TRANSFORMATIONS OF 2,4,5-TRISUBSTITUTED PYRIMIDINES. THE SYNTHESES AND TRANSFORMATIONS OF PYRIMIDO/4,5-d/PYRIMIDINE, 1,2,4-TRIAZOLO/4,3-a/PYRIMIDINE, TETRAZOLO/1,5-a/PYRIMIDINE, 1,2,4-TRIAZOLO/3,4-b/PURINE AND TETRAZOLO/5,1-b/PURINE DERIVATIVES

Uroš Urleb, Branko Stanovnik*, Vekoslava Stibilj, and Miha Tišler

Department of Chemistry, Edvard Kardelj University of Ljubljana, 61000 Ljubljana, Yugoslavia

Abstract - Some new approaches for the syntheses of pyrimido-/4,5-d/pyrimidines 3, 4, 9, and 10, 5,6-disubstituted 1,2,4-triazolo/4,3-a/pyrimidines 13, 15, 16, 17, 19, and 20, 5,6-disubstituted tetrazolo/1,5-a/pyrimidine 21, 1,2,4-triazolo-/3,4-b/purines 25, 26, and 28, and tetrazolo/5,1-b/purine 27 from 2,4,5-trisubstituted pyrimidines 2 and 12 are described.

Polysubstituted pyrimidines are versatile synthons for various heterocyclic systems. Recently, 2-substituted 4-amino-5-cyanopyrimidines have been used for the preparation of pyrimidinecarboxamide oximes and 5-(1,2,4-oxadiazol-3-yl)-pyrimidines in our laboratory.[1]

In this communication we report on the syntheses of substituted pyrimido/4,5-d/pyrimidines, 5,6-disubstituted 1,2,4-triazolo/4,3-a/pyrimidines, 5,6-disubstituted tetrazolo/1,5-a/pyrimidines, 1,2,4-triazolo/3,4-b/purines and tetrazolo/5,1-b/purines from 2-substituted 4-aminopyrimidine-5-carboxamides and -carbohydrazides.

The little known bicyclic system pyrimido/4,5-d/pyrimidine has been studied by several groups,[2-9] some of them have been interested also in its diuretic[3,4] and antibacterial activity[7] and structure-activity relationship.[10] Recently, several new approaches to this bicyclic system starting from the substituted pyrimidinylformamidines and pyrimidinylformamide oximes have been reported.[11]

On the other hand, there are many reports dealing with the synthesis of 1,2,4-triazolo/4,3-a/pyrimidines and tetrazolo/1,5-a/pyrimidines, mainly monosubstituted or symmetrically disubstituted. However, derivatives of unsymmetrically disubstituted pyrimidine ring are rare, most probably due to some difficulties encountered in structural assignments.[12]

Two trisubstituted pyrimidine derivatives, 4-amino-2-methylthiopyrimidine-5-carboxamide (2) obtained from 4-amino-5-cyano-2-methylthiopyrimidine (1) and 4-amino-2-hydrazinopyrimidine-5-carbohydrazide (12) obtained from 4-amino-5-ethoxycarbonyl-2-mercaptopyrimidine (11) were used as starting compounds. Reaction of 2 with (trisformamido)methane afforded 7-methylthiopyrimido/4,5-d/pyrimid-4(3H)-one, (3), identical with the compound obtained from 2 and triethyl orthoformate[3]. Methylation of 3 with N,N-dimethylformamide dimethyl acetal (DMFDMA)[13] gave the N_3-methylated product (4), the alternative N_1-methylated one (5) being not formed. The compound 4 was also obtained from 2 and DMFDMA. The structure of 4 was assigned on the basis of elemental analysis, ^1H nmr and mass spectra, and confirmed by its conversion upon treatment with aqueous sodium hydroxide to 4-amino-5-methylcarbamoyl-2-methylthiopyrimidine (6), identical with the compound prepared from 4-amino-5-ethoxycarbonyl-2-methylthiopyrimidine (7) and methylamine. The compound 6 underwent cyclization with triethyl orghoformate to give 4. The reaction of 4 with hydrazine hydrate resulted in substitution of the 7-methylthio group followed by ring opening to give 4-amino-2-hydrazino-5-methylcarbamoylpyrimidine (8), identical with the compound obtained from 6 and hydrazine hydrate. On the other hand, 4 did not undergo ring opening upon treatment with methylhydrazine to give 3-methyl-7-(1-methylhydrazino) pyrimido/4,5-d/pyrimid-4(3H)-one (9) only by substitution of the 7-methylthio group. This was then deamined with nitrous acid to give 3-methylaminopyrimido/4,5-d/pyrimid-4(3H)-one (10) (Scheme 1).

4-Amino-2-hydrazinopyrimidine-5-carbohydrazide (12) was transformed into a series of 1,2,4-triazolo/4,3-a/pyridine and tetrazolo/1,5-a/pyrimidine derivatives. Upon treatment of 12 with triethyl orthoformate the cyclization between the 2-hydrazino group and the 3-position and transformation of the 5-hydrazido group occurred to give 5-amino-6-ethoxycarbonyl-1,2,4-triazolo/4,3-a/pyrimidine (13), the isomeric 6,7-disubstituted derivative 14 being not produced. The compound 13 was converted with hydrazine hydrate into the corresponding hydrazide 15. The nitrosation of 15 with nitrous acid afforded 5-amino-6-azidocarbonyl-1,2,4-triazolo/4,3-a/pyrimidine (16). The reaction of 12 with triethyl orthoacetate also gave only 5-amino-6-(2-ethoxy)ethylidenecarbazoyl-3-methyl-1,2,4-triazolo/4,3-a)pyrimidine (17) and the isomeric ring closure product (18) was not obtained in this case, either. The structures of fused pyrimidines were assigned on the basis on elemental analysis and spectral assignment; the protons at position 3 in 13 and 15 were easily

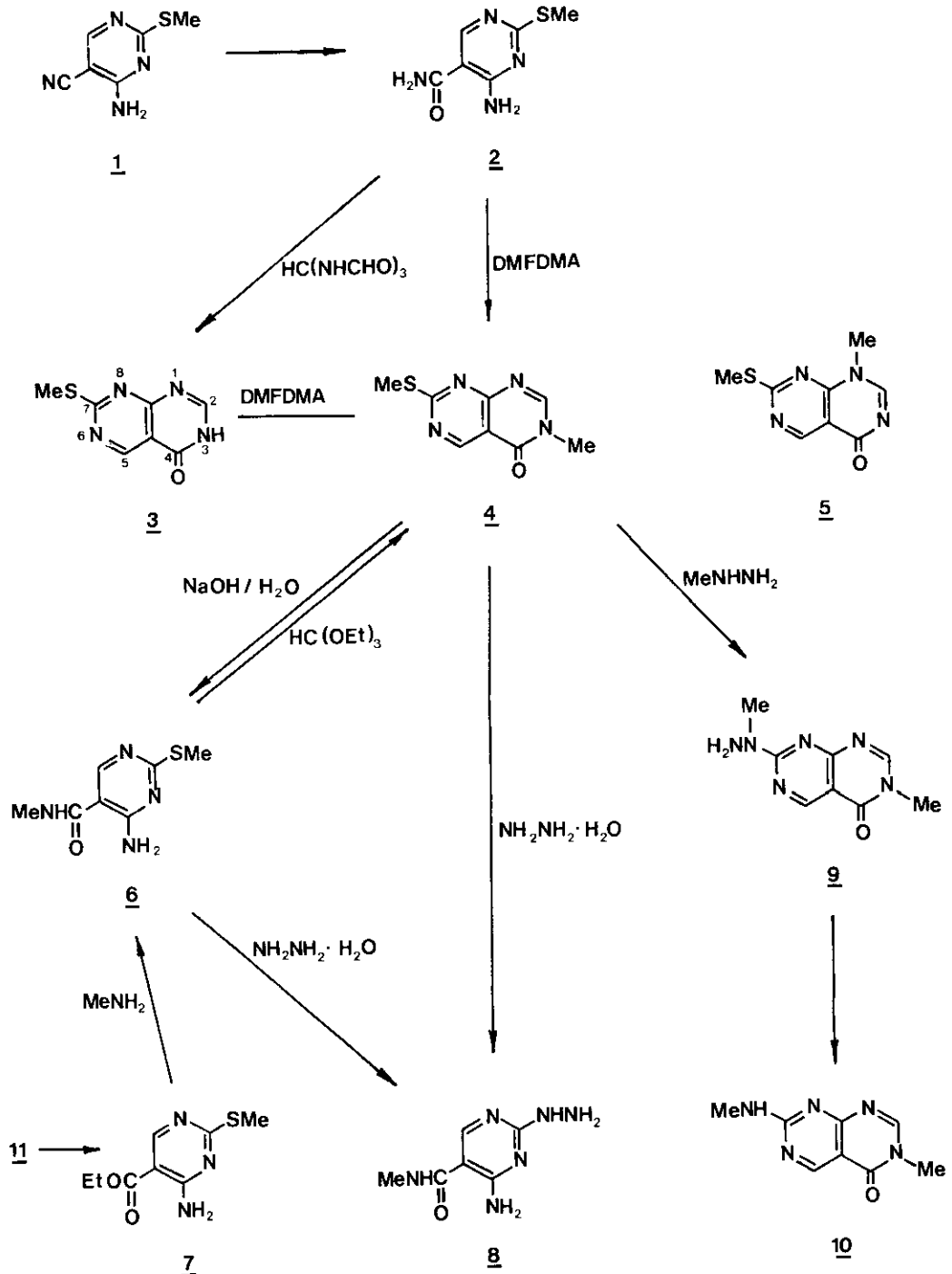
exchangeable with deuterium in basic solution, and the pyrimidine ring protons in triazolopyrimidines (13, 15, 16, 19, and 20) and tetrazolopyrimidine (21) appeared at δ 7.68-8.34, characteristic of H_7, while H_5 appears invariably above δ 8.60.[20] An attempt to prepare the corresponding hydrazide 19 from 17, as an intermediate in the preparation of 5-amino-6-azidocarbonyl-3-methyl-1,2,4-triazolo/4,3-a/pyrimidine (20), gave the compound 19 only in an inpure form. On the other hand, when 17 was hydrolyzed in aqueous hydrochloric acid at room temperature, followed by nitrosation with nitrous acid the compound 20 was obtained. By treatment of the compound 12 with nitrous acid 5-amino-6-azidocarbonyltetrazolo/1,5-a/pyrimidine (21) was produced. (Scheme 2).

Further evidence for this type of ring fusion was obtained by transformations of compounds 16, 20 and 21 into fused purines. Namely, the azidocarbonyl compounds 16, 20, and 21 were thermally transformed through the Curtius rearrangement into fused 1,2,4-triazolo/3,4-b/purin-7(8H)-one (25), 1-methyl-1,2,4-triazolo/3,4-b/purin-7(8H)-one (26) and tetrazolo/5,1-b/purin-7(8H)-one (27). Methylation of 25 with DMFDMA afforded 1,6,8-trimethyl-1,2,4-triazolo/3,4-b/purin-7(8H)-one (28). The intermediary isocyanates are usually not isolable in heterocyclic series. However, when 25 was heated in toluene for 2 h, isocyanate 16a was isolated, which showed a characteristic band in ir spectrum at ν_{NCO} = 2250 cm^{-1} [21] (Scheme 2). The chemical shifts for H_5 in the compounds 25-28, which fall in the range of δ = 8.26-8.72 ppm, are also in agreement with those for H_5 (δ = 8.86 ppm) in 1,2,4-triazolo/3,4-b/purine reported in a literature[22]. This supports also the angular structures of 25 - 28. The isomeric linear tricyclic structures 29 - 32 should be excluded in which a considerable downfield shift should be expected, since the H_8 appears at δ 10.26 in the parent tetrazolo/1,5-a/purine (31)[23].

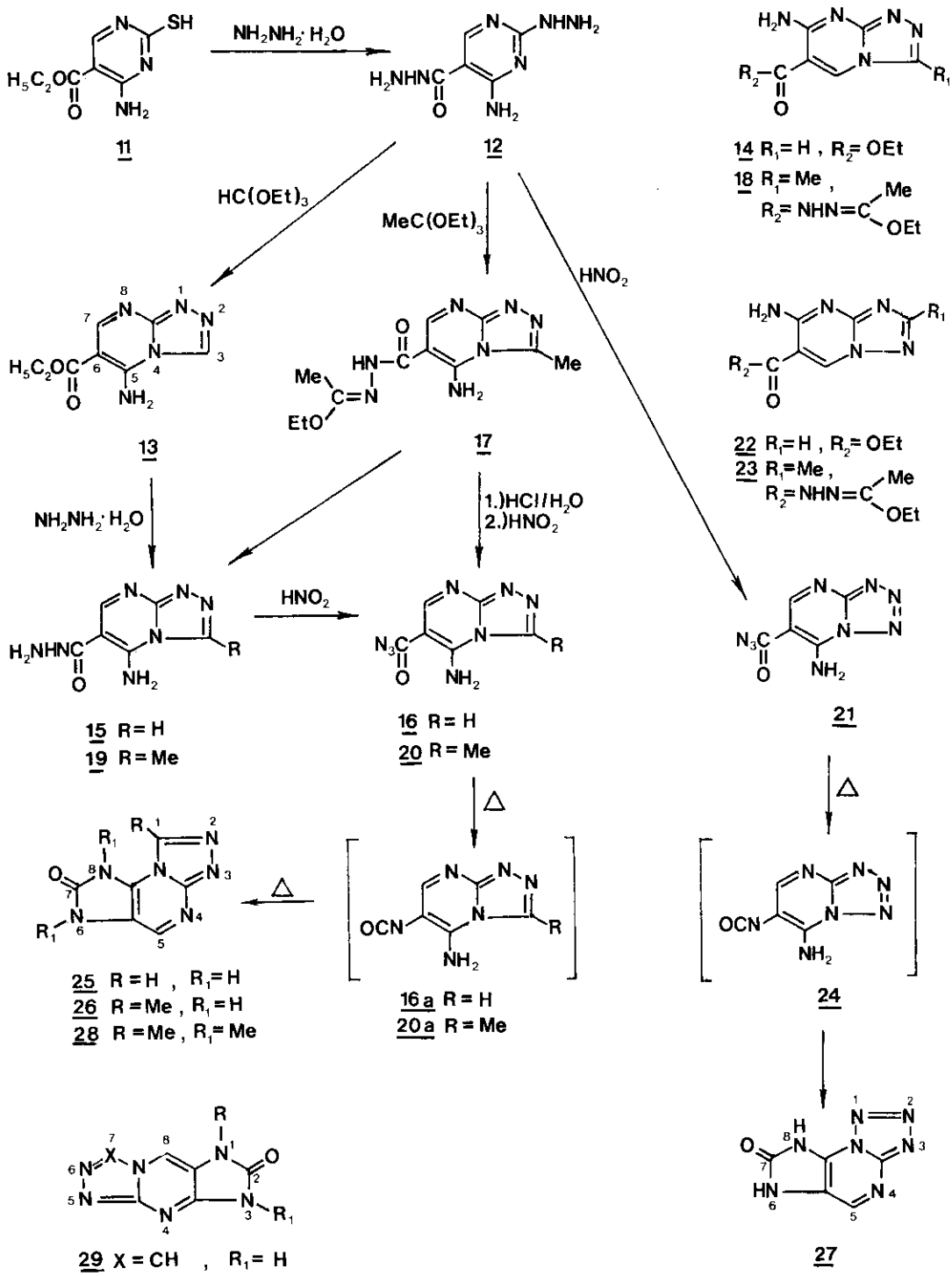
EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^1H nmr spectra were obtained on a JEOL JNM C60-HL spectrometer with TMS as internal standard, ir spectra on a PERKIN-ELMER instrument 727B, mass spectra on a HITACHI-PERKIN-ELMER mass spectrometer RMU-6L, and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 240C.

The following compound were prepared according to literature references: 4-amino-5-ethoxycarbonyl-2-mercaptopyrimidine (11)[24] and 4-amino-2-methylthiopyrimidine-5-


SMe
NC
NH2
1
H2NC
O
2
HC(NHCHO)3
DMFDMA
MeS
NH
3
DMFDMA
Me
4
5
NaOH / H2O
HC (OEt)3
MeNHNH2
MeNHC
6
NH2NH2· H2O
NH2NH2· H2O
MeNH2
9
11
EtOC
7
NHNH2
8
MeNH
10

SCHEME 1


NH2NH2·H2O
HC(OEt)3
MeC(OEt)3
HNO2
1.)HCl/H2O
2.)HNO2
Δ
11
12
13
17
14 R1=H , R2=OEt
18 R1=Me , R2=NHN=C(Me)(OEt)
22 R1=H , R2=OEt
23 R1=Me , R2=NHN=C(Me)(OEt)
15 R=H
19 R=Me
16 R=H
20 R=Me
21
16a R=H
20a R=Me
24
25 R=H , R1=H
26 R=Me , R1=H
28 R=Me , R1=Me
27
29 X=CH , R1=H
30 X=C-Me , R1=H
31 X=N , R1=H
32 X=Me , R1=Me

SCHEME 2

carboxamide (2)[25].

7-Methylthiopyrimido/4,5-d/pyrimid-4(3H)-one (3). - A mixture of 2 (80 mg) and $HC(NHCHO)_3$ (60 mg) was heated for 45 min at 180°C. After cooling, MeOH (3 ml) was added, the solid was filtered and recrystallized from DMF to give 3 in 66% yield, mp 280°C, lit.[3] mp 225-229°C, m/z 194 (M^+), nmr (DMSO-d_6/TMS, 100°C) δ: 2.6 (s, SMe), 8.33 (s, H_5), 9.15 (s, H_2). Anal.Calcd. for $C_7H_6H_4OS$: C, 43.29; H, 3.11; N, 28.85. Found: C, 43.34; H, 3.45; N, 28.67.

3-Methyl-7-methylthiopyrimido/4,5-d/pyrimidin-4(3H)-one (4). - a) A suspension of 1 (500 mg) in DMFDMA (4 ml) was refluxed for 6 h. The mixture was left in refrigerator for 12 h. The solid formed was filtered and recrystallized from DMF to give 4 in 39% yield, mp 252-253°C, m/z 208 (M^+), nmr (DMSO-d_6/TMS, 110°C) δ: 2.6 (s, SMe), 3.47 (s, NMe), 8.6 (s, H_5), 9.2 (s, H_2). Anal.Calcd.for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.90. Found: C, 46.35; H, 3.88; N, 26.75.

b) A suspension of 3 (90 mg) in DMFDMA (1.5 ml) was refluxed for 6 h. The precipitate was, after cooling, filtered, washed with MeOH and recrystallized from DMF to give 4 in 28% yield. The ir spectrum was identical with that of the compound described in a).

c) A suspension of 6 (100 mg) in $HC(OEt)_3$ (3 ml) was refluxed for 12 h. Methanol (3 ml) was added to the oily residue obtained after evaporation of the volatile components in vacuo. The solid was filtered and recrystallized from DMF to give 4 in 7% yield.

4-Amino-5-methylcarbamoyl-2-methylthiopyrimidine (6). - a) To a suspension of 4 (190 mg) in H_2O (4 ml) NaOH (300 mg) was added and the mixture was kept at room temperature for 4 h. The precipitate was filtered, washed with water and recrystallized from EtOH to give 6 in 66% yield, mp 185-190°C, m/z 198 (M^+), nmr(DMSO-d_6/TMS) δ : 2.4(s, SMe), 2.75 (d, NHMe), 7.85 (br s, NH), 8.45 (s, H_6), J_{NHMe} 3.75 Hz. Anal.Calcd.for $C_7H_{10}N_4OS$: C, 42.41; H, 5.08; N, 28.26. Found: C, 42.29; H, 5.21; N, 28.07.

b) A mixture of 7 (200 mg) and $MeNH_2$ (45% aq. solution, 5 ml) was refluxed for 5 h. The precipitate, which was formed in refrigerator after 48 h, was filtered, washed with H_2O and recrystallized from EtOH to give 6 in 34% yield.

4-Amino-5-ethoxycarbonyl-2-methylthiopyrimidine (7). - To a suspension of 11 (500 mg) in $PhCH_3$ (5 ml) DMFDMA (0.6 ml) was added and the mixture was refluxed for 20 h. The volatile components were evaporated in vacuo and H_2O (5 ml) and MeOH (3 ml) were

added. The precipitate was filtered and recrystallized from a mixture of $CHCl_3$ and MeOH to give 7 in 55% yield, mp 128°C, lit.[26] mp 126-127°C.

4-Amino-2-hydrazino-5-methylcarbamoylpyrimidine (8). - a) A mixture of 6 (100 mg) and $NH_2NH_2.H_2O$ (80%, 3 ml) in EtOH (2 ml) was refluxed for 15 h. The volatile components were evaporated in vacuo, H_2O (2 ml) was added, the precipitate was filtered and recrystallized from DMF to give 8 in 38% yield, mp 234-237°C, m/z 182(M^+), nmr (DMSO-d_6/TMS) δ : 2.65 (d, NHMe), 4.1 (br s, NH_2), 7.5 (br s, NH_2), 8.0 (br s, NH), 8.33 (s, H_6), J_{NHMe} 3.75 Hz. Anal.Calcd. for $C_6H_{10}N_6O$: C, 39.56; H, 5.49; N, 46.19. Found: C, 39.92; H, 5.47; N, 46.43.

b) A mixture of 4 (90 mg) and $NH_2NH_2.H_2O$ (80%, 1 ml) in EtOH (2 ml) was refluxed for 6 h. The precipitate was, after cooling, filtered and recrystallized from DMF to give 8 in 9% yield.

3-Methyl-7-(1-methylhydrazino)pyrimido/4,5-d/pyrimid-4(3H)-one (9). - A mixture of 4 (150 mg) and $MeHNNH_2$ (98%, 0.5 ml) in EtOH (2 ml) was refluxed for 6 h. The precipitate was, after cooling, filtered and recrystallized from MeOH to give 9 in 41% yield, mp 245-248°C, m/z 206 (M^+), nmr ($CDCl_3$/TMS) δ : 3.48 (s, NMe), 3.50 (s, NMe), 4.65 (br s, NH_2), 8.15 (s, H_5), 9.15 (s, H_2). Anal.Calcd for $C_8H_{10}N_6O$: C, 46.60; H, 4.89; N, 40.75. Found: C, 46.31; H, 5.15; N, 40.44.

3-Methyl-7-methylaminopyrimido/4,5-d/pyrimid-4(3H)-one (10). - To a solution of 9 (110 mg) in a mixture of AcOH (3 ml) and H_2O (2 ml), a solution of $NaNO_2$ (50 mg) in H_2O (4 ml) was added dropwise at 0°C. The solution was then neutralized with solid $NaHCO_3$ and extracted with $CHCl_3$ (5 times, 10 ml each time). The combined extracts were washed with H_2O and dried over anhyd.Na_2SO_4. The oily residue, obtained after evaporation of $CHCl_3$ in vacuo, solidified after addition of petroleum ether (5 ml). The solid was filtered and recrystallized from a mixture of $CHCl_3$ and MeOH to give 10 in 45% yield, mp 243-245°C, nmr ($CDCl_3$/TMS) δ: 2.05 (s, NMe), 2.9 (d, NHMe), 6.5 (br s, NHMe), 8.28 (s), 8.33 (s) (H_2,H_5). Anal. Calcd. for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.31; H, 4.44; N, 37.04.

4-Amino-2-hydrazinopyrimidine-5-carbohydrazide (12). - A mixture of 11 (500 mg) and $NH_2NH_2.H_2O$ (80%, 4 ml) in EtOH (5 ml) was refluxed for 5 h. The precipitate was, after cooling, filtered and recrystallized from DMF and EtOH to give 12 in 53% yield, mp 236-238°C, nmr (DMSO-d_6/TMS) δ: 7.67 (s, H_6), 8.6 (br s), 7.4 (br s), 6.9 (br s), 3.9 (br s), 3.2 (br s) (NH, NH_2). Anal.Calcd.for $C_5H_9N_7O$: C, 32.79; H, 4.91, N, 53.55; Found: C, 32.68; H, 4.78; N, 53.72.

5-Amino-6-ethoxycarbonyl-1,2,4-triazolo/4,3-a/pyrimidine (13). - A mixture of 12 (4 g) and $HC(OEt)_3$ (24 ml was refluxed for 9 h. The crude product was filtered and continuously extracted with $CHCl_3$ for 24 h to give 13 in 44% yield, mp 174-176°C (from a mixture of $CHCl_3$ and petroleum ether), m/z 207 (M^+), nmr $CDCl_3$/TMS) δ : 1.33 (t, $CH_2\underline{Me}$), 4.13 (q, $\underline{CH_2}Me$), 7.67 (s, H_7), 8.58 (s, H_3), J_{CH_2Me} 7.0 Hz. Anal.Calcd. for $C_8H_9N_5O_2$: C, 46.38; H, 4.35; N, 33.82. Found: C, 46.08; H, 4.14; N, 33.98.

5-Amino-1,2,4-triazolo/4,3-a/pyrimidine-6-carbohydrazide (15). - To a suspension of 13 (3 g) in EtOH (10 ml) $NH_2NH_2.H_2O$ (80 %, 6.7 ml) was added and the mixture was refluxed for 4 h. The product was, after cooling, filtered and purified by sublimation (110°C, 1 torr) to give 15 in 8% yield, mp 170-172°C, nmr (DMSO-d_6/TMS) δ : 7.68 (s, H_7), 7.70 (s, H_3), 5.80 (br s, NH, NH_2). Anal.Calcd. for $C_6H_7N_7O$: C, 37.31; H, 3.63; N, 50.78. Found: C, 37.51; H, 3.72; N, 51.01.

5-Amino-6-azidocarbonyl-1,2,4-triazolo/4,3-a/pyrimidine (16). - To a solution of 15 (103 mg) in aqueous HCl (1:1, 10 ml) a solution of $NaNO_2$ (69 mg) in H_2O (2 ml) was added dropwise at 0°C. The mixture was left for 30 min at 0°C and then neutralized with solid $NaHCO_3$. The precipitate was filtered and washed with ice-cold H_2O to give 16 in 60% yield, mp 160°C (decomp.), nmr (DMSO-d_6/TMS) δ : 7.75 (s, H_3, H_7). An analytically pure sample could not be obtained since the compound is thermally unstable in solutions.

5-Amino-6-(2-ethoxy)ethylidenecarbazoyl-1,2,4-triazolo/4,3-a/pyrimidine (17). - A mixture of 12 (435 mg) and $MeC(OEt)_3$ (4 ml) was refluxed for 9 h. The precipitate was, after cooling, filtered, washed with H_2O and recrystallized from a mixture of $CHCl_3$ and MeOH to give 17 in 65% yield, mp 143-146°C, nmr (DMSO-d_6/TMS) δ : 1.25 (t, $CH_2\underline{Me}$), 2.0 (s, 3-Me), 2.45 (s, C-Me), 4,1 (q, $\underline{CH_2}Me$), 7.37 (br s, NH_2), 8.75 (s, H_7), 10.55 (br s, NH). Anal.Calcd. for $C_{11}H_{15}N_7O_2$: N, 35.36. Found N, 35.06.

5-Amino-6-azidocarbonyl-3-methyl-1,2,4-triazolo/4,3-a/pyrimidine (20). - A mixture of 17 (300 mg) in aqueous HCl (1:1,18 ml) was kept at room temperature for 3 h. A solution of $NaNO_2$ (200 mg) in H_2O (3 ml) was added dropwise at 0°C. The mixture was left in refrigerator for 12 h and the precipitate formed was filtered to give the crude 20 in 62% yield. The compound is unstable and was immediately converted into 26.

5-Amino-6-azidocarbonyltetrazolo/1,5-a/pyrimidine (21). - To a solution of 12 (207 mg) in a mixture of aqueous HCl (35%, 1.5 ml) and H_2O (5 ml), a solution of $NaNO_2$ (173 mg) in H_2O (2 ml) was added dropwise at 0°C. The mixture was left at

0°C for 1 h and then neutralized with solid $NaHCO_3$. The precipitate was filtered and washed with ice-cold H_2O to give 21 in 56 % yield, mp 300°C (from EtOH), nmr (DMSO-d_6/TMS) δ : 8.03 (s, H_7). Anal. Calcd. for $C_5H_3N_9O$: C, 29.27; H, 1.46; N, 61.46. Found: C, 29.47; H, 1.86; N, 61.33.

1,2,4-Triazolo/3,4-b/purin-7(8H)-one (25). - A solution of 16 (213 mg) in toluene (20 ml) was refluxed for 6 h. The precipitate was filtered and the crude product was recrystallized from a mixture of DMF and H_2O to give 25 in 65 % yield, mp>300°C, m/z 176 (M^+), nmr (DMSO-d_6/TMS) δ : 7.8 (br s, NH), 8.2 (s, H_1), 8.72 (s, H_5). Anal. Calcd. for $C_6H_4N_6O$: C, 40.92; H, 2.29; N, 47.71. Found: C, 40.68; H, 2.34; N, 48.02.

1-Methyl-1,2,4-triazolo/3,4-b/purin-7(8H)-one (26). - A suspension of 20 (100 mg) in toluene (5 ml) was refluxed for 15 h. The precipitate was, after cooling, filtered and recrystallized from a mixture of AcOH and H_2O to give 26 in 64% yield, mp>350°C, nmr (CF_3COOH/TMS) δ: 2.77 (s, Me), 8.45 (s, H_5). Anal.Calcd. for $C_7H_6N_6O$: C, 44.21; H, 3.18; N, 44.19. Found: C, 44.19; H, 3.33; N, 44.00.

Tetrazolo/5,1-b/purin-7(8H)-one (27). - A suspension of 21 (615 mg) in toluene (5 ml) was refluxed for 3 h. The precipitate was filtered to give 27 in 55 % yield, mp >300°C (from a mixture of DMF and MeOH), nmr (DMSO-d_6/TMS) δ : 4.0 (br s, NH), 8.37 (s, H_5). Anal.Calcd. for $C_5H_3N_7O$: C, 33.90; H, 1.69; N, 55.37. Found: C, 33.73; H, 2.03; N, 55.48.

1,6,8-Trimethyl-1,2,4-triazolo/3,4-b/purin-7(8H)-one (28). - To a suspension of 26 (100 mg) in toluene (4 ml), DMFDMA (100 mg) was added and the mixture was refluxed for 4 h. The precipitate was, after cooling, filtered and recrystallized from a mixture of $CHCl_3$ and petroleum ether to give 28 in 44 % yield, mp 285-290°C, m/z 218 (M^+), nmr (DMSO-d_6/TMS, 125°C) δ : 2.53 (s, Me), 3.25 (s, N_6-Me, N_8-Me), 8.26 (s, H_5). Anal.Calcd. for $C_9H_{10}N_6O$: C, 49.54; H, 4.62; N, 38.51. Found: C, 49.32; H, 4.34; N, 38.19.

Hydrogen-deuterium exchange. - To a solution of 13 (50 mg) in DMSO-d_6 (0.7 ml), a solution of NaOD/D_2O (1 M, 0.3 ml) was added. The reaction was followed by ^1H nmr. After 3 h at 118°C 3-H was completely exchanged with deuterium.

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