable to the proton at the 4-position, in the ^{1}H-NMR ($CDCl_3$) spectrum. In addition, alkylation of **9** by shaking with



8	R	8	R
a	NHEt	e	OEt
b	$NH(CH_2)_2OH$	f	$O(CH_2)_2OH$
c	$N(Me)(CH_2)_2OH$	g	$S(CH_2)_2OH$
d	morpholino		

Scheme 1

ethyl iodide in 1N potassium hydroxide gave the corresponding 4-ethylthio-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (**11**) in 76% yield.



Scheme 2

The compounds reported in this paper were examined for the inhibitory activity against rabbit platelet aggregation induced by collagen by a turbidimetric method reported by Born and Cross[7] using an aggregometer, and were mostly found to be slightly less active than aspirin which was familiar as an anti-platelet agent.[8] Further investigations along this line are now in progress and the results of the inhibitory activities in this paper will be reported elsewhere.

All reagents were of commercial quality from freshly opened containers and were used without further purification. Dry solvents (pyridine, DMF, and 2-methoxyethanol) were prepared by molecular sieves. Dry $CHCl_3$ was prepared by distillation over P_2O_5. Reactions were monitored by analytical TLC performed on Wako 70 FM silica gel plates and products were visualized by UV light. Column chromatography was carried out with Kiesel gel 60 (70–230 mesh ASTM, Merck). Melting points were taken using a Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were obtained using a Yanagimoto MT-2 CHN Corder element analyser. Mass spectra were obtained using a VG-70SE spectrometer with FAB ionization or a Shimadzu LKB-9000 spectrometer with EI ionization. IR spectra were obtained using a JASCO IRA-102 spectrophotometer. ^1H-NMR spectra were obtained using a Varian VXR 200 MHZ spectrometer with TMS as the internal standard.

Ethyl 2-(Tosylamino)pyridine-3-carboxylate (2):
A mixture of ethyl 2-aminopyridine-3-carboxylate[9] (**1**; 15 g, 90 mmol) and TsCl (25.7 g, 135 mmol) in dry pyridine (80 mL) is heated with stirring at 40 °C for 50 h. After cooling, the precipitate is filtered off and the filtrate is concentrated under reduced pressure. The residual product is isolated by column chromatography on silica gel (400 g, $CHCl_3$) and recrystallized from EtOAc to give compound **2** as colorless needles; yield: 23.1 g (80%); bp 117–119 °C; R_f 0.75 ($CHCl_3$/acetone, 1 : 1).

$C_{15}H_{16}N_2O_4S$	calc.	C 56.24	H 5.03	N 8.74
(320.4)	found	56.08	5.13	8.61

IR (KBr): ν = 3190 (NH), 1685 (C=O), 1335 (as, SO_2), 1290 (as, COC), 1160 (s, SO_2), 1146 cm^{-1} (s, COC).

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.34 (t, 3H, J = 7.10 Hz, $CH_2C\underline{H}_3$), 2.36 (s, 3H, Tosyl-CH_3), 4.36 (q, 2H, J = 7.10 Hz, $C\underline{H}_2CH_3$), 7.11 (dd, 1H, J_{4-5} = 7.87 Hz, J_{5-6} = 4.83 Hz, H-5), 7.36 (d, 2H, J = 8.44 Hz, Tosyl-H-3,5), 7.93 (d, 2H, J = 8.44 Hz, Tosyl-H-2,6), 8.23 (dd, 1H, J_{4-5} = 7.87 Hz, J_{4-6} = 1.90 Hz, H-4), 8.35 (dd, 1H, J_{4-6} = 1.90 Hz, J_{5-6} = 4.83 Hz, H-6), 10.59 (br s, 1H, NH exchangeable with D_2O).

MS (FAB): m/z = 321 (MH^+).

Ethyl 2-[Tosyl(3-cyanopropyl)amino]pyridine-3-carboxylate (3):

A mixture of **2** (20 g, 62.4 mmol), 4-chlorobutyronitrile (15 g, 145 mmol), and anhydr. K_2CO_3 (34.6 g, 249.5 mmol) in dry DMF (300 mL) is heated with stirring at 110 °C for 24 h. The precipitate is filtered off and the filtrate is concentrated under reduced pressure. The product is isolated by column chromatography on silica gel (400 g, benzene/EtOAc, 7:1) and recrystallized from benzene/cyclohexane to give compound **3** as colorless needles; yield: 19.8 g (82 %); mp 73–75 °C; R_f 0.26 (benzene/EtOAc, 5:1).

$C_{19}H_{21}N_3O_4S$	calc.	C 58.90	H 5.46	N 10.85
(387.5)	found	58.80	5.40	10.62

IR (KBr): ν = 2250 (C≡N), 1714 (C=O), 1343 (as, SO_2), 1308 (as, COC), 1160 (s, SO_2), 1105 cm^{-1} (s, COC).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.47 (t, 3H, J = 7.16 Hz, $CH_2C\underline{H}_3$), 1.86 (m, 2H, $C\underline{H}_2CH_2CN$), 2.40 (s, 3H, Tosyl-CH_3), 2.71 (t, 2H, J = 7.45 Hz, CH_2CN), 3.80 (t, 2H, J = 5.98 Hz, NCH_2), 4.47 (q, 2H, J = 7.16 Hz, $C\underline{H}_2CH_3$), 7.18–7.39 (m, 5H, H-5, Ph-H), 8.24 (dd, 1H, J_{4-5} = 7.75 Hz, J_{4-6} = 1.96 Hz, H-4), 8.45 (dd, 1H, J_{4-6} = 1.96 Hz, J_{5-6} = 4.75 Hz, H-6).

MS (FAB): m/z = 388 (MH^+).

5-Hydroxy-9-tosyl-8,9-dihydro-7*H*-pyrido[2,3-*b*]azepine-6-carbonitrile (4):

To an ice-cooled solution of **3** (20 g, 51.6 mmol) in dry DMF (120 mL) is added NaH (14 g, 350 mmol, as 60 % oil dispersion) by portions with stirring, and the mixture is stirred at 25 °C for 3 h. After the reaction, the mixture is taken up in ice-water (300 mL) and acidified (pH ca. 5) with 10 % HCl. The mixture is extracted with EtOAc (4 × 150 mL). The combined organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), and concentrated in vacuo to yield the solid. The crude product is purified by column chromatography on silica gel (200 g, benzene/EtOAc, 7:1) and recrystallized from benzene to give compound **4** as colorless needles; yield: 11.5 g (65 %); mp 132–134 °C; R_f 0.31 (benzene/EtOAc, 5:1).

$C_{17}H_{15}N_3O_3S$	calc.	C 59.81	H 4.43	N 12.31
(341.4)	found	60.07	4.54	12.05

IR (KBr): ν = 2240 (C≡N), 1692 (C=O), 1350 (as, SO_2), 1170 cm^{-1} (s, SO_2).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.33 (t, 2H, J = 6.35 Hz, H-7), 2.41 (s, 3H, CH_3), 2.83 (t, 2H, J = 6.35 Hz, H-8), 7.43 (d, 2H, J = 8.14 Hz, Tosyl-H-3,5), 7.48 (dd, 1H, J_{2-3} = 4.80 Hz, J_{3-4} = 7.86 Hz, H-3), 7.95 (d, 2H, J = 8.14 Hz, Tosyl-H-2,6), 8.00 (dd, 1H, J_{2-4} = 1.89 Hz, J_{3-4} = 7.86 Hz, H-4), 8.49 (dd, 1H, J_{2-3} = 4.80 Hz, J_{2-4} = 1.89 Hz, H-2), 11.35 (br, 1H, OH exchangeable with D_2O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.43 (m, 1H, one of H-7), 2.45 (s, 3H, CH_3), 3.04–3.33 (m, 2H, each one of H-7 and H-8), 4.36 (m, 1H, one of H-8), 4.50 (dd, 1H, J = 6.93, 11.57 Hz, H-6, exchangeable with D_2O), 7.24 (dd, 1H, J_{2-3} = 4.71 Hz, J_{3-4} = 7.84 Hz, H-3), 7.37 (d, 2H, J = 8.32 Hz, Tosyl-H-3,5), 8.14 (d, 2H, J = 8.32 Hz, Tosyl-H-2,6), 8.23 (dd, 1H, J_{2-4} = 1.97 Hz, J_{3-4} = 7.84 Hz, H-4), 8.50 (dd, 1H, J_{2-3} = 4.71 Hz, J_{2-4} = 1.97 Hz, H-2).

MS (FAB): m/z = 342 (MH^+).

4-Amino-7-tosyl-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]-azepine (5):

A mixture of **4** (10 g, 29 mmol) and $HCONH_2$ (49.7 mL, 1.25 mol) is heated with stirring at 160 °C for ca. 12 h under NH_3 stream until the substrate **4** disappears. The reaction is monitored by TLC using MeOH as eluent and the product is visualized by UV light. The mixture is allowed to stand overnight in a refrigerator, and the resulting crystals are collected by filtration and recrystallized from MeOH to give **5** as brown needles. The mother liquor is extracted with EtOAc (3 × 20 mL). The combined organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), and concentrated in vacuo to yield a second crop; yield: 5.9 g (55 %); mp 265–267 °C; R_f = 0.55 (MeOH).

$C_{18}H_{17}N_5O_2S$	calc.	C 58.84	H 4.66	N 19.06
(367.4)	found	58.78	4.61	18.82

IR (KBr): ν = 3370 (as, NH_2), 3360 (s, NH_2), 1350 (as, SO_2), 1160 cm^{-1} (s, SO_2) and δ = 1665 cm^{-1} (NH_2).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.39 (s, 3H, CH_3), 2.63 (t, 2H, J = 6.35 Hz, H-5), 3.95 (t, 2H, J = 6.35 Hz, H-6), 7.01 (s, 2H, NH_2, exchangeable with D_2O), 7.37 (d, 2H, J = 8.10 Hz, Tosyl-H-3,5), 7.50 (dd, 1H, J_{9-10} = 4.70 Hz, J_{10-11} = 7.76 Hz, H-10), 7.81 (d, 2H, J = 8.10 Hz, Tosyl-H-2,6), 8.18 (dd, 1H, J_{9-11} = 1.90 Hz, J_{10-11} = 7.76 Hz, H-11), 8.37 (s, 1H, H-2), 8.50 (dd, 1H, J_{9-10} = 4.70 Hz, J_{9-11} = 1.90 Hz, H-9).

MS (FAB): m/z = 368 (MH^+)

6,7-Dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepin-4(3H)-one (6):

A solution of **5** (5 g, 14.6 mmol) in concentrated HCl (25 mL) and AcOH (25 mL) is heated under reflux for 49 h. To complete the reaction, further addition of concentrated HCl (3 × 25 mL) is necessary during the reaction. The resulting solution is concentrated to dryness in vacuo, and the residue is dissolved in H_2O (ca. 70 mL) and neutralized with $NaHCO_3$ under cooling. The precipitate formed is filtered by suction, washed with cold H_2O, and recrystallized from MeOH to give **6** as colorless needles; yield: 2.3 g (74 %); mp 296–298 °C; R_f 0.58 (MeOH).

$C_{11}H_{10}N_4O$	calc.	C 61.67	H 4.71	N 26.16
(214.2)	found	61.62	4.69	25.86

IR (KBr): ν = 3240, 3050 (NH), 1674 (C=O), 1348 cm^{-1} (C–N).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.82 (m, 2H, H-5), 3.42 (m, 2H, H-6), 6.66 (dd, 1H, J_{9-10} = 4.51 Hz, J_{10-11} = 7.93 Hz, H-10), 7.18 (t, 1H, J = 4.56 Hz, H-7, exchangeable with D_2O), 8.05 (dd, 1H, J_{9-10} = 4.51 Hz, J_{9-11} = 1.91 Hz, H-9), 8.09 (s, 1H, H-2), 8.42 (dd, 1H, J_{9-11} = 1.91 Hz, J_{10-11} = 7.93 Hz, H-11), 12.41 (br s, H-3, exchangeable with D_2O).

MS: m/z = 215 (MH^+).

4-Chloro-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (7):

To a stirred mixture of **6** (2 g, 9.34 mmol) in ethanol-free dry $CHCl_3$ (5 mL) is added $POCl_3$ (9 mL, 96.6 mmol), and the solution is heated under reflux for 12 h. After the reaction, the solution is concentrated to dryness in vacuo and ice-water (ca. 10 mL) is poured to the residue at once. The resulting solution is basified (pH ca. 8) with sat. aq $NaHCO_3$ to afford the solid, which is filtered by suction, washed with cold H_2O, and recrystallized from toluene to give **7** as yellow needles; yield: 1.67 g (77 %); mp 208–210 °C; R_f 0.63 (MeOH).

$C_{11}H_9ClN_4$	calc.	C 56.78	H 3.90	N 24.08
(232.7)	found	57.08	3.94	23.88

IR (KBr): ν = 3230 (NH), 763 cm^{-1} (C–Cl).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.28 (m, 2H, H-5), 3.73 (m, 2H, H-6), 5.67 (br, 1H, H-7, exchangeable with D_2O), 6.80 (dd, 1H, J_{9-10} = 4.63 Hz, J_{10-11} = 7.95 Hz, H-10), 8.22 (dd, 1H, J_{9-10} = 4.63 Hz, J_{9-11} = 1.85 Hz, H-9), 8.54 (dd, 1H, J_{9-11} = 1.85 Hz, J_{10-11} = 7.95 Hz, H-11), 8.85 (s, 1H, H-2).

MS (FAB): m/z = 233 (MH^+).

4-Ethylamino-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (8a):

A mixture of **7** (1 g, 4.3 mmol) and 70 % aq $EtNH_2$ (42.7 mL, 528 mmol) in dioxane (60 mL) is stirred at r.t. for 40 h. Concentration of the solution to dryness in vacuo and recrystallization of the residue from EtOAc gives **8a** as colorless needles; yield: 684 mg (66 %); mp 208–209 °C; R_f 0.26 (acetone/$CHCl_3$, 1:1).

$C_{13}H_{15}N_5$	calc.	C 64.71	H 6.27	N 29.03
(241.3)	found	64.60	6.55	28.90

IR (KBr): ν = 3340, 3250 cm^{-1} (NH).

^1H-NMR ($CDCl_3$/TMS): δ = 1.28 (t, 3 H, J = 7.20 Hz, CH_3), 2.75 (t, 2 H, J = 5.13 Hz, H-5), 3.54 (q, 2 H, J = 7.20 Hz, CH_2CH_3), 3.68 (dd, 2 H, J = 4.64, 9.96 Hz, H-6), 4.73 (br, 1 H, 4-NH, exchangeable with D_2O), 5.42 (br, 1 H, H-7, exchangeable with D_2O), 6.81 (dd, 1 H, J_{9-10} = 4.69 Hz, J_{10-11} = 7.86 Hz, H-10), 8.12 (dd, 1 H, J_{9-10} = 4.69 Hz, J_{9-11} = 1.82 Hz, H-9), 8.58 (s, 1 H, H-2), 8.60 (dd, 1 H, J_{9-11} = 1.82 Hz, J_{10-11} = 7.86 Hz, H-11).

MS (FAB): m/z = 242 (MH^+).

4-(2-Hydroxyethylamino)-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (8b):

A mixture of **7** (1 g, 4.3 mmol), 2-aminoethanol (1.31 g, 21.4 mmol), and anhydr. K_2CO_3 (1.19 g, 8.6 mmol) in dioxane (30 mL) is heated under reflux for 19 h. After the reaction, the precipitate is filtered off. The filtrate is concentrated in vacuo and treated with H_2O (40 mL) to yield the crystals, which are filtered by suction and recrystallized from EtOAc to afford **8b** as colorless prims; yield: 730 mg (66%); mp 206–208 °C; R_f 0.52 (MeOH).

$C_{13}H_{15}N_5O$	calc.	C 60.68	H 5.88	N 27.22
(257.3)	found	61.00	5.84	27.03

IR (KBr): ν = 3350 (OH), 3220 (NH), 1053 cm^{-1} (COH).

^1H-NMR (DMSO-d_6/TMS): δ = 2.77 (br t, 2 H, J = 5.02 Hz, H-5), 3.38–3.56 (m, 6 H, H-6, CH_2CH_2OH), 4.73 (t, 1 H, J = 5.37 Hz, OH, exchangeable with D_2O), 6.68 (dd, 1 H, J_{9-10} = 4.53 Hz, J_{10-11} = 7.81 Hz, H-10), 6.89 (br t, 1 H, J = 4.40 Hz, 4-NH, exchangeable with D_2O), 7.00 (br, t, 1 H, H-7, exchangeable with D_2O), 8.05 (dd, 1 H, J_{9-10} = 4.53 Hz, J_{9-11} = 1.76 Hz, H-9), 8.36 (s, 1 H, H-2), 8.42 (dd, 1 H, J_{9-11} = 1.76 Hz, J_{10-11} = 7.81 Hz, H-11).

MS (FAB): m/z = 258 (MH^+).

4-Methyl(2-hydroxyethyl)amino]-6,7-dihydro-5*H*-pyrido[2,3-*b*]-pyrimido[4,5-*d*]azepine (8c):

A mixture of **7** (1 g, 4.3 mmol) and 2-(methylamino)ethanol (1.82 g, 24.2 mmol) is heated with stirring at 60 °C for 1.5 h. After cooling, dilution of the solution with H_2O (50 mL) affords the crystals, which are filtered by suction, washed with cold H_2O, and recrystallized from EtOH to give **8c** as colorless needles; yield: 735 mg (63%); mp 160–162 °C; R_f 0.03 (EtOAc).

$C_{14}H_{17}N_5O$	calc.	C 61.97	H 6.32	N 25.81
(271.3)	found	62.05	6.33	25.58

IR (KBr): ν = 3410 (OH), 3230 (NH), 1040 cm^{-1} (COH).

^1H-NMR ($CDCl_3$/TMS): δ = 3.01 (m, 2 H, H-5), 3.06 (s, 3 H, CH_3), 3.64 (br t, 2 H, J = 4.67 Hz, CH_2CH_2OH), 3.72 (m, 2 H, H-6), 3.90 (t, 2 H, J = 4.67 Hz, CH_2OH), 5.48 (br t, 2 H, H-7, OH, exchangeable with D_2O), 6.79 (dd, 1 H, J_{9-10} = 4.69 Hz, J_{10-11} = 7.86 Hz, H-10), 8.15 (dd, 1 H, J_{9-10} = 4.69 Hz, J_{9-11} = 1.85 Hz, H-9), 8.42 (dd, 1 H, J_{9-11} = 1.85 Hz, J_{10-11} = 7.86 Hz, H-11), 8.55 (s, 1 H, H-2).

MS (EI): m/z (%) = 271 (M^+, 15), 256 ($M^+ - CH_3$, 11), 254 ($M^+ - OH$, 7), 240 ($M^+ - CH_2OH$, 100), 226 ($M^+ - CH_2CH_2OH$, 33), 197 ($M^+ - N(CH_3)CH_2CH_2OH$, 22).

4-Morpholino-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (8d):

A mixture of **7** (1 g, 4.3 mmol) and morpholine (4 mL, 45.9 mmol) is heated at 80 °C for 1 h. After cooling, the solution is diluted with H_2O (20 mL) to give the solid, which is filtered by suction. The filtrate is adjusted to pH 8 with AcOH and extracted with EtOAc (4 × 10 mL). The combined organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), and concentrated in vacuo to yield a second crop. The solids are recrystallized from benzen to yield **8d** as colorless needles; yield: 884 mg (73%); mp 197–198 °C; R_f 0.34 (acetone/$CHCl_3$, 1 : 1).

$C_{15}H_{17}N_5O$	calc.	C 63.58	H 6.05	N 24.72
(283.3)	found	63.72	6.18	24.75

IR (KBr): ν = 3230 cm^{-1} (NH).

^1H-NMR ($CDCl_3$/TMS): δ = 3.00 (m, 2 H, H-5), 3.30 (t, 2 H, J = 4.73 Hz, $H_{morpholine}$), 3.65 (m, 2 H, H-6), 3.84 (t, 2 H, J = 4.73 Hz, $H_{morpholine}$), 5.70 (br t, 1 H, H-7, exchangeable with D_2O), 6.77 (dd, 1 H, J_{9-10} = 4.66 Hz, J_{10-11} = 7.92 Hz, H-10), 8.14 (dd, 1 H, J_{9-10} = 4.66 Hz, J_{9-11} = 1.88 Hz, H-9), 8.47 (dd, 1 H, J_{9-11} = 1.88 Hz , J_{10-11} = 7.92 Hz, H-11), 8.72 (s, 1 H, H-2).

MS (FAB): m/z = 284 (MH^+).

4-Ethoxy-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (8e):

To a stirred solution of NaOEt prepared from Na (168 mg, 7.3 mmol) and abs. EtOH (60 mL) is added **7** (1 g, 4.3 mmol) by portions at 0–5 °C, and the solution is stirred at r.t. for 3 h. After the solution is further heated under reflux for 1 h, the precipitate is filtered off. The filtrate is concentrated in vacuo, treated with H_2O (30 mL), neutralized with AcOH, and extracted with EtOAc (4 × 15 mL). The combined organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), concentrated in vacuo, and recrystallized from EtOH to afford **8e** as colorless needles; yield: 677 mg (65%); mp 155–156 °C; R_f 0.03 (CH_2Cl_2).

$C_{13}H_{14}N_4O$	calc.	C 64.44	H 5.82	N 23.13
(242.3)	found	64.44	5.97	23.01

IR (KBr): ν = 3230 (NH), 1230 (as, =COC), 1028 cm^{-1} (s, =COC).

^1H-NMR ($CDCl_3$/TMS): δ = 1.43 (t, 3 H, J = 7.08 Hz, CH_3), 3.07 (t, 2 H, J = 4.90 Hz, H-5), 3.66 (dd, 2 H, J = 4.64, 9.82 Hz, H-6), 4.45 (q, 2 H, J = 7.08 Hz, CH_2CH_3), 5.50 (br t, 1 H, H-7, exchangeable with D_2O), 6.77 (dd, 1 H, J_{9-10} = 4.66 Hz, J_{10-11} = 7.90 Hz, H-10), 8.15 (dd, 1 H, J_{9-10} = 4.66 Hz, J_{9-11} = 1.88 Hz, H-9), 8.57 (dd, 1 H, J_{9-11} = 1.88 Hz, J_{10-11} = 7.90 Hz, H-11), 8.66 (s, 1 H, H-2).

MS (FAB): m/z = 243 (MH^+).

4-(2-Hydroxyethoxy)-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (8f):

A mixture of **7** (1 g, 4.3 mmol), ethylene glycol (20 mL, 359 mmol), and Et_3N (4 mL, 28.7 mmol) is stirred at 70–80 °C for 24 h. After the reaction, the solution is concentrated in vacuo to remove excess Et_3N, treated with H_2O (60 mL), and extracted with $CHCl_3$ (3 × 30 mL). The combined organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), concentrated in vacuo, and recrystallized from benzene to yield **8f** as colorless needles; yield: 778 mg (70%); mp 143–145 °C; R_f 0.23 (acetone/$CHCl_3$, 1 : 1).

$C_{13}H_{14}N_4O_2$	calc.	C 60.45	H 5.46	N 21.70
(258.3)	found	60.16	5.43	21.98

IR (KBr): ν = 3350 (OH), 3250 (NH), 1230 (as, =COC), 1068 (COH), 1020 cm^{-1} (s, =COC).

^1H-NMR ($CDCl_3$/TMS): δ = 2.84 (br, 1 H, OH, exchangeable with D_2O), 3.08 (br t, 2 H, J = 4.86 Hz, H-5), 3.65 (dd, 2 H, J = 4.64, 9.71 Hz, H-6), 3.99 (t, 2 H, J = 4.41 Hz, CH_2OH), 4.56 (t, 2 H, J = 4.41 Hz, OCH_2CH_2OH), 5.67 (br t, 1 H, H-7, exchangeable with D_2O), 6.78 (dd, 1 H, J_{9-10} = 4.64 Hz, J_{10-11} = 7.87 Hz, H-10), 8.15 (dd, 1 H, J_{9-10} = 4.64 Hz, J_{9-11} = 1.76 Hz, H-9), 8.60 (dd, 1 H, J_{9-11} = 1.76 Hz, J_{10-11} = 7.87 Hz, H-11), 8.65 (s, 1 H, H-2).

MS (FAB): m/z = 259 (MH^+).

4-(2-Hydroxyethylthio)-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (8g):

A mixture of **7** (1 g, 4.3 mmol) and 2-mercaptoethanol (6 mL, 85.6 mmol) in dry pyridine (2 mL) is heated under reflux with stirring for 6 h. After cooling, the solution is diluted with H_2O (20 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layer is washed with sat. aq NaCl, dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oily mass, which is recrystallized from EtOAc to yield **8g** as pale yellow needles; yield: 472 mg (40%); mp 182–184 °C; R_f 0.25 (acetone/$CHCl_3$, 1 : 1).

$C_{13}H_{14}N_4OS$	calc.	C 56.91	H 5.14	N 20.42
(274.3)	found	56.67	5.19	20.50

IR (KBr): ν = 3320 (OH), 3250 (NH), 1043 cm^{-1} (COH).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.94 (m, 2H, H-5), 3.30 (m, 2H, SCH_2), 3.49 (m, 2H, H-6), 3.63 (m, 2H, $C\underline{H}_2OH$), 5.02 (t, 1H, J = 5.54 Hz, OH, exchangeable with D_2O), 6.71 (dd, 1H, J_{9-10} = 4.50 Hz, J_{10-11} = 7.97 Hz, H-10), 7.32 (br t, J = 4.76 Hz, H-7, exchangeable with D_2O), 8.13 (dd, 1H, J_{9-10} = 4.50 Hz, J_{9-11} = 1.91 Hz, H-9), 8.49 (dd, 1H, J_{9-11} = 1.91 Hz, J_{10-11} = 7.97 Hz, H-11), 8.82 (s, 1H, H-2).

MS (EI): m/z (%) = 274 (M^+, 8), 257 (M^+ $-$OH, 8), 229 (M^+ $-CH_2CH_2OH$, 13), 197 (M^+ $-SCH_2CH_2OH$, 9), 40 (M^+ $-$234, 100).

6,7-Dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepin-4(3*H*)-thione (9):

A mixture of **7** (1 g, 4.3 mmol) with thiourea (1.64 g, 21.5 mmol) in dry 2-methoxyethanol (35 mL) is heated under reflux for 22 h. After the reaction, the mixture is concentrated in vacuo and 2N NaOH (40 mL) is added to the residue. Then, the mixture is stirred at r.t. for 1 h. Acidification (pH 4) of the mixture with AcOH deposites the solid, which is recrystallized from 2-methoxyethanol to give compound **9** as yellow needles; yield: 624 mg (63%); mp 268–270 °C; R_f 0.47 (acetone/$CHCl_3$, 1:1).

$C_{11}H_{10}N_4S$	calc.	C 57.37	H 4.38	N 24.33
(230.3)	found	57.11	4.45	24.51

IR (KBr): ν = 3200, 3140 (NH), 1228 cm^{-1} (C=S).

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.30 (m, 2H, H-5), 3.44 (m, 2H, H-6), 6.69 (dd, 1H, J_{9-10} = 4.49 Hz, J_{10-11} = 7.95 Hz, H-10), 7.36 (br t, 1H, H-7, exchangeable with D_2O), 8.13 (dd, 1H, J_{9-10} = 4.49 Hz, J_{9-11} = 1.90 Hz, H-9), 8.23 (s, 1H, H-2), 8.35 (dd, 1H, J_{9-11} = 1.90 Hz, J_{10-11} = 7.95 Hz, H-11), 13.96 (br s, 1H, H-3, exchangeable with D_2O).

MS (FAB): m/z = 231 (MH^+).

6,7-Dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (10):

A stirred mixture of **9** (1 g, 4.34 mmol) and wet Raney-Ni (5 mL, precipitate from MeOH suspension) in 2-methoxyethanol (100 mL) is heated under reflux for 8 h. After the reaction, Raney-Ni is filtered off and the filtrate is concentrated to dryness in vacuo. The residue is recrystallized from benzene to afford **10** as yellow needles; yield: 0.47 g (55%); mp 159–161 °C; R_f 0.2 (acetone/$CHCl_3$, 1:1).

$C_{11}H_{10}N_4$	calc.	C 66.65	H 5.09	N 28.27
(198.2)	found	66.76	5.17	27.98

IR (KBr): ν = 3240 cm^{-1} (NH).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.07 (br t, 2H, J = 4.61 Hz, H-5), 3.70 (m, 2H, H-6), 5.85 (br t, 1H, H-7, exchangeable with D_2O), 6.79 (dd, 1H, J_{9-10} = 4.61 Hz, J_{10-11} = 7.97 Hz, H-10), 8.20 (dd, 1H, J_{9-10} = 4.61 Hz, J_{9-11} = 1.66 Hz, H-9), 8.41 (br s, 1H, H-4), 8.68 (dd, 1H, J_{9-11} = 1.66 Hz, J_{10-11} = 7.97 Hz, H-11), 9.13 (br s, 1H, H-2).

MS (FAB): m/z = 199 (MH^+).

4-Ethylthio-6,7-dihydro-5*H*-pyrido[2,3-*b*]pyrimido[4,5-*d*]azepine (11):

A mixture of **9** (0.5 g, 2.17 mmol) and EtI (1.02 g, 6.51 mmol) in 1N KOH (3.26 mL, 3.26 mmol) is shaked at 4 °C for 10 h and at 20 °C for 5 h. The deposited crystals are filtered by suction and washed with cold H_2O. The filtrate (pH 4) acidified with AcOH is concentrated in vacuo and crystallized from H_2O to yield the second crop. The combined crystals are recrystallized from EtOAc to afford pure compound **11** as yellow needles; yield: 426 mg (76%); mp 186–187 °C; R_f 0.64 (acetone/$CHCl_3$, 1:1).

$C_{13}H_{14}N_4S$	calc.	C 60.44	H 5.46	N 21.69
(258.3)	found	60.32	5.52	21.61

IR (KBr): ν = 3230 cm^{-1}(NH).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.40 (t, 3H, J = 7.37 Hz, CH_3), 3.04 (t, 2H, J = 4.88 Hz, H-5), 3.24 (q, 2H, J = 7.37 Hz, $C\underline{H}_2CH_3$), 3.70 (dd, 2H, J = 4.64, 9.82 Hz, H-6), 5.52 (br t, 1H, H-7, exchangeable with D_2O), 6.79 (dd, 1H, J_{9-10} = 4.66 Hz, J_{10-11} = 7.87 Hz, H-10), 8.17 (dd, 1H, J_{9-10} = 4.66 Hz, J_{9-11} = 1.89 Hz, H-9), 8.52 (dd, 1H, J_{9-11} = 1.89 Hz, J_{10-11} = 7.87 Hz, H-11), 8.85 (s, 1H, H-2).

MS (FAB): m/z = 259 (MH^+).

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(1) Hirota, T.; Sasaki, K.; Ohtomo, H.; Uehara, A.; Nakayama, T. *Heterocycles* **1990**, *31*, 153.
(2) Sasaki, K.; Hirota, T.; Arimoto, Y.; Satoh, Y.; Ohtomo, H.; Nakayama, T. *J. Heterocycl. Chem.* **1990**, *27*, 1771.
(3) Sasaki, K.; Sekiya, Y.; Nagamatsu, T.; Ohtomo, H.; Nakayama, T.; Hirota, T. *J. Heterocycl. Chem.* **1991**, *28*, 503.
(4) Nagamatsu, T.; Kinoshita, K.; Sasaki, K.; Nakayama, T.; Hirota, T. *J. Heterocycl. Chem.* **1991**, *28*, 513.
(5) Nagamatsu, T.; Tsurubayashi, S.; Sasaki, K.; Hirota, T. *Synthesis* **1991**, 303.
(6) Nagamatsu, T.; Yamada, M.; Sasaki, K.; Ohtomo, H.; Nakayama, T.; Hirota, T. *Aust. J. Chem.* **1991**, submitted.
(7) Born, G.V.R.; Cross, M.J. *J. Physiol.* **1963**, *168*, 178.
(8) Mustard, J.F.; Packham, M.A. *Pharmacol. Rev. (USA)* **1970**, *22*, 97 and references therein.
(9) Fox, H.H. *J. Org. Chem.* **1952**, *17*, 547.