Purines XIV. [1]. Reactivity of 8-Bromo-3,9-dimethylxanthine Towards Some Nucleophilic Reagents

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The reactivity of 8-bromo-3,9-dimethylxanthine (**6**) towards a variety of nucleophilic reagents has been investigated. Nucleophilic displacements take place easily with aliphatic mercaptans and aliphatic alcohols, whereas aliphatic amines required more severe conditions. Prolonged heating of **6** with amines causes a new type of rearrangement from 3,9- to 3,7-dimethylxanthines due to a 1,3-sigmatropic shift of the N(9)-methyl group.

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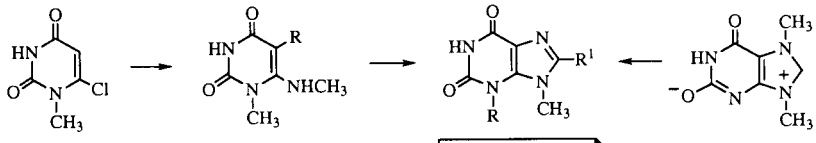
Introduction.

Nucleophilic displacement reactions in the purine series were first studied by Fischer [2] in determining the reactivity sequence of 2,6,8-trichloropurine towards various nucleophiles. More recent investigations [3-9] along the same lines all agree in the first findings showing that the chlorine atoms are substituted subsequently in the order 6-2-8 and based upon the anion formation theory which counteracts a nucleophilic attack at the negatively charged imidazole moiety to a large extent. On the other hand, fixation of the acidic imidazole H-atom by alkylation at N-7 or N-9 causes a change in reactivity according to the sequence 8-6-2 which results from the fact that the nucleophilic addition at the position 8 leads now to the most stable intermediate in this classical addition-elimination mechanism. The same mechanistic considerations guided us to the xanthine series to see whether 8-bromo-3,9-dimethylxanthine (**5**) will be prone to easy nucleophilic displacement reactions in position 8. from 6-chloro-1-methyluracil (**1**) [13] with methylamine to 6-methylamino-1-methyluracil (**2**) followed by nitrosation to **3**, then reductive formylation to **4** and finally ring closure with formamide giving **5** is most favoured. Bromination in glacial acetic acid proceeded well and gave a 90% yield of 8-bromo-3,9-dimethylxanthine (**6**). Biltz [14] attempted to brominate the alleged 3.9-dimethylxanthine but obtained 8-bromo-9-methylxanthine (**9**) instead. This result is easily understood on the basis of more recent findings [9] showing that the methylation product of 9-methylxanthine (**7**) is 7,9-dimethylxanthinium betaine (**10**) and not **5** or even 8,9-dimethylxanthine (**8**) as claimed by Biltz [14,15]. Bromination of **10** will then proceed most probably first by demethylation and followed by a normal electrophilic substitution at the position 8.

Reflux of **6** in alcoholic potassium hydroxide led in methanol and ethanol to 8-methoxy-**13** and 8-ethoxy-3,9-dimethylxanthine (**14**), respectively, whereas the same

Scheme 1



	R
2	H
3	NO
4	NHCHO

	R	R^1
5	CH_3	H
6	CH_3	Br
7	H	H
8	H	CH_3
9	H	Br

Since 3,9-disubstituted xanthine derivatives have not been studied in detail we hope that some of the currently synthesized derivatives will show potential biological activity in screening experiments.

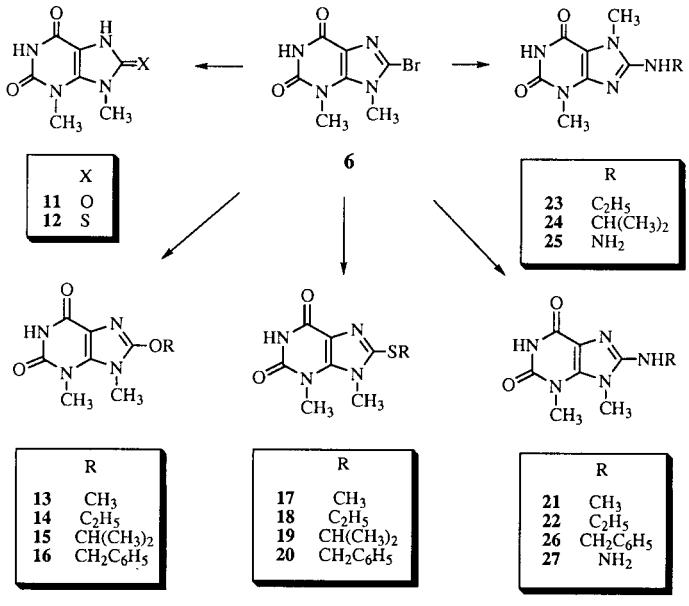
Results and Discussion.

The synthesis of 3,9-dimethylxanthine (**5**) has been performed by various approaches [10-12] but the sequence reaction in 2-propanol afforded a mixture of 8-isopropyloxy-**15** and 3,9-dimethyluric acid (**11**) [15]. Sodium benzyloxide in benzyl alcohol reacted well with **6** at 90° to give **16** in good yield. Sodium alkanethiolates behave analogously and gave on heating to 70-90° for 2-3 days the corresponding 8-alkylthio-3,9-dimethylxanthines **17-19**. Potassium benzylthiolate reacted at 120° exclusively to give 3,9-dimethyl-8-thiouric acid (**12**) and it is assumed that the

mechanism of this nucleophilic displacement reaction consisted first in the formation of 8-benzylthio-3,9-dimethylxanthine (**20**) which functions as an alkylation agent in the subsequent reaction with excess benzylthiolate. Reaction of sodium benzylthiolate with **6** at room temperature in dimethylformamide led in good yield to **20** which was also derived from benzylation of 3,9-dimethyl-8-thiouric acid (**12**).

The reactions with various primary amines also worked well under special conditions. Benzylamine gave on heating to 90° for several days expectedly 8-benzylamino-3,9-dimethylxanthine (**26**) and hydrazine converted **6** on reflux into 8-hydrazino-3,9-dimethylxanthine (**27**). Methyl-, ethyl- and isopropylamine, however, required more drastic conditions and reacted with **6** at 160° in an autoclave to 8-methylamino-3,9-dimethylxanthine (**21**) and surprisingly to a mixture of 8-ethylamino-3,9- **22** and 8-ethylamino-3,7-dimethylxanthine (**23**) as well as 8-isopropylamino-3,7-dimethylxanthine (**24**), respectively. We assume that this new type of purine rearrangement is due to an intramolecular 1,3-sigmatropic shift of the N(9)-methyl group to position N(7) in order to release the internal strain caused by the peri-located methyl groups. A Dimroth-type ring transformation is highly unlikely since no simple mechanism can be proposed.

Scheme 2



The compounds synthesized herein have been characterized by elemental analyses and spectral means such as ^1H nmr and uv spectra. Both methods allow a clear-cut differen-

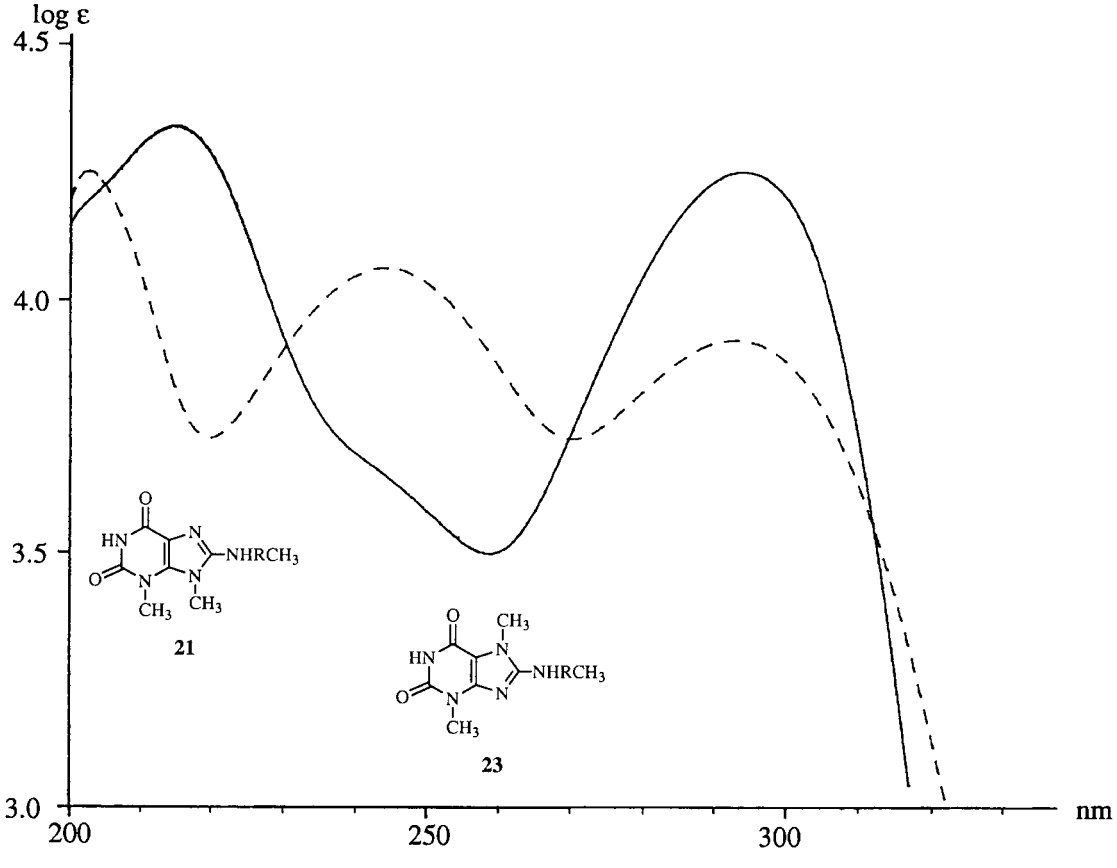


Figure 1. UV-Absorption spectra of 8-ethylamino-3,7- **23** and 8-methylamino-3,9-dimethylxanthine (**21**) in methanol.

tiation between the 3,9- and 3,7-dimethylxanthine series since the uv-spectra show either a three band or two band absorption curve (Figure 1), respectively, whereas the characteristic differences in the ^{1}H nmr spectra are seen in the chemical shifts of the two methyl groups in question.

The N(3)-methyl group of xanthines resonates in dimethyl-d_6 sulfoxide usually at 3.5-3.6 ppm and the N(7)-methyl group at higher field between 3.2 and 3.3 ppm. Peri-located methyl groups in 3- and 9-position come much closer to each other in the lower field area of 3.5-3.8 ppm (Table 1) indicating some steric interaction of the alkyl substituents. Comparisons of the chemical shifts of corresponding functionalities in **13-27** reflect also the structural relationships, so the H-N(1) is expectedly constant in the range of 10.5-11.1 and also the Me-N(3) vary only slightly between 3.61 and 3.51 ppm. The chemical shifts of Me-N(9), however, are much more influenced by the chemical nature of the C(8)-substituent. Alkoxy- and alkylthio groups cause an upfield shift of the Me-N(9) signal in **5** which is even more pronounced by the alkylamino and hydrazino substituents due to a stronger mesomeric interaction via the π-system. This effect is also reflected in the uv spectra where the long wavelength absorption of the 8-alkoxy-**13-16** and 8-alkylthio-3,9-dimethylxanthines **17-20** are found in the range of 274-280 nm but the 8-alkylamino and 8-hydrazino derivates **21-27** show a bathochromic shift to 289-296 nm.

Table 1

UV- and ^{1}H-NMR Data of 3,7- and 3,9-Dimethylxanthine Derivatives

Compound No.	UV-Absorption Spectra in Methanol λ_{max}				log ε		^{1}H-NMR Data MeN(3)	MeN(9)/(7)
13	208	234	277	3.92	3.94	3.97	3.55	3.64
14	204	234	277	4.15	3.99	3.98	3.55	3.64
15	208	234	279	3.83	3.88	3.86	3.55	3.62
16	203	234	278	4.36	4.03	3.94	3.56	3.68
17	204	257	[277]	4.20	4.08	[4.04]	3.59	3.79
18	205	259	[277]	4.22	4.10	[4.06]	3.60	3.81
19	206	261	274	4.18	4.06	4.04	3.61	3.86
20	203	[264]	280	4.48	[4.12]	4.13	3.57	3.71
21	203	245	294	4.25	4.06	3.92	3.55	3.58
22	203	246	295	4.24	4.06	3.90	3.57	3.60
26	204	247	294	4.31	4.01	3.83	3.56	3.65
23	216	[246]	295	4.34	[3.65]	4.25	3.52	3.28
24	216	[246]	296	4.09	[3.36]	4.02	3.50	3.25
25	213		291	3.88		3.75	3.52	3.29
27	204	242	289	4.20	3.91	3.94	3.56	3.59

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EXPERIMENTAL

General.

Melting points were determined with an electrothermal Gallenkamp apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Bruker AC 250 spectrometer in δ (ppm) and with tetramethylsilane as the internal standard. The uv spectra were determined with a Perkin Elmer, Lambda 5 or 15 spectrophotometer; λ_{max} in nm (log ε). The purity of the compounds was checked by tlc on silica gel plates (Schleicher & Schüll, F 1500 LS 254) and on cellulose plates (Schleicher & Schüll, F 1440 LS 254). The microanalyses were performed in the microanalytical laboratory of the department of chemistry, Konstanz university.

6-Chloro-1-methyluracil (**1**) [13,16].

A solution of 6-chlorouracil [17,18] (5.84 g, 40 mmoles) in dimethyl sulfoxide (25 ml) was treated with potassium carbonate (2.8 g, 20 mmoles) and methyl iodide (8 ml, 120 mmoles) by stirring at room temperature for 3 hours. Then water (30 ml) was added, cooled in the ice-box for several hours and the resulting precipitate collected. The product was recrystallized from methanol (40 ml) to give 3.34 g (72%) of colorless crystals of **1**, mp 186°, lit [13] mp 192-194°; uv (methanol): 207 (3.85), 268 (3.99).

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.40; H, 3.14; N, 17.45. Found: C, 37.53; H, 3.19; N, 17.45.

1-Methyl-6-methylaminouracil (**2**) [10].

A mixture of 6-chloro-1-methyluracil (**1**) (4.01 g, 25 mmoles) in ethanolic methylamine (40%, 10 ml) was heated under reflux for 15 minutes. After cooling the precipitate was collected and recrystallized from little water to give 2.98 g (77%) of colorless crystals of **2**, mp 275-277°, lit [10] mp 276°; uv (methanol): 203 (4.15), 265 (4.35).

1-Methyl-6-methylamino-5-nitrosouracil (**3**) [10].

A solution of **2** (3.1 g, 20 mmoles) in water (31 ml) was cooled to 0-5° and then sodium nitrite (1.51g, 22 mmoles) added. Dropwise addition of acetic acid (3 g, 60 mmoles) under stirring caused nitrosation with separation of violet crystals. The precipitate was collected and dried in a vacuum desiccator to give 3.24 g (88%) of **3**; 1. mp 180° with decoloration, solidification and 2. mp >330°; uv (methanol): 230 (4.11), 314 (3.80); ^{1}H nmr (dimethyl-d_6 sulfoxide): 15.29 (s, 1H, H-N), 11.28 (q, 1H, H-N), 3.41 (s, 3H, MeN(1)), 3.13 (d, 3H, C*H*$_3$NH(C-6)).

5-Formylamino-1-methyl-6-methylaminouracil (**4**) [10].

A stirred mixture of **3** (1.84 g, 10 mmoles) in formic acid (25 ml) was treated with zinc dust (3.9 g, 30 mmoles) by gradual addition and heating finally to reflux for 15 minutes. The precipitate of zinc and zinc formate was filtered from the hot solution and the filtrate evaporated to dryness. The residue was coevaporated with ethanol and then recrystallized from little water to give 1.20 g (61%) of colorless needles of **4**, first mp 240-250°, then solidification and 2nd mp 321°, lit [10] 1st mp 240-250° and 2nd mp 321-322°; uv (methanol): 205 (4.12), 271 (4.22); ^{1}H mnr (dimethyl-d_6 sulfoxide): 10.78 (s, 1H, H-N), 8.68 + 8.01 (d, 1H, H-N (C-5)), 8.33 + 7.76 (d, 1H, 5-CHO), 6.58 + 6.39 (q, 1H, H-N(C-6)), 3.24 (s, 3H, MeN(1)), 2.87 (d, 3H, C*H*$_3$NH(C-6)).

3,9-Dimethylxanthine (**5**) [10].

A mixture of **4** (0.99 g, 5 mmoles) in formamide (5 ml), water (0.25 ml) and formic acid (0.25 ml) was heated under reflux for 30 minutes. It was evaporated to dryness *in vacuo* and the precipitate recrystallized from water with little charcoal to give 0.72 g (80%) of colorless crystals of **5**, mp 336°, lit [10] mp 321-322°; uv (methanol): 202 (4.02), 235 (3.71), 265 (3.72); ^{1}H nmr

(dimethyl-d_6 sulfoxide): 11.02 (s, 1H, H-N(3)), 7.60 (s, 1H, H-C(8)), 3.90 (s, 3H, MeN(9)), 3.59 (s, 3H, MeN(3)).

8-Bromo-3,9-dimethylxanthine (**6**).

In glacial acetic acid (70 ml) 3,9-dimethylxanthine (**5**) (3.6 g, 20 mmoles) was dissolved by warming. At 60° a solution of bromine (3.5 ml) in acetic acid (10 ml) was added dropwise with stirring and after 1 hour the precipitate was collected, recrystallized from water and then dried in a vacuum desiccator to give 4.68 g (90%) of colorless crystals of **6**, mp 295-297°; uv (methanol): 203 (4.27), 242 (4.08), 268 (4.03); ^{1}H nmr (dimethyl-d_6 sulfoxide): 11.23 (s, 1H, H-N), 3.86 (s, 3H, MeN(9)), 3.60 (s, 3H, MeN(3)).

Anal. Calcd. for $C_7H_7BrN_4O_2$: C, 32.45; H, 2.72; N, 21.63. Found: C, 32.48; H, 2.74; N, 21.51.

3,9-Dimethyl-8-thiouric Acid (**12**).

Compound **6** (0.5 g, 1.9 mmoles) was heated with potassium hydroxide (2.5 g) in benzyl mercaptane (25 ml) at 120° for 5 hours in an oilbath with stirring. It was then evaporated *in vacuo* and the residue acidified by acetic acid. The precipitate was collected, washed with ether and recrystallized from water (120 ml) to give 0.26 g (64%) of yellowish crystals of **12**, mp 290-300° dec; uv (methanol): 202 (4.06), 226 (3.93), 272 (4.16), 310 (4.21); ^{1}H nmr (dimethyl-d_6 sulfoxide): 13.28 (s, 1H, H-N(7)), 11.41 (s, 1H, H-N(1)),3.86 (s, 3H, MeN(9)), 3.60 (s, 3H, MeN(3)).

Anal. Calcd. for $C_7H_8N_4O_2S$: C, 39.61; H, 3.79; N, 26.39. Found: C, 39.43; H, 3.84;N, 26.42.

8-Methoxy-3,9-dimethylxanthine (**13**).

Compound **6** (0.5 g, 1.9 mmoles) was heated in a mixture of potassium hydroxide (1 g) in methanol (10 ml) for 12 hours under reflux. The precipitate was filtered off and the filtrate acidified by acetic acid. The resulting solid was collected, washed with a small amount of water and then recrystallized from ethanol to give 0.145 (36%) colorless crystals of mp 316°; uv (methanol): 208 (3.92), 234 (3.94), 277 (3.97); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.97 (s, 1H, H-N), 3.96 (s, 3H, OMe), 3.64 (s, 3H, MeN(9)), 3.55 (s, 3H, MeN(3)).

Anal. Calcd. for $C_8H_{10}N_4O_3$: C, 45.72; H, 4.79; N, 26.65. Found: C, 45.57; H, 4.90; N, 26.01.

8-Ethoxy-3,9-dimethylxanthine (**14**).

Analogous to the preceding procedure with compound **6** by 3 hours reflux in ethanol; crystallization from ethanol gave 0.23 g (54%) of colorless crystals, mp 258-260°; uv (methanol): 204 (4.15), 234 (3.99), 277 (3.98); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.96 (s, 1H, H-N), 4.35 (q, 2H, O-CH_2), 3.64 (s, 3H, MeN(9)), 3.55 (s, 3H, MeN(3)), 1.34 (t, 3H, CMe).

Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.11; H, 5.36; N, 24.78.

3,9-Dimethyl-8-isopropoxyxanthine (**15**) and 3,9-Dimethyluric Acid (**11**).

Compound **6** (0.5 g, 1.9 mmoles) was heated in 2-propanol (25 ml) and potassium hydroxide (2.5 g) for 12 hours under reflux. The mixture was evaporated to dryness, the residue dissolved in water (15 ml) and then acidified by acetic acid. The precipitate was collected, then heated with ethanol (30 ml) and filtered from the insoluble material. This solid (18%) was identical with authentic 3,9-dimethyluric acid (**11**) [19], mp >320°. From the filtrate on partial evaporation 0.205 g (45%) of **15** crystallized as colorless crystals of mp >280° dec; uv (methanol): 208 (3.83), 234 (3.88), 279 (3.86); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.95 (s, 1H, H-N), 5.01 (sept, 1H, O-CH), 3.62 (s, 3H, MeN(9)), 3.55 (s, 3H, MeN(3)), 1.33 (d, 6H, 2 x Me).

Anal. Calcd. for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.51. Found: C, 50.30; H, 5.77; N, 23.80.

8-Benzyloxy-3,9-dimethylxanthine (**16**).

Compound **6** (1.0 g, 3.8 mmoles) was added to a solution of sodium hydride (0.5 g) in benzyl alcohol (25 ml) and then heated in an oil bath to 90° for 2 hours with stirring. After cooling the reaction mixture was poured into ether (150 ml) with stirring precipitating an amorphous solid. The precipitate was collected, dissolved in warm water (50 ml) and acidified with acetic acid to give a colorless solid (0.8 g). Recrystallization from ethanol (300 ml) gave 0.65 g (60%) of **16** as colorless needles, mp 227-229°; uv (methanol): 203 (4.36), 234 (4.03), 278 (3.94); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.95 (s, 1H, H-N), 7.47 (m, 2H, arom. H-C), 7.42 (m, 3H, arom. H-C), 5.40 (s, 2H, OCH_2), 3.68 (s, 3H, MeN(9)), 3.56 (s, 3H, MeN(3)).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.64. Found: C, 58.40; H, 4.91; N, 19.55.

3,9-Dimethyl-8-methylthioxanthine (**17**).

Compound **6** (0.5 g, 1.9 mmoles) was heated with sodium methanethiolate (0.42 g, 6 mmoles) in absolute ethanol (15 ml) for 24 hours under reflux with stirring. It was evaporated to dryness, water (15 ml) added and acidified with acetic acid. The precipitate was collected and recrystallized twice from ethanol/water 3:1 to give 0.12 g (28%) of **17** as colorless crystals, mp of 271-274°; uv (methanol): 204 (4.20), 257 (4.08), [277 (4.04)]; ^{1}H nmr (dimethyl-d_6 sulfoxide): 11.09 (s, 1H, H-N), 3.79 (s, 3H, MeN(9)), 3.59 (s, 3H, MeN(3)), 2.56 (s, 3H, MeS).

Anal. Calcd. for $C_8H_{10}N_4O_2S$; C, 42.46; H, 4.45; N, 24.76. Found: C, 42.55; H, 4.57; N, 24.56.

8-Ethylthio-3,9-dimethylxanthine (**18**).

Analogous to the preceding procedure with compound **6** (0.5 g, 1.9 mmoles), ethanethiol (0.84 g, 10 mmoles) and potassium hydroxide (0.54 g, 10 mmoles) were heated in ethanol (15 ml) under reflux in an oil bath with stirring for 36 hours. After workup the precipitate was recrystallized from ethanol/water 9:1 to give 0.347 g (76%) of colorless crystals of mp 280-283°; uv (methanol); 205 (4.22), 259 (4.10), [277 (4.06)]; ^{1}H nmr (dimethyl-d_6 sulfoxide): 11.11 (s, 1H, H-N), 3.81 (s, 3H, MeN(9)), 3.60 (s, 3H, MeN(3)), 3.07 (q, 2H, CH_2S), 1.27 (t, 3H, Me).

Anal. Calcd. for $C_9H_{12}N_4O_2S$: C, 44.98; H, 5.03; N, 23.31. Found: C, 44.86; H, 5.01; N, 23.11.

3,9-Dimethyl-8-isopropylthioxanthine (**19**).

As described above 2-propanethiol (0.96 g, 10 mmoles) gave 0.357 g (74%) of colorless crystals of mp 245-247°; uv (methanol): 206 (4.18), 261 (4.06), 274 (4.04) ; ^{1}H nmr (dimethyl-d_6 sulfoxide): 11.13 (s, 1H, H-N), 3.86 (s, 3H, MeN(9)), 3.61 (s, 3H, MeN(3)), 3.58 (m, 1H, H-C), 1.30 (d, 6H, 2xMe).

Anal. Calcd. for $C_{10}H_{14}N_4O_2S$: C, 47.22; H, 5.55; N, 22.03. Found: C,47.36; H, 5.68; N, 22.13.

8-Benzylthio-3,9-dimethylxanthine (**20**).

a).

3,9-Dimethyl-8-thiouric acid (0.212 g, 1 mmole) (**12**) was dissolved in water (20 ml) and potassium carbonate (0.19 g, 1.2

mmoles). Benzyl bromide (0.204 g, 1.2 mmoles) was added to the solution and after vigorous stirring for 2 hours the resulting precipitate collected. Crystallization from methanol gave 0.21 g (69%) of colourless crystals, mp 253-255°.

b).

To a solution of benzylmercaptan (0.99 g, 8 mmoles) in dry dimethyl-formamide (15 ml) was added sodium hydride (0.2 g, 8 mmoles) and 8-bromo-3,9-dimethylxanthine (**6**) (1.04 g, 4 mmoles) and then the suspension stirred at room temperature for 6 hours forming a voluminous precipitate. The mixture was diluted with water (50 ml), the precipitate collected and recrystallized from ethanol to give 0.85 g (70%) of colorless needles, mp 254-255°; uv (methanol): 203 (4.48), [264 (4.12)], 280 (4.13); ^{1}H nmr (dimethyl-d_6 sulfoxide): 11.15 (s, 1H, H-N), 7.30 (m, 5H, arom. H-C), 4.33 (s, 2H, CH_2), 3.71 (s, 3H, Me-N(9)), 3.57 (s, 3H, Me-N(3)).

Anal. Calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.67; N, 18.54. Found: C, 55.45; H,4.68; N, 18.46.

3,9-Dimethyl-8-methylaminoxanthine (**21**).

Compound **6** (0.5 g, 1.9 mmoles) was heated with ethanolic methylamine (15 ml, 33%) in an autoclave to 160° for 3 days. It was evaporated to dryness, the residue treated with ethanol, the solid collected and then recrystallized from water to give 0.135 g (34%) of a colorless powder, mp >320°; uv (methanol): 203 (4.24), 245 (4.04), 294 (3.89); pK_a 10.03; ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.77 (s, 1H, H-N), 6.19 (q, 1H, H-N(C8)), 3.58 (s, 3H, MeN(9)), 3.55 (s, 3H, MeN(3)), 2.57 (d, 3H, MeNH).

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.92; H, 5.29; N, 33.47. Found: C, 46.04; H, 5.33; N, 33.35.

8-Ethylamino-3,9-dimethylxanthine (**22**).

A mixture of compound **6** (0.45 g, 1.7 mmoles) and ethanolic ethylamine (15 ml, 50%) was heated in an autoclave to 160° for 30 hours. It was evaporated to a small volume, the precipitate consisting of a mixture of **22** and **23** was collected and the solid recrystallized from ethanol/water (2/1) to give as a first crop 36 mg (9%) of **23** and from the filtrate 0.12 g (31%) of **22** as colorless crystals, mp 317°; uv (methanol): 203 (4.21), 246 (4.06), 295 (3.90); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.72 (s, 1H, H-N), 6.13 (t, 1H, H-N), 3.60 (s, 3H, MeN(9)), 3.57 (s, 3H, MeN(3)), 3.31 (m, 2H, CH_2N), 1.16 (t, 3H, CMe).

Anal. Calcd. for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found; C, 48.32; H, 5.68; N, 31.17.

8-Ethylamino-3,7-dimethylxanthine (**23**).

A mixture of 8-chloro-3,7-dimethylxanthine (0.5 g, 2.3 mmoles) and ethanolic ethylamine (15 ml, 50%) was heated in an autoclave to 160° for 1 day. After cooling the resulting precipitate was filtered and recrystallized from ethanol/water (2/1) to give 0.23 g (45%) of colorless crystals, mp >330°; uv (methanol): 216 (4.28), [246 (3.60)], 294 (4.21); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.33 (s, 1H, H-N), 6.78 (t, 1H, H-N), 3.52 (s, 3H, MeN(3)), 3.37 (m, 2H, CH_2N), 3.28 (s, 3H, MeN(7)), 1.18 (d, 3H, MeC).

Anal. calcd. for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.21; H, 5.78; N, 31.20.

3,7-Dimethyl-8-isopropylaminoxanthine (**24**).

Compound **6** (0.5 g, 1.9 mmoles) was heated in an autoclave with ethanolic isopropylamine (15 ml, 33%) for 2 days to 160°. After evaporation the residue was recrystallized from ethanol to give 0.21 g (46%) of colorless crystals, mp 292-296°; uv (methanol): 216 (4.09), [246 (3.36)], 296 (4.02); pK_a 10.78; ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.57 (s, 1H, H-N), 6.67 (d, 1H, H-N), 3.98 (sept, 1H, CH), 3.50 (s, 3H, MeN(3)), 3.25 (s, 3H, MeN(7)), 1.19 (d, 6H, 2 x Me).

Anal. Calcd. for $C_{10}H_{15}N_5O_2$: C, 50.62; H, 6.37; N, 29.51. Found: C, 50.78; H, 6.41; N, 29.49.

8-Hydrazino-3,7-dimethylxanthine (**25**).

8-Chloro-3,7-dimethylxanthine (1.07 g, 5 mmoles) was heated in hydrazine hydrate (20 ml) for 20 minutes. The resulting precipitate was collected and recrystallized from water to give 0.74 g (70%) of colorless crystals, mp 290-294° dec; uv (methanol): 213 (3.88), 291 (3.75); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.63 (bs, 1H, H-N), 8.06 (s, 1H, H-N), 4.32 (s, 2H, NH_2), 3.52 (s, 3H, Me-N(3)), 3.29 (s, 3H, Me-N(7)).

Anal. Calcd. for $C_7H_{10}N_6O_2$: C, 40.00; H, 4.80; N, 39.99. Found: C, 39.86; H, 4.88; N, 39.73

8-Benzylamino-3,9-dimethylxanthine (**26**).

Compound **6** (0.5 g, 1.9 mmoles) was heated in benzylamine (15 ml) in an oil bath to 90° for 6 days. After cooling the precipitate was collected. The filtrate was evaporated *in vacuo*, the residue treated with ethanol, the solid filtered and then the united crops recrystallized from ethanol/water to give 0.24 g (43%) of colorless crystals, mp 295-305° dec; uv (methanol): 204 (4.31), 247 (4.01), 294 (3.83); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.78 (s, 1H, HN), 7.27 (m, 5H, C_6H_5), 6.81 (t, 1H, H-N), 4.40 (d, 2H, CH_2), 3.65 (s, 3H, MeN(9)), 3.56 (s, 3H, MeN(3)).

Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.94, H, 5.30; N, 24.54. Found; C, 58.50; H, 5.30; N, 24.26.

8-Hydrazino-3,9-dimethylxanthine (**27**).

Compound **6** (0.5 g, 1.9 mmoles) and hydrazine (6 ml, 99%) were heated in an oil bath to 80° for 15 hours. It was evaporated *in vacuo* and the residue recrystallized from water to give 0.25 g (62%) of a colorless powder, mp 260-264°; uv (methanol): 204 (4.20), 242 (3.91), 289 (3.94); ^{1}H nmr (dimethyl-d_6 sulfoxide): 10.83 (s, 1H, H-N), 7.33 (s, 1H, NH), 4.09 (s, 2H, NH_2), 3.59 (s, 3H, MeN(9)), 3.56 (s, 3H, MeN(3)).

Anal. Calcd. for $C_7H_{10}N_6O_2$: C, 39.99; H, 4.79; N, 39.98. Found: C, 40.12; H, 4.88; N, 39.75.

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