Monatshefte für Chemie 116, 341—351 (1985)

Monatshefte für Chemie
Chemical Monthly

2,6-Dialkoxy-7-methylpurines

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(Received 15 December 1983. Revised 17 April 1984. Accepted 8 May 1984)

The preparation of unsymmetrical 2,6-dialkoxy-7-methylpurines (**2**), and 2-alkoxy-1,7-dialkyl-6-oxo-1,6-dihydropurines (**5**) is described. In contrast to **1** and **2**, a facile thermal lactim-lactam rearrangement from hypoxanthines **5** and **7** into xanthines **6** was observed.

(Keywords: Nucleophilic heteroaromatic substitution; Thermal lactim-lactam rearrangement; [1,3] Sigmatropic shifts; Dialkoxy-7H-purines; Dialkyl-1H (or 3H), 7H-hypoxanthines; Trialkyl-7H-xanthines)

2,6-Dialkoxy-7-methylpurine

Die Darstellung von unsymmetrischen 2,6-Dialkoxy-7-methylpurinen (**2**) und 2-Alkoxy-1,7-dialkyl-6-oxo-1,6-dihydropurinen (**5**) wird beschrieben. Im Gegensatz zu den Verbindungen **1** und **2** erfolgt die thermische Lactim-Lactam-Umlagerung der Hypoxanthine **5** und **7** zu den Xanthinen **6** glatt.

Introduction

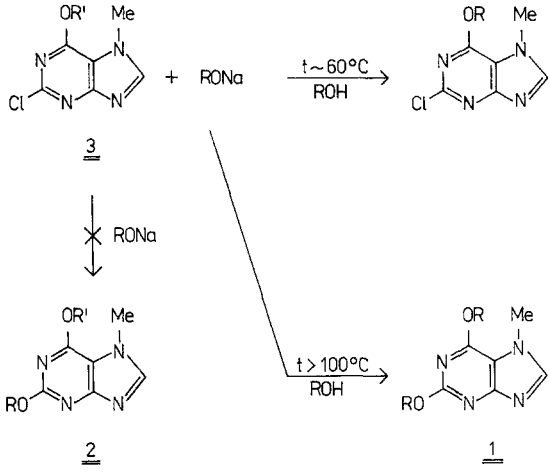
2,6-Dialkoxy-7-methylpurines **1** can serve as a source for the preparation of some important pharmacologically active 7*H*-xanthine derivatives[1–3]. The lactim-lactam rearrangement of dialkoxypurines **1** and **2**[1,2] seems to be a rather simple way of transforming these compounds into dialkylxanthines **6**. For this purpose we have synthetized several 2,6-dialkoxypurines of type **1** and **2** as well as hypoxanthines **5** and have attempted their direct transformation into xanthines **6**.

Results and Discussion

Synthesis of Purines **1** *and Hypoxanthines* **5**

The synthesis of only a few symmetrical 2,6-dialkoxy-7-methylpurines (**1**) – based on the reaction of 2,6-dichloro-7-methylpurine **8** with sodium alkoxide – has hitherto been described[1–3]. We had expected that unsymmetrical 2,6-dialkoxy-7-methylpurines (**2**) could be obtained from 2-chloro-6-alkoxy-7-methylpurines (**3**) and an equimolar amount of sodium alkoxide in alcoholic solution (Scheme 1).

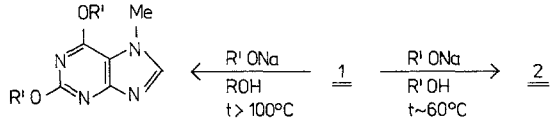
Scheme 1



The reaction proceeded however (at a temperature of about 60 °C) via an exchange of the 6-alkoxy group to yield another 2-chloro-6-alkoxy-7-methylpurine, in which the 2-chlorine substituent remained unaffected. At higher temperatures both the 6-alkoxy and 2-chlorine substituents were replaced by alkoxide ions with good yields, resulting in sym. 2,6-dialkoxy-7-methylpurines (**1**).

The reactivity of the 6-alkoxy substituent suggested that unsymmetrical 2,6-dialkoxy-7-methylpurines (**2**) might be prepared using symmetrical derivatives as substrates (Scheme 2).

Scheme 2



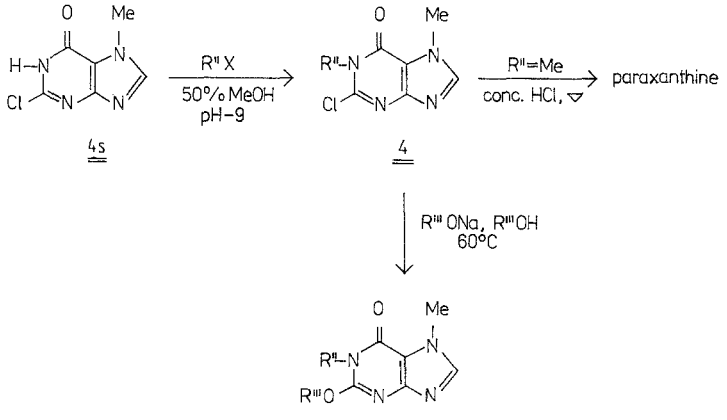
It has been found that at temperatures below 60 °C the unsymmetrical derivatives **2** were formed; when however the reaction temperature exceeded 60 °C the formation of symmetrical compounds **1** predominated. Two series of transformations of symmetrical dialkoxypurines **1** into unsymmetrical dialkoxypurines **2** were performed using the following substrates: for the first series the dimethoxy compound **1 a** and sodium alkoxide ($R = Et$, *n-Pr*, *i-Bu*, allyl) and for the second series dialkoxypurines **1 b**–**1 e** (R = *Et*, *n-Pr*, *i-Bu*, allyl) and sodium methoxide. Better yields of unsymm. dialkoxypurines **2** were obtained in the second series probably for steric reasons with the MeO^- ion being more reactive. The formation of unsymm. dialkoxypurines **2** was accompanied by the formation of high-melting products (m. p. 360 °C, ca. 10–15% of the obtained dialkoxypurines).

A comparison of the ^{1}H-NMR spectra of 2,6-dimethoxy-(**1 a**) 2-methoxy-6-ethoxy (**2 a**) and 6-methoxy-2-ethoxy-7-methylpurines (**2 e**) offers the possibility to resolve these spectra. α-Alkoxy-protons of the 6-alkoxy substituent were found to be more deshielded than 2-alkoxy ones.

Acid hydrolysis of all dialkoxypurines **1** and **2** yielded 7-methylxanthine. Attempts of alkaline hydrolysis failed since no formation of the previously reported[8] type of hypoxanthines **5** (R = H) was observed.

2-Alkoxy-1-alkyl-7-methyl-6-oxo-1,6-dihydropurines (**5**) were obtained by the action of sodium alkoxide on 2-chloro-6-oxo-1-alkyl-7-methylpurine (**4**) (see Scheme 3).

Scheme 3



N-1 alkylation of chlorohypoxanthine (**4**) was found to be the step which limits the effectivness of this process. Alkylation of the N-1 position with dimethyl sulfate in a 50% water-methanol solution at *pH*-9 gave the dimethyl compound **4a** with a yield of up to 51%. Thus, it becomes possible to obtain paraxanthine, starting from theobromine via 2,6-dichloro-7-methylpurine (**8**) with a total yield of 25%, whereas the total yield of paraxanthine obtained in the same way according to Ref.[5] was only 8.5%.

The structures of the 2-alkoxy-hypoxanthines **4** and **5** were confirmed by acid hydrolysis giving 1,7-dialkyl-xanthines.

It should also be noted that the 2-chlorine substituent in hypoxanthine derivatives such as 6-oxo-1,6-dihydropurine (**4**) and 2-chloro-3,7-dimethyl-6-oxo-3,6-dihydropurine is more reactive toward sodium alkoxides than in purines **3** or **8**.

Attempts of a Lactim-Lactam Rearrangement

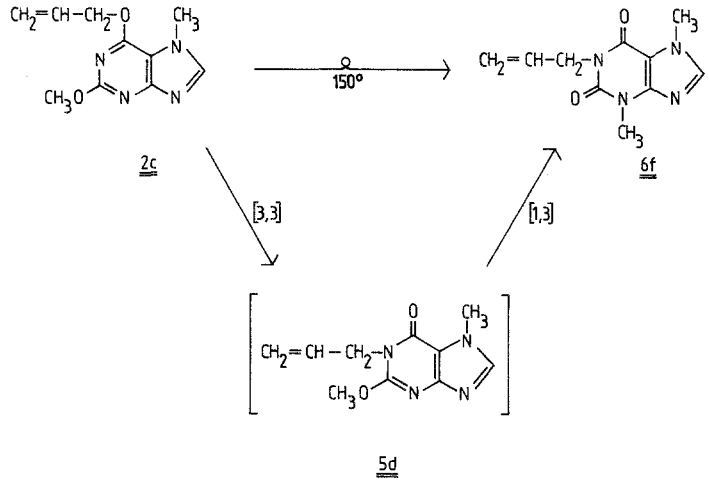
It has been shown that the thermally induced lactim-lactam rearrangement proceeds smoothly only in the case of 2,6-dimethoxy-7-methylpurine (**1a**) at 22 °C[1] and some allylic-type of symm. dialkoxy-7-methylpurines (150–160 °C)[2]. If ethoxy- and propoxy-substituents were present, a decomposition of dialkoxy-7-methylpurines took place. Similar results were obtained in the case of unsymm. 2,6-dialkoxy-7-methylpurines **2a**, **2b**, **2d**, **2e**, **2f** and **2h** which decomposed at 220 °C to give alkylamines; in the reaction mixtures the expected xanthines **6** could be detected by TLC and ^{1}H-NMR.

Interesting results were found in the rearrangement of methoxy-allyloxypurines **2c** and **2g**: The rearrangement of 6-allyloxy-2-methoxy-7-methylpurine (**2c**) proceeded as easily as with the 2,6-diallyloxy derivative (**1d**) at 150–160 °C with the formation of 1-allyl-3,7-dimethylxanthine (**6f**). A mechanistic sequence in the formation of **6f** from **2c** can be formulated with hypoxanthine **5d** as an intermediate, formed in the allylic hetero-*Claisen* rearrangement[6], proceeding as thermal [3,3] sigmatropic shift. The final product **6f** would then arise from **5d** as a result of the O^2-N-3 methyl-migration proceeding as a thermal [1,3] sigmatropic shift (Scheme 4).

The sequence **2c**→**5d**→**6f** suggests that hypoxanthines **5** are transformed into xanthines **6** more easily than dialkoxypurines **1** or **2**.

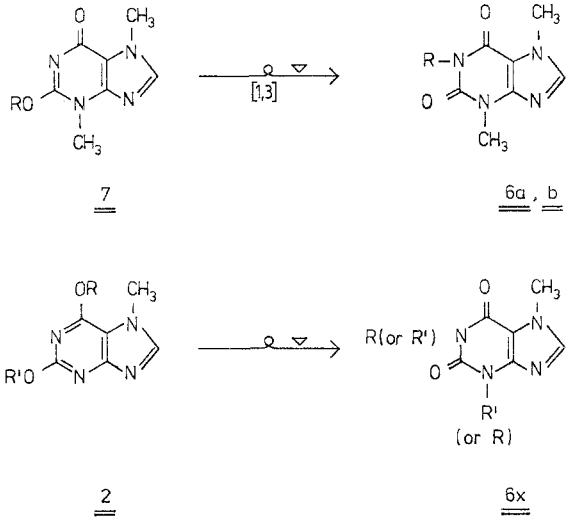
This hypothesis seems to be supported by the results of the lactim-lactam rearrangement of hypoxanthines **5b** and **5c** proceeding (O^2–N-3 alkyl migration) already at a temperature of 160–170 °C with the formation of trialkyxanthines **6a** and **6b** in yields of 50% (calc. per converted **5**). We have however also found, that the isomeric

Scheme 4



hypoxanthine-system **7** undergoes a rearrangement to give 1-alkyltheobromines **6d, 6e** (O^2–N-1 alkyl migration) as facile as **5b** and **5c** (Scheme 5).

Scheme 5



Taking into account the known thermal O→N alkyl rearrangement of 2,4-dialkoxypyrimidines[7], 4-alkoxypyridines[8] or quinolines[9] and the rearrangement of 2,6-dimethoxy- and 2,6-diallyloxy-7-methylpurines mentioned above[1,2] one may conclude that the transformation of purines **1 a** and **2** into the trialkylxanthine system **6 x** may proceed with O^6–N-1, O^2–N-3, O^2–N-1 alkyl migrations (thermal [1,3]sigmatropic shifts) and O^6→N-3 alkyl migration (thermal [1,5] sigmatropic shift). The results of the rearrangement of 2,6-diallyloxy-type purine derivatives, however, ought to be classified as thermal [3,3] sigmatropic shifts only. In the case of 6-allyloxyguanines O^6–N-3, O^6–N-7 and O^6–C-8 anionic pentenyl migrations were observed[10,11]; the O^6–N-3 and O^6–C-8 migrations were assumed to proceed via C-5 by two anionic [3,3] sigmatropic shifts, but O^6–N-7 migration was an anionic [3,3] one, followed by anionic [3,2] sigmatropic shifts.

In the course of our experiments in the case of **2 c**, **5 a**, **b**, **c**, **7 a**, **b**, and **c** O^2–N-3, O^2–N-1 alkyl and O^6–N-1 allyl migrations were observed, whereas in the rearrangement of **2 g** into xanthine **6 c** O^6–N-1 methyl and O^6–N-3 allyl migrations were found.

Considering all the observed types of O-alkyl N-alkyl migrations, the rearrangement of unsymm. 2,5-dialkoxy-7-methylpurines (**2**) will furnish all four possible trialkyxanthines **6 x**. This explains the problems of isolating pure compounds from the products of the rearrangement of dialkoxypurines **2**.

Experimental

The m.p.'s (uncorr.) were determined on a heated *Boetius* table. The ^{1}H-NMR spectra were recorded on a Varian Anaspect EM 360 spectrometer at 60 MHz in $CDCl_3$ solutions, *TMS* being applied as an internal standard. The mass spectra were taken on a LKB 9000 mass spectrometer at 15 and 70 eV and at a temp. of 60–100°. TLC analyses were performed employing Merck's silica gel G and a solution of methanol-chloroform 1 : 1 (*v/v*) as the developing system, chromatograms were visualised in UV light or by iodine vapour.

The substrates and standards were prepared by the reported methods: 2,6-dichloro-7-methylpurine **8**[4]; compounds **3 a** (*R′ = Me*)[1] and **3 b** (*R′ = Et*)[5]; compound **4 s**[5]; 2-chloro-3,7-dimethyl-6-oxo-3,6-dihydropurine[14]; compounds **7 a** (*R = Me*)[14], **7 b** (*R = Et*)—m.p. 149–151°, ^{1}H-NMR (δ, ppm): CH_2CH_2O 1.25 (t, $J = 6$ Hz, 3 H), CH_3CH_2O 4.35 (q, $J = 6$ Hz, 2 H), N_3-CH_3 3.45 (s, 3 H), N_7-CH_3 3.85 (s, 3 H), C_8-H 7.41 (s, 1 H), obtained according to[14], as well as in the way presented in sec. 1, **7 c** (*R = n-Pr*)[14]. N-alkyl-N′, N″-dimethyl-7 H-xanthines **6**: **6 a** (*R = Me, R′ = Et*)[12], **6 b** (*R = Me, R′ = n-Pr*)[15], **6 c** (*R = Me, R′* = allyl)[12], **6 d** (*R = Et, R′ = Me*)[12], **6 e** (*R = n-Pr, R′ = Me*)[16], **6 f** (*R* = allyl, *R′ = Me*)[13] were prepared from theobromine or paraxanthine, respectively.

1. Reaction of 2-Chloro-6-alkoxypurines **3** *or 2-Chloro-1-alkyl-7-methyl-6-oxo-1,6-dihydropurine* **4** *with Sodium Alkoxides*

Equimolar amounts (5 mmol) of 2-chloro-6-alkoxy-7-methylpurine **3** or 2-chloro-1-alkyl-7-methyl-6-oxo-1,6-dihydropurine **4** and sodium alkoxide in 30 ccm of anhydrous alcohol were stirred at 60° for 2 h. The alcohol was then distilled off in a vacuum and the residue was treated with 40 ccm of water and

neutralized with dil. hydrochloric acid. The resultant mixture was extracted with chloroform (3 × 15 ccm), the extracts being dried with anhydrous sodium sulfate, the solvent was then vacuum-evaporated at waterbath temperature. For the results see Table 1.

Table 1

Substrate				Product						
No.	*R'*	*R''*	*R'''* (alcohol)	No.	*R'*	*R''*	*R'''*	Yield %	m.p. °C	Ref.
3a	*Me*			**3b**	*Et*			75	240–242	[1]
3b	*Et*			**3d**	*Me*			83	215–217	[5]
4a		*Me*	*Me*	**5a**		*Me*	*Me*	77	188–190	
4a		*Me*	*Et*	**5b**		*Me*	*Et*	60	150–153	
4a		*Me*	*n-Pr*	**5c**		*Me*	*n-Pr*	45	86–88	

5a: ^{1}H-NMR (δ, ppm): N_7-CH_3 3.42 (s, 3 H); C_2-OCH_3 3.96 (s, 3 H); N_1-CH_3 4.04 (s, 3 H); C_8-H 7.63 (s, 1 H).

MS (70 eV): $m/e = 194$ (M^+, 100%).

5b: ^{1}H-NMR (δ, ppm): $C_2-OCH_2\mathbf{CH_3}$ 1.25 (t, $J = 6$ Hz, 3 H); $C_2-O\mathbf{CH_2}CH_3$ 4.35 (q, $J = 6$ Hz, 2 H); N_7-CH_3 3.30 (s, 3 H); N_1-CH_3 3.85 (s, 3 H); C_8-H 7.60 (s, 1 H).

MS (15 eV): $m/e = 208$ (M^+, 98%), 180 (M-C_2H_4, 100%).

5c: ^{1}H-NMR (δ, ppm): $C_2-OCH_2CH_2\mathbf{CH_3}$ 0.90 (t, $J = 6$ Hz, 3 H); $C_2-OCH_2\mathbf{CH_2}CH_3$ 1.65 (m, $J = 6$ Hz, 2 H); $C_2-O\mathbf{CH_2}CH_2CH_3$ 4.30 (t, $J = 6$ Hz, 2 H); N_7-CH_3 3.30 (s, $J = 6$ Hz, 3 H); N_1-CH_3 3.85 (s, 3 H); C_8-H 7.70 (s, 1 H).

MS (70 eV): $m/e = 222$ (M^+, 35%), 180 (M-C_3H_6, 100%).

5d*: ^{1}H-NMR (δ, ppm): N_7-CH_3, C_2-OCH_3, $N_1-CH_2CH=CH_2$ 3.75–4.15 (m, 8 H); $N_1-CH_2\mathbf{CH}=\mathbf{CH_2}$ 4.25–6.1 (m, 3 H); C_8-H 7.55 (s, 1 H).

MS (70 eV): $m/e = 220$ (M^+, 25%), 180 (M-C_3H_4, 100%).

The products resulting from the reaction performed in *Carius* tubes in alcohol solution were isolated in the same way: the reaction of compound **3a** and sodium ethoxide (100°, 3 h) yielded 2,6-diethoxy-7-methylpurine **1b** (57%), the reaction of **3b** and sodium methoxide (120°, 2 h) yielded 2,6-dimethoxy-7-methyl-purine **1a** (77%).

2. Symmetrical 2,6-Dialkoxy-7-methylpurines **1**

Symmetrical 2,6-dialkoxy-7-methylpurines **1** were prepared from the dichloro-compound **8** (40 g, 0,2 mol) and sodium alkoxide (0,42 mol) in 500 ccm of anhydrous alcohol by heating them in a 1 dm^3 rocking steel autoclave. After cooling, the solid was filtered off. The filtrate was vacuum-evaporated to dryness in a rotary evaporator. The residue – crude 2,6-dialkoxy-7-methylpurine (**1**) – was crystallized from alcohol or xylene. The results are listed in Table 2.

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* The compound was prepared from 2-chloro-7-methyl-6-oxo-1,6-dihydropurine 10 mmol, allyl bromide 10 mmol and sodium methoxide 20 mmol in anhydrous methanol. The product was isolated as presented above; yield 20%, m.p. 85–87° (from methanol).

Table 2

No.	*R*	Temp. °C	Time	Yield %	M.p. °C	Ref. m.p. °C
1a	*Me*	100	2 h	80	198–190	199[1]
1b	*Et*	115–120	3 h	76.5	146–148	147–149[3]
1c	*n-Pr*	130–140	12 h	77	88–90	92[2]
1d	allyl	100	3 h	40	104–106	111–112[2]
1e	*i-Bu*	135–140	18 h	46[a]	93–95	

[a] The reaction was carried out in *Carius* tubes.

1e: ^{1}H-NMR (δ, ppm): $-OCH_2CH(CH_3)_2$ 0.9 (d, $J=6$ Hz, 12 H); $-OCH_2CH(CH_3)_2$ 2.0 (m, $J=6$ Hz, 2 H); $-OCH_2CH(CH_3)_2$ 4.1 (d, $J=6$ Hz, 4 H); N_7-CH_3 3.75 (s, 3 H); C_8-H 7.7 (s, 1 H).

MS (70 eV): $m/e = 278$ (M^+, 19%), 166 ($M-2\times CH_4H_8$, 100%).

3. Unsymmetric 2,6-Dialkoxy-7-methylpurines **2**

Reactions were performed as presented in sec. 1 starting from the symmetric 2,6-dialkoxy compound **1** (5 mmol) and sodium alkoxide solution prepared from 11 mmol of sodium and 30 ccm of anhydrous alcohol. The product was crystallized from acetone, hexane or ether (see Table 3).

Table 3

No.	Products		M.p. °C	Yield %
	R	*R'*		
2a	*Me*	*Et*	183–185	75
2b	*Me*	*n-Pr*	125–127	80
2c	*Me*	allyl	130–132	80
2d	*Me*	*i-Bu*	141–143	72
2e	*Et*	*Me*	160–162	84
2f	*n-Pr*	*Me*	148–151	82
2g	allyl	*Me*	96–98	77
2h	*i-Bu*	*Me*	170–172	79

2a: ^{1}H-NMR (δ, ppm): $C_6-OCH_2CH_3$ 1.2 (t, $J=6$ Hz, 3 H); $C_6-OCH_2-CH_3$ 4.25 (q, $J=6$ Hz, 2 H); N_7-CH_3 3.75 (s, 3 H); C_2OCH_3 3.85 (s, 3 H); C_8-H 7.7 (s, 1 H).

MS (70 eV): $m/e = 208$ (M^+, 100%).

2b: ^{1}H-NMR (δ, ppm): $C_6OCH_2CH_2CH_3$ 0.85 (t, $J=6$ Hz, 3 H); $C_6-OCH_2CH_2CH_3$ 1.65 (m, $J=6$ Hz, 2 H); $C_6-OCH_2CH_2CH_3$ 4.25 (t, $J=6$ Hz, 2 H); N_7-CH_3 3.75 (s, 3 H); C_2-OCH_3 3.85 (s, 3 H): C_8-H 7.7 (s, 1 H).

MS (70 eV): $m/e = 222$ (M^+, 58%), 180 (M-C_3H_6, 100%).

2c: ^{1}H-NMR (δ, ppm): N_7-CH_3, C_2-OCH_3, $C_6-OCH_2CH=CH_2$ 3.75–3.97 (m, 8H); $C_6-OCH_2CH=CH_2$ 4.7–6.7 (m, 3H); C_8-H 8.2 (s, 1H).

MS (70 eV): $m/e = 220$ (M^+, 100%).

2d: ^{1}H-NMR (δ, ppm): $C_6-OCH_2CH(CH_3)_2$ 0.9 (d, $J = 6$ Hz, 6H); $C_6-OCH_2CH(CH_3)_2$ 1.95 (m, $J = J = 6$ Hz, 1H); $C_6-OCH_2CH(CH_3)_2$ 4.1 (d, $J = 6$ Hz, 2H); N_7-CH_3 3.85 (s, 3H); C_2-OCH_3 4.0 (s, 3H); C_8-H 8.1 (s, 1H).

MS (70 eV): $m/e = 236$ (M^+, 25%), 180 (M-C_4H_8, 100%).

2e: ^{1}-NMR (δ, ppm): $C_2-OCH_2CH_3$ 1.2 (t, $J = 6$ Hz, 3H); $C_2-OCH_2CH_3$ 4.25 (q, $J = 6$ Hz, 2H); $N-CH_3$ 3.75 (s, 3H); C_6-OCH_3 3.9 (s, 3H); C_8-H 7.7 (s, 3H).

MS (70 eV): $m/e = 208$ (M^+, 39%), 193 (M-CH_3, 100%).

2f: ^{1}H-NMR (δ, ppm): $C_2-OCH_2CH_2CH_3$ 0.85 (t, $J = 6$ Hz, 3H); $C_2-OCH_2CH_2CH_3$ 1.65 (m, $J = 6$ Hz, 2H); $C_2-OCH_2CH_2CH_3$ 4.2 (t, $J = 6$ Hz, 2H); N_7-CH_3 3.75 (s, 3H); C_6-OCH_3 3.95 (s, 3H); C_8-H 7.7 (s, 1H).

MS (70 eV): $m/e = 222$ (M^+, 12%), 180 (M-C_3H_8, 100%).

2q: ^{1}H-NMR (δ, ppm): N_7-CH_3, C_6-OCH_3, $C_2-OCH_2CH=CH_2$ 3.75–3.95 (m, 8H); $C_2-OCH_2CH_2CH=CH_2$ 4.8–5.5 (m, 3H), C_8-H 7.75 (s, 1H).

MS (70 eV): $m/e = 220$ (M^+, 51%), 205 (M-CH_3, 100%).

2n: ^{1}H-NMR (δ, ppm): $C_2-OCH_2CH(CH_3)_2$ 0.9 (d, $J = 6$ Hz, 6H); $C_2-OCH_2CH(CH_3)_2$ 1.85 (m, $J = 6$ Hz, 1H); $C_2-OCH_2CH(CH_3)_2$ 4.1 (d, $J = 6$ Hz, 2H); N_7-CH_3 3.75 (s, 3H); C_6-OCH_3 3.85 (s, 3H); C_8-H 7.7 (s, 1H).

MS (70 eV): $m/e = 236$ (M^+, 48%), 180 (M-C_4H_8, 100%).

4. Synthesis of Paraxanthine

6.5 g (55 mmol) of dimethyl sulfate and 5.5 ccm (55 mmol) of a 20% aqueous solution of potassium hydroxide were added dropwise to a solution of 2-chloro-6-oxo-1,6-dihydro-7-methylpurine (50 mmol) in 100 ccm of a 50% water-methanol solution at 30°, with the *pH* value kept at 9. Afterwards stirring was continued for 1 h. The resulting 2-chloro-6-oxo-1,6-dihydro-1,7-dimethylpurine (**4a**, $R = Me$) was filtered off. M.p. 224–226°, Ref. m.p. 222–224°[5], yield 51%.

The compound **4a** (46 mmol) was hydrolyzed with 96 ccm of conc. hydrochloric acid at an oil-bath temp. of 130° for 1.5 hours. The resulting solution was vacuum-evaporated to dryness. The residue was crystallized from water, neutralized with conc. NH_3 aq. to give paraxanthine m.p. 290–292° Ref. m.p. 293–295°[5] (yield 56% calc. per compound **4a**).

5. Acid-Hydrolyzed O-Dealkylation of 2,6-Dialkoxy-7-methylpurines **1**, **2** *and 2-Alkoxy-1,7-dialkyl hypoxanthines* **5a–5c**

Compound **1**, **2** or **5** (5 mmol) was refluxed with 10 ccm of 18% HCl aq in an oil-bath at 125–130° for 1.5 h and then vacuum-evaporated to dryness. The residue was suspended in water, neutralized with conc. NH_3 aq. and filtered off. Yield ca. 100% (see Table 4).

Paraxanthine was analysed by its m.p. and by means of TLC. Heteroxanthine was analysed making use of TLC and also as a sodium salt[5].

6. Attempts of Lactim-Lactam Rearrangement

2–3 mmol of compounds **5b**, **5c**, **7b**, **7c** were heated for 1 hour at a temp. of 165–170 °C in an oil-bath. Then the sample was dissolved in 3 ccm of ethanol and applied on a chromatography column (22 cm long, diameter 1 cm), filled with 11 g

Table 4

No.	Substrate				Product	R_f value
	R	*R'*	*R''*	*R'''*		
1a	*Me*	*Me*				
2a	*Me*	*Et*			heteroxanthine	0.23
5a			*Me*	*Me*		
5b			*Me*	*Et*	paraxanthine	0.37
5c			*Me*	*Pr*		

of silica gel (100–200 mesh). The compounds were eluted with chloroform collecting 2 ccm fractions. The progress of the separation was controlled by means of the TLC method mentioned above. The fractions Nos. 9–12 consisted of pure xanthines **6a**, **6b**, **6d**, **6e**, respectively. The fractions Nos. 13–28 containing mixtures of starting hypoxanthine **5** or **7** and xanthine **6** were collected together and evaporated to dryness. The content of xanthines **6** in the mixture with substrates was determined by means of the quantitative TLC method. In the analyses a 0.2 mm layer of silica gel was used. A linear correlation (± 3%) between the spot area and 3–15 μg of the amount of the applied compound **5**, **6** or **7** was found (see Table 5).

Table 5

No.	Substrate		No.	Products	Yield [a] %
	R_f value	Conversion %		R_f value	
5b	0.51	51	**6a**	0.58	22
5c	0.53	52	**6b**	0.60	25
7b	0.47	59	**6d**	0.61	23
7c	0.50	61	**6e**	0.63	25

[a] Calc. per used compound **5** or **7**.

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