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ADDITION OF ELECTROPHILIC RADICALS TO CAFFEINE : SYNTHETIC ASPECTS AND INFLUENCE OF THE PEROXIDIC INITIATORS

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Dedicated to Professor E. Lederer on the occasion of his 80th birthday

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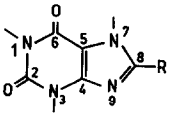
Abstract - Primary and secondary electrophilic radicals such as : $^{\bullet}CHRCO_2CH_3$ (R=H,CH_3,CO_2CH_3) and tertiary $^{\bullet}CCl_3$ radical were added directly at C-8 of the model purine compound, caffeine to give the corresponding 8-substituted derivatives in fairly good yields. Unexpected reaction of caffeine with oxy radicals from the initiators ($PhCO_2^{\bullet}$, t-BuOO$^{\bullet}$) gave rise to C-5 substituted 1,3,7-trimethyl-5,7-dihydrouric acid derivatives (C-5-R=CCl_3, CH_3, $C(CH_3)_2CO_2CH_3$) and to the spirodihydantoin C-8 adduct derivative of caffeine 11.

Since Linschitz and Connolly's first observation on the photochemically induced addition of α-hydroxyalkyl groups on the 6 position of the purine nucleus (1), the substitutions of purines, nucleosides or nucleotides involving radicals have attracted the attention of a number of research groups (2).

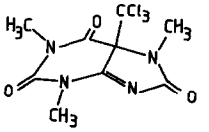
From the abondant investigations carried out in this field during the past two decades it has been established that : a) all the carbon centered radicals which were shown to react with a variety of purines have nucleophilic character ($^{\bullet}CH_3$, $^{\bullet}\overline{CR(CH_2)_n-O}$, $^{\bullet}\overline{CR(CH_2)_n-NH}$, $R\dot{C}=O$, $\dot{C}RROH$ ....); b) the reaction is analogous to the well documented homolytic heteroaromatic substitution reaction studied by Minisci and collaborators (2k, 3); c) the reactions can be induced directly by light or γ-ray, initiated by photochemical or thermal decomposition of peroxides, or in presence of redox systems ; d) among the carbons of the purine nucleus susceptible to be attacked by the free radical, C-6 and C-8, and to a lesser extent C-2, were the only ones which reacted ; no addition of the alkyl radical across the 4-5 double bond was reported ; e) in peroxidic-initiated reactions, addition of the oxy radical from the initiator was not found (2k). No report on the behavior of purine bases toward electrophilic carbon centered radicals was found in the literature (4).

In a preliminary communication we described for the first time the direct introduction of the electrophilic $^{\bullet}CCl_3$ radical on the model purine compound caffeine 1 (5). At that time we observed that the site of substitution by $^{\bullet}CCl_3$ was largely influenced by the peroxidic initiators used.

Thus when caffeine 1 was allowed to react with bromotrichloromethane in presence of excess commercial t-butyl peroxide, $(t\text{-BuO})_2$, two C-8 substituted products were obtained : compounds 2 and 3 , as well as the unexpected minor reaction product 4. However, with benzoyl peroxide 4 was the major product formed.



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



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At that time we suspected contamination of the $(t\text{-BuO})_2$ by traces of t-butylhydroperoxide to be responsible of the formation of 4. Obviously in both cases the initiator was involved in the reaction sequences which led to the C-5 susbstituted product.

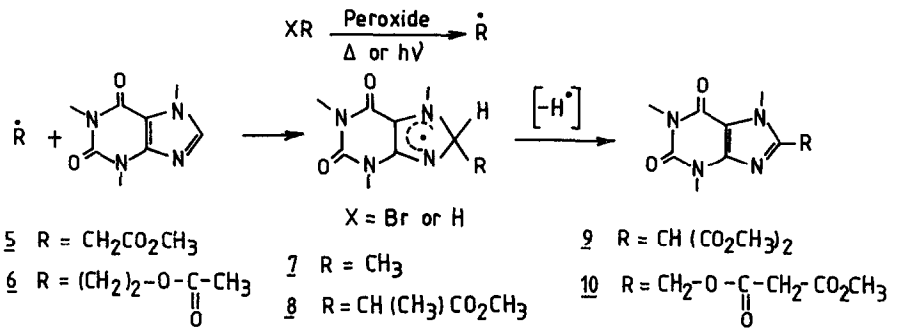
In the present paper we report the results of the work undertaken with the aim on one hand to extend our preliminary results to other electrophilic radicals and on the other hand to investigate the unexpected influence of the peroxidic initiator on the course of the reaction.

RESULTS AND DISCUSSION

Electrophilic radicals are characterized by the presence of electron withdrawing fonctions α to the carbon centered radical. In this respect, malonyl, $\dot{C}H(CO_2R)$, and carbomethoxymethyl, $\dot{C}H_2CO_2CH_3$, radicals have been shown to have electrophilic properties in addition reactions upon simple double bonds (6). We therefore considered the carbomethoxy-alkyl radicals such as $^{\bullet}CR_1R_2CO_2CH_3$ to be good candidates for testing the generality of direct introduction of such species on the purine nucleus.

- Reactions with primary and secondary carbomethoxy-alkyl radicals

Caffeine 1 solubilised directly in the ester was allowed to react with the alkyl radicals produced by abstraction of either bromide or hydrogen atom from the corresponding ester by the t-butoxy radical thermally or photochemically generated as depicted in Scheme 1 :



Scheme 1

The reactions investigated are summarized in table I. The products isolated were identified by means of their physical properties (microanalytical analysis, ^1H, ^{13}C NMR, mass spectra, U.V. absorption) which are reported in the experimental section.

Addition of the carbomethoxymethyl radical $\dot{C}H_2\text{-}CO_2CH_3$ proved to be quite satisfactory when the radical was produced from bromoacetate by thermal decomposition of $(t\text{-BuO})_2$ (Table I entry 1). The photochemical-induced reaction with bromoacetate or methyl acetate was less operating (entries 2, 3, 4).

From the photochemical reaction with methyl acetate compounds 5, 6, 7, were isolated. 8-methylcaffeine 7 was the result of attack at C-8 by methyl radicals produced through β scission of the t-BuO radicals. Compound 6 was certainly formed by coupling of the stabilized benzilic-type radical species $8\text{-}\dot{C}H_2$ derived from 8-methylcaffeine with radical $\dot{C}H_2\text{-O-COCH}_3$ produced by hydrogene abstraction on the methyl group of the methoxy moiety of the ester, as already reported by various authors (7).

Secondary radical from methyl-bromopropionate proved to add less readily than the primary radical ; longer reaction time was required to reach significant conversion of the substrate (comparison between entries 1 and 5). Replacement of the hydrogen atom at the radical center α to the carbonyl by a methyl group gives rise to a more developped captodative radical species which must be more stable and less electrophilic then the primary radical (6b). Nevertheless 75 % of the reacted caffeine was converted to expected derivative 8.

TABLE I

Substitution products of caffeine from primary and secondary esters in presence of $(t\text{-BuO})_2$

Entry	Esters (100 mmoles)	Caffeine (mmoles)	Peroxide (mmoles)	R	$\Delta/h\nu$	hrs	T (%)	Yield* (%)
1	$BrCH_2CO_2CH_3$	3.25	17.4	5 $CH_2CO_2CH_3$	Δ	8	82	77
2	$BrCH_2CO_2CH_3$	1.4	52.1	5 $CH_2CO_2CH_3$	+ hν	47	67	41
3	$HCH_2CO_2CH_3$	0.13	2.19	5 $CH_2CO_2CH_3$ 6 $CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$	hν	26	71	40 5
4	$HCH_2CO_2CH_3$	0.27	2.6	5 $CH_2CO_2CH_3$ 6 $CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$ 7 CH_3	hν	79	89	28 8 2
5	$BrCH(CH_3)CO_2CH_3$	2.9	15.3	8 $CH(CH_3)CO_2CH_3$	Δ	30	38	75
6	$BrCH(CO_2CH_3)_2$	3.4	18.1	9 $CH(CO_2CH_3)_2$ 5 $CH_2CO_2CH_3$	Δ	17	50	2 44
7	$HCH(CO_2CH_3)_2$	2.9	15.7	9 $CH(CO_2CH_3)_2$ 5 $CH_2CO_2CH_3$ 10 $CH_2-O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3$	Δ	17	56	8 15 18
8	$HCH(CO_2CH_3)_2$	0.84	9	9 $CH(CO_2CH_3)_2$ 10 $CH_2-O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3$	hν	15	100	59 traces

*: Yields based on reacted caffeine ; T: Reacted caffeine ; Δ: 105-107°C (see experimental section) ; hν: > 290 nm ; +: peroxide added by small portions during irradiation.

With bromomalonate and malonate methyl esters, the expected substitution product 9 was formed ; however the yields of isolated derivative was largely dependent of the experimental conditions used (entries 6, 7, 8). Thus, the thermally induced reactions led mainly to 5 since 9 revealed to be thermally unstable (8). With dimethyl malonate, 10 was also formed due to competitive hydrogen abstraction α to the carbonyl or on the $-O-CH_3$ function as already mentioned (7). The C-8 malonyl ester derivative 9 was obtained best by the photo-initiated reaction (entry 8), where lower temperature prevented dealkoxycarbonylation and favored more selective α-hydrogen abstraction.

Reactions with tertiary radicals

When caffeine was allowed to react with tertiary radicals derived from bromotrichloromethane, α-methyl-dimethylmalonate and methyl α-bromoisobutyrate in presence of $(t\text{-BuO})_2$ or benzoyl peroxyde, $(PhCO_2)_2$, interesting and unexpected results were obtained ; these are summarized in Table II.

As described previously (5), reaction of caffeine with tertiary $\dot{C}Cl_3$ radical produced from $BrCCl_3$ and t-BuO· gave, in the first stage of the reaction, 8-trichloromethylcaffeine 2. It was then shown that this derivative evolved, through chlorine abstraction followed by coupling of the resulting radical species with an other $\dot{C}Cl_3$ radical, to 8-pentachloroethylcaffeine 3 ; we recall that in these conditions traces of C-8 oxo C-5 substituted products 4 were also formed. This compound became the main reaction product isolated when $(t\text{-BuO})_2$ was replaced by $(PhCO_2)_2$.

When caffeine was reacted with either α-methyl dimethylmalonate or methyl α-bromoisobutyrate in presence of $(t\text{-BuO})_2$, no C-8 radical addition product of these esters was formed ; instead the adduct 11, the structure of which was established by single-crystal X-ray analysis (Fig. 1) (9), was formed independently of the ester used (Table II). The rearrangement of the spiro-moiety of

that adduct will be discussed later on. No definite conclusions could be reached as to the lack of reactivity of the α-methyl dimethylmalonate ester since degradation of the starting material was observed and furthermore non selective hydrogen abstraction could be expected. On the other hand, the poor reactivity of the tertiary dimethyl-carbomethoxymethyl radical ($\dot{C}(CH_3)_2CO_2CH_3$) toward C-8 carbon could be, more likely, the consequence of its decreasing polarity rather than its increasing bulkyness ; moreover, increasing stability of this tertiary radical might also contribute to a certain degree to the reversibility of the addition step.

However, when this ester was reacted in presence of benzoyl peroxide 5-(2dimethyl-carbomethoxymethyl)-1,3,7-trimethyl-5,7-dihydrouric acid 12 was obtained. The common feature between compounds 4 and 12, i.e., a carbonyl fonction at C-8 , and the formation of the highly oxidized spiro moiety of adduct 11, led us to consider that oxy radicals from the initiators used in large excess (5-10 times molar) must be involved in the introduction of an oxygen atom at C-8. Yet, the differences observed between $(t\text{-BuO})_2$ and $(PhCO_2)_2$ needed to be elucidated.

Table II : Reaction of caffeine with tertiary radicals in presence of $(t\text{-BuO})_2$ or $(PhCO_2)_2$

Entry	Reagent (100 mmoles)	Caffeine 1 (mmoles)	Peroxide (mmoles)	Temp. °C	hrs	Reacted 1 (mmoles)	Product (%)*
1	$BrCCl_3$	1.03	$(t\text{-BuO})_2$ 5.5	107	50	78.6	2 (43) 3 (31) 4 (3.5)
2	$BrCCl_3$	1.03	$(PhCO_2)_2$ 5.5	80	5	100	2 (5) 4 (67)
3	$BrC(CH_3)_2CO_2CH_3$	3.4	$(t\text{-BuO})_2$ 18	105	30	36	11 (14)
4	$BrC(CH_3)_2CO_2CH_3$	1.4	$(PhCO_2)_2$ 7.3	80	4	95	11 (trace) 12 (33)
5	$HC(CH_3)CO_2CH_3)_2$	3.7	$(t\text{-BuO})_2$ 19.6	105	17	43	11 (26)

* Yields based on reacted caffeine

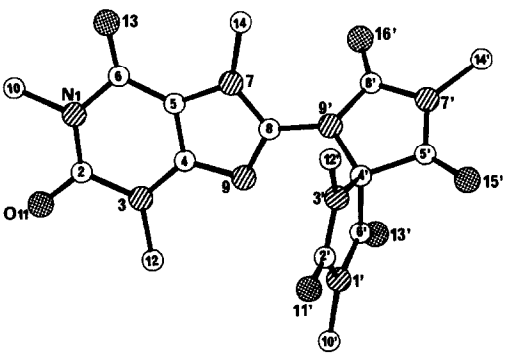
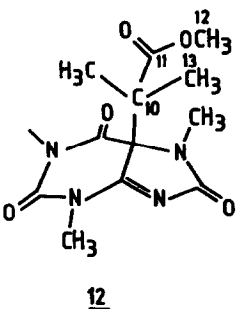


Figure 1: Perspective view of molecule 11



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Influence of the peroxides

Reactions with $(t\text{-BuO})_2$ and t-BuOOH

t-butoxy radicals (t-BuO·) are known to abstract allylic hydrogen atom rather than to add on alkene double bond (10) ; moreover homolytic aromatic substitution reactions by this radical species are unknown. Therefore, the possibility of direct oxidation at C-8 by the terbutoxy radical must be dismissed. Since commercial $(t\text{-BuO})_2$ contains about 5 % of t-butylhydroperoxide, more reasonable was to consider hydrogen abstraction from t-BuOOH by t-BuO· ; this reaction is known to be very fast (11). The resulting t-butylperoxy radical (t-BuOO·), a poor hydrogen abstracting species, does add to double bonds (12). Thus, the proportion of C-8 oxo C-5 substituted product 4 to C-8 substituted derivative 2 would depend upon the t-BuOO· radical concentration formed during the reaction. To test this hypothesis we examined the product distribution of reactions conducted with variable ratios of t-BuOOH/$(t\text{-BuO})_2$ in $BrCCl_3$; the results are depicted in Table III.

TABLE III

Reaction of caffeine (a) in $BrCCl_3$ at 107° C with variable ratios of $(t\text{-BuO})_2$/t-BuOOH (reaction time 50 h)

Entry	$(t\text{-BuO})_2$ (mmoles)	t-BuOOH (mmoles)	Reacted caffeine (%)	Yields* (%) 2	3	4
1	5.2	(b)	78	43	31	3.5
2	4.70	0.38	100	20	2	25
3	1.56	2.70	75	15	2	23
4	-	3.85	43	17	0.2	23
5[c]	-	-	10	10	-	-

* Yields based on reacted caffeine

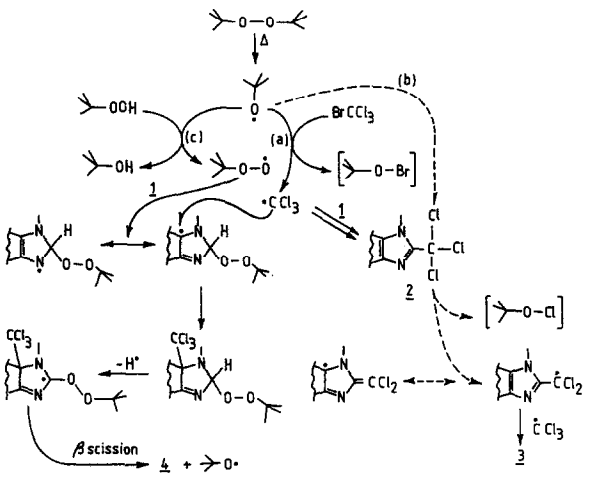
(a) Caffeine concentration : 1,03 mmoles in 10 ml $BrCCl_3$

(b) Commercial $(t\text{-BuO})_2$ containing t-BuOOH

(c) Blank experiment

The most notable feature observed was the higher yield of C-5 substituted derivative 4 as the amount of t-BuOOH was increased. Whereas in the initial reaction (Table III, entry 1) only 3.5 % of 4 was obtained against 74 % of C-8 polyhalogenoalkyl derivatives 2 and 3. The product composition was completely altered with large amount of t-BuOOH ; 4 representing then over 50 % of the products formed (entries 2, 3, 4). With t-butylhydroperoxide alone (entry 4), the lower conversion of the substrate for a given reaction time and temperature could be explained by the fact that homolysis rate constant of t-BuOOH is much lower than that of $(t\text{-BuO})_2$. Another relevant point which gives some insight about the competitive reactions of t-butoxy radical with the trichloromethyl derivative 2 on one hand, and with t-BuOOH on the other hand, was the supressed formation of 3. To explain these results the following sequence of reactions may be envisioned, Scheme 2.

Hydrogen abstraction from t-butylhydroperoxide (Scheme 2(c)) would generate t-butylperoxy radicals which add onto the C-8 carbon giving rise to a σ radical intermediate where the unpaired electron is delocalized leading to a persistant tertiary captodative radical at C-5 ; coupling of this intermediate with CCl_3· radical followed by oxidation and β scission of the peroxy bond would lead to 4. Accordingly, increasing t-BuOOH concentration would disfavor the competitive reactions of t-BuO· radicals with $BrCCl_3$ (a) and with 2 (b), thus lowering the yields of 2 and 3 as observed (13).



Scheme 2

Since adduct product 11 was obtained when caffeine was reacted with sluggish tertiary radicals, the above experiments were repeated in inert solvent without $BrCCl_3$. In these conditions one can expect reaction to take place only between the substrate and the peroxides. Two products were formed : adduct 11 and 8-methoxycaffeine 13, identified by comparison with an authentic sample synthesized according to Huston and Allen (14).

TABLE IV

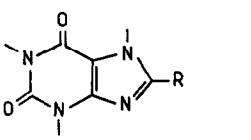
Reaction of caffeine (a) in chlorobenzene at 107° C with variable ratios of $(t\text{-BuO})_2$/t-BuOOH (reaction time 30 h)

Entry	$(t\text{-BuO})_2$ (mmoles)	t-BuOOH (mmoles)	Reacted caffeine (%)	Yields* (%) 11	Yields* (%) 13	11/13
1	5.22	(b)	54	9	34	0.26
2	4.70	0.38	50	13	27	0.48
3	3.66	1.16	50	21	19	1.11
4	2.61	1.92	50	24	14	1.71
5	1.56	2.7	50	30	7	4.29

* Yields based on reacted caffeine

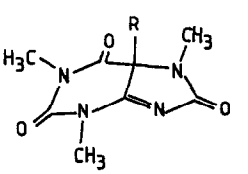
(a) Caffeine concentration 1.03 mmoles in 10 ml of chlorobenzene

(b) Commercial $(t\text{-BuO})_2$ containing t-BuOOH



13 R = OCH_3 14 R = O-C(=O)-Ph

15 R = OH



16 R = O-C(=O)-Ph

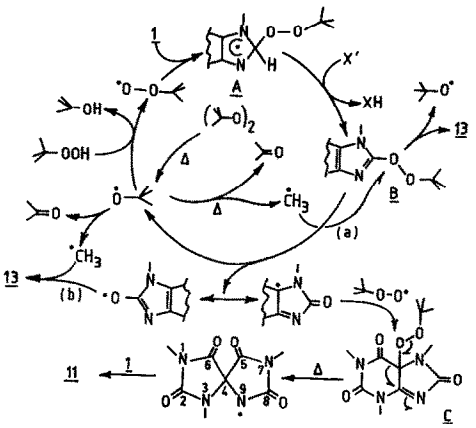
17 R = CH_3

The data reported in Table IV shows that with increasing t-BuOOH concentration the ratio of 11/13 is quite affected. These results can be rationalized by the sequence of reactions illustrated in Scheme 3.

The peroxo radical adduct A, which in the previous experiments combined with $\dot{C}Cl_3$ radical, would be oxidized, in the present case, to the corresponding labile 8-t-butylperoxocaffeine derivative B.

At low t-BuOOH concentration (which means high $\dot{C}H_3$ concentration) predominant C-8 methoxy derivative 13 is observed (entry 1), more likely through induced decomposition of B at the first stage of the reaction (pathway a) ; according to pathway b, some C-5 methylated derivative would be expected from the C-5 mesomeric radical intermediate ; none was found.

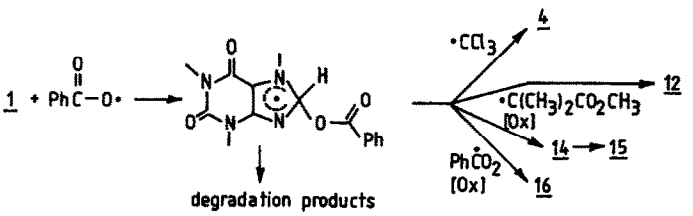
Conversely, with increasing t-BuOOH concentration induced decomposition is less effective ; thus B is thermally decomposed into the captodative C-5 radical intermediate which recombines with t-BuOO. After homolysis of C and ring contraction through cleavage of the C-5-C-6 bond (15), the spiro radical intermediate thus formed reacts with caffeine. We noticed that, in contrast to what happened with $BrCCl_3$, the conversion of caffeine remained constant.



Scheme 3

Reactions with benzoyl peroxide

The fact that in presence of benzoyl peroxide only C-5 alkylated products were obtained either with the very reactif $\dot{C}Cl_3$ radical or with the tertiary dimethyl-carbomethoxymethyl radical, chemically inert toward C-8 addition, is in good agreement with what is known about the facility for benzoyloxy radical to add on double bonds (16) or on aromatic nucleus (17). It was further shown that derivatives 14, 15 and 16 could be isolated from large-scale experiments (3 g of 1, 5 g of $(PhCO_2)_2$ in 50 ml of $BrCCl_3$), and that large amounts of non-characterized red degradation products (18) were formed when molar ratio of $(PhCO_2)_2$ to caffeine was inferior to 5.

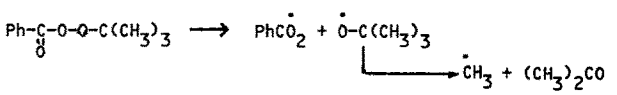


Synthesis of 1,3,5,7-tetramethyl-5,7-dihydrouric acid 17

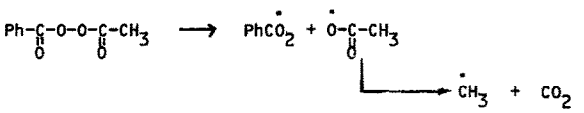
When crystallographic structure of 4 was published (5), the question arose as to the factors which contributed to the stability of this C-5 substituted derivative as compared to the unstability of the C-5 methylated purines which rearranged spontaneously to imidazotriazines (19). At that time it was not possible to reach a definite decision between the influence of the attracting trichloromethyl group at C-5 (instead of the CH_3 group) or the nature of the Sp^2 C-8 carbon engaged in an exocyclic double bond through the carbonyl fonction (in place of a second endocyclic double bond in the hypothetical C-5 methylated purine derivative). It was therefore challenging to attempt the synthesis of C-5 methylated analogue of 4 by the radical approach based on the present knowledge about the influence of the peroxide.

A prerequisite in order to achieve such synthesis was the simultaneous production of benzoyloxy and methyl radicals. To reach this goal two peroxides could be envisioned :

a) t-butyl peroxybenzoate



b) acetyl benzoyl peroxide



Since decarboxylation of acetyl radical (20) is known to be about 10^4 times faster than β-scission of t-butoxy radical (21), instantaneous $\dot{C}H_3$ concentration should be therefore more important with acetyl benzoyl peroxide. Thus concomitant $PhCO_2^{\cdot}$ and $\dot{C}H_3$ additions at C-8 and C-5 respectively would be expected to take place best with the second peroxide (b).

As reported recently (22) this was the case, 17 was obtained with fairly good yield (33 %) with acetyl benzoyl peroxide ; whereas t-butyl peroxybenzoate did not lead to the desired product. Instead adduct 11 and 8-methoxycaffeine 13 were formed. We could not and can not propose a plausible explanation for the origin of these two derivatives in the present experiment. Further investigations are necessary in order to elucidate this point.

Conclusion

In addition to what was already known about homolytic substitution of heteroaromatic bases by nucleophilic radicals, this work demonstrates that radicals having electrophilic character such as primary or secondary methyl-carbomethoxy radicals or tertiary trichloromethyl radical do react, in certain conditions, at C-8 of caffeine ; the corresponding substituted products being formed in good to fair yields. These results corroborate the fact that caffeine can be considered as an ambivalent compound having electron donating (23) or accepting (24) properties (25). Furthermore, a better understanding of the influence of the peroxidic initiator on the course of the reaction, in our experimental conditions, allowed us to elaborate a specific route to C-5 alkylation of caffeine by initial benzoyloxy radical addition at C-8 with concomitant alkyl coupling at C-5.

EXPERIMENTAL

Melting points, determined on a Leitz heating microscope apparatus, are uncorrected. Ultraviolet spectra from 95 % ethanol solutions were recorded on a Beckman Acta III spectrophotometer. I.R. spectra from chloroform solutions were recorded on a Perkin-Elmer-577 instrument. Mass spectra were measured on a AEI MS-9 Spectrometer under electron impact at 70 EV (E.I.) or chemical ionisation with NH_3 (C.I.). ^1H N.M.R. spectra were recorded on a Varian T60 or a Brucker WH-90 instrument from chloroform solutions (unless stated to the contrary) ; chemical shifts (δ) are expressed in ppm from tetramethylsilane as internal standard. Signals are described as S (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Likewise ^{13}C NMR were recorded on Varian CFT-20 or Brucker AM-300 Spectrometers ; ^{13}C data are reported in Table V (experimental section). Microanalytical analyses were determined by the "Service Central d'Analyse", C.N.R.S., Vernaison, France ; found values are presented in parentheses. Column chromatography (Merck, Kieselgel-60, 70-230 mesh) ; analytical thin layer chromatography, TLC, (Merck aluminium sheets silica-60F254 pre-coated) and preparative layer chromatography, PLC, (Merck glass silica-60 F 254 pre-coated, 2 mm) were developed with the appropriate following solvents : A (cyclohexane-ether 1/1) ; B (acetone-hexane 7/3) ; C (chloroform-methanol 99/1) ; D (acetone-hexane 6/4) ; E (ethyl acetate-methanol 99/1) ; F (cylohexane-ether 9/1) ; G (ethyl acetate-cyclohexane 7/3) ; H (Benzene-methanol 20/1.5) ; I (ethyl acetate-methanol 95/5).

Reagents : caffeine (Merck) ; methyl acetate, methyl bromoacetate, methyl DL-2-bromopropionate (Janssen) dimethyl bromomanolate, dimethyl malonate (Fluka) were used as such ; methyl malonic acid (Janssen) and α-bromoisobutyric acid (Fluka) were esterified to the corresponding esters (Eb. 78-80° C/70 mm ; Eb. 66-67° C/38 mm respectively). Bromotrichloromethane (Janssen) was distilled before use. 8-bromocaffeine and 8-methylcaffeine were prepared according to Klosa (26) and Kawazoe (2-i) respectively. Di-t-butyl peroxide, $(t\text{-}BuO)_2$, (Merck) and t-butylhydroperoxide 70 % (Triconox) were used as such, whereas t-butyl peroxybenzoate (Janssen) was distilled (Eb. 85-87° C/0.3 mm). Acetyl benzoyl peroxide was prepared according to Nedelec (27) ; CAUTION should be taken while distilling t-butyl perbenzoate or during synthesis of acetyl benzoyl peroxide since these compounds are known to react violently.

General procedure : caffeine was dissolved in the reacting component in the presence of appropriate peroxidic initiators. The progress of the reaction was followed by ascending TLC. Product separation was achieved by immediate column chromatography and if required further purified by PLC. The thermal reactions were conducted under argon, the stirred solution being immersed, in a thermostated oil bath. The photochemically induced reactions were carried out in a Pyrex immersion apparatus (procedure A) or in a vessel placed 10 cm away from the light source (procedure B), internal cooling was maintained with running water, irradiation was done using Hanau TQ high pressure mercury vapor lamps (500 or 150 W) under continuous bubbling of argon.

Reaction with $BrCCl_3$ and $(t\text{-}BuO)_2$: Caffeine (200 mg, 1.03 mmoles) in $BrCCl_3$ (10 ml, 100 mmoles) and t-butyl peroxide (1 ml, 5.5 mmoles) were allowed to react 50 hrs at 107° C. The compounds were eluted with solvent A : first 8-pentachloroethylcaffeine 3 (99 mg) was obtained (Rf : 0.19 solvent A, 0.55 solvent H) ; m.p. 254-257° C ; υmax 1660, 1705 cm^{-1} ; λmax 296 nm, ε = 9000 ; m/z (C.I.) : 395 (M + 1) ; Calc. for $C_{10}H_6N_4O_2Cl_5$: C, 30.44 (30.42) ; H, 2.29 (2.19) ; N, 14.20 (14.08) ; Cl, 44.94 (45.51) ; O, 8.13(7.80) ; NMR : 3.44, 3.56, 4.40 (3 CH_3, N-1,N-3,N-7). Next 8-trichloromethylcaffeine 2 (110 mg) was eluted (Rf : 0.18 solvent A, 0.52 solvent H) ; m.p. 190-192° C ; υmax : 1660, 1705 cm^{-1} ; λmax 296 nm, ε = 1300 ; m/z (C.I.) 312, (M + 1) ; calc. for $C_9H_9N_4O_2Cl_3$: C, 34.69 (34.06) ; H, 2.92 (2.79) ; N, 17.93 (17.51) ; Cl, 34.14 (35.55) ; O, 10.32 (10.09) ; NMR :

3.42, 3.60, 4.33 (N-1-CH_3, N-3-CH_3, N-7-CH_3) ; PLC were necessary for good separation of 2 and 3. Solvent B eluted 5-trichloromethyl-1,3,7-trimethyl-5,7-dihydrouric acid 4 (9,4 mg) Rf : 0.44 (solvent H) ; m.p. 200-303° C ; νmax : 1520, 1624, 1705, 1755 cm^{-1} ; λmax 254 nm (shoulder), ε = 6700; m/z (E.I.) : 327 (M), 209 (100 %, M-CCl_3) ; calc. for $C_9H_9N_4O_3Cl_3$: C, 32.97 (33.43) ; H, 2.74 (2.66) ; N, 17.09 (17.00) ; Cl, 32.38 (31.57) ; O, 14.82 (15.34) ; NMR : 3.34, 3.44, 3.54 (N-1-CH_3, N-3-CH_3, N-7-CH_3) ; for crystallographic data cf. refs 5 and 22. Finally 43 mg of unreacted caffeine were eluted with solvent C.

Reaction with $BrCCl_3$ and $(PhCO_2)_2$: (1) Caffeine (400 mg, 2.06 mmoles), $(PhCO_2)_2$ (2.64 mg, 11 mmoles, 22 eq.) in $BrCCl_3$ (20 ml) were kept at 80° C for 5 hrs. Compound 2 (32 mg) was eluted with solvent A, followed by compound 4 (451 mg) eluted with solvent C ; 25 mg of non identified products were also isolated. (2) Caffeine (3 g, 15.5 mmoles), $(PhCO_2)_2$ (5.4 g, 22.3 mmoles) in $BrCCl_3$ (50 ml) were kept at 80° C for 6 hrs. The reaction mixture was allowed to stand overnight at 5°C ; a precipitate was isolated, crystallization in ethyl acetate/methanol afforded 205 mg of trimethyluric acid 15 (Rf : 0.03 solvent H) ; m.p. 340-345° C ; m/z (C.I.) 211 (M + 1) ; calc. for $C_8H_{10}N_4O_3$: C, 45.71 (45.94) ; H, 4.80 (4.84) ; N, 26.66 (26.40) ; NMR (DMSO-d6) : 3.19, 3.32, 3.34 (N-1-CH_3, N-3-CH_3, N-7-CH_3). The filtrate was diluted with chloroform and washed with bicarbonate solution. The organic phase was evaporated under vacuum. The oily residue, taken up with ethyl acetate/ether, furnished 526 mg of 5-benzoyloxy-1,3,7-trimethyl-5,7-dihydrouric acid 16 (Rf : 0.7 solvent H) ; m.p. 171-173° C (ethyl acetate) ; calc. for $C_{15}H_{14}N_4O_5$: C, 54.54 (54.55) ; H, 4.27 (4.20) ; N, 16.96 (16.89) ; NMR : 3.21, 3.36, 3.55 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 8.07 (m-5H, C-5-O-CO-Ph). The mother-liquor was again washed with bicarbonate solution for removal of remaining benzoic acid. The organic phase was evaporated, taken up with ether, 647 mg of 4 were isolated. After chromatography of this last mother-liquor with solvents A and E 128 mg of 8-benzoyloxy-caffeine 14 was isolated (Rf : 0.51 solvent I) ; double m.p. 165-170° C sublimes, partial fusion around 200° C, complete fusion 345-346° C (possible thermal decomposition into trimethyluric acid); m/z (E.I.) : 314, 209, 105 ; N.M.R. : 3.44, 3.58, 3.84 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 8.02 (m-5H, C-8-O-COPh). The remaining products isolated were caffeine (344 mg) and non characterized red-violet pigments.

Reaction with esters

- *Methyl bromoacetate, $(t\text{-}BuO)_2$, thermal reaction* : caffeine (400 mg, 2.06 mmoles), bromoacetate (6 ml, 63.4 mmoles) and $(t\text{-}BuO)_2$ (2 ml, 11 mmoles) were heated at 105° C during 8 hrs. 345 mg of 8-carbomethoxy-methylcaffeine 5 were eluted with solvent D (Rf : 0.27 solvent I) ; m.p. 180-182° C (ethyl acetate) ; νmax : 1660, 1705, 1745 cm^{-1} ; λmax 277 nm, ε : 12000 ; m/z (E.I.) : 266(M^+) ; calc. for $C_{11}H_{14}N_4O_4$: C, 46.62 (46.59) ; H, 5.30(5.32) ; N, 21.04 (21.33) ; O, 24.04 (23.69) ; N.M.R. : 3.39, 3.55, 3.94 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 3.87 (S-2H, C-8-CH_2), 3.76 (S-3H, OCH_3). Solvent C eluted 73.5 mg of unreacted caffeine.

- *Methyl bromoacetate, $(t\text{-}BuO)_2$, Photochemical reaction, procedure B-500 W* : caffeine (400 mg, 2.06 mmoles) in methyl bromoacetate (14 ml, 147.84 mmoles) was irradiated during 47 hrs with addition of $(t\text{-}BuO)_2$ by small portions (total volume 14 ml, 77 mmoles). Solvent was partially evaporated and the residue chromatographed. Solvent B eluted 153 mg of 5, purified by PLC ; 130.3 mg of 1 was recovered with solvent C.

- *Methylacetate, $(t\text{-}BuO)_2$, photochemical reaction : (1) procedure A-150 W* : caffeine (1 g, 5.15 mmoles) in methylacetate (320 ml, 4.03 moles) was irradiated during 26 hrs ; peroxide (16 ml, 88 mmoles) was added during irradiation. Solvent was evaporated under vacuum. The products were separated by successive chromatography using solvants B and D ; were isolated : compound 5 (372 mg) and 8-(1 acetoxyl-ethylcaffeine 6 (52 mg) (Rf : 0.32, solvent I) ; m.p. 135.5-136.5° C ; νmax : 1660, 1705, 1745 cm^{-1} ; λmax 276 mm, ε = 24800 ; m/z (C.I.) : 281 (M + 1) ; N.M.R. : 3.40, 3.54, 3.95 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 3.08, 4.47 (t-2H, t-2H, C-8-CH_2 and CH_2-O- respectively), 2.04 (S-3H, OCH_3). *(2) procedure A 300 W* : caffeine (10 g, 51.5 mmoles) in methyl acetate (1.5 l, 18.9 moles) to which was added $(t\text{-}BuO)_2$ at intervals (total volume 90 ml, 495 mmoles) were, irradiated 79 hrs. Solvent was evaporated ; the oily residue taken up with ethyl acetate afforded, after crystallization 261 mg of 5 and 250 mg of caffeine. Chromatography of the mother-liquor with solvent A followed by ethyl acetate and finally solvent C furnished 3.1 g of 5, 1 g of 6 and 170 mg of 7 (N.M.R. : 3.38, 3.53, 3.90 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 2.47 (S-3H, C-8CH_3)).

- *Methyl DL-2-bromopropionate, $(t\text{-}BuO)_2$, thermal reaction* : The reaction was carried out as previously described with 4 ml of ester, caffeine (200 mg, 1.03 mmoles) and $(t\text{-}BuO)_2$ (1 ml, 5.5 mmoles), at 107° C for 30 hrs. Chromatography of the reaction mixture (solvent D) afforded 83 mg of 8-(2 carbomethoxy)-ethylcaffeine 8 (Rf : 0.42, solvent I) ; m.p. 160-163° C (ethyl acetate) ; νmax : 1650, 1697, 1735 cm^{-1} λmax 278 nm, ε = 12400 ; m/Z (C.I.) : 281 (M + 1) ; calc. for $C_{12}H_{16}N_4O_4$: C, 51.43 (51.63) ; H, 5.75 (5.82) ; N, 19.99 (19.90) ; O, 22.83 (22.90) ; N.M.R. : 3.40, 3.57, 3.96 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 3.95 (q-1H, C-8-CH-, 1.67 (d-3H, CH_3). Solvent C eluted 123.5 mg of caffeine.

- *Methyl bromomalonate, $(t\text{-}BuO)_2$, thermal reaction* : caffeine (200 mg), methyl bromomalonate (4 ml, 30.3 mmoles), $(t\text{-}BuO)_2$ (1 ml, 5.5 mmoles) were kept at 107° C for 17 hrs. Chromatography with solvent A eluted 17.4 mg of a fraction from which were obtained by crystallization in ethyl acetate 3.5 mg of 8-dicarbomethoxy-methylcaffeine 9 (Rf : 0.44, solvent I) ; m.p. 181.5-184° C ; νmax : 1658, 1702, 1743, 1752 cm^{-1} ; λmax 279 nm, ε = 12800 ; m/z (C.I.) : 325 (M + 1) ; calc. for $C_{13}H_{12}N_4O_6$: C, 48.15 (48.44) ; H, 4.97 (5.03) ; N, 17.28 (17.20) ; O, 29.60 (29.31) ; N.M.R. : 3,40, 3.55, 3.95 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 5.07 (S-1H, C-8-CH) ; 3.86 (S-6H, two OCH_3). Further elution with ethyl acetate and solvant E gave 60.5 mg of 5 and 100 mg of 1.

- *Dimethyl malonate, $(t\text{-}BuO)_2$ thermal reaction* : the same reaction conditions as above were used : caffeine (200 mg, 1.03 mmoles), dimethyl malonate (4 ml, 34.92 mmoles), $(t\text{-}BuO)_2$ (1 ml, 5.5 mmoles). 15 mg of 9 were isolated by crystallyzation from a fraction eluted by solvent A. Ethyl acetate eluted 33.6 mg of 8-(carbomethoxymethyl-carbonyloxy)-methylcaffeine 10 (Rf : 0.35 solvent I), m.p.

145.5-147° C ; νmax : 1658, 17.04, 1740, 1755 cm^{-1} ; λmax 279 nm, ε = 21500 ; m/z (C.I.) : 325 (M + 1) ; calc. for $C_{13}H_{16}N_4O_6$: C, 48.15 (48.08) ; H, 4.97 (4.98) ; N, 29.60 (29.67) ; O, 17.28 (17.35) ; N.M.R. : 3.39, 3.56, 4.02 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 5.26 (S-2H, C-8-CH_2-O-), 3.45 (S-2H, O=C-CH_2-C=O), 3.74 (S-3H, OCH_3).

- *Dimethyl malonate, $(t\text{-}BuO)_2$, photochemical reaction, procedure B-500 W* : caffeine (200 mg, 1.03 mmoles) dimethyl malonate (14 ml, 122 mmoles), $(t\text{-}BuO)_2$ (total volume 2 ml) were irradiated during 15 hrs. The products were eluted with solvents F, A and ethyl acetate ; 197 mg of 9 was isolated, 10 was detected by TLC as trace. The same reaction carried out on 1.2 g of 1 in 86 ml of dimethyl malonate and 26.5 ml of $(t\text{-}BuO)_2$ (irradiation 52 hrs) furnished after purification : 9 (666.5 mg), 10 (153 mg), 5 (25.2 mg) and 1 (483 mg).

- *Methyl bromoisobutyrate, $(PhCO_2)_2$, thermal reaction* : caffeine (200 mg, 1.03 mmoles), ester (10 ml, 76 mmoles), $(PhCO_2)_2$ (1.32 g, 5.45 mmoles) were kept at 80° C for 4 hrs. Remaining ester and benzoic acid were eluted with solvents F and A. Ethyl acetate eluted 151.6 mg of a fraction chich after PLC purification afforded 101 mg of 5-(2-dimethylcarbomethoxymethyl)1,3,7-trimethyl-5,7-dihydrouric acid 12 which did not crystallize ; λmax 244 nm (shoulder), ε = 6500 ; m/z (E.I.) : 310 (M^+) ; N.M.R. : 3.26, 3.33, 3.46 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 1.37, 1.25 (S-3H, C-5-C-$(CH_3)_2$), 3.69 (S-3H, OCH_3) ; 10 mg of caffeine were eluted with solvant C.

Reaction with t-butyl peroxybenzoate : caffeine (200 mg, 1.03 mmoles), t-butylperoxybenzoate 0.39 ml, 2.08 mmoles) in chlorobenzene (4 ml) were allowed to react at 105° C for 4 hrs. After chromatography (ethyl acetate) and further purification on PLC (solvent I), 42.8 mg of adduct 11 (Rf : 0.52, solvent I) ; m.p. 298-302° C ; νmax : 1520, 1665, 1709, 1739 cm^{-1} ; λmax 281, ε = 15500 (ε_{242} nm = 5400) ; m/z (E.I.) : 418 (M^+) ; N.M.R. : 2.99, 3.09, 3.28, 3.39, 3.47, 3.97 (S-3H respectively, six CH_3) ; further elution gave 29 mg of 8-methoxycaffeine 13 (Rf 0.42, solvent H) ; m.p. 179-182°C (lit. (13) 172.5-174° C) ; νmax : 1540, 1660, 1700 cm^{-1}, λmax 273 nm, ε = 13600 ; m/z (E.I.) : 224 (M^+) ; calc. for $C_9H_{12}N_4O_3$: C, 48.50 (48.58) ; H, 5.15 (5.17) ; N, 21.30 (21.23) ; O, 25.05 (25.02) ; N.M.R. : 3.41, 3.55, 3.72 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 4.16 (S-3H, C-8-OCH_3). Solvent C eluted next 100 mg of unreacted caffeine and 12 mg of unidentified by products.

Reaction with acetyl benzoyl peroxide : caffeine (200 mg, 1.03 mmoles), acetyl benzoyl peroxide (807.2 mg, 4.48 mmoles), in chlorobenzene (4 ml) were kept at 105° C for 1 hr. Ethyl acetate eluted 44.4 mg of 1,3,5,7-tetramethyl-5,7-dihydrouric acid 17 (Rf : 0.28, solvent H) ; m.p. 196-200° C (ethyl acetate). νmax : 1540, 1620, 1705, 1745 cm^{-1} ; λmax 242 (shoulder), ε= 5500 ; m/z (E.I.): 224 (M^+) ; N.M.R. : 3.22, 3.29, 3.52 (N-1-CH_3, N-3-CH_3, N-7-CH_3), 1.77 (S-3H, C-5 CH_3) ; for crystallographic data cf. ref. 22. 72 mg of caffeine and 14 mg of degradation products were eluted with solvent C.

Crystallographic study of 11, 8-[2,4,7,9-tetraoxo-3,6,8-trimethyl-1,3,6,8-tetraazaspiro (4-4) nonane-1γ]-caffeine :

$C_{16}H_{18}N_8O_6$, M = 418.38, orthorhombic, $p2_12_12_1$, Z = 8. Cell parameters : a = 13.502 (4), b = 15.444 (5), C = 18.450 (5) Å, V = 3866.05 $Å^3$, d_c = 1.44 gcm^{-3}, λ = 1.5418 Å (Cu Kα), μ = 8.62 cm^{-1}.

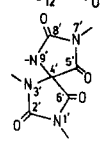
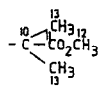
3705 intensity data were collected on a Philips PW1100 diffractometer using graphite monochromated Cu Kα radiation and the θ-2θ scan-technique up to θ = 65 °. The structure was solved by direct methods based on the random start multisolution using program SHELXS86 (28) and refined anisotropically byfull-matrix least-squares, minimizing the function $\Sigma w(Fo-|Fc|)^2$. The methyl hydrogen atoms were located on successive difference Fourier maps and introduced in calculations in idealized positions (d C-H = 1.0 Å) with an isotropic thermal factor greater than 20 % that of the carrying atom. Convergence was reached at R = 0.058 and Rw = 0.078 for the 2446 observed reflections having I > 2.5 σ(I), σ(I) derived from counting statistics (weighting scheme : $w = 1/\sigma^2(Fo) + 0.0056\ Fo^2$, Rw = $(\Sigma w(Fo-|Fc|)^2/\Sigma Fo^2)^{1/2}$, max Δρ on the final difference map : 0.22 $eÅ^{-3}$. Refinement performed with program SHELX76 (29) which also provided atomic scattering factors.
The two molecules of the asymmetric unit are two enantiomers with atom C-4' : R or S. It is interesting to note they do not adopt the same conformation along the C-8'-N-9' bond, the torsion angle N-7-C-8-N-9'-C-8' being respectively -53° in A, and -77° in B. For two enantiomers that angle should be of the same value with an opposite sign.

These molecules are staked in dimers, the purine bases being parallel with the aromatic six-membered rings superimposed and distant from 3.43 Å.

Correspondence between numbering of the atoms in figure 1 and those of the title name are as follows : N-9'=N-1 ; C-8'=C-2 ; N-7'=N-3 ; C-4'=C-5 ; N-3'=N-6 ; C-2'=C-7 ; N-1'=N-8 ; C-6'=C-9.

List of the atomic coordinates, bond distances and angles are available as Supplementary Material and have been deposited at the Cambridge Crystallographic Data Centre.

Table V : Characteristic ^{13}C NMR Spectra Data of C-8 and C-5 substituted caffeine derivatives (off-resonance decoupling)

compound C-8-R		C-2	C-4	C-5	C-6	C-8	N-1-CH_3	N-3-CH_3	N-7-CH_3	C-10	C-11	C-12	C-13 C-13'
H	1	150.38	148.53	107.36	155.19	141.37	29.55	27.71	33.41	-	-	-	-
$-CCl_3$	2	151.27	147.02	110.73	155.53	145.00	29.82	28.11	34.81	87.46	-	-	-
$-CH_2-C(=O)-OCH_3$	5	151,45	147.59	108.03	155.15	146.35	29.59	27.76	32.10	33.21 (t)	167.75	52.73	-
$-CH_2-CH_2-O-C(=O)-OCH_3$	6	151.78	150.57	107.76	155.47	148.13	29.83	28.01	31.98	26.54 (t)	170.79	61.85 (t)	20.97 (q)
$-CH_3$	7	151.20	150.46	106.92	154.68	147.45	29.32	27.51	31.57	12.82	-	-	-
$-CH(CH_3)-C(=O)-OCH_3$	8	151.00	147.75	107.46	155.30	147.62	29.71	27.79	31.84	37.91 (d)	170.79	52.77	14.97 (q)
$-CH(C(=O)-OCH_3)_2$	9	151.42	147.36	108.79	155.27	144.25	29.18	27.82	32.17	51.72 (d)	(C-11') 165.16	(C-12') 53.53	
$-CH_2-O-C(=O)-CH_2-C(=O)-OCH_3$	10	151.44	147.38	108.80	155.27	144.27	29.69	27.83	32.68	53.55 (t)	(C-11') 165.17	53.55	51.75 (t)
	11	*151.25 152.24	146.80 80.31	107.52 164.19	155.21 164.67	137.49 154.96	29.64 26.09	27.97 25.88	33.00 26.21				
$-OCH_3$	13	151.82	146.38	103.71	156.32	154.97	29.87	27.85	29.86	57.86	-	-	-
C-5-R													
$-CCl_3$	4	160.29	150.34	76.08	170.54	164.61	30.03	29.58	32.15	98.29	-	-	-
	12	164.39	150.52	75.95	172.35	164.91	30.17	29.01	31.61	53.50	174.87	53.99	22.16 21.34
$-CH_3$	17	164.56	150.62	65.37	177.07	167.46	29.10	27.26	31.38	25.51	-	-	-

* Chemical schifts of the caffeine moiety of the adduct

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