propanediol, (ii) Matteson's one-carbon homologation reaction (CH_2ClI/n-BuLi),[21] and (iii) oxidation (30% H_2O_2/2 N $KHCO_3$). The cyclopropylmethanol **11**, in turn, can be ring opened to *threo*-2-methyl-1,3-heptandiol in a regioselective and stereospecific manner,[20] the above conversion shows one way to extend the utility of this method in enantioselective organic synthesis.

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Supplementary Material Available: Representative procedures for the cyclopropanation of **1a–c**, the ring opening of **4a–c**, and the homologation of **10** and the spectral and physical properties as well as the analytical data of **1b**, **4a–c**, **6–8**, and **11** (6 pages). Ordering information is given on any current masthead page.

A Novel Oxidative Skeleton Rearrangement of the Caffeine System

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Summary: 8-(Disubstituted amino)- and 8-alkoxycaffeines react with 3-chloroperoxybenzoic acid to undergo a novel rearrangement giving spiro compounds of type **5**.

We report here on results of a peroxy acid oxidation of 8-(*N,N*-disubstituted amino)caffeines (systematic names: 8-(*N,N*-disubstituted amino)-3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-diones), **1**, and the related compounds **2**. Our initial objective in this area[1,2] was the synthesis of their *N*-oxide analogues as potential antitumor agents. Procedures for the synthesis of a number of purine *N*-oxides have been reported previously by several authors.[3-13] In particular, the preparation of several purine *N*-oxides by direct oxidation of the parent bases was first reported by von Euler[3] as well as by Brown.[4,5]

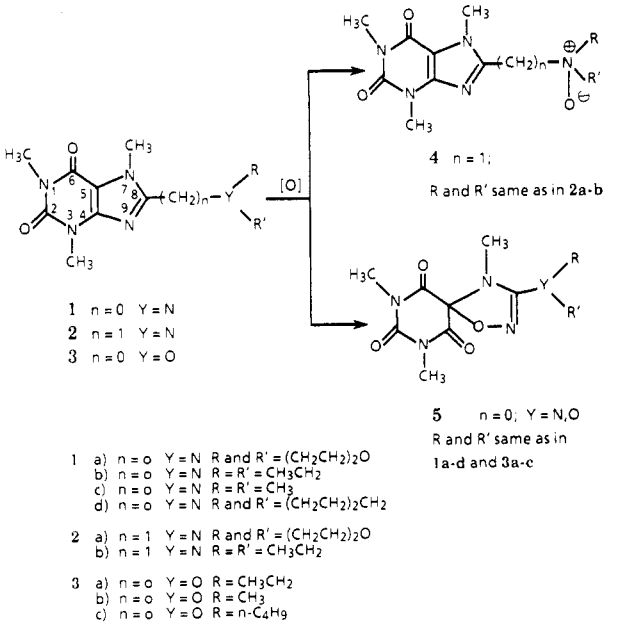
Based on literature precedent,[14] we envisioned that peracid oxidation of **1** with an amino function in the 8-position would yield *N*-oxides of type **4**. Instead, when type **1** compounds were treated with 3-chloroperoxybenzoic acid in a chloroform–water mixture, lemon-yellow products **5** were obtained in good yields (Table I). The elemental analyses and mass spectral data of these species showed that they possess two oxygen atoms more than the type **1** pecursors. ^1H and ^{13}C NMR spectral data of **5** showed symmetry in these products. Thus, in the ^1H NMR spectrum of **5a** the two singlets due to the *N*-CH_3 groups of the pyrimidine ring merged into one singlet. The decoupled ^{13}C NMR spectrum (75.5 MHz) of **1a** exhibits 10 singlets at δ 27.563, 29.510, 32.356, 49.868, 66.256, 104.972, 146.969, 151.262, 154.432, and 155.632 corresponding to N_7-CH_3, N_3-CH_3, N_1-CH_3, $C_{10,10'}$, $C_{11,11'}$, C_8, C_4, C_5, C_6, and C_2 respectively, while the decoupled ^{13}C NMR spectrum of **5a** shows only seven singlets at δ 29.440, 49.360, 65.948, 91.233, 149.864, 160.964, and 164.463. These data could

Table I. 3-(*N,N*-Disubstituted amino)-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-triones and Their 3-Alkoxy Analogues[27]

compd	Y	R	R′	mp,[a] °C (uncorr)	yield, % (isolated)
5a	N	$-(CH_2CH_2)_2O$		224	61
5b	N	CH_3CH_2	CH_3CH_2	135	57
5c	N	CH_3	CH_3	149	33
5d	N	$-(CH_2CH_2)_2CH_2$		176	51
5e	O	CH_3CH_2	–	176	41
5f	O	CH_3	–	188	58
5g	O	n-C_4H_9	–	158	27

[a] Recrystallized from ethanol.

Scheme I



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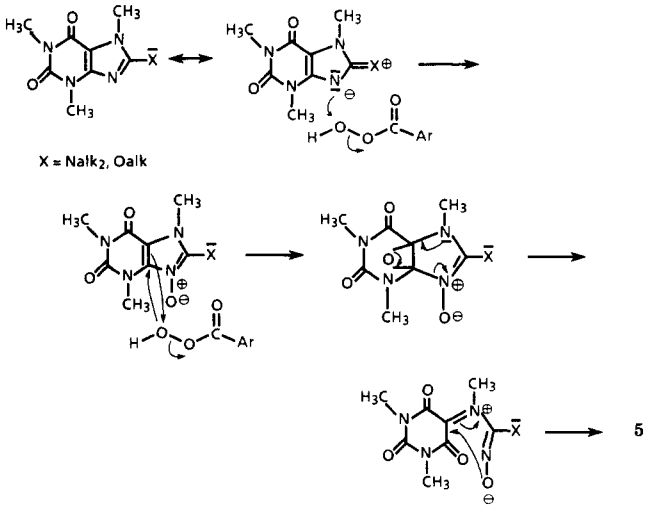
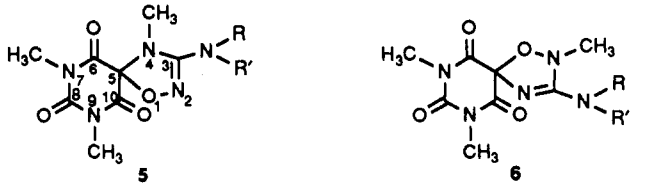
Scheme II



be interpreted to belonging to a number of structures with **5** and **6** being the most likely ones.



Furthermore, vigorous refluxing of these oxidized products of type **1** with 1,2-phenylenediamine in dilute HCl yielded 1,3-dimethylalloxazine (**7**), whose structure was proven by independent synthesis through methylation of the known alloxazine.[15]

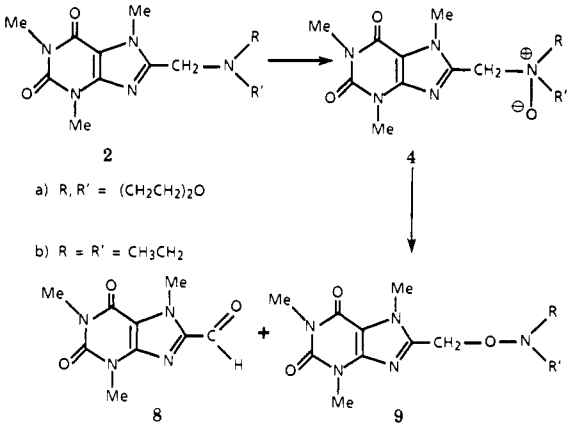
However, the spectroscopic data as well as the results of the chemical degradation were not sufficient to distinguish unambiguously between structures **5** and **6**. Therefore, the structure of compound **5a** was proven by X-ray crystallographic analysis.[16]

This novel rearrangement occurs only if a nitrogen or an oxygen atom is adjacent to the 8-position of the caffeine molecule (Scheme I). Thus, 8-alkylcaffeines and 8-bromocaffeine were shown to be inert toward 3-chloroperoxybenzoic acid. 8-Caffeinyl phenyl thioether was oxidized by 3-chloroperoxybenzoic acid to a mixture of the corresponding sulfone and sulfoxide. If the nitrogen or oxygen atom is separated by a CH_2 group from the 8-position of the caffeinyl moiety, as in the type **2** compounds, normal N-oxidation instead of the novel rearrangement on treatment with 3-chloroperoxybenzoic acid occurs.

These experimental facts lead to a tentative mechanism for this rearrangement in which the initial step is peracid attack at either N-9 or C-5 (Scheme II).

The structure of type **4** species was inferred from elemental analyses and spectroscopic data. In addition,

Scheme III



compound **4** undergoes normal *N*-oxide decomposition to afford 8-formylcaffeine (**8**)[17] and the O-substituted hydroxylamine **9** via Cope elimination and Meisenheimer rearrangements, respectively (Scheme III).

The skeletal rearrangement reported here is different from all other known oxidative reactions of caffeine.[18-26] The application of this simple reaction for the preparation of similar spirocyclic compounds is in progress as are attempts to establish the exact mechanism of this novel rearrangement.

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Supplementary Material Available: X-ray data for **5a** including atomic coordinates and equivalent isotropic displacement parameters, anisotropic temperature parameters, hydrogen atom coordinates and isotropic displacement parameters, bond lengths and angles, and tables giving spectroscopic characterization and analytical data of all new compounds (13 pages); observed and calculated structure factors (4 pages). Ordering information is given on any current masthead page.

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(16) Crystal data of **5a**: $C_{12}H_{17}N_5O_5$, orthorhombic space group $P2_12_12_1$, a = 11.520 (2) Å, b = 12.532 (2) Å, c = 9.706 (1) Å, Z = 4. A total of 1108 reflections with $3 \leq 2\theta \leq 45°$ were observed. Standard direct and difference Fourier methods and least-squares refinement led to final values of R = 0.0364 and R_w = 0.0532.

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(27) Typical experimental procedure: To a solution of **1** or **3** (0.01 mol) in chloroform (100 mL) in a three-neck round-bottom flask equipped with reflux condenser leading to a pressure release valve was added water (50 mL) followed by dropwise addition of 0.5 M 3-chloroperoxybenzoic acid (0.02 mol) in wet chloroform ($CHCl_3$–H_2O = 50:1). The mixture was stirred until TLC showed the disappearance of the starting material (~48 h). The chloroform layer was separated, washed with buffer solution (pH 10) and water, and dried over anhydrous Na_2SO_4. After evaporation of chloroform under reduced pressure, **5** was obtained and purified by recrystallization from ethanol.