Tetrahedron Letters,Vol.30,No.51,pp 7161-7164,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

A NOVEL RING SYSTEM ARISING FROM INTRAMOLECULAR OXIDATIVE CYCLIZATION OF 8-(4-PENTENYL)DIHYDROBERBERINE

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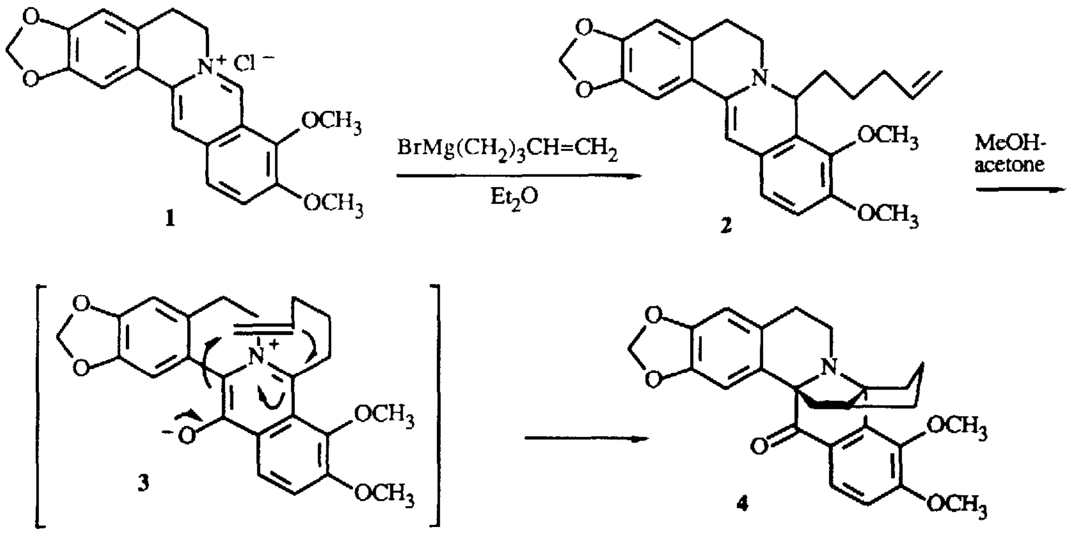
Abstract: An unusual oxidative cyclization reaction was observed in the course of studies on the synthesis of berberine linked to oligonucleotides at the 8-position. The novel ring structure of the oxidative cyclization product was confirmed using X-ray crystallography.

Our laboratory is investigating general methods for the conjugation of berberine alkaloids to oligonucleotides. Our approach to the development of a general method for attaching terminally hydroxylated polymethylene linker chains of various lengths to the 8-position of berberine involves first addition of a Grignard reagent bearing a terminal double bond, followed by hydroboration-oxidation of the latter functionality to yield an 8-alkyldihydroberberine with a terminally hydroxylated side chain.



Scheme 1

Reaction of berberine chloride (**1**, Scheme 1) with the Grignard reagent prepared from 5-bromo-1-pentene gave the expected pentenyldihydroberberine **2** in 76-94% crude yield.[1] However, the attempted purification of the crude product by recrystallization from methanol-acetone resulted in the formation of a new compound in 26% yield, with respect to berberine.[2] The same transformation was observed upon attempted chromatography of the crude product on silica gel (5% yield).

Spectral data strongly suggested that the new compound was structure **4**. ^{1}H-NMR showed that the latter compound had no resonances between δ 3.92 and 5.92; *i.e.*, the resonances of 8-H, 13-H and the three terminal olefin protons of **2** were absent from the spectrum of **4**. The 12-H had shifted from δ 6.73 in **2** to 7.80 in **4**, and there was a net loss of two protons relative to **2**. The exact mass measurement showed that the gain of 14 mass units relative to **2** was due to the gain of one oxygen atom and the loss of two hydrogen atoms. IR (1676 cm^{-1}) and ^{13}C-NMR data (δ 199) established the presence of an α,β-unsaturated ketone.

This proposed structure was confirmed by X-ray crystallography (Figure 1). Compound **4** ($C_{25}H_{25}NO_5$), crystallized from chloroform-ethyl acetate in the monoclinic space group $P2_1/n$ with $a = 9.4418(7)$, $b = 7.853(2)$, $c = 27.005(3)$ Å, $\beta = 92.922(7)^\circ$, $Z = 4$. 2873 unique reflections were collected on an Enraf-Nodius diffractometer using monochromatic Mo$K\alpha$ ($\lambda = 0.71073$ Å) radiation and the $\omega/2\theta$ scan technique. The raw data was corrected for polarization effects. 2007 reflections were considered to be observed, $I>3\sigma(I)$. The structure was solved by direct methods using SHELX, and all calculations were performed on a VAX computer using SDP/VAX.[3] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in calculated positions. Full matrix least squares refinement of 280 parameters led to an R value of 0.041 and an R_w value of 0.052 (using the weighing scheme defined by Killean and Lawrence).[4]

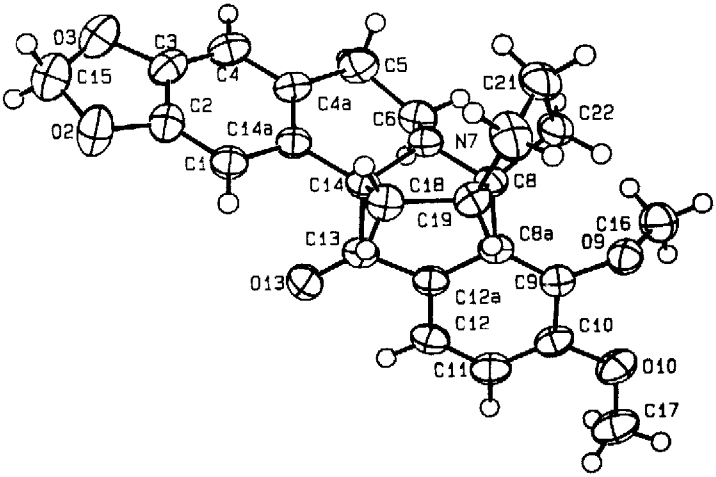
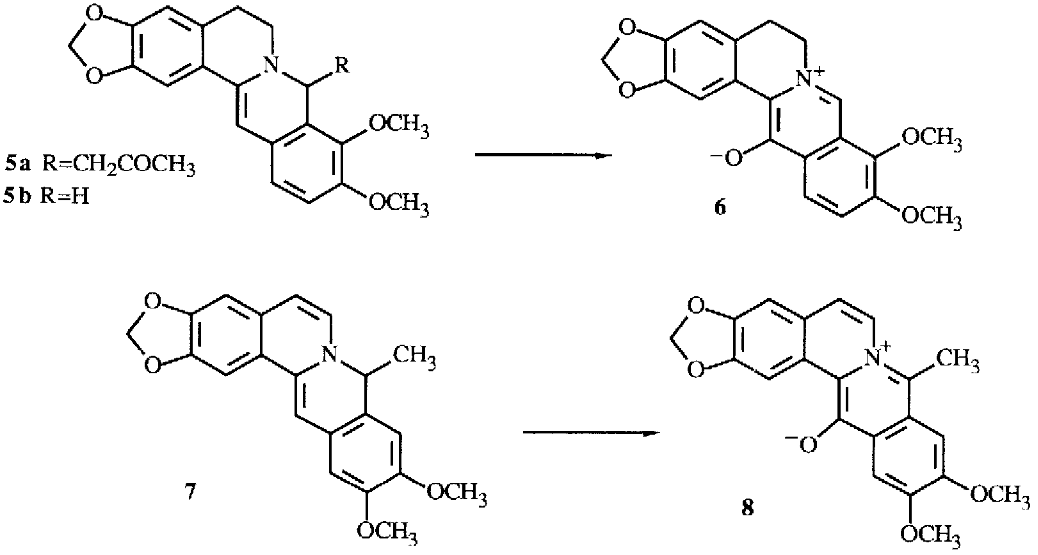


Figure 1 ORTEP plot of **4**

Of the mechanisms considered for this transformation, the most plausible involves a concerted, intramolecular 1,3-dipolar cycloaddition of the postulated phenolbetaine intermediate **3** (Scheme 1). The existence of a phenolbetaine intermediate is based on the fact that phenolbetaines of the protoberberine alkaloids have been synthesized from dihydroberberines in numerous ways. Berberine phenolbetaine (**6**, Scheme 2) has been prepared by oxidation of 8-

acetonyldihydroberberine (**5a**) with potassium permanganate or osmium tetroxide,[5] as well as by *m*-chloroperbenzoic acid oxidation [6] or by dye-sensitized photo-oxidation of dihydroberberine (**5b**).[7] In addition, coralynephenolbetaine (**8**) has been prepared by refluxing an ethanolic solution of dihydrocoralyne (**7**, a 5,6-dehydro analog of dihydroberberine) in the dark under aerated conditions. This latter example points to the possibility of the formation of intermediate **3** from **2** when the latter is dissolved in refluxing methanol during the attempted recrystallization process.

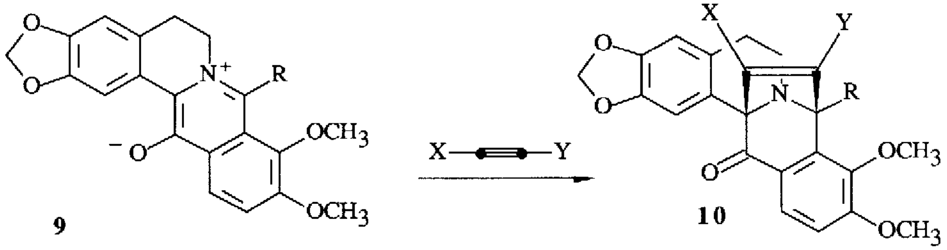


Scheme 2

The synthesis of five-membered heterocycles *via* the "1,3-dipolar cycloaddition" of a "heteroallyl anion" to a multiple bond system has been reviewed by Huisgen,[8] who has proposed a concerted mechanism for such transformations. The 1,3-dipolar cycloadditions of *N*-substituted 3-oxidopyridiniumbetaines to various alkenes bearing an electron-withdrawing substituent have been investigated by Katritzky *et al.* [9] These studies suggested a concerted mechanism driven by the donation of electrons from the betaine to the olefin, as applied in Scheme 1. Hanaoka *et al.*[10] have reported the reaction of the berberinephenolbetaines **9a**, **9b** and **9c** with various alkynes bearing at least one electron-withdrawing substituent to give a series of bridged 1,3-dipolar cycloadducts **10a, 10b** and **10c** (Scheme 3). In contrast to the reports of Katritzky and Hanaoka, the present work demonstrates the possibility of an analogous 1,3-dipolar cycloaddition involving a dipolarophile which contains no electron-withdrawing substituent.

In summary, we now report the formation of a novel ring system whose structure has been confirmed by X-ray crystallography. This transformation, which involves a serendipitously generated phenolbetaine intermediate, appears to be the first intramolecular 1,3-dipolar cycloaddition reaction involving a protoberberine.

Acknowledgement: This research was supported by NIH Grant AI25712.



9

10

a **R= OCH_3**
b **R= H**
c **$R=CH_2COCH_3$**

Scheme 3

References and Notes

1. mp 72-80 °C; IR (KBr) 3421, 3144, 3077, 2935, 2906, 2827, 2364, 1641, 1620, 1595, 1551, 1487, 1449, 1415, 1383, 1345, 1283, 1233, 1204, 1171, 1153, 1131, 1110, 1073, 1030, 998, 970, 937, 868, 852, 825, 791, 772 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$) δ 7.14 (s, 1 H), 6.73 (s, 2 H), 6.59 (s, 1 H), 5.94 (s, 2 H), 5.80 (s, 1 H), 5.69 (m, 1 H), 4.88 (m, 2 H), 4.72 (t, J = 6.0 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.48 (m, 1 H), 3.26 (m, 1 H), 2.83 (m, 2 H), 1.92 (m, 2 H), 1.69 (m, 2 H), 1.36 (m, 2 H). High resolution EIMS, calcd for $C_{25}H_{27}NO_4$: *m/e* 405.1940. Found: *m/e* 405.1935.
2. mp 244.5-245.5 °C; IR (KBr) 3002, 2940, 2864, 2838, 2794, 1676, 1654, 1648, 1582, 1506, 1482, 1434, 1380, 1337, 1309, 1270, 1257, 1237, 1199, 1184, 1163,1126, 1116, 1079, 1069, 1058, 1041, 1022, 1002, 983, 958, 939, 912, 896, 860, 824, 805, 792, 776, 762, 649 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 8.7 Hz, 1 H), 6.90 (s, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 6.55 (s, 1 H), 5.92(d, J = 2.7 Hz, 2 H), 3.92 (s, 3 H), 3.78 (s, 3 H), 2.88 (m, 3 H), 2.53 (m, 5 H), 2.06 (m, 3 H), 1.80 (m, 2 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 199.01, 158.67, 146.45, 145.27, 145.27, 137.64, 129.53, 127.47, 125.07, 125.07, 109.71, 109.07, 108.07, 107.56, 100.66, 92.55, 74.53, 61.18, 55.78, 51.86, 41.98, 40.15, 33.79, 32.36, 30.11, 25.89. .High resolution EIMS, calcd for $C_{25}H_{25}NO_5$: *m/e* 419.1733. Found: *m/e* 419.1730. Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.19; H, 6.07; N, 3.27.
3. B.A. Frenz, "The Enraf-Nodius CAD 4 SDP--A Real-time System for Concurrent X-Ray Data Collection and Crystal Structure Determination," in *Computing in Crystallography*, H. Schenk, R. Olthof-Hazelkamp, H. vanKonigsveld, and G.C. Bassii, Eds., Delft University Press. Delft, Holland, 1978, pp 64-71.
4. R.C.G. Killean, J.L. Lawrence, *Acta. Crys., B* **1969**, *25*, 1750.
5. J. Iwasa, S. Naruto, *J. Pharm. Soc. Jap.* **1966**, *86*, 534 ; Chem. Abstr. **1966**, *65*, 12247b.
6. M. Hanaoaka, C. Mukai, K. Nagami, K. Okajima, S. Yasuda, *Chem. Pharm. Bull.* **1984**, *32*, 2230.
7. Y. Kondo, J. Imai, H. Inoue, *J. Chem. Soc., Perkin Trans.. I* **1980,** 911.
8. R. Huisgen, J. Org. Chem **1976**, *41*, 403.
9. N. Dennis, A.R. Katritzky, Y. Takeuchi, *Angew. Chem. Int. Ed. Eng.* **1976**, *15*, 1.
10. M. Hanaoka, A. Wada, S. Yassuda, C. Mukai, T. Imanishi, *Heterocycles* **1979**, *12*, 511.

(Received in USA 1 September 1989)