Synthesis of 8-Substituted Xanthines and Their Oxidative Skeleton Rearrangement to 1-Oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones

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The synthesis of a number of 8-(dialkylamino)- and 8-alkoxyxanthines (**3** and **6**, respectively) is described. Treatment of **3** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave by a novel rearrangement 3-(disubstituted amino)-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones **10**. Also, the corresponding 3-alkoxy-subtituted spiro compounds **12** were obtained by an analogus treatment of 8-alkoxyxanthines **6**. In attempts to elucidate a tentative mechanism for this rearrangement 8-[(dialkylamino)methyl]caffeines **7** when treated with *m*-CPBA did not undergo the rearrangement but only yielded the expected *N*-oxide derivatives **16**. This result seems to indicate that a necessary structure element for this rearrangement to occur is an atom with an unshared pair of electrons to be attached to the 8-position of the investigated xanthines. In agreement with this statement is the fact that *N*-oxides of 8-[(dialkylamino)methyl]caffeines **16** do not undergo the novel rearrangement but rather give the expected Meisenheimer rearrangement or the Cope elimination depending upon reaction conditions.

Introduction

Compounds based on the xanthine skeleton have always been of great interest for their biological activities. Thus, 8-(disubstituted amino)-1,3,7-trisubstituted xanthines belong to a pharmacologically important subclass of xanthine.[1−5] A recent preliminary report from our research group[6] described a novel rearrangement of these compounds to 3-(disubstituted amino)-4,7,9-trisubstituted-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones while attempting to convert these 8-amino-substituted species to the corresponding *N*-oxides by using *m*-chloroperoxybenzoic acid as oxidizing agent. Interestingly and important for the elucidation of the mechanism of this new rearrangement is the observation that it does not occur if the dialkylamino moiety is separated by a $-CH_2-$ unit from the xanthine ring (Scheme 1). In the following report we describe the result of our continuing efforts to investigate the scope and limitation of this novel rearrangement.

Results and Discussions

Synthesis of 8-Functionally Substituted Xanthine Derivatives

While 1,3,7-trimethylxanthine (caffeine) (**1a**) is commercially available, 1,3,7-triethylxanthine (**1b**) could be prepared by direct ethylation of xanthine as reported earlier by Ogilvie et al.[7] 1,3-Di-*n*-propylxanthine (**1c**) and 1,3-di-*n*-butylxanthine (**1d**) were synthesized following a pathway which is very similar to the synthesis by Traube.[8][9] Ethylation of the 7-position of **1c** afforded **1e**.

Toward the syntheses of 8-dialkylamino-1,3,7-trisubstituted xanthines, compounds **1a**,**b**,**d**,**e** were brominated using elemental bromine in nitrobenzene to give **2a−d**. Synthesis of 1,3-di-*n*-butyl-7-ethylxanthine (**2e**) was achieved by bromination of **1d** followed by ethylation. Substitution at the 8-position of substituted xanthine by dialkylamino groups was done by previously reported procedures,[10−14] namely by a direct nucleophilic substitution reaction between dialkylamines and the 1,3,7-trialkyl-8-bromoxanthine **2** to furnish compounds **3** (Equation 1). In an attempt to include functionally substituted dialkylamino groups in the reaction Scheme we chose a number of different substituents of this type. Therefore we elected to condense **2a** with a number of alkyamino acids. Thus, *N*-methylsarcosine and proline gave the anticipated products; however, *N*-methylhistidine, even under pressure (ca. 50 ψ), did not condense with **2a**, possibly due to steric hindrance. 8-(*N*′-Acetylpiperazino)caffeine (**3r**), another substituent in the 8-position with two N atoms, was obtained by acetylation of **3l** with acetyl chloride in dimethylformamide. Acetylation of 8-(2,2-di-

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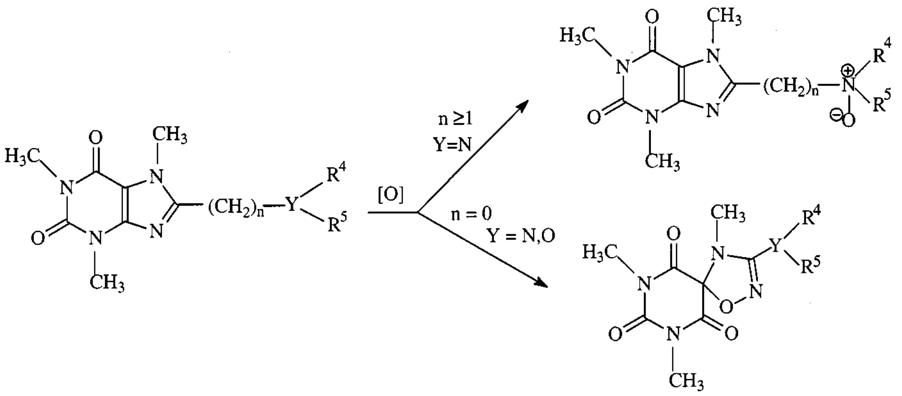
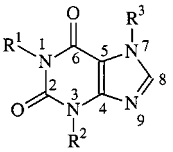


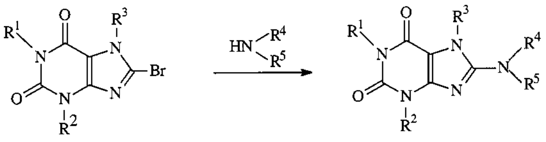
Scheme 1. Oxidation of 8-dialkylaminocaffeines by *m*-CPBA



1

1	**a**	**b**	**c**	**d**	**e**
$\mathbf{R^1}$	Me	Et	*n*-Prop	*n*-Bu	*n*-Prop
$\mathbf{R^2}$	Me	Et	*n*-Prop	*n*-Bu	*n*-Prop
$\mathbf{R^3}$	Me	Et	H	H	H

Figure 1. 1,3,7-Trialkylcaffeines



2 **3**

(eq. 1)

3	**a**	**b**	**c**	**d**	**e**	**f**	**g**
$\mathbf{R^1}$	Me	Me	Me	Me	Me	Me	Me
$\mathbf{R^2}$	Me	Me	Me	Me	Me	Me	Me
$\mathbf{R^3}$	Me	Me	Me	Me	Me	Me	Me
$\mathbf{R^4}$	Me	Et	$-(CH_2)_2Cl$	$CH_2C_6H_5$	H	$-(CH_2)_2OH$	$-(CH_2)_2$ O
$\mathbf{R^5}$	Me	Et	$-(CH_2)_2Cl$	$CH_2C_6H_5$	C_6H_5	$-(CH_2)_2OH$	$-(CH_2)_2$

3	**h**	**i**	**j**	**k**	**l**	**m**
$\mathbf{R^1}$	Me	Me	Me	Me	Me	Me
$\mathbf{R^2}$	Me	Me	Me	Me	Me	Me
$\mathbf{R^3}$	Me	Me	Me	Me	Me	Me
$\mathbf{R^4}$	$-(CH_2)_2$ CH_2	$-(CH_2)_3$ $CH\text{-}CH_3$	*i*-Bu	*n*-Pent	$-(CH_2)_2$ N	Me
$\mathbf{R^5}$	$-(CH_2)_2$	$-(CH_2)_3$	*i*-Bu	*n*-Pent	$-(CH_2)_2$	$-(CH_2)_2N(CH_3)_2$

3	**n**	**o**	**p**	**q**
$\mathbf{R^1}$	Me	Me	Me	Me
$\mathbf{R^2}$	Me	Me	Me	Me
$\mathbf{R^3}$	Me	Me	Me	Me
$\mathbf{R^4}$	Me	Me	$-(CH_2)_3$ $CHCO_2$-*n*-Bu	Me
$\mathbf{R^5}$	$(CH_2)_3N(CH_3)_2$	CH_2CO_2-*n*-Bu	$-(CH_2)_3$	C_6H_5

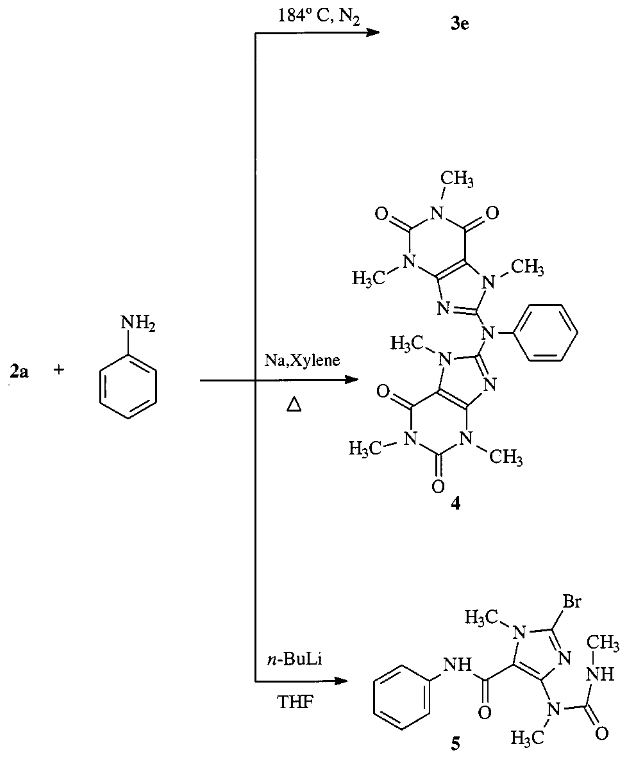
3	**r**	**s**	**t**	**u**
$\mathbf{R^1}$	Me	Me	Et	Et
$\mathbf{R^2}$	Me	Me	Et	Et
$\mathbf{R^3}$	Me	Me	Et	Et
$\mathbf{R^4}$	$(Et)_2NC(O)CH_3$	$(CH_2)_2OC(O)CH_3$	$-(CH_2)_2$ O	*n*-Bu
$\mathbf{R^5}$	$(Et)_2NC(O)CH_3$	$(CH_2)_2OC(O)CH_3$	$-(CH_2)_2$	H

hydroxyethylamino)caffeine (**3f**) with acetic anhydride in the presence of pyridine at 145°C for 3 h afforded the diacetate **3s**.

Obtaining of 8-(*N*-methylanilino)caffeine (**3q**) was thought best to be accomplished by methylation of 8-anilinocaffeine[11] (**3e**). Compound **3q** was chosen as an example with an aromatic substituent at the N atom of the 8-position. Thus, a reaction of **2a** with aniline was carried out as reported earlier[11] to afforded **3e** in good yield. In order to optimize the yield of **3e**, aniline was converted into its sodium salt by dissolving it in a sodium suspension in boiling xylene; however, the expected amination of **2a** did not occur but instead *N*,*N*-bis(8-caffeinyl)aniline (**4**) was isolated (Scheme 2). Likewise, treatment of an aniline solution in tetrahydrofuran (at −78°C) with *n*-butyllithium followed by addition of **2a** did not yield the expected **3e** but 2-bromo-4-(1,3-dimethylureidyl)-1-methyl-5-(*N*-phenylformamidyl)-imidazole (**5**) was the product of this reaction. The structural assignment of **5** is not only based on ^1H-NMR and MS spectral data as well as elemental analysis, but its structure was unequivocally secured by an X-ray crystallographic analysis (Figure 2). While performing these reactions attempts for direct coupling between 8-bromocaffeine and *N*-methylaniline went without difficulty to afford **3q** in good yield.

Refluxing 8-bromo-1,3,7-triethylxanthine (**2b**) with dimethyl- or diethylamine in boiling butanol failed to afford the corresponding 8-(dialkylamino) analogs. On the other hand **2b** reacted with morpholine to give the expected 8-morpholino compound **3t** in moderate yield. However, under the same condition as mentioned above, **2b** reacted with *n*-butylamine to afford **3u** in good yield. In order to prepare the 8-(dialkylamino) compound **3v**, an ethylation attempt of **3u** was made using diethyl sulfate in tetrahydrofuran. However, no reaction took place. Replacing the solvent with higher boiling *N*,*N*-dimethylformamide and increasing the diethyl sulfate concentration led to the formation of the expected 8-[(*n*-butyl)(ethyl)amino]-1,3,7-triethylxanthine (**3v**) and 8-[(*n*-butyl)(formyl)amino]-1,3,7-triethylxanthine (**3w**) (Equation 2).

The 8-alkoxyxanthines **6a−g** were synthesized basically by following the previously described procedure.[15−17]



Scheme 2. Reaction of 8-bromocaffeine with aniline

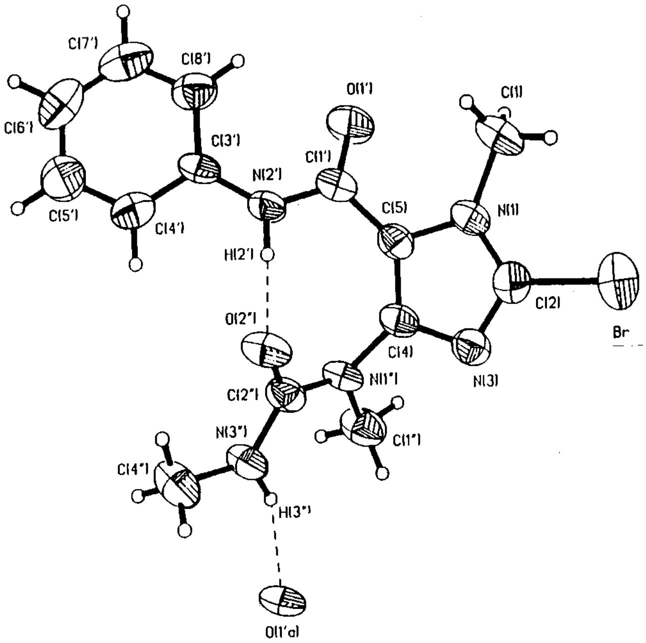
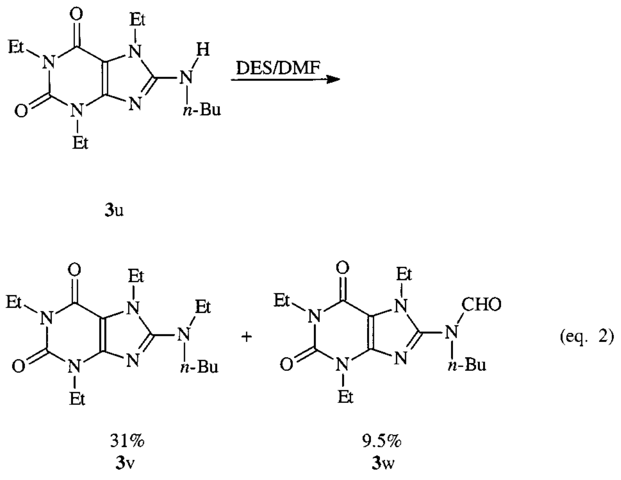
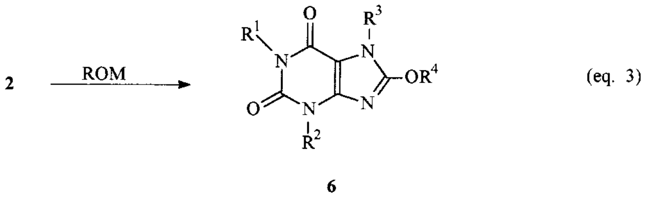


Figure 2. Molecular structure of **5** in the crystal

Thus, refluxing **2** with sodium or lithium alkoxides using an appropriate solvent afforded the desired **6a−g** in good yields (Equation 3).

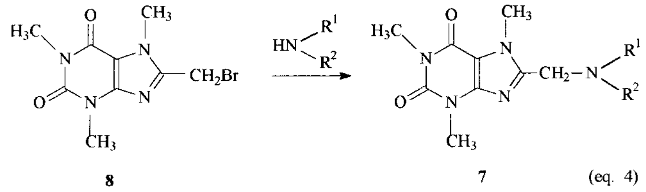
The desired 8-[(dialkylamino)methyl]caffeines **7** were obtained by a modified procedure introduced by Golovchinskaya[18] using (bromomethyl)caffeine[13] (**8**) (Equation 4). Refluxing this compound with the appropriate dialkylamine in n-butanol furnished compounds **7a−e** in good yields (Equation 4).





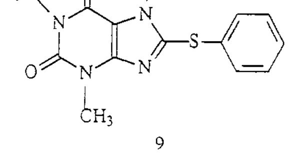
6

6	a	b	c	d	e	f	g
R^1	Me	Me	Me	Me	Me	Prop	Bu
R^2	Me	Me	Me	Me	Me	Prop	Bu
R^3	Me	Me	Me	Me	Me	Et	Et
R^4	Me	Et	n-Bu	CH_2CF_3	$CH_2CH_2N(Me)_2$	CH_2CF_3	CH_2CF_3



7	a	b	c	d	e
R^1	CH_2CH_2 O	Et	Prop	Bu	i-Pent
R^2	CH_2CH_2	Et	Prop	Bu	i-Pent

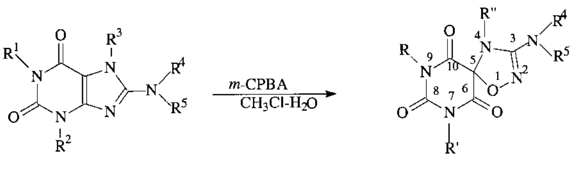
When instead of the earlier reported method, using aqueous-alcoholic sodium hydroxide[19] equivalent amounts of **2a** and thiophenol in the presence of triethylamine were refluxed in n-butanol, 8-(phenylthio)caffeine **9** was obtained.



9

Oxidation of 8-Substituted Xanthines

All 8-substituted xanthines were subjected to *m*-chloroperoxybenzoic acid oxidation in a water/chloroform solvent mixture. Straight-chain as well as branched-chain 8-(dialkylamino)caffeines underwent smoothly the novel skeleton rearrangement to the hitherto unknown 3-(disubstituted amino)-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones **10a−n** (Equation 5). The rearranged products could be easily recognized by their ^{1}H-NMR spectra, which showed two singlets with an integral ratio of 2:1. This is due to the fact that the methyl groups in positions 1 and 3 (δ = 3.30−3.40) of the starting materials became equivalent in the rearranged products. The remaining singlet (δ = 2.80−2.90) arises from the methyl group at position 4 of **10**. The upfield shift of this observation can be rationalized by the loss of the aromatic character of the caffeine system. Similarly, compound **3t** was transformed to **10o**.



$R^1, R^2 \neq Nalk_2$ **10** (eq. 5)

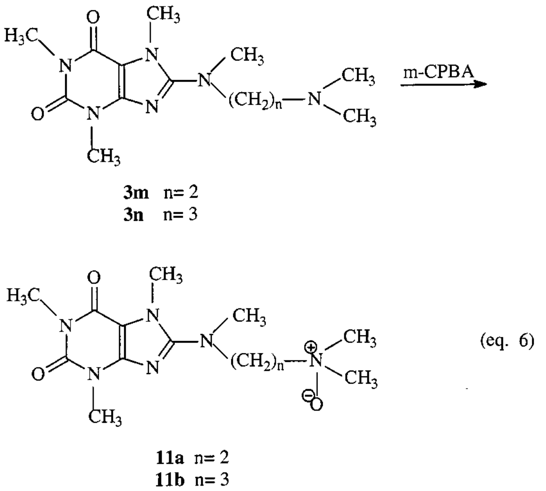
10	a	b	c	d	e	f	g
R¹	Me	Me	Me	Me	Me	Me	Me
R²	Me	Me	Me	Me	Me	Me	Me
R³	Me	Me	Me	Me	Me	Me	Me
R⁴	Me	Et	$(CH_2)_2Cl$	Bz	$-(CH_2)_2\diagdown O$	$-(CH_2)_2\diagdown CH_2$	$-(CH_2)_3\diagdown CH\text{-}CH_3$
R⁵	Me	Et	$(CH_2)_2Cl$	Bz	$-(CH_2)_2\diagup$	$-(CH_2)_2\diagup$	$-(CH_2)_3\diagup$

10	h	i	j	k
R¹	Me	Me	Me	Me
R²	Me	Me	Me	Me
R³	Me	Me	Me	Me
R⁴	$CH_2CH(CH_3)_2$	$CH_2(CH_2)_3CH_3$	Me	$-(CH_2)_3\diagdown CHCO_2\text{-}n\text{-}Bu$
R⁵	$CH_2CH(CH_3)_2$	$CH_2(CH_2)_3CH_3$	$CH_2CO_2\text{-}n\text{-}Bu$	$-(CH_2)_3\diagup$

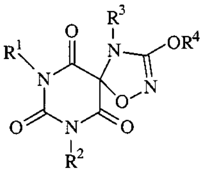
10	l	m	n	o
R¹	Me	Me	Me	Et
R²	Me	Me	Me	Et
R³	Me	Me	Me	Et
R⁴	Me	$-(CH_2)_2\diagdown NC(O)CH_3$	$-(CH_2)_2OC(O)CH_3$	$-(CH_2)_2\diagdown O$
R⁵	C_6H_5	$-(CH_2)_2\diagup$	$-(CH_2)_2OC(O)CH_3$	$-(CH_2)_2\diagup$

Attempts to rearrange 8-substituted caffeines with a second amino function in the side chain employing the same conditions were not successful. Thus, *N*′-(8-caffeinyl)-*N*,*N*,*N*′-trimethyl-1,2-ethylenediamine (**3m**) and *N*′-(8-caffeinyl)-*N*,*N*,*N*′-trimethyl-1,3-propylenediamine (**3n**) gave only the mono-*N*-oxides **11a** and **11b** as reaction products (Equation 6).

The position of the *N*-oxidation was found to be at the terminal tertiary nitrogen atom and not at the nitrogen atom adjacent to the ring. This assignment is based on the significant downfield shift of the signals of the methyl groups of the terminal dimethylamino group in the ^{1}H-NMR spectra of **11a** and **11b**. While the chemical shift for these protons are δ = 2.27 for **3m** and δ = 2.20 for **3n**, they shifted to δ = 3.27 and 3.22 in the mono-*N*-oxidized derivatives **11a** and **11b**. However, when the second N atom of the side chain at the 8-position belongs to an amido group rather than an amino group such as the one of **3r**, the novel rearrangement did occur. This is probably due to the decreased nucleophilicity of the second N atom because of its resonance involvement with the amido carbonyl group.



Similarly, 3-alkoxy-4,7,9-trialkyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones **12a−f** were obtained by rearrangement of the appropriate 8-alkoxyxanthines **6a−d**,**f**,**g** (Figure 3).



12

12	a	b	c	d	e	f
R¹	Me	Me	Me	Me	*n*-Prop	*n*-Bu
R²	Me	Me	Me	Me	*n*-Prop	*n*-Bu
R³	Me	Me	Me	Me	Et	Et
R⁴	Me	Et	*n*-Bu	CH_2CF_3	CH_2CF_3	CH_2CF_3

Figure 3. Molecular structure of **12**

The structural assignment for these spiro compounds is also based on spectral data analysis, elemental analysis, and secured by an X-ray analysis of compound **12c** as a prototype (Figure 4).

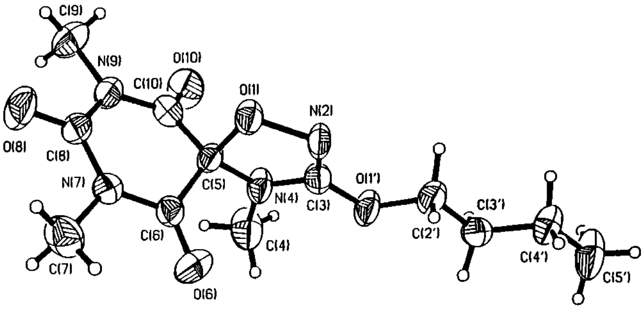
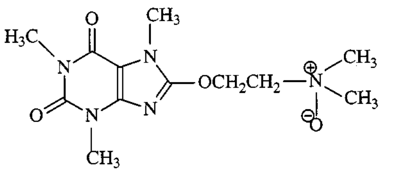


Figure 4. Molecular structure of **12c** in the crystal



13

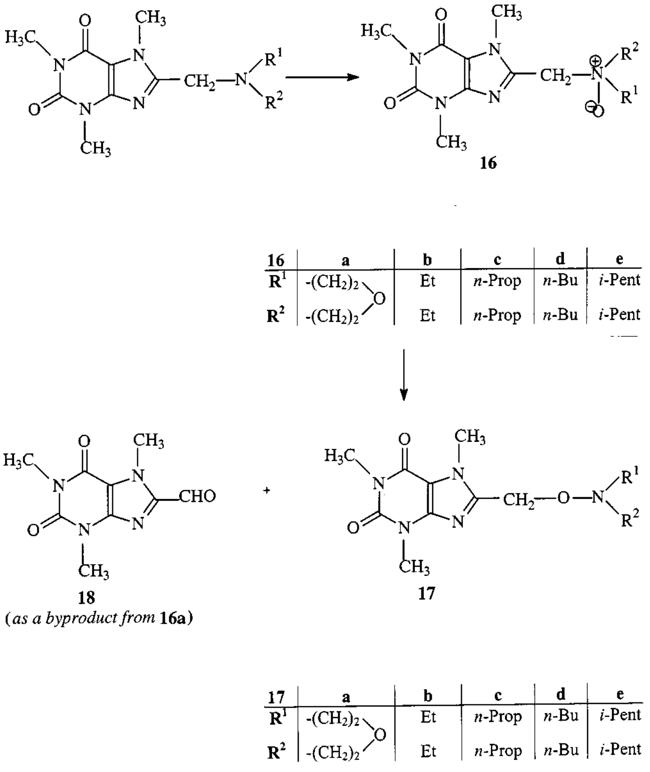
Figure 5. Molecular structure of **13**

Again, introducing an amino function to the alkoxy group led in a normal reaction only to the *N*-oxide at this nitrogen atom. Thus, when 8-[2-(dimethylamino)ethoxy]caffeine (**6e**) was treated with *m*-CPBA only its *N*-oxide **13** was isolated (Figure 5). No trace of a rearranged product could be detected. At present we do not have a satisfactory explanation for the failure of the rearrangement to occur in these compounds.

From these results it seems to become evident that for the observed rearrangement to happen the atom attached to the 8-position of the xanthine system has to have an unshared pair of electrons available, moreover it has also to be divalent, since **2** under the same condition did not rearrange because the bromine atom is not capable of being part of the five-membered ring of the newly formed spiro compound. These prerequisites for the rearrangement are not in disagreement with the fact that **9** did not rearrange in spite of the fact that the sulfur atom attached to the 8-position of caffeine possesses an unshared pair of electrons. But under these conditions the sulfur atom is oxidized by *m*-CPBA to the sulfoxide **14** and the sulfone **15**. Apparently, these oxidations occur faster than the described rearrangement.

Though we did not attempt to elucidate in detail the mechanism of the reported novel rearrangement, the mechanism as depicted in Scheme 3 seems to us the most logical one. It explains the decisive role of the unshared pair of electrons on the atom at the 8-position which renders the N atom at the 9-position highly nucleophilic, and thus initiates the oxidative rearrangement. A second equivalent of peracid then reacts with the 5,6-carbon−carbon double bond of the intermediately formed 9-oxide followed by opening of the imidazole ring to give, by the postulated oxirane and subsequent ring-closure, the final spiro compound.

Another strong evidence for the necessity of an atom with an unshared pair of electrons adjacent to the xanthine system is based on the failure of the 8-[(dialkylamino)methyl]caffeines **7a−e** to rearrange when treated with *m*-CPBA. Compounds of type **7** yielded only the corresponding *N*-oxides **16** (Scheme 3). As expected they underwent a normal *N*-oxide decomposition to give the *O*-substituted hydroxyamines **17a−e**. The 8-formylcaffeine **18** was isolated as a by-product in case of **16a**. The formation of **17a−e** can be explained by a Meisenheimer rearrangement[20] (namely, by a bond cleavage/recombination mechanism) followed by a Cope elimination[21] to yield **18**.



16

16	a	b	c	d	e
R^1	$-(CH_2)_2$ O	Et	*n*-Prop	*n*-Bu	*i*-Pent
R^2	$-(CH_2)_2$	Et	*n*-Prop	*n*-Bu	*i*-Pent

18
(*as a byproduct from* **16a**)

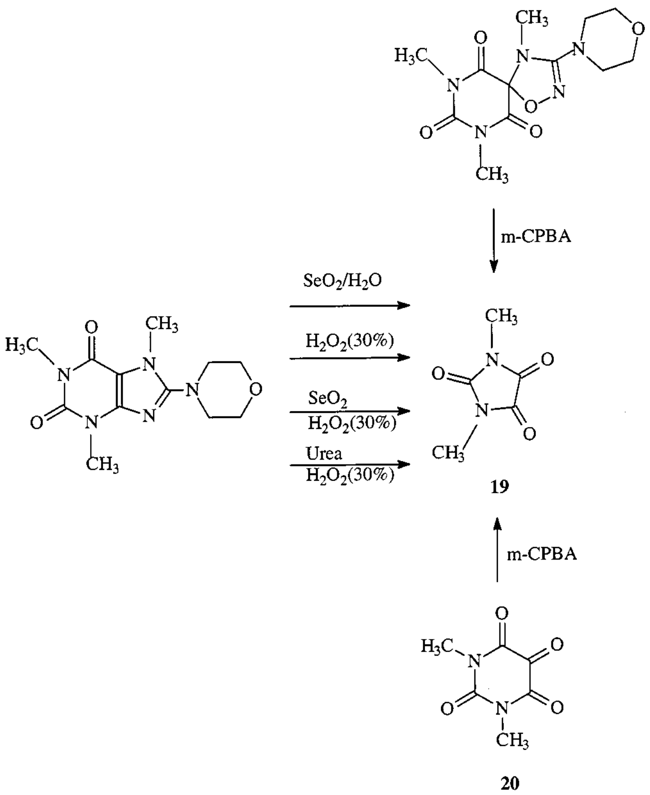
17

17	a	b	c	d	e
R^1	$-(CH_2)_2$ O	Et	*n*-Prop	*n*-Bu	*i*-Pent
R^2	$-(CH_2)_2$	Et	*n*-Prop	*n*-Bu	*i*-Pent

Scheme 3. Course of oxidation of 8-dialkylaminomethylcaffeine *N*-oxide

Since there are a variety of chemical oxidation reactions of purine analogs described in earlier literature[22−32] and since none of these oxidations led to our novel rearrangement, it seemed reasonable to investigate the action of other oxidizing agents, in order to learn about the role − if any − of such agents. Thus, using 8-morpholinocaffeine as a prototype, this compound was utilized to investigate the result of oxidations with a number of different oxidizing agents. Selenium dioxide, hydrogen peroxide, and a mixture of selenium dioxide and hydrogen peroxide, as well as a mixture of urea and hydrogen peroxide were employed in this study. In each case 1,3-dimethylparabanic acid (**19**) was obtained as the sole reaction product (Scheme 4). This acid also is the product of the exhaustive oxidation of caffeine using hydrogen peroxide. Later it was found that the labile *m*-CPBA can be replaced by the magnesium salt of monoperoxyphthalic acid.[33]

These preceding experiments show that with different oxidizing agents, two different products were formed, namely 1-oxa-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione and 1,3-dimethylparabanic acid. To demonstrate the intermediacy of the novel species in the oxidative process a spiro compound was subjected to further treatment with an excess of *m*-CPBA at room temperature in the two-phase system chloroform/water. The rapid formation of 1,3-dimethylparabanic acid (**19**) under these conditions was verified by thin-layer chromatography (Scheme 4). Likewise, when 1,3-dimethylalloxan (**20**), which was isolated earlier as an oxidation product of caffeine,[24] was subjected to the oxidation with *m*-CPBA, **19** was the only identifiable product



Scheme 4. Oxidation of 8-morpholinocaffeine by different oxidizing agents

(Scheme 4). It therefore seems that this compound is the end product of oxidations of caffeine and also of 8-substituted dialkylaminocaffeines. It is interesting to note that the pyrimidine ring of caffeine apparently does not survive strong oxidizing conditions, since 1,3-dimethylparabanic acid is also formed by oxidation of **20** with *m*-CPBA.

A number of the novel spiro compounds, including the two amino acid derivatives **10j** and **10k**, were tested by the NIH for cancerostatic activity but were found to be inactive.

Experimental Section

Melting points were measured in a capillary tube. ^{1}H- and ^{13}C-NMR spectra were recorded with a 250-MHz instrument (Bruker Ac 250) with tetramethylsilane as an internal standard. TLC and column chromatography were carried out using SiO_2. Elemental analyses were obtained by M-H-W laboratories, Phoenix, AZ.

1,3,7-Trialkyl-8-(dialkylamino)xanthines 3i−r. − General Procedure: Compounds **3a−h** were prepared according to published procedures[10−14] from the appropriate 1,3,7-trialkyl-8-bromoxanthine **2** and dialkylamine. Compounds **3i−s** were not described so far, therefore their relevant properties are reported here.

8-(2-Methylpiperidino)caffeine (3i): Yield 41%, m.p. 125°C (hexane). − ^{1}H NMR: δ = 1.06 (d, 3 H), 1.67 (m, 6 H), 3.09 (m, 2 H), 3.39 (s, 3 H), 3.47 (m, 1 H), 3.54 (s, 3 H), 3.75 (s, 3 H). − MS; *m*/*z* (%): 291 (100) $[M^+]$, 275 (58), 262 (20), 222 (17). − $C_{14}H_{21}N_5O_2$ (291.36): calcd. C 57.71, H 7.27; found C 58.00, H 7.22.

8-(Diisobutylamino)caffeine (3j): Yield 48%, m.p. 135−136°C (EtOH). − ^{1}H NMR: δ = 0.87 (d, 12 H), 1.88 (m, 2 H), 3.12 (d, 4 H), 3.39 (s, 3 H), 3.52 (s, 3 H), 3.76 (s, 3 H). − MS; *m*/*z* (%): 321 (10) $[M^+]$, 321 (49), 278 (40), 222 (100), 82 (20). − $C_{16}H_{27}N_5O_2$ (321.42): calcd. C 59.79, H 8.47; found C 60.00, H 8.19.

8-(Di-*n*-amylamino)caffeine (3k): Yield 28%, m.p.73°C (EtOH/EtOAc, 1:1). − ^{1}H NMR: δ = 0.89 (t, 6 H), 1.28 (m, 8 H), 1.55 (m,4 H), 3.24 (t, 4 H), 3.39 (s, 3 H), 3.52 (s, 3 H), 3.74 (s, 3 H). − MS; *m*/*z* (%): 349 (100) $[M^+]$, 292 (17), 278 (17), 236 (66). − $C_{18}H_{31}N_5O_2$ (349.48): calcd. C 61.86; H 8.94; found C 61.68, H 8.79.

8-Piperazinocaffeine (3l): Yield 48%, m.p.179°C (EtOH). − ^{1}H NMR: δ = 1.64 (s, 1 H), 2.90−3.15 (m, 4 H), 3.15−3.35 (m, 4 H), 3.39 (s, 3 H), 3.52 (s, 3 H), 3.76 (s, 3 H). − HRMS; *m*/*z*: 276.1432 (calcd. for $C_{13}H_{18}N_5O_2$: 276.146049).

***N*′-(8-Caffeinyl)-*N*,*N*,*N*′-trimethyl-1,2-ethanediamine (3m):** Yield 49%, m.p. 97°C (hexane/*n*-butanol). − ^{1}H NMR: δ = 2.27 (s, 6 H), 2.50 (t, 2 H), 3.01 (s, 3 H), 3.40 (t, 2 H), 3.39 (s, 3 H), 3.51 (s, 3 H), 3.78 (s, 3 H). − $C_{13}H_{22}N_6O_2$ (294.36): calcd. C 53.04; H 7.53, N 28.55; found C 52.85, H 7.32, N 28.44.

***N*-(8-Caffeinyl)-*N*,*N*′,*N*′-trimethyl-1,3-propanediamine (3n):** Yield 48%, m.p. 44−5°C (column chromatography using methanol as eluent). − ^{1}H NMR: δ = 1.55−1.95 (m, 2 H), 2.20 (s, 6 H), 2.30 (t, 2 H), 2.98 (s, 3 H), 3.35 (t, 2 H), 3.39 (s, 3 H), 3.51 (s, 3 H), 3.78 (s, 3 H). − $C_{14}H_{24}N_6O_2$ (308.39): calcd. C 54.53, H 7.84, N 27.25; found C 54.25, H 7.59, N 26.97.

Butyl *N*-(8-caffeinyl)sarcosinate (3o): Yield 70%, m.p.106°C (hexane). − ^{1}H NMR: δ = 0.90 (t, 3 H), 1.45 (m, 4 H), 3.15 (s, 3 H), 3.38 (s, 3 H), 3.47 (s, 3 H), 3.85 (s, 3 H), 4.07 (s, 2 H), 4.14 (t, 2 H). − MS; *m*/*z* (%): 337 (74) $[M^{+}\cdot]$, 236 (100), 122 (20). − $C_{15}H_{23}N_5O_4.0.5\ H_2O$ (346.39): calcd. C 52.01, H 6.98; found C 51.80, H 6.98.

Butyl *N*-(8-caffeinyl)prolinate (3p): Yield 54%, m.p. 104°C (hexane). − ^{1}H NMR: δ = 0.90 (t, 3 H), 1.40 (m, 4 H), 2.10 (m, 4 H), 3.35 (s, 3 H), 3.42 (s, 3 H), 3.69 (m, 2 H), 3.85 (s, 3 H), 4.12 (t, 2 H), 4.70 (t, 1 H). − MS; *m*/*z* (%): 363 (28) $[M^{+}\cdot]$, 70(91), 57 (80), 41 (100). − $C_{17}H_{25}N_5O_4$ (363.42): calcd. C 56.18, H 6.93; found C 55.93, H 7.04.

8-(*N*-Methylanilino)caffeine (3q): Yield 38%, m.p. 149−150°C (EtOH). − $C_{15}H_{17}N_5O_2$ (299.33): calcd. C 60.19, H 5.72, N 23.40; found C 60.55, H 5.93, N 23.02.

8-(*N*′-Acylpiperazino)caffeine (3r): A mixture of **3l** (1.39 g, 5 mmol), triethylamine (5 mL) and *N*,*N*-dimethylformamide (50 mL) was heated to 80°C. Acetyl chloride (0.43 mL, 6 mmol) was then added dropwise with stirring. After stirring at 80°C for 1 h, the solvent was removed under reduced pressure and the remaining residue was dissolved in water (20 mL) and refluxed for 2 min. The solution was allowed to cool and extracted with chloroform. The organic phases were dried with Na_2SO_4. The solvent was then removed in vacuo and the crude product was recrystallized from ethanol to give **3r** (1.43 g, 89% yield), m.p. 147°C . − ^{1}H NMR: δ = 2.14 (s, 3 H), 3.30 (m, 4 H), 3.39 (s, 3 H), 3.51 (s, 3 H), 3.75 (m, 4 H), 3.78 (s, 3 H). − $C_{14}H_{20}N_6O_3$:(320.35): calcd. C 52.49, H 6.29, N 26.23; found C 52.51, H 6.17, N 26.04.

8-[Bis(2-acetyloxyethyl)amino]caffeine (3s): A solution of **3f** (0.99 g, 3.3 mmol), acetic anhydride (0.65 mL, 6.6 mmol) and pyridine (0.65 mL) was refluxed under stirring at 145°C for 3 h. The mixture was poured into ice-cold water (25 mL) and extracted with ether and chloroform. The collected organic layers were washed with 10% HCl solution (2 × 20 mL) followed by saturated sodium carbonate solution (20 mL) and then dried with $MgSO_4$ to give **3s** as a colorless solid in 57% yield, m.p. 98−99°C. − ^{1}H NMR: δ =

2.01 (s, 6 H), 3.39 (s, 3 H), 3.51 (s, 3 H), 3.56 (t, 4 H), 3.78 (s, 3 H), 4.23 (t, 4 H). − MS; *m/z* (%): 381 (18) [$M^{+\cdot}$], 274 (21), 272 (24), 116 (21), 43 (100). − $C_{16}H_{23}N_5O_6$ (381.39): calcd. C 50.39, H 6.08; found C 50.16, H 6.38.

1,3,7-Triethyl-8-morpholinoxanthine (3t): Yield 55%, m.p.139°C. −^{1}H NMR: δ = 1.35 (m, 9 H), 3.23 (m, 4 H), 3.85 (m, 4 H), 4.11 (m, 6 H).

8-(*n*-Butylamino)-1,3,7-triethylxanthine (3u): Yield 78%, m.p. 172°C. − ^{1}H NMR: δ = 0.77−1.75 (m, 16 H), 3.47 (m, 2 H), 4.07 (m, 7 H).

8-[(*n*-Butyl)(ethyl)amino]-1,3,7-triethylxanthine (3v): To a solution of **3u** (0.24 g, 0.78 mmol) in *N*,*N*-dimethylformamide (5 mL) was added diethyl sulfate (1 mL). The mixture was heated with stirring to reflux for 6 h. After cooling, water (20 mL) and ether (20 mL) were added. The ether layer was separated, dried with anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (ethyl acetate/chloroform, 1:1). Compound **3v** was isolated in 31% yield as colorless oil. − ^{1}H NMR: δ = 0.83−1.75 (m, 19 H), 3.25 (m, 4 H), 4.12 (m, 6 H). − $C_{17}H_{29}N_5O_2$ (335.45): calcd.C 60.87, H 8.71, N 20.88;. found C 60.67, H 8.50, N 20. 80.

8-[(*n*-Butyl)(formyl)amino]-1,3,7-triethylxanthine (3w): This compound was isolated from the above crude product by column chromatography in 9.5% yield, m.p. 71°C. − ^{1}H NMR: δ = 0.85−1.56 (m, 16 H), 3.75 (m, 2 H), 4.15 (m, 6 H), 8.34 (s, 1 H). − $C_{16}H_{25}N_5O_3$ (335.41): calcd. C 57.30, H 7.51, N 20.88; found C 57.45, H 7.46, N 20.66.

***N*,*N*-Bis(8-caffeinyl)aniline (4):** To a suspention of sodium (4.6 g, 0.20 mol) in boiling xylene (120 mL) was added aniline (18.2 mL, 0.20 mol) and the mixture refluxed for 2 h, then **2a** (27.3 g, 0.10 mol) was added in one portion, and the mixture refluxed for an additional 40 h. After cooling, a saturated aqueous solution of ammonium chloride was added and the precipitate was fitered off, washed with ether and dried. After purifying it by column chromatography using ethyl acetate as eluent, 12.5 g of **4** was isolated (50% yield), m.p. 285°C. − ^{1}H NMR: δ = 3.40 (s, 6 H), 3.49 (s, 6 H), 3.67 (s, 3 H), 7.20−7.40, 7.77−7.92 (2 m, 5 H). − $C_{22}H_{23}N_9O_4$ (477.48): calcd. C 55.34, H 4.86, N 26.40; found C 55.13, H 5.03, N 26.18.

2-Bromo-4-(1,3-dimethylureidyl)-1-methyl-5-(*N*-phenylformamidyl)-imidazole (5): To a solution of 0.6 N *n*BuLi (12.5 mL, 20 mmol) in THF (50 mL) was added aniline (1.82 mL, 20 mmol) (N_2, −78°C). The mixture was stirred for 30 min, then treated with **2a** (2.73 g, 10 mmol) and refluxed for 6 h. After removing the solvent, 0.1 N HCl (20 mL) was added to the residue. It was collected, extracted with chloroform and recrystallized twice from ethanol to give **5** in 36% yield, m.p. 184°C (EtOH). − ^{1}H NMR: δ = 2.87 (d, 3 H), 3.20 (s, 3 H), 3.88 (s, 3 H), 5.15 (br. s, 1 H), 7.05−7.65 (m, 5 H), 9.00 (br. s, 1 H). − FAB MS; *m/z*: 366, 368 [MH^+]. − $C_{14}H_{16}BrN_5O_2$ (366.22): calcd. C 45.92, H 4.40, N 19.12; found C 46.28, H 4.67, N 19.00.

1,3,7-Trialkyl-8-(2′,2′,2′-trifluoroethoxy)xanthines (6d,f,g). − General Procedure: To a cold suspension (0°C) of sodium (140 mg, 6 mmol) in THF (4.5 mL) was added with stirring 2,2,2-trifluoroethanol (1.5 mL, 19 mmol). Stirring was continued until all sodium had reacted. The above solution was added dropwise to a stirred solution of the appropriate 1,3,7-trialkyl-8-bromoxanthine **2** (4 mmol) in THF (40 mL). The reaction mixture was refluxed for 10 h, filtered and after evaporating the solvent, the remaining light yellow residue was dissolved in $CHCl_3$ and washed with saturated Na_2CO_3 solution. The solvent was removed to give **6**.

8-(2′,2′,2′-Trifluoroethoxy)caffeine (6d): Yield 73%, m.p. 151°C. − ^{1}H NMR: δ = 3.39 (s, 3 H), 3.50 (s, 3 H), 3.76 (s, 3 H), 4.87 (q, 2 H). − MS; *m/z* (%): 292 (100) [$M^{+\cdot}$], 209 (69), 124 (17), 83 (62). − $C_{10}H_{11}F_3N_4O_3$ (292.22): calcd. C 41.10, H 3.79, N 19.17; found C 41.00, H 4.00, N 19.14.

7-Ethyl-1,3-di-*n*-propyl-8-(2′,2′,2′-trifluoroethoxy)xanthine (6f): Yield 58%, m.p. 54°C. − ^{1}H NMR: δ = 0.96 (t, 6 H), 1.40 (t, 3 H), 1.70 (m, 4 H), 3.96 (m, 4 H), 4.21 (q, 2 H), 4.87 (q, 2 H). − MS; *m/z* (%): 362 (54) [$M^{+\cdot}$], 320 (19), 292 (18), 278 (100), 248 (27), 83 (17). − $C_{15}H_{21}F_3N_4O_3$ (362.35): calcd. C 49.72, H 5.84, N 15.46; found C 49.75, H 6.00, N 15.36.

1,3-Di-*n*-butyl-7-ethyl-8-(2′,2′,2′-trifluororethoxy)xanthine (6g): Yield 68%, m.p. 63°C. − ^{1}H NMR: δ = 0.96 (m, 6 H), 1.39 (m, 7 H), 1.67 (m, 4 H), 3.99 (q, 4 H), 4.21 (q, 2 H), 4.87 (q, 2 H). − MS; *m/z* (%): 390 (99) [$M^{+\cdot}$], 373 (74), 370 (53), 292 (100), 278 (64). − $C_{17}H_{25}F_3N_4O_3$ (390.41): calcd. C 52.30,H 6.45, N 14.35; found C 52.45, H 6.49, N 14.45.

8-[(Dialkylamino)methyl]caffeines 7. − General Procedure: To a solution of 8-(bromomethyl)caffeine (**8**) (8.7 mmol) in *n*-butanol (100 mL) was added the appropriate dialkylamine (17 mmol). This mixture was refluxed for 12 h. Finally, the solvent was evaporated and the product was isolated by column chromatography using EtOAc as mobile phase.

8-(Morpholinomethyl)caffeine (7a): Yield 70%, m.p. 223°C. − ^{1}H NMR: δ = 2.48−2.52 (m, 4 H), 3.40 (s, 3 H), 3.57 (s, 3 H), 3.66 (s, 2 H), 3.68−3.72 (m, 4 H), 4.04 (s, 3 H). − $C_{13}H_{19}N_5O_3$ (293.33): calcd. C 53.23, H 6.53, N 23.88; found C 53.06, H 6.54, N 24.01.

8-[(Diethylamino)methyl]caffeine (7b): Yield 75%, m.p. 112°C (ref.[18] 108−111°C). − ^{1}H NMR: δ = 1.00−1.06 (m, 6 H), 2.49−2.58 (m, 4 H), 3.40 (s, 3 H), 3.57 (s, 3 H), 3.71 (s, 2 H), 4.04 (s, 3 H). − $C_{13}H_{21}N_5O_2$ (279.34): calcd. C 55.90, H 7.58, N 25.07; found C 56.08, H 7.54, N 25.16.

8-[(Di-*n*-propylamino)methyl]caffeine (7c): Yield 63%, m.p. 84°C. − ^{1}H NMR: δ = 0.81−0.87 (m, 6 H), 1.38−1.52 (m, 4 H), 2.36- 2.42 (m, 4 H), 3.40 (s, 3 H), 3.57 (s, 3 H), 3.91 (s, 2 H), 4.04 (s, 3 H). − $C_{15}H_{25}N_5O_2$ (307.40): calcd. C 58.61, H 8.20, N 22.78; found C 58.16, H 8.12, N 23.00.

8-[(Di-*n*-butylamino)methyl]caffeine (7d): 62% yield, m.p. 65°C (ref.[15] 160°C). − ^{1}H NMR: δ = 0.87 (m, 6 H), 1.28 (m, 4 H), 1.40 (m, 4 H), 2.42 (m, 4 H), 3.41 (s, 3 H), 3.57 (s, 3 H), 4.04 (s, 3 H), 3.70 (s, 2 H). − $C_{17}H_{29}N_5O_2$ (335.45): calcd. C 60.87, H 8.71, N 20.88; found C 60.69, H 8.57, N 20.99.

8-[(Diisoamylamino)methyl]caffeine (7e): 55% yield, m.p. 43°C. − ^{1}H NMR: δ = 0.87 (m, 12 H), 1.41 (m, 6 H), 2.37 (m, 4 H), 3.40 (s, 3 H), 3.57 (s, 3 H), 3.73 (s, 2 H), 4.03 (s, 3 H). − $C_{19}H_{33}N_5O_2$ (363.51): calcd. C 62.78, H 9.15, N 19.27; found C 63.06, H 8.93, N 19.28.

8-Caffeinyl Phenyl Thioether (8): A mixture consisting of **2a** (2.73 g, 10 mmol), thiophenol (1 mL) and triethylamine (1.2 mL) was dissolved in *n*-butanol (50 mL) and refluxed for 16 h. Upon cooling a colorless precipitate was obtained, yield 76%, m.p. 141−144°C (EtOH) (ref.[19] 147°C). − ^{1}H NMR: δ = 3.41 (s, 3 H), 3.67 (s, 3 H), 3.93 (s, 3 H), 7.33 (m, 5 H).

Oxidation with *m*-Chloroperoxybenzoic Acid. − General Procedure: In a three-necked, round-bottom flask, equipped with a magnetic stirrer, dropping funnel and reflux condenser, one equivalent of starting material was dissolved in a two-phase system of chloroform and water (10 mL of chloroform and 10 mL of water per 1 mmol of starting material). To this was added dropwise a solution two equivalents of *m*-CPBA in chloroform (2 mL of chloroform per 1 mmol of *m*-CPBA). The solution was stirred at room temperature for 4 d. For isolating the rearranged products, the chloroform layers were separated and washed with a solution of sodium bicarbonate. After drying with anhydrous sodium sulfate and flash evaporation of the solvent, the rearranged product was isolated by column chromatography and purified by recrystallization.

3-(Dimethylamino)-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (10a): Yield 61%, m.p. 148−50°C. − ^{1}H NMR: δ = 2.80 (s, 6 H), 2.87 (s, 3 H), 3.37 (s, 6 H). − MS; *m/z* (%): 269 (12) [M$^{+\cdot}$], 239 (100), 237 (33), 222 (20), 182 (22), 167 (11), 142 (46), 127 (45). − $C_{10}H_{15}N_5O_4$ (269.26): calcd. C 44.61, H 5.62, N 26.01; found C 44.40, H 5.68, N 25.97.

10b: Yield 60%, m.p. 133°C (aq. EtOH). − ^{1}H NMR: δ = 1.2 (t, 6 H), 2.80 (s, 3 H), 3.11 (q, 4 H), 3.32 (s, 6 H). − MS; *m/z* (%): 297 (12) [M$^{+\cdot}$], 267 (100), 210 (11), 182 (12). − $C_{12}H_{19}N_5O_4$ (297.32): calcd. C 48.48, H 6.44, N 23.56; found C 48.66, H 6.41, N 23.65.

10c: Yield 48%, m.p. 118°C (chromatography with $CHCl_3$/CH_3CO_2Et, 1:1). − ^{1}H NMR: δ = 2.89 (s, 3 H), 3.35 (s, 6 H), 3.5−3.7 (m,8 H). − $C_{12}H_{17}Cl_2N_5O_4$ (366.20): calcd. C 39.36, H 4.68, N 19.12; found C 39.54, H 4.88, N 19.00.

10d: Yield 70%, m.p. 130−131°C (cyclohexane). − $C_{22}H_{23}N_5O_4$ (421.46): calcd. C 62.70, H 5.50, N 16.62; found C 63.13, H 5.45, N 16.35.

10e: Yield 61%, m.p. 231°C (MeOH). − ^{1}H NMR: δ = 2.86 (s, 3 H), 3.17 (m, 4 H), 3.35 (s, 6 H), 3.79 (m,4 H). − MS: *m/z* (%): 311 (13) [M$^{+\cdot}$], 281 (100), 224 (16), 169 (20), 142 (39). − $C_{12}H_{17}N_5O_5$ (311.30): calcd. C 46.30, H 5.50, N 22.50; found C 46.46, H 5.62, N 22.52.

10f: Yield 48%, m.p. 170°C (aq. MeOH). − ^{1}H NMR: δ = 1.67 (m, 6 H), 2.85 (s, 3 H), 3.10 (m, 4 H), 3.35 (s, 6 H). − MS; *m/z* (%): 309 (2) [M$^{+\cdot}$], 279 (100), 222 (12), 112 (28). − $C_{13}H_{19}N_5O_4$ (309.33): calcd. C 50.48, H 6.19, N 22.64; found C 50.28, H 6.33, N 22.39.

10g: Yield 35%, m.p. 138°C (EtOH). − ^{1}H NMR: δ = 1.25 (d, 3 H), 1.65 (m, 6 H), 2.82 (s, 3 H), 3.01 (m, 1 H), 3.14 (m, 1 H), 3.33 (s, 3 H), 3.35 (s, 3 H) 3.45 (m, 1 H). − MS; *m/z* (%): 323 (8) [M$^{+\cdot}$], 293 (100), 166 (30), 154 (21). − $C_{14}H_{21}N_5O_4$ (323.35): calcd. C 52.00, H 6.55, N 21.66; found C 52.13, H 6.58, N 22.05.

10h: A yellow oil in 54% yield. − ^{1}H NMR: δ = 0.90−0.96 (d, 12 H), 1.96−2.10 (m, 2 H), 2.83 (s, 3 H), 2.88−2.91 (d, 4 H), 3.34 (s, 6 H). − MS; *m/z* (%): 353 (12) [M$^{+\cdot}$], 323 (100), 254 (32), 210 (18), 127 (18). − $C_{16}H_{27}N_5O_4$ (353.42): calcd. C 54.38, H 7.70; found C 54.19, H 7.53.

10i: A yellow oil in 42% yield. − ^{1}H NMR: δ = 0.88−0.94 (t, 6 H), 1.20−1.49 (m, 8 H), 1.59−1.67 (m, 4 H), 2.82 (s, 3 H), 3.00−3.09 (t, 4 H), 3.34 (s, 6 H). − MS; *m/z* (%): 365 (37) [M$^{+\cdot}$ − 18], 348 (15), 336 (14), 322 (24), 320 (28), 308 (33), 295 (56), 267 (38), 252 (70), 152 (100). − $C_{18}H_{31}N_5O_4$ (381.48): calcd. C 56.67, H 8.19; found C 56.48, H 7.97.

10j: Yield 35%, m.p. 136−8°C (EtOH). − ^{1}H NMR: δ = 0.95 (t, 3 H), 1.45 (m, 4 H), 2.89 (s, 3 H), 2.92 (s, 3 H), 3.34 (s, 6 H), 3.82 (s,2 H), 4.18 (t, 2 H). − MS; *m/z* (%): 369 (8) [M$^{+\cdot}$], 339 (100), 83 (26). − C15H23N5O6·0.75H_2O (382.89): calcd. C 47.05, H 6.45, N 18.29; found C 47.22, H 6.37, N, 18.45.

10k: Yield 26%, m.p. 88°C (EtOH). − ^{1}H NMR: δ = 0.90 (t, 3 H), 1.45 (m, 4 H), 2.05 (m, 4 H), 2.89 (s, 3 H), 3.30 (s, 6 H), 3.57 (t, 2 H), 4.15 (t, 2 H), 4.35 (t, 1 H). − MS; *m/z* (%): 395 (6) [M$^{+\cdot}$], 365 (53), 41 (100). − $C_{17}H_{25}N_5O_6$ (395.42): calcd. C 51.64, H 6.37; found C 51.59, H 6.45.

10l: Yield 50%, m.p. 165−166°C (MeOH) (ref.[33] 167°C).

10m: Yield 14%, m.p. 218°C (EtOH). − ^{1}H NMR: δ = 2.10 (s, 3 H), 2.86 (s, 3 H), 3.00−3.30 (m, 4 H), 3.34 (s, 6 H), 3.45−3.80 (m, 4 H). − $C_{14}H_{20}N_6O_5$ (352.35): calcd. C 47.72, H 5.72, N 23.85; found C 47.57, H 5.88, N 23.74.

10n: A yellow oil in 21% yield. − ^{1}H NMR: δ = 2.08 (s, 6 H), 2.85 (s, 3 H), 3.35 (s, 6 H), 3.39−3.44 (t, 4 H), 4.27−4.31 (t, 4 H). − MS; *m/z* (%): 413 (4) [M$^{+\cdot}$], 383 (41), 139 (23), 43 (100). − $C_{16}H_{23}N_5O_8$ (413.39): calcd. C 46.49, H 5.61; found C 46.35, H 5.69.

10o: A yellow oil in 22% yield. − ^{1}H NMR: δ = 1.06 (t, 3 H), 1.24 (t, 6 H), 3.10−3.21 (m, 4 H), 3.35 (q, 2 H), 3.73−3.84 (m, 4 H), 3.98 (q, 4 H). − $C_{15}H_{23}N_5O_5$ (353.38): calcd. C 50.98, H 6.56, N 19.81; found C 50.64, H 6.56, N 19.62.

***N*-Caffeinyl-*N,N′,N′*-trimethyl-1,2-ethanediamine *N*-Oxide (11a):** The *N*-oxidation of **3m** (0.59 g, 2 mmol) and *m*-CPBA (0.70 g, 2 mmol) was conducted according to the general procedure. The product, however, was found to be distributed in both the organic and the aqueous phase. After separation of the two layers and drying the organic phase with anhydrous Na_2SO_4, both solutions were flash-concentrated. The *N*-oxide was obtained in 63% by silica gel column chromatography of the combined residues using a mixture of ethyl acetate and chloroform (1:1) to elute the *m*-CPBA; a mixture of methanol and water (5:1) was used to separate **11a** from a small amount of unchanged **3m**, m.p. 141−142°C. − ^{1}H NMR: δ = 2.65 (br. s, 3.5 H, D_2O exchangeable), 3.05 (s, 3 H), 3.27 (s, 6 H), 3.38 (s, 3 H), 3.45 (t, 2 H), 3.49 (s, 3 H), 3.80 (s, 3 H), 3.90 (t, 2 H). − C13H22N6O3·1.75H_2O (341.88): calcd. C 45.67, H 7.51, N 24.58; found C 45.75, H 7.20, N 24.57.

***N*-Caffeinyl-*N,N′,N′*-trimethyl-1,3-propanediamine *N*-Oxide (11b):** As described above but using **3n**. The isolated yellowish oily product was purified by silica gel column chromatography using a mixture of methanol and water (5:2) as eluent in 36% yield. − ^{1}H NMR: δ = 2.32 (m, 2 H), 2.70 (br. s, 3.5 H, D_2O exchangeable), 3.01 (s, 3 H), 3.22 (s, 6 H), 3.30 (t, 2 H), 3.38 (s, 3 H), 3.44 (t, 2 H), 3.51 (s, 3 H), 3.79 (s, 3 H). − C14H24N6O3·1.75H_2O (355.91): calcd. C 47.25, H 7.79, N 23.61; found C 47.32, H 7.92, N 23.61.

3-Methoxy-4,7,9-trimethyl-1-oxotetraspiro[4,5]dec-2-ene-6,8,10-trione (12a): Yield 58%, m.p. 188°C (EtOH). − ^{1}H NMR: δ = 2.79 (s, 3 H), 3.34 (s, 6 H), 3.95 (s, 3 H). − MS; *m/z* (%): 256 (57) [M$^{+\cdot}$], 226 (57), 184 (14), 142 (50), 58(100). − $C_9H_{12}N_4O_5$ (256.22): calcd. C 42.19, H 4.72, N 21.87; found C 42.31, H 4.46, N 21.89.

12b: Yield 41%, m.p. 176°C (EtOH). − ^{1}H NMR: δ = 1.42 (t, 3 H), 2.80 (s, 3 H), 3.35 (s, 6 H), 4.26 (q, 2 H). − MS; *m/z* (%): 270 (47) [M$^{+\cdot}$], 240 (20), 212 (36), 156 (49), 58 (100). − $C_{10}H_{14}N_4O_5$ (270.25): calcd. C 44.44, H 5.22, N 20.73; found C 44.48, H 5.30, N 20.80.

12c: Yield 27%, m.p. 158°C. − ^{1}H NMR: δ = 0.96 (t, 3 H), 1.20−1.85 (m, 4 H), 2.79 (s, 3 H), 3.33 (s, 6 H), 4.21 (t, 2 H). − MS; *m/z* (%): 298 (34) [M$^{+\cdot}$], 242 (42), 212 (52), 156 (42), 57 (86), 41 (100). − $C_{12}H_{18}N_4O_5$ (298.30): calcd. C 48.32, H 6.08, N 18.78; found. C 48.12, H 5.99, N 18.67

12d: Yield 70%, m.p. 123°C [column chromatography using a mixture of $CHCl_3$ and EtOAc (4:1) as eluent]. − ^{1}H NMR: δ = 2.85 (s, 3 H), 3.36 (s, 6 H), 4.54 (q, 2 H). − MS; *m/z* (%): 324 (23) [M$^{+\cdot}$], 211 (33), 210 (56), 56 (100). − $C_{10}H_{11}F_3N_4O_3$ (324.21): calcd. C 37.05, H 3.42, N 17.28; found C 37.21, H 3.37, N 17.11.

8-[2-(Dimethylamino)ethoxy]caffeine *N*-Oxide (13): It was prepared in 28% yield form **6e** according to the procedure given for the synthesis of **11**, m.p. 115°C. − ^{1}H NMR: δ = 2.67 (br. s, 4 H, D_2O exchangable), 3.31 (s, 6 H), 3.38 (s, 3 H), 3.50 (s, 3 H), 3.70 (s, 3

H), 3.72 (t, 2 H), 5.15 (t, 2 H). − C12H19N5O4·2H2O (333.34): calcd. C 43.24, H 6.95, N 21.01; found C 43.35, H 6.62, N 21.22.

8-Caffeinyl Phenyl Sulfoxide (14): According to the usual procedure **9** (0.3 g, 0.96 mmol) was oxidized by *m*-CPBA (0.4 g, 2.1 mmol). The obtained product was recrystallized from abs. ethanol and purified by column chromatography using EtOAc as mobile phase, yield 75%, m.p. 224°C . − ^{1}H NMR: δ = 3.37 (s, 3 H), 3.56 (s, 3 H), 4.09 (s, 3 H), 7.50−7.75 (m, 5 H). − $C_{14}H_{14}N_4O_3S$ (318.36): calcd. C 52.82, H 4.43, N 17.60, S 10.07; found C 52.73, H 4.70, N 17.49, S 9.85.

8-Caffeinyl Phenyl Sulfone (15): A small amount of **15** was isolated from the above reaction mixture, m.p. 240°C (ref.[19] 230°C). − ^{1}H NMR: δ = 3.37 (s, 3 H), 3.51 (s, 3 H), 4.33 (s, 3 H), 7.67, 8.05 (2 m, 5 H).

8-(Morpholinomethyl)caffeine *N*-Oxide (16a): It was prepared in 77% yield from the oxidation of **7a** following the general procedure, m.p. 168°C. − ^{1}H NMR: δ = 3.41 (s, 3 H), 3.55 (s, 3 H), 3.84 (m, 8 H), 4.27 (s, 3 H), 4.50 (s, 2 H). − $C_{13}H_{19}N_5O_4$ (309.33): calcd. C 50.48, H 6.19, N 22.64; found C 50.33, H 6.26, N 22.48.

8-[(Diethylamino)methyl]caffeine *N*-Oxide (16b): It was prepared in 84% from the oxidation of **7b** following the general procedure, m.p. 111°C. − ^{1}H NMR: δ = 1.41 (t, 6 H), 1.85 (br. s, 4 H, D_2O exchangeable), 3.37 (q, 4 H), 3.40 (s, 3 H), 3.55 (s, 3 H), 4.26 (s, 3 H), 4.43 (s, 2 H). − C13H21N5O3·2H2O (331.37): calcd. C 47.12,H 7.60, N 21.13; found C 46.91, H 7.37, N 20.65.

16c: It was prepared in 74% by oxidation of **7c** following the general procedure, m.p. 117°C. − ^{1}H NMR: δ = 1.00 (t, 6 H), 1.89 (m, 4 H), 3.21 (m, 4 H), 3.40 (s, 3 H), 3.55 (s, 3 H), 4.27 (s, 3 H), 4.41 (s, 2 H). − $C_{15}H_{25}N_5O_3$ (323.40): calcd. C 55.71, H 7.79, N 21.66; found C 55.62, H 7.79, N 21.79.

16d: It was prepared in 78% by oxidation of **7d** following the general procedure, m.p. 103°C. − ^{1}H NMR: δ = 1.00 (t, 6 H), 1.41 (m, 4 H), 1.83 (m, 4 H), 3.25 (m, 4 H), 3.40 (s, 3 H), 3.54 (s, 3 H), 4.27 (s, 3 H), 4.41 (s, 2 H). − $C_{17}H_{29}N_5O_3$ (351.45): calcd. C 58.11, H 8.26, N 19.94; found C 58.02, H 8.59, N 19.76.

16e: It was prepared in 84% fby oxidation of **7e** following the general procedure, m.p. 104°C. − ^{1}H NMR: δ = 0.98 (d, 12 H), 1.72 (m, 6 H), 3.26 (m, 4 H), 3.40 (s, 3 H), 3.54 (s, 3 H), 4.27 (s, 3 H), 4.40 (s, 2 H). − $C_{19}H_{33}N_5O_3$ (379.50): calcd. C 60.13, H 8.76, N 18.45; found C 60.11, H 8.52, N 18.50.

***N*-(8-Caffeinylmethoxy)morpholine (17a):** A suspension of **16a** (0.25 g, 0.8 mmol) in benzene (50 mL) was heated for 12 h under reflux. A mixture of two products was produced. The two products were separated by column chromatography using EtOAc as mobile phase to give **17a** in 56% yield and **18** (yield 8%) as a minor product. − M.p. 176°C. − ^{1}H NMR: δ = 2.70 (m, 4 H), 3.09 (m, 4 H), 3.41 (s, 3 H), 3.58 (s, 3 H), 4.05 (s, 3 H), 4.84 (s, 2 H). − $C_{13}H_{19}N_5O_4$ (309.33): calcd. C 50.48, H 6.19, N 22.64; found C 50.42, H 6.22, N 22.54.

***O*-(8-Caffeinylmethyl)-*N*,*N*-diethylhydroxylamine (17b):** It was prepared in 54% yield from **16b** following the above procedure. − M.p. 98°C. − ^{1}H NMR: δ = 1.07 (t, 6 H), 2.73 (q, 4 H), 3.41 (s, 3 H), 3.58 (s, 3 H), 4.06 (s, 3 H), 4.81 (s, 2 H). −$C_{13}H_{21}N_5O_3$ (295.34): calcd. C 52.87, H 7.17, N 23.71; found C 52.91, H 7.25, N 23.78.

***O*-(8-Caffeinylmethyl)-*N*,*N*-di-*n*-propylhydroxylamine (17c):** It was prepared in 42% yield from **16c** following the above procedure. − M.p. 83°C. − ^{1}H NMR: δ = 0.90 (t, 6 H), 1.49 (m, 4 H), 2.65 (m, 4 H), 3.41 (s, 3 H), 3.58 (s, 3 H), 4.04 (s, 3 H), 4.79 (s, 2 H). − $C_{15}H_{25}N_5O_3$ (323.40): calcd. C 55.71, H 7.79, N 21.66; found C 56.00, H 7.89, N 21.90.

***O*-(8-Caffeinylmethyl)-*N*,*N*-di-*n*-butylhydroxylamine (17d):** It was prepared in 42% yield from **16d** following the above procedure. − M.p. 65°C. − ^{1}H NMR: δ = 0.88 (t, 6 H), 1.29 (m, 4 H), 1.38 (m, 4 H), 2.67 (t, 4 H), 3.41 (s, 3 H), 3.58(s, 3 H), 4.04 (s, 3 H), 4.78 (s, 2 H). − $C_{17}H_{29}N_5O_3$ (351.45): calcd. C 58.10, H 8.32, N 19.93; found C 58.31, H 8.43, N 20.11.

***O*-(8-Caffeinylmethyl)-*N*,*N*-diisoamylhydroxylamine(17e):** It was prepared in 42% yield from **16e** following the above procedure. − M.p. 65°C. − ^{1}H NMR: δ = 0.87 (d, 12 H), 1.37 (m, 4 H), 1.55 (m, 2 H), 2.68 (m, 4 H), 3.42 (s, 3 H), 3.59 (s, 3 H), 4.05 (s, 3 H), 4.79 (s, 2 H). − $C_{19}H_{33}N_5O_3$ (379.51): calcd. C 60.13, H 8.76, N 18.45; found C 60.30, H 8.70, N 18.57.

Oxidation of 8-Morpholinocaffeine with Selenium Dioxide and Hydrogen Peroxide to Dimethylparabanic Acid: A mixture of **3g** (1.4 g, 5 mmol), *n*-butanol (15 mL) and the appropriate oxidizing agent was heated to reflux for 10 h. The oxidizing agents were: a) selenium dioxide (1.11 g, 10 mmol) and water (1 mL); b) 30% hydrogen peroxide (1.13 g, 10 mmol); c) selenium dioxide (10 mmol) and 30% hydrogen peroxide (10 mmol). In the cases a) and c) the solution was cooled to 0°C for 1 d before filtration and removal of the solvent under reduced pressure. The residue was separated by silica gel column chromatography using a mixture of EtOAc and $CHCl_3$ (1:1) as eluent. Unreacted starting material and 1,3-dimethylparabanic acid were isolated, m.p. 152°C (ref.[34] 148−149°C).

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