Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 696–707
Tetrahedron
www.elsevier.com/locate/tet

Oxidative alkylamination of azinones as a direct route to aminoazinones: study of some condensed diazinones

Anna V. Gulevskaya*, Oleg N. Burov, Alexander F. Pozharskii, Mikhail E. Kletskii, Inna N. Korbukova

Department of Organic Chemistry, Southern Federal University, Zorge 7, Rostov-on-Don 344090, Russian Federation

Received 2 August 2007; received in revised form 22 October 2007; accepted 8 November 2007
Available online 12 November 2007

Abstract

Oxidative alkylamination of azinones is a promising method for the preparation of a great variety of alkylaminoazinones. Treatment of 6,8-dimethyl-2-*R*-pyrimido[4,5-*c*]pyridazin-3,5,7(2*H*,6*H*,8*H*)-triones **7**, 1,3-dimethyl-5-*R*-pteridin-2,4,6(1*H*,3*H*,6*H*)-triones **8** and 1,3,6-trimethylpyrimido[4,5-*d*]pyrimidin-2,4,7(1*H*,3*H*,6*H*)-trione **9** with alkylamine/$AgPy_2MnO_4$ or alkylamine/$KMnO_4$ has been shown to produce their 4-, 7- and 5-alkylamino derivatives, respectively, in good yields. While 1-methylquinoxalin-2(1*H*)-one **10** is smoothly alkylaminated under the above conditions giving 3-alkylamino derivatives, quinoxaline itself does not take part in this reaction. Factors influencing oxidative alkylamination of azinones and a regioselectivity of the process are discussed.

Keywords: Nucleophilic aromatic substitution of hydrogen; Oxidative alkylamination; Azinones; Alkylaminoazinones

1. Introduction

Aminoazinones are compounds of a great biological importance. Two of them, cytosine **1** and guanine **2**, are the commonest known nitrogen bases of the nucleic acids (Fig. 1). Many others display a wide range of pharmacological activities.[1a–c,2,3a,4a,b] Some aminoazinones are already introduced in medicine practice. The most famous among them are the antivirus drug acyclovir **3**, immunomodulatory agent bropirimine **4**, used in the treatment of AIDS, lamivudine **5** and zalcitabine **6**.[5] The key properties of aminoazinones, such as their acid–base character, ability to self-organization via hydrogen binding and metal ions complexation, originate from the presence of the amide functionality and an external amino group in their structure.

All known synthetic methods for amino- and alkylaminoazinones may be divided into two major groups: (i) formation of the hetero-ring carrying an amino or alkylamino substituent

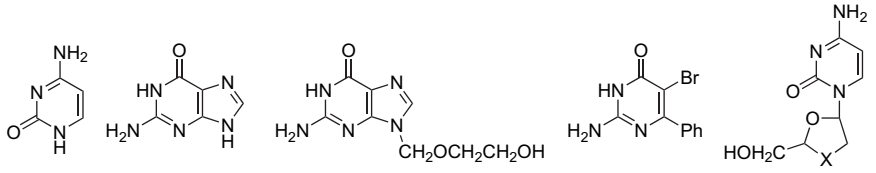
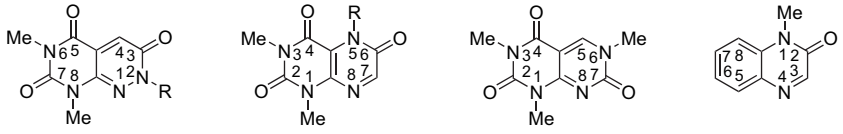


Figure 1. Cytosine (**1**), guanine (**2**), acyclovir (**3**), bropirimine (**4**), lamivudine (**5**) and zalcitabine (**6**).

* Corresponding author. Tel./fax: +7 863 297 5146.
E-mail address: agulevskaya@rsu.ru (A.V. Gulevskaya).

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.11.029



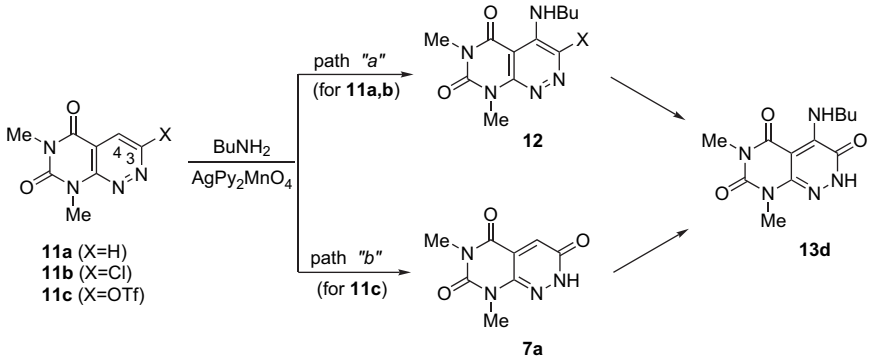
7a (R = H)
7b (R = Me)

8a (R = H)
8b (R = Me)

9

10

Figure 2.



11a (X=H)
11b (X=Cl)
11c (X=OTf)

12

13d

7a

Scheme 1.

by a heterocyclization reaction, and (ii) functionalization of already existing azinones via nucleophilic aromatic substitution of a halo, alkylthio, cyano or some other leaving groups.[1–5] The majority of these methods are rather time-consuming and not very selective. Therefore, development of efficient synthetic protocols for the preparation of aminoazinones remains a challenging problem.

Herein, for the first time we report the preparation of alkylaminoazinones by the direct oxidative alkylamination of azinones using an alkylamine/oxidant system. Uracil-fused diazinones **7**–**9** and quinoxalinone **10** were employed as the substrates (Fig. 2). A theoretical approach to some peculiarities of the reaction is also discussed.

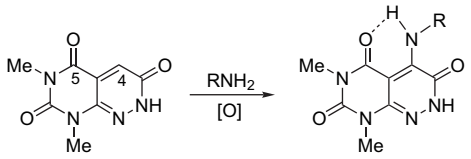
2. Results and discussion

2.1. Oxidative alkylamination

The idea behind this work has primarily arisen from an accidental observation. Following successful oxidative amination and alkylamination of pyridazinouracils **11a** and **11b**[6] we expected that treatment of triflate **11c** with butylamine in the presence of $AgPy_2MnO_4$ should give aminotriflate **12**. Instead, 4-butylaminopyridazinone **13d** was isolated in 72% yield as a single product (Scheme 1). A priori, the formation of **13d** could originate either from hydrolysis of the triflate group in the target product **12** (pathway 'a') or from initial hydrolysis of the starting compound **11c** with subsequent oxidative alkylamination of thus formed pyridazinone **7a** (pathway 'b'). At first glance, the latter possibility looked less probable since: (1) addition of a nucleophile to the C(3)=O group of **7a** could not be excluded and (2) pyridazinone **7a**, being NH-acid, might be converted by alkylamine into an anion inert to further nucleophilic attack. Nevertheless, we proved that the reaction can proceed via pathway 'b'.

It was found that 6,8-dimethylpyrimido[4,5-*c*]pyridazin-3,5,7(2*H*,6*H*,8*H*)-trione **7a** being treated with an excess of primary alkylamines in the presence of an oxidant ($KMnO_4$ or $AgPy_2MnO_4$) affords 4-alkylamino derivatives **13a**–**f** in moderate to good yields (Table 1). Though potassium permanganate is the most commonly used oxidant for the oxidative amination,[7] its drawback is a lowered solubility in alkylamines. To overcome this difficulty, we recently offered for this purpose, a more soluble complex oxidant $AgPy_2MnO_4$.[8] As seen from Table 1, the latter provides higher yields of aminoazinones and shorter reaction time comparing with $KMnO_4$. Reaction of **7a** with benzylamine is especially noteworthy. When carried

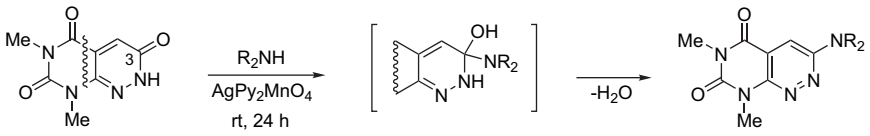
Table 1
Oxidative alkylamination of pyridazinone **7a**



7a **13a-g**

Alkylamine	Product	$AgPy_2MnO_4$ (1.2 equiv, rt, 2–2.5 h)	$KMnO_4$ (2 equiv, rt, overnight)
		Yield %	Yield %
$EtNH_2$	**13a**	68[a]	54[a]
$PrNH_2$	**13b**	64	52
i-$PrNH_2$	**13c**	57	47
$BuNH_2$	**13d**	68	64
t-$BuNH_2$	**13e**	67	56
cyclo-$C_6H_{11}NH_2$	**13f**	42	23
$PhCH_2NH_2$	**13g**	46	Trace

[a] Reaction was carried out at −3 to 0 °C.



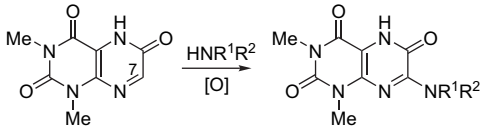
Scheme 2.

out with $KMnO_4$, the oxidation of alkylamine takes place, whereas the use of $AgPy_2MnO_4$ gives 4-benzylaminopyridazinone **13g** in 46% yield.

Reaction of pyridazinone **7a** with secondary amines (piperidine and morpholine) and $AgPy_2MnO_4$ proceeds exclusively at position 3 (Scheme 2). The corresponding 3-alkylaminopyridazines **14a** and **14b**[6a] were isolated in 13–15% yields as the sole reaction product. Apparently, in this case the oxidant does not participate in the process, which develops as a nucleophilic addition to the carbonyl group, with loss of water. We observed a similar difference in the regioselectivity depending on the alkylamine nature in the oxidative alkylamination of **11a** and **11b**.[6a,c]

Then we found that isomeric 1,3-dimethylpteridin-2,4,6-(1*H*,3*H*,5*H*)-trione **8a** also enters oxidative alkylamination with results summarized in Table 2. There are some peculiarities in the behaviour of both diazinones. At first, reactions of pyrazinone **8a** with primary and secondary alkylamines, unlike **7a**, proceed in the same direction to produce 7-alkylamino derivatives **15a–i**. The second difference deals with work-up of the reaction mixture. Upon amination of **8a** with alkylamine/$KMnO_4$ the reaction product is usually separated as the potassium salt and, therefore, further acidification is needed. We were unable to isolate any product of alkylamination of **8a** with propylamine or *tert*-butylamine using $AgPy_2MnO_4$, though full conversion of the starting material took place.

Table 2
Oxidative alkylamination of pyrazinone **8a**



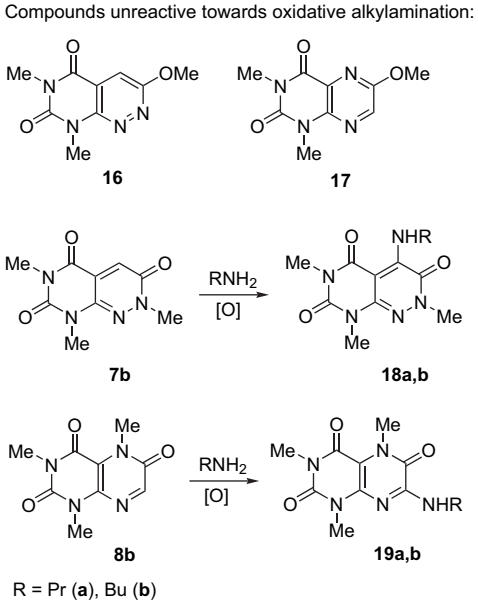
Alkylamine	Product	$AgPy_2MnO_4$ (1.2 equiv, rt, 3.5–4 h)	$KMnO_4$ (2 equiv, rt, overnight)
		Yield %	Yield %
$EtNH_2$	**15a**	59[a]	42[a]
$PrNH_2$	**15b**	[b]	54
i-$PrNH_2$	**15c**	71	50
$BuNH_2$	**15d**	68	52
t-$BuNH_2$	**15e**	[b]	45
cyclo-$C_6H_{11}NH_2$	**15f**	43	23
Piperidine	**15g**	51	40
Morpholine	**15h**	57	41
Et_2NH	**15i**	28	Trace

[a] Reaction was carried out at −3 to 0 °C.
[b] No product was isolated.

A possible reason of this seems to be a formation of insoluble silver salts of the desired aminoazinones **15b** and **15e**.

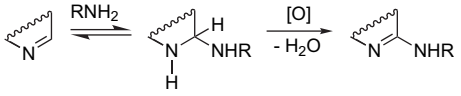
2.2. Factors influencing oxidative alkylamination of azinones

An intriguing question is whether the azinones **7a** and **8a** react with amines as one of two possible tautomeric forms (lactam or lactim) or as the anion. To shed light on this, we have prepared and examined fixed derivatives of each tautomer **7b**, **8b**, **16** and **17** (Scheme 3). It was proved that methoxyazines **16** and **17** are inert towards alkylamines, whereas isomeric *N*-methylazinones **7b** and **8b** are smoothly converted into alkylamino derivatives **18** (31–36%) and **19** (55–56%) after 2–2.5 h stirring with the alkylamine/$AgPy_2MnO_4$ system at room temperature. These experiments clearly demonstrate that azinones **7a** and **8a** react with alkylamines in the neutral lactam form.



Scheme 3.

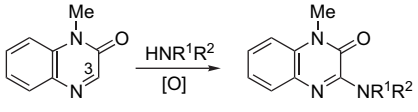
The next point for consideration is concerned with the role of the amide carbonyl group in this process. Mechanistically, an oxidative alkylamination consists of σ^H-adduct formation followed by oxidative aromatization (Scheme 4).[7] It is well known that incorporation of a carbonyl group into an azine ring considerably decreases the aromaticity of the latter.[9] As a consequence, addition of a nucleophile and, thus, σ^H-adduct formation is facilitated.



Scheme 4.

This can be illustrated by the comparative behaviour of quinoxaline and 1-methylquinoxalin-2(1*H*)-one **10**. We have found that quinoxaline does not enter alkylamination whereas quinoxalinone **10** reacts with primary and secondary alkylamines in the presence of an oxidant to yield 3-alkylamino derivatives **20a–h** (Table 3).

Table 3
Oxidative alkylamination of quinoxalinone **10**

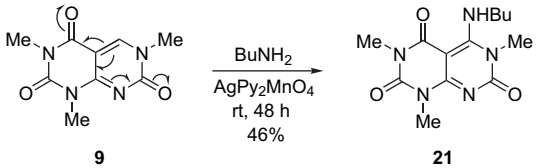


10 **20a-i**

Alkylamine	Product	$AgPy_2MnO_4$ (1.2 equiv, rt, 6 h)	$KMnO_4$ (2 equiv, rt, overnight)
		Yield %	Yield %
$MeNH_2$	**20a**	—	25[a]
$EtNH_2$	**20b**	68[b]	43[b]
$PrNH_2$	**20c**	61	44
i-$PrNH_2$	**20d**	64	42
$BuNH_2$	**20e**	66	48
cyclo-$C_6H_{11}NH_2$	**20f**	54[c]	15
Piperidine	**20g**	48[c]	Trace
Morpholine	**20h**	45[c]	Trace
Et_2NH	**20i**	0	0

[a] Reaction was carried out at −40 to −30 °C.
[b] Reaction was carried out at −3 to 0 °C.
[c] Reaction was carried out using $AgPy_2MnO_4$/alkylamine/THF.

Noteworthy, alkylamination of **10** proceeds slower than that of substrates **7** and **8**. This reduced reactivity can be attributed to the lower π-deficiency of the reaction site of **10**. Unlike **10**, the reacting carbon atom of **7** and **8** is conjugated with the uracil carbonyl group C(5)=O and C(4)=O, respectively. Interestingly, isomeric pyrimidinone **9**, where the reaction centre is activated by the C(4)=O and C(7)=O groups at once, is also able to interact with butylamine/$AgPy_2MnO_4$ producing 5-butylamino derivative **21** (Scheme 5). This is the reason why alkylamination proceeds even at sterically hindered position 5.



9 **21**

Scheme 5.

Apparently, the presence of the aza group adjacent to (or conjugated with) the reaction site is another essential factor contributing to the reactivity of azinones. Indeed, unlike 1-methylquinoxalin-2(1*H*)-one **10**, 1-methylquinoline-2(1*H*)-one as we have shown does not enter oxidative alkylamination.

The experimental data in Tables 1–3 show that for all studied azinones (with exception of **9**) alkylamination occurs at the position α to the amide carbonyl. This is a rather rare type of reactivity for azinones.[10] Nucleophilic attack on the carbonyl carbon atom or carbon atom β to the carbonyl group is more characteristic for these substrates.[9] For example, 2- and 4-pyridones both undergo the Chichibabin reaction to give the 6- and 2-amino derivatives, respectively.[11] In order to rationalize our observations DFT calculations on the B3LYP/6-31G** level of theory using the Gaussian 03 program complex[12] have been performed. At first we tried to explain the regioselectivity of the oxidative alkylamination of azinones **7–10** by calculating and analyzing the global and local electrophilicity indices ω and ω_k[13] for preliminary optimized structures. The obtained results are given in Figure 3. It can be clearly seen that for all tested azinones **7**, **8** and **10** the largest ω_k value corresponds to the carbon atom α to the carbonyl group. Note, the local electrophilicity at this atom of **7** and **8** is at least twice the value of ω_k for other electrophilic sites of the molecule. This picture is in complete agreement with the total regioselectivity of alkylamination of these substrates observed experimentally. In the case of pyrimidinone **9** the maximum of ω_k corresponds to the C(5) atom, which is indeed the reaction site.

Parameter of the global electrophilicity ω reflects a relative activity of the studied azinones towards alkylamination (substrate selectivity). The global electrophilicity value of pyridazinone **7** is the largest in the series. The presence of a uracil ring in the substrates **7**, **8** and **9** is responsible, obviously, for their higher electrophilicity as compared to quinoxalinone **10**. Reducing the ω value for **10** agrees with its less reactivity. Though the global electrophilicity of unreactive quinoxaline **22** is somewhat larger than that for quinoxalinone **10**, the value of ω_k for the latter is twice the largest local electrophilicity of **22**.

For a deeper insight into the regiochemistry of the alkylamination reaction we also carried out the theoretical analysis for the σ-adducts of azinones **7–10** with methylamine differing by the addition place. The relative energies E_{rel} (in kcal/mol), obtained by comparing the calculated total energies of the starting materials and σ-adducts, are summarized in Figure 4. All

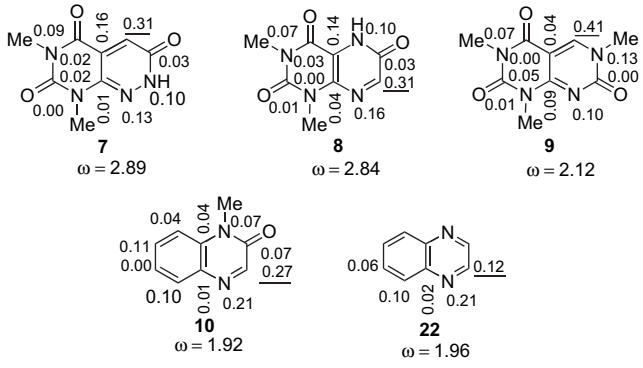


Figure 3. Calculated global electrophilicity values (ω, in eV) and local electrophilicity indices (ω_k, given at each ring atom, in eV).

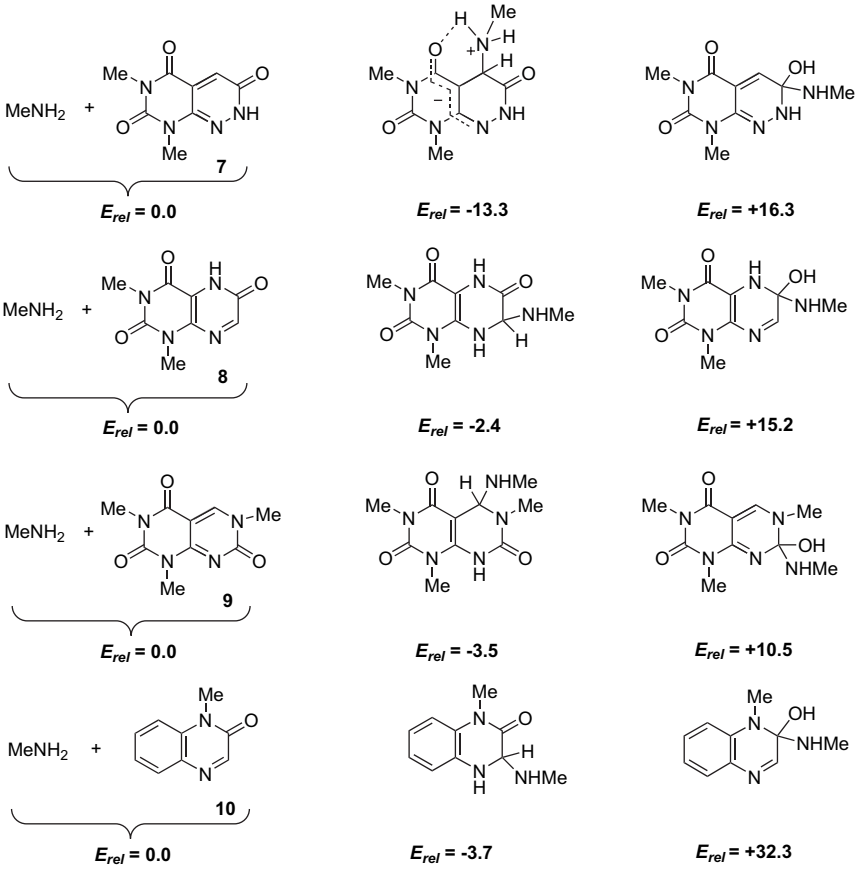


Figure 4. Calculated relative energies (in kcal/mol) for the methylamino-σ-adducts of azinones **7**–**10**.

σ-adducts under consideration correspond to minima on the potential energy surface. As one can see in all cases formation of the methylamino-σ^H-adduct via nucleophilic attack on the carbon atom α to the carbonyl group (or conjugated with the latter as in the case of **9**) is exothermic. The methylamino-σ^H-adduct of pyridazinone **8** is 10–11 kcal/mol more stable than those for other substrates. This exceptionally high value is likely caused by the stabilization of the above adduct by intramolecular hydrogen bonding between the methylamino and C(5)=O groups. In none of the other cases such stabilization has been obtained. In contrast, addition of methylamine to the carbonyl carbon atom of azinones **7**–**10** is strongly unprofitable, apparently, due to considerable energy loss at disruption of the amide resonance in the corresponding adducts.

2.3. Structure of alkylaminoazinones

The structural assignment for alkylaminoazinones, apart from elemental analysis, was based on the following evidences. The mass spectra of all samples show the corresponding molecular ion of a high intensity. Like the parent azinones **7a** and **8a**, alkylaminoazinones **13** and **15** exist in the lactam form. Thus, the UV spectra of **13** and **15** are similar to that of *N*-methylated compounds **18** and **19** (Table 4).

The ^{1}H NMR and IR spectra confirm this conclusion. In the IR spectra of the uracil-fused aminoazinones **13** and **15** there are three intensive bands in the 1630–1720 cm^{-1} region assigned to the carbonyl stretching vibration and two bands in the N–H stretching region (3130–3330 cm^{-1}). The amide proton N(2)–H of alkylaminopyridazinones **13** reveals itself as a broad singlet at 9.6–10.3 ppm. For these compounds as well as for **18**, the chemical shift of the NH-proton of the alkylamino group is from 10.2 to 10.6 ppm. Obviously, this high δ value arises from the intramolecular hydrogen bonding between this proton and the C(5)=O carbonyl group. Noteworthy, the α-CH_2 (or α-CH) protons of **13** and **18** experience a strong deshielding influence of the adjacent C(3)=O group that brings their chemical shifts to δ 4.0–5.4 ppm. Alkylaminopyrazinones **15** and **19**, evidently, are not chelated because

Table 4
Selected UV spectral data of alkylaminoazinones ($CHCl_3$)

Compound	λ_{max}, nm (log ε)	Compound	λ_{max}, nm (log ε)
13d	303 (3.66)	**18b**	305 (3.72)
	315 (3.62)		315 (3.69)
	360 (3.91)		362 (3.88)
	376 (3.93)		376 (3.93)
	397 sh (3.71)		396 sh (3.74)
15d	261 (4.23)	**19b**	258 (4.08)
	296 (3.87)		291 (3.65)
	358 (4.23)		351 (4.13)
	372 (4.27)		367 (4.17)
	390 (4.08)		390 (3.90)

observed δ values for the NH-protons of their alkylamino groups are significantly lower (7.1–7.8 ppm) than those for **13** and **18**. Interestingly, the α-CH_2 and α'-CH_2 protons of 7-piperidino, 7-morpholino and 7-diethylamino substituents of **15g**, **15h** and **15i** are non-equivalent and reveal themselves as two different signals at 3.7–4.0 and 4.2–4.7 ppm. This seems to be a reflection of the restricted rotation around C(7)–N(*exo*) bond caused by the strong conjugation of the 7-alkylamino group and the C(4)=O fragment. Compound **21** displays the lowest δ value of the NH-proton (5.4 ppm). In this case formation of the intramolecular hydrogen bond similar to that of **13** and **18** is sterically hindered.

As expected, alkylaminoquinoxalinones **20** show one characteristic band of the C=O group (1650–1670 cm^{-1}) and one band in the 3310–3350 cm^{-1} region arisen from the absorption of N–H bond. A 0.6–0.8 ppm upfield shift of the NH-protons of the alkylamino groups in these compounds comparing with this of **20** reflects a slight fusion ring effect.

3. Conclusions

In summary, a simple and convenient synthetic route to alkylaminodiazinones via oxidative alkylamination of diazinones using alkylamine/$KMnO_4$ or (better) alkylamine/$AgPy_2MnO_4$ system has been developed. The reaction proceeds as a nucleophilic aromatic substitution of hydrogen at the α position to the amide carbonyl group of azinone. This is an example of a very rare reaction type in the azinone series. Both NH-unsubstituted and *N*-methylated diazinones undergo oxidative alkylamination whereas methoxyazines are unreactive. This evidences that NH-azinones enter the reaction in tautomeric lactam form. A role of the amide carbonyl group consists in the lowering of the ring aromaticity that promotes formation of the σ^H-adduct. Another essential structural factor is the presence of the aza group in the substrate molecule that additionally facilitates nucleophilic addition. Further studies on the scope and mechanistic aspects of the reaction are underway.

4. Experimental

4.1. General

Proton (^1H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-250 (250 MHz) and Unity-300 (300 MHz) spectrometers with $CDCl_3$ as a solvent. Infrared (IR) spectra were recorded on a Specord IR-71 spectrometer using Nujol. Ultraviolet absorption (UV) spectra were registered on a Specord M-40 and Specord UV–vis spectrophotometers with $CHCl_3$ as a solvent. Mass spectra were measured on a Finnigan MAT INCOS 50 spectrometer. Melting points were determined in glass capillaries and are uncorrected. Al_2O_3 (III–IV activity of Brockman) was used for chromatographic separations.

DFT (density functional theory) calculations have been carried out using the B3LYP[12a,b] exchange-correlation functionals, together with the standard 6-31G** basic set.[12c] The optimization of the geometries was done by the Berny method of analytical calculation of gradients. The nature of stationary points was determined on the basis of the vibration analysis. Minimum energy paths of reactions (MEPR) were calculated by means of gradient descent from the transition state structures in forward and backward direction of a transition vector. All calculations were carried out with the use of the Gaussian 03 program complex.[12d]

4.2. Synthesis of the starting compounds

Compounds **7a**,[14] **8a**,[15] **8b**,[16] **9**,[17] **10**[18] and **11c**[14] were synthesized in accordance with known procedures.

4.2.1. 2,6,8-Trimethylpyrimido[4,5-c]pyridazin-3,5,7-(2H,6H,8H)-trione (*7b*)

To a stirred solution of *t*-BuOK (67 mg, 0.6 mmol) in dry DMSO (6 mL) at room temperature, **7a** (104 mg, 0.5 mmol) and MeI (95 mg, 0.04 mL, 0.67 mmol) were added. After 20 min, the solvent was removed under reduced pressure. The residue was ground with Al_2O_3 (3–4 g), loaded onto a column with Al_2O_3 (3×20 cm) and purified by flash column chromatography with $CHCl_3$ as the eluent. The yellowish fraction with R_f 0.8 gave **7b**. Recrystallization from *i*-PrOH yielded **7b** (71 mg, 64%) as yellowish crystals, mp 194–197 °C (lit.[19] 190–193 °C); [found: C, 48.7; H, 4.4; N, 25.3. $C_9H_{10}N_4O_3$ requires C, 48.65; H, 4.54; N, 25.21%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 378 (3.43), 394 (3.46), 412 sh nm (3.31); ν_{max} (Nujol) 3047 (C–H arom.), 1720, 1680 and 1667 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.72 (1H, s, 4-H), 3.83 (3H, s, 2-Me), 3.53 (3H, s, 8-Me), 3.44 (3H, s, 6-Me).

4.3. Oxidative alkylamination of triflate (*11c*)

A solution of **11c** (170 mg, 0.5 mmol) in butylamine (10 mL) was stirred at 10 °C for 10–15 min. To the resulting yellowish solution $AgPy_2MnO_4$ (231 mg, 0.6 mmol) was added in small portions over a 30 min period. After 1.5 h, the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was ground with silica (3–4 g), loaded onto a column with silica (3×20 cm) and purified by flash column chromatography with $CHCl_3$–MeOH (5:1) as the eluent. The fraction with R_f 0.35 gave **13d**. The product was crystallized from *i*-PrOH to give 100 mg (72%) of **13d**. Yellowish crystals, mp 180–181 °C; [found: C, 51.6; H, 6.0; N, 25.0. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]. For spectral data, see Section 4.4.4.

4.4. General procedure for the oxidative alkylamination of pyridazinone (*7a*)

Method A. A solution of **7a** (208 mg, 1 mmol) in the appropriate alkylamine (40 mL) was stirred at room temperature for 10–15 min. To the resulting yellowish solution $AgPy_2MnO_4$ (462 mg, 1.2 mmol) was added in small portions over a 30 min period. After 2–2.5 h, the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was ground with Al_2O_3 (3–4 g), loaded onto a column

with Al_2O_3 (3×20 cm) and purified by flash column chromatography with $CHCl_3$–MeOH (10:1) as the eluent. The fraction with R_f ~0.1 gave **13**. The product was crystallized from *i*-PrOH or CCl_4 to give **13a–g** with the yield indicated in Table 1. Reaction with $EtNH_2$ was carried out in a similar way at −3 to 0 °C for 3.5–4 h. Reaction with piperidine and morpholine providing **14a** and **14b** was carried out in a similar way at room temperature for 24 h.

Method B. A solution of **7a** (208 mg, 1 mmol) in the appropriate alkylamine (40 mL) was stirred at room temperature for 10–15 min. To the resulting yellowish solution $KMnO_4$ (316 mg, 2 mmol) was added. After stirring overnight the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was extracted with boiling *i*-PrOH (100 mL). The solvent was subsequently removed under reduced pressure. The crude product was crystallized from *i*-PrOH or CCl_4 to give **13a–g** with the yield indicated in Table 1. Reaction with $EtNH_2$ was carried out in a similar way at at −3 to 0 °C.

*4.4.1. 6,8-Dimethyl-4-ethylaminopyrimido[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**13a**)*

Yellowish crystals, mp 269–271 °C (*i*-PrOH); [found: C, 48.0; H, 5.2; N, 27.8. $C_{10}H_{13}N_5O_3$ requires C, 47.81; H, 5.22; N, 27.87%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 302 (3.63), 315 (3.60), 360 (3.92), 376 (3.94), 398 sh nm (3.67); ν_{max} (Nujol) 3247 and 3127 (N–H), 1700, 1673 and 1647 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.32 (1H, m, N*H*CH_2Me), 9.63 (1H, br s, 2-NH), 4.22 (2H, m, *C*H_2Me), 3.41 (3H, s, 8-Me), 3.37 (3H, s, 6-Me), 1.34 (3H, t, *J* 7.3 Hz, CH_2*Me*); *m/z* (EI) 251 (100 M^+), 236 (90), 234 (25), 223 (24), 209 (37), 195 (13), 179 (16), 166 (13), 151 (15), 93 (12), 80 (23), 66 (13), 58 (10), 44 (14%).

*4.4.2. 6,8-Dimethyl-4-propylaminopyrimido[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**13b**)*

Yellowish crystals, mp 205–207 °C (*i*-PrOH); [found: C, 50.0; H, 5.7; N, 26.5. $C_{11}H_{15}N_5O_3$ requires C, 49.81; H, 5.70; N, 26.40%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 305 (3.65), 316 (3.62), 361 (3.85), 376 (3.87), 398 sh nm (3.67); ν_{max} (Nujol) 3240 and 3140 (N–H), 1700, 1660 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.38 (1H, m, *NH*$(CH_2)_2$Me), 9.93 (1H, br s, 2-NH), 4.16 (2H, m, *C*$H_2$$CH_2$Me), 3.41 (3H, s, 8-Me), 3.36 (3H, s, 6-Me), 1.72 (2H, m, CH_2*C*H_2Me), 1.02 (3H, t, *J* 7.3 Hz, $(CH_2)_2$*Me*); *m/z* (EI) 265 (41 M^+), 236 (100), 223 (40%).

*4.4.3. 4-Isopropylamino-6,8-dimethylpyrimido[4,5-c]-pyridazin-3,5,7(2H,6H,8H)-trione (**13c**)*

Yellowish crystals, mp 186–187 °C (*i*-PrOH); [found: C, 49.8; H, 5.6; N, 26.5. $C_{11}H_{15}N_5O_3$ requires C, 49.81; H, 5.70; N, 26.40%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 303 (3.64), 316 (3.61), 361 (3.88), 376 (3.91), 397 sh nm (3.69); ν_{max} (Nujol) 3233 and 3140 (N–H), 1700, 1660 and 1627 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.34 (1H, m, *NH*$CHMe_2$), 10.18 (1H, br s, 2-NH), 5.45 (1H, m, *CH*Me_2), 3.41 (3H, s, 8-Me), 3.36 (3H, s, 6-Me), 1.33 (6H, d, *J* 6.4 Hz, $CHMe_2$); *m/z* (EI) 265 (57 M^+), 250 (100), 223 (32), 194 (10), 80 (19), 66 (11), 58 (20), 41 (22%).

*4.4.4. 4-Butylamino-6,8-dimethylpyrimido[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**13d**)*

Yellowish crystals, mp 180–181 °C (*i*-PrOH); [found: C, 51.7; H, 6.0; N, 25.1. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 303 (3.66), 315 (3.62), 360 (3.91), 376 (3.93), 397 sh nm (3.71); ν_{max} (Nujol) 3227 and 3133 (N–H), 1693, 1660 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.37 (1H, m, *NH*$(CH_2)_3$Me), 9.90 (1H, br s, 2-NH), 4.20 (2H, m, *C*$H_2$$(CH_2)_2$Me), 3.41 (3H, s, 8-Me), 3.36 (3H, s, 6-Me), 1.67 (2H, m, CH_2*C*$H_2$$CH_2$Me), 1.46 (2H, m, $(CH_2)_2$*C*H_2Me), 0.97 (3H, t, *J* 7.3 Hz, $(CH_2)_3$*Me*); *m/z* (EI) 279 (59 M^+), 262 (13), 236 (100), 223 (40), 82 (12), 80 (13%).

*4.4.5. 4-tert-Butylamino-6,8-dimethylpyrimido-[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**13e**)*

Yellowish crystals, >265 °C decomp. (*i*-PrOH); [found: C, 51.7; H, 6.1; N, 25.0. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 302 (3.63), 319 (3.60), 360 (3.83), 377 (3.86), 397 sh nm (3.68); ν_{max} (Nujol) 3250 and 3160 (N–H), 1700, 1667 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 11.03 (1H, br s, *NH*Bu-*t*), 9.64 (1H, br s, 2-NH), 3.39 (3H, s, 8-Me), 3.35 (3H, s, 6-Me), 1.61 (9H, s, *t*-Bu); *m/z* (EI) 279 (10 M^+), 223 (100), 194 (13), 110 (12), 82 (10), 80 (20), 67 (16), 56 (15), 52 (11), 41 (60%).

*4.4.6. 4-Cyclohexylamino-6,8-dimethylpyrimido-[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**13f**)*

Off-white crystals, mp 286–287 °C decomp. (CCl_4); [found: C, 55.1; H, 6.2; N, 23.0. $C_{14}H_{19}N_5O_3$ requires C, 55.07; H, 6.27; N, 22.94%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 305 (3.66), 319 (3.63), 362 (3.93), 377 (3.96), 398 sh nm (3.75); ν_{max} (Nujol) 3293 and 3127 (N–H), 1700, 1673 and 1647 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.45 (1H, m, *NH*C_6H_{11}-*cyclo*), 9.80 (1H, br s, 2-NH), 5.12 (1H, m, 1′-H cyclohexyl), 3.41 (3H, s, 8-Me), 3.37 (3H, s, 6-Me), 2.10 (2H, m, cyclohexyl), 1.78 (2H, m, cyclohexyl), 1.35 (6H, m, cyclohexyl); *m/z* (EI) 305 (30 M^+), 262 (27), 223 (100), 208 (10), 100 (10), 81 (33), 67 (10), 55 (25), 41 (33%).

*4.4.7. 4-Benzylamino-6,8-dimethylpyrimido[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**13g**)*

Yellowish crystals, >230 °C decomp. (*i*-PrOH); [found: C, 57.6; H, 4.9; N, 22.3. $C_{15}H_{15}N_5O_3$ requires C, 57.50; H, 4.83; N, 22.35%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 303 (3.74), 315 (3.70), 362 (3.94), 377 (3.96), 398 sh nm (3.72); ν_{max} (Nujol) 3300 and 3133 (N–H), 1700, 1667 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.62 (1H, m, *NH*CH_2Ph), 10.31 (1H, br s, 2-NH), 7.35 (5H, m, Ph), 5.44 (2H, d, *J* 6.2 Hz, *C*H_2Ph), 3.42 (3H, s, 8-Me), 3.34 (3H, s, 6-Me); *m/z* (EI) 313 (100 M^+), 296 (13), 236 (14), 104 (10), 91 (71), 79 (15), 65 (14%).

*4.4.8. 3-Piperidino-6,8-dimethylpyrimido[4,5-c]pyridazin-5,7(6H,8H)-dione (**14a**)*

Compound **14a** was obtained as yellow crystals with mp 156–159 °C (*i*-PrOH), identical in properties to the compound earlier synthesized by us.[6]

*4.4.9. 3-Morpholino-6,8-dimethylpyrimido[4,5-c]pyridazin-5,7(6H,8H)-dione (**14b**)*

Compound **14b** was obtained as yellow crystals with mp 211–214 °C (*i*-PrOH), identical in properties to the compound earlier synthesized by us.[6]

*4.5. General procedure for the oxidative alkylamination of pyridazinone (**7b**)*

A solution of **7b** (222 mg, 1 mmol) in the appropriate alkylamine (40 mL) was stirred at room temperature for 10–15 min. To the resulting yellowish solution $AgPy_2MnO_4$ (462 mg, 1.2 mmol) was added in small portions over a 30 min period. After 2 h, the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was ground with Al_2O_3 (3–4 g), loaded onto a column with Al_2O_3 (3×20 cm) and purified by flash column chromatography with $CHCl_3$ as the eluent. The fraction with R_f 0.8 gave **18**. The product was crystallized from *i*-PrOH.

*4.5.1. 2,6,8-Trimethyl-4-propylaminopyrimido[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**18a**)*

Compound **18a** was obtained in 31% yield as yellowish crystals, mp 115–117 °C (*i*-PrOH); [found: C, 51.6; H, 6.0; N, 25.00. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 306 (3.75), 317 (3.72), 362 (3.83), 375 (3.91), 396 sh nm (3.74); ν_{max} (Nujol) 3140 (N–H), 1700, 1687 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.24 (1H, m, *NH*$(CH_2)_2$Me), 4.14 (2H, m, *CH*$_2$CH$_2$Me), 3.64 (3H, s, 2-Me), 3.40 (3H, s, 8-Me), 3.34 (3H, s, 6-Me), 1.69 (2H, m, CH$_2$*CH*$_2$Me), 0.99 (3H, t, *J* 7.3 Hz, $(CH_2)_2$*Me*); *m/z* (EI) 279 (45 M^+), 250 (100), 237 (64), 80 (23), 67 (17), 58 (22), 56 (21), 53 (13), 42 (47), 39 (20%).

*4.5.2. 4-Butylamino-2,6,8-trimethylpyrimido[4,5-c]pyridazin-3,5,7(2H,6H,8H)-trione (**18b**)*

Compound **18b** was obtained in 36% yield as yellowish crystals, mp 50–52 °C (*i*-PrOH); [found: C, 53.3; H, 6.4; N, 24.0. $C_{13}H_{19}N_5O_3$ requires C, 53.23; H, 6.53; N, 23.88%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 305 (3.72), 315 (3.69), 362 (3.88), 376 (3.93), 396 sh nm (3.74); ν_{max} (Nujol) 3113 (N–H), 1687, 1647 and 1633 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.21 (1H, m, *NH*$(CH_2)_3$Me), 4.17 (2H, m, *CH*$_2$$(CH_2)_2$Me), 3.63 (3H, s, 2-Me), 3.38 (3H, s, 8-Me), 3.33 (3H, s, 6-Me), 1.65 (2H, m, CH$_2$*CH*$_2$CH$_2$Me), 1.43 (2H, m, $(CH_2)_2$*CH*$_2$Me), 0.95 (3H, t, *J* 7.3 Hz, $(CH_2)_3$*Me*); *m/z* (EI) 293 (45 M^+), 264 (11), 250 (11), 237 (76), 80 (12), 42 (10%).

*4.6. General procedure for the oxidative alkylamination of 1,3-dimethylpteridin-2,4,6(1H,3H,5H)-trione (**8a**)*

Method A. A solution of **8a** (208 mg, 1 mmol) in the appropriate alkylamine (40 mL) was stirred at room temperature for 15–20 min. To the resulting yellowish solution $AgPy_2MnO_4$ (462 mg, 1.2 mmol) was added in small portions over a 30 min period. After 3.5–4 h, the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was extracted with boiling *i*-PrOH (100 mL). The solvent was subsequently removed under reduced pressure. The crude product was crystallized from *i*-PrOH or CCl_4 to give **15a–e** with the yield indicated in Table 2. Compounds **15f–h** were purified by flash column chromatography on a column with Al_2O_3 and $CHCl_3$–MeOH (5:1) as the eluent followed by recrystallization. Reaction with $EtNH_2$ was carried out in a similar way at −3 to 0 °C.

Method B. A solution of **8a** (208 mg, 1 mmol) in the appropriate alkylamine (40 mL) was stirred at room temperature for 15–20 min. To the resulting yellow solution $KMnO_4$ (316 mg, 2 mmol) was added in small portions over a 30 min period. After stirring overnight the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was extracted with boiling *i*-PrOH (100 mL). The solvent was removed under reduced pressure. The residue was mixed with water (5 mL), acidified by concd HCl to pH 2–3 and heated to 70 °C. The mixture was cooled and extracted with $CHCl_3$ (2×15 mL). The solvent was subsequently removed under reduced pressure. The crude product was crystallized from *i*-PrOH or CCl_4 to give **15** with the yield indicated in Table 2. Reaction with $EtNH_2$ was carried out in a similar way at −3 to 0 °C.

*4.6.1. 7-Ethylamino-1,3-dimethylpteridin-2,4,6(1H,3H,5H)-trione (**15a**)*

Beige crystals, mp 304–305 °C (*i*-PrOH); [found: C, 47.8; H, 5.1; N, 27.9. $C_{10}H_{13}N_5O_3$ requires C, 47.81; H, 5.22; N, 27.87%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 263 (4.12), 287 (3.78), 364 (4.14), 379 (4.19), 395 nm (4.01); ν_{max} (Nujol) 3333 and 3153 (N–H), 1713, 1680 and 1633 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 9.53 (1H, br s, 5-NH), 7.14 (1H, m, *NH*CH$_2$Me), 3.60 (3H, s, 1-Me), 3.59 (2H, m, *CH*$_2$Me), 3.42 (3H, s, 3-Me), 1.32 (3H, t, *J* 7.3 Hz, CH$_2$*Me*); *m/z* (EI) 251 (100 M^+), 236 (24), 223 (16), 208 (20), 195 (13), 110 (12), 95 (10), 82 (51), 71 (10), 68 (45), 58 (17), 56 (23), 53 (33), 44 (37), 41 (38%).

*4.6.2. 1,3-Dimethyl-7-propylaminopteridin-2,4,6(1H,3H,5H)-trione (**15b**)*

Off-white crystals, mp 274–275 °C (*i*-PrOH); [found: C, 49.8; H, 5.6; N, 26.5. $C_{11}H_{15}N_5O_3$ requires C, 49.81; H, 5.70; N, 26.40%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 263 (4.17), 288 (3.95), 362 (4.13), 377 (4.18), 393 nm (4.00); ν_{max} (Nujol) 3287 and 3153 (N–H), 1707, 1680 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.02 (1H, br s, 5-NH), 7.53 (1H, m, *NH*$(CH_2)_2$Me), 3.59 (3H, s, 1-Me), 3.53 (2H, m, *CH*$_2$CH$_2$Me), 3.42 (3H, s, 3-Me), 1.73 (2H, m, CH$_2$*CH*$_2$Me), 0.99 (3H, t, *J* 7.4 Hz, $(CH_2)_2$*Me*); *m/z* (EI) 265 (81 M^+), 250 (70), 236 (100), 223 (51), 207 (21), 195 (21), 152 (19), 148 (14), 123 (14), 109 (16), 94 (14), 82 (64), 67 (40), 58 (18), 53 (18), 41 (19%).

*4.6.3. 7-Isopropylamino-1,3-dimethylpteridin-2,4,6(1H,3H,5H)-trione (**15c**)*

Off-white crystals, mp 304–305 °C (*i*-PrOH); [found: C, 49.8; H, 5.6; N, 26.3. $C_{11}H_{15}N_5O_3$ requires C, 49.81; H, 5.70; N, 26.40%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 263 (4.10), 287

(3.81), 362 (4.17), 376 (4.22), 393 nm (4.01); ν_{max} (Nujol) 3280 and 3167 (N–H), 1707, 1680 and 1647 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 10.94 (1H, br s, 5-NH), 7.77 (1H, d, *J* 7.8 Hz, *NH*CHMe$_2$), 4.32 (2H, m, *CH*Me$_2$), 3.58 (3H, s, 1-Me), 3.42 (3H, s, 3-Me), 1.33 (6H, d, *J* 6.5 Hz, CH*Me*$_2$); *m/z* (EI) 265 (61 M^+), 250 (100), 223 (39), 194 (18), 138 (10), 110 (12), 80 (27), 67 (18), 58 (45), 42 (25%).

*4.6.4. 7-Butylamino-1,3-dimethylpteridin-2,4,6-(1H,3H,5H)-trione (**15d**)*

Off-white crystals, mp 240–242 °C (*i*-PrOH); [found: C, 51.6; H, 6.1; N, 25.0. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 261 (4.23), 296 (3.87), 358 (4.23), 372 (4.27), 390 nm (4.08); ν_{max} (Nujol) 3327–3113 and 3167 (N–H), 1700, 1687 and 1660 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 9.99 (1H, br s, 5-NH), 7.47 (1H, m, *NH*(CH$_2$)$_3$Me), 3.61 (3H, s, 1-Me), 3.57 (2H, m, *CH*$_2$(CH$_2$)$_2$Me), 3.44 (3H, s, 3-Me), 1.71 (2H, m, CH$_2$*CH*$_2$CH$_2$Me), 1.44 (2H, m, (CH$_2$)$_2$*CH*$_2$Me), 0.98 (3H, t, *J* 7.3 Hz, (CH$_2$)$_3$*Me*); *m/z* (EI) 279 (72 M^+), 250 (100), 236 (50), 223 (28), 207 (12), 82 (18%).

*4.6.5. 7-tert-Butylamino-1,3-dimethylpteridin-2,4,6-(1H,3H,5H)-trione (**15e**)*

Off-white crystals, mp 288–289 °C (*i*-PrOH); [found: C, 51.6; H, 6.0; N, 25.2. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 261 (3.62), 286 (3.23), 360 (3.71), 372 (3.76), 390 nm (3.57); ν_{max} (Nujol) 3280 and 3213–3187 (N–H), 1700, 1673 and 1647 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 9.66 (1H, br s, 5-NH), 7.08 (1H, br s, *NH*Bu-*t*), 3.59 (3H, s, 1-Me), 3.42 (3H, s, 3-Me), 1.52 (9H, s, *t*-Bu); *m/z* (EI) 279 (30 M^+), 223 (100), 195 (15), 138 (11), 110 (10), 82 (25), 68 (19), 57 (23), 55 (11), 53 (13), 42 (37), 39 (13%).

*4.6.6. 7-Cyclohexylamino-1,3-dimethylpteridin-2,4,6-(1H,3H,5H)-trione (**15f**)*

Off-white crystals, mp 295–297 °C decomp. (*i*-PrOH); [found: C, 54.9; H, 6.2; N, 22.9. $C_{14}H_{19}N_5O_3$ requires C, 55.07; H, 6.27; N, 22.94%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 262 (3.94), 288 sh (3.68), 362 (4.12), 376 (4.16), 390 nm (3.97); ν_{max} (Nujol) 3273 and 3167 (N–H), 1700, 1673 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 9.66 (1H, br s, 5-NH), 7.13 (1H, d, *J* 7.7 Hz, *NH*C_6H_{11}-*cyclo*), 3.96 (1H, m, cyclohexyl), 3.58 (3H, s, 1-Me), 3.41 (3H, s, 3-Me), 2.03 (2H, m, cyclohexyl), 1.78 (2H, m, cyclohexyl), 1.65 (2H, m, cyclohexyl), 1.37 (4H, m, cyclohexyl); *m/z* (EI) 305 (45 M^+), 223 (100), 195 (21), 138 (13), 110 (12), 82 (13), 67 (19), 50 (26), 41 (26%).

*4.6.7. 1,3-Dimethyl-7-piperidinopteridin-2,4,6-(1H,3H,5H)-trione (**15g**)*

Yellow crystals, mp 243–244 °C decomp. (CCl_4); [found: C, 53.6; H, 6.0; N, 24.1. $C_{13}H_{17}N_5O_3$ requires C, 53.60; H, 5.88; N, 24.04%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 277 (4.07), 301 (4.00), 370 (4.39), 392 (4.48), 408 nm (4.31); ν_{max} (Nujol) 3140 (N–H), 1700, 1673 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 9.38 (1H, br s, 5-NH), 4.49 (2H, br m, α-CH_2 piperidino), 3.93 (2H, br m, α-CH_2' piperidino), 3.54 (3H, s, 1-Me), 3.42 (3H, s, 3-Me), 1.74 (6H, m, β- and γ-CH_2 piperidino); *m/z* (EI) 291 (100 M^+), 236 (12), 223 (62), 207 (14), 195 (23), 180 (17), 95 (16), 84 (30), 67 (25), 55 (14), 41 (23%).

*4.6.8. 1,3-Dimethyl-7-morpholinopteridin-2,4,6-(1H,3H,5H)-trione (**15h**)*

Yellow crystals, mp 295–298 °C decomp. (CCl_4); [found: C, 49.3; H, 5.2; N, 24.0. $C_{12}H_{15}N_5O_4$ requires C, 49.14; H, 5.16; N, 23.88%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 277 (3.76), 302 (3.60), 372 (4.20), 391 (4.31), 408 nm (4.16); ν_{max} (Nujol) 3140 (N–H), 1707, 1673 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 8.97 (1H, br s, 5-NH), 4.66 (2H, m, NCH_2 morpholino), 4.00 (2H, m, NCH_2' morpholino), 3.84 (4H, m, O(CH$_2$)$_2$ morpholino), 3.55 (3H, s, 1-Me), 3.43 (3H, s, 3-Me); *m/z* (EI) 293 (100 M^+), 250 (10), 236 (22), 222 (46), 208 (34), 180 (33), 95 (13), 67 (13%).

*4.6.9. 1,3-Dimethyl-7-diethylaminopteridin-2,4,6-(1H,3H,5H)-trione (**15i**)*

Yellow crystals, mp 300–301 °C decomp. (*i*-PrOH); [found: C, 51.5; H, 6.0; N, 24.9. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 275 (3.81), 300 (3.60), 367 (4.08), 391 (4.18), 408 nm (4.01); ν_{max} (Nujol) 3167 (N–H), 1693, 1673 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 8.94 (1H, br s, 5-NH), 4.18 (2H, m, NCH_2 diethylamino), 3.68 (2H, m, NCH_2' diethylamino), 3.55 (3H, s, 1-Me), 3.41 (3H, s, 3-Me), 1.32 (6H, m, N(CH$_2$*Me*)$_2$); *m/z* (EI) 279 (56 M^+), 264 (11), 250 (100), 236 (28), 207 (11), 82 (15), 67 (12%).

*4.7. General procedure for the oxidative alkylamination of 1,3,5-trimethylpteridin-2,4,6(1H,3H,5H)-trione (**8b**)*

A solution of **8b** (222 mg, 1 mmol) in the appropriate alkylamine (40 mL) was stirred at room temperature for 15–20 min. To the resulting yellowish solution $AgPy_2MnO_4$ (462 mg, 1.2 mmol) was added in small portions over a 30 min period. After 2–2.5 h, the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was extracted with boiling *i*-PrOH (100 mL). The solvent was subsequently removed under reduced pressure. The crude product was crystallized from *i*-PrOH to give **19** in 55–56% yield.

*4.7.1. 1,3,5-Trimethyl-7-propylaminopteridin-2,4,6-(1H,3H,5H)-trione (**19a**)*

Beige crystals, mp 210–213 °C (*i*-PrOH); [found: C, 51.6; H, 6.0; N, 25.1. $C_{12}H_{17}N_5O_3$ requires C, 51.60; H, 6.14; N, 25.08%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 259 (3.97), 292 (3.45), 355 (3.95), 370 (4.03), 390 nm (3.85); ν_{max} (Nujol) 3287 (N–H), 1700, 1645 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.12 (1H, m, *NH*(CH$_2$)$_2$Me), 4.01 (3H, s, 5-Me), 3.59 (3H, s, 1-Me), 3.49 (2H, m, *CH*$_2$CH$_2$Me), 3.39 (3H, s, 3-Me), 1.70 (2H, m, CH$_2$*CH*$_2$Me), 0.99 (3H, t,

J 7.5 Hz, $(CH_2)_2$*Me*); *m/z* (EI) 279 (55 M^+), 250 (48), 237 (20), 96 (11), 82 (94), 67 (100), 55 (13), 54 (17), 41 (75%).

*4.7.2. 7-Butylamino-1,3,5-trimethylpteridin-2,4,6-(1H,3H,5H)-trione (**19b**)*

Beige crystals, mp 164–167 °C (*i*-PrOH); [found: C, 53.2; H, 6.5; N, 23.8. $C_{13}H_{19}N_5O_3$ requires C, 53.23; H, 6.53; N, 23.88%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 258 (4.08), 291 sh (3.65), 351 (4.13), 367 (4.17), 390 nm (3.90); ν_{max} (Nujol) 3293 (N–H), 1700, 1653 and 1640 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.10 (1H, br s, *NH*$(CH_2)_3$Me), 4.00 (3H, s, 5-Me), 3.59 (3H, s, 1-Me), 3.53 (2H, m, *CH*$_2(CH_2)_2$Me), 3.39 (3H, s, 3-Me), 1.65 (2H, m, CH_2*CH*$_2CH_2$Me), 1.40 (2H, m, $(CH_2)_2$*CH*$_2$Me), 0.95 (3H, t, *J* 7.3 Hz, $(CH_2)_3$*Me*); *m/z* (EI) 293 (100 M^+), 264 (13), 250 (68), 237 (27), 208 (13), 108 (11), 82 (63), 67 (68), 55 (27), 41 (63%).

*4.8. General procedure for the oxidative alkylamination of 1-methylquinoxalin-2(1H)-one (**10**)*

Method A. A solution of **10** (160 mg, 1 mmol) in the appropriate alkylamine (30 mL) was stirred at room temperature for 15–20 min. To the resulting yellowish solution $AgPy_2MnO_4$ (462 mg, 1.2 mmol) was added in small portions over a 30 min period. After 6 h overall stirring the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was ground with Al_2O_3 (3–4 g), loaded onto a column with Al_2O_3 (3×20 cm) and purified by flash column chromatography with $CHCl_3$ as the eluent. The fraction with R_f ~0.8 gave **20**. The product was crystallized from *i*-PrOH to give **20a–e** with the yield indicated in Table 3. Reaction with $EtNH_2$ was carried out in a similar way at −3 to 0 °C.

Method B. To a stirred solution of **10** (160 mg, 1 mmol) and alkylamine (3 mL) in THF (10 mL) at room temperature, $AgPy_2MnO_4$ (385 mg, 1 mmol) was added in small portions over a 30 min period. After 12 h, $AgPy_2MnO_4$ (385 mg, 1 mmol) was added in small portions over a 30 min period. After 12 h, the excess amount of the alkylamine was subsequently removed under reduced pressure. Products **20f–h** were isolated similarly to method A with the yield indicated in Table 3.

Method C. To a stirred solution of **10** (160 mg, 1 mmol) in the appropriate alkylamine (30 mL) at room temperature, $KMnO_4$ (316 mg, 2 mmol) was added. After stirring overnight the excess amount of the alkylamine was subsequently removed under reduced pressure. Products **20a–h** were isolated similarly to method A with the yield indicated in Table 3. Reaction with $EtNH_2$ was carried out in a similar way at −3 to 0 °C.

*4.8.1. 1-Methyl-3-methylaminoquinoxalin-2(1H)-one (**20a**)*

Yellowish crystals, mp 147–149 °C (*i*-PrOH); [found: C, 63.4; H, 5.7; N, 22.3. $C_{10}H_{11}N_3O$ requires C, 63.48; H, 5.86; N, 22.21%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 260 (4.06), 325 (4.08), 342 (4.20), 357 nm (4.08); ν_{max} (Nujol) 3340 (N–H), 1647 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.55 (1H, m, 5-H), 7.15–7.25 (3H, m, 6-, 7- and 8-H), 6.40 (1H, m, *NH*Me), 3.68 (3H, s, 1-Me), 3.10 (3H, d, *J* 5.1 Hz, NH*Me*); *m/z* (EI) 189 (100 M^+), 174 (27), 161 (16), 147 (16), 131 (20), 119 (20), 95 (13), 90 (10), 77 (15), 51 (12), 39 (10%).

*4.8.2. 1-Methyl-3-ethylaminoquinoxalin-2(1H)-one (**20b**)*

Yellowish crystals, mp 114–116 °C (*i*-PrOH); [found: C, 65.2; H, 6.2; N, 20.5. $C_{11}H_{13}N_3O$ requires C, 65.01; H, 6.45; N, 20.68%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 252 (4.34), 327 (3.90), 342 (4.04), 357 nm (4.01); ν_{max} (Nujol) 3130 (N–H), 1647 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.54 (1H, m, 5-H), 7.10–7.32 (3H, m, 6-, 7- and 8-H), 6.32 (1H, m, *NH*CH_2Me), 3.69 (3H, s, 1-Me), 3.57 (2H, m, *CH*$_2$Me), 1.29 (3H, t, *J* 7.3 Hz, CH_2*Me*); *m/z* (EI) 203 (100 M^+), 188 (79), 175 (53), 161 (22), 148 (21), 131 (22), 119 (27), 102 (25), 92 (22), 90 (36), 77 (37), 65 (16), 51 (22), 44 (43), 39 (11%).

*4.8.3. 1-Methyl-3-propylaminoquinoxalin-2(1H)-one (**20c**)*

Yellowish crystals, mp 100–102 °C (*i*-PrOH); [found: C, 66.5; H, 7.0; N, 19.4. $C_{12}H_{15}N_3O$ requires C, 66.34; H, 6.96; N, 19.34%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 260 (3.97), 327 (4.08), 340 (4.21), 357 nm (4.01); ν_{max} (Nujol) 3347 (N–H), 1653 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.53 (1H, m, 5-H), 7.15–7.25 (3H, m, 6-, 7- and 8-H), 6.37 (1H, m, *NH*$(CH_2)_2$Me), 3.69 (3H, s, 1-Me), 3.49 (2H, m, *CH*$_2$$CH_2$Me), 1.70 (2H, m, CH_2*CH*$_2$Me), 1.0 (3H, t, *J* 7.4 Hz, $(CH_2)_2$*Me*); *m/z* (EI) 217 (61 M^+), 188 (78), 175 (100), 161 (19), 148 (22), 131 (16), 119 (20), 104 (17), 90 (31), 77 (53), 65 (20), 58 (13), 51 (33), 41 (38), 38 (28%).

*4.8.4. 3-Isopropylamino-1-methylquinoxalin-2(1H)-one (**20d**)*

Yellowish crystals, mp 132–134 °C (*i*-PrOH); [found: C, 66.3; H, 6.7; N, 19.5. $C_{12}H_{15}N_3O$ requires C, 66.34; H, 6.96; N, 19.34%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 257 (3.91), 327 (3.97), 340 (4.12), 357 nm (4.00); ν_{max} (Nujol) 3340 (N–H), 1660 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.55 (1H, m, 5-H), 7.20–7.31 (3H, m, 6-, 7- and 8-H), 6.26 (1H, d, *J* 6.7 Hz, *NH*$CHMe_2$), 4.32 (1H, m, *CH*Me_2), 3.72 (3H, s, 1-Me), 1.32 (6H, d, *J* 6.7 Hz, $CHMe_2$); *m/z* (EI) 217 (91 M^+), 202 (100), 175 (88), 161 (10), 148 (28), 131 (11), 119 (21), 90 (16), 77 (24), 58 (32), 51 (16), 44 (32), 41 (27), 39 (25%).

*4.8.5. 3-Butylamino-1-methylquinoxalin-2(1H)-one (**20e**)*

Yellowish crystals, mp 73–75 °C (*i*-PrOH); [found: C, 67.4; H, 7.5; N, 18.3. $C_{13}H_{17}N_3O$ requires C, 67.51; H, 7.41; N, 18.17%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 252 (3.91), 260 (3.92), 328 (3.98), 340 (4.09), 353 nm (4.00); ν_{max} (Nujol) 3340 (N–H), 1660 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.53 (1H, m, 5-H), 7.17–7.28 (3H, m, 6-, 7- and 8-H), 6.34 (1H, m, *NH*$(CH_2)_3$Me), 3.69 (3H, s, 1-Me), 3.52 (2H, m, *CH*$_2(CH_2)_2$Me), 1.64 (2H, m, CH_2*CH*$_2CH_2$Me), 1.43 (2H, m, $(CH_2)_2$*CH*$_2$Me), 0.95 (3H, t, *J* 7.3 Hz, $(CH_2)_3$*Me*); *m/z* (EI) 231 (51 M^+), 202 (16), 188 (71), 175 (100), 161 (32), 148 (27), 131 (16), 119 (21), 104 (14), 90 (19), 77 (29), 65 (10), 51 (14), 41 (18%).

*4.8.6. 3-Cyclohexylamino-1-methylquinoxalin-2(1H)-one (**20f**)*

Off-white crystals, mp 163–165 °C (*i*-PrOH); [found: C, 70.2; H, 7.2; N, 16.5. $C_{15}H_{19}N_3O$ requires C, 70.01; H, 7.44; N, 16.33%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 260 (3.97), 330 (4.09), 344 (4.21), 352 nm (4.08); ν_{max} (Nujol) 3340 (N–H), 1673 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.52 (1H, m, 5-H), 7.15–7.26 (3H, m, 6-, 7- and 8-H), 6.30 (1H, d, *J* 7.6 Hz, *NH*C_6H_{11}-*cyclo*), 4.02 (1H, m, 1′-H cyclohexyl), 3.69 (3H, s, 1-Me), 2.07 (2H, m, cyclohexyl), 1.74 (2H, m, cyclohexyl), 1.20–1.55 (6H, m, cyclohexyl); *m/z* (EI) 257 (38 M^+), 200 (29), 175 (100), 148 (31), 146 (17), 131 (10), 119 (16), 90 (11), 77 (17), 55 (16), 41 (29), 39 (18%).

*4.8.7. 1-Methyl-3-piperidinoquinoxalin-2(1H)-one (**20g**)*

Yellowish crystals, mp 84–86 °C (*i*-PrOH); [found: C, 69.2; H, 6.8; N, 17.4. $C_{14}H_{17}N_3O$ requires C, 69.11; H, 7.04; N, 17.27%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 253 (4.25), 348 sh (4.01), 362 (4.58), 375 sh nm (4.45); ν_{max} (Nujol) 1673 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.50 (1H, m, 5-H), 7.12–7.26 (3H, m, 6-, 7- and 8-H), 3.84 (4H, m, α-CH_2 piperidino), 3.64 (3H, s, 1-Me), 1.68 (6H, m, β- and γ-CH_2 piperidino); *m/z* (EI) 243 (100 M^+), 228 (44), 214 (26), 200 (62), 188 (33), 175 (39), 160 (21), 148 (15), 131 (43), 119 (11), 104 (18), 90 (24), 84 (100), 77 (28), 65 (10), 56 (15), 51 (15), 41 (29), 39 (22%).

*4.8.8. 1-Methyl-3-morpholinoquinoxalin-2(1H)-one (**20h**)*

Yellowish crystals, mp 93–95 °C (*i*-PrOH); [found: C, 63.6; H, 6.1; N, 17.2. $C_{13}H_{15}N_3O_2$ requires C, 63.66; H, 6.16; N, 17.13%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 262 (3.97), 346 sh (4.00), 360 (4.01), 378 sh nm (4.01); ν_{max} (Nujol) 1673 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 7.52 (1H, m, 5-H), 7.15–7.30 (3H, m, 6-, 7- and 8-H), 3.93 (4H, m, $N(CH_2)_2$ morpholino), 3.82 (4H, m, $O(CH_2)_2$ morpholino), 3.65 (3H, s, 1-Me); *m/z* (EI) 245 (69 M^+), 214 (22), 200 (40), 188 (37), 175 (29), 160 (100), 145 (10), 131 (84), 118 (12), 107 (49), 105 (40), 90 (54), 86 (31), 77 (70), 63 (28), 56 (24), 51 (44), 42 (34), 39 (30%).

*4.9. 5-Butylamino-1,3,6-trimethylpyrimido[4,5-d]-pyrimidin-2,4,7(1H,3H,6H)-trione (**21**)*

A solution of **9** (222 mg, 1 mmol) in butylamine (50 mL) was stirred at room temperature for 15–20 min. To the resulting yellow solution $AgPy_2MnO_4$ (578 mg, 1.5 mmol) was added in small portions over a 1 h period. After 2 days overall stirring the excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was extracted with boiling $CHCl_3$ (100 mL). The solvent was removed under reduced pressure. The crude product was crystallized from *i*-PrOH to give **21** with the 46% yield. Colourless crystals, mp 282–284 °C decomp. (*i*-PrOH); [found: C, 53.4; H, 6.5; N, 23.8. $C_{13}H_{19}N_5O_3$ requires C, 53.24; H, 6.48; N, 23.89%]; UV–vis ($CHCl_3$) λ_{max} (log ε): 253 (3.93), 293 nm (4.15); ν_{max} (Nujol) 3300 (N–H), 1720, 1680 and 1627 cm^{-1} (C=O); δ_H (250 MHz, $CDCl_3$) 5.41 (1H, m, *NH*$(CH_2)_3$Me), 3.55 (2H, m, *CH*$_2(CH_2)_2$Me), 3.53 (3H, s, 1-Me), 3.38 (3H, s, 3-Me), 3.35 (3H, s, 6-Me), 1.66 (2H, m, CH_2*CH*$_2CH_2$Me), 0.96 (3H, t, *J* 7.1 Hz, $(CH_2)_3$*Me*), 1.40 (2H, m, $(CH_2)_2$*CH*$_2$Me); *m/z* (EI) 293 (100 M^+), 264 (42), 251 (13), 237 (85), 221 (67), 208 (18), 182 (14), 180 (15), 124 (11), 107 (13), 96 (64), 93 (13), 82 (84), 72 (18), 69 (45), 67 (26), 56 (68), 42 (91%).

Acknowledgements

This work was supported by the Russian Foundation for Basic Research (grant no. 07-03-00485-a).

References and notes

1. 3-Amino- and 3-alkylaminopyrazin-2-ones, synthesis and antithrombotic activity: (a) Nantermet, P. G.; Selnick, H. G. *Tetrahedron Lett.* **2003**, *44*, 2401; (b) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Nantermet, P. G.; Selnick, H. G.; Isaacs, R. C. A.; Dale Lewis, S.; Lucas, B. J.; Krueger, J. A.; Singh, R.; Miller-Stein, C.; White, R. B.; Wong, B.; Lyle, E. A.; Stranieri, M. T.; Cook, J. J.; McMasters, D. R.; Pellicore, J. M.; Pal, S.; Wallace, A. A.; Clayton, F. C.; Bohn, D.; Welsh, D. C.; Lynch, J. J., Jr.; Yan, Y.; Chen, Z.; Kuo, L.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1353; (c) Sanderson, P. E. J.; Lyle, T. A.; Cutrona, K. J.; Dyer, D. L.; Dorsey, B. D.; McDonough, C. M.; Naylor-Olsen, A. M.; Chen, I.-W.; Chen, Z.; Cook, J. J.; Cooper, C.; Gardell, S. J.; Hare, T. R.; Krueger, J. A.; Dale Lewis, S.; Lin, J. H.; Lucas, B. J.; Lyle, E. A.; Lynch, J. J., Jr.; Stranieri, M. T.; Vastag, K.; Yan, Y.; Shafer, J. A.; Vacca, J. P. *J. Med. Chem.* **1998**, *41*, 4466; (d) Isabel, E.; Aspiotis, R.; Black, W. C.; Colucci, J.; Fortin, R.; Giroux, A.; Grimm, E. L.; Han, Y.; Mellon, C.; Nicholson, D. W.; Rasper, D. M.; Renaud, J.; Roy, S.; Tam, J.; Tawa, P.; Vaillancourt, J. P.; Xanthoudakis, S.; Zamboni, R. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1671; (e) Kuse, M.; Kondo, N.; Ohyabu, Y.; Isobe, M. *Tetrahedron* **2004**, *60*, 835; (f) Chung, J. Y. L.; Cvetovich, R. J.; Tsay, F.-R.; Dormer, P. G.; DiMichele, L.; Mathre, D. J.; Chilenski, J. R.; Mao, B.; Wenslow, R. *J. Org. Chem.* **2003**, *68*, 8838; (g) Isaacs, R. C. A.; Solinsky, M.; Cutrona, K. J.; Newton, C. L.; Naylor-Olsen, A. M.; Krueger, J. A.; Dale Lewis, S.; Lucas, B. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 338; (h) Nantermet, P. G.; Burgey, C. S.; Robinson, K. A.; Pellicore, J. M.; Newton, C. L.; Deng, J. Z.; Selnick, H. G.; Dale Lewis, S.; Lucas, B. J.; Krueger, J. A.; Miller-Stein, C.; White, R. B.; Wong, B.; McMasters, D. R.; Wallace, A. A.; Lynch, J. J., Jr.; Yan, Y.; Chen, Z.; Kuo, L.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P.; Lyle, T. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2771.
2. 4(5)-Amino- and 4(5)-alkylaminopyridazin-3-ones, synthesis, anti-arrhythmic properties and in vitro ability to inhibit aldose reductase (ALR2): (a) Dal Piaz, V.; Vergelli, C.; Giovannoni, M. P.; Scheideler, M. A.; Petrone, G.; Zaratin, P. *Il Farmaco* **2003**, *58*, 1063; (b) Costantino, L.; Rastelli, G.; Gamberini, M. C.; Giovannoni, M. P.; Dal Piaz, V.; Vianello, P.; Barlocco, D. *J. Med. Chem.* **1999**, *42*, 1894; (c) Károlyházy, L.; Szabó, D.; Anwair, M. A. S.; Borosy, A. P.; Takács-Novák, K.; Mátyus, P. *J. Mol. Struct. (Theochem)* **2002**, *578*, 89; (d) Anwair, M. A. S.; Károlyházy, L.; Szabó, D.; Balogh, B.; Kovesdi, I.; Harmat, V.; Krenyácz, J.; Gellért, Á.; Takács-Novák, K.; Mátyus, P. *J. Agric. Food Chem.* **2003**, *51*, 5262.
3. 3-Amino- and 3-alkylaminoquinoxalin-2(1*H*)-ones, synthesis and CNS activity: (a) Csikós, É.; Gönczi, C.; Podányi, B.; Tóth, G.; Hermecz, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1789; (b) Moustafa, O. S. *J. Chin. Chem. Soc.* **2000**, *47*, 351.
4. 2-Amino- and 2-alkylaminoquinazolin-4(3*H*)-ones, synthesis, hypotensive activity and ability to inhibit the glucose-induced insulin release: (a) Somers, F.; Ouedraogo, R.; Antoine, M.-H.; De Tullio, P.; Becker, B.; Fontaine, J.; Damas, J.; Dupont, L.; Rigo, B.; Delarge, J.; Lebrune, P.; Pirotte, B. *J. Med. Chem.* **2001**, *44*, 2575; (b) Hess, H. J.; Cronin, T. H.; Scriabine, A. *J. Med. Chem.* **1968**, *11*, 130; (c) Kundu, B.; Partani, P.; Duggineni, S.; Sawant, D. *J. Comb. Chem.* **2005**, *7*, 909; (d) Connoly,

D.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153.

5. 2-Amino- and 2-arylaminopyrimidin-4(3*H*)-ones, synthesis and biological activity: (a) Hannah, D. R.; Sherer, E. C.; Davies, R. V.; Titman, R. B.; Laughton, C. A.; Stevens, M. F. G. *Bioorg. Med. Chem.* **2000**, *8*, 739; (b) Rose, Y.; Ciblat, S.; Reddy, R.; Belley, A. C.; Dietrich, E.; Lehoux, D.; McKay, G. A.; Poirier, H.; Rafai Far, A.; Delorme, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 891; 4-Alkylaminopyrimidin-2(1*H*)-ones: (c) Zechel, C.; Backfisch, G.; Delzer, J.; Geneste, H.; Graef, C.; Hornberger, W.; Kling, A.; Lange, U. E. W.; Lauterbach, A.; Seitz, W.; Subkowski, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 165; 5-Alkylaminopyrimidin-4(3*H*)-ones: (d) Akahoshi, F.; Ashimori, A.; Yoshimura, T.; Imada, T.; Nakajiama, M.; Mitsutomi, N.; Kuwahara, S.; Ohtsuka, T.; Fukaya, C.; Miyazaki, M.; Nakamura, N. *Bioorg. Med. Chem.* **2001**, *9*, 301; 5-Aminopyrimidin-2(1*H*)-ones: (e) Luo, G. *Tetrahedron Lett.* **2004**, *45*, 8331.
6. (a) Gulevskaya, A. V.; Besedin, D. V.; Pozharskii, A. F. *Russ. Chem. Bull., Int. Ed.* **1999**, *48*, 1150; (b) Besedin, D. V.; Gulevskaya, A. V.; Pozharskii, A. F. *Mendeleev Commun.* **2000**, *10*, 150; (c) Gorunenko, V. V.; Gulevskaya, A. V.; Pozharskii, A. F. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 846.
7. Van der Plas, H. C. *Adv. Heterocycl. Chem.* **2004**, *86*, 1.
8. (a) Pozharskii, A. F.; Gulevskaya, A. V.; Kuz'menko, V. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1988**, *24*, 1404; For the comparison of $AgPy_2MnO_4$ versus $KMnO_4$ at the oxidative alkylamination, see: (b) Gulevskaya, A. V.; Maes, B. U. W.; Meyers, C.; Herrebout, W. A.; Van der Veken, B. J. *Eur. J. Org. Chem.* **2006**, 5305.
9. Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Amsterdam, 2000; pp 43–52, 195–220, 272–276.
10. (a) Coates, W. J.; McKillop, A. *Heterocycles* **1989**, *29*, 1077; (b) Coates, W. J.; McKillop, A. *Heterocycles* **1993**, *35*, 1313; (c) Ostrowicz, A.; Bałoniak, S.; Mąkosza, M.; Rykowski, A. *Tetrahedron Lett.* **1992**, *33*, 4787; (d) Chupakhin, O. N.; Sidorov, E. O.; Postovskii, I. J. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1974**, *10*, 867.
11. (a) Bojarska-Dahlig, H.; Nautka-Namirski, P. *Roczniki Chemii* **1956**, *30*, 461; *Chem. Abstr.* **1957**, *51*, 14722; (b) Chichibabin, A. E. Germany Patent 374291; *Chem. Abstr.* **1924**, *18*, 2176.
12. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785; (c) Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, NY, 1986; (d) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, revision C.01*; Gaussian: Wallingford CT, 2004.
13. The global electrophilicity index ω measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment has been given by the following expression: $\omega=\mu^2/2\eta$ in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, E_{HOMO} and E_{LUMO}, as $\mu\approx(E_{HOMO}+E_{LUMO})/2$ and $\eta\approx E_{HOMO}-E_{LUMO}$, respectively. The local electrophilicity index ω_k condensed to atom k is obtained by projecting the global quantity onto any atomic centre k in the molecule by using the electrophilic Fukui function (i.e., the Fukui function for nucleophilic attack, f_k^+), resulting in: $\omega_k=f_k^+\ \omega$. The Fukui function for nucleophilic attack f_k^+ is defined as $f_k^+=\rho_{N+1}(k)-\rho_N(k)$, where $\rho_N(k)$ is the electron density at a point k in space around the molecule, N corresponds to the number of electrons in the neutral molecule and $N+1$ refers to the number of electrons in the corresponding radical anion (obtained by adding an electron to the LUMO of the neutral molecule). (a) Parr, R. G.; von Szetpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922; (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512; (c) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *J. Phys. Chem. A* **2002**, *106*, 6871; (d) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2003**, *59*, 3117.
14. Gorunenko, V. V.; Gulevskaya, A. V.; Pozharskii, A. F. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 441.
15. Steppan, H.; Hammer, J.; Baur, R. H.; Gotlieb, R.; Pfleiderer, W. *Liebigs Ann. Chem.* **1982**, *67*, 2135.
16. Heckel, A.; Pfleiderer, W. *Helv. Chim. Acta* **1986**, *69*, 704.
17. Gulevskaya, A. V.; Pozharskii, A. F.; Shorshnev, S. V.; Zheltushkina, E. A. *Chem. Heterocycl. Compd.* **1994**, *30*, 1083.
18. Bassindale, A. R.; Parker, D. J.; Patel, P.; Taylor, P. G. *Tetrahedron Lett.* **2000**, *41*, 4933.
19. Nishigaki, S.; Ichiba, M.; Senga, K. *J. Org. Chem.* **1983**, *48*, 1628.