Tetrahedron Letters,Vol.25,No.37,pp 4161-4162,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

BIOMIMETIC SYNTHESIS OF NEODIHYDROTHEBAINE AND BRACTAZONINE FROM THEBAINE

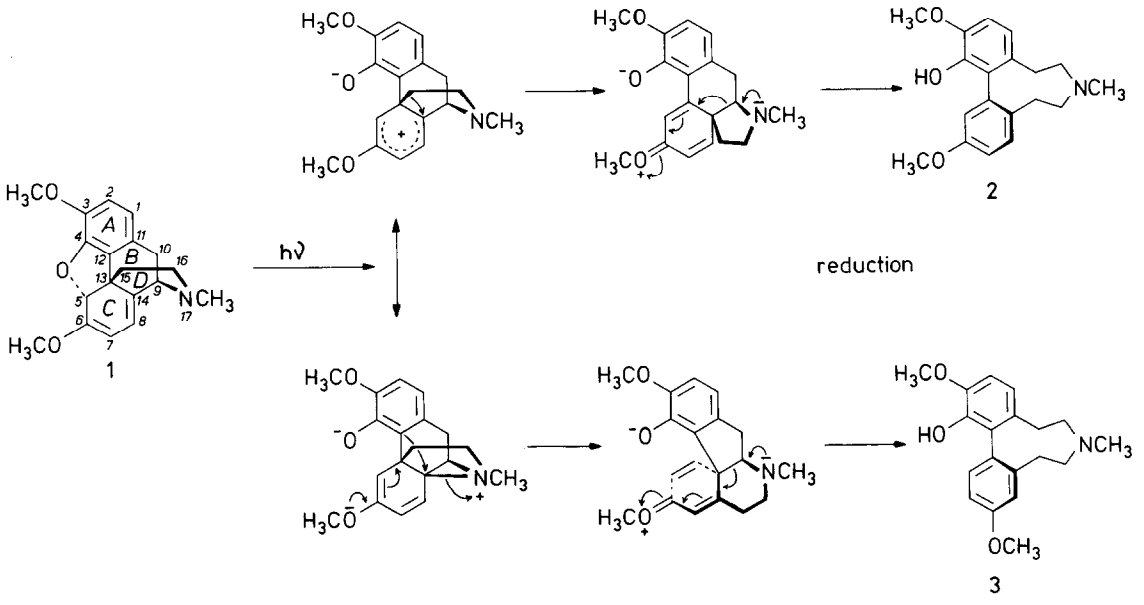
Hubert G. Theuns*[@], Guus F. La Vos[#], Michael C. ten Noever de Brauw[#] and Cornelis A. Salemink[@]
[@]Organic Chemical Laboratory, State University of Utrecht, Utrecht, The Netherlands
[#]Central Institute for Nutrition and Food Research, Zeist, The Netherlands

Abstract: Photochemical irradiation of the morphinan alkaloid thebaine 1, followed by reduction, affords the dibenz[d,f]azonine alkaloids neodihydrothebaine 2 and bractazonine 3, in a sequence paralleling the proposed biosynthesis of these alkaloids in Papaver bracteatum.

Recently, we reported the finding of two unusual alkaloids in *Papaver bracteatum* Lindl., both belonging to the class of the dibenz[*d,f*]azonine alkaloids.[1] Their biogenesis from thebaine 1, the major alkaloid of this species, is considered probable. Here we wish to report on a biomimetic synthesis of these alkaloids, neodihydrothebaine 2 and bractazonine 3, from thebaine 1.

The biogenesis of bractazonine supposedly requires the coercion of the nitrogen lone pair to create a quaternary aziridinium ion,[1] in which aryl migration is said to be favored.[2] For such nitrogen participation that lone pair must be available. Furthermore, in the known neospirine rearrangement of thebaine, triggered by the action of a (Lewis) acid, like MgI_2[3] or CF_3COOH,[4] only 2 is observed upon reduction as a reaction product. The ring A aryl group is present as an undissociated phenolic group, which obviously has a low migratory aptitude. If,

Scheme I: Proposed mechanisms for the photo rearrangements of thebaine



on the other hand, the ring A aryl group would be present as a phenolate anion, such group would be expected to have a stronger 'nucleophilic push' to rearrange to the erythrinadienone intermediate, which is thought to yield bractazonine 3. Thebaine, however, is a stable compound under alkaline conditions.

In our hands, photochemical irradiation of thebaine in MeOH containing NaOH and $NaBH_4$ for 2.5 h using a 125-W high pressure mercury lamp in a quartz immersion apparatus, while a stream of N_2 was passed through the solution, provided an effective means for opening of the C-4/C-5 oxygen bridge.[5] Chromatographic separation of the products afforded neopinone dimethyl acetal[6,7] (yield 37%; identified by ^{1}H- and ^{13}C-NMR[6,8], and by comparison of its mass spectrum with that of neopine methyl ether[9]), and an inseparable mixture[1] of neodihydrothebaine 2 and bractazonine 3 (4:1; yield 19%), next to unreacted thebaine (40%). In capillary GC/MS[1] the identities of 2 and 3 were confirmed. Neopinone dimethyl acetal was already known to result from photochemical addition of the solvent methanol to the 6,7-double bond of the diene system of thebaine.[7] The irradiation is essential for the formation of the dibenz[*d,f*]azonines in this reaction: without irradiation pure thebaine was recovered. In the absence of $NaBH_4$ only neopinone dimethyl acetal and thebaine were detected in GLC. Upon subsequent reduction also both dibenz[*d,f*]azonines 2 and 3 were obtained in yields comparable to those of the *in situ* reduction procedure.

The reaction sequence described here mimics the biogenesis of the dibenz[*d,f*]azonine alkaloids neodihydrothebaine 2 and bractazonine 3 from thebaine 1. Moreover, it is shown that the neospirine rearrangement may proceed under alkaline conditions as well.

Acknowledgement — Thanks are due to Ir.E.Buurman, Diosynth B.V., Apeldoorn, The Netherlands, for a generous supply of thebaine, to Mr.A.V.E.George, for recording ^{1}H-NMR, to Dr.U.Weiss, National Institute of Arthritis and Metabolic Diseases, National Institute of Health, Bethesda, Maryland, U.S.A., for an authentic sample of neopine methyl ether, and to Prof.Dr.H.J.T.Bos, for valuable discussions. This work forms part of the thesis by H.G.Theuns (in preparation).

References and Notes

(1) H.G.Theuns, H.B.M.Lenting, C.A.Salemink, H.Tanaka, M.Shibata, K.Ito and R.J.J.Ch.Lousberg, *Phytochemistry* 23 (1984), 1157.

(2) S.M.Kupchan and C.-k.Kim, *J.Amer.Chem.Soc.* 97 (1975), 5623.

(3) K.W.Bentley, *J.Amer.Chem.Soc.* 89 (1967), 2464.

(4) R.T.Channon, G.W.Kirby and S.R.Massey, *J.Chem.Soc. (D)* (1969), 92.

(5) Photo rearrangements are proposed to operate in the biogenesis of certain alkaloids; See, for example: S.Fazal Hussain, M.Tariq Siddiqui, G.ManiKumar and M.Shamma, *Tetrahedron Lett.* 21 (1980), 723.

(6) W.Fleischhacker and H.Markut, *Monatsh.Chem.* 102 (1971), 569.

(7) W.G.Dauben, C.P.Baskin and H.C.H.A.van Riel, *J.Org.Chem.* 44 (1979), 1567.

(8) H.G.Theuns, R.H.A.M.Janssen, H.W.A.Biessels and C.A.Salemink, *Org.Magn.Res.* (in press).

(9) L.F.Small, *J.Org.Chem.* 20 (1955), 953. Neopinone dimethyl acetal: GC/MS *m/z* (relative intensity) 344(22),343(100),329(10),328(50),312(21),268(18),255(33),254(84),226(12),225(43). Neopine methyl ether: GC/MS *m/z* (relative intensity) 314(22),313(100),298(21),282(12),255 (21),254(64),225(13),42(10).

(Received in UK 4 July 1984)