Purines, pyrimidines, and fused systems based on them

16.* Oxidative amination of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione

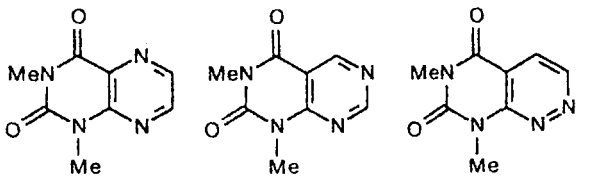
*A. V. Gulevskaya, D. V. Besedin, and A. F. Pozharskii**

Rostov State University,
7 ul. Zorge, 344090 Rostov-on-Don, Russian Federation.
Fax: +7 (863 2) 28 5667. E-mail: pozharsk@pozhar.rnd.runnet.ru

6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione reacts with ammonia or primary amines in the presence of an oxidant to give the corresponding 4-amino derivatives. Reactions with secondary amines (dimethylamine, piperidine, or morpholine) proceed with difficulty, resulting in 3-amino derivatives.

Key words: 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione, nucleophilic substitution, oxidative amination, hetarylamines.

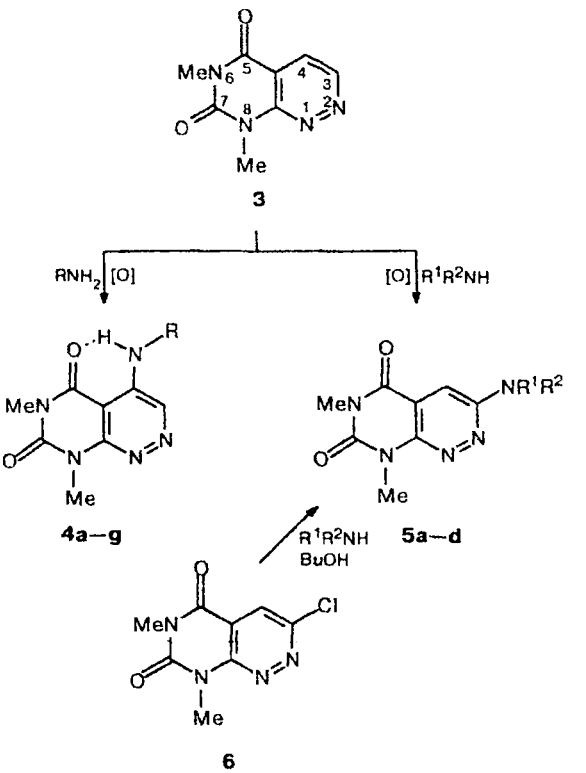
Previously, we reported the oxidative amination of 1,3-dimethylpteridine-2,4(1*H*,3*H*)-dione (1,3-dimethyllumazine, **1**)[2] and isomeric 1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**2**)[3]. It was shown that the direction and ease of the reaction largely depend on the relative values of the positive π charges on the carbon atoms of the azine ring. In a continuation of these investigations, in the present work we studied oxidative amination of 6,8-dimethylpyrimido[4,5-*c*]-pyridazine-5,7(6*H*,8*H*)-dione (**3**), yet another representative of this series.



1 **2** **3**

Compound **3** reacts with an excess of liquid ammonia or primary alkylamines in the presence of $KMnO_4$ or the $AgPy_2MnO_4$ complex at −78 to 20 °C (depending on the boiling point of the amine) to give 4-amino derivatives **4a—g** in 53—90% yields. Reactions with secondary amines (dimethylamine, piperidine, or morpholine) occur much more difficultly under the same conditions and result in the corresponding 3-amino derivatives **5a—c** in only 5—13% yields.

The structures of compounds **4** and **5** were established using UV, IR, and ^1H NMR spectroscopy (Table 1). 4-Amino derivatives **4** are colorless solids (λ_{max} 324—343 nm), while 3-aminopyridazinouracils **5** are bright yellow compounds (λ_{max} 404—423 nm). In the ^1H NMR spectra of amines **4**, a signal for the single H(3) aromatic proton is observed at δ 8.6—8.9, which agrees with the published data for 4-alkylamino-5-azacinnolines.[5] Signals for the protons of the amino groups are shifted downfield (δ 8.9—9.5) compared to analogous signals for



3

4a—g **5a—d** **6**

4: R = H (**a**), Me (**b**), Et (**c**), Pr (**d**), Bu^t (**e**), $PhCH_2$ (**f**), cyclohexyl (**g**);
5: NR^1R^2 = NMe_2 (**a**), piperidino (**b**), morpholino (**c**), $NHCH_2Ph$ (**d**)

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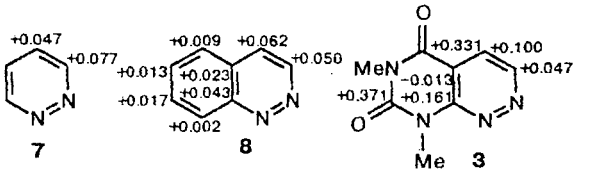
alkylamino derivatives of lumazine **1** (δ 4.9—6.8)[2,6] and pyrimidouracil **2** (δ 5.9—6.2).[3] Apparently, this is due to the formation of an intramolecular hydrogen bond between the C(5)=O carbonyl group and the H atoms of the alkylamino group. It is interesting that the NH_2 protons in compound **4a** are magnetically nonequivalent and hence manifest themselves in the ^1H NMR spectrum as two different signals at δ 5.3 and 8.4 (in $CDCl_3$) and at δ 8.08 and 8.18 (in DMSO-d_6); these signals coalesce in DMSO-d_6 at 55 °C.

The ^1H NMR spectra of 3-amino derivatives **5** exhibit a signal for the H(4) proton at δ 7.45—7.60. The structures of compounds **5** were conclusively proved by their independent synthesis from 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**6**). Heating of the latter with piperidine, morpholine, or benzylamine in butanol gave compound **5b—d** in 73—77% yield; the reaction product with benzylamine **5d** differed from 4-benzylamino derivative **4f**.

Pyridazine (**7**) and cinnoline (**8**) are known to undergo oxidative amination at position 4.[4,5] For cinnoline **8**, this correlates both with relative values of the effective π charges on the C(3) and C(4) atoms and with the energies of anion localization (L^-_n) (HMO calculations). In the molecule of pyridazine **3**, the C(3) atom is more electron-deficient, but the L^-_3 and L^-_4 values suggest that substitution at position 4 is somewhat preferred. Thus, compound **3** resembles cinnoline more closely. In its molecule, the positive charge on the C(4) atom is much higher than that on the C(3) atom, and the energy of anion localization (corresponding to the addition of a nucleophile at position 4) is significantly lower.



7 **8** **3**

$L^-_3 = 2.36\beta$, $L^-_4 = 2.35\beta$ $L^-_3 = 2.41\beta$, $L^-_4 = 2.10\beta$ $L^-_3 = 2.33\beta$, $L^-_4 = 2.07\beta$

Table 1. Physicochemical characteristics of compounds **4** and **5**

Compound	IR, ν/cm^{-1}			^1H NMR ($CDCl_3$), δ (*J*/Hz)					UV, λ_{max}/nm (log ε)
	Ring	C=O	N—H	8-Me	6-Me	H-3[a]	NH	R	
4a	1620	1660 1700	3260 3367	3.41 3.21[b]	3.76 3.53	8.51 8.54	5.30, 8.40 8.08, 8.17	— —	228 (4.51) 273 (3.74) 324 (3.90)
4b	1580	1640 1690	3290	3.39	3.74	8.62	8.89	3.09 (d, 3 H, NH<u>Me</u>, *J* = 5.2)	231 (4.44) 340 (3.97)
4c	1610	1660 1700	3305	3.39	3.74	8.62	8.95	1.39 (t, 3 H, C—Me, *J* = 7.2); 3.46 (m, 2 H, NH—<u>CH_2</u>)	230 (4.40) 341 (3.94)
4d	1590	1660 1690	3290	3.39	3.74	8.61	8.98	1.03 (t, 3 H, C—Me, *J* = 7.6); 1.74 (m, 2 H, C—CH_2, *J* = 7.3); 3.36 (m, 2 H, N—CH_2, *J* = 7)	230 (4.48) 341 (4.04)
4e	1600	1660 1700	3220	3.38	3.73	8.84	9.45	1.52 (s, 9 H, CMe_3)	230 (4.38) 343 (3.96)
4f	1555	1620 1660	3280	3.40	3.75	8.61	9.37	4.61 (d, 2 H, N—CH_2, *J* = 5.86) 7.25—7.40 (m, 5 H, C_6H_5)	231 (4.50) 339 (4.04)
4g	1590	1645 1675	3275	3.39	3.73	8.61	9.00	1.41, 1.75, 2.00 (m, 10 H, cyclohexyl); 3.62 (m, 1 H, H-1, cyclohexyl)	230 (4.48) 343 (4.08)
5a	1620	1660 1700	—	3.50	3.77	7.60	—	3.21 (s, 6 H, NMe_2)	249 (4.11) 269 (4.12) 423 (3.14)
5b	1600	1635 1675	—	3.49	3.81	7.60	—	1.71 (m, 6 H, β- and γ-CH_2, piperidine); 3.70 (m, 4 H, α-CH_2, piperidine)	252 sh (4.33) 273 (4.38) 421 (3.26)
5c	1600	1640 1670	—	3.46	3.78	7.60	—	3.62 (t, 4 H, $N(CH_2)_2$, *J* = 5.2); 3.86 (t, 4 H, $O(CH_2)_2$, *J* = 5.2)	218 (4.58) 240 sh (4.20) 425 (3.76)
5d	1600	1630 1660	3320	3.41 3.25[b]	3.76 3.55	7.37 7.43	5.33 (t, *J* = 5.72) 7.60 (t, *J* = 5.68)	4.65 (t, 2 H, NH—<u>CH_2</u>, *J* = 5.72); 7.26—7.36 (m, 5 H, C_6H_5) 4.64 (t, 2 H, NH—<u>CH_2</u>, *J* = 5.68); 7.23—7.38 (m, 5 H, C_6H_5)	245 (4.66) 264 sh (4.56) 404 (3.59)

[a] H(4) for compounds **5**.
[b] In DMSO-d_6.

Table 2. Conditions for oxidative amination of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**3**). Properties, yields, and data from elemental analysis of compounds **4** and **5**

Compound	Reaction conditions			Yield (%)	M.p. /°C	R_f[a]	Found (%) / Calculated			Molecular formula
	Amine (*V*/mL)	*T*/°C	Oxidant				C	H	N	
4a	NH_3 (30)	−78 to −70	$KMnO_4$	70	264—266	0.05	46.20 46.38	4.43 4.35	33.71 33.56	$C_8H_9N_5O_2$
4b	$MeNH_2$ (30)	−22 to −20	$KMnO_4$	90	234—237	0.39	48.92 48.87	5.00 4.98	31.45 31.67	$C_9H_{11}N_5O_2$
4c	$EtNH_2$ (30)	−15 to −10	$AgPy_2MnO_4$	85	220—223	0.41	51.20 51.06	5.35 5.53	29.70 29.78	$C_{10}H_{13}N_5O_2$
4d	$PrNH_2$ (25)	18—20	$AgPy_2MnO_4$	60	179—182	0.39	52.92 53.01	6.25 6.02	28.03 28.11	$C_{11}H_{15}N_5O_2$
4e	Bu^tNH_2 (25)	18—20	$AgPy_2MnO_4$	63	190—192	0.55	54.95 54.71	6.40 6.46	26.84 26.61	$C_{12}H_{17}N_5O_2$
4f	$PhCH_2NH_2$ (20)	18—20	$AgPy_2MnO_4$	51	173—174	0.32	60.61 60.67	5.24 5.06	23.41 23.57	$C_{15}H_{15}N_5O_2$
4g	Cyclohexylamine (15)	18—20	$AgPy_2MnO_4$	53	231—233	0.36	57.80 57.73	7.03 7.21	24.31 24.05	$C_{14}H_{21}N_5O_2$
5a	Me_2NH (30)	−28 to −24	$AgPy_2MnO_4$	13	158—160	0.80	51.00 51.06	5.38 5.53	29.80 29.78	$C_{10}H_{13}N_5O_2$
5b	Piperidine (30)	18—20	$AgPy_2MnO_4$	10	154—156	0.79	56.54 56.73	6.12 6.18	25.70 25.45	$C_{13}H_{17}N_5O_2$
5c	Morpholine (30)	18—20	$AgPy_2MnO_4$	5	211—214	0.42	52.03 51.99	5.27 5.41	25.38 25.27	$C_{12}H_{15}N_5O_3$
5d	$PhCH_2NH_2$ (20)	18—20	—	77[b]	167—169	0.29	60.45 60.67	5.21 5.06	23.65 23.57	$C_{15}H_{15}N_5O_2$

[a] R_f of the initial compound **3** is 0.67.
[b] With respect to compound **6**.

The tendency toward increasing the positive π charge on the C(4) atom in fused pyridazines is noteworthy; in the case of pyridazinouracil **3**, this can be additionally favored by the −M effect of the C(5)=O group conjugated with position 4.

Thus, the calculated data correlate well with the direction of amination of compound **3** with primary alkylamines or ammonia. Apparently, the absence of such a correlation for secondary alkylamines may be explained, as in the case of compounds **1** and **2**, by a steric factor: since position 4 is sterically hindered, bulkier secondary amines are forced to attack the less electron-deficient but more accessible C(3) atom.

From the viewpoint of reactivity, 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**3**) is intermediate between 1,3-dimethylpyrimido[4,5-*c*]pyrimidine-2,4(1*H*,3*H*)-dione (**2**), which is the most reactive in the oxidative amination, and 1,3-dimethylumazine (**1**).

Experimental

IR spectra were recorded on a UR-20 instrument (Vaseline oil). ^1H NMR spectra were recorded on a Unity-300 spectrometer (300 MHz) with Me_4Si as the internal standard. UV spectra were obtained with a Specord M-40 instrument in methanol. Al_2O_3 (Brockmann activity IV—V) was used for chromatography. Melting points were measured on a PTP instrument in glass capillaries and are not corrected.

Physicochemical characteristics of the compounds obtained are presented in Table 1. Data from elemental analysis are given in Table 2.

Synthesis of 4-amino- and 4-alkylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (4a—g). Compound **3** [7] (0.3 g, 1.5 mmol) was dissolved in 15—30 mL of ammonia or alkylamine and stirred for 15—20 min at the temperature indicated in Table 2. An oxidant (2.5 mmol) was added, and stirring was continued at the same temperature for an additional 30—40 min (in the case of benzylamine and cyclohexylamine, the solutions were additionally kept at 20 °C for one day). The reaction mixture was concentrated to dryness, and the products were extracted from the residue with 50 mL of boiling $CHCl_3$. The extract was concentrated to ~5 mL and chromatographed on a column with Al_2O_3 (1×40 cm) in chloroform to give a colorless fraction (for R_f values, see Table 2). The product was recrystallized from ethanol. Compounds **4a—g** are colorless needle-shaped crystals. The physicochemical characteristics are given in Table 1.

Synthesis of 3-alkylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (5a—d). *A.* Compounds **5a—c** were obtained by analogy with compounds **4** (see Table 2). The reaction products were purified by column chromatography (Al_2O_3, a 2 : 1 toluene—$CHCl_3$ mixture as the eluent). Compounds **5a—c** are bright yellow needle-shaped crystals. The

physicochemical characteristics are given in Table 1.

B. A mixture of compound **6** (0.23 g, 1 mmol)[8] and the corresponding alkylamine (3 mmol) in 4 mL of BuOH was refluxed for 12 h. After cooling, the precipitate of alkylamino derivative **5b—d** was filtered off and recrystallized from ethanol. The filtrate containing both products **5** and the initial compound **6** was concentrated to dryness. The residue was dissolved in a minimum amount of $CHCl_3$ and chromatographed on a column with Al_2O_3 in $CHCl_3$. A bright yellow fraction (for R_f values, see Table 2) was collected. The total yield was 73—77%. The samples of compounds **5b,c** obtained by methods *A* and *B* are identical.

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