Free Radical Alkylation of 1,3-Dimethyluracils and Caffeine with Benzoyl Peroxide

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Reaction of 1,3-dimethyluracil and 1,3,6-trimethyluracil with benzoyl peroxide in cyclohexane, ethyl acetate, and acetonitrile gave the corresponding 5-alkyl-1,3-dimethyluracils, although a steric effect of the methyl group at 6-position complicated the reaction. On the other hand, a similar treatment of 1,3-dimethylthymine led to alkylation of the methyl group at 5-position. The reaction of caffeine gave 8-alkylcaffeines and alkyl acetates were used as favorable solvents with respect to synthesis of 8-alkylcaffeines.

In recent years increasing interest has been shown in the role of free radical reaction on organic synthesis[1] and in biological system.[2] Reaction of purine and pyrimidine bases with free radicals has also been of importance in connection with the damage of nucleic acids. Although the reaction of purine bases with alkyl radicals, e.g., the UV-radiation[3-6] in alcohols,[3] ethers,[4] and amines,[5] has been extensively investigated,[3-7] the reaction of pyrimidine bases is not sufficiently revealed. While the reaction of thymine and uracil with hydroxyl radical led to the addition of the radical at the 5-position of pyrimidine ring,[8] the γ-radiation of thymine in ethanol[9] and UV-radiation of uracil in 2-propanol,[3f-g] and tetrahydrofuran[10] gave the corresponding 6-alkyl-5,6-dihydrouracils but UV-induced reaction of thymine in 2-propanol was reported to give 5-(2-hydroxy-2-methylpropyl)uracil.[3f-g] On the other hand, we reported the free radical alkylation of uracil and 1,3-dimethyluracil (**1a**) with benzoyl peroxide.[11] The present investigation was undertaken to compare the reaction of 1,3-dimethylthymine (**1b**) and 1,3,6-trimethyluracil (**2a**) with that of **1a**, in order to elucidate the effect of methyl group at 5- and 6-positions of pyrimidine ring on the free radical reaction. We further compared the reaction of caffeine (**5a**) as a purine base with that of the uracils.

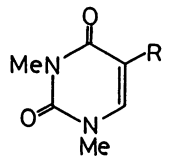
Results and Discussion

When **1a** was treated with benzoyl peroxide in cyclohexane, ethyl acetate, and acetonitrile at ca. 80 °C under nitrogen atmosphere, it reacted with alkyl radicals formed by abstraction of hydrogen atom from the solvents to be converted into the corresponding 5-alkyl-1,3-dimethyluracils (**1c**), (**1d**), (**1e**), and (**1f**).[11] The compound **2a** also underwent the similar reaction, although a steric effect of the methyl group at 6-position somewhat complicated the reaction, i.e., the treatment of **2a** gave (**2c**), (**2d**), and (**2f**) together with small amounts of (**2j**), (**3**), and (**4**). On the other hand, a similar treatment of **1b** gave (**1g**), (**1h**), and (**1i**) as main products, suggesting that the reaction mainly led to an alkylation

Table 1. Alkylation of 1,3-Dimethyluracils and Caffeine with Benzoyl Peroxide[a]

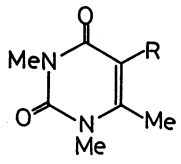
Substrate	Solvent[a]	Conversion	Products
		%	Isolated yield, %[b]
1a	Cyclohexane	52	**1c**/96
1a	Ethyl acetate	72	**1d**/55; **1e**/36
1a	Acetonitrile	21	**1f**/91
2a	Cyclohexane	20	**2c**/50; **3**/20
2a	Ethyl acetate	38	**2d**/57; **2j**/5; **4**/8
2a	Acetonitrile	14	**2f**/79
1b	Cyclohexane	30	**1g**/30; **1h**/4
1b	Ethyl acetate	18	**1i**/67
1b	Acetonitrile	8	**1h**/63
5a	Cyclohexane	49	**5c**/97
5a	Ethyl acetate	42	**5d**/64; **5e**/26
5a	Acetonitrile	20	**5f**/75
5a	1,2-Dimethoxyethane	16	**5k**/91
5a	1,2-Diacetoxyethane	74	**5l**/42; **5m**/48
5a	Butyl acetate	53	**5n**/19; **5o**/32; **5p**/11; **5q**/24
5a	*t*-Butyl acetate	28	**5r**/79

a) Reaction conditions are shown in Experimental section except the amount of solvent used; cyclohexane (125 ml) and the other solvents (50 ml). b) Yield based on the substrate consumed.



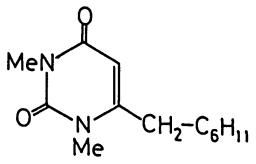
1

1a : R = H
1b : R = Me
1c : R = C_6H_{11}
1d : R = CH_2COOEt
1e : R = CHMeOAc
1f : R = CH_2CN
1g : R = CH_2-C_6H_{11}
1h : R = CH_2OCOPh
1i : R = $CH_2CHMeOAc$



2

2a : R = H
2c : R = C_6H_{11}
2d : R = CH_2COOEt
2f : R = CH_2CN
2j : R = Ph



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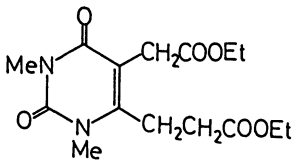
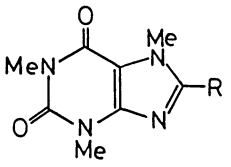


4

C_6H_{11} = cyclohexyl

Fig. 1.



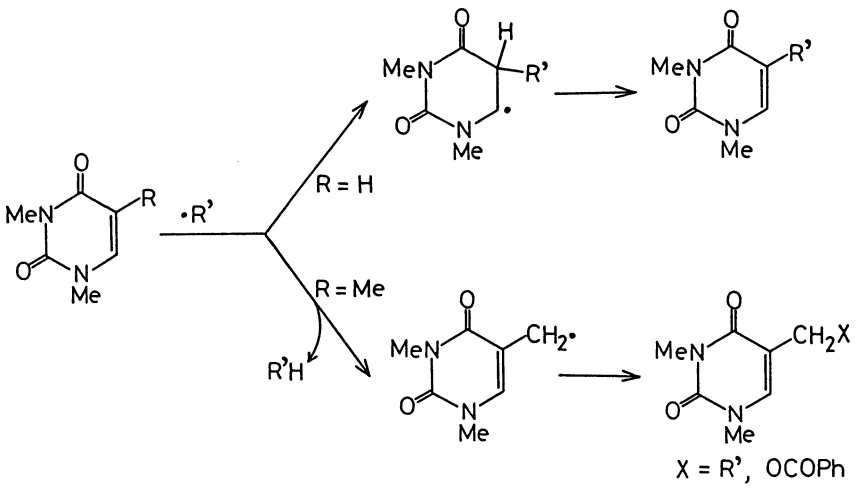
5

5a : R = H
5c : R = C_6H_{11}
5d : R = CH_2COOEt
5e : R = CHMeOAc
5f : R = CH_2CN
5k : R = $CH(OMe)CH_2OMe$
5l : R = $CH_2COOCH_2CH_2OAc$
5m : R = $CH(OAc)CH_2OAc$
5n : R = CH_2COOBu^n
5o : R = $CHPr^nOAc$
5p : R = $CHEtCH_2OAc$
5q : R = $CHMeCH_2CH_2OAc$
5r : R = CH_2COOBu^t

Fig. 2.

of the methyl group at 5-position. The reaction of **5a** gave 8-alkylcaffeines (**5c**), (**5d**), (**5e**), and (**5f**) in good yields. These results are summarized in Table 1.

Table 1 indicates that the treatment of **1a**, **2a**, and **5a** with benzoyl peroxide in ethyl acetate efficiently gave the alkylated products. Therefore, reaction of **5a** with benzoyl peroxide in some alkyl acetates was compared with that in ethers, because the abstraction of hydrogen atom from ethers by the radicals derived from benzoyl peroxide is well-known.[12] While treatment of **5a** with benzoyl peroxide in 1,2-dimethoxyethane only gave a small amount of 8-(1,2-dimethoxyethyl)caffeine (**5k**), a similar treatment in 1,2-diacetoxyethane achieved its efficient conversion into (**5l**) and (**5m**). When **5a** was reacted with benzoyl peroxide in butyl acetate, unexpected products (**5p**) and (**5q**) were obtained together with expected products (**5n**) and (**5o**). On the other hand, **5a** was almost unreactive to benzoyl peroxide in dibutyl ether. Reaction of **5a** in *t*-butyl acetate gave (**5r**) in good yield based on **5a** consumed. We further



Scheme 1.

studied the reaction of **5a** with benzoyl peroxide in some ketones and alkanes such as 2-pentanone, 2-hexanone, octane, and 2,2,4-trimethylpentane, but almost no reaction occurred on those treatment. These observations suggest that alkyl acetates were favorable solvents for the present free radical alkylation with benzoyl peroxide.

The structures of products were determined on the basis of ^{1}H NMR, ^{13}C NMR, and mass spectral data and elemental analyses except for **1e**, **1g**, **1i**, and the known compounds. The compounds **1e** and **1g** were confirmed by ^{1}H NMR, ^{13}C NMR, mass, and high-resolution mass spectral data. The structural speculation of **1i** was estimated by ^{1}H NMR, ^{13}C NMR, ^{1}H–^{13}C COSY NMR, and mass spectral data, although the molecular ion peak was weak.

From the results shown in Table 1, it seems most reasonable to conclude that the alkyl radicals preferentially made an attack on the 5-position of the pyrimidine ring. In spite of a steric effect of methyl group at the 6-position of **2a**, the reaction of **2a** was similar to that of **1a**. However the methyl group at 5-position of **1b** obviously hindered the free radical alkylation at the 5-position of pyrimidine ring and therefore the reaction of **1b** resulted in the alkylation of the 5-methyl group. In view of the above considerations, the reaction of 1,3-dimethyluracils with alkyl radicals (carbon centered radicals) is explained as shown in Scheme 1.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were obtained with a JEOL GSX400 (400 MHz) or a JEOL PMX60A (60 MHz) spectrometers using tetramethylsilane as an internal standard. ^{13}C NMR spectra ($CDCl_3$) were obtained with a JEOL GSX400 (100 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL JMS-D300 spectrometer. The elemental analyses were performed by the Analytical Center of Kyoto University.

The preparation of **1a** and **2a** were carried out according to the procedure described before for that of **1b**.[13] Benzoyl peroxide (with 25% water) was obtained commercially and was used without further purification for the reaction.

General Procedure for the Alkylation of 1,3-Dimethyluracils (1a, 1b, and 2a) and Caffeine (5a) with Benzoyl Peroxide. A solution of the substrate **1a**, **1b**, **2a**, and **5a** (1 mmol) and benzoyl peroxide (1 mmol) in solvent such as cyclohexane, ethyl acetate, 1,2-dimethoxyethane, 1,2-diacetoxyethane, butyl acetate and *t*-butyl acetate was heated at 80 °C (or at reflux temperature when the solvents were acetonitrile and ethyl acetate) under nitrogen (or argon) atmosphere. The reaction mixture was evaporated to give a residue, which was then chromatographed on silica gel (Fuji gel packed column NQ-2, 24 mmϕ×360 mm), eluted with hexane and ethyl acetate, with low-pressure pump (Chemco Low-prep pump 81-M-2R) and UV-monitor (Shimadzu UV-detector SPD-6A, detected at 250 nm), to give the products and recovered substrate. The results are shown in Table 1. The spectral data of the products are given below.

5-Cyclohexyl-1,3-dimethyluracil (1c): Mp 104.5—105.5 °C; ^{1}H NMR δ=6.87 (s, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.6 (m, 1H), 1.9—1.7 (m, 5H), 1.4—1.3 (m, 2H), 1.3—1.1 (m, 3H); ^{13}C NMR δ=163.39, 151.62, 137.75, 119.19, 36.85, 35.60, 32.47, 27.92, 26.61, 26.20; MS *m/z* (rel intensity) 222 (M^+, 100). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60%. Found: C, 64.76; H, 8.23; N, 12.60%.

5-Ethoxycarbonylmethyl-1,3-dimethyluracil (1d): Mp 79—80 °C (lit,[14] mp 78—80 °C); ^{1}H NMR δ=7.29 (s, 1H), 4.17 (q, 2H, *J*=7 Hz), 3.42 (s, 3H), 3.34 (s, 5H), 1.27 (t, 3H, *J*=7 Hz); ^{13}C NMR δ=170.90, 163.26, 151.69, 141.70, 106.87, 61.15, 36.96, 32.36, 28.00, 14.15; MS *m/z* (rel intensity) 226 (M^+, 38), 153 (100).

5-(1-Acetoxyethyl)-1,3-dimethyluracil (1e): Oil; ^{1}H NMR δ=7.26 (s, 1H), 5.81 (q, 1H, *J*=7 Hz), 3.43 (s, 3H), 3.34 (s, 3H), 2.08 (s, 3H), 1.50 (d, 3H, *J*=7 Hz); ^{13}C NMR δ=169.93, 161.95, 151.50, 140.22, 113.41, 66.60, 37.16, 27.86, 21.50, 19.79; MS *m/z* (rel intensity) 226 (M^+, 4), 183 (100). Found: *m/z* 226.0953. Calcd for $C_{10}H_{14}N_2O_4$, M, 226.0953.

5-Cyanomethyl-1,3-dimethyluracil (1f): Mp 120—121 °C (lit,[14] mp 116—118 °C); ^{1}H NMR δ=7.39 (s, 1H), 3.49 (s, 5H), 3.37 (s, 3H); ^{13}C NMR δ=162.10, 151.33, 140.84, 116.65, 103.43, 37.25, 28.19, 16.15; MS *m/z* (rel intensity) 179 (M^+, 100). Anal. Calcd for $C_8H_9N_3O_2$: C, 53.62; N, 5.06; N, 23.45%. Found: C, 53.85; H, 4.95; N, 23.24%.

5-Cyclohexylmethyl-1,3-dimethyluracil (1g): Oil; ^{1}H NMR δ=6.90 (s, 1H), 3.38 (s, 3H), 3.35 (s, 3H), 2.18 (d, 2H, *J*=7 Hz), 1.8—1.5 (m, 6H), 1.3—1.1 (m, 3H), 0.9—0.8 (m, 2H); ^{13}C NMR and ^{1}H–^{13}C COSY NMR δ=163.82, 151.88, 139.61 (C-6), 112.31 (C-5), 36.76 (CH_3), 36.50 (C_6H_{11}), 35.31 (CH_2), 33.16 (2×C_6H_{11}), 27.96 (CH_3), 26.48 (C_6H_{11}), 26.13 (2×C_6H_{11}); MS *m/z* (rel intensity) 236 (M^+, 28), 154 (100). Found: *m/z* 236.1524. Calcd for $C_{13}H_{20}N_2O_2$: M, 236.1524.

5-Benzoyloxymethyl-1,3-dimethyluracil (1h): Mp 145—146 °C; ^{1}H NMR δ=8.03 (dd, 2H, *J*=8 and 1 Hz), 7.54 (tt, 1H, *J*=8 and 1 Hz), 7.52 (s, 1H), 7.42 (t, 2H, *J*=8 Hz), 5.15 (s, 2H), 3.42 (s, 3H), 3.37 (s, 3H); ^{13}C NMR δ=166.82, 162.80, 151.60, 144.22, 133.21, 129.93, 129.72, 128.41, 108.24, 59.71, 37.17, 28.02; MS *m/z* (rel intensity) 274 (M^+, 2), 169 (100). Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21%. Found: C, 61.04; H, 4.99; N, 10.02%.

5-(2-Acetoxypropyl)-1,3-dimethyluracil (1i): Oil ^{1}H NMR δ=7.02 (s, 1H), 5.06 (tdd, 1H, *J*=6, 5, and 8 Hz), 3.39 (s, 3H), 3.35 (s, 3H), 2.66 (dd, 1H, *J*=14 and 5 Hz), 2.48 (dd, 1H, *J*=14 and 8 Hz), 2.01 (s, 3H), 1.25 (d, 3H, *J*=6 Hz); ^{13}C NMR and ^{1}H–^{13}C COSY NMR δ=170.47, 163.54, 151.74, 140.66 (C-6), 109.54 (C-5), 69.65 (CH), 36.87 (N-CH_3), 33.44 (CH_2), 28.05 (N-CH_3), 21.30 (CO-CH_3), 19.81 (CH_3); MS *m/z* (rel intensity) 240 (M^+, 1), 180 (100).

5-Cyclohexyl-1,3,6-trimethyluracil (2c): Mp 179—181 °C; ^{1}H NMR δ=3.44 (s, 3H), 3.33 (s, 3H), 2.29 (s, 3H), 2.7—2.6 (m, 1H), 2.15—2.0 (m, 2H), 1.85—1.6 (m, 3H), 1.55—1.45 (m, 2H), 1.35—1.2 (m, 3H); ^{13}C NMR δ=162.33, 152.14, 146.49, 115.84, 32.22, 29.93, 28.06, 27.24, 25.87, 16.52; MS *m/z* (rel intensity) 236 (M^+, 92), 167 (100). Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86%. Found: C, 66.00; H, 8.65; N, 11.61%.

5-Ethoxycarbonylmethyl-1,3,6-trimethyluracil (2d): Mp 144—146 °C; ^{1}H NMR δ=4.16 (q, 2H, *J*=7 Hz), 3.53 (s, 2H), 3.46 (s, 3H), 3.36 (s, 3H), 2.25 (s, 3H), 1.27 (t, 3H, *J*=7 Hz); ^{13}C NMR δ=171.06, 162.62, 151.99, 149.50, 105.36, 61.09, 32.26, 31.68, 28.43, 17.05, 14.21; MS *m/z* (rel intensity) 240

(M^+, 26), 167 (100). Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66%. Found: C, 54.88; H, 6.78; N, 11.71%.

5-Cyanomethyl-1,3,6-trimethyluracil (2f): Mp 104—105.5 °C; ^{1}H NMR δ=3.62 (s, 2H), 3.48 (s, 3H), 3.38 (s, 3H), 2.39 (s, 3H); ^{13}C NMR δ=161.55, 151.57, 150.46, 117.19, 101.87, 32.43, 28.69, 17.20, 14.67; MS *m/z* (rel intensity) 193 (M^+, 100). Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75%. Found: C, 55.97; H, 5.71; N, 21.74%.

1,3,6-Trimethyl-5-phenyluracil (2j): Mp 85—87 °C (lit,[15] 88 °C); ^{1}H NMR δ=7, 45—7.15 (m, 5H), 3.50 (s, 3H), 3.40 (s, 3H), 2.15 (s, 3H); ^{13}C NMR δ=162.28, 152.19, 148.33, 134.14, 130.79, 128.47, 127.77, 114.27, 32.32, 28.42, 18.12.

6-Cyclohexylmethyl-1,3-dimethyluracil (3): Mp 96—97 °C; ^{1}H NMR δ=5.56 (s, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 2.34 (d, 2H, *J*=7 Hz), 1.8—1.45 (m, 6H), 1.3—0.9 (m, 5H); ^{13}C NMR δ=162.47, 153.43, 152.92, 101.66, 40.66, 35.98, 33.12, 31.76, 27.95, 26.08, 25.99; MS *m/z* (rel intensity) 236 (M^+, 1), 154 (100). Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86%. Found: C, 65.45; H, 8.44; N, 11.68%.

6-[2-(Ethoxycarbonyl)ethyl]-5-ethoxycarbonylmethyl-1,3-dimethyluracil (4): Mp 90—92 °C; ^{1}H NMR δ=4.18 (q, 2H, *J*=7 Hz), 4.16 (q, 2H, *J*=7 Hz), 3.52 (s, 2H), 3.48 (s, 3H), 3.36 (s, 3H), 2.93 (t, 2H, *J*=8 Hz), 2.57 (t, 2H, *J*=8 Hz), 1.28 (t, 6H, *J*=7 Hz); ^{13}C NMR δ=171.14 (2C), 162.64, 152.13, 150.81, 106.25, 61.33, 61.23, 32.16, 31.82, 31.77, 28.48, 25.12, 14.17 (2C); MS *m/z* (rel intensity) 326 (M^+, 34), 280 (99), 253 (100). Calcd for $C_{15}H_{22}N_2O_6$: C, 55.20; H, 6.80; N, 8.58%. Found: C, 55.20; H, 6.86; N, 8.54%.

8-Cyclohexylcaffeine (5c): Mp 205—207 °C (lit,[6d] 205—207 °C); ^{1}H NMR δ=3.94 (s, 3H), 3.56 (s, 3H), 3.37 (s, 3H), 2.7 (m, 1H), 1.95—1.8 (m, 4H), 1.8—1.6 (m, 3H), 1.45—1.3 (m, 3H); ^{13}C NMR δ=157.98, 155.43, 151.75, 148.10, 106.98, 35.80, 31.38, 30.96, 29.69, 27.78, 26.01, 25.60; MS *m/z* (rel intensity) 276 (M^+, 92), 221 (100).

8-(Ethoxycarbonylmethyl)caffeine (5d): Mp 143—144 °C; ^{1}H NMR δ=4.23 (q, 2H, *J*=7 Hz), 3.95 (s, 3H), 3.87 (s, 2H), 3.56 (s, 3H), 3.41 (s, 3H), 1.29 (t, 3H, *J*=7 Hz); ^{13}C NMR δ=167.36, 155.40, 151.66, 147.79, 146.58, 108.24, 62.06, 33.64, 32.24, 29.75, 27.92, 14.14; MS *m/z* (rel intensity) 280 (M^+, 88), 207 (100). Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99%. Found: C, 51.25; H, 5.57; N, 19.76%.

8-(1-Acetoxyethyl)caffeine (5e): Mp 146.5—148 °C; ^{1}H NMR δ=5.98 (q, 1H, *J*=7 Hz), 4.03 (s, 3H), 3.57 (s, 3H), 3.38 (s, 3H), 2.12 (s, 3H), 1.70 (d, 3H, *J*=7 Hz); ^{13}C NMR δ=170.12, 155.54, 151.64, 151.02, 147.66, 107.93, 63.40, 32.02, 29.80, 27.94, 20.83, 18.68; MS *m/z* (rel intensity) 280 (M^+, 32), 237 (100). Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99%. Found: C, 51.56; H, 5.78; N, 20.19%.

8-(Cyanomethyl)caffeine (5f): Mp 229—232 °C (lit,[16] 232—234 °C); ^{1}H NMR δ=4.05 (s, 3H), 3.95 (s, 2H), 3.56 (s, 3H), 3.40 (s, 3H); ^{13}C NMR δ=155.25, 151.47, 147.60, 141.68, 113.13, 108.73, 32.39, 29.82, 28.04, 17.19; MS *m/z* (rel intensity) 233 (M^+, 100).

8-(1,2-Dimethoxyethyl)caffeine (5k): Mp 131—132 °C; ^{1}H NMR δ=4.71 (t, 1H, *J*=5 Hz), 4.08 (s, 3H), 3.80 (d, 2H, *J*=5 Hz), 3.57 (s, 3H), 3.40 (s, 9H); ^{13}C NMR δ=155.45, 151.65, 150.26, 147.68, 108.53, 76.49, 73.47, 59.44, 57.61, 32.58, 29.80, 27.92; MS *m/z* (rel intensity) 282 (M^+, 16), 237 (100). Calcd for $C_{12}H_{18}N_4O_4$: C, 51.05; H, 6.43; N, 19.85%. Found: C, 50.97; H, 6.46; N, 19.78%.

8-[(2-Acetoxyethoxy)carbonylmethyl]caffeine (5l): Mp 146—147.5 °C; ^{1}H NMR δ=4.36 (m, 4H), 3.96 (s, 3H), 3.91 (s, 2H), 3.55 (s, 3H), 3.40 (s, 3H), 2.07 (s, 3H); ^{13}C NMR δ=170.63, 167.29, 155.34, 151.62, 147.75, 146.16, 108.25, 63.66, 61.71, 33.35, 32.21, 29.72, 27.92, 20.75; MS *m/z* (rel intensity) 338 (M^+, 52), 87 (100). Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56%. Found: C, 49.60; H, 5.30; N, 16.31%.

8-(1,2-Diacetoxyethyl)caffeine (5m): Mp 125.5—126.5 °C; ^{1}H NMR δ=6.10 (t, 1H, *J*=5 Hz), 4.58 (m, 2H), 4.06 (s, 3H), 3.56 (s, 3H), 3.40 (s, 3H), 2.15 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ=170.44, 170.02, 155.50, 151.58, 147.74, 147.32, 108.17, 64.23, 53.61, 32.16, 29.83, 27.98, 20.68, 20.65; MS *m/z* (rel intensity) 338 (M^+, 28), 236 (100). Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56%. Found: C, 49.72; H, 5.30; N, 16.42%.

8-(Butoxycarbonylmethyl)caffeine (5n): Mp 119.5—120.5 °C; ^{1}H NMR δ=4.17 (t, 2H, *J*=7 Hz), 3.95 (s, 3H), 3.87 (s, 2H), 3.56 (s, 3H), 3.40 (s, 3H), 1.64 (tt, 2H, *J*=7 and 7 Hz), 1.37 (tq, 2H, *J*=7 and 7 Hz), 0.93 (t, 3H, *J*=7 Hz); ^{13}C NMR δ=167.47, 155.37, 151.64, 147.76, 146.62, 108.19, 65.93, 33.60, 32.23, 30.50, 29.73, 27.94, 19.03, 13.63; MS *m/z* (rel intensity) 308 (M^+, 100), 207 (85). Calcd for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17%. Found: C, 54.35; H, 6.56; N, 17.95%.

8-(1-Acetoxybutyl)caffeine (5o): Mp 100—100.5 °C; ^{1}H NMR δ=5.80 (t, 1H, *J*=7 Hz), 4.06 (s, 3H), 3.57 (s, 3H), 3.39 (s, 3H), 2.11 (s, 3H), 2.11 (m, 1H), 1.99 (m, 1H), 1.43 (m, 1H), 1.30 (m, 1H), 0.97 (t, 3H, *J*=7 Hz); ^{13}C NMR δ=170.40, 155.54, 151.66, 150.89, 147.85, 107.70, 66.66, 35.10, 32.05, 29.83, 27.92, 20.77, 18.84, 13.65; MS *m/z* (rel intensity) 308 (M^+, 36), 265 (100). Calcd for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17%. Found: C, 54.60; H, 6.51; N, 18.34%.

8-[1-(Acetoxymethyl)propyl]caffeine (5p): Mp 120—121.5 °C; ^{1}H NMR δ=4.39 (dd, 1H, *J*=10 and 6 Hz), 4.28 (t, 1H, *J*=10 Hz), 4.00 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H), 3.14 (m, 1H), 2.01 (s, 3H), 1.85 (m, 2H), 0.89 (t, 3H, *J*=7 Hz); ^{13}C NMR δ=170.65, 155.43, 154.35, 151.73, 148.26, 107.26, 66.48, 38.17, 31.57, 29.76, 27.85, 24.01, 20.83, 11.62; MS *m/z* (rel intensity) 308 (M^+, 32), 248 (100). Calcd for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17%. Found: C, 54.56; H, 6.62; N, 17.84%.

8-(3-Acetoxy-1-methylpropyl)caffeine (5q): Mp 65—66 °C; ^{1}H NMR δ=4.15 (dt, 1H, *J*=11 and 6 Hz), 3.96 (m, 1H), 3.94 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 3.10 (m, 1H), 2.24 (m, 1H), 2.03 (s, 3H), 2.01 (m, 1H), 1.35 (d, 3H, *J*=7 Hz); ^{13}C NMR δ=170.85, 157.09, 155.40, 151.75, 148.14, 107.11, 62.23, 34.14, 31.41, 29.75, 28.15, 27.85, 20.90, 19.44; MS *m/z* (rel intensity) 308 (M^+, 37), 235 (100). Calcd for $C_{14}H_{20}N_4O_4$: 54.53; H, 6.54; N, 18.17%. Found: C, 54.38; H, 6.61; N, 18.33%.

8-(*t*-Butoxycarbonylmethyl)caffeine (5r): Mp 194.5—195.5 °C; ^{1}H NMR δ=3.94 (s, 3H), 3.80 (s, 2H), 3.56 (s, 3H), 3.39 (s, 3H), 1.48 (s, 9H); ^{13}C NMR δ=166.52, 155.32, 151.62, 147.74, 147.18, 108.08, 82.92, 34.84, 32.17, 29.70, 27.99, 27.88; MS *m/z* (rel intensity) 308 (M^+, 65), 208 (100). Calcd for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; H, 18.17%. Found: C, 54.39; H, 6.40; N, 18.39%.

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