Aminolysis of Methoxy Groups in Pyrimidine Derivatives. Activation by 5-Nitroso Group

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The nucleophilic substitution of 2-methoxy groups in pyrimidine derivatives was strongly activated by introduction of a 5-nitroso group on to the pyrimidine ring. The aminolysis of several 2-methoxy-5-nitrosopyrimidine derivatives was performed at room temperature in hydroxylic as well as in non-hydroxylic media with different primary amines in short time and good yields. The aminolysed substrates include 6-[(per-*O*-acetyl)glycosyl]aminopyrimidines which afforded the corresponding 2-aminopyrimidines without harming the acetyl protecting groups of the sugar moiety.

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Introduction.

The chemistry of pyrimidine derivatives is of particular interest in the preparation of bioactive (natural as well as synthetic) compounds because of the ubiquitous occurrence of this heterocyclic nucleus in living systems either by itself or as part of other fused heterocyclic systems (*i.e.*, purines and pteridines). In pyrimidine chemistry, nucleophilic substitution is one of the most widely used procedures to elaborate the ring functionalisation [1]. This is undoubtedly due to the intrinsic π-deficiency of this diazine, which makes it prone to suffer nucleophilic displacement of a great variety of groups linked to its carbon atoms, particularly to the most electron deficient, C(2) and C(4)/C(6) [1]. Halogenides (especially chloride), being good leaving groups, have been preferred for synthetic purposes, but many other groups have been displaced under appropriate conditions, including nitro, sulfones, sulfoxides, cyano, thiocyanato, acyloxy, alkylthio, alkoxides, alkylsilyloxides and amines. With reference to alkoxy groups, it is well documented that the poor leaving ability of alkoxides requires the participation of strong nucleophiles (such as other alkoxides) and/or severe reaction conditions (typically high temperatures) to successfully achieve their substitution [2]. This has rendered the alkoxide substitution in pyrimidine rings of little synthetic application except for simple non-labile substrates.

On the other hand, it has been recognized that activation towards nucleophilic substitution is enhanced by introduction of an electron-withdrawing group at C(5) of the pyrimidine ring. The most studied (and the most synthetically employed) activating group has been the strong electron withdrawing nitro group, whose profound activating effect on the aminolysis of 2- and 4-methoxy groups has been described [3]. Thus 2-(or 4-/6)-chloro-5-nitropyrimidines are commonly used as precursors to obtain other functionalised 5-nitropyrimidine derivatives through nucleophilic displacement of chloride under soft conditions [4].

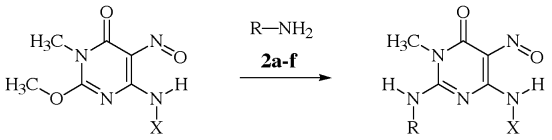
However, another strong electron-withdrawing group, the nitroso group, has received little attention as an activator of nucleophilic substitution, even when it is one of the most widely employed to introduce a nitrogen functionalisation at C(5) in pyrimidine derivatives during the synthesis of azaheterocycles fused with pyrimidine (*i.e.*, purines, 8-azapurines, pteridines, *etc*.). There are some precedents [5-6] indicating that a 5-nitroso group can act as strong activator of nucleophilic substitution of alkylthio groups from pyrimidines. However, the studies have not been, to our knowledge, extended to the activation of other leaving groups.

In this article we report on the very high activation towards aminolysis of methoxy groups found in 2-methoxy-5-nitrosopyrimidine derivatives, which has been shown to be due to the existence of the 5-nitroso functionalisation. The scope and synthetic application of this reaction are explored.

Results and Discussion.

During our work with 5-nitrosopyrimidines as intermediates in the preparation of binuclear fused pyrimidines [7-8], we found that treatment of 6-amino-2-methoxy-3-methyl-5-nitrosopyrimidin-4(3*H*)-one, **1a**, with concentrated aqueous ammonia at room temperature afforded, in a short time, a pink solid which was identified as 2,6-diamino-3-methyl-5-nitrosopyrimidin-4(3*H*)-one hydrate, **3a** (see Scheme 1). The mild reaction conditions and the good yield of this transformation (up to 96 %, see Table 1) prompted us to explore the synthetic applicability of this aminolysis reaction. Then, the ability of different primary amines, **2b**-**g** (including alkylamines, aminoacid potassium salts and aniline, see Scheme 1) to replace the 2-methoxy group of **1a** was tested. In all cases, hydroxylic media (methanol, water or acetonitrile-water mixtures) and room temperature were chosen as reaction conditions, under which the reactions proceeded in suspension.

Scheme 1

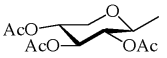


1a-c **3a-j**

1	X
a	-H
b	Xylo(OAc)$_3$
c	Gluco(OAc)$_4$

2	R
a	-H
b	-CH_3
c	-CH_2-Ph
d	-*n*-Bu
e	-CH_2-COO^-K^+
f	(S) -CH(-CH_3)-COO^-K^+
g	

3	R	X
a	-H	-H
b	-CH_3	-H
c	-CH_2-Ph	-H
d	-*n*-Bu	-H
e	-CH_2-COOH	-H
f	(S) -CH(-CH_3)-COO^-K^+	-H
g	-H	Xylo(OAc)$_3$
h	-CH_2-Ph	Xylo(OAc)$_3$
i	-*n*-Bu	Xylo(OAc)$_3$
j	-H	Gluco(OAc)$_4$

Xylo(OAc)$_3$ = 

Gluco(OAc)$_4$ = 

Table 1

Synopsis of Reaction Conditions and Yields for the Aminolysis Reactions

Product	Solvent	Molar ratio 2/1	Temp.	Time (min)	Yield (%)
3a	H_2O [a]	[b]	r.t.	105	96
3b	H_2O [a]	4.4	r.t.	35	90
3c	MeOH [a]	1.2	r.t.	420	86
3c	H_2O [a]	4.0	r.t.	20	84
3d	MeOH [a]	1.2	r.t.	90	91
3d	H_2O [a]	4.0	r.t.	35	72
3e	CH_3CN/H_2O [a]	1.0	70°	50	76
3f	CH_3CN/H_2O [a]	1.0	r.t.	1080	71
3g	CH_2Cl_2	excess [c]	r.t.	60	87
3h	CH_2Cl_2	1.5	r.t.	30	80
3h	H_2O	4.0	r.t.	10	80
3i	CH_2Cl_2	1.5	r.t.	45	91
3j	CH_2Cl_2	excess [b]	r.t.	35	53

[a] The reaction proceeds in suspension; [b] large excess; 20 % aqueous ammonia was used as NH_3 source, see experimental; [c] a slight current of gaseous ammonia was used as NH_3 source.

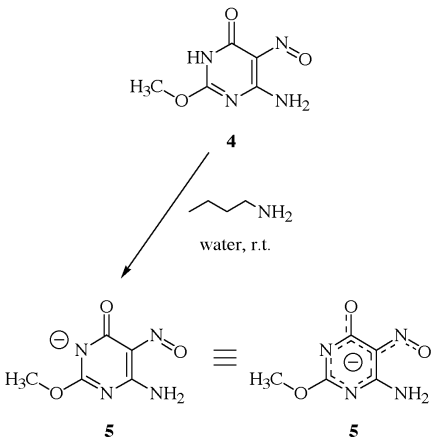
For alkylamines and aminoacid derivatives, **2b-f**, the results were clean nucleophilic substitutions to afford the corresponding 2-aminopyrimidine derivative **3b-f** in good to very good yields after reaction times ranging from 35 minutes to 18 hours. All the resulting products, **3b-f**, were fully characterized through elemental analysis, spectroscopic properties (ir, uv-vis, ms, ^{1}H-nmr and ^{13}C-nmr, see Experimental and Table 2) and single crystal X-ray diffraction analysis of one of them (**3e**) [9]. A remarkable structural feature of compounds **3a-g** (also observed in their precursors, **1a-c**) is the strong intramolecular hydrogen bond established between the 5-nitroso and the 6-NH groups, which causes the pmr signal of the involved NH proton to be displaced up to 10.84-10.94 ppm for **3a-f** and even further (up to

12.10-12.22) for the 6-*N*-glysosyl derivatives **3g-j** (see Experimental). Besides, compounds **3a,g,j** show distinguishable pmr signals for each of the two 2-NH_2 protons, which appear in the range 7.79-8.64 ppm and are displaced *ca.* 0.45 ppm one from the other in all the three cases. This effect points to a high double bond character for the N^2-C(2) bond as a consequence of the participation of the N^2 lone pair in the push-pull system originated by the 2-amino and 5-nitroso substituents in relative *para*- positions of the pyrimidine ring. The relative short N^2-C(2) distance (1.319 Å) measured in the single crystal X-ray diffraction analysis of **3e** also supports this hypothesis.

With reference to the less nucleophilic aniline, **2g**, while it was unable to displace the 2-methoxy group of **1a** in water at room temperature, under reflux the result was a complex mixture of fluorescent compounds of no practical value for our purpose.

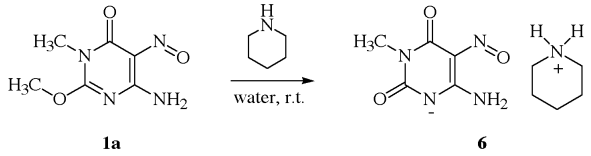
The easy substitution of such a poor leaving group as is methoxide, proved to be due to the strong activation produced by the 5-nitroso group in **1a**, because the corresponding non-nitrosated pyrimidine derivative, 6-amino-2-methoxy-3-methylpyrimidin-4(3*H*)-one [10] remained unaltered after treatment with butylamine (4 mol equivalents) in water at room temperature for 48 hours. Moreover, the nitrosoderivative 6-amino-2-methoxy-5-nitrosopyrimidin-4(3*H*)-one, **4** [10], did not experience substitution of its 2-methoxy group by similar treatment with butylamine (4 mol equivalents, water, room temperature). In this case the only observed transformation was the solution of the original water suspension of **4** after butylamine addition. This observation, and the inability of **4** to suffer methoxide displacement was interpreted as a consequence of the acidity of its amide tautomerizable hydrogen, which can be removed by butylamine. After deprotonation, the resulting water soluble anionic species, **5**, has its negative charge delocalized along the pyrimidine nucleus, which consequently becomes deactivated towards nucleophilic attack (see Scheme 2).

Scheme 2



Secondary amines, being more nucleophilic than primary and still possessing a hydrogen atom linked to nitrogen, apparently comply with the requirements to accomplish the aminolysis of **1a**. However, treatment with piperidine in water resulted in hydrolysis of **1a** instead of aminolysis, thus affording the piperidinium salt of 4-amino-1-methyl-5-nitrosouracil-3-yde, **6**, in good yield (see Scheme 3). Specially helpful for the characterization of **6** was its single crystal X-ray diffraction analysis [11] (see Figure 1), because the spectroscopic data did not allow definitive discrimination between the actual structure and the hypothetical one, 2-(piperidin-1-yl)-5-nitrosopyrimidine derivative, resulting from piperidine substitution of the 2-methoxy group of **1a**, in a similar way to that observed for primary amines.

Scheme 3



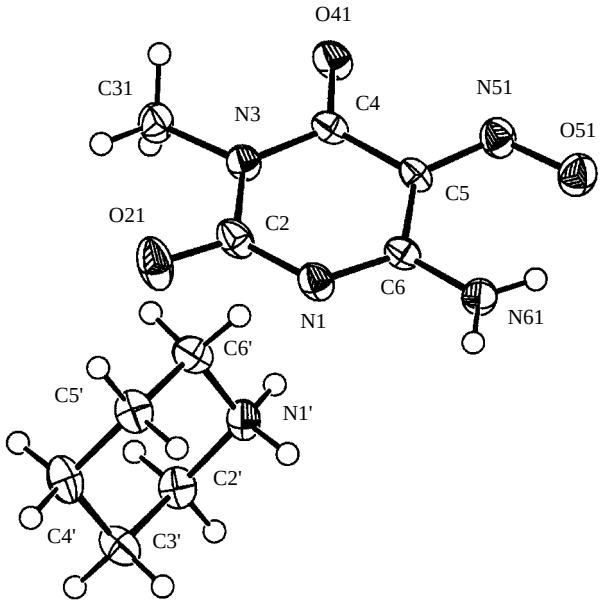


Figure 1. ORTEP plot of **6**. Displacement ellipsoids are represented at the 30 % probability level.

The reason why treatment with piperidine produced hydrolysis instead of aminolysis remains uncertain, but a probable explanation can be found in the steric hindrance

Table 2

^{13}C-NMR Chemical Shifts [a] for Compounds **3a-j** [b]

Compound	Pyrimidine moiety 3-CH_3	C-5	C-6	C-2	C-4	Other
3a	27.8	141.8	150.6	156.8	161.5	----
3b	28.3	141.7	149.6	154.7	161.2	26.9 (q)
3c	27.4	142.1	149.9	154.7	161.6	40.5 (t), 127.0 (d), 127.4 (d), 128.3 (d),138.4 (s)
3d	27.7	142.3	150.4	154.8	162.0	14.1 (q), 19.8 (t), 31.2 (t), 41.6 (t)
3e	27.4	142.0	149.6	154.9	161.4	42.9 (t), 170.47 (s)
3f	26.6	141.9	150.3	152.7	161.5	18.8 (q), 52.3 (d), 172.7 (s)
3g	28.0	140.9	149.4	157.0	161.0	20.1(q), 20.3(q), 20.4 (q), 62.9 (t), 67.8 (d), 69.6 (d), 70.6 (d), 77.2 (d), 169.1 (s), 169.3 (s),169.4 (s)
3h	27.7	140.8	149.8	155.0	162.2	*Benzyl* 46.4 (t), 127.7 (d), 127.9 (d), 128.5 (d), 137.4 (s). *Sugar* 20.6 (q), 20.8 (q), 63.5 (t), 68.2 (d), 69.5 (d), 70.8 (d), 78.2 (d), 169.6 (s), 169.8 (s), 169.9 (s)
3i	27.5	141.2	148.8	154.5	161.1	*Butyl* 13.8 (q), 19.4 (t), 31.0 (t), 41.7 (t) *Sugar* 20.3 (q), 20.4 (q), 20.5 (q), 63.0 (t), 68.4 (d), 69.8 (d), 71.2 (d), 77.8 (d), 169.4 (s); 169.6 (s)
3j	28.0	140.7	149.4	157.0	160.9	20.1 (q), 20.2 (q), 20.3 (q), 20.4 (q), 61.6 (t), 67.7 (d), 70.3 (d), 72.0 (d), 72.7 (d), 77.1 (d), 169.1 (s), 169.2 (s) 169.5 (s), 170.0 (s)

[a] All spectra acquired in DMSO-d_6 (except for **3h**, that was acquired in $CDCl_3$); [b] Chemical shift δ in ppm relative to TMS as internal standard.

caused by the 3-methyl substituent of the pyrimidine ring, which should prevent the piperidine moiety from being accommodated at C(2) of the pyrimidine nucleus. Under these circumstances water, or hydroxyls liberated after protonation of piperidine, should be able to compete with the amine for nucleophilic displacement of the 2-methoxy group.

The synthetic usefulness of the aminolysis under discussion is well exemplified by its application on glycosides **1b,c**, whose sugar hydroxyls are fully protected as acetates. The reactions were performed in dry dichloromethane at room temperature in times ranging from 30 minutes to 1 hour, without any interference with the ester protecting groups on the sugar for the xyloside as well as for the glucoside [12], as revealed by tlc analysis of the crude reaction mixtures. Moreover, benzylamine accomplished substitution on a suspension of **1b** in water in only 10 minutes with a final isolated yield of **3h** similar to that obtained in dichloromethane (see Scheme1 and Table 1)

Conclusions.

The introduction of a nitroso group on C(5) of a pyrimidine nucleus highly activates it towards nucleophilic substitution. This enables easy and selective aminolysis of methoxy groups in hydroxylic as well as non hydroxylic media under mild conditions whenever relatively acidic amide-imide tautomerizable groups are absent from the pyrimidine ring. As nitrosopyrimidines are useful intermediates in common synthetic routes to purines and pteridines, the nitroso stage can be used to elaborate functionalisation on the heterocyclic nucleus through nucleophilic substitution under soft conditions prior to ring completion. The application of this methodology to prepare fused pyrimidines, including nucleoside analogues, [7-8] is currently under study in our laboratory.

Acknowledgements.

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EXPERIMENTAL

Melting points were determined in an Electrothermal IA9000 melting point apparatus and are uncorrected. The ir spectra were recorded in a Perkin-Elmer 1760X FT-IR spectrophotometer as potassium bromide pellets. Ultraviolet and visible spectra were measured in a GBC UV/VIS 911 spectrophotometer. The ^{1}H and ^{13}C nmr were obtained with a Bruker DPX-300 instrument in dimethylsulfoxide-d_6 or deuteriochloroform and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Electron-impact (70 eV) mass spectra were obtained in a Hewlett-Packard HP-5989-B spectrometer. Optical rotation was measured in a Perkin-Elmer 241 polarimeter. The elemental analyses were performed in a Perkin-Elmer 240 C instrument from "Servicios Técnicos de la Universidad de Granada". Thin layer chromatography was performed on Merck Silica Gel 60GF_{254} aluminium precoated foils (0.2 mm) with fluorescent indicator and spots were visualized by ultraviolet irradiation. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). The X-ray diffraction data were collected at the EPSRC,X-ray Crystallographic Service, University of Southampton using an Enraf Nonius Kappa-CCD diffractometer.

2,6-Diamino-3-methyl-5-nitrosopyrimidin-4(3*H*)-one Hydrate (**3a**).

Finely powdered **1a** [13] (5.500 g, 27.20 mmoles) was suspended in 20% aqueous ammonia (70 mL) and the mixture stirred at room temperature for 1 hour and 45 minutes. The pink solid in suspension was collected by filtration, washed successively with water, ethanol and ethyl ether, and dried by suction to give 4.870 g (26.02 mmoles, 96 %) of **3a**, mp >330°; ir (potassium bromide): 3355, 3272, 3146, 1652, 1559, 1516, 1287, 1236, 1144, 1052 cm^{-1}; uv-vis (methanol-water, 8:2, v/v): λ max (log ε): 542 (1.84), 327 (4.20), 299 (shoulder), 246 (shoulder), 230 (3.94) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.32 (s, 3H, CH_3), 7.79 (br s, 1H, 2-NHa), 8.07 (br s, 1H, 6-NHa), 8.23 (br s, 1H, 2-NHb), 10.84 (br s, 1H, 6-NHb); ms: m/z (%) 169 (M^+, 21), 124 (4), 111(2), 95 (2), 68 (27), 56 (40), 53 (44), 43 (100).

Anal. Calcd. for $C_5H_7N_5O_2 \cdot H_2O$: C, 32.09; H, 4.85; N, 37.42. Found: C, 31.90; H, 4.71; N, 37.80.

6-Amino-3-methyl-2-(methylamino)-5-nitrosopyrimidin-4(3*H*)-one (**3b**).

Methylamine (1.87 mL of 40% aqueous solution, 21.72 mmoles) was added to a suspension of **1a** (1.00 g, 4.95 mmoles) in water (25 mL), and the mixture was stirred at room temperature for 35 minutes. The pink solid in suspension was collected by filtration, washed with plenty of water and dried *in vacuo* at 78° to give 0.817 g (4.46 mmoles, 90 %) of **3b** under the form of a very insoluble pink fine powder of coherent spectroscopic data. For analytical purposes a sample was recrystallized from hot dimethyl sulfoxide, mp 312°; ir (potassium bromide): 3451, 3297, 3143, 3060, 2965, 2909, 1688, 1607, 1496, 1470, 1454, 1414, 1367, 1292, 1227 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.93 (s, 3H, 2-NCH_3), 3.31 (s, 3H, 3-CH_3), 7.87 (br s, 1H, 2-NH), 8.02 (br s, 1H, 6-NHa), 10.93 (br s, 1H, 6-NHb); ms: m/z (%) 183 (M^+, 100), 166 (55), 138 (51), 125 (42), 109 (44), 83 (22), 69 (36), 57 (92).

Anal. Calcd. for $C_6H_9N_5O_2$: C, 39.34; H, 4.95; N, 38.23. Found: C, 39.45; H, 5.07; N, 37.87.

6-Amino-2-(benzylamino)-3-methyl-5-nitrosopyrimidin-4(3*H*)-one (**3c**).

Benzylamine (0.65 mL, 5.94 mmoles) was added to a suspension of **1a** (1.00 g, 4.95 mmoles) in methanol (25 mL) and the mixture stirred at room temperature for 7 hours. The solid in suspension was collected by filtration, washed with methanol and dried under vacuum at 78° to give 1.109 g (4,28 mmoles, 86 %) of **3c**, mp 267° (dec); ir (potassium bromide): 3264, 1672, 1613, 1590, 1554, 1515, 1454, 1372, 1221 cm^{-1}; uv-vis (methanol), λ max (log ε): 540 (1.87), 330 (4.35), 254 (3.77), 233 (4.02) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.39 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 7.20-7.45 (m, 5H, phenyl protons), 8.31 (br s, 1H, 6-NHa), 8.58 (br s, 1H, 2-NH), 10.91 (br s, 1H, 6-NHb); ms: m/z (%) 259 (M^+, 21), 242 (100), 215 (18), 91 (71), 77 (6).

Anal. Calcd. for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.67; H, 5.21; N, 26.77.

6-Amino-2-(butylamino)-3-methyl-5-nitrosopyrimidin-4(3*H*)-one (**3d**).

Butylamine (0.59 mL, 5.94 mmoles) was added to a suspension of **1a** (1.00 g, 4.95 mmoles) in methanol (25 mL) and the mixture stirred at room temperature for 1.5 hours. The crude, containing a red crystalline precipitate, was concentrated under reduced pressure to *ca*. 10 mL, then water (50 mL) was added and the mixture concentrated again to half its volume and finally stored in the refrigerator at 4° overnight. The crystalline red solid was collected by filtration, washed with water and dried *in vacuo* at 78° to give 0.900 g (4.00 mmoles) of **3d**. By concentration of the mother liquors another 0.110 g (0.49 mmoles) of **3d** were obtained. Global yield: 91 %, mp 227° (dec); ir (potassium bromide): 3432, 3312, 3243, 3078, 2955, 2931, 2872, 1685, 1620, 1586, 1499, 1469, 1427, 1379, 1220 cm^{-1}; uv-vis (methanol), λ max (log ε): 544 (1.84), 330 (4.33), 255 (3.73), 233 (3.96) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.88 (t, 3H, butyl CH_3, J = 7.4 Hz), 1.28 (m, 2H, $CH_2CH_2\mathit{CH}_2CH_3$), 1.53 (tt, 2H, $CH_2\mathit{CH}_2CH_2CH_3$, J = 7.2, 7.4 Hz), 3.31 (s, 3H, 3-CH_3), 3.38 (t, 2H, N-CH_2-, J = 7.2 Hz), 8.03 (br s, 1H, 2-NH), 8.24 (d, 1H, 6-NHa, J = 4.5 Hz), 10.90 (d, 1H, 6-NHb, J = 4.5 Hz); ms: m/z (%) 225 (M^+, 32), 208 (100), 182 (87), 152 (23), 124 (15), 111(17), 95 (13).

Anal. Calcd. for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 47.56; H, 6.82; N, 30.75.

2-[(4-Amino-3-methyl-5-nitroso-6-oxo-1,6-dihydro)pyrimidin-2-yl]aminoacetic Acid Dihydrate (**3e**).

A solution of glycine (0.751 g, 10.0 mmoles) in water (20 mL) was treated with 1 *N* KOH (10 mL). To the resulting solution, **1a** (2.02 g, 10.00 mmoles) and acetonitrile (30 mL) were added and the mixture stirred at 70° for 50 minutes. The crude was cooled at room temperature, acidified to pH 3 by dropwise addition of acetic acid and left in the refrigerator at 4° for 24 hours. The orange crystalline solid was collected by filtration, washed successively with water, ethanol and ethyl ether, and dried by suction to give 1.99 g (7,56 mmoles, 76 %) of **3e**, mp 133° (dec); ir (potassium bromide): 3475, 1706, 1570, 1463, 1299, 1262 cm^{-1}; uv-vis (water), λ max (log ε): 530 (1.82), 327 (4.33), 262 (3.67), 228 (3.89), 204 (4.39) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.38 (s, 3H, CH_3), 4.07 (d, 2H, N-CH_2-, J = 3.6 Hz), 8.35 (d, 1H, 6-NHa, J = 4.5 Hz), 8.44 (br s, 1H, 2-NH), 10.90 (d, 1H, 6-NHb, J = 4.5 Hz).

Anal. Calcd. for $C_7H_9N_5O_4 \cdot 2H_2O$: C, 31.93; H, 4.94; N, 26.60. Found: C, 32.05; H, 4.77; N, 26.87.

Potassium (*S*)-2-[(4-Amino-3-methyl-5-nitroso-6-oxo-1,6-dihydro)pyrimidin-2-yl]aminopropanoate Dihydrate (**3f**).

A solution of L-alanine (0.45 g, 5.0 mmoles) in water (5 mL) was treated with 1 *N* KOH (5 mL). To the resulting solution, **1a** (1.02 g, 5.00 mmoles) and acetonitrile (15 mL) were added and the mixture stirred at room temperature for 18 hours. The solvent was eliminated under reduced pressure. Acetonitrile (35 mL) and ethyl ether (75 mL) were added and the mixture containing an abundant precipitate was kept in the freezer at -15° overnight. The pink solid precipitate was collected by filtration, washed with ethyl ether and immediately introduced in a desiccator while the solid was still wet with ether. Drying *in vacuo* at 78° afforded 0.997 g (3.57 mmoles, 71 %) of **3f**, mp 250°; $[\alpha]_{436}^{23}$ + 355.2 (c = 0.125, water); ir (potassium bromide): 3347, 1691, 1630, 1603, 1045, 1293, 1266 cm^{-1}; uv-vis (water), λ max (log ε): 525 (1.90), 328 (4.36), 263 (3.68), 228 (3.92), 204 (4.33) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.36 (d, 3H, -CHCH_3, J = 6.9 Hz), 3.39 (s, 3H, 3-CH_3), 4.00 (q, 1H, N-CH, J = 6.9 Hz), 7.70 (br s, 1H, 2-NH), 8.41 (br s, 1H, 6-NHa), 10.94 (br s, 1H, 6-NHb)

Anal. Calcd. for $C_8H_{10}N_5O_4K \cdot 2H_2O$: C, 30.47; H, 4.48; N, 22.21. Found: C, 30.68; H, 4.42; N, 21.84.

2-Amino-3-methyl-5-nitroso-6-[(tri-*O*-acetyl)-β-D-xylopyranosyl]aminopyrimidin-4(3*H*)-one (**3g**).

Through a solution of **1b** [14] (1.00 g, 2.26 mmoles) in dichloromethane (10 mL), a slight current of gaseous ammonia was continuously bubbled at room temperature for 1 hour. The resulting mixture, containing a blue-pink solid in suspension, was evaporated to dryness under reduced pressure. The residue was boiled with methanol (25 mL) for 5 minutes, and then left to stand at room temperature overnight. The solid in suspension was collected by filtration, washed successively with methanol and ethyl ether, and dried by suction to give 0.809 g (1.89 mmoles) of **3g**. Concentration of the mother liquors gave another 0.043 g (0.1 mmoles) of **3g**. Global yield: 87 %, mp 296 (dec); ir (potassium bromide): 3503, 3405, 3144, 2944, 1757, 1623, 1550, 1506, 1371, 1252, 1221, 1180, 1068 cm^{-1}; uv-vis (methanol), λ max (log ε): 554 (1.82), 332 (4.27), 304 (shoulder), 253 (shoulder), 234 (4.07) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.93, 2.02, 2.11 (3s, each, 3H, acetates), 3.32 (s, 3H, 3-CH_3), 3.48 (dd, 1H, 5'-Hα, J = 9.1, 11.7 Hz), 3.98 (dd, 1H, 5'-Hβ, J = 4.9, 11.7 Hz), 4.91 (psdt, 1H, 4'-H, J = 4.9, 8.8 Hz), 5.0 (pst, 1H, 2'-H, J = 8.2 Hz), 5.24 (pst, 1H, 3'-H, J = 8.5 Hz), 5.64 (pst, 1H, 1'-H, J = 8.5 Hz), 8.18 (br s, 1H, 2-NHa), 8.63 (br s, 1H, 2-NHb), 12.22 (d, 1H, 6-NH, J = 9.0 Hz); ms: m/z (%) 410 (2), 248 (2), 231 (15), 181 (9), 157 (6), 139 (6), 97 (10), 60 (10), 43 (100).

Anal. Calcd. for $C_{16}H_{21}N_5O_9$: C, 44.97; H, 4.95; N, 16.39. Found: C, 44.79; H, 4.98; N, 16.24.

2-(Benzylamino)-3-methyl-5-nitroso-6-[(tri-*O*-acetyl)-β-D-xylopyranosyl]aminopyrimidin-4(3*H*)-one Hydrate (**3h**).

Benzylamine (0.37 mL, 3.39 mmoles) was added to a solution of **1b** (1.00 g, 2.26 mmoles) in dichloromethane (25 mL) and the mixture was stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel (eluent dichloromethane-ethanol, 95:5, v/v) to obtain one fraction containing 1.179 g of chromatographically pure material which, after recrystallization from methanol afforded, in two crops, 0.968 g (1.81 mmoles, 80 %) of **3h**, mp 218º (dec); ir (potassium bromide): 3389, 3269, 2945, 1756, 1677, 1593, 1555, 1525, 1455, 1372, 1226 cm^{-1}; uv-vis (methanol), λ max (log ε): 557 (1.83), 336 (4.32), 256 (3.77), 236 (4.04) nm; ^1H nmr (deuteriochloroform): δ 1.97, 2.11, 2.18 (3s, each, 3H, acetates), 3.38 (dd, 1H, 5'-Hα, J = 8.9, 11.9 Hz), 3.47 (s, 3H, 3-CH_3), 4.04 (dd, 1H, 5'-Hβ, J = 4.9, 11.9 Hz), 4.59 (dd, 1H, 2-N-CHa, J = 5.1, 14.9 Hz), 4.73 (dd, 1H, 2-N-CHb, J = 5.1, 14.9 Hz), 4.96 (m, 2H, 4'-H and 2'-H), 5.24 (pst, 1H, 3'-H, J = 8.0), 5.53 (pst, 1H, 1'-H, J = 8.1 Hz), 7.13-7.40 (m, 5H, phenyl protons), 8.64 (br s, 1H, 2-NH), 12.18 (d, 1H, 6-NH, J = 8.3 Hz); ms: m/z (%) 500 (17), 398 (9), 270 (12), 254 (52), 242 (31), 139 (9), 97 (15), 91 (28), 43 (100).

Anal. Calcd. for $C_{23}H_{27}N_5O_9 \cdot H_2O$: C, 51.59; H, 5.46; N, 13.08. Found: C, 51.65; H, 5.54; N, 13.05.

2-(Butylamino)-3-methyl-5-nitroso-6-[(tri-*O*-acetyl)-β-D-xylopyranosyl]aminopyrimidin-4(3*H*)-one Hemihydrate (**3i**).

Butylamine (0.34 mL, 3.39 mmoles) was added to a solution of **1b** (1.00 g, 2.26 mmoles) in dichloromethane (15 mL) and the mixture was stirred at room temperature for 45 minutes. The solvent was removed under reduced pressure and the residue triturated with methanol (5 mL) for 10 minutes. The solid in suspension was collected by filtration, washed successively with methanol and ethyl ether and dried by suction to give 0.861 g (1.71 mmoles) of **3i**. By concentration of the mother liquors another 0.153 g (0,31 mmoles) of **3i** were obtained. Global yield: 91 %, mp 224º (dec); ir (potassium bromide): 3409, 3286, 2958, 2864, 1752, 1696, 1607, 1558, 1523, 1467, 1438, 1372, 1225, 1163, 1115, 1072, 1037 cm^{-1}; uv-vis (methanol), λ max (log ε): 552 (1.85), 335 (4.33), 266 (3.76), 237 (3.99) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.89 (t, 3H, butyl CH_3, J = 7.3 Hz), 1.33 (m, 2H, -$CH_2CH_2CH_2CH_3$), 1.56 (m, 2H, -CH_2CH_2-CH_2CH_3), 1.92, 1.99, 2.05 (3s, each, 3H, acetates), 3.35 (m, 1H, N-CHa), 3.36 (s, 3H, 3-CH_3), 3.55 (m, 1H, N-CHb), 3.58 (m, 1H, 5'-Hα), 3.91 (dd, 1H, 5'-Hβ, J = 5.2, 11.2 Hz), 4.89 (psdt, 1H, 4'-H, J = 5.2, 9.1 Hz), 5.01 (pst, 1H, 2'-H, J = 8.7 Hz), 5.38 (pst, 1H, H'-3, J = 8.8 Hz), 5.71 (pst, 1H, 1'-H, J = 8.6), 8.41 (br s, 1H, 2-NH), 12.10 (d, 1H, 6-NH, J = 8.7 Hz); ms: m/z (%) 466 (26), 406 (11), 236 (18), 220 (31), 208 (17), 182 (11), 157 (18), 139 (21), 97 (21), 43 (100).

Anal. Calcd. for $C_{20}H_{29}N_5O_9 \cdot 1/2H_2O$: C, 48.78; H, 6.14; N, 14.22. Found: C, 48.66; H, 6.22; N, 14.16.

2-Amino-3-methyl-5-nitroso-6-[(tetra-O-acetyl)-β-D-glucopyranosyl]aminopyrimidin-4-(3*H*)-one Hydrate (**3j**).

Through a solution of **1c** [14] (1.00 g, 1.94 mmoles) in dichloromethane (30 mL), a slight current of gaseous ammonia was continuously bubbled at room temperature for 35 minutes. A blue clear solution was obtained which rapidly gels when manually stirred. The gel was almost completely dissolved by addition of acetonitrile and sonication for 10 minutes at room temperature. The solvent was eliminated under reduced pressure and the resulting blue solid residue recrystallized from hot methanol to give, in two crops, 0.654 g (1.26 mmoles, 65 %) of **3j**, mp 227º (dec); ir (potassium bromide): 3047, 3095, 2947, 1757, 1733, 1546, 1369, 1249, 1225 cm^{-1}; uv-vis (methanol), λ max (log ε): 554 (1.84), 330 (4.26), 301 (shoulder), 252 (shoulder), 234 (4.07) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.98, 1.90 (2s, each, 3H, acetates), 2.01 (s, 6H, acetates), 3.32 (s, 3H, 3-CH_3), 4.00 (m, 2H, 5'-H and 6'-Ha), 4.17 (dd, 1H, 6'-Hb, J= 4.6, 12.1 Hz), 5.02 (pst, 1H, 4'-H, J = 9.5 Hz), 5.04 (pst, 1H, 2'-H, J = 9.4 Hz), 5.36 (pst, 1H, 3'H, J = 9.5 Hz), 5.75 (pst, 1H, 1'-H, J = 9.1 Hz), 8.19 (br s, 1H, 2-NHa), 8.64 (br s, 1H, 2-NHb), 12.22 (d, 1H, 6-NH, J = 9.0 Hz); ms: m/z (%) 169 (6), 115 (7), 98 (8), 60 (8) 43 (100).

Anal. Calcd. for $C_{19}H_{25}N_5O_{11} \cdot H_2O$: C, 44.10; H, 5.26; N, 13.53. Found: C, 44.04; H, 5.32; N, 13.43.

Piperidinium 6-Amino-3-methyl-5-nitrosouracil-1-ide (**6**).

Piperidine (2.00 mL, 19.8 mmoles) was added to a suspension of **1a** (1.00 g, 4.95 mmoles) in acetonitrile/water (20 mL, 3:1, v/v) and the mixture stirred at room temperature for 2.5 hours. The solvent was removed under reduced pressure and the residue treated with ethanol (5 mL) and evaporated to dryness twice. The final solid residue was recrystallized from methanol-water (25 mL, 50:1 v/v) and the resulting red crystalline solid was collected by filtration, washed with methanol and dried by suction to give 0.635 g (2.48 mmoles, 50 %) of **6**, mp 217º; ir (potassium bromide): 3319, 3253, 2949, 2840, 2809, 2739, 1688, 1631, 1610, 1476, 1438, 1384, 1341, 1281, 1267, 1235, 1084 cm^{-1}; uv-vis (methanol), λ max (log ε): 509 (1.88), 318 (4.24), 245 (shoulder), 225 (3.92) nm; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.56 (m, 2H, piperidinium 4-CH_2), 1.65 (m, 4H, piperidinium 3-and 5- CH_2),

3.03 (pst, 4H, piperidinium 2- and 5-CH_2, J = 5.55 Hz), 3.16 (s, 3H, 3-CH_3), 7.50 (br s, 3H, piperidinium NH_2^+ and 6-NHa), 10.66 (br s, 1H, 6-NHb); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 21.63 (t), 22.17 (t), 26.73 (q), 43.70 (t), 140.85 (s), 153.39 (s), 156.83 (s), 164.39 (s); ms: m/z (%) 170 (29), 153 (43), 112 (23), 110 (23), 96 (69), 85 (67), 84 (100), 70 (37), 56 (67).

Anal. Calcd. for $C_{10}H_{18}N_5O_3$: C, 47.05; H, 6.71; N, 27.43. Found: C, 47.13; H, 6.87; N, 27.39.

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