Purines. XIV [1]. Synthesis and Properties of 8-Nitroxanthine and its *N*-Methyl Derivatives

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Dedicated to the memory of Dr. Roland K. Robins

Xanthine (**1**) and its *N*-methyl derivatives **2-16** have been nitrated to the corresponding 8-nitro derivatives **17-32** under different reaction conditions. Nitration in glacial acetic acid with nitric acid works well with the N-7 unsubstituted and some of the 9-methylxanthines, respectively, whereas the 7-methylxanthine derivatives react best with nitronium tetrafluoroborate in sulfolane or glacial acetic acid. The 8-nitro group can be displaced nucleophilically to form 8-chloro-, **33**, **34**, 8-ethoxy-, **35**, **36**, and uric acid derivatives **37-40**, respectively. The newly synthesized 8-nitroxanthines have been characterized by elemental analyses, p*K*-determinations and uv and ^{1}H-nmr spectra.

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Introduction.

The purine ring system can be regarded as a composite of a π-electron-deficient pyrimidine- and a π-electron-excessive imidazole ring inducing some polarity into the molecule which is due to the sharing of the imidazole ring π-electrons by the pyrimidine moiety. This balance can, however, be disturbed by insertion of appropriate strong electron-attracting or -withdrawing groups into either ring. As a consequence of the partial localization of π-electrons around the ring nitrogen atoms, the adjacent carbon atoms show a pronounced degree of electrophilic character. Electronegative heteroatoms or groups attached to these positions will undergo a broad variety of nucleophilic displacement reactions. Even purine itself is aminated in a Chichibabin reaction to give in excellent yield adenine [2]. On the other hand, introduction of one or better two electron-releasing groups into the pyrimidine ring activates the 8-position for the attack of electrophiles. Since the majority of purine metatheses in literature [3] are of the nucleophilic displacement type we have focused our interest to electrophilic substitutions by investigating the nitration of xanthine and its *N*-alkyl derivatives. The presence of two amide functions in the pyrimidine moiety counteract the inherent π-electron deficiency to such an extent that the ring nitrogens can be considered as electronically neutralized giving rise to a benzene-like character of the six-membered heterocycle.

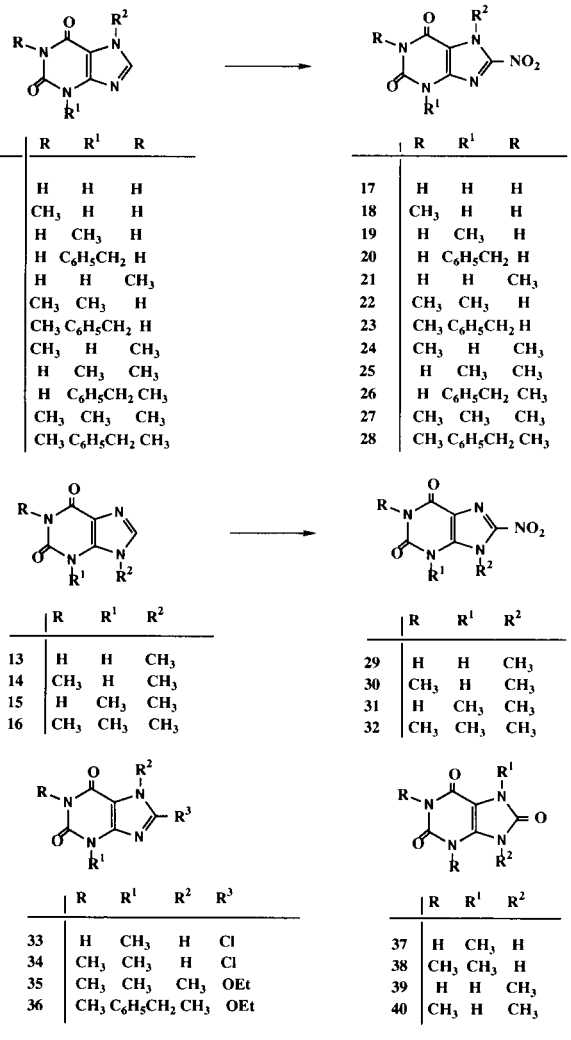
Results and Discussion.

Despite the fact that xanthines are prone to easy electrophilic substitution reactions in position 8 of the nucleus it is to some extent surprising that only a few direct nitrations have been described in literature. Only theophylline (**6**) [4-6], theobromine (**9**) [4,7-9], caffeine (**11**) [6,10,11], 3-methylxanthine (**3**) [12] and 9-methylxanthine (**13**) [13] have been converted directly by various types of nitric acid into their 8-nitro derivatives whereby in most cases no yields and detailed physical data have been reported. There is also the possibility to displace in 8-diazoxanthines the nitrogen function by the nitrite group yielding 8-nitroxanthines as shown with 8-diazoxanthine and 8-diazotheophylline [13]. Furthermore 8-nitroxanthine (**17**) and 1-methyl-8-nitroxanthine (**18**) have also been obtained besides various other reaction products on treatment of 3-acetoxy- and 3-acetoxy-1-methylxanthine, respectively, with sodium nitrite in water at room temperature [14].

We concentrated our efforts first towards the direct nitration of xanthine and its various *N*-methyl derivatives using dilute to concentrated and fuming nitric acid, respectively under a variety of reaction conditions. Xanthine (**1**) is difficult to nitrate due to its low solubility and its sensitivity to oxidations yielding alloxan and urea. Treatment of **1** in glacial acetic acid with 100% nitric acid at 120° gave 8-nitroxanthine (**17**) in 45% yield as yellowish crystals from 0.5 *N* hydrochloric acid. Similarly 1-methyl- **2**, 3-methyl- **3**, 3-benzyl- **4**, 9-methyl- **13**, 1,3-dimethyl- **6**, 3-benzyl-1-methyl- **7** and 1,9-dimethylxanthine (**14**) form in an analogous manner the corresponding 8-nitro derivatives **18-20**, **29**, **22**, **23** and **30** in yields of 40-70%, respectively. Strangely enough caffeine (**11**) reacted under the same reaction conditions in only 25% yield to 8-nitrocaffeine (**27**) whereby a series of side products have been detected chromatographically as noticed also by Kozuka *et al.* [11]. Even more difficulties arose on nitration of theobromine (**9**) according to literature [4,7-9] yielding mainly starting material contaminated with small amounts of 8-nitrotheobromine (**25**) which could not be isolated in pure form applying various chromatographical methods. 7-Methyl- **5**, 1,7-dimethyl- **8**, 3-benzyl-7-methyl- **10** and 3-benzyl-1,7-dimethylxanthine (**12**) also failed to form the corresponding 8-nitro derivatives presumably due to the fact that the 7-methylxanthines, in general, are easily oxi-

dized by nitric acid to alloxans and further breakdown products.

Scheme 1



	R	R^1	R
1	H	H	H
2	CH_3	H	H
3	H	CH_3	H
4	H	$C_6H_5CH_2$	H
5	H	H	CH_3
6	CH_3	CH_3	H
7	CH_3	$C_6H_5CH_2$	H
8	CH_3	H	CH_3
9	H	CH_3	CH_3
10	H	$C_6H_5CH_2$	CH_3
11	CH_3	CH_3	CH_3
12	CH_3	$C_6H_5CH_2$	CH_3

	R	R^1	R
17	H	H	H
18	CH_3	H	H
19	H	CH_3	H
20	H	$C_6H_5CH_2$	H
21	H	H	CH_3
22	CH_3	CH_3	H
23	CH_3	$C_6H_5CH_2$	H
24	CH_3	H	CH_3
25	H	CH_3	CH_3
26	H	$C_6H_5CH_2$	CH_3
27	CH_3	CH_3	CH_3
28	CH_3	$C_6H_5CH_2$	CH_3

	R	R^1	R^2
13	H	H	CH_3
14	CH_3	H	CH_3
15	H	CH_3	CH_3
16	CH_3	CH_3	CH_3

	R	R^1	R^2
29	H	H	CH_3
30	CH_3	H	CH_3
31	H	CH_3	CH_3
32	CH_3	CH_3	CH_3

	R	R^1	R^2	R^3
33	H	CH_3	H	Cl
34	CH_3	CH_3	H	Cl
35	CH_3	CH_3	CH_3	OEt
36	CH_3	$C_6H_5CH_2$	CH_3	OEt

	R	R^1	R^2
37	H	CH_3	H
38	CH_3	CH_3	H
39	H	H	CH_3
40	CH_3	H	CH_3

In order to achieve nitration at the more sensitive *N*-substituted xanthine derivatives nitronium tetrafluoroborate was applied in various solvents at elevated temperatures. 3,9-Dimethyl- **15** and 1,3,9-trimethylxanthine (isocaffeine) (**16**) reacted in glacial acetic acid and sulfolane, respectively, in moderate yields to the corresponding 8-nitro derivatives **31** and **32**. The same method was proven to be also successful with all 7-substituted xanthines like 7-methyl- **5**, 1,7-dimethyl- **8**, 3,7-dimethyl- (theobromine) (**9**), 3-benzyl-7-methyl- **10**, 1,3,7-trimethyl- (caffeine) (**11**) and 3-benzyl-1,7-dimethylxanthine (**12**) which showed nitration at C-8 to give **21** and **24–28** in 25-40% yield. Since 8-nitrocaffeine (**27**) could only be obtained in 39% by the direct nitration procedure also methylation of the easily available 8-nitrotheophylline (**22**) was achieved by methyl iodide in DMF and in the presence of potassium carbonate to get 60% recrystallized material.

The nitro group is also susceptible to nucleophilic displacement reactions as shown by Cacace and Masironi [8]. 3-Methyl-8-nitroxanthine (**19**) and 8-nitrotheophylline (**22**) led on heating in concentrated hydrochloric acid in an acid catalyzed reaction to the corresponding 8-chloro derivatives **33** and **34**. Blocking of the acidic H-atom at the imidazole moiety by alkylation allows also substitutions by basic nucleophiles. Nitrocaffeine (**27**) and 3-benzyl-1,7-dimethyl-8-nitroxanthine (**28**) reacted with the ethoxy ion to 8-ethoxycaffeine (**35**) and 3-benzyl-8-ethoxy-1,7-dimethylxanthine (**36**), respectively. Furthermore basic hydrolysis in 1*N* sodium hydroxide resulted in the formation of uric acids (**37–40**) starting from 7-methyl- **21**, 1,3,7-trimethyl- **27**, 9-methyl- **29**, and 1,3,9-trimethyl-8-nitroxanthine (**32**). This reaction can also be followed spectrophotometrically converting **27** at *p*H 11 into 1,3,7-trimethyluric acid (**38**) within 3 hours at room temperature (Figure 1).

Physical Data.

The introduction of a strong electron-attracting group into the 8-position of the xanthine nucleus is directly associated with a more or less dramatic change in acidity of these compounds in comparison to the 8-unsubstituted xanthines. The determination of the acidic pK_a's was achieved by the spectrophotometric method [15] and revealed interesting correlations (Table 1).

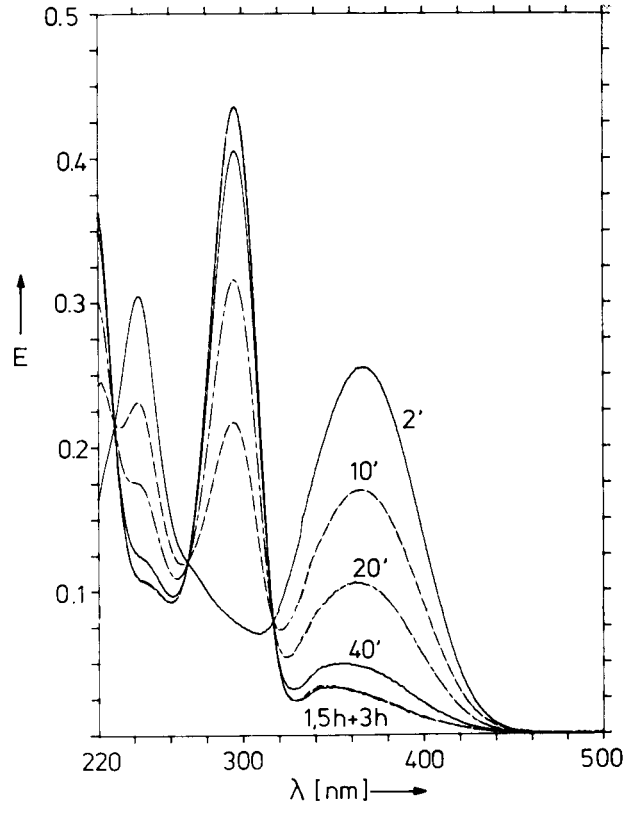
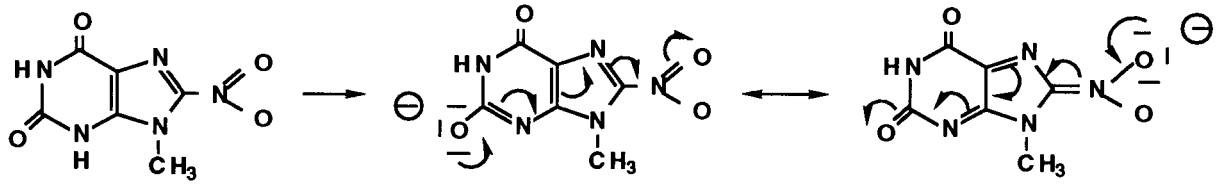


Figure 1. Interconversion of 8-Nitrocaffeine (**27**) into 1,3,7-Trimethyluric Acid (**38**) at *p*H 11.

Table 1
Physical Data of 8-Nitroxanthine and its *N*-Methyl Derivatives

-8-Nitroxanthine	pK_a in H_2O	UV absorption spectra λ max (nm)				UV absorption spectra log ε				*p*H	molecular form
unsubstituted	2.12	203	320		358	4.11	4.03		4.04	0.0	o
(**17**)	9.84	205	244		377	4.18	386		4.07	6.0	-
		226	260	[304]	423	4.02	397	[3.41]	4.02	13.0	--
1-Methyl- (**18**)	2.01	209	236		359	3.99	3.98		4.01	0.0	o
	10.15		234	[286]	381		3.94	[3.29]	4.09	8.0	-
		229	259	[302]	430	3.99	3.98	[3.51]	4.04	13.0	--
3-Methyl- (**19**)	1.80	211	237		363	4.06	4.03		3.97	0.0	o
	11.48		244		382		3.92		4.07	8.0	-
		235	237	[291]	414	3.80	3.88	[3.44]	4.16	14.0	--
3-Benzyl- (**20**)	1.67	205	239		362	4.25	4.11		3.94	-1.0	o
	11.21	224	244		381	4.02	3.97		4.06	4.0	-
			250	[292]	412		3.94	[3.46]	4.15	13.0	--
7-Methyl- (**21**)	7.13	206	232		356	4.11	4.03		3.94	5.0	o
		218	257	[291]	408	4.11	4.09	[3.48]	3.82	10.0	-
9-Methyl- (**29**)	4.11	229	253		354	3.97	3.65		4.06	1.0	o
	13.22	223	250	[294]	407	4.02	3.99	[2.99]	4.07	10.0	-
		237	250	[310]	448	3.89	3.93	[3.38]	4.18	2N NaOH	--
1,3-Dimethyl-(**22**)	2.08	210	245		370	3.99	4.06		4.02	0.0	o
		203	239	[286]	387	4.19	3.95	[3.32]	4.08	6.0	-
3-Benzyl-1-methyl- (**23**)	1.90		241	[278]	364		4.12	[3.44]	3.95	0.0	o
		226	244	[285]	384	4.00	4.01	[3.36]	4.08	5.0	-
1,7-Dimethyl- (**24**)	7.30		236	265	360		3.96	3.72	3.87	4.0	o
		214	259	[290]	413	4.16	4.03	[3.71]	3.74	10.0	-
1,9-Dimethyl- (**30**)	4.19	223	256		355	3.97	3.52		4.08	2.0	o
		226	253	[294]	412	3.96	4.04	[3.17]	4.10	7.0	-
3,7-Dimethyl- (**25**)	9.45	210	239		367	4.11	4.09		3.93	7.0	o
			244	[268]	389		3.93	[3.68]	4.00	12.0	-
3-Benzyl-7-methyl- (**26**)	9.00		240	[276]	362		4.09	[3.56]	3.90	7.0	o
			246	[275]	388		3.96	[3.69]	3.96	11.0	-
3,9-Dimethyl- (**31**)	8.93		238	258	358		3.88	3.71	4.00	7.0	o
		206	248	[291]	388	4.26	3.87	[3.31]	4.10	11.0	-
1,3,7-Trimethyl- (**27**)		218	240		360	3.89	3.98		3.92	MeOH	o
3-Benzyl-1,7-dimethyl- (**28**)			242	360			4.13		3.91	MeOH	o
1,3,9-Trimethyl- (**32**)			240	358			3.93		4.02	MeOH	o



The nitro group causes a strong increase in acidity in general and changing the ionisation sequence of the acidic hydrogens in xanthine from N-3, N-7, N-1 to N-7, N-3, N-1 in 8-nitroxanthine. All 8-nitroxanthines carrying an N-H function at the imidazole moiety are relatively strong acids with p*K*a values of about 2 which is 6 p*K*-units more acidic than their 8-unsubstituted counterparts as seen, for example, from a comparison of theophylline (8.68) and 8-nitrotheophylline (2.08) (**22**). This first step of ionisation is associated with a bathochromic shift of about 20 nm of the long wavelength absorption band of the uv spectrum. Fixation of the imidazole proton by a methyl group influences the acidity of the N-H functions of the pyrimidine part in dependence of the site of methylation. 7-Methyl-8-nitroxanthine (**19**) shows a p*K*a of 7.13 whereas 9-methyl-8-nitroxanthine (**29**) is 3 p*K*-units more acidic. This effect is the result of a strong resonance stabilization in the monoanion of **29** which is of only inductive nature in **19**.

It is interesting to note that monoanion formation of 7-methyl- **21** and 9-methyl-8-nitroxanthine (**29**) is accompanied with a strong bathochromic shift in the uv spectrum of about 50 nm which is also observed in changing from the mono- to the dianion in 8-nitroxanthine and its 1-methyl derivative. The closely related second p*K*a values of 8-nitroxanthine (**17**) and 1-methyl-8-nitroxanthine (**18**) as well as their highly similar uv spectra of the dianions *versus* those of 3-methyl-8-nitroxanthine (**19**) clearly prove the ionisation sequence of the acidic hydrogens according to N-7, N-3, N-1.

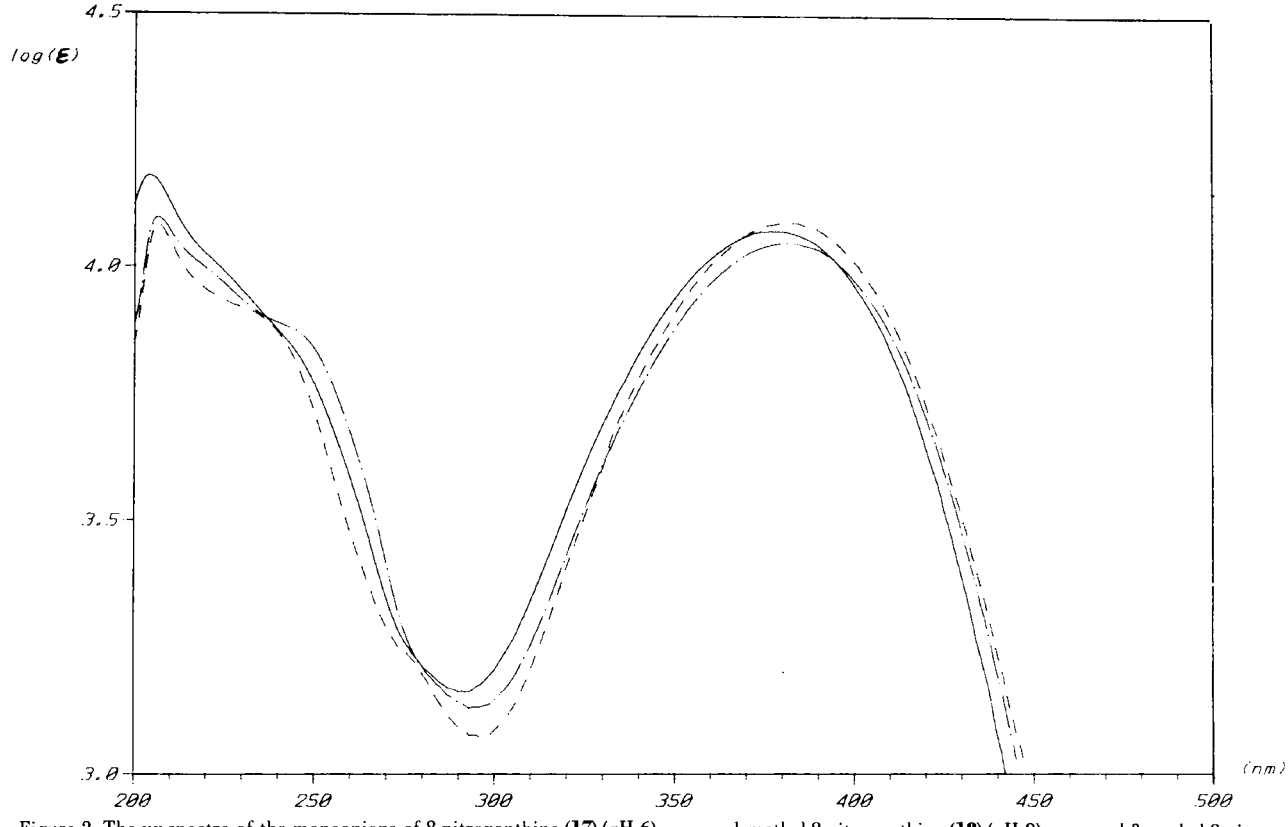


Figure 2. The uv-spectra of the monoanions of 8-nitroxanthine (**17**) (*p*H 6) _____ 1-methyl-8-nitroxanthine (**18**) (*p*H 8) ------ and 3-methyl-8-nitroxanthine (**19**) (*p*H 8) .....

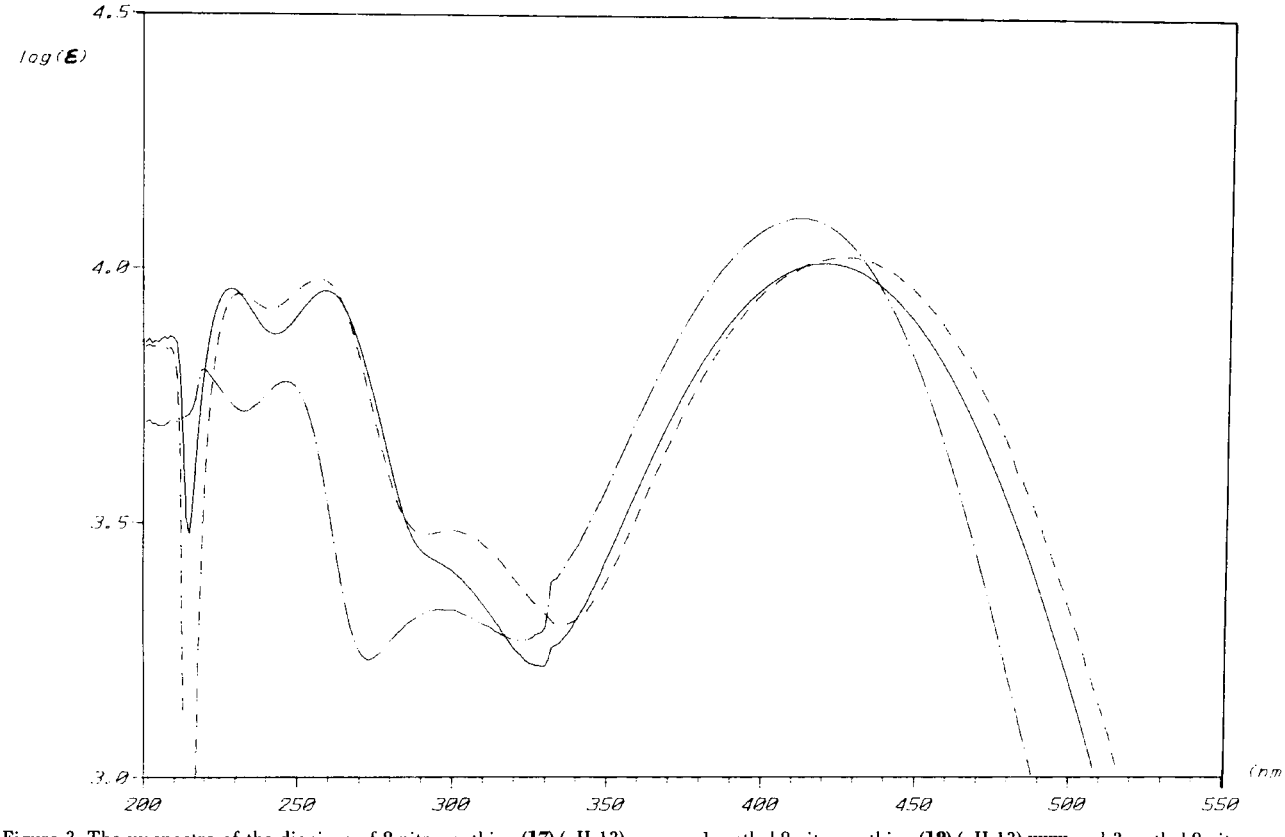


Figure 3. The uv-spectra of the dianions of 8-nitroxanthine (**17**) (*p*H 13) _____ 1-methyl-8-nitroxanthine (**18**) (*p*H 13) ------ and 3-methyl-8-nitroxanthine (**19**) (*p*H 14) .....

Table 2

^{1}H-NMR Data of 8-Nitroxanthine and its *N*-methyl Derivatives in DMSO-d_6

-8-Nitroxanthine	δ (ppm) N_1-CH_3 (s, 3H)	N_3-CH_3 (s, 3H)	N_7-CH_3 (s, 3H)	N_9-CH_3 (s, 3H)	Various Signals
unsubstituted **17**					12.2 (s, 1H, NH), 10.4 (s, 1H, NH), 7.15 (s, 1H, NH),
1-Methyl **18**	3.25				12.82 (s, 1H, NH), 10.1 (s, 1H, NH)
3-Methyl- **19**		3.36			11.47 (s, 1H, NH), 7.80 (s, 1H, NH)
7-Methyl- **21**			4.20		11.30 (s, 1H, NH), 10.80 (s, 1H, NH)
9-Methyl- **29**				3.80	13.20 (s, 1H, NH), 11.89 (s, 1H, NH)
1,3-Dimethyl- **22**	3.25	3.43			8.39 (s, 1H, NH)
1,7-Dimethyl- **24**	3.40		4.20		12.60 (s, 1H, NH)
1,9-Dimethyl- **30**	3.22			3.95	13.45 (s, 1H, NH)
3,7-Dimethyl- **25**		3.36	4.24		11.72 (s, 1H, NH)
3,9-Dimethyl- **31**		3.75		4.15	12.35 (s, 1H, NH)
1,3,7-Trimethyl- **27**	3.22	3.40	4.35		
1,3,9-Trimethyl- **32**	3.18	3.40	4.35		
3-Benzyl- **20**					11.55 (s, 1H, NH), 8.20 (s, 1H, NH), 7.25 (m, 5H, Ph), 5.09 (s, 2H, CH_2)
3-Benzyl-1-methyl- **23**	3.26				7.25 (m, 5H, Ph), 5.59 (s, 1H, NH), 5.10 (s, 2H, CH_2)
3-Benzyl-7-methyl- **26**			4.40		11.90 (s, 1H, NH), 7.30 (m, 5H, Ph), 5.20 (s, 2H, CH_2)
3-Benzyl-1,7-Dimethyl- **28**	3.40		4.40		7.45 (m, 5H, Ph), 5.30 (s, 2H, CH_2)

The ^{1}H nmr spectra of the 8-nitroxanthines reveal corresponding chemical shifts of the methyl protons according to the site of attachment. Structural assignments can be based on these signals of which only the 3-methyl signal in 3,9-dimethyl- **31** and 1,3,9-trimethyl-8-nitroxanthine **(32)** is shifted more strongly to lower field due to some steric interaction of the peri-located methyl groups.

EXPERIMENTAL

General.

The tlc were accomplished with precoated silica gel thin-layer sheets F 1500 LS254 and cellulose thin-layer sheets F 1440 LS 254 from Schleicher & Schüll. Melting points are uncorrected and were taken on a Büchi apparatus, model Dr. Tottuli. The p*K* determinations were done by spectrophotometric methods [15]. The uv-visible spectra were determined on Uvikon 820, Kontron, and Lambda 5 (Perkin Elmer) spectrometers, reported as λ max (log ε). The ^{1}H-nmr were obtained on a Bruker-WN-250 spectrometer and reported in δ (ppm) relative to TMS.

1,9-Dimethylxanthine **(8)** [16].

In a mixture of formamide (140 ml), water (5 ml) and formic acid (5 ml) was heated 5-formylamino-6-methylamino-3-methyluracil [19] for 30 minutes under reflux. After cooling it was diluted with water (120 ml), chilled in the ice-box for several hours and then the precipitate collected and dried in the oven (13.6 g, 75%). The crude material was recrystallized from a mixture of water (1.5 *l*) and concentrated hydrochloric acid (10 ml) to give colorless crystals in 60% (10.9 g) yield, mp >340°, lit [16] 350-351°; uv (*p*H 3): 235 (3.87), 263 (4.00).

Anal. Calcd. for $C_7H_8N_4O_2$ (mol wt 180.2): C, 46.65; H, 4.48; N, 31.09. Found: C, 46.51; H, 4.44; N, 31.06.

8-Nitroxanthine (**17**).

Xanthine (2.26 g, 14.9 mmoles) **(1)** was heated in glacial acetic acid (19 ml) to 120° in an oil-bath and then 100% nitric acid (3 ml, 71.4 mmoles) was added dropwise with stirring. The suspension was refluxed for 1 hour. After cooling the precipitate was collected, washed and dried at 100°. The solid was recrystallized from 0.5 *N* hydrochloric acid (300 ml) to give a yellowish crystal powder in 45% (1.33 g) yield, mp >300°.

Anal. Calcd. for $C_5H_3N_5O_4$ (mol wt 197.1): C, 30.47; H, 1.53; N, 35.53. Found: C, 30.27; H, 1.69; N, 34.98.

1-Methyl-8-nitroxanthine (**18**).

1-Methylxanthine (1.66 g, 10 mmoles) **(2)** was suspended in glacial acetic acid (50 ml), then heated to 100° and 65% nitric acid (1.5 ml, 33.3 mmoles) was added dropwise with stirring. After 30 minutes the reaction mixture was heated to reflux for 15 minutes and after cooling evaporated to dryness. The residue was treated with water (10 ml) for a few minutes and then the precipitate was collected by suction. The crude product (1.59 g, 75%) was recrystallized from water (200 ml)/concentrated hydrochloric acid (5 ml) to give yellow crystals in 62% (1.30 g) yield, mp >300°.

Anal. Calcd. for $C_6H_5N_5O_4$ (mol wt 211.1): C, 34.13; H, 2.39; N, 33.17. Found: C, 33.85; H, 2.37; N, 32.86.

3-Methyl-8-nitroxanthine (**19**).

In glacial acetic acid (30 ml) was heated 3-methylxanthine (1.66 g, 10 mmoles) **(3)** to 100° and then 65% nitric acid (1.5 ml, 33.3 mmoles) was added dropwise. The mixture was kept at 100° for 30 minutes and was then refluxed for 15 minutes. It was then evaporated in vacuum, the residue was treated with water (10 ml) and then the precipitate was collected. The crude product (1.69 g, 80%) was recrystallized from 0.5 *N* hydrochloric acid (400 ml) to give yellow crystals in 63% (1.32 g) yield, mp >300°.

Anal. Calcd. for $C_6H_5N_5O_4$: C, 34.13; H, 2.39; N, 33.17. Found: C, 34.31; H, 2.43; N, 32.84.

3-Benzyl-8-nitroxanthine (**20**).

A mixture of 3-benzylxanthine (3.0 g, 12.4 mmoles) **(4)** in glacial acetic acid (15 ml) was heated in an oil-bath of 120° and then 65% nitric acid (3 ml) was added dropwise with stirring. Heating was continued for 30 minutes and after cooling the precipitate was collected, washed with water and dried in the oven (2.8 g,

79%). The reaction filtrate was evaporated to dryness, the residue treated with water (10 ml) to give another precipitate (0.3 g, 8%). The crude product was recrystallized from water (150 ml/concentrated hydrochloric acid) (1 ml) to give yellowish crystals in 70% (2.5 g) yield, mp 299-301°.

Anal. Calcd. for $C_{12}H_9N_5O_4$ (mol wt 287.3): C, 50.17; H, 3.14; N, 24.39. Found: C, 50.27; H, 3.25; N, 24.24.

7-Methyl-8-nitroxanthine (**21**).

In glacial acetic acid (20 ml) was dissolved nitronium tetrafluoroborate (532 mg, 4 mmoles) and then 7-methylxanthine (332 mg, 2 mmoles) (**5**) [1] was added gradually with stirring. The mixture was then heated to 120° for 1 hour, cooled to room temperature and evaporated to dryness. The residue was treated with ice (20 g), the resulting precipitate collected, washed with little water and dried (0.18 g, 43%). Recrystallization from water (30 ml) and 5 drops of concentrated hydrochloric acid gave yellowish crystals in 38% (0.16 g) yield, mp >300°.

Anal. Calcd. for $C_6H_5N_5O_4$ (mol wt 211.1): C, 34.13; H, 2.39; N, 33.17. Found: C, 34.07; H, 2.24; N, 32.18.

1,3-Dimethyl-8-nitroxanthine (**22**) [5].

In acetic anhydride (50 ml) theophylline (5.4 g, 30 mmoles) (**6**) was suspended and after cooling to 0-5°, 65% nitric acid (4.5 ml, 10 mmoles) was added dropwise with stirring. The material dissolved and then a yellowish solid precipitated gradually. After 2 hours stirring in the ice-bath, the mixture was heated to 40° for 10 minutes, then cooled to room temperature, ethanol/water (1:1, 100 ml) added and the precipitate of chromatographically pure material (5.06 g, 75%) was collected. A recrystallized sample was obtained from 0.5 *N* hydrochloric acid in the form of yellowish crystals, mp 283° dec, lit [5] mp 282°.

Anal. Calcd. for $C_7H_7N_5O_4$ (mol wt 225.2): C, 37.34; H, 3.14; N, 31.11. Found: C, 37.38; H, 3.34; N, 31.60.

3-Benzyl-1-methyl-8-nitroxanthine (**23**).

In glacial acetic acid (20 ml) was suspended 3-benzyl-1-methylxanthine (**7**) [17] and after heating to 120°, 65% nitric acid (1.6 ml) was added dropwise with stirring. It was refluxed for 20 minutes, then cooled to room temperature, the precipitate (1.4 g) was collected, the filtrate evaporated and the residue treated with water to give another 0.12 g. The crude material was recrystallized from water/ethanol (1:1, 80 ml) to give yellowish crystals in 59% (1.38 g) yield, mp 221-222°.

Anal. Calcd. for $C_{13}H_{11}N_5O_4$ (mol wt 301.3): C, 51.83; H, 3.68; N, 23.25. Found: C, 51.87; H, 3.72; N, 23.03.

1,7-Dimethyl-8-nitroxanthine (**24**).

a) 1,7-Dimethylxanthine (0.18 g, 1 mmole) (**8**) [1] in sulfolane (3 ml) was treated at room temperature with a 0.5 *M* solution of nitronium tetrafluoroborate in sulfolane (4 ml) by dropwise addition with stirring. The solution was then heated to 120° for 30 minutes. Evaporation under vacuum and subsequent addition of ethanol (5 ml) led to a precipitate which was collected and gave after recrystallization from ethanol (20 ml) yellow crystals in 38% (0.08 g) yield, mp 234-235°.

b) To a solution of nitronium tetrafluoroborate (226 mg, 2 mmoles) in glacial acetic acid (10 ml) was added 1,7-dimethylxanthine (0.18 g, 1 mmole) (**8**) with stirring. The mixture was heated to 100° for 30 minutes and then evaporated under vacuum. The residue was treated with water (5 ml), the precipitate collected and then recrystallized from ethanol (20 ml) to give yellow crystals in 35% (78 mg) yield, mp 234-235°.

Anal. Calcd. for $C_7H_7N_5O_4$ (mol wt 225.2): C, 37.34; H, 3.13; N, 31.11. Found: C, 37.50; H, 3.02; N, 30.42.

3,7-Dimethyl-8-nitroxanthine (**25**).

To a solution of nitronium tetrafluoroborate (266 mg, 2 mmoles) in glacial acetic acid (10 ml) was added theobromine (188 mg, 1 mmole) (**9**) with stirring. The mixture was then heated to 120° for 1 hour and after cooling evaporated to dryness. The residue was treated with ice (10 g) for a few minutes and the precipitate collected. Recrystallization from ethanol/water (1:1, 40 ml) and addition of 3 drops of concentrated hydrochloric acid gave yellow crystals in 30% (68 mg) yield, mp 287-290°.

Anal. Calcd. for $C_7H_7N_5O_4$ (mol wt 225.2): C, 37.34; H, 3.14; N, 31.11. Found: C, 37.70; H, 3.18; N, 30.84.

3-Benzyl-7-methyl-8-nitroxanthine (**26**).

To a solution of nitronium tetrafluoroborate (266 mg, 2 mmoles) in glacial acetic acid (10 ml) was added 3-benzyl-7-methylxanthine (256 mg, 1 mmole) (**10**) [1] with stirring. The reaction mixture was heated to 120° for 1 hour under anhydrous conditions and was then evaporated to dryness in vacuum. The residue was treated with ice (10 g) by stirring for 30 minutes. The precipitate was collected and gave after recrystallization from 0.5 *N* hydrochloric acid (30 ml) yellow crystals in 27% (80 mg) yield, mp 223-225°.

Anal. Calcd. for $C_{13}H_{11}N_5O_4$ (mol wt 301.3): C, 51.83; H, 3.69; N, 23.25. Found: C, 51.70; H, 3.60; N, 22.98.

1,3,7-Trimethyl-8-nitroxanthine (**27**) [10,11].

a) In glacial acetic acid (5 ml) was dissolved caffeine (1.94 g, 10 mmoles) (**11**) at 100° and then 65% nitric acid (2 ml, 44.4 mmoles) was added dropwise with stirring. It was heated to 100° for 1 hour, evaporated in vacuum, the residue treated with 1 *N* sodium bicarbonate (20 ml), then extracted with chloroform (2 x 50 ml), the organic layer dried over sodium sulfate and finally evaporated again. The residue was recrystallized from methanol (30 ml) to give yellowish crystals in 25% (0.6 g) yield, mp 173°, lit [11] 171-172°.

b) To a solution of nitronium tetrafluoroborate (266 mg, 1 mmole) in glacial acetic acid (5 ml) was added caffeine (194 mg, 1 mmole) (**11**) with stirring. The mixture was heated to 90° for 1 hour, then evaporated to dryness, the residue treated with 0.5 *N* sodium bicarbonate (40 ml) and finally extracted with chloroform (2 x 50 ml). The chloroform extract was dried over sodium sulfate, evaporated, the residue stirred with methanol (5 ml) and the solid collected by suction. Recrystallization from methanol (10 ml) gave yellow crystals in 39% (94 mg) yield, mp 173°.

c) In anhydrous DMF (30 ml) 1,3-dimethyl-8-nitroxanthine (1.5 g, 6.7 mmoles) (**22**), potassium carbonate (1 g) and methyl iodide (1 ml, 16 mmoles) were heated to 80° for 30 minutes and subsequently stirred at room temperature for a few hours. The reaction solution was diluted with water (30 ml) whereby a precipitate separated out. The solid was collected, washed with little water and methanol and dried at 80° (1.13 g, 71%). Workup of the filtrate gave another crop (0.1 g, 6%). The crude material was recrystallized from methanol (60 ml) to give yellow crystals in 60% (1.23 g) yield, mp 173°.

All three products prepared by different methods turned out to be chromatographically and spectrophotometrically identical.

3-Benzyl-1,7-dimethyl-8-nitroxanthine (**28**).

a) A suspension of 3-benzyl-1,7-dimethylxanthine (0.27 g, 1 mmole) (**12**) [1] in sulfolane (3 ml) was treated with a 0.5 *M* solution of nitronium tetrafluoroborate (4 ml) in sulfolane by dropwise addition. It was stirred at room temperature for 30 minutes and then heated to 120° for 30 minutes. The mixture was evaporated in vacuum to dryness, the residue treated with ethanol (5 ml) and the precipitate collected. Recrystallization from ethanol (20 ml) gave yellowish crystals in 29% (90 mg) yield, mp 182-183°.

b) To a solution of nitronium tetrafluoroborate (266 mg, 2 mmoles) in glacial acetic acid (5 ml) was added 3-benzyl-1,7-dimethylxanthine (0.27 g, 1 mmole) (**12**) [1] and then the mixture heated to 100° for 30 minutes. After evaporation to dryness the residue was treated with water (5 ml), the precipitate collected and recrystallized from ethanol (20 ml) to give yellow crystals in 30% (95 mg) yield, mp 182°.

Anal. Calcd. for $C_{14}H_{13}N_5O_4$ (mol wt 315.3): C, 53.33; H, 4.16; N, 22.22. Found: C, 53.33; H, 4.12; N, 21.92.

9-Methyl-8-nitroxanthine (**29**) [13].

In glacial acetic acid (40 ml) was suspended 9-methylxanthine (2.0 g, 12 mmoles) (**13**) [18] and then 65% nitric acid (4 ml, 89 mmoles) was added dropwise with stirring. The mixture was subsequently heated to 100° for 30 minutes and to 120° for 15 minutes. After evaporation the residue was treated with water (20 ml), the precipitate collected and then recrystallized from 0.5 *N* hydrochloric acid (100 ml) to give yellow crystals in 40% (1.02 g) yield, mp >300°.

Anal. Calcd. for $C_6H_5N_5O_4$ (mol wt 211.1): C, 34.13; H, 2.39; N, 33.17. Found: C, 34.16; H, 2.41; N, 32.90.

1,9-Dimethyl-8-nitroxanthine (**30**).

A suspension of 1,9-dimethylxanthine (1.8 g, 10 mmoles) (**14**) in glacial acetic acid (10 ml) was treated with 65% nitric acid (1.8 ml, 40 mmoles) at 90° for 15 minutes with stirring. The adduct dissolved after 5 minutes and shortly later a yellow precipitate was formed. The reaction mixture was chilled in an ice-bath, then the solid collected, washed with water and dried in the oven (1.62 g, 72%). Recrystallization from 0.5 *N* hydrochloric acid (200 ml) gave yellow crystals in 63% (1.42 g) yield, mp >300°.

Anal. Calcd. for $C_7H_7N_5O_4$ (mol wt 225.2): C, 37.34; H, 3.14; N, 31.11. Found: C, 37.23; H, 3.11; N, 30.92.

3,9-Dimethyl-8-nitroxanthine (**31**).

a) To a solution of nitronium tetrafluoroborate (266 mg, 2 mmoles) in glacial acetic acid (5 ml) was added 3,9-dimethylxanthine (0.18 g, 1 mmole) (**15**) [16] and the mixture heated to 100° for 1 hour with stirring. After evaporation the residue was treated with water (5 ml), the precipitate collected and recrystallized from a mixture of water (20 ml) and 3 drops of concentrated hydrochloric acid to give yellowish crystals in 40% (90 mg) yield, mp 276°.

b) A suspension of 3,9-dimethylxanthine (0.18 g, 1 mmole) (**15**) in sulfolane (3 ml) was treated by dropwise addition of a 0.5 *M* solution of nitronium tetrafluoroborate (4 ml, 2 mmoles) with stirring at room temperature. The mixture was then heated to 120° for 30 minutes, evaporated and the residue treated with ethanol (5 ml). The precipitate was collected and gave on recrystallization from water (30 ml) and a few drops of concentrated hydrochloric acid yellowish crystals in 42% (95 mg) yield, mp 275-277°.

Anal. Calcd. for $C_7H_7N_5O_4$ (mol wt 225.2): C, 37.34; H, 3.14; N, 31.11. Found: C, 37.17; H, 2.85; N, 30.72.

1,3,9-Trimethyl-8-nitroxanthine (**32**).

To glacial acetic acid (20 ml) was added subsequently nitronium tetrafluoroborate (1.06 g, 8 mmoles) and isocaffeine (776 mg, 4 mmoles) (**16**) with stirring. The mixture was then heated to 80° for 1 hour. After cooling the reaction solution was evaporated, the residue treated with water (60 ml) and then extracted with dichloromethane (300 ml). The dichloromethane extract was dried over sodium sulfate, filtered, again evaporated and finally the residue recrystallized from ethanol (20 ml). Yellow crystals were obtained in 23% (0.22 g) yield, mp 232-233°.

Anal. Calcd. for $C_8H_9N_5O_4$ (mol wt 239.2): C, 40.17; H, 3.79; N, 29.28. Found: C, 40.00; H, 3.84; N, 28.85.

8-Chloro-3-methylxanthine (**33**) [20,21].

In concentrated hydrochloric acid (20 ml) was refluxed 3-methyl-8-nitroxanthine (0.3 g, 1.42 mmoles) (**9**) for 15 minutes whereby the yellow solution became colorless and a precipitate separated out. The reaction mixture was evaporated to dryness, the residue treated with water (10 ml), the solid collected and dried (0.27 g, 95%). Recrystallization from water gave a colorless crystal powder in 88% (0.25 g) yield, mp 330°, lit [20] 340-345°.

Anal. Calcd. for $C_6H_5ClN_4O_2$ (mol wt 200.7): C, 35.92; H, 2.51; N, 27.93. Found: C, 35.67; H, 2.70; N, 27.78.

8-Chloro-1,3-dimethylxanthine (**34**) [8,20].

In concentrated hydrochloric acid (15 ml) was refluxed 1,3-dimethyl-8-nitroxanthine (0.3 g, 13.3 mmoles) (**22**) for 30 minutes. The reaction mixture was evaporated to dryness, the residue treated with water (10 ml) and the *p*H adjusted to 5 by ammonia. The precipitate was collected and gave on recrystallization from water (20 ml) colorless crystals in 59% (0.16 g) yield, mp 310-311°, lit [20] 300°; uv (*p*H 13): 216 (4.17), 276 (4.05); ^{1}H-nmr (DMSO-d_6): 16.4 (s, 1 H, 7-NH), 3.40 (s, 3H, 3-CH_3), 3.20 (s, 3H, 1-CH_3).

8-Ethoxy-1,3,7-trimethylxanthine (**35**) [22].

A suspension of 8-nitrocaffeine (0.12 g, 0.5 mmole) (**27**) in ethanol (5 ml) was combined with a solution of sodium (20 mg) in absolute ethanol (10 ml) and then stirred at room temperature. After 15 minutes a clear solution was obtained from which a colorless solid separated. The reaction mixture was evaporated after 2 hours, the residue was treated with a mixture of water (20 ml) and acetic acid (5 ml) and the solid collected. Recrystallization from methanol (8 ml) gave colorless crystals in 79% (94 mg) yield, mp 143°, lit [22] 140°; uv (methanol): 205 (4.33), 278 (4.11); ^{1}H-nmr (DMSO-d_6): 4.44 (q, 2H, CH_2), 3.53 (s, 3H, 7-CH_3), 3.26 (s, 3H, 3-CH_3), 3.14 (s, 3H, 1-CH_3), 1.35 (t, 3H, C-CH_3).

Anal. Calcd. for $C_{10}H_{14}N_4O_3$ (mol wt 238.6): C, 50.42; H, 5.88; N, 23.53. Found: C, 50.61; H, 6.00; N, 23.66.

3-Benzyl-8-ethoxy-1,7-dimethylxanthine (**36**).

In a mixture of 10% potassium hydroxide (5 ml) and ethanol (15 ml) 3-benzyl-1,7-dimethylxanthine (0.15 g, 0.48 mmole) (**28**) was dissolved at 50° with stirring. After 15 minutes it was neutralized with acetic acid to *p*H 6, the precipitate collected and recrystallized from ethanol (8 ml) to give colorless crystals in 54% (80 mg) yield, mp 134-135°; uv (methanol): 206 (4.48), 278 (4.13); ^{1}H-nmr (DMSO-d_6): 7.28 (m, 5H, Ph), 5.08 (s, 2H, CH_2 (benzyl)), 4.46 (q, 2H, CH_2 (ethyl)), 3.57 (s, 3H, 7-CH_3), 3.18 (s, 3H, 1-CH_3), 1.35 (t, 3H, C-CH_3).

Anal. Calcd. for $C_{16}H_{18}N_4O_3$ (mol wt 314.3): C, 61.13; H, 5.77; N, 17.83. Found: C, 61.14; H, 5.87; N, 17.79.

7-Methyluric Acid (**37**) [23,24].

In 1 *N* sodium hydroxide (10 ml) 7-methyl-8-nitroxanthine (80 mg, 0.38 mmole) (**21**) was heated to 90° for 30 minutes with stirring. The hot solution was acidified to *p*H 2 and the precipitate collected after cooling to room temperature. The solid was reprecipitated from 1 *N* sodium hydroxide with 1 *N* hydrochloric acid from hot solution to give a colorless crystal powder in 37% (25 mg) yield, mp >300°; uv (*p*H 13): 220 (4.45), [250] (3.52), 296 (4.10).

1,3,7-Trimethyluric Acid (**38**) [23,24].

In 1 *N* sodium hydroxide (20 ml) 8-nitrocaffeine (239 mg, 1 mmole) (**27**) was heated to 90° for 15 minutes with stirring. The hot solution was acidified to *p*H 2, after cooling the precipitate was collected and dried at 100° (126 mg, 60%). Recrystallization from water (50 mg/ml) gave a colorless crystal powder in 43% (90 mg) yield, mp >310°, lit [23] >300°; uv (*p*H 9): 216 (4.15), 248 (3.58), 295 (4.23).

9-Methyluric Acid (**39**) [24,25].

In 2 *N* sodium hydroxide (20 ml) 9-methyl-8-nitroxanthine (211 mg, 1 mmole) (**29**) was heated to 80-90° for 2 hours with stirring. The hot solution was acidified to *p*H 1 with hydrochloric acid and the precipitate was collected after cooling to room temperature. Reprecipitation from 1 *N* sodium hydroxide and 2 *N* hydrochloric acid in hot solution gave a colorless powder in 35% (64 mg) yield, mp >300°, lit [25] >300°; (*p*H 14): 247 (3.90), 298 (4.05).

1,3,9-Trimethyluric Acid (**40**) [24,26].

In 1 *N* sodium hydroxide (5 ml) 8-nitro-1,3,9-trimethylxanthine (90 mg, 0.38 mmole) (**32**) was heated to 90° for 1 hour and then the hot solution acidified to *p*H 1 with hydrochloric acid. The solution was evaporated to dryness, the residue treated with water (5 ml), the precipitate was collected and then recrystallized from water/charcoal to give 10% (8 mg) isolated yield, mp >300°, lit [24] 335° dec.

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