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CHEMISTRY OF NITROENAMINES. PART 2. SYNTHESIS OF SATURATED PYRROLO-PYRIMIDINES AND -PYRAZINES

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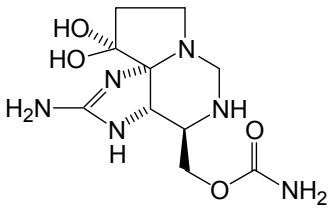
Abstract – New saturated pyrrolo-pyrimidines and pyrrolo-pyrazines were synthesized from 2-nitromethylene-pyrrolidine. Additionally, some simple aminomethylated derivatives of Mannich type were prepared. The nitro compounds were reduced into diastereomeric amines, which were separated and characterized structurally.

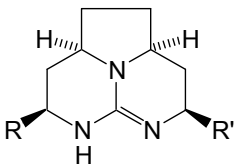
INTRODUCTION

Due to their push pull electronic structure the nitroenamines[1] can readily undergo chemical transformations providing a wide spectrum of various heterocycles. Thus in our preceding papers we have described the preparation of divers pyrrolizines[2] and indolizidines[3] starting from 2-nitromethylene-pyrrolidine (**1**). Enaminoesters, *e.g.* pyrrolidin-2-ylidene-acetic acid ethyl ester[7] were also subjected to similar Mannich reactions, providing ester derivatives in moderate yields.

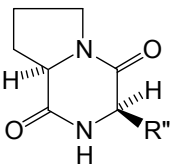
Although the thoroughly studied saxitoxin,[4] an extremely toxic substance of marine organisms incorporates a pyrrolo-pyrimidine part in its tricyclic structure, simple pyrrolo-pyrimidines are less investigated. Based on the enhanced reactivity of the nitroenamines, in this paper we report the synthesis of some saturated pyrrolo-pyrimidines, along with some new pyrrolo-pyrazines, occurring as subunits in the molecules of some natural products, *e.g.* batzelladines[5] and naseseazines.[6]



saxitoxin



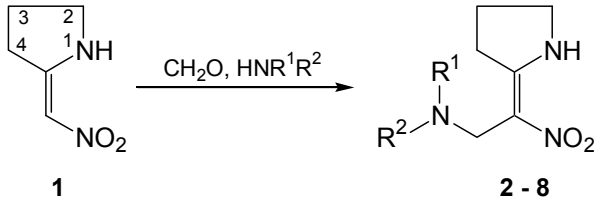
batzelladines



naseseazines

RESULTS AND DISCUSSION

Using the nitroenamine **1** as a C-H acid reactant several Mannich reactions were accomplished (Scheme 1). The reactions with various secondary amines in ethanol at room temperature led to formation of aminomethylated products in good yields (Table 1). Instead of formaldehyde and dimethylamine the Eschenmoser salt was also applied successfully.

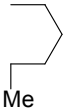
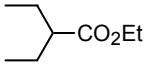


1 **2 - 8**

Scheme 1. Mannich reaction of the nitroenamine **1**

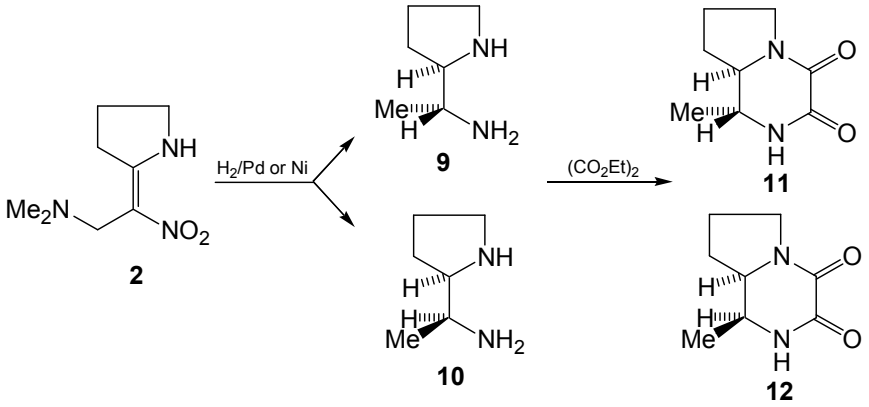
As previously noted[2] the high chemical shift (~9 ppm) of the NH proton may indicate the *Z* arrangement of the double bond in **1**. We confirmed this configuration by NOE experiments showing interaction between the olefinic =CH and 4-CH_2 protons. In compounds **2-8** the δNH chemical shifts appeared also at ~9 ppm proving the unchanged configuration.

Table 1. Mannich products obtained from the nitroenamine **1** with secondary amines

Amine	Product		yield	mp, °C
	Compound No	R^1, R^2		
dimethylamine	**2**	Me, Me	93	165
N-methyl-benzylamine	**3**	Me, $CH_2C_6H_5$	71	110
sarcosine	**4**	Me, CH_2CO_2H	90	171 (dec)
morpholine	**5**		71	152
piperidine	**6**		92	150-51
2-methylpiperidine	**7**		93	96
ethyl isonipecotate	**8**		44	110-112

Catalytic reduction of **2** gave the mixture of diastereomeric diamines **9** and **10** in comparable amounts. Noteworthy, that reductive removal of the dimethylamino group proceeded simultaneously. For the sake of clarity only the enantiomers (5*R*,5*aR*) and (5*R*,5*aS*) are shown in Scheme 2. In case of the nitroalkenes **3-8** no such removal of the amine component was observed. Upon treatment with diethyl oxalate at 60 °C

the mixture of diamines **9** and **10** gave the pyrrolo-piperazine derivatives **11** and **12** (Scheme 2). Recrystallization led to a nearly pure substance containing the isomers **11** and **12** in a ratio *ca.* 97:3, respectively.



Scheme 2. Reduction of the Mannich product **2** and its subsequent cyclization

The stereochemistry of **11** and **12** was established by comprehensive one- and two-dimensional NMR methods using widely accepted strategies.[8] The results are displayed in Figure 1.

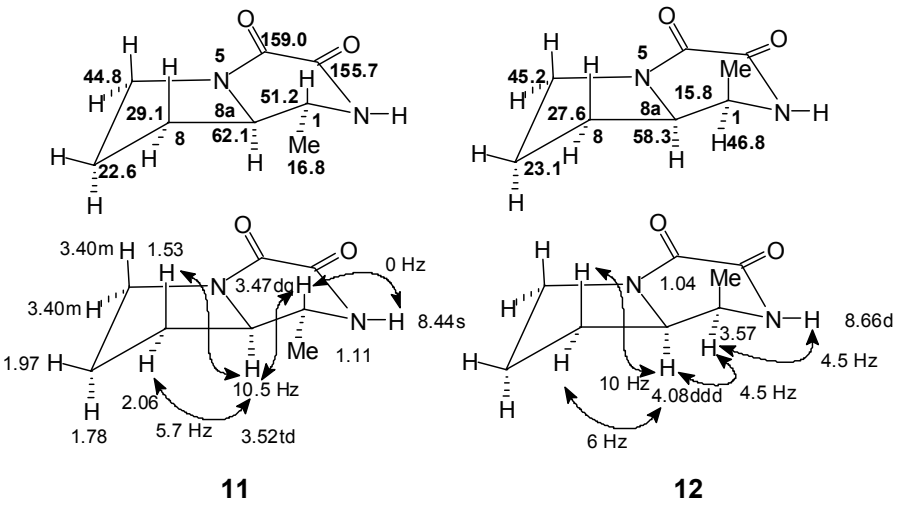
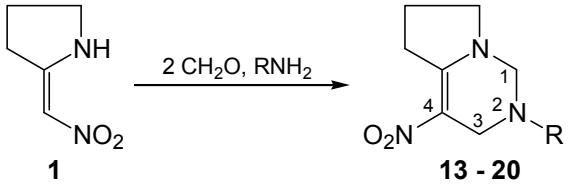


Figure 1. Stereochemistry of **11** (H-1,H-8*a trans*) and **12** (H-1,H-8*a cis*). Bold numbers above denote the ^{13}C chemical shifts, ^{1}H data are down. The arrows refer to the characteristic ^{3}J (H,H) coupling constants.

Based on the significantly different ^{3}J (H-1,H-8*a*) coupling constants **11** and **12** were identified unambiguously. The value of 10.5 Hz in **11** proves the antiperiplanar arrangement of H-1 and H-8*a* atoms, whereas the value of 4.5 Hz in **12** supports their *gauche* position.

The Mannich reactions of the nitroenamine **1** with primary amines gave the pyrrolo-pyrimidines **13-20** in good yields (Scheme 3, Table 2).

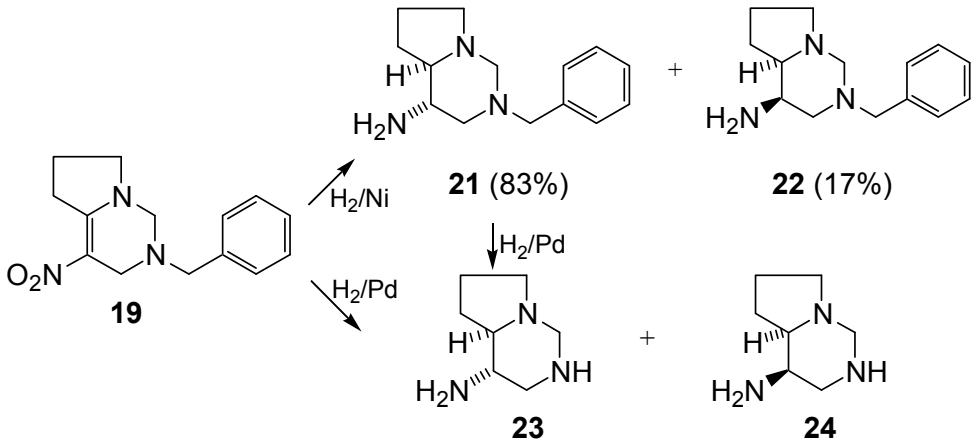


Scheme 3. Mannich reaction of **1** with primary amines

Table 2. Mannich products obtained from the nitroenamine **1** with primary amines

Primary amine	Product		yield, %	mp, ^{o}C
	Compound No	R		
methylamine	**13**	-Me	66	152
isopropylamine	**14**	-$CHMe_2$	95	89
tert-butylamine	**15**	-CMe_3	93	137
cyclopropylamine	**16**	-$CH(CH_2)_2$	57	125-26
colamine	**17**	-$(CH_2)_2OH$	81	90
2-methoxy-ethylamine	**18**	-CH_2CH_2OMe	71	78-79
benzylamine	**19**	-$CH_2C_6H_5$	81	123-24
3,4-dimethoxy-β-phenyl-ethylamine	**20**	-$CH_2CH_2C_6H_3(3,4\text{-}OMe)_2$	83	169-71

Reduction of **19** with Raney-Ni led to a mixture of diastereomers **21** and **22,** with equatorial and axial C(4)-NH_2 group, respectively, that was subjected column chromatography affording the pure isomers in a ratio 83:17 (Scheme 4).



Scheme 4. Reduction of **19**

The NMR signal assignments and the C(4) and C(4*a*) configurations were determined by $^{1}H,^{13}C$, DEPT, $^{1}H,^{1}H$-COSY, $^{1}H,^{13}C$-HSQC, $^{1}H,^{1}H$-NOESY and selective ^{1}H-NOESY experiments in $CDCl_3$. The conformation and the characteristic NMR correlations are depicted in Figure 2.

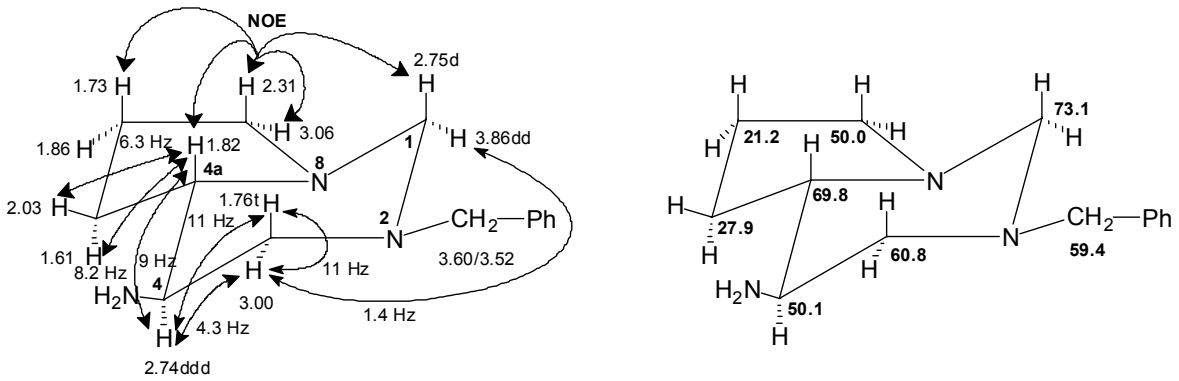


Figure 2. Stereochemistry of the *trans* diastereomer **21**. a) ^{1}H data. Arrows refer to the characteristic ^{3}J (H,H) coupling constants (Hz); arrows marked with NOE show the sterically close ^{1}H atoms observed upon selective irradiation of H-7β at δ 2.31; b) ^{13}C chemical shifts.

The H-4 signal at δ 2.74 ppm appeared with a *ddd* multiplicity. The measured *J* (H-4,H-4*a*) = 9.0 Hz and *J* (H-4,H-3β) = 11.0 Hz coupling constants are in accordance with their antiperiplanar arrangements, whereas the value of *J* (H-4,H-3α) = 4.3 Hz supports their *gauche* relation.

Hydrogenation of **19** with Pd/C catalyst led to formation of a mixture containing **23** predominantly and **24** in negligible amount. These diastereomers were not separated, the structure of **23** was proven by debenzylation of **21**.

In conclusion we have demonstrated the synthetic usefulness of the nitroenamine **2** in preparation of various Mannich compounds. These primary products were reduced enabling us to prepare new pyrrolo-pyrazines and pyrrolo-pyrimidines.

EXPERIMENTAL

General. Commercially available (Aldrich, Alfa Aesar) reagents were used. Prior the use the solvents were redistilled. The reaction mixtures and the purity of the products were checked by analytical TLC performed on precoated Merck aluminum sheets (DC-Alufolien Kieselgel 60 F_{254}). The spots were visualized by iodine vapor or Dragendorff reagent. Melting points were determined on a Büchi 20SchmP apparatus and are uncorrected. HRMS were determined with a Waters LCT Premier XE instrument. IR

spectra were obtained with a Perkin-Elmer 1600 FT/IR instrument (KBr pellet or liquid film). NMR spectra were recorded at ambient temperature on a Varian UNITY spectrometer (300 MHz for ^{1}H-spectra, 75 MHz for ^{13}C spectra) and compounds **1**, **11**, **12**, **19** and **21** on a Bruker Avance spectrometer (500 MHz and 125 MHz, resp.). Chemical shifts, given on the δ scale, were referenced to the solvent ($CDCl_3$: δ_C = 77.0 and δ_H = 7.27; DMSO-d_6: δ_C = 39.5 and δ_H = 2.50, resp.). In the 1D measurements (^{1}H, ^{13}C, DEPT-135), 64K data points were used for the FID. The pulse programs [gs-COSY, gs-HSQC, gs-HMBC, 1D NOESY (mixing time = 350 ms), 2D NOESY (mixing time = 400 ms)] were taken from the Bruker software library.

2-Nitromethylenepyrrolidine (**1**). The mixture of 2-methoxypyrroline (135.1 g, 1.36 mol) and nitromethane (166.1 g, 2.72 mol) was heated under reflux for 20 h. The red solution was concentrated to give a dark viscous residue which was purified by column chromatography using silica (100 g) and EtOAc - CH_2Cl_2 (1:1) eluent mixture. Evaporation furnished an orange solid, 90.2 g (51.8%); an analytical sample was obtained by recrystallization from ethyl acetate. Pale yellow crystals; mp 109-110 °C (lit.,[9] 108 °C). IR (KBr) ν_{max} 3261 (NH), 1611, 1359 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14 (2H, m), 2.72 (2H, t, *J* = 7.8 Hz), 3.73 (2H, t, *J* = 7.2 Hz), 6.63 (s, 1H), 9.20 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 31.3, 48.4, 106.7, 162.8.

General procedure for the preparation of compounds 2-8

A mixture of 128 mg (1.0 mmol) of **1**, 150 mg (5 mmol) of paraformaldehyde and 1.0 mmol of a secondary amine in 6 mL EtOH was stirred at room temperature for 5 h. The crystalline product was either filtered off, or the reaction mixture was concentrated and the residue was crystallized. The products were purified by recrystallization using common alcohols. Yields and melting points are given in Table 1.

Dimethyl-(2-nitro-2-pyrrolidin-2-ylideneethyl)amine (**2**)**.** Using dimethylamine hydrochloride (Scheme 1) **2**·HCl was isolated. Mp 165 °C. The free base **2** was obtained by treatment with aqueous solution of potassium carbonate and subsequent extraction with dichloromethane. IR (KBr) ν_{max} 3295 (NH), 1604, 1338 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.07 (2H, m), 2.13 (6H, s), 2.88 (2H, t, *J* = 7.8 Hz), 3.27 (2H, s), 3.68 (2H, t, *J* = 7.2 Hz), 9.8 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ 21.3, 32.1, 44.8, 48.6, 56.0, 115.8, 165.0; HRMS: calculated for $C_8H_{15}N_3O_2$ $[MH]^+$ 186.1243, found 186.1242.

2·HI was obtained in reaction of **1** with equimolar amount of dimethyl methylene ammonium iodide (Eschenmoser salt) in EtOH at 20 °C for 4 h. White powderlike product (80%), recryst. from 95% EtOH, mp 200 °C.

Benzylmethyl-(2-nitro-2-pyrrolidin-2-ylideneethyl)amine (**3**)**.** Pale yellow plates. IR (KBr) ν_{max} 3304 (NH), 1606, 1350 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.13 (2H, m), 2.18 (3H, s), 2.88 (2H, t, *J* = 7.8 Hz), 3.50 (2H, s), 3.50 (2H, s), 3.52 (2H, s), 3.73 (2H, t, *J* = 7.3 Hz), 7.10-7.30 (5H, m), 9.80 (1H, bs);

^{13}C-NMR ($CDCl_3$) δ 21.5, 32.0, 42.0, 48,7, 54.3, 61.8, 116.2, 126.9, 128.1, 128.9, 139.4, 165.4; HRMS: calculated for $C_{14}H_{19}N_3O_2$ $[MH]^+$ 262.1556, found 262.1556.

[Methyl-(2-nitro-2-pyrrolidin-2-ylideneethyl)amino]acetic acid (**4**)**.** White solid. IR (KBr) ν_{max} 3264 (NH), 1630 (COOH), 1593, 1371 (NO_2) cm^{-1}; ^{1}H-NMR (D_2O) δ 2.04 (2H, m), 2.77 (3H, s), 2.91 (2H, t, *J* = 7.7 Hz), 3.59 (2H, s), 3.71 (2H, t, *J* = 7.4 Hz). 4.19 (2H, s); ^{13}C-NMR (D_2O) δ 23.3, 37.0, 44.0, 52.2, 53.4, 58.7, 60.6, 112.0, 171.3, 173.0; HRMS: calculated for $C_9H_{15}N_3O_4$ $[MH]^+$ 230.1141, found 211.1155.

4-(2-Nitro-2-pyrrolidin-2-ylideneethyl)morpholine (**5**)**.** Pale yellow crystals. IR (KBr) ν_{max} 3321, 3280 (NH), 1611, 1345 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.16 (2H, m), 2.38-2.45 (4H, m), 2.97 (2H, t, *J* = 7.9 Hz), 3.44 (2H, s), 3.58-3.65 (4H, m), 3.76 (2H, t, *J* = 7.3 Hz), 9.82 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ 21.4, 32.2, 48.7, 53.0, 55.5, 67.0, 115.1, 165.1; HRMS: calculated for $C_{10}H_{17}N_3O_3$ $[MH]^+$ 228.1348, found 228.1346.

1-(2-Nitro-2-pyrrolidin-2-ylideneethyl)piperidine (**6**)**.** Yellowish white crystals. IR (KBr) ν_{max} 3304 (NH), 1604, 1352 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30-1.60 (6H, m), 2.15 (2H, m), 2.30-2.46 (4H, m), 2.99 (2H, t, *J* = 7.9 Hz), 3.41 (2H, s), 3.76 (2H, t, *J* = 7.2 Hz), 9.80 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ 21.5, 24.4, 26.1, 32.1, 48.7, 54.0, 55.8, 116.1, 165.3; HRMS: calculated for $C_{11}H_{19}N_3O_2$ $[MH]^+$ 226.1556, found 226.1549.

2-Methyl-1-(2-nitro-2-pyrrolidin-2-ylideneethyl)piperidine (**7**)**.** Yellowish white crystals. IR (KBr) ν_{max} 3230 (NH), 1607, 1351 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, d, *J* = 6.3 Hz), 1.10-1.60 (6H, m), 1,85-2.30 (4H, m), 2.50 - 3.35 (4H, m), 3.65-3.82 (3H, m), 9.91 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ 18.3, 21.3, 23.5, 25.9, 32.1, 34.4, 48.6, 50.8, 51.1, 56.6, 116.1, 165.4; HRMS: calculated for $C_{12}H_{21}N_3O_2$ $[MH]^+$ 240.1712, found 240.1701.

1-(2-Nitro-2-pyrrolidin-2-ylideneethyl)piperidine-4-carboxylic acid ethyl ester (**8**)**.** Yellowish white crystals. IR (KBr) ν_{max} 3334 (NH), 1720 (C=O), 1616, 1352 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.23 (3H, t, *J* = 7.1 Hz), 1.55-2.33 (9H, m), 2.72-2.83 (2H, m), 2.98 (2H, t, *J* = 7.9 Hz), 3.44 (2H, s), 3.76 (2H, t, *J* = 7.3 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 9.85 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ 14.2, 21.4, 28.4, 32.1, 41.2, 48.7, 52.4, 55.3, 60.2, 115.7, 165.4, 175.3; HRMS: calculated for $C_{14}H_{23}N_3O_4$ $[MH]^+$ 298.1767, found 298.1762.

1-Pyrrolidin-2-yl-ethylamines (**9** and **10**)**. 2** (0.37 g, 2.0 mmol) in 20 mL EtOH was hydrogenated at 25 ^{o}C under 0.8 MPa in presence of Pd/C catalyst for 3 h, followed by filtration and evaporation to yield a colourless oil (0.16 g, 70 %) as a mixture of **9** and **10**. These diastereomers were not separated. IR (liquid film) ν_{max} 3366 br (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.03 and 1.08 (dublets, *J* = 6.0 Hz, 3H), 1.25-1.90 (4H, m), 2.40-3.00 (7H, m); ^{13}C-NMR ($CDCl_3$) two series of signals: δ 20.7, 26.0, 28.3, 46.4, 51.4, 65.7; and δ

20.9, 25.4, 26.8, 46.6, 50.2, 64.9.

Trans- and **c*is*-1-Methyl-1-hexahydropyrrolo[1,2-*a*]pyrazine-3,4-dione** (**11** and **12**)**.** To a mixture of **9** and **10** (540 mg, 3.43 mmol) diethyl oxalate (502 mg, 3.43 mmol) was added. The reaction mixture was stirred at 60 ^{o}C for 3 h, and the white solid formed upon cooling was separated (230 mg, 40.0%). Recrystallization from isopropyl alcohol gave the *trans* diastereomer **11** containing about 3% of **12** (estimated by NMR signal intensities). IR (KBr) ν_{max} 3430, 3200 (NH), 1689, 1678 (amide-I) cm^{-1}; NMR data, Figure 1.

General procedure for the preparation of 13-20.

The solution of **1** (1.0 mmol), a primary amine (1.0 mmol) and 0.18 g of 35% formaline (2.0 mmol) in 5 mL MeOH was stirred at 25 ^{o}C for 4-6 h. After a complete reaction monitored by TLC, the solvent was evaporated in vacuo, and the residue was crystallized and/or recrystallized. Yields and melting points are given in Table 2.

2-Methyl-4-nitro-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (**13**)**.** Pale yellow crystals. IR (KBr) ν_{max} 1573, 1374 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (2H, m), 2.44 (3H, s), 3.48 (2H, t, *J* = 7.5 Hz), 3.56 (2H, t, *J* = 7.3 Hz), 3.78 (2H, s), 4.02 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.3, 34.1, 41.4, 50.3, 52.4, 67.2, 113.7, 159.5; HRMS: calculated for $C_8H_{14}N_3O_2$ $[MH]^+$ 184.1086, found 184.1091.

2-Isopropyl-4-nitro-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (**14**)**.** Pale yellow crystals. IR (KBr) ν_{max} 1575, 1349 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.12 (6H, d, *J* = 6.5 Hz), 2.10 (2H, m), 2.89 (1H, h, *J* = 6.5 Hz), 3.43 (2H, t, *J* = 7.7 Hz), 3.56 (2H, t, *J* = 7.4 Hz), 3.86 (2H, s), 4.10 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.3 (overlapped C-7 and CH_3 signals), 34.2, 45.3, 51.2, 52.1, 63.0, 115.0, 160.6; HRMS: calculated for $C_{10}H_{18}N_3O_2$ $[MH]^+$ 212.1399, found 212.1399.

2-*tert*-Butyl-4-nitro-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (**15**)**.** Pale yellow crystals. IR (KBr) ν_{max} 1588, 1363 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (9H, s), 2.11 (2H, m), 3.43 (2H, t, *J* = 7.8 Hz), 3.58 (2H, t, *J* = 7.4 Hz), 3.85 (2H, s), 4.07 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.3, 26.9, 34.2, 43.0, 52.2, 54.1, 60.8, 116.1, 160.6; HRMS: calculated for $C_{11}H_{20}N_3O_2$ $[MH]^+$ 226.1556, found 226.1559.

2-Cyclopropyl-4-nitro-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (**16**)**.** Pale yellow crystals. IR (KBr) ν_{max} 1575, 1365 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.5-0.6 (4H, m), 2.00 (1H, m), 2.13 (2H, m), 3.49 (2H, t, *J* = 7.8 Hz), 3.58 (2H, t, *J* = 7.4 Hz), 3.94 (2H, s), 4.15 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.3, 34.1, 41.4, 50.3, 52.4, 67.2, 113.7, 159.5; HRMS: calculated for $C_{10}H_{16}N_3O_2$ $[MH]^+$ 210.1243, found 210.1249.

2-(4-Nitro-3,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-2-yl)ethanol (**17**)**.** Pale yellow crystals. IR (KBr) ν_{max} 3384 (OH), 1577, 1367 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (2H, m), 2.59 (1H, bs), 2.66 (2H, t, *J* =

5.1 Hz), 3.44 (2H, t, *J* = 7.8 Hz), 3.55 (2H, t, *J* = 7.2 Hz), 3.67 (2H, t, *J* = 5.1 Hz), 3.84 (2H, s), 4.15 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.1, 34.3, 48.1, 52.4, 55.0, 59.4, 66.2, 113.5, 160.3; HRMS: calculated for $C_9H_{15}N_3O_3$ $[MH]^+$ 214.1192, found 214.1187.

2-(2-Methoxy-ethyl)-4-nitro-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (18). Pale yellow crystals. IR (KBr) ν_{max} 1576, 1351 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (2H, m), 2.70 (2H, t, *J* = 5.1 Hz), 3.34 (3H, s), 3.43 (2H, t, *J* = 7.8 Hz), 3.52 (2H, t, *J* = 5.1 Hz), 3.55 (2H, t, partly overlapped, *J* = 7.2 Hz), 3.86 (2H, s), 4.17 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.2, 34.2, 48.9, 52.3, 52.7, 58.9, 66.0, 71.0, 113.6, 160.1; HRMS: calculated for $C_{10}H_{17}N_3O_3$ $[MH]^+$ 228.1358, found 228.1347.

2-Benzyl-4-nitro-1,2,3,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (19). Pale yellow crystals. IR (KBr) ν_{max} 1579, 1371 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10 (2H, m), 3.46 (2H, t, *J* = 7.5 Hz), 3.47 (2H, t, *J* = 7.5 Hz), 3.69 (2H, s), 3.93 (2H, s), 4.04 (2H, s), 7.25 - 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.3, 34.2, 48.7, 52.2, 57.6, 64.5, 113.9, 127.7, 128.5, 128.8, 137.1, 160.1; HRMS: calculated for $C_{14}H_{18}N_3O_2$ $[MH]^+$ 260.1399, found 260.1406.

2-[2-(3,4-dimethoxyphenyl)ethyl]-4-nitro-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine (20). Pale yellow crystals. IR (KBr) ν_{max} 1577, 1365 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (2H, m), 2.69-2.83 (4H, m), 3.42-3.52 (4H, m), 3.84 (3H, s), 3.86 (3H, s), 3.96 (2H, s), 4.09 (2H, s), 6.69-6.81 (3H, m); ^{13}C NMR ($CDCl_3$) δ 20.2, 34.2, 34.4, 48.0, 52.3, 55.1, 55.9, 66.3, 111.4, 112.0, 113.8, 120.5, 132.0, 147.6, 149,0, 160.0; HRMS: calculated for $C_{17}H_{24}N_3O_4$ $[MH]^+$ 334.1767, found 334.1763.

2-Benzyloctahydropyrrolo[1,2-*c*]pyrimidin-4-ylamine (21 and **22).** The solution of **19** (1.30 g, 5.0 mmol) in EtOH (30 mL) was hydrogenated with Raney-Ni catalyst (1.1 g) under pressure (initial pressure 0.9 MPa) at 23 °C for 6 h. After removal of the catalyst the solvent was evaporated to yield a pale yellow oily residue (1.15 g, practically complete conversion). The crude product (1.10 g) was chromatographed using an eluent mixture (EtOAc - CH_2Cl_2 - isopropylamine, 40/10/3) to produce the diastereomer **21** (595 mg), white crystals, mp 63-64 °C, IR (KBr) ν_{max} 3344, 3249, 3167 (NH), 1609, 1495 (C=C) cm^{-1}; NMR data of **21**: *s*. Figure 2. and diastereomer **22** (74 mg), as a pale yellow oil. IR (liquid film) ν_{max} 3400 br (NH_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.60-2.20 (9H, m), 2.37-2.44 (1H, m), 3.30-3.50 (3H, m), 3.47 (2H, s), 3.86 (1H, d), 7.20-7.40 (5H, m) ^{13}C NMR ($CDCl_3$) δ 21.0, 24.9, 46.9, 50.6, 59.6, 59.7, 66.8, 75.5, 126.9, 128.1, 128.7, 138.1.

Octahydropyrrolo[1,2-*c*]pyrimidin-4-ylamine (23 and **24).** The solution of the nitro compound **19** (2.20 g, 8.5 mmol in 20 mL EtOH) was hydrogenated in presence of 10% Pd/C (1.45 g) at 0.8 MPa and 20 °C. As the hydrogen consumption ceased (about 3 h), the catalyst and the solvent was removed to yield a colorless oil (1.0 g, 83%), predominantly the diastereomer **23**.

The solution of **21** (190 mg) in EtOH (15 mL) was hydrogenated in presence of 10% Pd/C catalyst (120

mg) at 0.8 MPa and 23 ^{o}C. As the hydrogen absorption ceased, the catalyst and the solvent were removed to furnish **23** as a colorless oil (115 mg, in quantitative yield). ^{1}H-NMR ($CDCl_3$) δ 1.35-1.7 (4H, m), 1.90-2.45 (8H, m), 2.85-2.95 (2H, m), 3.82 (1H, d); ^{13}C NMR ($CDCl_3$) δ 20.2, 28.2, 49.8, 52.7, 53.4, 66.8, 70.4; HRMS: calculated for $C_7H_{16}N_3$ $[MH]^+$ 142.1344, found 142.1336.

^{13}C NMR signals of the minor component **24** ($CDCl_3$) δ 22.7, 23.2, 40.2, 46.3, 52.9, 57.1, 68.3.

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