Tetrahedron Letters, Vol.22, No.33, pp 3131 - 3134, 1981
Printed in Great Britain

0040-4039/81/333131-04$02.00/0

AN EFFICIENT CONVERSION OF BERBERINE INTO A RHOEADINE VIA AN INDENOBENZAZEPINE

Natesan Murugesan, Gábor Blaskó,[1] Robert D. Minard and Maurice Shamma*,

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802, U.S.A.

Treatment of ketoaziridine 4 with aqueous formaldehyde gives the unusual bridged indenobenzazepine derivative 6 whose reduction with sodium cyanoborohydride produces trans ketol 8. In the presence of hydrochloric acid, 8 undergoes irreversible conversion to the more stable cis ketol 10. Periodate oxidation of 8 supplies γ-lactone 11. $NaBH_4$ reduction of 11 followed by acid treatment affords δ-lactone 12 which upon reduction and O-methylation furnishes cis rhoeadine analog 14.

Current developments in the chemistry of berbinoids have centered largely upon the chemistry of berberinephenolbetaine (2)[2] and 8-methoxyberberinephenolbetaine (3).[3] One of the more interesting synthetic routes to the spirobenzylisoquinolines rests upon the existence of a photoequilibrium between berberinephenolbetaine (2), readily available from berberine (1), and the isolable ketoaziridine 4. Regioselective cleavage of the benzylic N-7 to C-8 bond of 4 upon treatment with ethyl chloroformate in refluxing benzene led to the spirobenzylisoquinoline 5.[4] We became interested, therefore, in the selective fission of the alternate benzylic N-7 to C-14 linkage of 4 as a possible route to the indenobenzazepines and the rhoeadines.

Irradiation with sunlight for a period of 6 h of a methanolic solution of berberinephenolbetaine (2) containing aqueous formaldehyde and a little rose bengal under nitrogen supplied, through the intermediacy of the ketoaziridine 4, a 60% yield of the unusual bridged indenobenzazepine derivative 6, $C_{21}H_{19}NO_6$, mp 223-224° C (MeOH-$CHCl_3$). Species 6 may also be represented by conformational expression 6a in which the seven membered ring exists in a stable chair form. Alternatively, treatment of a methanolic solution of 4 with aqueous formaldehyde at room temperature for 6 h resulted in formation of 6 in 90% yield. The nmr spectrum of the bridged intermediate 6 shows a characteristic H-8 singlet at δ4.80, while the methylene protons of the OCH_2N bridge appear as an AB quartet at δ4.17 and 4.93, J_{gem} 7 Hz.

The alternate structure 7 for the product of the formaldehyde reaction was ruled out since it would involve a highly strained system incorporating two trans-fused five membered rings. An indication of the more stable arrangement represented by stereo expression 6a for the bridged compound is the fact that actual recovery of the melt following heating to slightly above 224° C of compound 6 showed that it still consisted almost exclusively of unchanged material.

Reduction of the bridged indenobenzazepine derivative 6 with sodium cyanoborohydride at pH ≈3 in aqueous methanol gave a near quantitative yield of ketol 8, $C_{21}H_{21}NO_6$, mp 182-183° C (EtOH), whose nmr spectrum shows characteristic H-1 and H-8 singlets at δ7.17 and 4.40, respectively. Alternatively, the conversion of 6 to 8 could be realized with sodium cyanoborohydride in the presence of dry hydrogen chloride dissolved in either dry methanol or methylene chloride. It

follows that 8 must have the B/C trans fused stereochemistry indicated, corresponding to that prevailing in the racemic bridged intermediate 6.

The O-acetyl derivative 8a, $C_{23}H_{23}NO_7$, mp 186-187° C (MeOH), formed by treatment of 8 with acetic anhydride in pyridine at room temperature overnight, exhibits an nmr spectrum which includes an O-acetyl singlet at δ2.00.

The trans ketol 8 undergoes an irreversible conversion to the thermodynamically more stable cis ketol 10, $C_{21}H_{21}NO_6$, mp 192-193° C (EtOH), when treated with aqueous hydrochloric acid at room temperature. The reaction intermediate must be the resonance stabilized cation 9. The nmr spectrum of cis ketol 10 includes H-1 and H-8 singlets at δ7.30 and 4.59, respectively. The material acetylates slowly over a period of several days to furnish O-acetyl derivative 10a, $C_{23}H_{23}NO_7$, mp 178-181° C (MeOH), whose nmr spectrum shows O-acetyl and H-1 singlets at δ2.21 and 7.33, respectively.

Oxidative cleavage of the trans ketol 8 using sodium metaperiodate in dilute hydrochloric acid and methanol supplied the γ-lactone 11, $C_{21}H_{19}NO_6$, mp 179-180° C (EtOH), in 50% yield. This lactone is colorless in neutral solution, but a yellow color develops in acid due to cleavage of the lactone ring accompanied by iminium ion formation.

The remaining steps in the synthesis follow well established precedents.[5] Reduction of 11 with methanolic sodium borohydride containing a little hydrochloric acid generated a crude product which was refluxed for one hour with dilute hydrochloric acid to furnish in 82% yield the amorphous cis δ-lactone 12, $C_{21}H_{21}NO_6$. Dibal in toluene reduction of 12 at -10° C supplied as expected the amorphous hemiacetal 13 (94%), $C_{21}H_{23}NO_6$. O-Methylation with methyl orthoformate then gave rise to the desired rhoeadine analog 14, $C_{22}H_{25}NO_6$, in 90% yield, mp 160-162° C (MeOH).[6]

The present sequence represents a simple and efficient transformation of a protoberberinium salt into a cis fused rhoeadine, thus supplying a facile entry to the non-natural rhoeadines substituted at C-10,11 rather than at the more usual C-12,13 sites. Almost as importantly, we have here a route to indenobenzazepine derivatives of known stereochemistry, such as 8 and 10, which incorporate a ketone at C-13 and a tertiary alcohol at C-14.

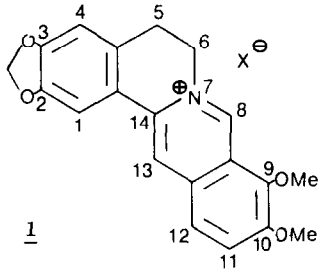
Physical and Spectral Data[7]

Bridged Intermediate 6: λmax 232, 292 nm (log ε 3.94, 3.83); νmax 1710 cm^{-1}; nmr (60 MHz) δ3.93 (6H, s, 2xOCH_3), 4.17 and 4.93 (2H, ABq, J 7 Hz, OCH_2N), 4.80 (1H, s, H-8), 5.87 (2H, s, OCH_2O), 6.62 (1H, s, H-4), 7.03 (1H, d, J 8 Hz, H-11), 7.05 (1H, s, H-1), 7.61 (1H, d, J 8 Hz, H-12); ms m/e 381 (M^+, 54), 353 (100), 352 (63), 324 (50), 297 (52), 148 (20); R_f 0.72.

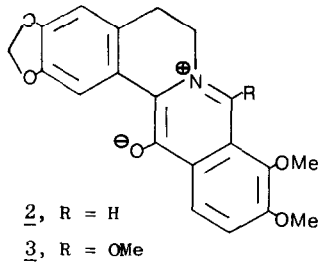
trans Ketol 8: λmax 232, 292 nm (log ε 4.04, 3.95); νmax 1705, 3500 cm^{-1}; nmr (360 MHz) δ2.79 (3H, s, NCH_3), 3.84 (3H, s, 9-OCH_3), 3.97 (3H, s, 10-OCH_3), 4.41 (1H, s, H-8), 5.89 and 5.91 (2H, ABq, J 1.5 Hz, OCH_2O), 6.67 (1H, s, H-4), 7.09 (1H, d, J 8.5 Hz, H-11), 7.17 (1H, s, H-1), 7.71 (1H, d, J 8 Hz, H-12); ms m/e 383 (M^+, 49), 365 (91), 349 (55), 324 (100), 190 (54), 177 (93), 176 (80), 165 (59), 149 (47); R_f 0.49.

trans Acetate 8a: νmax 1705, 1760 cm^{-1}, nmr (360 MHz) δ2.00 (3H, s, CH_3COO), 2.85 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.98 (1H, s, H-8), 5.92 and 5.94 (2H, q, J 1.2 Hz, OCH_2O), 6.65 (1H, s, H-4), 7.06 (1H, d, J 8.5 Hz, H-11), 7.64 (1H, s, H-1), 7.68 (1H, d, J 8.5 Hz, H-12); ms m/e 425 (M^+, 3), 365 (100), 349 (33), 334 (39), 177 (50); R_f 0.71.

cis Ketol 10: λmax 237, 291 nm (log ε 4.12, 4.15); νmax 1705, 3540 cm^{-1}; nmr (360 MHz) δ2.65 (3H, s, NCH_3), 3.93 (3H, s, 9-OCH_3), 4.01 (3H, s, 10-OCH_3), 4.59 (1H, s, H-8), 5.93 and 5.95 (2H, ABq, J 1.5 Hz, OCH_2O), 6.56 (1H, s, H-4), 7.09 (1H, d, J 8.2 Hz, H-11), 7.30 (1H, s, H-1), 7.65

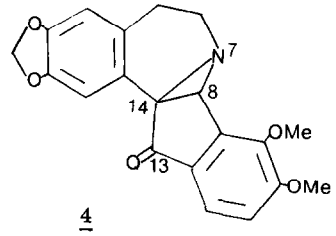


1

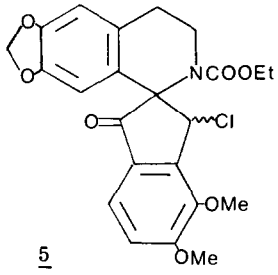


2, R = H

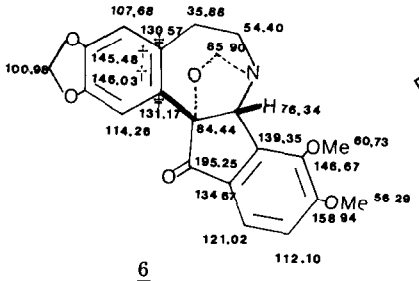
3, R = OMe



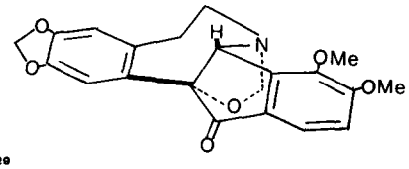
4



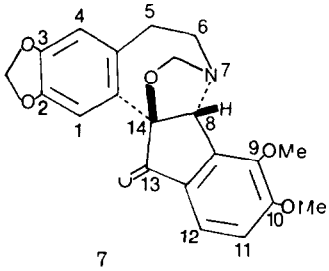
5



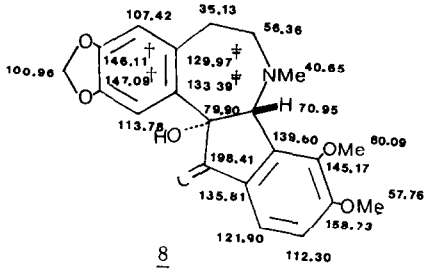
6



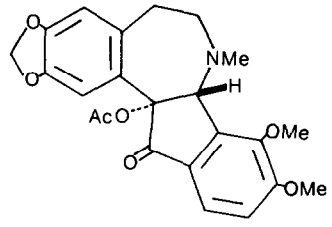
6a



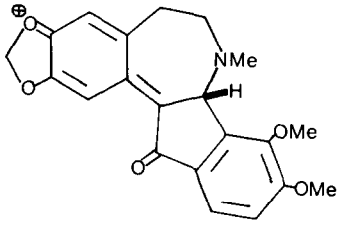
7



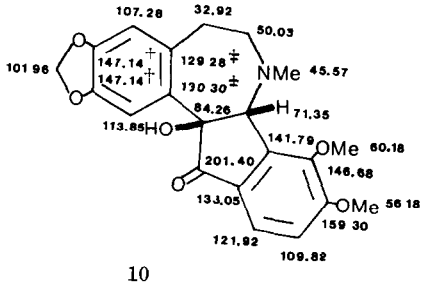
8



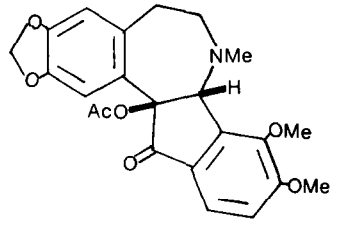
8a



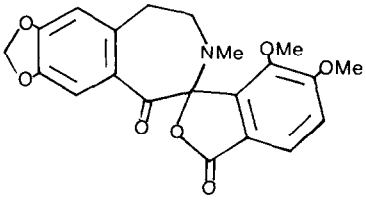
9



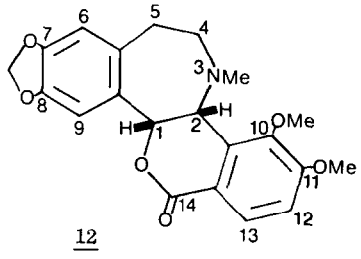
10



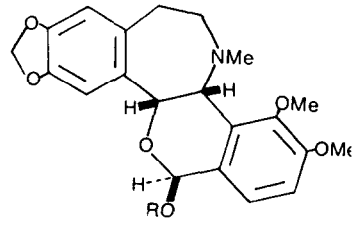
10a



11



12



13, R = H

14, R = Me

(1H, d, J 8.2 Hz, H-12); ms m/e 383 (M^+, 33), 368 (22), 365 (31), 349 (24), 324 (51), 190 (15), 177 (100), 149 (25); R_f 0.51.

cis-Acetate 10a: ν max 1710, 1735 cm^{-1}; nmr (360 MHz) δ2.21 (3H, s, CH_3COO), 2.78 (3H, s, NCH_3), 3.93 (3H, s, 9-OCH_3), 4.00 (3H, s, 10-OCH_3), 4.97 (1H, s, H-8), 5.91 and 5.94 (2H, ABq, J 1.5 Hz, OCH_2O), 6.48 (1H, s, H-4), 7.03 (1H, d, J 8.2 Hz, H-11), 7.33 (1H, s, H-1), 7.60 (1H, d, J 8.2 Hz, H-12); ms m/e 425 (M^+, 13), 365 (100), 349 (36), 334 (34), 177 (55); R_f 0.71.

γ-Lactone 10: λ max 245 sh, 267, 322 nm (log ε 4.32, 4.28, 3.85); ν max 1685, 1755 cm^{-1}; nmr (200 MHz) δ2.27 (3H, s, NCH_3), 3.80 (3H, s, 9-OCH_3), 3.95 (3H, s, 10-OCH_3), 6.00 and 6.02 (2H, ABq, J 1.5 Hz, OCH_2O), 6.70 (1H, s, H-4), 7.00 (1H, s, H-1), 7.12 (1H, d, J 8.5 Hz, H-11), 7.62 (1H, d, J 8.5 Hz, H-12); ms m/e 397 (M^+, 53), 369 (54), 324 (95), 294 (88), 176 (100), 148 (82); R_f 0.64.

δ-Lactone 11: λ max 260, 285 nm (log ε 4.05, 3.97); ν max 1725 cm^{-1}; nmr (200 MHz) δ2.15 (3H, s, NCH_3), 3.81 (1H, d, J < 1 Hz, H-2), 3.89 (3H, s, 10-OCH_3), 3.97 (3H, s, 11-OCH_3), 5.07 (1H, d, J <1 Hz, H-1), 5.96 (2H, s, OCH_2O), 6.65 (1H, s, H-6), 6.66 (1H, s, H-9), 7.01 (1H, d, J 8.5 Hz, H-12), 7.88 (1H, d, J 8.5 Hz, H-13); ms m/e 383 (M^+, 13), 206 (72), 190 (100), 177 (24); R_f 0.56.

Hemiacetal 12: nmr (200 MHz) δ2.26 (3H, s, NCH_3), 3.50 (1H, s, OH), 3.71 (1H, d, J < 1 Hz, H-2), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.48 (1H, d, J < 1 Hz, H-1), 5.90 (1H, s, HCOH), 5.93 and 5.95 (2H, ABq, J 1.3 Hz, OCH_2O), 6.63 (1H, s, H-6), 6.67 (1H, s, H-9), 6.92 (1H, d, J 8.5 Hz, H-12), 7.07 (1H, d, J 8.5 Hz, H-13); ms m/e 385 (M^+, 1.1), 384 (4), 366 (9), 222 (100), 179 (43); R_f 0.37.

Rhoeadine 13: λ max 228, 285 nm (4.27, 3.84); nmr (60 MHz) δ2.30 (3H, s, NCH_3), 3.50 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.96 (1H, d, J < 1 Hz, H-2), 4.83 (1H, d, J < 1 Hz, H-1), 5.63 (1H, acetal H), 5.88 (2H, s, OCH_2O), 6.60 (1H, s, H-6), 6.70 (1H, s, H-9), 6.86 (1H, d, J 8.5 Hz, H-12), 7.06 (1H, d, J 8.5 Hz, H-13); ms m/e 399 (M^+, 65), 384 (70), 349 (32), 222 (20), 190 (20), 177 (100); R_f 0.36.

Acknowledgment: This research was supported by grant NS15437, NINCDS, USPHS. G.B. is the recipient of an IREX fellowship.

References and Footnotes[7,8]

1. Permanent address: Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1025 Budapest, Hungary.
2. H.L. Holland, D.B. MacLean, R.G.A. Rodrigo and R.H.F. Manske, Tetrahedron Lett., 4323 (1975); and Y. Kondo, M. Inoue and J. Imai, Heterocycles, 6, 953 (1977).
3. J.L. Moniot and M. Shamma, J. Am. Chem. Soc., 98, 6714 (1976), and J. Org. Chem., 44, 4337 (1979); and M. Hanaoka and C. Mukai, Heterocycles, 6, 1981 (1977).
4. M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima and T. Imanishi, Tetrahedron Lett., 3749 (1979).
5. W. Klötzer, S. Teitel, J.F. Blount and A. Brossi, J. Am. Chem. Soc., 93, 4321 (1971).
6. For a discussion of the relative stereochemistry of the rhoeadines, see M. Shamma, J.A. Weiss, S. Pfeifer and H. Döhnert, Chem. Commun., 212 (1968). For a review of other synthetic routes to the rhoeadines, see M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York (1972), pp. 410-412; and M. Shamma and J.L. Moniot, Isoquinoline Alkaloids Research, 1972-1977, Plenum Press, New York (1978), pp. 337-346.
7. The numbering system adopted here for the indenobenzazepine derivatives is in accord with that for the protoberberines and spirobenzylisoquinolines. TLC was on Merck Silica Gel F-254 glass plates, and the developing solvent was MeOH-$CHCl_3$ 4:96 v/v. UV spectra are in EtOH, and ir spectra are in $CHCl_3$. All nmr spectra were obtained in $CDCl_3$ solution using TMS as the internal standard.
8. All compounds are racemates.

(Received in USA 4 March 1981)