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FREE RADICAL ADDITION OF TRICHLOROMETHYL TO CAFFEINE ACCESS TO C-8 POLYHALOGENOALKANE DERIVATIVES AND TO UNEXPECTED 5-TRICHLOROMETHYL-1,3,7 TRIMETHYL-5,7-DIHYDROURIC ACID

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Abstract : The "Electrophilic" trichloromethyl radical was introduced directly into the model purine compound, caffeine, leading to products 2 and 3 (the former being smoothly converted to the corresponding carboxy ester derivative) and to the unexpected C-5 substituted title compound 4.

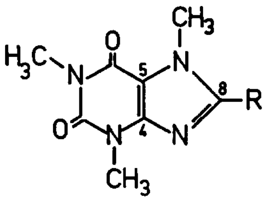
Extensive investigations have been carried out during the last two decades on the homolytic substitution of purine bases by nucleophilic radicals. It has been shown that the C-6, C-8 and to a lesser extent C-2 positions of the purines are the main sites of radical attack[1]. One of the most convincing demonstrations of the potentiallity of this particular reactivity is the smooth introduction of the 2-propanol radical into the nucleosidic constituents of DNA[2]. Other synthetic applications have been reported, such as the direct replacement of the H-8 hydrogen of CGMP by acyl substituants[3], and the synthesis of cyclo 5'-8 adenosine derivatives[4]. However recorded examples of radical addition across the 4-5 double bound[5] and/or direct introduction of electrophilic radicals into the purine bases[6] are quite limited.

We report here new examples of homolytic substitution of model purine compound caffeine 1 at C-8 by the "electrophilic" $\dot{C}Cl_3$ radical and the solvolysis of the trichloromethyl derivative, as well as the unexpected reactivity of the 4-5 double bound, consecutive to oxidation at C-8.

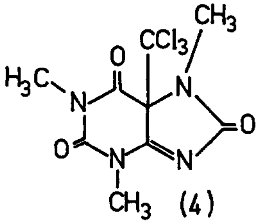
Thus, on refluxing caffeine 1 in bromotrichloromethane in the presence of diterbutylperoxide*, $(tBuO)_2$, two major derivatives were formed : 8-trichloromethyl caffeine 2 (m.p. 190-192° C) and 8-pentachloroethyl caffeine 3 (m.p. 254-257° C). Among the minor reaction products, we were able to isolate and identify, on the basis of its analytical and mass spectroscopic analysis, racemic compound 4** (m.p. 200-202° C).

In this non-chain radical addition of $\dot{C}Cl_3$ to caffeine initiated by $(tBuO)_2$, longer reaction times result in greater conversion of caffeine but no increase in formation of 2 ; secondary by-products formation was favoured instead (Table 1).The following results indicate that 3 derives most probably from initially formed compound 2 and not from $\cdot C_2Cl_5$ radical addition to caffeine. Thus, when 2 was refluxed in $BrCCl_3$ and $(tBuO)_2$, 3 was formed along with some unidentified secondary products ; moreover, when caffeine was allowed to react with a three mole excess of hexachloroethane in $BrCCl_3$ and $(tBuO)_2$, virtually the some proportions of 2, 3 and 4 were observed as in the standard procedure.

The reactivity of 8-trichloromethyl caffeine was demonstrated by its easy conversion into the corresponding methyl ester 5 (m.p. 208-209° C) either by refluxing 2 in a chloroform-methanol solution or by exposure to light. Synthesis of 8-carboxy ester purines by electrophylic substitution of 8-lithio purine trimethysilyl nucleosides were recently reported[7]. Here direct radical trichloromethylation followed by solvolysis represents a novel way for regioselective introduction of ester fonctions.



1 R = H
2 R = CCl_3
3 R = C_2Cl_5
5 R = CO_2CH_3



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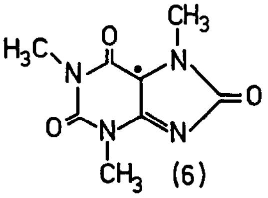

(6)

Interestingly, when the radical addition was initiated by dibenzoyl-peroxide*, $(BzO_2)_2$ compound 4 was the principal product (table 1). The pathway that leads to this unexpected reaction product remains for the moment uncertain. Oxidation, either by benzoyl peroxide or, in the previous experiments, by hydroperoxide contaminating the $(tBuO)_2$ might lead to a 8-oxo-intermediate with a captodatif carbon radical[8] centered at C-5. This hypothetical labile specie 6 would readily combine with CCl_3 radical leading to the C-5 substituted derivative 4, reminicent of the oxidative transformation product of uric acid[9].

Unequivalent proof of the structure of 4 was provided by a single crystal X-ray analysis (Fig. 1). Two independent molecules are present in the asymmetric unit of the unit-cell.

Crystal data : Crystals of 4 belong to the monoclinic system, space group P2/c, Z = 8, a = 14.278 (3), b = 8.417 (2), c = 22.994 (5) Å, β = 105.87° (5). V = 2658 Å³.

Intensity data were measured on a Philips PW1100 diffractometer, using graphite-monochromated Cu Kα radiation (λ = 1.518 Å) and the θ-2θ scan technique up to θ = 65°. Of the 4353 collected reflections, of which 3936 unique, 1682 were considered as observed with I > 2.5 ρ (I), ρ (I) derived from counting statistics. Lorentz-polarization and empirical absorption corrections were applied[10].

*The structure was solved by direct methods and refixed by least-squares technic, with anisotropic thermal parameters for non-hydrogen atoms. All hydrogen atoms were introduced geometrically (d_{C-H} = 1.0 Å) and assigned the equivalent isotropic thermal parameter of the attached atom. The final R value is 0.080****. The bond distances and angles of the two crystallographic independent molecules are in good agreement with each other.*

The six- and the five-membered rings are approximately planar ; the dihedral angle between their mean planes is 151°.

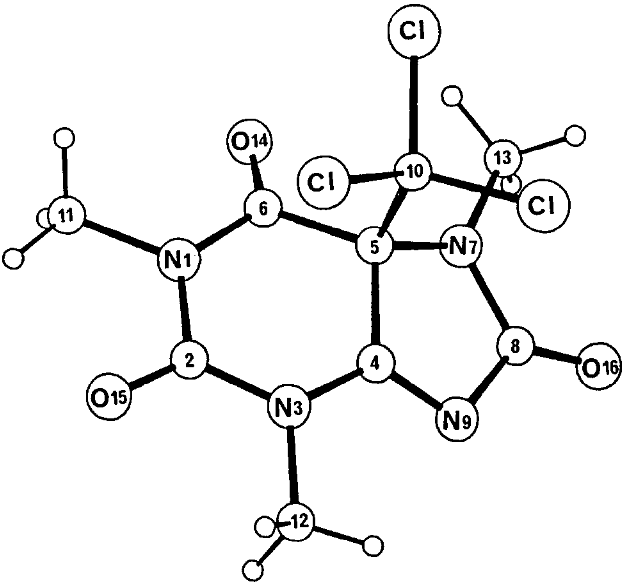

Figure 1 : Perspective view of the molecule. For the two independent molecules : salient bond distance : C(5)-C(10) : 1.592(17), 1.575(18) Å; intramolecular distances : C(10)... O(14) : 3.28, 3.23, C(10)...(13) : 3.25, 3.23 Å ; torsinal angles in six-membered rings : N(1)-C(6) : -17, -28°, C(6)-C(5) : 34, 40°, C(5)-(4) : -39, -40°, C(4)-N(3) : 23, 24°, N(3)-C(2) : -3, -5°, C(2)-C(1) : 0, 8°, five-membered rings : C(4)-C(5) : 12, 16°, C(5)-N(7) : -14, -15° - N(7)-C(8) : 13, 12°, C(8)-N(9) : -6, -1°, N(9)-C(4) : -5, -9°.

Initiator (mmoles)	Time Hours	Yield %			Conversion %	
		$(2)^{bc}$	$(3)^{bc}$	$(4)^{d}$	c	d
$(tBuO)_2(O)^a$	72	≅ 10	-	-	≅ 10	
" (5.5)	24	62	28	-	40	
	48	52	37	-	67	
	69	45	40	3	83	80
" (11)	24	78	22	-	44	
	48	50	36	-	78	
	51	48	36	3	79	68
" (16,5)	24	76	23	-	58	
	48	50	40	-	86	
	62	45	42	3	90	77
$(BzO)_2(5.5)^e$	5	≅ 5	-	67		≅ 100^f
"$(0.1)^{eg}$	5	-	-	-		≅ 5

Table 1 : a : 1.03 mmoles of 1 in 10 ml of $BrCCl_3$ at 107° C ; b : yields bases on reacted 1 ; c : from nmr analysis of N-7 methyl signal intergration curve ± 5 % (60 MHz) ; d : calculated from isolated products ; e : 80°C ; f : no caffeine was recovered ; g : 2.5 ml of 0.04 M solution in $BrCCl_3$ added gradually, 95 % 1 recovered.

We are currently investigating the mecanism of formation of 4 and the reactivity of 2 towards various nucleophiles.

We thank Dr D. Lefort and J.Y. Nedelec for helpful discussions.

Notes

* Comparable results were obtained when the reaction was conducted under an argon atmosphere.

** All compounds described where fully characterised spectroscopically (I.R., mass and NMR***) and by elementary analysis.

*** ^{1}H nmr (90 MHz $CDCl_3$) : (2) 4.33 (N-7 CH_3), 3.61, 3.43 (N-1, N-3 CH_3) ; (3) 4.40 (N-7 CH_3) ; 3.56, 3.42 (N-1, N-3 CH_3) ; (4) 3.56, 3.46 3.37 (N-1, N-3, N-7 CH_3) ; 4.39 (N-7 CH_3), 4.03 (C-8 CO_2CH_3), 3.63, 3.44 (N-1, N-3 CH_3).

**** Calculations were performed with programs SHELX76[11], DEVIN[12] and ORTEP[13] for the drawing of the molecule (fig. 1). The atomic coordinates for molecules I and II, anisotropic thermal parameters, bond lengths and angles and a table of observed and calculated structure factors, have been deposited at the Cambridge Crystallographic Data Centre.

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