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# AN APPROACH TO THE MECHANISM OF PHOTOOXIDATION OF BERBERINE UNDER BASIC CONDITIONS

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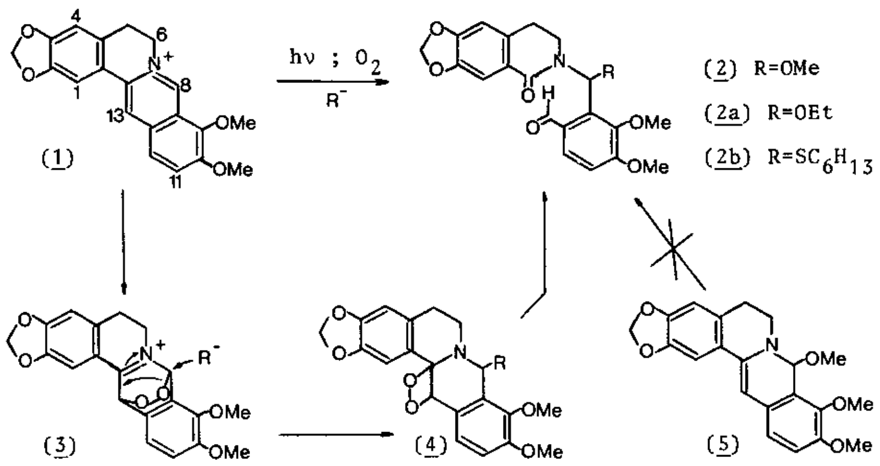
Abstract — The unsensitized photooxidation of berberine (1) catalyzed by basic reagents such as $^-SC_6H_{13}$, $^-N_3$, $Et_3N$, $^-OCH_3$ or $^-OC_2H_5$, in solution, is described. As a possible mechanism, the formation of an initial berberine-oxygen exciplex followed by a nucleophilic attack to intermediate (3) and rearrangement of this compound to dioxetane (4) is proposed taking in consideration the new isolated lactamic aldehyde structures (2a) and (2b) from the bulk of the reaction. The intervention of both singlet oxygen and the dihydroberberine (5) in these reactions is disregarded.

Photooxidation has proved to be a useful tool in organic synthesis[1]. Recent reviews indicate its value and possibilities in the field of terpenes[2], alkaloids[3] and other natural products[4,5]. In function of the substrate structure and the reaction conditions, hydroperoxides, dioxetanes, endoperoxides or their derivatives, can be obtained[6].

The Rose Bengal sensitized photooxygenation of berberine[7] and dihydroberberine[8] gives the corresponding berberinephenolbetaine in good yields. In the absence of any sensitizer the photochemical oxidation of dihydroberberine produces principally berberine[8]. In contrast, berberine (1) does not react in similar unsensitized conditions unless sodium methoxide is present in the bulk of the reaction, and then, the lactamic aldehyde (2) is formed[9] (see Scheme I). The structure of this compound strongly suggests the participation of a dioxetane precursor (compound (4)) probably originating either via formation of singlet oxygen[10] or via another active species that can be transformed into it.

Scheme I. Proposed mechanism of photooxidation of berberine under basic conditions (R represents a nucleophilic species).



In this communication the results of the non sensitized photochemical oxidation of berberine chloride in the presence of different basic conditions, with and without typical quenchers of singlet oxygen, in alcoholic solvents, are presented and discussed. Participation of both dihydroberberine (5) and singlet oxygen as reactive species is disregarded. In contrast, formation of an exciplex berberine-oxygen followed by a nucleophilic displacement is proposed.

Thus the irradiation of a 6 mM methanolic solution of berberine containing 4 times molar excess of either triethylamine, sodium azide, sodium n-hexylmercaptide or sodium methoxide gives reproducible and comparative yields of the lactamic aldehyde (2). However, a new lactamic aldehyde, (2a), having an ethoxy group at the 8-position is obtained if an ethanolic solution is used instead of a methanolic one. In addition, in the presence of fifty fold molar excess of sodium n-hexylmercaptide, compound (2b) was formed together with di-n-hexylsulfide. The reactions were carried out in a 75 ml immersion quartz reactor with a 125 W Medium Pressure Hg lamp (Hanovia) cooled by water, and although they were insensitive to temperature changes between 10° and 38°C, most of them were done at 14°C, under $O_2$ bubbling until total conversion (60-70 min) as observed by tlc. The final solution was evaporated under vacuum and the principal product purified by two consecutive column chromatography separations over silica gel G60 eluted with $CHCl_3$, the first of them under $N_2$ pressure; the yield of the ether crystallized products was 45-55%. Compound (2b), was further purified by preparative tlc. The principal properties of them are given below.

Compound (2).- Identical as previously informed[9].

Compound (2a).- mp 208-210°C; $\nu_{max}^{KBr}$ cm$^{-1}$ : 1710 (ArCHO), 1675 (lactam); $\lambda_{max}^{EtOH}$ nm (log ε) : 234 (4.32), 269 (4.17), 318 (3.74); $^1$H-nmr ($CDCl_3$, TMS) δ : 10.20 (s, 1H, CHO), 7.53 (d, J=8Hz, 1H, H-12), 7.34 (s, 1H, H-1), 7.06 (d, J=8Hz, 1H, H-11), 6.83 (s, 1H, H-4), 6.06 (s, 2H, $OCH_2O$), 5.90 (s, 1H, H-8), 4.02 & 3.95 (2 x s, 6H, 2 x $OCH_3$), 3.00-3.56 (m, 6H, $CH_2O$, $H_2$-6, $H_2$-5), 1.14 (t, J=7Hz, 3H, $CH_3$); m/e (70 eV) : 413 ($M^+$).

Compound (2b).- mp 127-128°C; $\nu_{max}^{KBr}$ cm$^{-1}$ : 1690 (ArCHO), 1660 (lactam), 735 (C-S); $\lambda_{max}^{EtOH}$ nm (log ε) : 264 (3.00), 311 (2.74); $^1$H-nmr ($CDCl_3$, TMS) δ : 10.19 (s, 1H, CHO), 7.55 (s, 1H, H-1), 7.34 & 7.07 (2 x d, J=8Hz, 2H, H-11, H-12), 6.76 (s, 1H, H-4), 6.09 & 6.00 (2 x d, J=6Hz, 2H, $OCH_2O$), 5.93 (s, 1H, H-8), 4.02 & 3.96 (2 x s, 6H, 2 x $OCH_3$), 3.30-3.70 (m, 4H, $H_2$-5, $H_2$-6), 2.95 (t, J=7Hz, 2H, $CH_2$-S), 1.28 (m, 8H, 4 x $CH_2$), 0.91 (t, J=5Hz, 3H, $CH_3$); 2,4-dinitrophenylhydrazone : mp 265.5 - 266.5°C.

Compound (5), 8-methoxydihydroberberine, was prepared by stirring a 6 mM methanolic solution of dry berberine (180 mgr in 75 ml abs. MeOH) containing Na (8 mgr) for 24 h under a $N_2$ atmosphere. After concentration, careful dilution with water (60 ml) and extraction with ether, the organic layer was dried and concentrated providing light yellow plates (160 mg, 89%), mp 125-127°C; $\nu_{max}^{KBr}$ cm$^{-1}$; 1620 and 1600; $\lambda_{max}^{EtOH}$ nm (log ε) : 276 (4.09), 286 sh (4.04), 352 (4.30); $^1$H-nmr ($CDCl_3$, TMS) δ: 7.12 (s, 1H, H-1), 6.87 (s, 2H, H-11, H-12), 6.57 (s, 1H, H-4), 6.21 (s, 1H, H-8), 6.05 (s, 1H, H-13), 5.89 (s, 2H, $OCH_2O$), 3.89 & 3.83 (2 x s, 6H, 2 x $OCH_3$), 3.49 (br t, J=6Hz, 2H, $H_2$-6), 3.00 (s, 3H, 8-$OCH_3$), 2.82 (br t, J=6Hz, 2H, $H_2$-5).

On the basis that compound (2) was obtained by direct photooxidation of berberine, only in the presence of a basic reagent, it was initially thought[9] that a 8-substituted dihydroberberine as compound (5), coming from a nucleophilic attack to the berberine structure could be formed in the first steps of the reaction. Also, it was supposed that this compound could further react with oxygen to produce dioxetane (4), the precursor of compound (2).

In our reaction conditions, singlet oxygen could be formed by an energy transfer process from berberine; but, the fact that neither the conversion rate of berberine (1) or the formation rate of the lactamic aldehyde (2) was affected by the presence of typical quenchers of singlet oxygen, clearly deny its participation in these reactions. As quenchers we used sodium azide and triethylamine ($k_Q$ = 2.1 x $10^6$

1 $mol^{-1}$ $sec^{-1}$)[11] in a molar excess of 5 to 12 times (16 to 48 mM). On the other hand, compound (2) has never been found as a product of reaction of either berberine[7], dihydroberberine[8,12], or their corresponding betaines[13] under singlet oxygen influence.

Participation of compound (5) as an intermediate was also disregarded. We have prepared the 8-methoxydihydroberberine (5). Its unsensitized photochemical conversion in the analogous conditions described for (1) did not produce the expected compound (2) with and without the presence of sodium methoxide. The same occurred when a mixture of (1) and (5) was irradiated in methanol, in the absence of sodium methoxide, disregarding in this way the participation of (5) in any other possible reaction with (1) leading to compound (2).

Although the presence of a nucleophilic species in the bulk of the reaction is essential for the formation of compound (2), there is no direct reaction between the berberine molecule and the nucleophile itself for the structure of compound (2) is not altered by using different basic systems and, in addition, compound (5) is not formed.

From the analysis of all these facts it seems reasonable to consider first the formation of an exciplex berberine-oxygen; such an exciplex could form compound (3), an 8,13-endoperoxide, which in the absence of a base probably goes back to the initial compounds. *Solvolysis reaction of the endoperoxide* (3) catalyzed by each of the chosen basic reagents could in principle explain the formation of dioxetane (4); as we used triethylamine, sodium n-hexylmercaptide and sodium azide —a hard, a soft and a borderline base respectively[14]— different reaction rates could be expected; however, that was not the case. Moreover this type of catalysis should involve a termolecular reaction and so seems improbable.

A direct nucleophilic substitution, $S_N2$ type, at the $C_8$ of intermediate (3) followed by an internal rearrangement to dioxetane (4) as is shown in Scheme I is probably a more adequate interpretation of our results.

It was observed that in all the cases studied only the methoxy group behaves like the active species under the basic concentrations used. That could be explained considering that, although the azide ion $N_3^-$ is a better carbocation-attacking-nucleophile than the methoxy group ($N_+$ : 7.6 vs 7.3)[15], *its nucleophilic constant* ($n_{CH_3I}$) is somewhat lower than that of the methoxy group (5.8 vs 6.3)[16]. The $Et_3N$ is more nucleophilic than the methoxy group ($n_{CH_3I}$ : 6.7 vs 6.3)[16] but it is more difficult to stabilize the ammonium ion that should be formed by attack of this reagent to (3), if the steric effect allows that to occur. The sodium mercaptide is also more nucleophilic[17] than the methoxy group because sulfur is in a lower position than oxygen in the Periodic Table. It seems that in this case, it is just a matter of relative concentrations.

Consistently, the increase of the concentration of sodium n-hexylmercaptide to the order of 0.36 M in the methanolic solution allows competition to be effective between the $^-OCH_3$ and the $^-SC_6H_{13}$ species by the $C_8$ of compound (3). Under this reaction condition compound (2b) was obtained in 15-20% yield. When the reaction was done using sodium ethoxide in ethanol, compound (2a) was isolated in 46% yield.

Thus, it is probable that the photooxidation of berberine in basic medium involves an exciplex between berberine and oxygen in the first steps of the reaction. Participation of both singlet oxygen and 8-methoxydihydroberberine is excluded. Therefore, formation of compound (2) is proposed as coming from a preferential nucleophilic attack of methoxy anion to the 8-position of intermediate (3). Favorable conditions for the presence of an ethoxy or a n-hexylmercaptide anion or potentially any nucleophilic species permit these groups to be incorporated at the 8-position of the lactamic aldehyde which is of considerable importance in the synthesis of other related alkaloid derivatives.

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