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PHOTOCHEMISTRY OF 4-PYRIMIDINONES IN AQUEOUS SOLUTION. ISOLATION OF REVERSIBLE PHOTOHYDRATES

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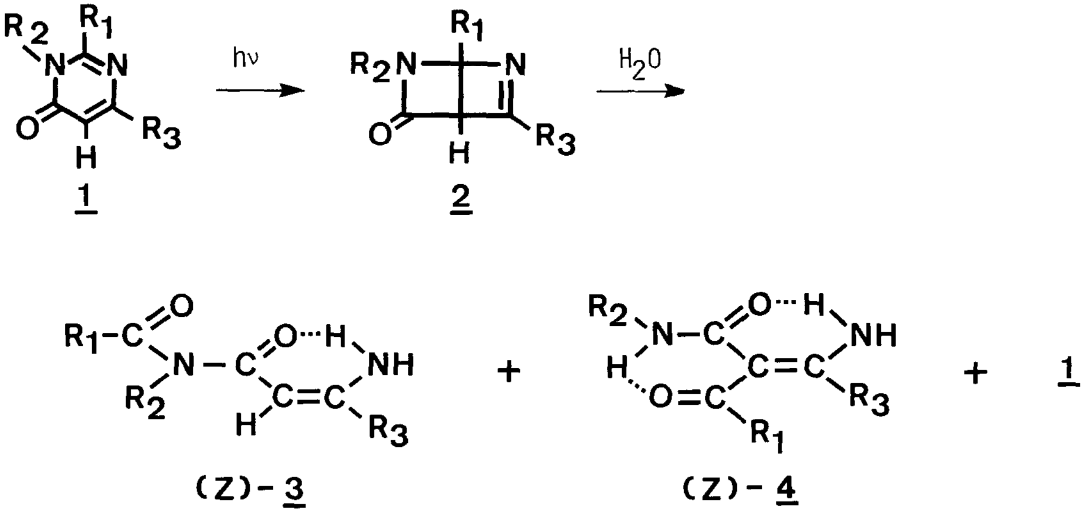
Abstract: Both the irradiation of 4-pyrimidinones (1a-c) and the reaction of the isolated Dewar 4-pyrimidinones (2a-c) in aqueous solution gave the corresponding photohydrates (3a-c) which reverted spontaneously to the starting 1a-c in the dark reaction. The photohydrates were isolated in crystalline form and their physical properties were determined.

Photochemistry of nucleic acids has been extensively studied since Sinsheimer and Hastings reported the photolysis of uracil and uridine in aqueous solution and the thermal reversal of the photoproducts to the original compounds.1) The structures of the photoproducts were assigned as 6-hydroxy-5,6-dihydropyrimidines (photohydrates).2) The photohydrates are known to play important roles in the inactivation and mutation of living organisms by ultraviolet irradiation.3) The photochemistry of 4-pyrimidinones in aqueous solution is of interest since these are model compounds closely related to nucleic acid pyrimidine bases, and isolation of the intermediates may provide insight into the photohydration reactions of the pyrimidine derivatives. With this prospect, we have now undertaken the photochemistry of 4-pyrimidinone (1) in aqueous solution.

When a water-acetonitrile (85:15 V/V) solution of 1a [$\lambda_{max}(H_2O)$ 269 nm (ε 4860) and 225 nm (ε 5850)] was irradiated at 2°C with a 100-W high-pressure mercury lamp through quartz under an argon atmosphere for 7 h, changes occurred in its ^{1}H NMR spectrum which suggests that a mixture of 1a (57%) and photoproduct (3a) (43%) was formed. New signals of 3a in the ^{1}H NMR spectrum ($CDCl_3$) appeared at δ 2.03 (s, 3H), 2.42 (s, 3H), 3.20 (s, 3H), and 5.02 (s, 1H). After irradiation, the intensities of the new signals decreased with the passage of time, while those of the signals in the spectrum of 1a increased. After 12 h, the new signals disappeared completely at 20°C. The result indicated that the photoproduct (3a) reverted spontaneously to the starting 1a in the dark reaction. Attempts to isolate the unstable product (3a) on alumina and Sephadex LH-20 columns were unsuccessful.

The primary photochemical reaction of 4-pyrimidinone (1) is the formation of the Dewar 4-pyrimidinone (2) which undergoes the SN1 and nucleophilic addition reactions.[4)] Recently, we have isolated the Dewar isomer (2) and expected that the photoproduct (3) would be obtained by the reaction of the Dewar isomer (2) with water. The Dewar isomers (2a-c) in aqueous solution gave the mixtures of the major products (3a-c), minor products (4a and 4b), and secondary reaction products (1a-c).



The ratios of the products (1a-c) to (3a-c) varied with the amount of 2a-c, concentration of water, reaction time, and temperature. A variety of conditions were investigated and the following set of conditions led to the isolation of the products (3a-c): A solution of the Dewar isomer (2) (40-150 mg) in 10.0 mL of acetone containing water (10 V/V %) was allowed to stand for 1-2 h at 15-21°C.[5)] The products (3b and 3c) were isolated by crystallization from carbon tetrachloride-pentane. In the case of the reaction of 2a, the product (3a) was separated on a column (150×2.5 cm) of Sephadex LH-20 (180 g of dry gel) with chloroform-hexane (4:1 V/V) as an eluant. The crystalline products (3a-c) and 4-pyrimidinones (1a-c) were obtained in yields of 46-74% and 18-33%, respectively.[6)] The products (3a-c) were single geometrical isomers. The minor products (4a and 4b) could not be isolated under the conditions. The products (3a-c) were the hydrates which were confirmed by the elemental analyses and were identical with the compounds observed in the photolysis of 1 in aqueous solution.

The structure of 3b was deduced from spectral data. The IR spectrum ($CHCl_3$) exhibited a stretching frequency of the primary amino group at 3520 cm^{-1} and two amide carbonyl frequencies at 1660 cm^{-1} and 1630 cm^{-1}. The UV maximum (CH_3CN) at 302 nm (ε 22200) indicated the presence of an enamino ketone moiety. The ^1H NMR spectrum (Me_2SO-d_6) showed signals at δ 1.18 (s, 9H, tert-Bu), 2.26 (s, 3H, CH_3),

Table I. Yields of the Products (3 and 1)

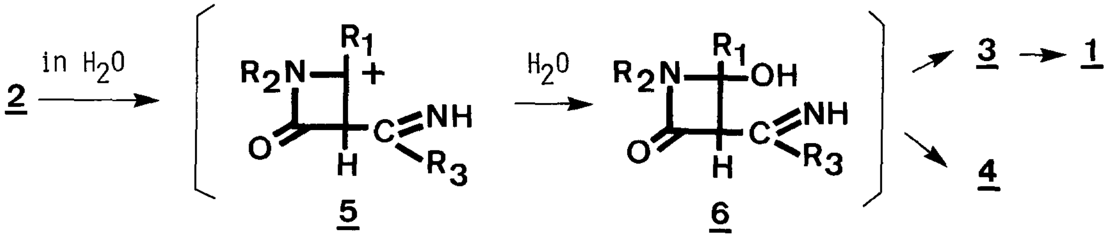
starting material	R_1	R_2	R_3	3 yield (%)	3 mp (°C)	1 yield (%)
2a	CH_3	CH_3	CH_3	46	71-74	33
2b	CH_3	CH_3	t-Bu	74	104-107	18
2c	$-(CH_2)_4-$		t-Bu	65	91-93	32

3.09 (s, 3H, NCH_3), 5.08 (s, 1H, CH), 7.3-7.5 (br, 1H, HNH), and 9.2-9.4 (br, 1H, HNH), and the ^{13}C NMR spectrum ($CDCl_3$) exhibited resonances at δ 25.7 (q), 28.8 (q), 32.2 (q), 36.4 (s), 83.3 (d), 172.7 (s), 172.8 (s), and 175.1 (s). From these data, the structure of 3b was assigned to N-acetyl-N-methyl-3-amino-4,4-dimethyl-2-pentenamide. The ^1H NMR spectrum (δ 9.2-9.4) showed the presence of an intramolecular hydrogen bonding between one of the carbonyl groups and one of the amine hydrogens, which indicated a Z configuration about the C-C double bond of 3b.$^{7)}$ The structures of other hydrates (3a and 3c) were assigned from their spectral data in comparison with those for (Z)-3b.

The hydrates (3a-c) in methanol at 16-23°C reverted to the parent 4-pyrimidinones (1a-c) after 2-7 days in 96-98% yields. The results lead to the conclusion that the isolated imides (3a-c) are the intermediates which regenerate the original compounds after irradiation of 1a-c in aqueous solution.

When the Dewar isomer (2a) in aqueous solution was allowed to stand for 39 h at 16°C, the resulting hydrate (3a) reverted to 1a and the careful separation on a column of alumina gave 1a (63%) and the minor product (4a) (19%). Similarly, the separation of the reaction mixture from 2b gave 1b (79%) and 4b (9%).$^{6)}$ The Dewar isomer (2c) did not give the product corresponding to 4a and 4b. The minor product (4a) was spectroscopically identical with (Z)-N-methyl-2-acetyl-3-amino-crotonamide$^{8)}$ synthesized from the hydrolysis of N-methyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone on alumina. The structure (4b) was assigned from the spectral data in comparison with those for (Z)-4a. The minor products (4a and 4b) are the primary products from 2 because the major products (3a and 3b) reverted quantitatively to the 4-pyrimidinones (1a and 1b) and did not give 4a and 4b.

Irradiation of 1 gives a singlet excited molecule which leads to an electrocyclic reaction to form the Dewar isomer (2). The formation of the products (3 and 4) from the Dewar isomer (2) can be explained by solvolysis to an intermediate carbocation (5), which reacts with water to give the β-hydroxy-β-lactam (6). The cleavage of the C(3)-C(4) bond of 6 gives the major product (3) and the cleavage of the N(1)-C(4) bond gives the minor product (4). The ring-opened water adduct (3) undergoes an intramolecular cyclization to give 1.



Recently, similar ring-opened amine adducts have been reported in the photochemistry of thymidine in aqueous solution containing alkylamines.$^{9)}$ A Dewar intermediate has been assumed to be involved in the formation of a ring-opened enamine in the photolysis of 1,3-dimethyluracil in methanol.$^{10)}$

References and Notes

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5) The thermal isomerization of 2 to 1 was not observed in C_6D_6 at 20°C for 2 h.

6) Satisfactory spectral and analytical data were obtained for each new compound. Complete spectroscopic details will be provided in a later publication.

7) We could not observe the formation of (E)-3b by the direct and the acetone-d_6-sensitized photolysis of (Z)-3b. The E isomer of 3b may be isomerized to the stable Z isomer via the enamine-imine tautomerization when (E)-3b was formed photochemically.

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(b) The configuration of 4a was deduced from that of (Z)-N-methyl-3-amino-2-formylcrotonamide (7). The configuration and two intramolecular hydrogen bonds of 7 were determined by the X-ray crystallographic analysis: Hirokami, S.; Nagata, M.; Yamazaki, T.; Date, T., unpublished results.

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