NEW TRICYCLIC COMPOUNDS : PYRIDO[2',3':4,5]- AND PYRIDO[3',2':4,5]-IMIDAZO[1,2-a]PYRIMIDINES

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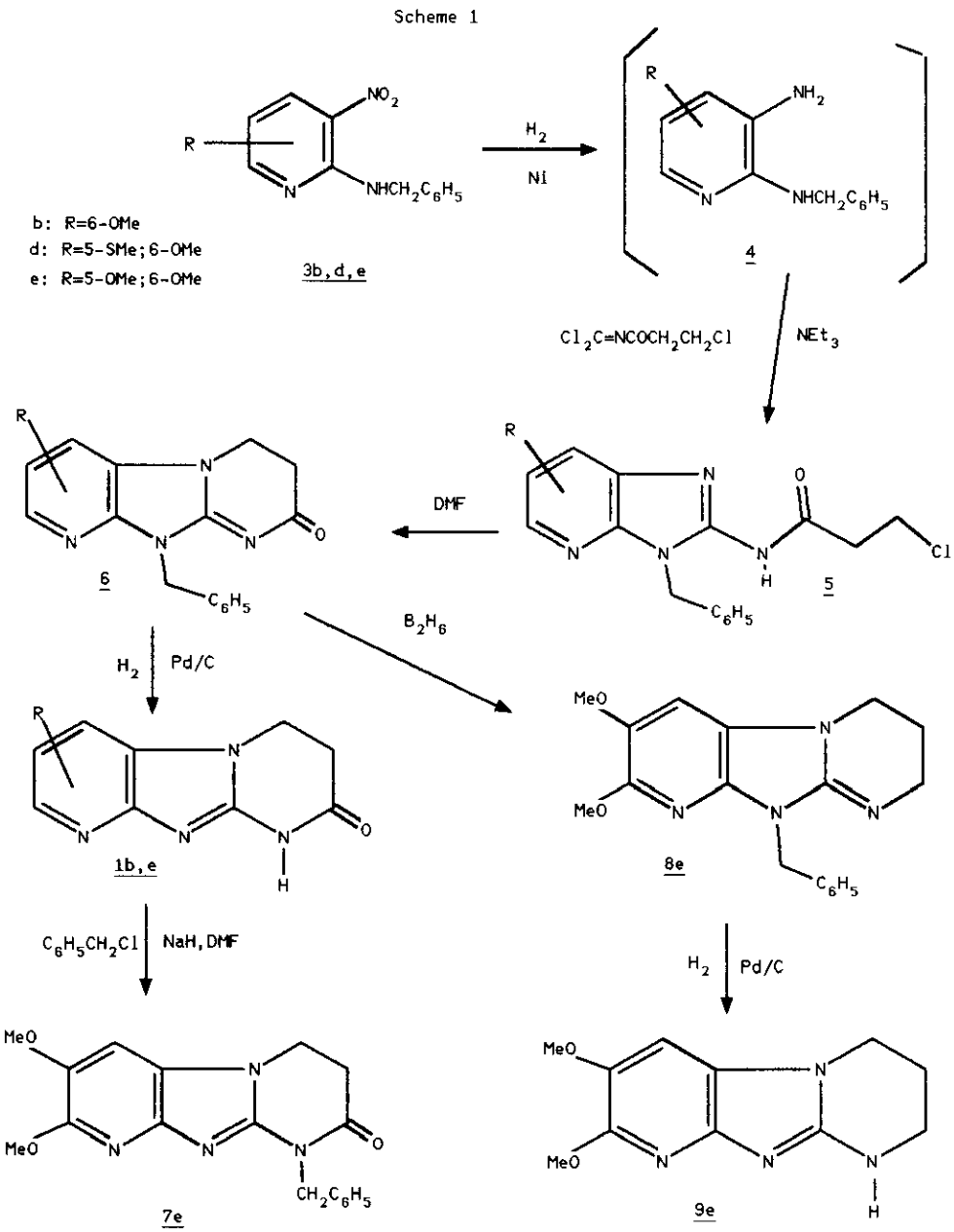
Abstract - 1,2,3,4-Tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-ones 1 are synthesized from 3-amino-2-benzylaminopyridines by condensation with N-(3-chloropropanoyl)carbonimidic dichloride and subsequent cyclisation . 1,2,3,4-Tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-ones 2 are prepared from methyl N-(3-amino-2-pyridyl)-3-aminopropanoates by condensation with N-acetylcarbonimidic dichloride, hydrolysis and cyclisation. Alkylation of pyridoimidazo[1,2-a]pyrimidin-2-ones 1 or 2 gives the corresponding 1-alkyl derivatives.

In a former paper,[1] we described the preparation of pyrimido[1,2-a]benzimidazole from o-phenylenediamine and N-(3-chloropropanoyl)carbonimidic dichloride. We report in the present note the synthesis of 1,2,3,4-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-ones 1 , 1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-ones 2 and some derivatives. Condensation of N-(3-chloropropanoyl)carbonimidic dichloride with 2,3-diaminopyridine gave 2-(3-chloropropanoylamino)imidazo[4,5-b]pyridine; we could hope a selective cyclisation of this compound to 1,2,3,4-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-one 1 or 1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one 2 , but heating 2-(3-chloropropanoylamino)imidazo[4,5-b]pyridine in DMF led, in any case, to a mixture of compounds 1 and 2 . Since compounds 1 and 2 were not easily separable, we devised selective syntheses of these compounds.

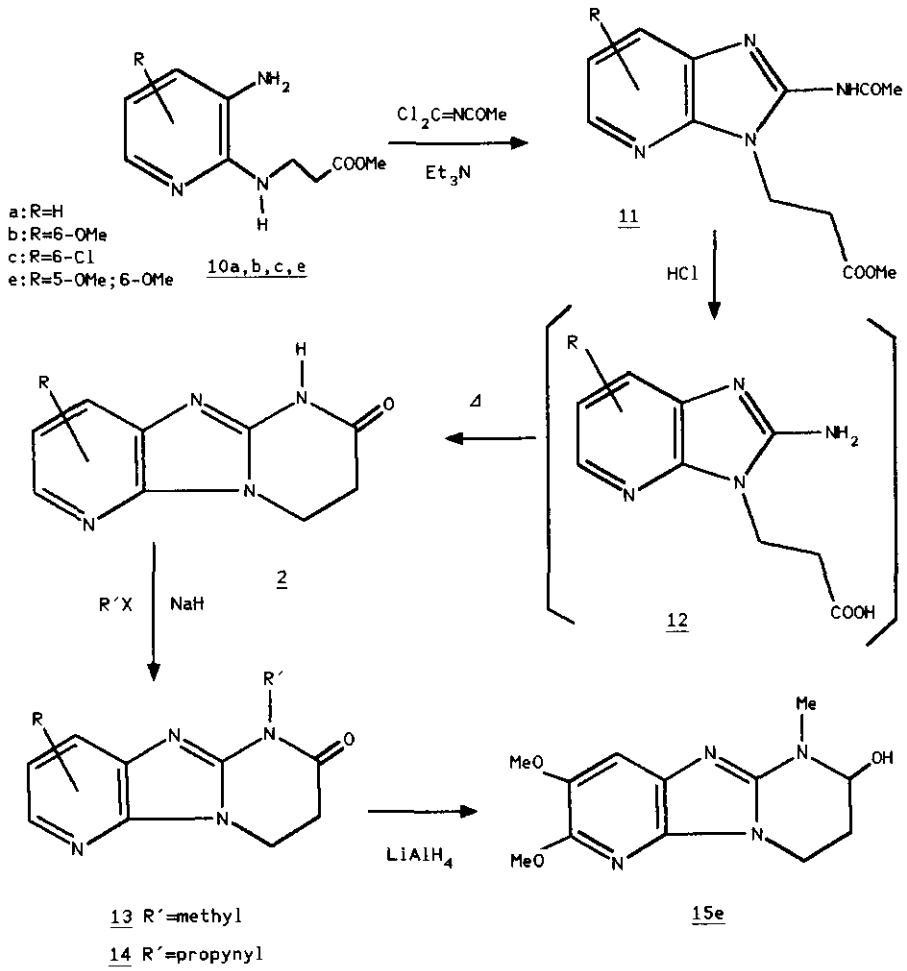
Synthesis of compounds 1 was achieved starting from 3-amino-2-benzylaminopyridines 4 prepared from 2-benzylamino-3-nitropyridines 3.[2,3] Condensation of 4 with N-(3-chloropropanoyl)carbonimidic dichloride in the presence of triethylamine gave 1-benzylamino-2-(3-chloropropanoylamino)imidazo[4,5-b]pyridines 5, and subsequent heating of 5 in DMF afforded 10-benzyl-2,3,4,10-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-ones 6, in a similar manner to the formation of pyrimidobenzimidazole.[1] Catalytic hydrogenolysis of the benzyl group of 6b,e gave 1b,e, but the benzyl group of 6d could not be removed by this method. Benzylation of 1e gave the 1-benzyl derivative 7e. On other hand, reduction of compound 6e with diborane in tetra-

Scheme 1


b: R=6-OMe
d: R=5-SMe; 6-OMe
e: R=5-OMe; 6-OMe
3b,d,e
H2
Ni
4
Cl2C=NCOCH2CH2Cl
NEt3
5
DMF
6
B2H6
H2
Pd/C
1b,e
8e
C6H5CH2Cl
NaH, DMF
7e
9e

hydrofuran afforded the de-oxo derivative 8e, which was catalytically hydrogenated to the 1,2,3,4-tetrahydro derivative 9e (Scheme 1). Diborane reduction of 1 was unsuccessful. Synthesis of isomeric pyrido[3',2':4,5]imidazo[1,2-a]pyrimidines 2 was effected by a different reaction sequence starting from methyl N-(3-amino-2-pyridyl)-3-aminopropanoates 10. Thus, 2-halogeno-3-nitropyridines[4-6] were treated with methyl 3-aminopropanoate to give the corresponding N-(nitropyridyl)-3-aminopropanoates, which were hydrogenated to 10. Condensation of 10 with N-acetylcarbonimidic dichloride[7] in the presence of triethylamine provided the imidazopyridines 11. Hydrolysis of 11 with hydrochloric acid gave the carboxylic acids 12, which were successfully cyclised to the desired pyridoimidazopyrimidines 2 upon heating under

Scheme 2



reduced pressure. Alkylation of 2 gave 1-alkyl derivatives, 13 and 14; lithium aluminium hydride reduction of 13e afforded the aminoalcohol 15e though in low yield (Scheme 2).
In conclusion, substituted pyrido[2',3':4,5]- and pyrido[3',2':4,5]imidazo[1,2-a]pyrimidines were easily synthesized by cyclisation of 2-aminoimidazo[4,5-b]pyridines obtained from condensation of alkanoylcarbonimidic dichlorides with appropriate 2-protected 2,3-diamino-pyridines .

EXPERIMENTAL

Melting points were determined on a Gallenkampf open capillary melting point apparatus and were uncorrected. Ir spectra were recorded on a Perkin Elmer Model 257 spectrophotometer. ^1H Nmr spectra were registered on a Varian T-60 (60 MHz) spectrometer. Elemental analysis were carried out either by CNRS Service Central d'Analyse F-69300 VERNAISON (France) or by Analytische laboratorien Postfach 135 D-5250 ENGELSKIRCHEN (Germany).

10-Benzyl-7,8-dimethoxy-2,3,4,10-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-one (6e). A solution of 2-benzylamino-5,6-dimethoxy-3-nitropyridine (3e, 9.7 g, 0.033 mol) in THF (80 ml) was hydrogenated in the presence of Raney Nickel (5 g) at 60°C. After removal of the catalyst by filtration, NEt_3 (3.4 g, 0.033 mol) and then N-(3-chloropropanoyl)carbonimidic dichloride (6.3 g, 0,033 mol) were added at a temperature below 40°C. The mixture was stirred for 30 min. The solid product was isolated by suction, washed with water and with ether and dried under reduced pressure to afford imidazopyridine 5e (7.9 g, 63 %). This solid was heated in boiling DMF (200 ml) for 2 h. The solvent was then removed under reduced pressure and the product was washed with water and dried to afford 6e (5.4 g, 74 %) , mp 231-233°C. This product was purified by chromatography on aluminium oxide (50 g, CH_2Cl_2 as mobile phase) : mp 234-236°C. Ir (KBr) 1640 cm^{-1}. ^1H Nmr ($CDCl_3$); δ 2.8 (t, 2H, J=7 Hz), 3.8-4.2 (m, 8H), 5.3 (s, 2H), 7.1 (s, 1H), 7.1-7.7 (m, 5H).

10-Benzyl-8-methoxy-2,3,4,10-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-one (6b). In the same way, from 2-benzylamino-6-methoxy-3-nitropyridine (3b), 6b was prepared in 29% yield, mp 243-245°C (EtOH). Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22 ; H, 5.23 ; N, 18.17. Found : C, 66.09 ; H, 5.08; N, 18.31.

10-Benzyl-8-methoxy-7-methylthio-2,3,4,10-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-one (6d). From 2-benzylamino-6-methoxy-5-methylthio-3-nitropyridine (3d), 6d was prepared in 18% yield, mp 209-211°C (EtOH). Anal. Calcd for $C_{18}H_{18}N_4O_2S$: C, 61.00, H, 5.11, N, 15.80, S, 9.04. Found : C, 60.96 ; H, 5.07 ; N, 15.84 ; S, 8.95.

7,8-Dimethoxy-1,2,3,4-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-one (1e). A

solution of the N-benzyl derivative 6e (3.8 g, 0.011 mol) in acetic acid (80 ml) was hydrogenated at 80°C in the presence of 10 % palladium on carbon (0.5 g). The heated mixture was then filtered, the solvent was evaporated, and the residue was washed with water and then with ether to afford lactam 1e (2g, 74 %). Recrystallization from DMF afforded an analytical sample, mp 280-282°C. Ir (KBr) 1695 cm^{-1}. ^1H Nmr (CF_3COOD) ; δ 1.9 (t, 2H, J=7 Hz), 2.6 (s, 3H), 2.7 (s, 3H), 3.2 (t, 2H, J=7Hz), 6.1 (s, 1H). Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 53.22 ; H, 4.87 ; N, 22.57. Found : C, 53.36 ; H, 5.05 ; N, 22.58.

8-Methoxy-1,2,3,4-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidin-2-one (1b).From 6b, 1b was similarly prepared in 37 % yield, mp 278-280°C (DMF). Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04 ; H, 4.62 ; N, 25.68. Found : C, 54.97 ; H, 4.62 ; N, 25.82.

Methyl (2-acetamido-5,6-dimethoxy-3H-imidazo[4,5-b]pyridyl)-3-propanoate (11e). A solution of methyl N-(5,6-dimethoxy-3-nitro-2-pyridyl)-3-aminopropanoate (7.2 g, 0.025 mol) in THF (75 ml) was hydrogenated in the presence of Raney Nickel (5 g). The catalyst was then filtered off and NEt_3 (5 g, 0.05 mol) and N-acetylcarbonimidic dichloride (3.5 g, 0.025 mol) were successively added to the stirred filtrate at a temperature below 40°C. Stirring was continued for 1 h and the solid product was isolated by suction, washed with water and with ether and dried to afford ester 11e (4.6 g, 57 %). Recrystallization from MeOH afforded an analytical sample, mp 176-178°C. Ir (KBr) 3300, 1740, 1630 cm^{-1}. ^1H Nmr ($CDCl_3$) ; δ 2.4 (s, 3H), 3.1 (t, 2H, J=6Hz), 3.7 (s, 3H), 4 (s, 3H), 4.1 (s, 3H), 4.5 (t, 2H, J=6Hz), 7.4 (s, 1H), 8.5- 10.0 (m, 1H). Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63 ; N, 17.38. Found : C, 52.26 ; H, 5.66 ; N, 17.54.

7,8-Dimethoxy-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2:a]pyrimidin-2-one (2e). The ester 11e (2.9 g, 0.009 mol) was heated in 5N HCl (60 ml) for 1 h. The solvent was evaporated under reduced pressure and the residual product was heated under reduced pressure at 180-200°C. DMF (70 ml) was then added and the mixture was heated for 1 h at reflux and filtered. The filtrate was then cooled to 0°C and the resultant brown precipitate was filtered to give 2e (1.4 g, 63%) , mp 310-312°C. Ir (KBr) ; 1675, 1690 cm^{-1}. ^1H Nmr (CF_3COOD); δ 2.0 (t, 2H, J=6Hz), 2.7 (s, 3H), 2.9 (s, 3H), 3.4 (t, 2H, J=6Hz), 6.3 (s, 1H). Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22 ; H, 4.87 ; N, 22.57. Found : C, 52.95, H, 4.61 ; N, 22.66.

1,2,3,4-Tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (2a). From ester 11a, 2a was similarly prepared in 67 % yield, mp 310-311°C (DMF). Anal. Calcd for $C_9H_8N_4O$: C, 57.44 ; H, 4.28 ; N, 29.77. Found : C, 57.15 ; H, 4.3 ; N, 29.71.

7-Methoxy-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (2b). From ester 11b, 2b was similarly prepared in 76 % yield, mp 295°C (DMF). Anal Calcd. for $C_9H_{10}N_4O_2$: C, 55.04 ; H, 4.62 ; N, 25,67. Found C, 54.92 ; H, 4.53 ; N, 25.34.

7-Chloro-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (2c). From ester 11c, 2c was similarly prepared in 68 % yield, mp >340°C. Anal. Calcd for $C_9H_7ClN_4O$: C, 48.55, H, 3.17 ; N, 25.16 ; Cl, 15.92. Found : C, 48.50 ; H, 3.23 ; N, 25.18 ; Cl 16.17.

1-Benzyl-7,8-dimethoxy-1,2,3,4-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyridin-2-one (7e). Lactam 1e (5.1 g, 0.02 mol) was added to a stirred suspension of NaH (50 % in oil, 1g, 0.02 mol) in DMF (60 ml), and the mixture was heated at 70-80°C for 1 h. Benzyl chloride (3.5g, 0.02 mol) was then added at 30° and then heating was continued for 3 h at 70°C. The solvent was evaporated and the residue was poured into water and the solid was filtered and washed with ether to afford 7e (3 g, 43 %), mp 173-175°C. Recrystallization from EtOH afforded an analytical sample (1.7 g, 24 %), mp 218-220°C. Ir (KBr) 1680 cm^{-1}. ^1H Nmr ($CDCl_3$); δ 3.0 (t, 2H, J=7Hz), 3.9 (s, 3H), 4.15 (t, 2H, J=7Hz), 4.2 (s, 3H), 5.4 (s, 2H), 7.0 (s, 1H), 7.2-7.7 (m, 5H). Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89 ; H, 5.36 ; N, 16.55. Found : C, 64.00 ; H, 5.24 ; N, 16.48.

1-Methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (13a). Lactam 2a was treated with MeI in the same way to give 13a in 43 % yield, mp 172-174°C (MeOH). Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.39 ; H, 4.98 ; N, 27.71. Found : C, 59.60 ; H, 5.13 ; N, 28.01.

7,8-Dimethoxy-1-methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (13e). From lactam 2e, 13e was prepared in 58% yield, mp 207-209°C (DMF). Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.96 ; H, 5.38 ; N, 21.36. Found : C, 54.53 ; H, 5.35 ; N, 21.43.

7-Methoxy-1-methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (13b). From 2b, 13b was prepared in 53 % yield, mp 163-166°C (MeOH). Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.99 ; H, 5.21 ; N, 24.12. Found : C, 56.46, H, 5.12 ; N, 23.79.

7-Methoxy-1-(3-propynyl)-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (14b). From lactam 2b and 3-bromopropyne, 14b was similarly prepared in 33 % yield, mp 178-180°C (MeOH). Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.92 ; H, 4.72 ; N, 21.86. Found : C, 60.85 ; H, 4.74 ; N, 21.67.

7-Chloro-1-methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-one (13c). From 2c and MeI, 13c was similarly prepared in 53 % yield, mp 212-213°C (MeOH). Anal. Calcd for $C_{10}H_9N_4ClO$: C, 50,74 ; H, 3.83 ; N, 23.67 ; Cl, 14.98. Found : C, 50.90 ; H, 3.69 ; N, 23.92 ; Cl 14.74.

10-Benzyl-7,8-dimethoxy-2,3,4,10-tetrahydro[2',3':4,5]imidazo[1,2-a]pyrimidine (8e). A suspension of lactam 6e (4.8 g, 0,014 mol) in THF (50 ml) was heated at reflux for 30 min and a solution of diboran-THF (2M, 10.5 ml, 0.021 mol) was added. Heating was continued for 1.25 h ; after cooling, 20% hydrochloric acid (2.5 ml) was added at 20°C. The resulting mixture was refluxed for 15 min, 30% NaOH (10 ml) was then added and the solution was

extracted with chloroform. The chloroform extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residual solid was washed with ether to afford pyrimidine 8e (3.7 g, 82 %). Recrystallization from MeOH afforded an analytical sample, mp 144-146°C. ^1H Nmr ($CDCl_3$); δ 1.7-2.3 (m,2H), 3.5-4.1 (m,4H), 3.9 (s,3H), 4.1 (s,3H), 5.1 (s,2H), 6,8 (s,1H), 7.2-7.7 (m,5H).

7,8-Dimethoxy-1,2,3,4-tetrahydropyrido[2',3':4,5]imidazo[1,2-a]pyrimidine (9e). A solution of N-benzyl derivative 8e (8.4 g, 0.026 mol) in acetic acid (80 ml) was hydrogenated at 120°C in the presence of 30 % palladium hydroxide on carbon (2 g). The mixture was then filtered, the solvent was evaporated and the residue was recrystallized from EtOH to afford the amine 9e (2.4 g, 40 %), mp 238-240°C. ^1H Nmr ($CDCl_3$); δ 2-2.5 (m, 2H), 3.4-3.7 (m, 2H), 3.9 (s, 3H), 4.1 (s, 3H), 6.85 (s, 1H), 6.7-7.3 (m, 1H). 9e in EtOH-$CHCl_3$ was treated with HCl to afford the HCl salt 9e.HCl : mp 240-242°C (EtOH). Anal. Calcd for $C_{11}H_{15}ClN_4O_2$: C, 48.80 ; H, 5.58 ; Cl, 13.09 ; N, 20.69. Found : C, 48.72 ; H,5.44 ; Cl, 13.25 ; N, 20.54.

7,8-Dimethoxy-1-methyl-1,2,3,4-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrimidin-2-ol (15e). Imidazopyridine 13e (5.12 g, 0.02 mol) was slowly added to a suspension of $LiAlH_4$ (1.14 g, 0.03 mol) in THF (110 ml). The mixture was refluxed for 4.5 h, then cooled, water (7 ml) and 5N NaOH (7 ml) were successively added with cooling ; the resulting precipitate was filtered and the filtrate was evaporated under reduced pressure ; the residue was washed with water and dried to afford the imidazopyridine 15e (1.3 g, 25 %). Recrystallization from EtOH provided an analytical sample, mp 180-182°C. ^1H Nmr (DMSO-d_6); δ 2.0-2.4 (m, 2H), 3.15 (s, 3H), 3.8 (s, 3H), 3.95 (s, 3H), 3.9-4.1 (m, 2H), 4.95-5.1 (m, 1H), 6.25 (d, 1H, J=5Hz, OH), 7.4 (s, 1H). Anal. Calcd for $C_{12}H_{16}NO_3$: C, 54.53 ; H, 6.10 ; N, 21.20. Found : C, 54.61 ; H, 6.18 ; N, 20.96.

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3.Compound 3d was prepared by thiocyanation of 2-benzylamino-6-methoxy-3-nitropyridine followed by methylation with methyl iodide in KOH-MeOH.

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