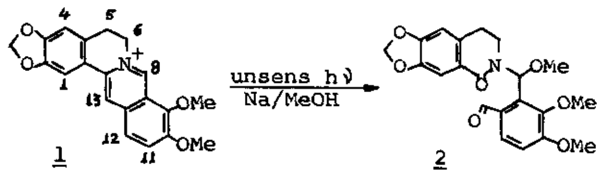
HETEROCYCLES, Vol 16, No 10, 1981

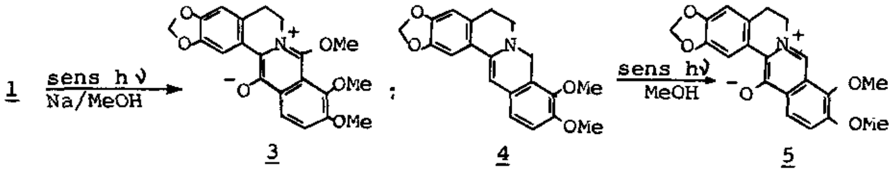
A NEW PRODUCT IN THE PHOTOOXIDATION OF BERBERINE: A LACTAMIC ALDEHYDE

M. Leonor Contreras* and Roberto Rozas
Dept. of Chemistry, Univ. of Santiago of Chile, Casilla 5659,
Santiago-2, Chile

Berberinium chloride (1) unsensitized photooxidation in the presence of sodium methoxide affords the lactamic aldehyde (2) in contrast to the already informed sensitized reaction that furnishes the betaine (3).

Applications of synthetic aspects of organic photochemistry in the natural product field is widely recognized.[1,2] Alkaloids constitute a major and interesting group of compounds of this field in terms of their significant pharmacological activity. Direct and sensitized photochemical transformations of alkaloids, have demonstrated to furnish a wide range of different structures.[3] In particular, sensitized photooxidation of berberinium chloride (1) provides[4] the 5,6-dihydro-13-hydroxy-8,9,10-trimethoxybenzo[g]-1,3-benzodioxolo [5,6-a] quinolizinium hydroxide inner salt (3) a useful intermediate for many berbine derivatives such as phthalideisoquinoline,[5] spirobenzylisoquinoline,[6] 13-hydroxyberbines,[4] 8,14-ethenoberbines[7] and aziridine derivatives.[8]

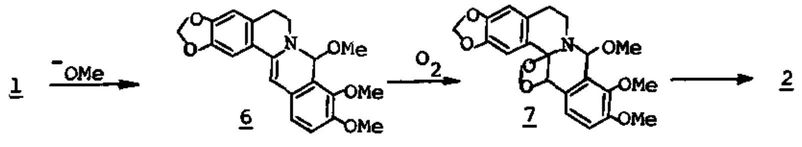




The present communication deals with the direct photochemical oxidation of (1) in the presence of sodium methoxide as a way of finding additional new transformations of this alkaloid.[9] Surprisingly the stable lactamic aldehyde compound (2), that had not been observed before as a photooxidation product of berberine or its derivatives, was obtained in one step.

Irradiations of 6 mM methanolic solution of (1) were made with a 125 W medium pressure Hg lamp immersed in a 75 ml quartz reactor, in the presence of sodium methoxide (10-20mM) and oxygen bubbling at 14°. Complete transformation of the starting material was observed after 75 min. In the absence of sodium no reaction took place.[10] The yellow final solution[11] was evaporated under vacuum and then purified over a silica column eluted with $CHCl_3$. Ether crystallization of the obtained yellow solid afforded 76 mg (45% yield) of the white compound (2), mp 138.5-140°; ν_{max}^{KBr} cm^{-1}: 1705 (ArCHO), 1678 (lactam); λ_{max}^{MeOH} nm(log ε): 233(4.34), 269(4.17), 318(3.75); ^{1}H-nmr ($CDCl_3$; TMS) δ: 10.33(s, 1H, CHO), 7.52(d, J=8, 1H, H-12), 7.29 (s, 1H, H-1), 7.04(d, J=8, 1H, H-11), 6.80(s, 1H, H-4), 6.03(s, 2H, OCH_2O), 5.88 (s, 1H, H-8), 3.94 & 3.99 (2 x s, 6H, 2 x OCH_3), 3.2-3.6 (m, 4H, H_2-5 & H_2-6), 2.96(s, 3H, N-C-OCH_3); ^{13}C-nmr ($CDCl_3$; TMS) δ: 189.7(Ar-CHO), 167.4(Ar-CO-N), 155.6, 152.5, 147.3, 145.1, 138.8, 130.8, 128.9, 126.1, 119.1, 113.8, 111.1, 110.1 (aromatic), 102.1(O-C-O), 85.5(N-C-OCH_3), 60.4 & 56.3 (Ar-OCH_3), 49.8(OCH_3), 41.4 (CH_2N), 31.0($ArCH_2$); m/e (40 eV): 399 (M^+). This compound afforded the 2,4-dinitrophenylhydrazone, mp 212-215°.

The sensitized photooxidation of berberine (1) with sodium methoxide[4] and dihydroberberine (4) without it[12] produces the corresponding berberinephenolbetaines (3) and (5). The direct reaction of (4) in the absence of sodium methoxide has proved to furnish mostly compound (1).[12] However, according to our results, none of these tendences seem to occur in the direct photooxidation of (1). As there is no reaction in the absence of sodium, it is presumed that the first step could be the methoxy nucleophilic attack at the more reactive position 8 of berberine[13] to generate (6) and then formation of the lactamic aldehyde (2) *via* the dioxetane (7) generated by the reaction between oxygen and the enamine (6).[15]



Under direct and Rose Bengal sensitized conditions, photooxidation of the berberinephenolbetaine (3) produces[6] three compounds: a spirobenzylisoquinoline, an imide-ester and methoxyberberal, the first two compounds by an initial attack of oxygen at 8- and 14- positions of (3) and the last one by attack of oxygen at the 13- and 14- positions of (3).[6] The direct reaction afforded the lower yields of products, specially in the formation of methoxyberberal which decreased from a 10% yield in the sensitized reaction to 1% in the direct one. That means that the 13- and 14- positions of (3) are much less attacked by oxygen under direct photooxidation conditions.

The fact that compound (2) has a carbonyl group at the 13- and 14- initial positions of berberine lets dioxetane (7) as its most probable precursor[16] and as a strong indication that the oxygen attack to those positions of (6) has been favored under unsensitized conditions of reaction even in the case of the primary formation of a zwitterionic species,[16] in contrast with the unsensitized reaction tendences showed by (3).[6] These observations and the different reaction product distribution seem to demonstrate that direct and sensitized photooxidation of berberine proceed through different pathways.

From a synthetical point of view, photochemical transformations of berberine allow different kind of cyclic structures to be obtained.[8] Thus, photocleavage of the C-ring of berberine derivatives yield compounds like imide-methyl ketones (22%),[8] imide-esters (10%)[6] or imide-aldehydes (3%).[12] By direct photooxidation of berberine in the presence of sodium methoxide we have extended this kind of reaction to the obtention of a lactamic aldehyde (45%) in one step from berberinium chloride. This compound represents a controlled[16] berberine oxidation product, which due to its particular structure could be a useful synthon for a number of alkaloid derivatives.

ACKNOWLEDGEMENTS: The authors wish to thank the Phytochemistry Group of our University for their kind donation of the berberinium chloride used in this study and to DICYT for finnancial support. We are deeply obliged to Prof. R. C. Cookson, Chem. Dept., Southampton Univ., for making possible the determination of the nmr and mass spectras and his encouraging suggestions.

REFERENCES:

1. H. A. J. Carless, Chem. Brit., 1980, 16, 456.

2. J. Kossanyi, Pure Appl. Chem., 1979, 51, 181.

3. S. P. Singh, V. I. Stenberg and S. Parmar, Chem. Rev., 1980, 80, (3) 269.

4. M. Hanaoka, C. Mukai and Y. Arata, Heterocycles, 1977, 6, 895.

5. J. L. Moniot and M. Shamma, J. Am. Chem. Soc., 1976, 98, 6714.

6. M. Hanaoka and C. Mukai, Heterocycles, 1977, 6, 1981.

7. M. Hanaoka, A. Wada, S. Yasuda, C. Mukai and T. Imanishi, Heterocycles, 1979, 12, 511.

8. M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima and T. Imanishi, Tet. Lett., 1979, 39, 3749.

9. The berberinium chloride used in this study was obtained from Berberis Buxifolia occurring at the South of Chile.

10. The reaction was monitored by t. l. c. (silica gel 60 F254 on Al and $CHCl_3$:EtOH = 87.5:12.5; Dragendorff reagent).

11. Similar results were obtained using ethanol or isopropanol-methanol (3:1) mixture, the transformation being faster in ethanol (50 min).

12. Y. Kondo, J. Imai and H. Inoue, J. Chem. Soc., Perkin I, 1980, 911.

13. It is known that berberine reacts at the 8- position with nucleophilic species, in the dark, to produce 7,8-dihydro-8-substituted berberines.[14]

14. M. Shamma and J. L. Moniot, 'Isoquinoline Alkaloids Research 1972-1977', Plenum Press, New York and London, 1978, 19, 234-5.

15. M. V. George and V. Bhat, Chem. Rev., 1979, 79, (5), 447.

16. A. A. Primer, ibid., 359.

17. Permanganate oxidation of 8-substituted compounds, with similar structures to (6), in the dark produces a lactamic acid[14] with the same carbon skeleton as compound (2).

Received, 16th June, 1981