Tetrahedron Letters,Vol.29,No.17,pp 2055-2058,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Controlled C-5 methylation of caffeine by benzoyloxy radical addition at C-8

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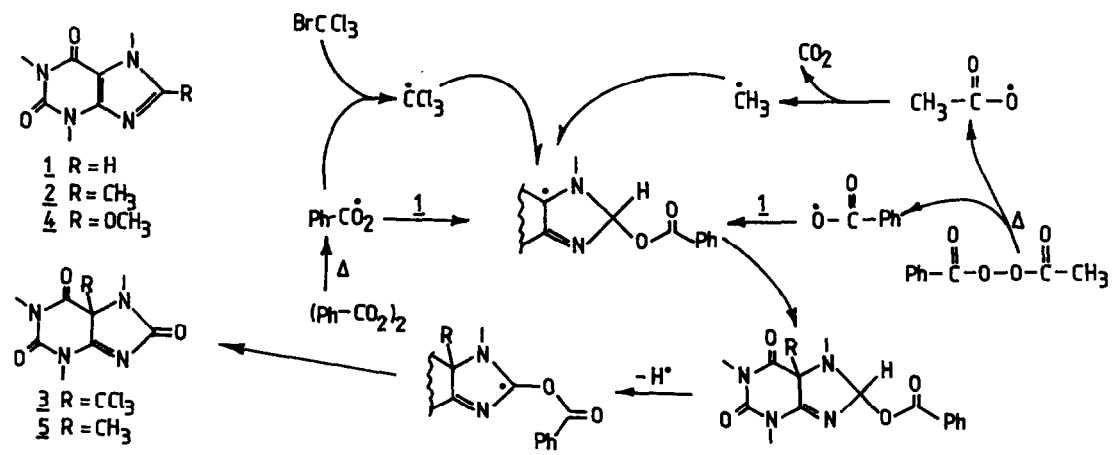
Summary : C-5 methylation of the model purine compound caffeine by acetyl benzoyl peroxide is the result of preferential addition of the electrophilic benzoyloxy radical at C-8 in neutral medium. X-ray structure and molecular orbital calculations on 1,3,5,7-tetramethyl-5,7-dihydrouric acid are presented.

Nucleophilic radicals add readily to the purine nucleus (1), in a reaction analogous to the homolytic alkylation of heteroaromatic bases developped by Minisci (2). The free radical additions of alcools (3), ethers (4), amines (5), or methyl (6), were initiated through decomposition of peroxides. Radical alkylation takes place preferentially at C-8 carbon of 6-substituted purines (7) ; and these reactions are enhanced by protonation. Thus, Wong et al. obtained 8-methyl caffeine 2 as the sole reaction product when an aqueous solution of caffeine 1 was treated with t-butyl peracetate as $\cdot CH_3$ radical source (8) ; no combination with oxy radicals was reported.

As part of our general study on homolytic substitution of caffeine 1 by electrophilic radicals, as well as on the influence of the peroxidic initiators on the course of the reaction (9), we reported in a previous communication (10) the predominant formation of 5-trichloromethyl-1,3,7-trimethyl-5-7-dihydrouric acid 3 when 1 was allowed to react with benzoyl peroxide in bromotrichloromethane. In this aprotic neutral medium, the peroxidic initiator (11) was obviously involved, not only in the production of $\cdot CCl_3$ radicals but also in the initial step of the substitution reaction.

In contrast with Wong's earlier observation (8), in our case preferential attack at C-8 carbon by the acyloxy radical (12) would produce a σ radical complex where the unpaired electron is stabilized on the C-5 captodative carbon. This radical intermediate consequently combines with $\cdot CCl_3$ radical prior to the oxidation step which is followed by β-scission of the oxygen-carbonyl bond as represented in the following Scheme :



C-5 alkylated purine molecules, more particularly C-5 methylated adenine or guanine, are postulated by N.J. Leonard et al., on the basis of semiempirical molecular orbital calculations, to be unstable intermediates which rearrange spontaneously to imidazotriazine derivatives (13).

Since benzoyloxy radical addition to C-8 triggers off the site of alkylation at C-5, one would expect that in the presence of methyl radicals, in neutral medium, C-5 methylated analogue of 3 would be obtained.

Thus methyl and benzoyloxy radicals were generated simultaneously by the thermal decomposition of either t-butyl perbenzoate or acetyl benzoyl peroxide (14a) in chlorobenzene in presence of caffeine 1 (14b).

Whereas the reaction with t-butyl perbenzoate leads to a mixture of two unexpected compounds : a dimer (15), the structure of which is under investigation, and compound 4 identified by comparison with an authentic sample synthesized according to Huston and Allen (16), we successfully isolated from the reaction with acetyl benzoyl peroxide the desired product ; the X-ray crystallographic analysis established unambiguously that this compound is the C-8 oxo, C-5 methyl derivative 5 (Fig. 1) (17). Two facts could account for the relatively fair conversion of 1 to 1,3,5,7-tetramethyl-5,7-dihydrouric acid 5 : a) the activation of the reaction due to a more favourable intramolecular association between caffeine and the less bulky aromatic peroxide (18) and b) the very fast decarboxylation of the acetyl radical (19) as compared to the slower rate of β-scission of the t-butoxy radical into acetone and $^{\cdot}CH_3$ ($k = 1,6 \times 10^9\ s^{-1}$ and $\times 10^5\ s^{-1}$ respectively at 60° C). The formation of the methoxy derivative 4 is not well understood for the moment and is under further investigation.

Semiempirical molecular orbital calculations MNDO using program MOPAC (20) were performed on the C-5 methyl derivative in order to compare the molecular equilibrium geometry with that observed in the crystal, and on the 5-methyl-5H-adenine to compare with Leonard's calculations (13). It is interesting to note that all intracyclic calculated bond lengths in the 5-methyl derivative are longer than the observed ones by 0.05 Å. So, the interpretation of the results determined by semiempirical molecular orbital methods on such a strained molecule must take this error into account. The experimental and calculated bond lengths are compared in Table 1.

Crystallographic study of 5 : C9 H9 O3 N4, Mr= 221.2, *Monoclinic, space group* P21, Z= 4 : *cell parameters* : a= 6.635(4), b= 16.490(6), c= 10.133(5) Å, β=106.93(2)°, V= 1060.6 Å^3, dc=1.39 g.cm^{-3}, λ = 1.5418 Å (Cu Kα), μ= 8.15cm^{-1}.

1971 intensity data were collected on a Philips PW 1100 diffractometer using graphite-monochromated Cu Kα radiation and the θ-2θ scan technique up to θ= 65°. The structure was solved by direct methods using program DEVIN (21), and refined anisotropically by full matrix least-squares minimizing the function $\Sigma w (Fo-|Fc|)^2$. *Hydrogen atoms were located on successive difference Fourier maps and introduced in the refinement in idealized positions (d C-H=1.00 Å) with an isotropic temperature factor equivalent to that of the bonded carbon atom. Final R was 0.041, Rw= 0.057* [$Rw= (\Sigma w (Fo-|Fc|)^2/\Sigma Fo^2)^{1/2}$ *with* $w= 1/\sigma^2(Fo)+0.0027\ Fo^2$] *calculated with the 1526 observed reflections having* $I>3\sigma(I)$, $\sigma(I)$ *from counting statistics. No residual higher than 0.16 eÅ*$^{-3}$ *in the final difference Fourier map. Calculations performed with program SHELX76 (22), (23).*

The two molecules of the asymmetric unit are shown in the Fig. 1. ; they are of opposite chirality. Superimposing each molecule on the enantiomer of the other one, the average of the shifts does not exceed 0.021 Å (H atoms excluded), with a maximum deviation (0.050 Å) for the C-15 methyl groups. Unsuccessful attempts were made to relate these molecules through a crystallographic inversion centre. The equivalent bond distances and angles and torsion angles are very similar (absolute values). The dihedral angle of the two planes (the six- and the five- membered rings) is 153.1°. These values are very close to that found precedently in the trichloromethyl compound 3 (10) (Table 1).

We thank Dr D. LEFORT for helpful discussions.

Table 1 : Comparison of observed and calculated bond lengths (in Å)

	a	b	c	d	e
N1-C2	1.39	1.393	1.43	1.41	1.39
N1-C6	1.38	1.382	1.44	1.33	1.31
C2-N3	1.36	1.397	1.43	1.32	1.31
N3-C4	1.37	1.348	1.39	1.40	1.37
C4-C5	1.50	1.496	1.55	1.56	1.57
C4-N9	1.27	1.290	1.31	1.31	1.30
C5-C6	1.54	1.515	1.55	1.54	1.56
C5-N7	1.43	1.451	1.48	1.48	1.47
C5-C13	1.58	1.536	1.56	1.55	1.56
N7-C8	1.40	1.368	1.44	1.31	1.30
C8-N9	1.40	1.425	1.44	1.43	1.45
N1-C10	1.49	1.477	1.48		
N3-C12	1.48	1.470	1.48		
N7-C15	1.46	1.448	1.47		
C8-O16	1.21	1.215	1.22		

a : 5-trichloromethyl-1,3,7-trimethyl-5,7-dihydrouric acid 3 (X-rays)
b : 1,3,5,7-tetramethyl-5,7-dihydrouric acid 5 (X-rays, this work)
c : 1,3,5,7-tetramethyl-5,7-dihydrouric acid 5 calculated by MOPAC
d : 5-methyl-5H-adenine calculated by MOPAC
e : 5-methyl-5H-adenine calculated by Leonard (MINDO/3 ref. 13)

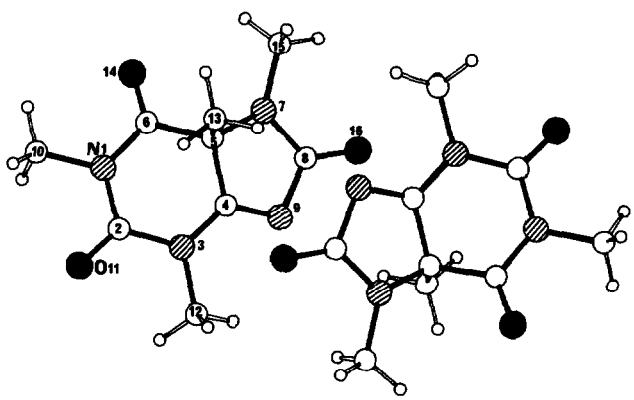


Figure 1

REFERENCES AND NOTES

1. T. Itahara, Y. Seto ; Chem. Letters 1441, (1985) ; Y. Maki, K. Kameyama, M. Sako, K. Hirota ; Tetrahedron Lett., 24, 799 (1983) E. Livneh, S. Tel-Or, J. Sperling, D. Elad ; Biochemistry, 21, 3698 (1982) and references cited therein.

2. A. Citterio, F. Minisci, O. Porta, F. Sesara ; J. Am. Chem. Soc. 99, 7960, (1977).

3. J. Salomon, D. Elad ; J. Org. Chem. 38, 3420, (1973).