Tetrahedron Vol 25, pp. 541 to 547 Pergamon Press 1969. Printed in Great Britain

PHOTOINDUCED REACTIONS—XXIV

PHOTOSENSITIZED OXYGENATION OF HYDROXYLATED 9-PHENYLPURINES[1,2]

T. MATSUURA and I. SAITO

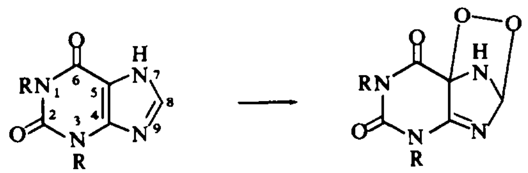
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Kyoto, Japan

(*Received in Japan* 24 *July* 1968; *Received in the UK for publication* 23 *August* 1968)

Abstract—Photosensitized oxygenation of 1,3-dimethyl-9-phenylxanthine (**5a**) and 9-phenylxanthine (**5b**) in methanol in the presence of rose bengal gave as the major products the corresponding 4,5-dimethoxyuric acid derivatives **9a** and **9b**, respectively. Under similar conditions, 1,3-dimethyl-9-phenyluric acid (**7a**) and 9-phenyluric acid (**7b**) yielded **9a** and **9b**, respectively. In the case of **7a**, 1,3-dimethyl-4-hydroxy-5-methoxy-9-phenyluric acid (**10**) was also obtained. Possible mechanisms involving peroxide intermediates, a 4,8-*endo*-peroxide **6** from **5** and a 4-hydroperoxide **8** from **6**, are discussed.

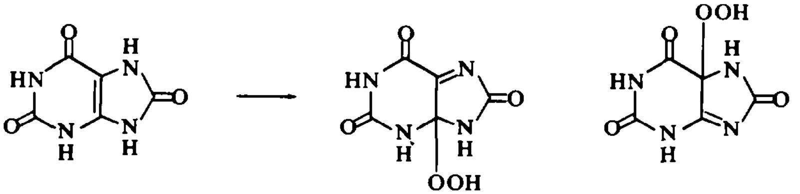
IN PREVIOUS papers,[3,4] it has been shown that the photosensitized oxygenation of hydroxylated purines, including xanthine (**1a**) and uric acid (**2**), in an aqueous alkaline solution gives various products which are possibly formed *via* a peroxide intermediate. We have postulated a 5,8-*endo*-peroxide **3a** for the intermediate from **1a** and a hydroperoxide **4a** or **4b** from **2**. The formation of 1,3-dimethylallantoin in the photosensitized oxygenation of theophylline (**1b**)[5] can be also rationalized by considering a similar peroxide intermediate **3b**. The peroxides **3** and **4** are analogous to photoperoxides obtained from cyclic conjugated dienes[6] and from olefins bearing an allylic hydrogen, $(-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H- \rightarrow -\overset{|}{C}(OOH)-\overset{|}{C}=\overset{|}{C}-)^7$ respectively. In contrast to purine derivatives such as **1** in which two double bonds of the imidazole ring are fixed at 4,5- and 8,9-positions, 9-N-substituted purines such as **5** have two double bonds fixed at 4,5- and 7,8-positions. In the latter case it might be expected to result in the initial formation of a 4,8-*endo*-peroxide **6** analogous to **3**. On the other hand, photosensitized oxygenation of 8-oxo-9-N-substituted purines such as **7**, in which a double bond is located only at 4,5-position as in **2**, would give a 4-hydroperoxy intermediate **8** analogous to **4a**.

When a methanol solution of 1,3-dimethyl-9-phenylxanthine (**5a**) was irradiated with a high-pressure mercury lamp (Pyrex) in the presence of rose bengal, 1·3 moles of oxygen was consumed and a crystalline product $C_{15}H_{18}N_4O_5$ was obtained in 23% yield. Irradiation with visible light in the presence of the sensitizer gave essentially identical results. The NMR spectrum ($CDCl_3$) of the product shows four singlets of two N-Me's and two OMe's at τ 6·48, 6·54, 6·80, and 7·45 in addition to a singlet at τ 3·75 and a multiplet centering at τ 2·78 corresponding to an NH and a Ph group. The IR spectrum exhibits intense absorptions at 1720 and 1675 cm^{-1}. Treatment of the product with hydriodic acid gave 1,3-dimethyl-9-phenyluric acid (**7a**) Chemical and spectral properties are compatible with structure **9a** for the photoproduct. This assignment was confirmed by an independent synthesis of **9a** which was obtained by



1a: R = H
1b: R = Me

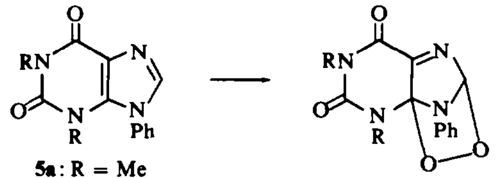
3a: R = H
3b: R = Me



2

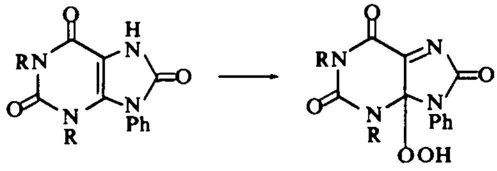
4a

4b



5a: R = Me
5b: R = H

6



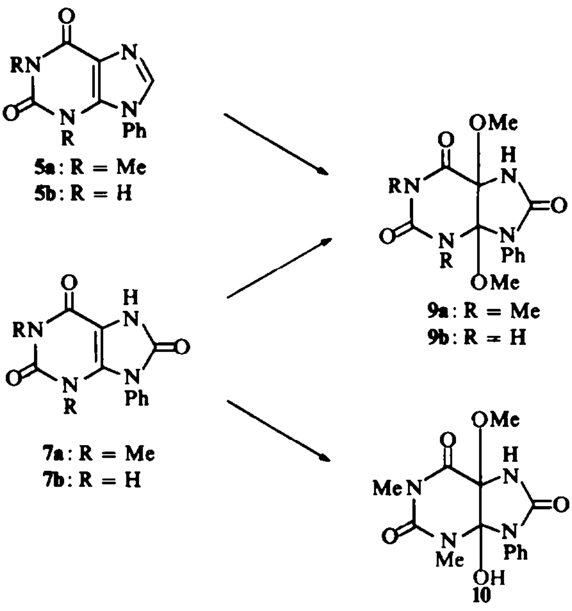
7a: R = Me
7b: R = H

8

the reaction of **7a** with chlorine in methanol applying the known method for the synthesis of 1,3,7,9-tetramethyl-4,5-dimethoxyuric acid from 1,3,7,9-tetramethyluric acid.[8]

Photosensitized oxygenation of 9-phenylxanthine (**5b**) in the same manner yielded, after the consumption of 1·1 moles of oxygen, a compound $C_{13}H_{14}N_4O_5$ in 58% yield. The molecular formula was confirmed by the appearance of its mass parent peak at *m/e* 306. The NMR spectrum (DMSO-d_6) exhibits two OMe singlets at τ 6·35 and 6·54, three singlets of three NH protons at τ 0·75, 3·20, and 3·45, and a multiplet of a Ph group centering at τ 2·73. The spectral data suggest structure **9b** for the photoproduct. This was confirmed by the methylation of the product with diazomethane yielding **9a**.

Photosensitized oxygenation of 9-N-substituted uric acid derivatives (**7**) also proceeded smoothly. Thus, 9-phenyluric acid (**7b**) gave, after the consumption of 1·1 moles of oxygen, 4,5-dimethoxy-9-phenyluric acid (**9b**) in 46% yield. In a similar way, 1,3-dimethyl-9-phenyluric acid (**7a**) absorbed 1·1 moles of oxygen to give **9a** (2%) and a compound $C_{14}H_{16}N_4O_5$ (11%). The NMR spectrum ($CDCl_3$) of the latter



5a: R = Me
5b: R = H

7a: R = Me
7b: R = H

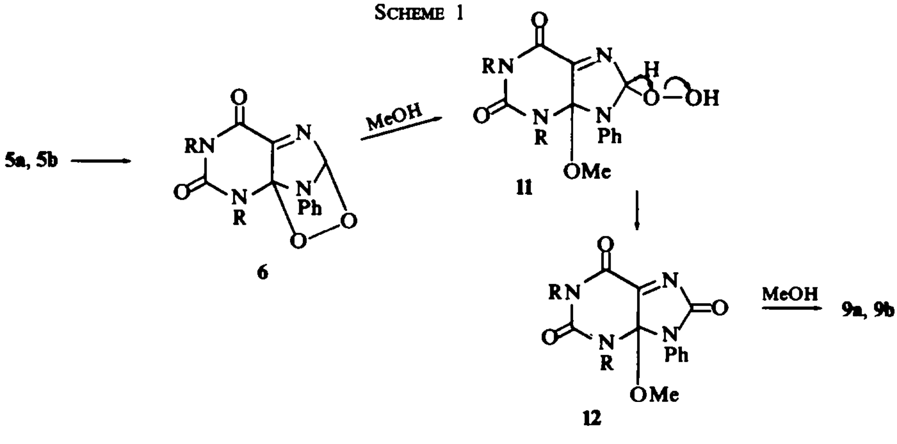
9a: R = Me
9b: R = H

10

product shows, in addition to a multiplet of a Ph group centering at τ 3·0 and two singlets at τ 2·76 and 3·47 corresponding to OH and NH protons, respectively, a singlet of nine protons at τ 6·66 suggesting the presence of two N-Me and an O-Me groups. Partial hydrolysis of **9a** with 2N HCl give this trimethylated compound for which, therefore structure **10** was assigned. In the course of the hydrolysis of **9a** to **10**, a OMe group at 4-position, which is highly deshielded by a Ph group at 9-position, might be selectively hydrolyzed.

Although both **5** and **7** give rise to **9**, different mechanisms must be considered for the formation of **9**. As was expected, the formation of **9** from **5** can be rationalized by a 4,8-*endo*-peroxide intermediate **6**. Such an *endo*-peroxide has been postulated as the intermediate in the photooxidation of some 5-membered nitrogen heterocycles, i.e. pyrroles,[9] oxazoles,[10] and isoindoles.[11] The initially formed *endo*-peroxide **6** could be solvolyzed by methanol to a methoxy-hydroperoxide **11** which is dehydrated

SCHEME 1



6

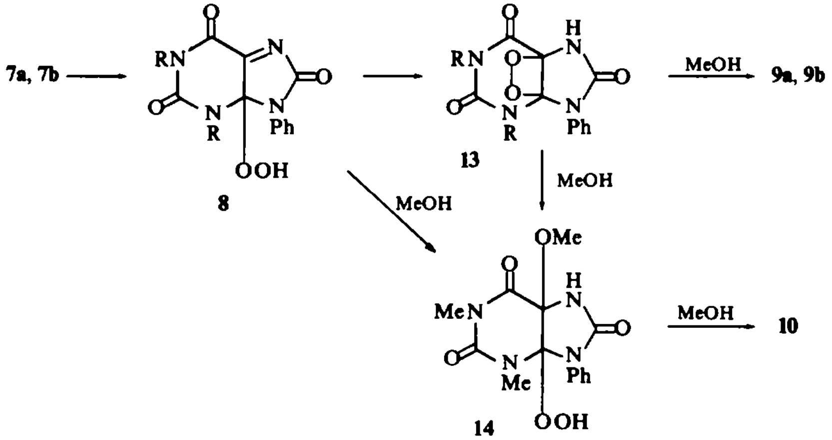
11

12

to give a 8-keto compound **12**. Such a process is well known in the photosentized oxygenation of furan which, in methanol, gives 4-methoxy-2-butenolide *via* a 1,4-*endo*-peroxide.[12] Our previous result that xanthine (**1a**) gives allantoin provides an analogous example.[3,4] Addition of methanol to a C=N bond of **12** finally leads to the 4,5-dimethoxyuric acid derivative **9** (Scheme 1). A similar mechanism has been proposed for the photosensitized oxygenation of 2-methyl-5-phenyloxazole.[10a]

On the other hand, a hydroperoxide **8** analogous to **4** can be considered to account for the formation of **9** from **7**.* This type of hydroperoxide is generally accepted as an intermediate in the photooxygenation of certain N-heterocycles bearing a —C=C—NH— moiety.[13] Hydroperoxide 8 could rearrange to a 4-membered cyclic peroxide **13** which, in the presence of methanol, undergoes reductive cleavage to give **9** (Scheme 2).

SCHEME 2



Such a process involving reductive cleavage of a cyclic peroxide by methanol to a dimethoxy compound has analogy in the photosensitized oxygenation of a cyclophane derivative.[14] A methoxy-hydroperoxide **14**, which might be formed either from the cyclic peroxide **13** by methanolysis or directly from hydroperoxide **8** by addition of methanol to a C=N double bond, can account for the formation of **10** from 1,3-dimethyl-9-phenyluric acid (**7a**).

Recently involvement of singlet oxygen in dye-sensitized photooxygenation of olefinic compounds[15] including oxazoles[16] has been shown by several workers. In order to ascertain the participation of singlet oxygen in the present reactions, we carried out reaction of **5b** with chemically generated singlet oxygen. Treatment of **5b**

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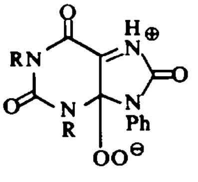
* We have proposed a zwitterionic structure **I** for the initially formed peroxides from **7a** and **7b** in a previous communitation.[2] Peroxide **I** can also rearrange to the four-membered cyclic peroxide **13**. Although our experimental data can not distinguish between structures **8** and **I**, the hydroperoxide structure **8** is more favorable considering from other examples.[13]



with hydrogen peroxide and sodium hypochlorite in an aqueous methanolic solution at pH 8·4 afforded a complex mixture of products from which only a small amount of 4,5-dimethoxy-9-phenyluric acid (**9b**) was detected. The low yield of **9b** is probably due to instability of **9b** under conditions employed. At pH 8·4 **5b** was quite stable to hydrogen peroxide alone, but was oxidized with hypochlorite to give unidentified products from which no **9b** could be detected. However, it is probable that singlet oxygen is involved in the present photosensitized oxygenation. Further studies on this point will be described in a subsequent paper.

EXPERIMENTAL

1,3-*Dimethyl-9-phenylxanthine* (**5a**)

To a suspension of 9-phenylxanthine[17] (1·0 g, 4·4 mmoles) in 100 ml abs MeOH, an ether soln of diazomethane (prepared from 5 g of nitrosomethylurea) was added. After removal of the solvent, a solid insoluble in MeOH was again methylated in a similar manner. Following removal of the solvent, the residue was extracted with $CHCl_3$ and the extract was evaporated. Crystallization of the residue gave 0·13 g (11·5%) of **5a**, m.p. 305–307° (dec); λ_{max}^{EtOH} 265 mμ (ε 21,200), ν_{max}^{Nujol} 1690, 1650 cm^{-1}, NMR ($CDCl_3$); τ 2·45–2·85 (5H, m,* phenyl), 2·50 (1H, s, —CH=N—), 6·65 (3H, s, >N—CH_3), (3H, s, >N—CH_3). (Found: C, 60·46; H, 4·85; N, 21·41. $C_{13}H_{12}N_4O_2$ requires C, 60·93; H, 4·72; N, 21·87%).

Photosensitized oxygenation of 1,3-*dimethyl-9-phenylxanthine* (**5a**)

A soln of 100 mg (0·4 mmole) of **5a** and rose bengal (10 mg) in 100 ml abs MeOH was irradiated with a 100 W high-pressure mercury lamp for 1 hr as described previously,[4] until 12 ml (0·50 mmole) O_2 was consumed. After removal of the solvent, the residual oil was purified by preparative TLC on silica gel using a mixture of $CHCl_3$ and EtOH (20:1). The zone of R_f-value 0·30 was collected and eluted with acetone. From the eluate 30 mg (23%) of **9a** was obtained as crystals. Recrystallization from MeOH gave fine needles, m.p. 223–225°, which were identical with an authentic sample prepared below (by mixture m.p. and IR); λ_{max}^{EtOH} 220 mμ (ε, 29,800), 275 mμ (ε, 1500), ν_{max}^{Nujol} 1720, 1675 cm^{-1}. (Found: C, 53·55; H, 5·41; N, 16·69. $C_{15}H_{18}N_4O_5$ requires C, 53·88; H, 5·43; N, 16·76%).

Reduction of 1,3-*dimethyl-4,5-dimethoxy-9-phenyluric acid* (**9a**) with HI

The reduction of **9a** was carried out according to the method of Biltz.[18] A soln of 150 mg (0·45 mmole) of **9a** obtained above in conc HI (5 ml) was warmed at 60° for 3 hr. Following removal of the solvent *in vacuo*, the residual oil was triturated with MeOH (20 ml) under ice-cooling to deposit 65 mg (53%) of **7a** as crystals, m.p. >300°, which were identified by IR.

1,3-*Dimethyl-4,5-dimethoxy-9-phenyluric acid* (**9a**)

According to the procedure reported by Biltz.[8] a suspension of 1·0 g (3·7 mmoles) of **7a**[19] in 20 ml abs MeOH was cooled on an ice–salt bath. Cl_2 gas was bubbled through the suspension yielding a clear soln. In order to remove excess Cl_2, a stream of N_2 was bubbled through the soln, depositing a white ppt. Crystallization from MeOH gave 0·61 g (50%) of **9a** as fine needles, m.p. 223–225°.

1,3,7-*Trimethyl-4,5-dimethoxy-9-phenyluric acid*

According to the above procedure, this compound was synthesized from 1,3,7-trimethyl-9-phenyluric acid[20] in 49% yield. Recrystallization from MeOH gave fine needles, m.p. 138°; λ_{max}^{EtOH} 221 mμ (ε35,600), 275 mμ (ε 2400), ν_{max}^{Nujol} 1740, 1680 cm^{-1}, NMR ($CDCl_3$); τ 2·87 (5H, m, phenyl), 6·55, 6·61, 6·80, 7·17, 7·45 (all s, each 3H, >N—CH_3 and —O—CH_3). (Found: C, 55·31; H, 5·64; N, 15·96. $C_{16}H_{20}N_4O_5$ requires C, 55·16; H, 5·79; N, 16·08%).

This compound was also obtained from **9a** in 55% yield by treatment with ethereal diazomethane.

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* m = multiplet; s = singlet, etc.

Photosensitized oxygenation of 9-*phenylxanthine* (**5b**).

A suspension of **5b** (2·0 g; 8·8 mmoles) in abs MeOH (400 ml) containing rose bengal (20 mg) was irradiated with a 100 W high-pressure mercury lamp for 3 hr as described. During irradiation, the CO_2 liberated was trapped as $BaCO_3$ (0·73 g, 2·5 mmoles). After 232 ml (9·7 mmoles) O_2 had been consumed, the mixture was concentrated *in vacuo* to 10 ml, then treated with Norit to remove the sensitizer. On cooling in an ice box overnight 0·52 g of **9b** was deposited as crystals. The mother liquor was evaporated and the residue was chromatographed on a silica gel column (40 g). Elution with $CHCl_3$–acetone (10:1) yielded 1·05 g (total yield, 58%) of **9b**. Recrystallization from MeOH gave crystals, m.p. 190–191°; λ_{max}^{EtOH} 218 mμ (ε 36,000), 248 (shoulder, 18,800), ν_{max}^{Nujol} 1770, 1670 cm^{-1}. (Found: C, 50·54; H, 4·82; N, 17·81. $C_{13}H_{14}N_4O_5$ requires: C, 50·98; H, 4·61; N, 18·28%).

Methylation of 4,5-*dimethoxy*-9-*phenyluric acid* (**9b**).

An excess of ethereal diazomethane was added to a soln of **9b** (100 mg). After removal of the solvent, the residue was again treated with ethereal diazomethane. The mixture was found by TLC to consist of several products, from which 5 mg of **9a** was isolated by preparative TLC using silica gel plates and $CHCl_3$–EtOH (10:1) as an eluting solvent, and the compound was identical with a sample obtained above (by IR).

Photosensitized oxygenation of 1,3-*dimethyl*-9-*phenyluric acid* (**7a**).

A suspension of **7a** (1·0 g; 3·7 mmoles) in 280 ml MeOH containing 20 mg rose bengal was photooxidized as described (photooxidation of **5a**). After 95 ml (4·0 mmoles) O_2 had been consumed, the mixture was evaporated. The residue was chromatographed on a silica gel column (20 g). Elution with 200 ml $CHCl_3$ yielded 25 mg (2·1%) of **9a** which was identified by IR. Elution with $CHCl_3$–acetone (20:1) yielded 132 mg (12%) of **10** as crystals. Recrystallization from acetone gave crystals, m.p. 201–202°; λ_{max}^{EtOH} 232 mμ (ε 27,700) and 271 (1700); λ_{max}^{Nujol} 3300–3400, 1750 (shoulder), 1690, and 1655 cm^{-1}. (Found: C, 52·50; H, 4·96; N, 17·51. $C_{14}H_{16}N_4O_5$ requires: C, 52·49; H, 5·04; N, 17·49%).

Partial hydrolysis of 1,3-*dimethyl*-4,5-*dimethoxy*-9-*phenyluric acid* (**9a**).

A suspension of **9a** (100 mg; 0·3 mmole) in 3 ml 2N HCl was boiled for 1 min. After cooling, the deposited solid was collected by filtration and crystallized from acetone to give 15 mg (15%) **10** as crystals, m.p. 200–202°, which were identical with the acid **10** obtained from **7a** (by IR).

Photosensitized oxygenation of 9-*phenyluric acid* (**7b**)

A suspension of **7b**[20] (1·5 g; 6·3 mmoles) in 200 ml abs MeOH containing 20 mg rose bengal was photooxidized for 4 hr as described. After 180 ml (7·1 mmoles) O_2 had been consumed, the mixture was evaporated *in vacuo* to 15 ml. The crystals deposited (0·86 g, 46%) were identified as **9b** (by IR and mixture m.p.).

Oxidation of 9-*phenylxanthine* (**5b**) *with hydrogen peroxide and sodium hypochlorite*

The oxidation was carried out by the procedure reported by Foote *et al.*[15] To a soln of **5b** (1.0 g; 4·4 mmoles) in 300 ml MeOH, 30% H_2O_2 (2·5 ml; 22·5 mmoles) was added. The mixture was cooled in an ice-bath and 14 ml (17 mmoles) 9% NaOCl aq was added dropwise with stirring in the course of 1 hr. To the reaction mixture (pH 8·4), 500 ml $CHCl_3$ and 500 ml water was added. The organic layer was separated and evaporated *in vacuo* to dryness. The residue was found by TLC to consist of at least 7 compounds. One of the compounds was identified by a TLC (silica gel, $CHCl_3$–EtOH (10:1)) and by PPC (n-BuOH–AcOH–H_2O (5:4:1) as **9b**.

At the same pH (8·4) **5b** was recovered unchanged on treatment with H_2O_2. Reaction of **5b** with an excess NaOCl was also carried out. To a soln of **5b** (100 mg; 0·44 mmole) in 100 ml of MeOH, 5 ml (6 mmoles) 9% NaOCl aq was added. The mixture was extracted with $CHCl_3$ as described. The extract was found by TLC to consist of mainly two products, which were not identical with **9b**.

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