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Photochemistry of Purine Systems, Part III[1] Photoreactions of Theophylline with Alcohols in the Presence of Aliphatic Ketones

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Photochemical reactions of theophylline with primary and secondary alcohols in the presence of aliphatic ketones result in substitution of an α-hydroxyalkyl group for the hydrogen atom at C-8 position. The results indicate that both the α-hydroxyalkyl radicals derived by H-abstraction from alcohol and the ketyl radicals generated by photoreduction of ketone are involved in the reactions.

(Keywords: Theophylline; Photoreduction; Photosubstitution)

Photochemie des Purinsystems, 3. Mitt.: Photochemische Reaktionen von Theophyllin mit Alkoholen in Gegenwart von aliphatischen Ketonen

Photochemische Reaktionen von Theophyllin mit primären und sekundären Alkoholen in Gegenwart von aliphatischen Ketonen liefern C-8-Substitutionsprodukte. Die Ergebnisse sprechen dafür, daß an den Reaktionen sowohl die durch H-Abstraktion aus Alkoholen gebildeten α-Hydroxyalkylradikale als auch die durch Photoreduktion von Ketonen entstandenen Ketylradikale beteiligt sind.

Introduction

Numerous studies have been made in an effort to explain the participation of purines and purine nucleosis in photochemical and γ-ray-induced reactions. Thus, while UV-light induced reactions of purine itself and purine riboside with a variety of alcohols resulted in the addition of the alcohol free radicals across the 1,6-double bond[2] similar reactions of substituted purines—such as caffeine, hypoxanthine, adenine and guanosine—led to substitution[3] of an α-hydroxyalkyl group for the hydrogen atom at C-8 position.

An exception was found, however, for 2-aminopurine[4] which underwent a primary attack at C-6 followed by one at C-8. With 6-ethoxypurine the primary substitution at C-8 was followed by one at C-2. It is suggested[5] that the reactivities of the various sites of the purines in photochemical reactions with alcohols follow the order: C-6 > C-8 > C-2.

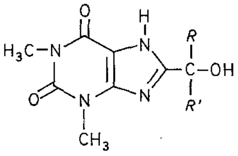
Since the use of acetone for reactions of 2-propanol under irradiation with UV-light (λ > 290 nm) has led to higher yields of the corresponding purine C-8 substitution products, *Elad* et al.[5] concluded that in such reactions the ketone behaves as a "classical" triplet sensitizer. The excited acetone could transfer the excitation energy to purine which abstracts an α-alkyl hydrogen atom from alcohol and generates α-hydroxyalkyl radicals. In view of the well known photoreduction ability of ketones by alcohols the authors feel that another route for the generation of alcohol free radicals may also operate in the reaction. The excited ketone would eventually abstract a hydrogen atom from the alcohol which serves as a solvent. However, it was impossible to differentiate between these two routes in *Elad's* experiments; 2-propanol was the only one alcohol, and acetone the only one ketone used in a mixture for photochemical reactions with the purines and identical radicals $CH_3\dot{C}(OH)CH_3$ were formed in both routes.

In order to obtain further insight into the role of ketones and to mechanistic aspects of photosubstitution in the purine system we have decided to study UV-induced reactions of theophylline with seven primary and secondary alcohols in the presence of several aliphatic ketones.

Results

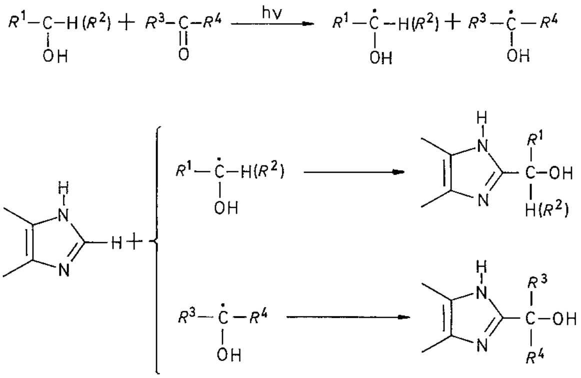
It has been fount that theophylline undergoes photoreactions when irradiated with UV-light (λ > 290 nm) in a mixture of alcohol—ketone 1 : 1 (*v*/*v*). The reactions resulted in substitution at the C-8 position and compounds **1**–**7** were obtained.

	R	*R'*
1	H	H
2	CH_3	H
3	CH_2CH_3	H
4	CH_3	CH_3
5	$(CH_2)_2CH_3$	H
6	CH_2CH_3	CH_3
7	$(CH_2)_2CH_3$	CH_3



Only one photoproduct was found in each case when α-hydroxyalkyl radicals derived from both alcohol and ketone were identical. These results were observed after irradiation of theophylline with: (a) 2-propanol in the presence of acetone, (b) 2-butanol in the presence of butanone, and (c) 2-pentanol in the presence of 2-pentanone. In all other systems alcohol : ketone studied (Table 1) always two products were isolated according to Scheme 1.

Scheme 1



Discussion

The photoreactions of theophylline with various primary and secondary alcohols in the presence of aliphatic ketones were performed with UV-light ($\lambda > 290$ nm). Spectral estimations indicate that under such experimental conditions most of the incident radiation is absorbed by the ketone.

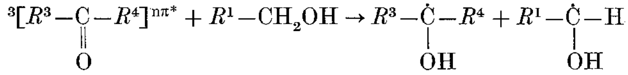
Although the intermediacy of the nπ* triplet state (T_1) of alkanones in their photoreduction by hydrogen donors seems to be well established recent results reported by *Henne* and *Fischer*[8] suggest that the reactivities and efficiences of acetone nπ* singlet state (S_1) and the triplet state (T_1) may be roughly equal in the reactions with 2-propanol. Since a successful quenching (97.4%) was obtained in our experiments when *cis*-1,3-pentadiene was added ($2 \cdot 10^{-2}\,M$) to the irradiated solution of theophylline containing 2-propanol and acetone we can conclude that in the initial step the ketone reacts predominantly from the triplet state (T_1).

Table 1. *Products of reactions of theophylline with alcohols in the presence of ketones (percentage yields are given in parentheses)*

	Methanol	Ethanol	1-propanol	2-propanol	1-butanol	2-butanol	2-pentanol
Acetone	**1** (3) **4** (80)	**2** (28) **4** (66)	**3** (23) **4** (68)	**4** (94)	**5** (19) **4** (72)	**6** (26) **4** (65)	**7** (23) **4** (69)
Butanone	**1** (1) **4** (7)	**2** (17) **6** (15)	**3** (8) **6** (13)	**4** (38) **6** (16)	**5** (12) **6** (16)	**6** (32)	**7** (15) **6** (18)
2-pentanone	**1** (1) **7** (7)	**2** (21) **7** (16)	**3** (13) **7** (18)	**4** (39) **7** (17)	**5** (15) **7** (20)	**6** (19) **7** (16)	**7** (40)

The results of elemental analyses and the spectroscopic data (UV, IR, ^{1}H-NMR, MS) of the photoproducts **1**–**7** were in good agreement with previously characterized authentic samples[6,7].

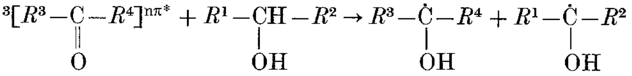
Chemical deactivation of the excited alkanone by primary alcohol leads to the formation of ketyl radical **A** and α-hydroxyalkyl radical **B**:



$${}^{3}[R^3-\underset{\displaystyle O}{\underset{\|}{C}}-R^4]^{n\pi^*} + R^1-CH_2OH \rightarrow R^3-\underset{\displaystyle OH}{\underset{|}{\dot{C}}}-R^4 + R^1-\underset{\displaystyle OH}{\underset{|}{\dot{C}}}-H$$

A **B**

However, when the excited ketone reacts with a secondary alcohol two ketyl radicals **A** and **C** are formed:



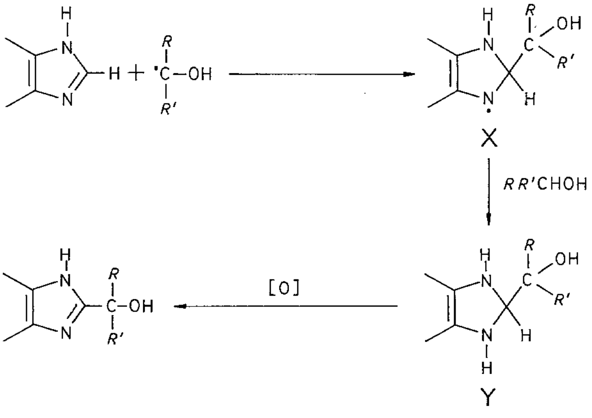
$${}^{3}[R^3-\underset{\displaystyle O}{\underset{\|}{C}}-R^4]^{n\pi^*} + R^1-\underset{\displaystyle OH}{\underset{|}{CH}}-R^2 \rightarrow R^3-\underset{\displaystyle OH}{\underset{|}{\dot{C}}}-R^4 + R^1-\underset{\displaystyle OH}{\underset{|}{\dot{C}}}-R^2$$

A **C**

In some cases this process may produce identical ketyl radicals. This will happen when the carbonyl carbon atom of a ketons is bonded to the same alkyl groups as they are attached to C-α of a secondary alcohol. Such a particular case took place in the work of *Elad* et al.[5] when purines were irradiated in a 2-propanol/acetone photosystem. This did not provide the opportunity to compare the participation of both reactants in photosubstitution of the purine system.

The subsequent step of the reactions with theophylline involves the attack of the radicals on the imino —C=N— group of imidazole moiety, which serves as a radical scavenger[9]. This attack yields the radicals **X** which abstracts a hydrogen atom to yield the "dihydro" type compounds **Y**. These intermediates are very sensitive to oxygen and upon work-up gave the corresponding C-8 substituted theophyllines (Scheme 2).

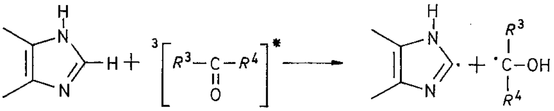
Scheme 2



Two different products were always identified after irradiation of theophylline in a solution of a primary alcohol and a ketone (Table 1). It is thus evident that both the ketyl radicals **A** and the α-hydroxyalkyl radicals **B** contribute independently to the reactions studied.

Similarly, two photoproducts were obtained after irradiation of theophylline with secondary alcohol and a ketone, except for the pairs: 2-propanol/acetone, 2-butanol/butanone, and 2-pentanol/2-pentanone, i.e., when identical radicals **A** and **C** were generated.

In most cases the yields for the formation of ketone derivatives of theophylline were appreciably higher than the yields of simultaneously formed theophylline-alcohol substitution products. This can imply that the excited ketone might react with theophylline alone producing two radicals:



The subsequent reaction between these radical species would lead to C-8 substitution products and the yield of the corresponding ketonic derivative would be enhanced. Such a possibility has been suggested by *Charlier* and *Helene*[10] for the photosensitized reaction of benzophenone with purine derivatives.

One cannot neglect the mechanism in which the alkanone behaves as a sensitizer in physical sense. Energy of the first excited triplet state for saturated aliphatic ketones (293–335 kJ mol^{-1}) is somewhat higher than that of theophylline (292 kJ mol^{-1}). Hence, the excited alkanone may transfer the excitation energy to theophylline which abstracts a hydrogen atom from the alcohol and produces α-hydroxyalkyl radicals. Such radicals would react with a ground state theophylline molecule in a similar manner as given in Scheme 2. However, this potentially probable route would lead to theophylline derivatives substituted by an alcohol rest exclusively. In view of significantly higher yields of ketonic derivatives actually observed, this route appears to play a minor role, if it takes place at all.

The results reported here indicate that in ketone photosensitized reactions occuring in the presence of hydrogen donating solvents radical reactions are at least as important as those involving triplet energy transfer. In the system: theophylline—alcohol—aliphatic ketone, the reactions involving α-hydroxyalkyl radicals (derived from alcohol) and ketyl radicals (generated by photoreduction of the excited ketone) are even the main reactions.

Acknowledgement

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Experimental

A solution of theophylline (2 g) in 250 ml of alcohol and 250 ml of the corresponding ketone (pairs of solvents are specified in Table 1) was irradiated with UV-light at controlled temperature (25° ± 1 °C) under argon using a Pyrex filtered Hanau Q-400 high-pressure mercury vapour immersion lamp. Progress of the reaction was observed by tlc on silica gel plates (E. Merck, DC-Fertigplatten Kieselgel 60 F_{254}) using a solvent mixture: 2-propanol—$CHCl_3$—acetone—NH_3aq. (4 : 3 : 3 : 1 *v/v*). Irradiation time ranged from 60–80 h.

Excess reagents were removed under reduced pressure on a rotating evaporator and the products were isolated by preparative tlc on silica gel (E. Merck, PSC-Fertigplatten Kieselgel 60 F_{254}, eluent as above) and recrystallized from acetonitrile.

Melting points, the results of elemental analyses, mass spectra, and UV, IR and PMR spectra of the products were in good agreement with those of authentic samples obtained previously[7].

For quantitative yield estimations the evaporated reaction mixture was analyzed by glc on a Pye-Unicam GCV chromatograph using "on column" methylation technique[12] with trimethyl-anilinium hydroxide (*TMAH*, Pierce Eurochemie). Condition of analyses: FID, glass column (2 m × 4 mm ID) filled with 3% SE 30 on Diatomite CQ 100–120 mesh (Pye-Unicam), carrier gas argon (37 ml min^{-1}), injector temperature 270 °C, column temperature 210 °C, detector temperature 250 °C, sensitivity $1.6 \cdot 10^{-10}$ AFS. Calculations were performed with a pre-programmed DP 101 Computing Integrator (Spectra Physics, California).

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