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A CONTROLLED OXIDATION OF BISBENZYLISOQUINOLINES[1]

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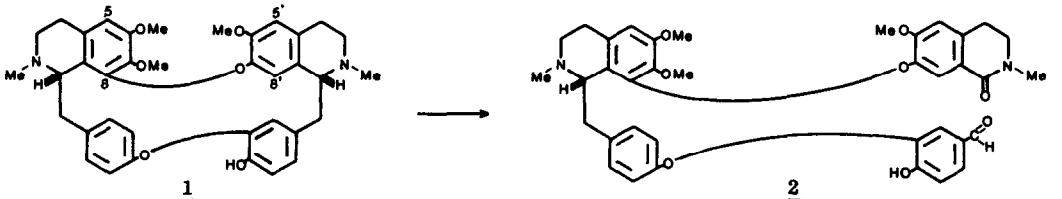
In the course of a recent investigation of the unusual dimeric isoquinoline alkaloid baluchistanamine (2), obtained from Berberis baluchistanica Ahrendt (Berberidaceae), it was found that this base could also be obtained in vitro by potassium permanganate in acetone oxidation of the accompanying bisbenzylisoquinoline alkaloid oxyacanthine (1).[2]

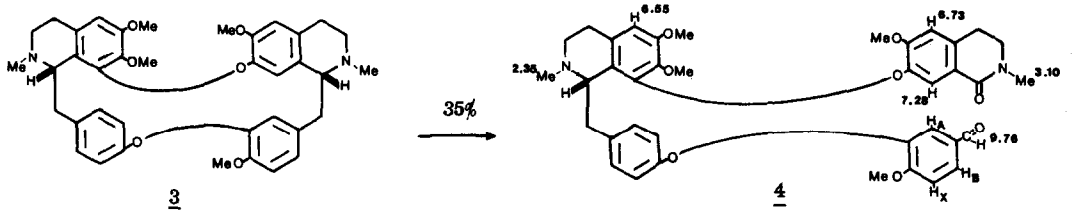


1 2

We have now completed a systematic study of the potassium permanganate in acetone oxidation of eight bisbenzylisoquinolines which, beside pointing to the generality of this controlled oxidative method, shows that in every case cleavage occurs at the benzylic bond of the isoquinoline moiety which is unsubstituted at C-8' (or C-8). Relative stereochemistry does not determine the site of the oxidation. Permanganate in acetone oxidation thus becomes useful as an alternate structural probe for bisbenzylisoquinolines. The dimeric bases oxidized in the present study include (+)-obaberine (3), (+)-isotetrandrine (5) and its diastereoisomer (+)-tetrandrine (7), (+)-hernandezine (9), (-)-nortenuipine acetate (11), (+)-rodiasine acetate (13), (+)-isotrilobine (15), and (+)-O,O-dimethyltubocurine (17).[3]

In each case, oxidation affords a tertiary lactam ($\nu_{max}^{CHCl_3}$ 1640-1645 cm^{-1}) and an aromatic aldehyde ($\nu_{max}^{CHCl_3}$ 1690-1720 cm^{-1}). The aromatic proton signals in the nmr spectra of bisbenzylisoquinolines generally overlap and are difficult to assign. On the other hand, the aromatic proton signals of the oxidized products are spread over a larger range and are generally easier to identify. In particular, there is a downfield shift of the aromatic protons belonging to the isoquinolone and aldehyde rings. The readily assignable singlet proton nmr chemical shifts for the products obtained are indicated in the following diagrams.

In the case of the oxidation product 4 obtained from obaberine (3), the C-5 and C-5' protons appear at δ6.55 (1H, s) and 6.73 (1H, s), respectively; the C-8' proton peri to the lactam carbonyl is at δ7.28 (1H, s), appreciably further downfield from the corresponding proton in obaberine which is situated at δ5.48; the aromatic protons of the benzaldehyde moiety are at



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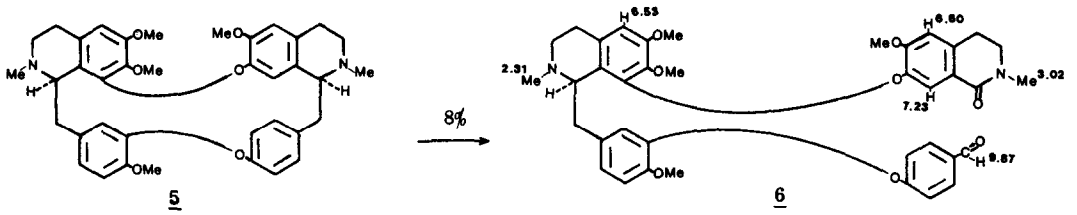

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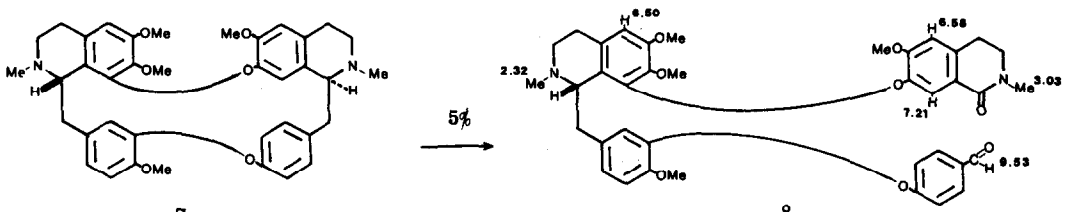

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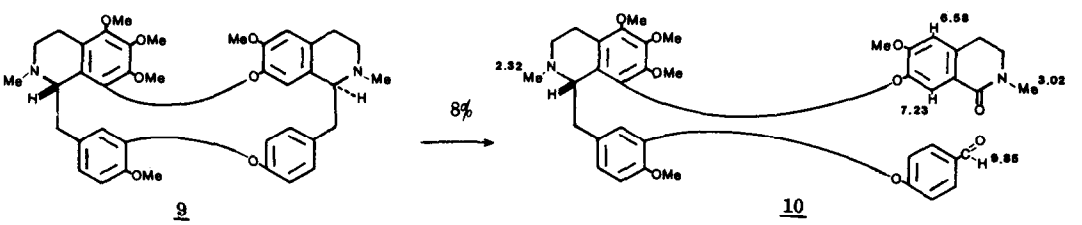


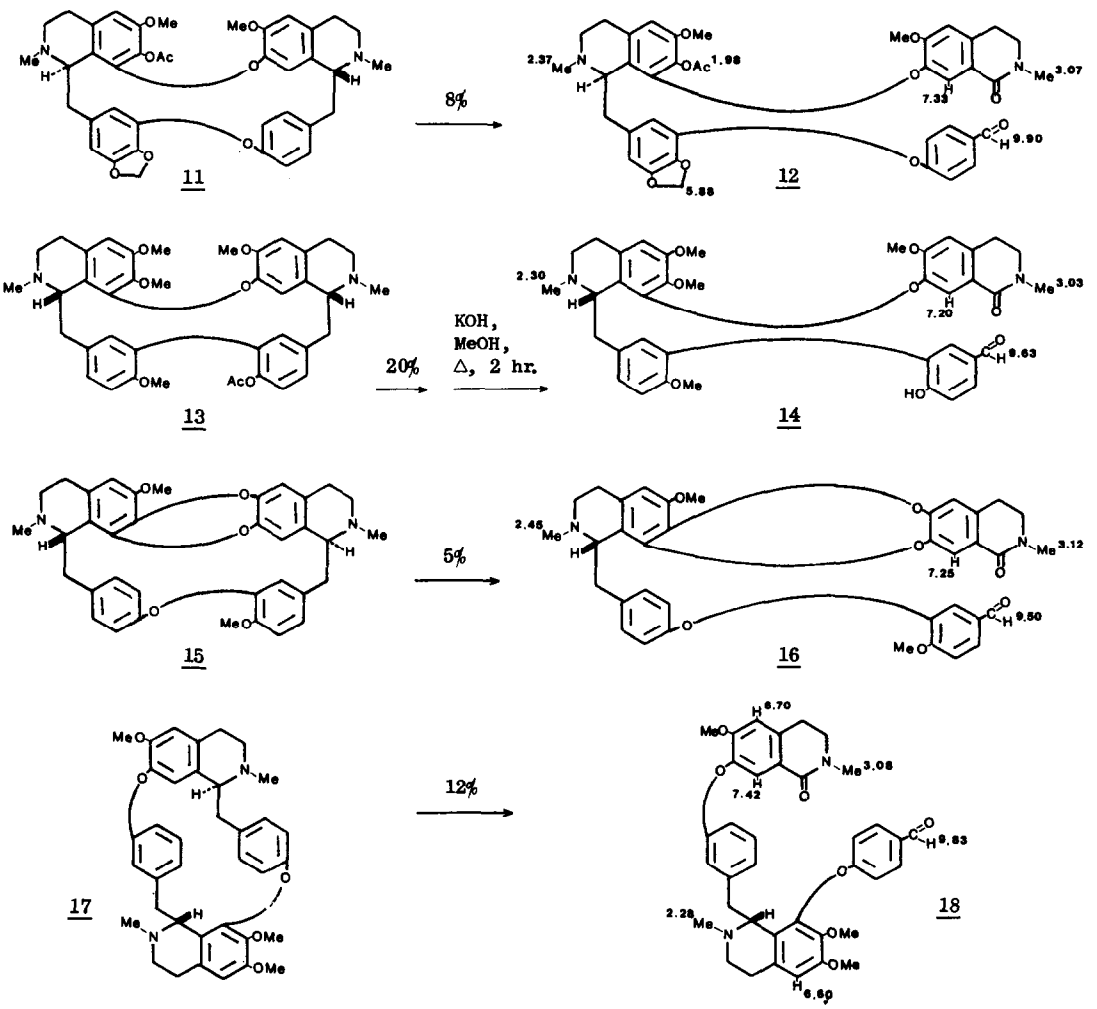
9 8% 10

Compd 4: λ_{max}^{EtOH} 226, 262, 270, 283sh, 292sh and 305sh nm (log ε 4.58, 4.12, 4.10, 3.99, 3.85 and 3.77); m/e 652 (M^+, $C_{38}H_{40}N_2O_8$), 411 (base), 241, 206 and 204.

Compd 6: λ_{max}^{EtOH} 232, 265, 272, 285 and 292sh nm (log ε 4.54, 4.08, 4.09, 4.07 and 4.03); m/e 652 (M^+, $C_{38}H_{40}N_2O_8$), 411 (base), 241, 206 and 204.

Compd 8: λ_{max}^{EtOH} 242, 262, 272 and 285 nm (log ε 4.52, 4.19, 4.19 and 3.96); m/e 652 (M^+, $C_{38}H_{40}N_2O_8$), 411 (base), 241, 206 and 204.

Compd 10: λ_{max}^{EtOH} 230, 265, 272, 284, 290sh and 305sh nm (log ε 4.52, 3.97, 4.01, 3.92, 3.90 and 3.56). m/e 682 (M^+, $C_{39}H_{42}N_2O_8$), 431 (base), 241, 236 and 234.



11 12 13 14 15 16 17 18

Compd 12: λ_{max}^{EtOH} 242, 261, 272 and 285sh nm (log ε 4.55, 4.22, 4.20 and 4.05);
m/e 694 (M^+, $C_{39}H_{38}N_2O_{10}$), 439 (base), 255, 192 and 190.

Compd 14: λ_{max}^{EtOH} 223, 275, 287 and 295sh nm (log ε 4.22, 3.67, 3.70 and 3.65);
m/e 652 (M^+, $C_{38}H_{40}N_2O_8$), 411 (base), 241, 206 and 204.

Compd 16: λ_{max}^{EtOH} 232, 260sh and 280sh nm (log ε 4.56, 4.06 and 3.93);
m/e 606 (M^+, $C_{36}H_{34}N_2O_7$), 365 (base), and 241.

Compd 18: λ_{max}^{EtOH} 228, 272 and 282 nm (log ε 4.58, 4.13 and 4.03);
m/e 652 (M^+, $C_{38}H_{40}N_2O_8$), 326 (base), 324, 206 and 204.

δ7.02 (X), 7.41 (A), and 7.66 (B) (3H, ABX, J_{AB} = 2 Hz, J_{AX} < 1 Hz, J_{BX} = 8.5 Hz); while the protons of the other bottom aromatic ring appear at δ 6.80 and 7.18 (4H, A_2B_2, J_{AB} = 8.5 Hz). The methoxyl singlets are at δ3.62, 3.85, 3.90 and 3.94.

A somewhat different pattern emerges for the oxidation product 6 of isotetrandrine (5). The C-5 and C-5' protons occur at δ6.53 (1H, s) and 6.60 (1H, s), respectively; the C-8' peri proton is at δ7.23 (1H, s), downfield from the corresponding proton in 5 which is at δ5.98; the aromatic protons of the benzaldehyde ring are present at δ6.92 and 7.77 (4H, A_2B_2, J_{AB} = 8.5 Hz); and the protons of the other bottom aromatic ring form an ABC pattern centered at δ6.92 (1H) and 6.97 (2H). The methoxyl singlets are at δ3.63, 3.70, 3.82 and 3.83.

When a phenolic group is present in the starting bisbenzylisoquinoline, O-acetylation, permanganate oxidation, and ester hydrolysis, yield a phenolic aldehydo lactam. This route affords a higher yield than direct oxidation of the phenol.[2] In case the phenolic group is located para to the aldehyde function, a very large bathochromic shift in the uv spectrum occurs upon addition of base.[4] To cite an example, the phenolic aldehydo lactam 14 derived from rodiasine acetate (13) shows $\lambda_{max}^{EtOH-OH^-}$ 270, 285, 300sh and 350 nm (log ε 3.41, 3.30, 3.26 and 3.46). The present oxidative method can, therefore, assist in locating the phenolic function of a new bisbenzylisoquinoline alkaloid.

In a typical experiment, 100 mg of the bisbenzylisoquinoline was dissolved in 150 ml acetone, and a solution of 40 mg $KMnO_4$ in 100 ml acetone added dropwise with stirring at room temperature over 45 min. Stirring was continued for an additional 6 hr. Filtration to remove MnO_2, followed by preparative tlc on Merck silica gel plates using 10% MeOH in $CHCl_3$ yielded the desired product as a high R_f component. Yields usually ranged from 5-35%. Low yield reactions could be improved by recycling of starting material, 25-50% of which could be recovered.[5]

In the same way that baluchistanamine (2) accompanies oxyacanthine (1) in B. baluchistanica, it would be expected that some of the aldehydo lactams produced here or by in vitro oxidation of other bisbenzylisoquinoline alkaloids will eventually be found as natural products.

References

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2. M. Shamma, J.E. Foy and G.A. Miana, J. Amer. Chem. Soc., 96, 7809 (1974).
3. For the actual nmr spectra of several bisbenzylisoquinoline alkaloids, see a monograph of 201 pages, in Japanese, honoring Professor M. Tomita, published in 1967 by a Committee for the Retirement of Professor Tomita.
4. A.I. Scott, U.V. Spectra of Natural Products, Macmillan Company, New York (1964), p. 109.
5. Nmr spectra were obtained at 60 MHz in $CDCl_3$, with TMS as internal standard.