Synthesis of Paraxanthine and Isoparaxanthine Analogs (1,7- and 1,9-Substituted Xanthine Derivatives)†

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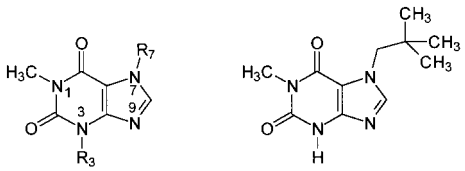
Abstract: A general, convenient method for the preparation of 1,7- and 1,9-disubstituted xanthine derivatives (paraxanthine and isoparaxanthine analogs) was developed starting from 6-amino-2-methoxypyrimidin-4-one. Alkylation with alkyl halides in acetone/potassium carbonate in the presence of a phase-transfer catalyst (PTC) yielded an equimolar mixture of N3- and O^4-alkylated products, which could be separated by dry column chromatography. The N3-alkylated uracil derivatives were converted to the corresponding 1-alkyl-2-methoxypurin-6-ones by standard procedures. PTC alkylation yielded an equimolar mixture of 7- and 9-alkylated isomers, which were again conveniently separated by dry column chromatography. The title compounds were obtained after acid hydrolysis of the 2-methoxy group in satisfactory yields.

Key words: paraxanthine, isoparaxanthine, xanthine synthesis, alkylation, phase transfer catalysis

Paraxanthine (1,7-dimethylxanthine, **1**) is the major metabolite of caffeine in humans (ca. 70–80%) and is believed to contribute to the physiological effects of caffeine.[1] Paraxanthine has been reported to exhibit a number of pharmacological effects, including stimulation of locomotor activity, stimulation of thermogenesis, and an increase in blood pressure.[1–3] One mechanism of action, by which **1** may exert its effects, is adenosine antagonism.[1,4] Paraxanthine is a potent adenosine receptor antagonist, comparable to caffeine and theophylline at A_1-, A_{2A}-, and A_{2B}-AR.[5]



1 Paraxanthine R_3=H, R_7=CH_3
2 Caffeine R_3=R_7=CH_3
3 Theophylline R_3=CH_3, R_7=H

4 MX-2/120

While a vast number of theophylline and caffeine analogs have been synthesized and pharmacologically evaluated, particularly for their adenosine receptor blocking activity, only few paraxanthine analogs have been investigated to date, probably due to the difficult synthetic access to this class of compounds. 3-Unsubstituted xanthines in general have been difficult to prepare, and general access to 1-monosubstituted and 1,8-disubstituted xanthine derivatives has only recently been achieved.[6–9] Despite many efforts over the decades to prepare paraxanthine and some of its analogs, only few analogs have been made available so far. Most syntheses described resulted in low yields, are laborious, time-consuming, multistep procedures, applying circumstantial protection strategies, and are limited to certain substituents, such as methyl. Several reports describe the synthesis of paraxanthine, but not the preparation of analogs, and some of them may be limited to the dimethyl derivative.[10–16] General strategies for the preparation of paraxanthine have been: (a) synthesis starting from an imidazole precursor;[12,13,17] (b) synthesis starting from a pyrimidine precursor or a xanthine derivative, in which the nitrogen atom, which is to remain unsubstituted, has to be protected;[11,14–19] and (c) selective alkylation of xanthines achieved by other methods than using protecting groups.[8,17,20] One report described the preparation of 7-substituted 1-methylxanthines by simple alkylation of 1-methylxanthine using alkyl iodides/sodium hydroxide in dimethyl sulfoxide followed by separation of the resulting mixture of 1,3-di-, 1,7-di-, and 1,3,7-trisubstituted xanthines by means of TLC and HPLC; no yields were reported.[21]

Recently we described a new synthesis of paraxanthine analogs by regioselective alkylation of 1-monosubstituted xanthines after silylation.[8] This reaction was, however, limited to certain alkylating agents, such as methyl iodide and propargyl bromide, while more reactive reagents resulted in 7,9-bisalkylation. More recently, during the course of our work presented here, Agostini et al. reported on the synthesis of a 7-neopentyl analog **4** of paraxanthine **1**, using a benzyl group for protection of the 3-position, which could successfully be removed in the final step by treatment with the Lewis acid aluminum chloride or by catalytic hydrogenation, respectively.[19] Compound **4** (MX-2/120) was found to be a potent bronchospasmolytic agent with few side effects and is currently being developed as a drug.[22]

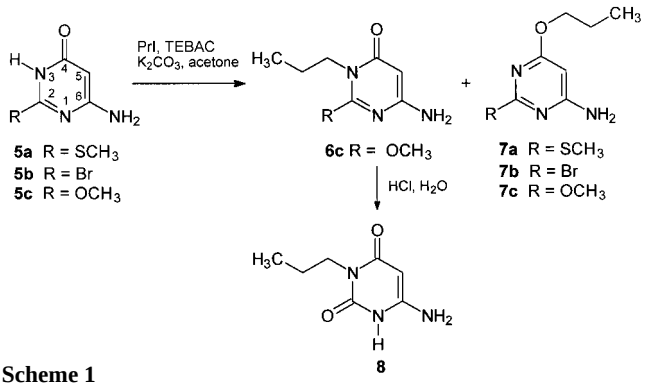
Isoparaxanthine (1,9-dimethylxanthine) is the unnatural isomer of paraxanthine. Only few analogs of isoparaxanthine have been synthesized via 6-(ar)alkylamino-substituted uracil [pyrimidine-2,4(1*H*,3*H*)-dione] derivatives; mainly 1-methyl derivatives bearing various substituents in the 9-position have been obtained.[23–26]

Our goal was to develop new, general and convenient procedures for the preparation of paraxanthine analogs and their 1,9-disubstituted isomers, the isoparaxanthines. The new compounds are of interest due to their potential pharmacological activities, and they will be useful as standard compounds for studying the metabolism of xanthine drugs. Furthermore, paraxanthine analogs can be used as starting compounds for the preparation of caffeine ana-

logs by simple alkylation in the 3-position,[13, 27] thereby offering access to new caffeine analogs, which are difficult or impossible to obtain by standard procedures.

Our strategy for the synthesis of 1,7- and 1,9-disubstituted xanthines (7*H*-imidazo[4,5-*d*]pyrimidine-2,6(1*H*,3*H*)-diones) included protection of the uracil nitrogen N1 from alkylation. As starting compounds we selected 2-substituted 6-aminopyrimidin-4-ones **5** (Scheme 1), bearing a methylthio **5a**, a bromo **5b**, or a methoxy group **5c** in the 2-position. These compounds are readily available[28–30] and the protecting groups can easily be hydrolyzed to obtain the desired 2-oxo derivatives in the last reaction step. At first we developed and optimized conditions for N3-alkylation of pyrimidin-4-one derivatives, and investigated which starting compound was most suitable for our purposes.

Most alkylations of such 2-substituted pyrimidin-4-one derivatives have only been performed with methylating reagents, such as methyl iodide, dimethyl sulfate, or trimethyl phosphate, respectively, under basic conditions.[31–33] Methylation was described as requiring fairly drastic reaction conditions, and appeared not to be applicable to alkylation with less reactive or sensitive alkylating agents.[33] We performed initial experiments using the moderately reactive propyl iodide for alkylation of pyrimidine derivatives **5a–c** (Scheme 1). Under usual reaction conditions, in basic aqueous or alcoholic solution or in dimethylformamide as solvent, alkylation required harsh reaction conditions, which led to partial degradation, and resulted in low yields. Therefore we looked for milder and, at the same time, more effective alkylation methods. A mild, convenient procedure for the alkylation of uracil and some of its derivatives, e.g. 6-aminouracil, includes silylation of the starting compound, by which the reactivity of the heterocycle towards electrophilic attack is increased, followed by reaction with alkyl halide, and subsequent hydrolysis of the remaining silyl groups.[34] Alkylation of 2-methylthio-6-(trimethylsilylamino)-4-(trimethylsilyloxy)pyrimidine with methyl iodide resulted in a high yield of 6-amino-3-methyl-2-(methylthio)pyrimidin-4-one (unpublished result), but alkylation with higher



Scheme 1

homologs, including propyl iodide, was not successful. The 2-bromo derivative **5b** gave only very low yields and was sensitive to degradation when alkylated with propyl iodide after silylation. The 2-methoxy derivative **5c** did react under the same conditions, but during the reaction, the methyl ether was cleaved and thus, the protecting group was lost.

An alternative mild procedure for the alkylation of heterocyclic compounds involves phase transfer catalysis. Results of our optimized experiments using this method are summarized in Table 1 (see also Schemes 1 and 2).

Alkylations were performed with starting compounds **5a–c** and initially with the moderately reactive alkylating agent propyl iodide (in various amounts). Reactions took place in dilute solutions (ca. 1 mmol of **5** in 5 mL of solvent). As solvents dichloromethane, acetone, acetonitrile, or dimethylformamide were used and finely ground potassium carbonate, fluoride, or hydroxide, respectively, (1–3 equiv) was added. Investigated phase-transfer catalysts (PTC) included the quarternary ammonium salts (0.1, 0.5, or 1.0 equiv, or only traces) tetrabutylammonium bromide (TBAB) and benzyltriethylammonium chloride (TEBAC), and the crown ether 18-crown-6 (0.1 equiv). As a comparison, analogous reactions were performed without the addition of PTC. We found that the addition of 1.5–2.0 equivalents of alkylating agent was optimal. This was true for the moderately reactive propyl iodide,

Table 1. Alkylation of 2-Substituted 6-Aminopyrimidin-4-ones using Phase Transfer Catalysis: Optimized Reaction Conditions

Substrate	Reaction Conditions	Alkylating Agent	Isolated Yields (%)		mp (°C)
			N3-Substituted Product	O^4-Substituted Product	
5a	acetone, K_2CO_3, reflux, 14 h (Method A)	PrI	–[a]	**7a**: 73%	**7a**: 124
5a	acetone, K_2CO_3, TEBAC, reflux, 7 h (Method B)	PrI	–[a]	**7a**: 75%	
5a	MeCN, K_2CO_3, TEBAC, 85 °C, 4.5 h (Method C)	PrI	–[a]	**7a:** 80%	
5b	acetone, K_2CO_3, TEBAC, reflux, 12 h	PrI	–[a]	**7b**: 60%	**7b**: 155
5c	acetone, K_2CO_3, TEBAC, reflux, 12 h	PrI	**6c**: 34%	**7c**: 40%	**6c**: 152 **7c**: 105
5c	acetone, K_2CO_3, TEBAC, reflux, 45 min, or r.t., 3 h	$CH{\equiv}CCH_2Br$	**6d**: 37.5%	**7d**: 35%	**6d**: 168 **7d**: 45

[a] Traces were detected by TLC.

and also for the more reactive propargyl bromide. Reactions took place at room temperature in most cases, but were accelerated by elevated temperatures without causing considerable side reactions. Acetone, acetonitrile, and dichloromethane were suitable solvents, while dimethylformamide gave only low yields. Acetone was selected for further reactions. Potassium carbonate as a base was superior to the fluoride and the hydroxide, both of which resulted in incomplete reactions. The best PTC in our reactions was TEBAC in a concentration of 0.5 equivalents. Regioselectivity of the alkylation was not influenced by the nature of the applied PTC. Alkylations proceeded under mild conditions, thus avoiding extreme temperatures or pH values. In all cases two products could be detected by TLC, the N3- and the O^4-alkylated isomers.

Alkylation of 2-methylthio derivative **5a** with propyl iodide yielded the O^4-propyl derivative **7a** as the main product and only traces of the desired N3-propyl isomer (Table 1). The percentage of N3 isomer formed was slightly higher at increased temperatures, or if the more reactive propargyl bromide was used as alkylating agent. Interestingly, the use of a PTC was found to be not essential for alkylation of **5a**. Alkylation of the bromo derivative **5b** also resulted in predominant *O*-alkylation to **7b**. Yields were lower due to partial degradation of **5b** and/or **7b** during the reaction. The addition of PTC was a prerequisite for successful alkylation of **5b**, in contrast to the alkylation of **5a** (see above). Reaction of alkyl halides with 2-methoxy derivative **5c** resulted in a mixture of about equal amounts of *N*- and *O*-alkylated products (Table 1). The percentage of *N*-alkylation was somewhat higher with the more reactive propargyl bromide than with propyl iodide. The addition of a PTC was necessary to achieve alkylation of **5c**. Reaction with propargyl bromide was completed after three hours at room temperature, or after 45 minutes at reflux temperature, while propyl iodide gave no reaction at room temperature and required a reaction time of 12 hours under reflux conditions (Table 1).

It had been observed earlier that 2-substituted pyrimidin-4-one derivatives exhibit an increased tendency towards O^4-alkylation, compared to uracil and its N1-, 5-, and/or 6-substituted derivatives, in which *N*- rather than *O*-alkylation is generally observed.[35, 36] Reasons for a tendency towards *O*-alkylation could be: (a) steric hindrance; and (b) electronic factors of the 2-substituent influencing reactivity of the neighboring nitrogen atom.

In order to find an explanation for the regioselectivity of alkylation of the 6-aminopyrimidin-4-one derivatives **5a–c**, we performed quantumchemical calculations. The semiempirical method MOPAC/PM3[37] was used to calculate the charge distribution and the heats of formation of the N–H and O–H tautomeric forms, respectively (Table 2).

As a first result, one can see that the nature of the substituent in the 2-position has only a very small effect on the electronic properties of the carbonyl oxygen atom (O^4). Consequently, *O*-alkylation is not directly influenced by the substituent in position 2. In contrast, the competing *N*-alkylation appears to show a strong dependence on a change of substitution at C2. The heteroaromatic ring system of compound **5c** shows a different pattern of atomic partial charges compared with **5a** and **5b**. Although the total electronic density and the mean bond order in the aromatic system is lower for compound **5c**, it shows a slightly higher negative charge at atom N3 and a much higher positive charge at atom C2 for both tautomeric forms. (Table 2)

Table 2. Results of the Semiempirical Quantumchemical Calculations for both Tautomeric Forms of Compounds **5a**, **5b** and **5c**.

	5a		**5b**		**5c**	
	N–H	O–H	N–H	O–H	N–H	O–H
Atomic Partial Charges [e^-]:						
N1	–0.21	–0.23	–0.14	–0.17	–0.27	–0.27
C2	–0.11	–0.02	–0.08	0.01	0.14	0.21
N3	0.09	–0.22	0.09	–0.21	0.06	–0.27
H–N3	0.11	–	0.11	–	0.11	–
C4	0.30	0.21	0.30	0.20	0.31	0.22
O=C4	–0.38	–0.22	–0.37	–0.22	–0.38	–0.22
H–O–C4	–	0.23	–	0.23	–	0.23
C5	–0.35	–0.30	–0.35	–0.29	–0.39	–0.34
C6	0.02	0.03	0.01	0.02	0.05	0.05
H_2N–C6	0.11	0.11	0.12	0.12	0.11	0.12
Mean Bond Order in Heterocycle:						
	1.27	1.33	1.28	1.37	1.25	1.30
Final Heat of Formation [kJ/mol]:						
	–62.68	–65.52	–33.20	–37.68	–244.72	–244.13

The differences in the charge distribution of the molecules also affect the relative stability of the tautomeric forms of **5a–c**. The ratio of tautomers can be estimated from the calculated heat of formation. (Table 2) We found a theoretical percentage for the N–H tautomer of 24% for **5a**, 14% for **5b** and 56% for **5c**. The calculated values are in agreement with experimental data: **5a** and **5b** are preferably *O*-alkylated, while **5c** actually gives a mixture of *N*- and *O*-alkylated products. (Table 1)

Although we had to neglect some important effects, like solvation of the tautomeric forms and the charged transition states, we were able to show, that the preferred position of alkylation of compounds **5a–c** appears to correlate with typical patterns of charge distribution in the molecules, that can be calculated with simple semiempirical quantumchemical calculations.

In order to prove that *N*-alkylation of **5c** had actually occurred at N3 rather than N1, **6c** was treated with aqueous hydrochloric acid solution to hydrolyze the methyl ether (Scheme 1). The resulting 6-aminouracil derivative **8** could unambiguously be identified as 3-propyl-substituted derivative by its analytical and spectral data. A convenient way to distinguish between 1- and 3-substituted 6-aminouracil derivatives is the shift for the protons of the

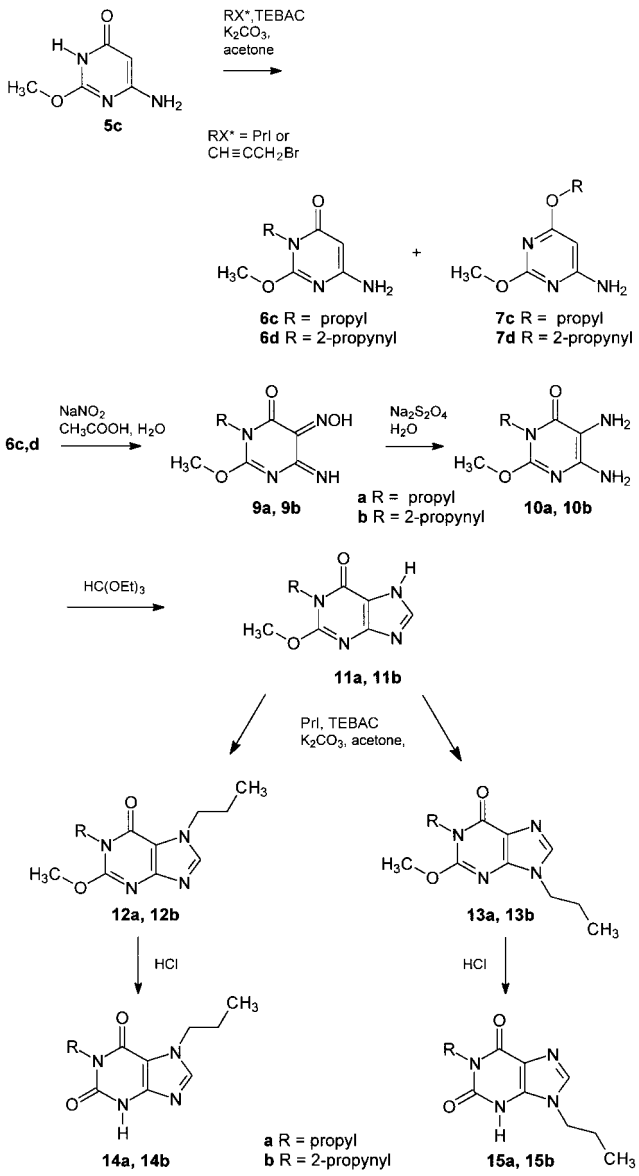
amino group in the ^{1}H NMR spectrum.[34] Compound **8** showed a signal at δ = 6.19 for the amino group (in DMSO-d_6) in accordance with the proposed structure, while the 1-substituted isomer would show a downfield shift of ca. 0.6 ppm and appear at δ = 6.74.[34]

Based on these results methoxy derivative **5c** was selected as a starting compound for the synthesis of 1,7- and 1,9-disubstituted xanthine derivatives. The formation of isomers upon alkylation of **5c** reduces the yields of compounds **6**, but this drawback is compensated for by the fact that alkylation can be performed almost quantitatively under mild conditions without limitations regarding the substituents to be introduced (reactive, less reactive, sensitive), and the isomers can easily be separated.

3-Substituted 6-amino-2-methoxypyrimidin-4-one derivatives **6c** and **6d** were converted to the purine derivatives following the classical Traube purine synthesis (Scheme 2). Nitrosation in the 5-position gave the 5-hydroxyimino-6-iminopyrimidin-4-one derivatives **9a** and **9b** as blue needles in high yields. Reduction had to be performed under mild conditions in order to prevent cleavage of the 2-methoxy group. Sodium dithionite reduction at 4°C resulted in almost quantitative yields of diaminouracils **10a** and **10b**. Ring closure to the purines **11a** and **11b** using triethyl orthoformate was completed within 1 to 1.5 hours at 110–120°C. In the following step a 7- or 9-substituent, respectively, had to be introduced. Alkylation of purines is usually performed under mild conditions in dimethylformamide/potassium carbonate using alkyl halides.[39] This procedure led to a number of byproducts when applied to the alkylation of purines **11a** and **11b**. Therefore, we decided to alkylate using PTC, the method which had already proven to be successful in the alkylation of uracil derivatives **5**. In xanthines alkylation at N7 rather than N9 is observed. In crystals of xanthines as well as in solution the N7–H tautomers are the only isomers observed.[38] In 2-substituted purin-4-one derivatives, such as **11a** and **11b**, however, an equilibrium of about equal amounts of N7–H and N9–H tautomers is observed, as can be seen in the ^{1}H NMR spectra (Table 4), and alkylation is expected to result in a mixture of N7- and N9-substituted isomers. Alkylation of **11a** and **11b** with propyl iodide in acetone/potassium carbonate/TEBAC proceeds smoothly and fast, and the expected mixtures of isomers, **12a**, **12b** and **13a**, **13b** are obtained. Isomers are conveniently separated by dry column chromatography, despite very close R_f values.

The disadvantage of the formation of isomers is again compensated for by the easy and fast method for their separation. Both isomers are accessible by this method. Due to the high reactivity of the imidazole nitrogen atoms the method is not limited to reactive alkylating agents, but will be generally applicable.

In the last step the methyl ether was cleaved by hydrolysis with aqueous hydrochloric acid. It was observed that 9-substituted isomers require harsher conditions for cleavage as compared to 7-substituted isomers. Novel paraxanthine analogs **14a**, **14b** and isoparaxanthine analogs **15a**, **15b** were obtained in fair yields (Table 3).



Scheme 2

The described synthetic method could also be used to prepare 1-monosubstituted xanthines, by subjecting purine derivatives, such as **11a** or **11b**, respectively, to acid hydrolysis of the 2-methoxy group. Recently, however, more convenient procedures have been developed for this class of compounds.[6, 7, 9]

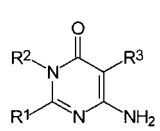
^{1}H and ^{13}C NMR spectral data for pyrimidine derivatives **5–10** are listed in Tables **4** and **5**. *N*- and *O*-Alkylated products can easily be distinguished by the proton shifts for the substituents. The O–CH_2 group appears at lower field (ca. 0.4 ppm) than N–CH_2 (Table 4). Similar effects are observed in the ^{13}C NMR spectra, where the difference between O–CH_2 and N–CH_2 for propyl and propargyl substituents is ca. 25 ppm (Table 5). Another indicator for the discrimination between N3- and O^4-substituted de-

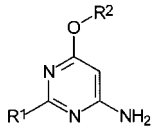
Table 3. Yields and Selected Analytical Data of Pyrimidine and Purine Derivatives **8–15**

Compound	Yield (%)	mp (°C)	MS (EI) *m/z* (%)	IR (KBr) ν (cm^{-1})
8	70	271[a]	–	–
9a	81	145	212.1 (100)	3289, 3154, 2959, 1695, 1583, 1498, 1262, 1088, 968, 787, 648
9b	87	172	209.1 (100), 153.9 (40), 135.9 (30)	–
10a	86	–[b]	–	–
10b	86	–[b]	–	–
11a	77	198	208.2 (50), 166.1 (100), 135.9 (80), 109.0 (40)	2964, 2535, 1699, 1563, 1526, 1391, 1200, 993, 619
11b	85	193	204.1 (100), 190.0 (50), 108.0 (30)	3256, 1698, 1563, 1524, 1381, 1277, 1204, 998
12a	30	154	–	–
12b	29	176	–	–
13a	30	186	–	–
13b	22	185	–	–
14a	75	137	236.2 (40), 194.1 (90), 178.1 (80), 151.9 (100)	–
14b	76	153	–	2969, 1712, 1680, 1388, 1206, 1122, 764
15a	58	257	236.2 (60), 194.1 (100), 178.1 (60), 152.1 (40), 123.0 (30), 109.1 (40)	–
15b	48	242		2649, 1676, 1442, 1301, 1121, 936, 769, 722

[a] Lit. [39] mp 275 °C.
[b] Compounds were not purified, raw products were subsequently used in the following step.

Table 4. ^{1}H NMR Spectral Data of Pyrimidine Derivatives





Compound	^{1}H NMR (DMSO-d_6) δ, *J* (Hz)			
	R^1	C6–NH_2[a] or C6=NH[b]	C5–H or R^3	R^2
5a	2.41	6.42	4.91	11.51
7a	2.38	6.56	5.41	0.89 (t, 3 H, CH_3) 1.63 (sext, 2 H, CH_2), 4.11 (t, 2 H, O-CH_2)
5b	–	6.66	5.41	11.61
7b	–	7.03	5.64	0.89 (t, 3 H, CH_3), 1.63 (sext, 2 H, CH_3), 4.06 (t, 2 H, O–CH_2)
5c	3.76	6.37	4.75	10.93
6c	3.66	6.32	4.84	0.80 (t, 3 H, CH_3), 1.47 (sext, 2 H, CH_2), 3.70 (t, 2 H, NCH_2)
6d	3.91	6.49	4.85	3.06 (t, 1 H, CH), 4.52 (d, 2 H, N–CH_2)
7c	3.74	6.49	5.41	0.85 (t, 3 H, CH_3) 1.69 (sext, 2 H, CH_2), 4.06 (t, 3 H, O-CH_2)
7d	3.75	6.64	5.41	3.43 (t, 1 H, CH), 4.94 (d, 2 H, O–CH_2)
9a	4.01	8.99	11.13[c]	0.88 (t, 3 H, CH_3), 1.61 (sext, 2 H, CH_2), 3.86 (t, 3 H, N-CH_2)
9b	4.07	9.19	11.15[c]	3.28 (t, *J* = 2.3, 1 H, CH), 4.70 (d, *J* = 2.3, 2 H, CH_2)
10a	3.82	5.63	3.38[d]	0.80 (t, 3 H, CH_3), 1.50 (sext, 2 H, CH_2), 3.76 (t, 2 H, N–CH^2)
10b	3.86	5.79	3.38[d]	3.06 (t, *J* = 2.4, 1 H, CH), 4.57 (d, *J* = 2.4, 2 H, CH_2)

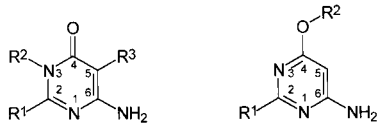
[a] All compounds except for **9a** and **9b**: s, 2H.
[b] Compounds **9a** and **9b**: s, 1 H.
[c] s, 1 H, C5=N–OH.
[d] s, 2 H, NH_2.

rivatives is the signal for the C5-hydrogen atom (Table 4). O^4-Substitution results in a downfield shift of ca. 0.5 ppm compared to unsubstituted or N3-substituted derivatives (Table 4). Furthermore, C4 is shifted downfield in *O*^{4}-alkylated compounds **7a–c** in comparison with *N*-alkylated or unsubstituted analogs **6c,d**, **5a–c**.

Bromo derivative **5b** exhibits shifts for C5–H at δ = 5.4 and for C4 at δ = 168, which is in the range of O^4-substituted rather than N3-substituted derivatives. This may be an indication that **5b** is present as the OH tautomer in dimethyl sulfoxide solution, while **5a** and **5c** appear to be present as NH tautomers according to the NMR spectral data (Table 4 and 5). Nitrosated products **9a** and **9b** may exhibit 5-hydroxyimino-4-oxo structure as shown in Scheme 2, or the tautomeric 4-hydroxy-5-nitroso structure.

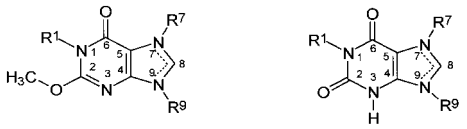
^{1}H and ^{13}C NMR spectral data for purine derivatives are listed in Table 6 and 7 and compared with data for paraxanthine **(1)**[8] and 9-methylxanthine, a commercially available 9-substituted xanthine derivative. The 2-methoxy substituent has a deshielding effect leading to a downfield shift of the 8-hydrogen (ca. 0.1–0.2 ppm) and other hydrogen atoms (Table 6), and also for the carbon atoms, connected to the methoxy group directly or by conjugation of double bonds (Table 7): C2 (ca. 3 ppm), C4 (5–7 ppm), C5 (ca. 4 ppm), and C8 (ca. 2 ppm). N7- and N9-Substituted isomers can be distinguished by the shifts of the 8-hydrogen in the ^{1}H NMR spectra. N9-Substitution causes an upfield shift in comparison with 9-unsubstituted, 7-substituted or 7-unsubstituted xanthines of ca. 0.2–0.3 ppm (Table 6). Thus, the 8-H signal of paraxanthine

Table 5. ^{13}C NMR Spectral Data of Pyrimidine Derivatives **5–10**



Compound	^{1}H NMR (DMSO-d_6) δ			
	R^1	C2, C4, C6	C5	R^2
5a	12.6	162.9, 163.5, 164.3	81.2	–
7a	13.0	165.1, 168.8, 169.6	81.5	10.2, 21.8, 66.9
5b	–	148.1, 165.9, 168.3	83.5	–
7b	–	150.2, 166.2, 169.3 (C4)	84.1	10.1, 21.7, 67.8
5c	54.0	158.2, 164.2, 164.2	79.3	–
6c	55.2	156.6, 162.0, 162.3	79.3	11.05, 21.4, 41.0
6d	55.4	155.9, 160.9, 162.1	79.3	28.7, 72.7, 78.5
7c	53.5	165.2, 166.9, 171.1 (C4)	79.8	10.2, 22.1, 67.0
7d	53.6	164.7, 167.0, 169.4	79.3	52.9, 77.2, 79.8
9a	56.7	148.3, 158.3, 161.7	142.9	11.1, 21.0, 42.2
9b	57.1	148.2, 157.4, 160.9	142.7	30.2, 74.0, 78.4
10a	54.7	147.0, 149.4, 157.4	102.6	11.0, 21.3, 42.0
10b	55.1	147.5, 149.0, 156.4	102.3	30.0, 73.1, 79.4

Table 6. ^{1}H NMR Spectral Data of Purine Derivatives



Compound	^{1}H NMR (DMSO-d_6) δ				
	C2–OCH_3 or N3–H[a]	R^1	R^7	R^9	C8–H
11a	3.95	0.81, 1.54, 3.88	–	–	7.94
11b	4.02	3.20, 4.73	7.91 (0.5 H)[a]/8.12 (0.5 H)[a]		7.99
12a	3.98	0.87, 1.59, 3.92	0.87, 1.78, 4.22	–	8.11
12b	3.98	3.20, 4.72	0.80, 1.80, 4.22	–	8.15
13a	3.96	0.84, 1.51, 3.85	–	0.84, 1.74, 3.98	7.86
13b	4.06	3.19, 4.72	–	0.84, 1.81, 4.01	7.95
14a	11.81	0.84, 1.53, 3.77	0.84, 1.73, 4.16	–	7.97
14b	11.93	3.06, 4.55	0.87, 1.78, 4.17	–	8.02
15a	12.21	0.85, 1.54, 3.78	–	0.85, 1.65, 3.97	7.70
15b	–[b]	3.06, 4.55	–	0.82, 1.67, 4.04	7.73
1	11.82	3.15	3.84	–	7.90
9-methylxanthine	11.92	10.74[a]	–	3.60	7.61

[a] Exchangeable.
[b] Signal could not be detected due to rapid exchange.

and analogs is found at ca. δ = 8.0 (compounds **1**, **14a**, **14b**) while that for isoparaxanthine analogs is found at δ = 7.7. The ^{13}C NMR spectra are also suitable for discrimination between regioisomers: the imidazole carbon atoms are shifted downfield by 9-alkylation, C4 (7–9 ppm), C5 (ca. 8 ppm), and C8 (5–6 ppm), in comparison with 9-unsubstituted xanthines with or without 7-substituent (Table 7).

In conclusion, we developed a general access to paraxanthine and isoparaxanthine analogs. The new compounds have been tested for pharmacological activity, and results from those studies will be published elsewhere.

Mps were measured with a Büchi 510 apparatus and were not corrected. The following instruments were used for recording spectra: IR: Perkin–Elmer 1750, MS: Varian MAT 711, ^{1}H and ^{13}C NMR: Bruker WP-80 or Bruker AC-250; DMSO-d_6 was used as solvent unless otherwise noted; TMS served as internal standard.
TLC was performed on silica gel coated aluminum plates 60 F_{254} (Merck). Compounds were detected by UV (254 nm) or by spraying with neutral, sat. $KMnO_4$ soln. As eluent mixtures of CH_2Cl_2 and MeOH (3:1; 9:1; or 99:1), or EtOAc, respectively, were used.
Satisfactory microanalyses were obtained for isolated compounds: C ±0.4, H ±0.40, N ±0.4, Br ±0.60, S ±0.26, unless otherwise indicated.
2-Substituted pyrimidin-4-one derivatives **5a–c** were prepared according to published procedures.[28–30]

6-Amino-2-methylthio-4-propoxypyrimidine (7a):
Method A: Compound **5a** (0.4 g, 2.5 mmol) was suspended in acetone (15 mL) and, after the addition of K_2CO_3 (1 g, 7.2 mmol) and PrI (0.4 mL, 4.1 mmol), heated to reflux for 14 h. Then, undissolved compound was filtered off. The filtrate was evaporated to dryness in vacuo and the oily residue recrystallized (EtOH). Alternatively, the volume of the filtrate was reduced in vacuo, and the product precipitated by the addition of water.

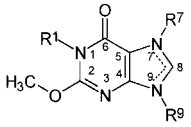
Method B: Compound **5a** (1.57 g, 10 mmol) was suspended in acetone (50 mL). After the addition of K_2CO_3 (4 g, 30 mmol), TEBAC (1.14 g, 5 mmol), and PrI (1.5 mL, 15 mmol) the mixture was heated to reflux for 7 h. Isolation of the product was performed as described above.

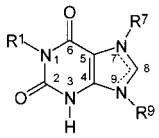
Method C: Compound **1** (0.8 g, 5.1 mmol) was dissolved in MeCN (20 mL). After the addition of K_2CO_3 (2 g, 14.5 mmol), TEBAC (0.57 g, 2.5 mmol), and PrI (0.9 mL, 9 mmol), the mixture was stirred for 4.5 h at 85 °C. Isolation of the product was performed as described above.
IR (KBr): ν = 3414, 3169, 2959, 1646, 1512, 1285, 1213, 1067, 809 cm^{-1}.
MS (EI): *m/z* (%) = 199 (40), 157 (100).

6-Amino-2-bromo-4-propoxypyrimidine (7b):
To a suspension of **5b** (1 g, 5 mmol), K_2CO_3 (2 g, 15 mmol), and TEBAC (0.57 g, 2.5 mmol) in acetone (25 mL) was added PrI (1 mL, 10 mmol) and the mixture was heated to reflux for 12 h. Then, the volume was reduced in vacuo to ca. 10 mL and water (50 mL) was added. The mixture was cooled to 4 °C for 2 h and the precipitate was collected by filtration.
IR (KBr): ν = 3307, 3164, 2965, 1641, 1591, 1264, 1216, 1040, 801 cm^{-1}.

6-Amino-2-methoxy-3-propylpyrimidin-4(3*H*)-one (6c) and 6-Amino-2-methoxy-4-propoxypyrimidine (7c):
Compound **5c** (5.65 g, 40 mmol) was dissolved in acetone (200 mL). After the addition of K_2CO_3 (16.6 g, 0.12 mol), TEBAC (4.56 g, 20 mmol) and PrI (6 mL, 62 mmol) the mixture was heated to reflux for 12 h. After cooling insoluble salts were filtered off and the volume of the filtrate reduced by rotary evaporation to a clear, saturated solution. Silica gel (ca. 2 g, 0.05–2 mm) was added and the solvent was

Table 7. ^{13}C NMR Spectral Data of Selected Purine Derivatives





Compound	^{13}C NMR (DMSO-d_6) δ								
	2-OCH_3	R^1	R^7	R^9	C2	C4	C5	C6	C8
11a	55.7	11.0, 21.2, 42.2	–	–	154.2	151.3	114.0	155.0	139.7
12a	55.7	11.0, 21.3, 42.2	10.5, 23.9, 47.6	–	153.9	153.9	109.9	155.3	144.0
12b	56.0	30.1, 73.5, 78.9	10.5, 23.8, 47.7	–	153.3	153.0	109.7	155.5	144.4
13a	55.9	11.0, 21.2, 42.2	–	10.9, 22.7, 44.5	154.7	146.6	118.5	156.2	139.3
13b	56.3	30.2, 73.4, 79.0	–	10.9, 22.6, 44.6	154.2	146.8	118.3	155.3	139.7
14a	–	11.1, 20.8, 41.2	10.5, 23.6, 47.5	–	150.8	147.7	105.9	155.0	142.6
14b	–	29.2, 72.5, 79.8	10.5, 23.5, 47.6	–	150.5	148.1	105.7	154.3	143.1
15a	–	11.2, 20.8, 41.4	–	10.5, 23.0, 45.2	150.7	138.6	115.0	157.3	137.0
15b	–	29.4, 72.4, 80.0	–	10.5, 23.0, 45.3	150.4	139.7	114.7	156.6	137.4
1	–	26.7	32.9	–	151.1	147.7	106.5	155.3	143.0

slowly and carefully removed by rotary evaporation in order to obtain a homogenous mixture of compounds and silica gel.

Separation of Isomers by Dry Column Chromatography:
A straight-sided sintered glass filter (height: 6 cm, radius: 7 cm) was filled with silica gel H (Stahl) (ca. 100 g). During the process of filling, vacuum was applied and at the same time the silica gel was pressed from above by means of a flat tool in order to obtain a dense, regular packing of the stationary phase. The silica gel was conditioned with the more lipophilic component of the eluent, petroleum ether. Then, the mixture of products and silica gel was added to the top of the column applying the same technique as described for the filling of the column. The height of this layer should only be a few millimeters, max 0.5 cm, and the layer must be even and uniform. Elution was performed first with petroleum ether, then with petroleum ether containing increasing proportions of EtOAc (5% steps). The more lipophilic compound **7c** was eluted first. Isomer **6c** was finally obtained by elution with pure EtOAc. The solutions were evaporated to dryness. The obtained, relatively pure products were recrystallized from acetone, MeOH or EtOH, respectively.

6-Amino-2-methoxy-3-(prop-2-ynyl)pyrimidin-4(3*H*)-one (6d) and 6-Amino-2-methoxy-4-(prop-2-ynyloxy)pyrimidine (7d):
6-Amino-2-methoxypyrimidin-4(3*H*)-one **(5c)** (5.65 g, 40 mmol) was suspended in acetone (200 mL) and finely ground K_2CO_3 (16.6 g, 1.12 mol), TEBAC (4.56 g, 20 mmol) and prop-2-ynyl bromide (5–6 mL, ca. 60 mmol) were added. The mixture was heated to reflux for 1 h on a water bath. Isolation and purification was achieved as described for compounds **6d** and **7d**.

6d:
IR (KBr): ν = 3353, 3192, 1647, 1571, 1469, 1366, 1143, 1051, 953, 813 cm^{-1}.
MS: *m/z* (%) = 179.1 (10), 156.1 (90), 126.0 (100), 110.9 (50), 69.1 (40), 43.0 (40).

7d:
IR (KBr): ν = 3462, 3297, 3150, 1645, 1572, 1467, 1431, 1365, 1343, 1205, 1051 cm^{-1}.
MS**:** *m/z* (%) = 180.1 (10), 178.1 (100), 120.8 (40), 111.1 (80), 109.7 (90), 82.1 (40), 67.0 (50).

6-Amino-3-propyluracil (8):
Compound **6c** (0.5 g, 2.7 mmol) was dissolved in concd HCl (4 mL) and the mixture was stirred at r.t. for 15 h. Then the solution was neutralized by the addition of sat. $NaHCO_3$, the volume was reduced by rotary evaporation, and the formed precipitate was collected by filtration.
^{1}H NMR (DMSO-d_6): δ = (compare ref.[39])
0.79 (t, 3H, CH_3); 1.40 (sext., 2H, CH_3–CH_2–); 3.59 (t, 2H, N–CH_2); 4.55 (s, 1H, C5-H); 6.19 (br s, 2H, C6-NH_2); 10.35 (s, 1H, N1-H).
^{13}C NMR (DMSO-d_6): δ = 11.1 (CH_3); 20.9 (CH_3–CH_2–); 40.2 (N–CH_2); 74.2 (C5); 151.0 (C2); 153.6 (C6); 163.1 (C4).

5-Hydroxyimino-6-imino-2-methoxy-3-propylpyrimidin-4(3*H*)-one (9a) and 5-Hydroxyimino-6-imino-2-methoxy-3-(prop-2-ynyl)pyrimidin-4(3*H*)-one (9b); General Procedure:
Aminouracil **6c**, or **6d**, respectively, (5 mmol) was suspended in water (20 mL) and the mixture was heated to a temperature of 50–55 °C on a water bath. AcOH (4 mL) was added, the mixture was stirred until a clear solution was obtained, and then sat. aq $NaNO_2$ (0.6 g, 8.7 mmol) was added slowly over 20 min. Initially the color of the solution turned violet. After the addition of about half of the $NaNO_2$, **9b** started to precipitate as blue crystals, while **9a** remained in solution. The mixture was stirred for a further 30 min, and **9b** was collected by filtration. For the isolation of **9a** the volume of the mixture was reduced by rotary evaporation until the product crystallized and was collected by filtration. The products were washed with water and dried in a vacuum desiccator.

5,6-Diamino-2-methoxy-3-propylpyrimidin-4(3*H*)-one (10a) and 5,6-Diamino-2-methoxy-3-(prop-2-ynyl)pyrimidin-4(3*H*)-one (10b); General Procedure:
Compound **9a**, or **9b**, respectively (5 mmol) was suspended in water (15 mL) and cooled to 4 °C upon stirring. A solution of $Na_2S_2O_4$ (7 g, 40 mmol) in water (20 mL) was added over a period of 20 min. The volume of the discolored solution was reduced by rotary evaporation until product started to precipitate. The mixture was again cooled to 4 °C and the precipitate was collected by filtration and washed with cold water. The volume of the filtrate was reduced again, cooled, and a second precipitate was collected.

2-Methoxy-1-propylpurin-6-one (11a) and 2-Methoxy-1-(prop-2-ynyl)purin-6-one (11b):
Compound **10a** or **10b**, respectively, (5 mmol) was suspended in triethyl orthoformate (15 mL) and stirred at 100–125 °C for 4 h. After cooling, the formed precipitate was filtered off, and washed with Et_2O.
11b: Anal. calcd C 52.94, found 52.27.

2-Methoxy-1,7-dipropylpurin-6-one (12a), 2-Methoxy-1,9-dipropylpurin-6-one (13a), 2-Methoxy-7-propyl-1-(prop-2-ynyl)purin-6-one (12b), 2-Methoxy-9-propyl-1-(prop-2-ynyl)purin-6-one (13b); General Procedure:
Compound **11a** (for **12a**,**13a**) or **11b** (for **12b**,**13b)**, respectively, (4 mmol), was dissolved in acetone (10 mL). After the addition of K_2CO_3 (1.6 g, 12 mmol), TEBAC (0.45 g, 2 mmol) and PrI (1 mL, 10 mmol) the mixture was heated to reflux on a water bath for 4 h. After cooling, insoluble salts were filtered off and the solvent was removed by rotary evaporation.

Separation of Isomers by Dry Column Chromatography:
A straight-sided, sintered glass filter (height: 5 cm, radius: 5.5 cm) was filled with silica gel H (according to Stahl) with application of vacuum. Compression of the silica gel was increased by pressing the top surface using a flat tool. The silica gel was washed with petroleum ether several times. Then, the mixture of products, dissolved in acetone (5–7 mL), was carefully poured on the column with the application of vacuum. Elution was performed under vacuum, first with petroleum ether (3 fractions of 40 mL each), then with petroleum ether containing increasing proportions of EtOAc (5% steps, 20 fractions of 40 mL each) and finally with EtOAc (20 fractions of 40 mL each). The more lipophilic 7-substituted isomers were eluted with mixtures of petroleum ether and EtOAc, while the more polar 9-substituted isomers were eluted with pure EtOAc. The product containing fractions were evaporated to dryness.
12b: Anal. calcd H 5.73, found 5.21.
13a: Anal. calcd C 57.58, found 57.01, N calcd 22.39, found 21.88.
13b: Anal. calcd N 22.75, found 22.21.

1,7-Dipropylxanthine (14a), 1,9-Dipropylxanthine (15a), 7-Propyl-1-(prop-2-ynyl)xanthine (14b), and 9-Propyl-1-(prop-2-ynyl)-xanthine (15b); General Procedure:
Compound **12a** (for **14a**), **12b** (for **14b**), **13a** (for **15a**) or **13b** (for **15b**), respectively, (0.8 mmol) was dissolved in water (2 mL), and concd HCl (4 mL) was added. The resulting clear solution was heated on an oil bath to 120 °C (**12a**, **13a**), or 90 °C (**12b**, **13b**), respectively, for 1.5 h. After cooling, a pH value of 5–6 was obtained by the addition of sat. aq $NaHCO_3$. The formed white precipitate was collected by filtration. The volume of the filtrate was reduced by rotary evaporation and further precipitate was obtained and filtered off.
15b: Anal. calcd C 56.87, found 56.12.

Semiempirical Calculations:
Molecules were built using the molecular modelling program Sybyl®[40] on an Evans & Sutherland ESV 3/32 graphics workstation. The structures, electronic densities and heats of formation were calculated with the parameter set PM3 as implemented in the program package MOPAC 6.0[37, 41] on a convex C3860 computer server. The keywords "PRECISE T=3600 NOINTER PM3 ESP" were used. The program integration and network setup was performed by using the molecular modelling integration platform marvin.[42] The atomic point charges were derived, using the ESP-algorithm of Besler, Merz and Kollman.[43]

We would like to thank Katharina Bauer for supplying and pre-processing the three-dimensional molecular structures and for assistance in the molecular modelling studies. MP was on leave from the Jagiellonian University of Cracow, Collegium Medicum, Department of Pharmaceutical Chemistry, Cracow, Poland, with support of the DFG (Deutsche Forschungsgemeinschaft), which is gratefully acknowledged. C.E.M. is grateful for support given by the Fonds der Chemischen Industrie.

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