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PHOTOINDUCED REACTIONS—XXVI

PHOTOSENSITIZED OXYGENATION OF 8-ALKOXYCAFFEINES AND RELATED COMPOUNDS[1]

T. MATSUURA and I. SAITO

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

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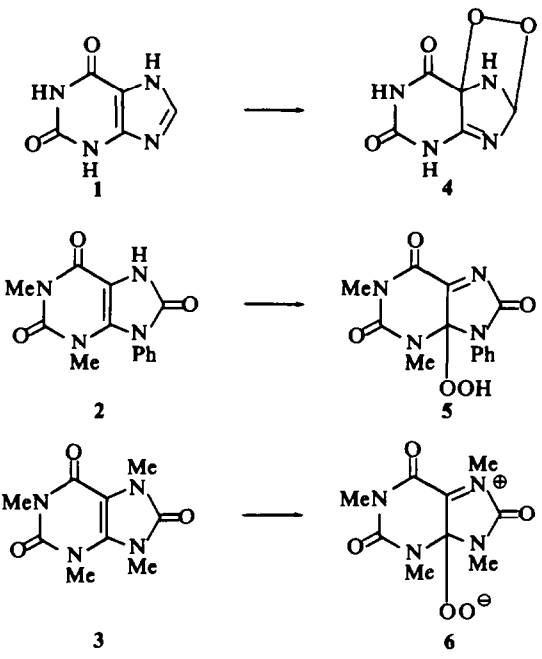
Abstract—Photosensitized oxygenation of 8-methoxycaffeine (**7a**) in methanol containing rose bengal yielded carbon dioxide and 1-methyl-2,2-dimethoxy-4-methylamino-3-imidazolin-5-one (**8a**) in good yield. Similarly, **7a** in methanol gave carbon dioxide, ethyl N-methylcarbamate, and 1-methyl-2-ethoxy-2-methoxy-4-methylamino-3-imidazolin-5-one (**8c**). The imidazolinone **8c** was also obtained by the photosensitized oxygenation of 8-ethoxycaffeine (**7b**) in methanol. Photooxygenation of other N-alkylated 8-alkoxyxanthines, **7c** and **7d**, which gave the corresponding imidazolinones **8**, was carried out in connection with the mechanism of these reactions.

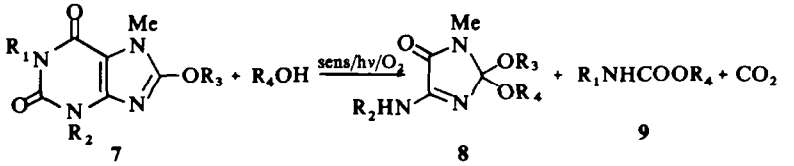
PHOTOSENSITIZED oxygenation of purine derivatives is of interest because of its significance in connection with the photodynamic degradation of guanine residues in deoxyribonucleic acids.[2] In order to contribute to the elucidation of this degradation, we have carried out the photosensitized oxygenation of various types of purine derivatives, including xanthine (**1**),[3] 1,3-dimethyl-9-phenyluric acid (**2**),[4,5] and 1,3,7,9-tetramethyluric acid (**3**).[1,4] To account for the products obtained from these reactions we proposed that the reaction proceeds *via* a peroxide intermediate which may be formed by the attack of singlet oxygen on the substrate. The nature of the peroxide depends upon the structural feature of the imidazole moiety of the purines. Thus, **1**, **2**, and **3** give a cyclic peroxide **4**, a hydroperoxide **5**, and a zwitterionic peroxide **6**, respectively. In this paper we report results on the photosensitized oxygenation of 8-alkoxycaffeines and related compounds, which provided further information concerning with structure of the peroxide intermediate and the manner of its decomposition.

Although caffeine easily suffers photosensitized oxygenation in alkaline media,[6] it does not undergo degradation in a neutral organic solvent such as methanol and chloroform. However, 8-alkoxycaffeines are very sensitive to photosensitized oxygenation even in methanol. This is consistent with the electrophillic character[7] of singlet oxygen which is regarded as the reactive species in dye-sensitized photooxygenation.[8] Substitution of an electron donating alkoxy group to the 8-position of caffeine may cause an increase of electron densities in the system. A similar effect has been observed in the photooxygenation of 1,4-dimethoxy-9,10-diphenylanthracene which does not give a usual 9,10-endo-peroxide but only a 1,4-endo-peroxide.[9]

When a solution of 8-methoxycaffeine (**7a**) in methanol-chloroform (20:1) was irradiated in the presence of rose bengal under bubbling oxygen, 0·8 mole of oxygen was consumed and liberation of 0·6 mole of carbon dioxide was observed. From the reaction mixture a crystalline product, $C_7H_{13}N_3O_3$, was obtained in 78% yield. Its UV spectrum shows a maximum at 218 mμ (ε 28,000) with a shoulder at 252 mμ



(ε 6200), and the IR spectrum shows bands at 3350 (NH), 1750, and 1665 cm^{-1}. The NMR spectrum (Table 1) suggests the presence of —NH—Me, $\rangle$N—Me, and two equivalent —OMe groups. These spectral data are compatible with structure **8a** for the product, but clarification depended on (i) whether one of the 2-OMe groups of **8a** comes from the solvent methanol, (ii) which N-Me group of **7a** is expelled in the course of the reaction, and (iii) which N-Me group of **7a** is converted to the 4-methylamino group in **8a**. The structural assignment for **8a** was confirmed by results obtained in the photosensitized oxygenation of various N-alkylated 8-alkoxyxanthines. The results are summarized in Table 1 which includes also the NMR data of the products.



7a: $R_1 = R_2 = R_3 = Me$
7b: $R_1 = R_2 = Me$; $R_3 = Et$
7c: $R_1 = Et$; $R_2 = R_3 = Me$
7d: $R_1 = R_2 = Et$; $R_3 = Me$

8a: $R_2 = R_3 = R_4 = Me$
8b: $R_2 = R_3 = Me$; $R_4 = CD_3$
8c: $R_2 = Me$; $R_3 = Et$ (or Me); $R_4 = Me$ (or Et)
8d: $R_2 = Me$; $R_3 = Et$, $R_4 = CD_3$
8e: $R_2 = Me$; $R_3 = R_4 = Et$
8f: $R_2 = Et$; $R_3 = R_4 = Me$
8g: $R_2 = Et$, $R_3 = Me$, $R_4 = CD_3$

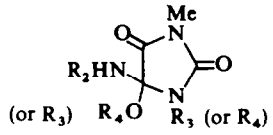
Photosensitized oxygenation of **7a** in methanol-d_4 and in ethanol yielded the corresponding products **8b** (28%) and **8c** (33%), respectively. The NMR spectra of **8b** and **8c** are virtually the same as that of **8a** except that one of the two equivalent OMe groups (τ 6·80) of **8a** is replaced by a OMe:d_3 group in **8b** and by an OEt group in **8c**. It is, therefore, obvious that the solvent alcohol has been incorporated into one of the two alkoxy groups of **8a**, **8b**, and **8c**. From the above results and the fact that the two OMe groups of **8a** is magnetically equivalent, it could be suggested that the alkoxy group incorporated from the solvent alcohol is introduced at the same position as the 8-OMe group being originally present in **7a**, provided that a drastic skeletal change of the imidazole moiety of **7a** does not occur in the course of the reaction. This was further supported by the following experiments.

Photooxygenation of 8-ethoxycaffeine (**7b**) in methanol yielded a product (71%) which was identical with **8c**. Under similar conditions **7b** afforded **8d** (24%) in methanol-d_4 and **8e** (25%) in ethanol. The NMR spectra of these two products are analogous to those of the imidazolinones **8a**, **8b**, and **8c** (Table 1). Furthermore, in the NMR spectrum of **8e** signals attributed to the OEt groups appear magnetically equivalent to the two OMe group of **8a**.

Similarly, 1-ethyl-3,7-dimethyl-8-methoxyxanthine (**7c**) gave **8a**, identical with the product obtained from **7a** in methanol, in 28% yield. The result clearly indicates that the 1-N-Et group was expelled in the course of the formation of **8a** from **7c**. In the case of the photosensitized oxygenation of **7a** in ethanol, the fate of the 1-N-Me group was linked to the formation of ethyl N-methylcarbamate (**9**; R_1 = Me, R_4 = Et) which was obtained in 68% yield.

In order to gain information on the origin of the N-methylamino group (—NH—R_2 in formula **8**) of the imidazolinone **8a**, **8b**, **8c**, **8d**, and **8e**, the photooxygenation of 1,3-diethyl-7-methyl-8-methoxyxanthine (**7d**) was carried out. Thus **7d** gave **8f** (57%) in methanol and **8g** (83%) in methanol-d_4. The UV, IR, and NMR spectra of both products are analogous to those of the imidazolinones obtained above, but the NMR spectra of **8f** and **8g** exhibit signals attributed to an —NH—Et group (Table 1). The results established that the 4-alkylamino group (—NH—R_2) of the imidazolinones **8a** –**8g** is derived from the 3-N-alkyl group of the starting xanthine derivatives **7a**–**7d**.

Although the above results strongly support structure **8** for the imidazolinones, if we assume that drastic skeletal changes did occur in the course of the photooxygenation, other possible structures **10**, **11**, and **12** for the photooxidation product should also be taken into consideration. Compounds, **10**, **11**, and **12** are ruled out since photooxygenation of **7b** in methanol afforded **8c** identical with the product obtained from **7a** in ethanol.



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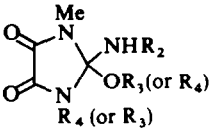

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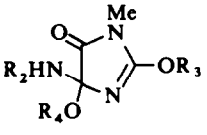

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The imidazolinones **8** are extremely sensitive to hydrolysis. Thus, on treatment with aqueous acetic acid at room temperature **8a**, **8c**, and **8e** yielded 1,3-dimethylparabanic acid (**13a**) in 91, 54, and 45% yield, respectively. On the other hand **8f** was

TABLE 1. THE FORMATION OF THE IMIDAZOLINONES 8 FROM 7 AND THE NMR DATA OF 8

7	Solvent (R_4OH)	O_2 consumed (mmole)	CO_2 evolved (mmole)	Yield of 8 (%)	8	NMR data for protons of 8[a]				
7a	MeOH	0·81	0·60	78	**8a**	7·18 s	4·10	7·00 d (J = 5)	6·80 s	6·80 s
7c	MeOH	1·23	1·10	28	**8a**					
7a	MeOH-d_4	0·57	ND[c]	28	**8b**	7·19 s	4·15	7·02 d (J = 5)	6·82 s	—
7a	EtOH	0·80	ND	33	**8c**	7·18 s	4·15	7·02 d (J = 5)	6·83 s	8·73 t (J = 7) 6·38 qd (J = 7, J' = 9)[d]
7b	MeOH	1·04	0·57	71	**8c**					6·72 qd (J = 7, J' = 9)[d]
7b	MeOH-d_4	0·58	ND	24	**8d**	7·20 s	4·40	7·03 d (J = 5)	8·81 t (J = 7) 6·60 m	—
7b	EtOH	0·71	0·73	25	**8e**	7·18 s	4·20	7·05 d (J = 5)	8·82 t (J = 7) 6·60 m	8·82 t (J = 7) 6·60 m
7d	MeOH	0·76	1·20	57	**8f**	7·22 s	4·35	8·75 t (J = 7) 6·58 qd (J = 7, J' = 5)	6·84 s	6·84 s
7d	MeOH-d_4	0·84	ND	83	**8g**	7·20 s	4·25	8·75 t (J = 7) 6·60 qd (J = 7, J' = 5)	6·84 s	—

[a] Chemical shifts were given by τ-value. Coupling constants (parentheses) were given by c/s. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

[b] These NH-protons appeared as a broad singlet.

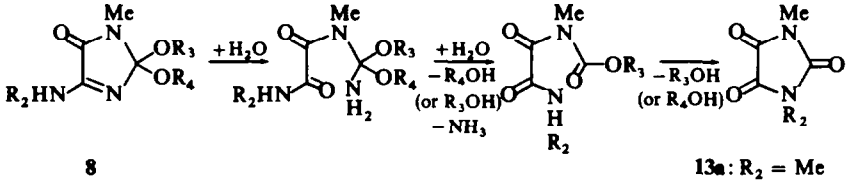
[c] Not determined.

[d] This signal was analysed by decoupling experiments.

hydrolyzed under similar conditions to give no 1,3-dimethylparabanic acid (**13a**) but only 1-ethyl-3-methylparabanic acid (**13b**) (26%). The results can be explained by a mechanism shown in Chart 1. The mechanism was supported by a tracer experiment using [8-^{14}C]-labeled 8-methoxycaffine (**7a***).

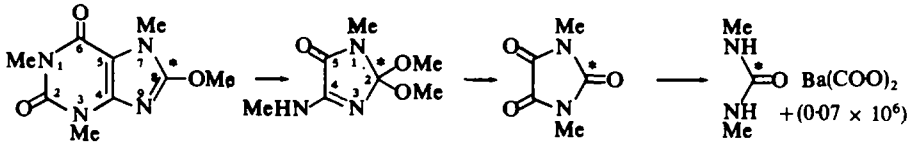
The [8-^{14}C]-labeled 8-methoxycaffeine (**7a***) was prepared, and it was submitted to photosensitized oxygenation under the standard conditions. The radioactive imidazolinone (**8a***) obtained was hydrolysed with aqueous acetic acid to yield the active 1,3-dimethylparbanic acid (**13a***) which was then hydrolysed with baryta to active 1,3-dimethylurea (**14a***) and practically inactive barium oxalate.[10] The data are shown in Chart 2. The results clearly demonstrate that the 2-C atom of **8a** was derived from the 8-C atom of **7a**.

CHART 1



8 **13a**: R_2 = Me; **13b**: R_2 = Et

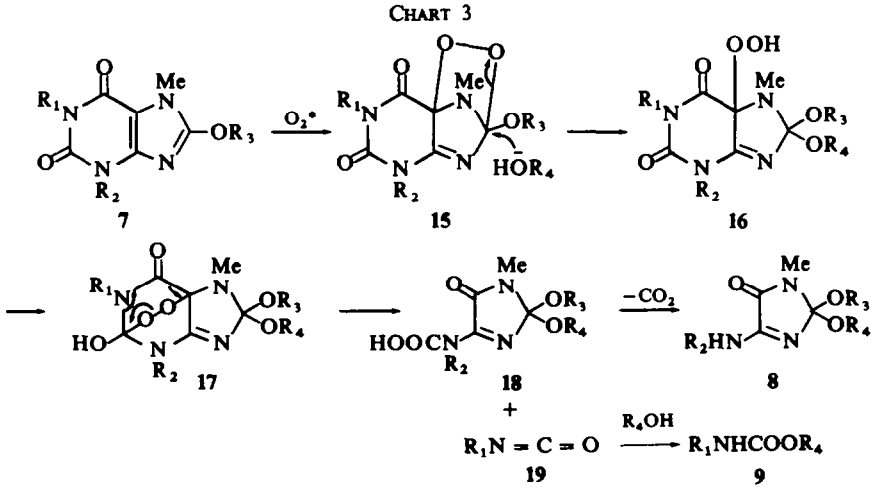
CHART 2



7a*	**8a**	**13a***	**14a***
(3·26 × 10^6 cpm/mmole)	(3·01 × 10^6)	(2·80 × 10^6)	(2·70 × 10^6)

The formation of the imidazolinones **8** from the trialkyl-8-alkoxyxanthines **7** can be rationalized by a scheme shown in Chart 3. On the basis of the previous findings,[1,4,5] it is most probable that singlet oxygen attacks the starting material **7**

CHART 3



7 **15** **16** **17** **18** **8** **19** **9**

to form a 5,8-endo-peroxide intermediate (**15**). Such a cyclic peroxide has been proposed for the initial intermediate in the photosensitized oxygenation of xanthine (**1**),[3] 9-phenylxanthine,[4,5] and 1,3-dimethyl-9-phenylxanthine.[4,5] The solvent alcohol (R_4OH) adds to the intermediate peroxide **15** to form an alkoxy hydroperoxide **16** which is, then, tautomerized to a 6-membered cyclic peroxide **17**. A similar mechanism involving such a tautomerization has been proposed for reactions involving a ketone hydroperoxide.[1,11,12] Peroxide **17** loses alkyl isocyanate (**19**) to give **18** which can be decarboxylated to form the imidazolinone **8**. The alkyl isocyanate reacts with the solvent alcohol to give alkyl N-alkyl-carbamate (**9**) which was isolated from the reaction mixture in one case.

EXPERIMENTAL

Photosensitized oxygenation of 8-*methoxycaffeine* (**7a**)

A. *In* MeOH. A soln of **7a**[13] (1·00 g, 4·46 mmoles) in MeOH–$CHCl_3$ (20:1, 100 ml) containing rose bengal (50 mg) was irradiated at room temp by a 100 W high-press mercury lamp through a Pyrex cooling jacket. During the irradiation O_2 was bubbled by a circulating pump through a sintered-glass joint which was attached at the bottom of the reaction vessel. O_2 consumption was manometrically followed. CO_2 liberated was trapped with $Ba(OH)_2$ aq. O_2 consumption was ceased after O_2 (90 ml, 3·6 mmoles) had taken up in 1 hr. CO_2 was determined by weighing the $BaCO_3$ precipitated. After removal of the solvent *in vacuo*, the residue was dissolved in 20 ml of acetone–ether (1:3). The soln, when cooled at −70° with a dry ice–acetone bath, deposited crystals (0·65 g, 78%). Recrystallization from acetone gave **8a**, m.p. 114–115°; λ_{max}^{EtOH} 218 mμ (ε 28,000), 252 mμ (ε 6200), ν_{max}^{Nujol} 3350, 1750, and 1665 cm^{-1}. (Found: C, 44·91; H, 7·06; N, 22·49. $C_7H_{13}N_3O_3$ requires: C, 44·91; H, 7·06; N, 22·45%).

When the irradiation was made with a tungsten lamp, virtually the same results were obtained. In the absence of rose bengal no O_2 consumption was observed and the starting material was recovered quantitatively.

B. *In* CD_3OD. A soln of **7a** (0·40 g, 1·8 mmoles) in CD_3OD (9 ml) containing rose bengal (5 mg) was photooxidized under similar conditions. The mixture was worked up as described above to give **8b** (90 mg, 28%), m.p. 114–115°.

C. *In* EtOH. A soln of **7a** (4·00 g, 17·8 mmoles) in EtOH (100 ml) and $CHCl_3$ (20 ml) containing rose bengal (50 mg) was photooxidized in the standard manner for 3 hr. VPC analysis (silicon DC at 70°, with DMF as an internal standard) of the mixture revealed that the mixture contained **9** (1·25 g, 68%). Fractional distillation of the mixture at the ordinary atmosphere gave pure ethyl N-methylcarbamate, b.p. 170°, which was identical with an authentic sample (by IR and VPC). The residue was chromatographed on a neutral alumina column (60 g). Elution with $CHCl_3$ (180 ml) gave **13a** (0·12 g, 5%). Further elution with $CHCl_3$ (300 ml) gave a semisolid (2·8 g). Recrystallization from acetone gave **8c** (1·20 g, 33%), m.p. 103–104°; λ_{max}^{EtOH} 218 mμ (ε 27,800), 252 mμ (ε 6200), ν_{max}^{Nujol} 3300, 1730, and 1665 cm^{-1}. (Found: C, 47·63; H, 7·63; N, 20·59. $C_8H_{15}N_3O_3$ requires: C, 47·75; H, 7·51; N, 20·88%).

Photosensitizied oxygenation of 8-*ethoxycaffeine* (**7b**)

A. *In* MeOH. A soln of **7b**[13] (2·00 g, 8·4 mmoles) in MeOH–$CHCl_3$ (20:1, 100 ml) containing rose bengal (50 mg) was photooxidized for 1 hr. The solvent was evaporated *in vacuo* and the residue was crystallized from acetone–ether (3:1, 20 ml). Recrystallization from acetone yielded **8c** (1·20 g, 71%), m.p. 103–104°, which were identical with **8c** obtained above (by mixture m.p., IR and NMR).

B. *In* CD_3OD. A soln of **7b** (0·30 g, 1·3 mmoles) in CD_3OD (9 ml) containing rose bengal (10 mg) was photooxidized as usual. After treatment of the mixture as described above, **8d** (60 mg, 24%) was obtained, m.p. 103–105°.

C. *In* EtOH. A soln of **7b** (2·00 g, 8·35 mmoles) in EtOH (150 ml) and $CHCl_3$ (5 ml) containing rose bengal (20 mg) was photooxidized using a tungsten lamp for 5 hr. After removal of the solvent *in vacuo*, the residue was chromatographed on a neutral alumina column (50 g). Elution with $CHCl_3$ (250 ml) gave a semisolid. Recrystallization from acetone yielded **8e** (0·45 g, 25%), m.p. 108–109°; λ_{max}^{EtOH} 218 mμ (ε 28,000), 252 mμ (ε 6240), ν_{max}^{Nujol} 3300, 1715, and 1650 cm^{-1}.

Photosensitized oxygenation of 1-*ethyl*-3,7-*dimethyl*-8-*methoxyxanthine* (**7c**)

A soln of **7c** (0·70 g, 2·9 mmoles) in MeOH (80 ml) and $CHCl_3$ (5 ml) containing rose bengal (20 mg) was photooxidized in the standard manner for 3 hr. After removal of the solvent, the residue was chromatographed on a neutral alumina column (15 g). Elution with $CHCl_3$ (200 ml) gave crystals (0·15 g, 28%), m.p. 113–114°, which were identical with **8a** (by mixture m.p., IR, and NMR).

1,3-*Diethyl*-7-*methyl*-8-*methoxyxanthine* (**7d**)

This compound was prepared from 1,3-diethylxanthine[15] by the known method for the synthesis of 8-alkoxycaffeine;[13] m.p. 143–147°, NMR ($CDCl_3$), τ 8·70 (tr (J = 6·5 c/s), 3H $\rangle N—CH_2—Me$), 8·67 (tr (J = 6·5 c/s), 3H, $\rangle N—CH_2—Me$), 6·34 (s, 3H, $\rangle N—Me$), 5·90 (s, 3H, —OMe), 5·90–6·20 (m, 4H, $\rangle N—CH_2—Me$). (Found: C, 52·06; H, 6·40; N, 22·29. $C_{11}H_{16}N_4O_3$ requires: C, 52·37; H, 6·39; N, 22·21%).

Photosensitized oxygenation of 1,3-*diethyl*-7-*methyl*-8-*methoxyxanthine* (**7d**)

A. *In* MeOH. A soln of **7d** (1·00 g, 4·0 mmoles) in MeOH (50 ml) and $CHCl_3$ (5 ml) containing rose bengal (20 mg) was photooxidized under the standard conditions for 2 hr. After removal of the solvent *in vacuo*, the residue was chromatographed on a neutral alumina column (20 g). Elution with 50 ml benzene–$CHCl_3$ (1:1) yielded an oil (0·45 g, 57%), which crystallized upon standing overnight. Attempts to recrystallization were unsuccessful. In order to obtain an analytical sample, the crystals were again chromatographed on an alumina column to give pure **8f** m.p. 75–77°; λ_{max}^{EtOH} 218 mμ (26,000), 253 mμ (ε 6000), ν_{max}^{Nujol} 3300, 1725, and 1655 cm^{-1}. (Found: C, 47·43; H, 7·49; N, 20·51. $C_8H_{15}N_3O_3$ requires: C, 47·75; H, 7·51; N, 20·88%).

B. *In* CD_3OD. A soln of **7d** (0·50 g, 2 mmoles) in CD_3OD (18 ml) containing rose bengal (10 mg) was photooxidized under the standard conditions. The solvent was removed *in vacuo* and the residue was chromatographed on a neutral alumina column (10 g). Benzene (50 ml) eluted **8g** (0·34 g, 83%), which crystallized upon standing overnight, m.p. 74–75°.

Hydrolysis of **8** *with aqueous acetic acid*

A soln of **8a** (40 mg) in H_2O containing three drops AcOH was kept at room temp for 24 hr. To the soln H_2O (50 ml) and $CHCl_3$ (50 ml) was added. The chloroform layer was separated and evaporated to dryness. Crystallization of the residue from acetone gave **13a** (28 mg, 91%). Similarly, **8c** and **8e** was hydrolysed with aqueous AcOH to give **13a** in 54 and 45% yield, respectively, but no 1-ethyl-3-methylparabanic acid could be detected on TLC. On similar treatment with aqueous AcOH, **8f** (50 mg) afforded **13b** (10 mg, 26%). Recrystallization from acetone gave crystals, m.p. 45–48° (lit.[16] m.p. 44°). No 1,3-dimethylparabanic acid was detected by TLC analysis of the mother liquor.

[8-^{14}C]-8-*Methoxycaffeine* (**7a***)

Theophylline labeled at 8-position with ^{14}C was prepared from 1,3-dimethyl-4,5-diaminouracil[15] and formic acid containing 0·5 mc [^{14}C]-formic acid according to the method of Speer *et al.*[15] Methylation of [8-^{14}C]-theophylline with Me_2SO_4 gave [8-^{14}C]-caffeine which, on chlorination and subsequent methoxylation according to the method of Huston,[13] gave **7a*** (3·26 × 10^6 cpm/mmole).

Photosensitized oxygenation of [8-^{14}C]-8-*methoxycaffeine* (**7a***) *in methanol*

A soln of **7a*** (4·00 g, 16·8 mmoles, 3·26 × 10^6 cpm/mmole) in MeOH–$CHCl_3$ (6:1, 200 ml) containing rose bengal (50 mg) was photooxidized under the standard conditions. CO_2 liberated was trapped as $BaCO_3$ (1·70 g, 48%, 660 cpm/mmole). Recrystallization of the product gave [2-^{14}C]-**8a** (2·32 g, 69%, 3·01 × 10^6 cmp/mmole), m.p. 113–114°.

Acid hydrolysis of [2-^{14}C]-1-*methyl*-2,2-*dimethoxy*-4-*methylamino*-3-*imidazolin*-5-*one* (**8a***)

A soln of **8a*** (2·00 g, 10·7 mmoles) in aqueous AcOH was treated as described above to give **13a*** (1·05 g, 69%, 2·804 × 10^6 cpm/mmole). A soln of **15a*** (0·95 g, 6·7 mmoles) in 3% $Ba(OH)_2$ aq (100 ml) was kept at 40–50° for 15 min according to the procedure of Behrend *et al.*[10] Barium oxalate (1·45 g, 95%, 7·05 × 10^4 cpm/mmole) precipitated was collected by filtration. The filtrate was evaporated *in vacuo* to dryness. The residue was extracted with acetone (50 ml). After removal of the solvent, the residue was crystallized from benzene to give [^{14}C]-N,N-dimethylurea (0·17 g, 29%, 2·698 × 10^6 cpm/mmole).

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