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TRANSFORMATIONS OF 13-OXOPROTOBERBERINIUM METHO SALTS III: BIOGENETICALLY PATTERNED CONVERSIONS TO RHOEADINES

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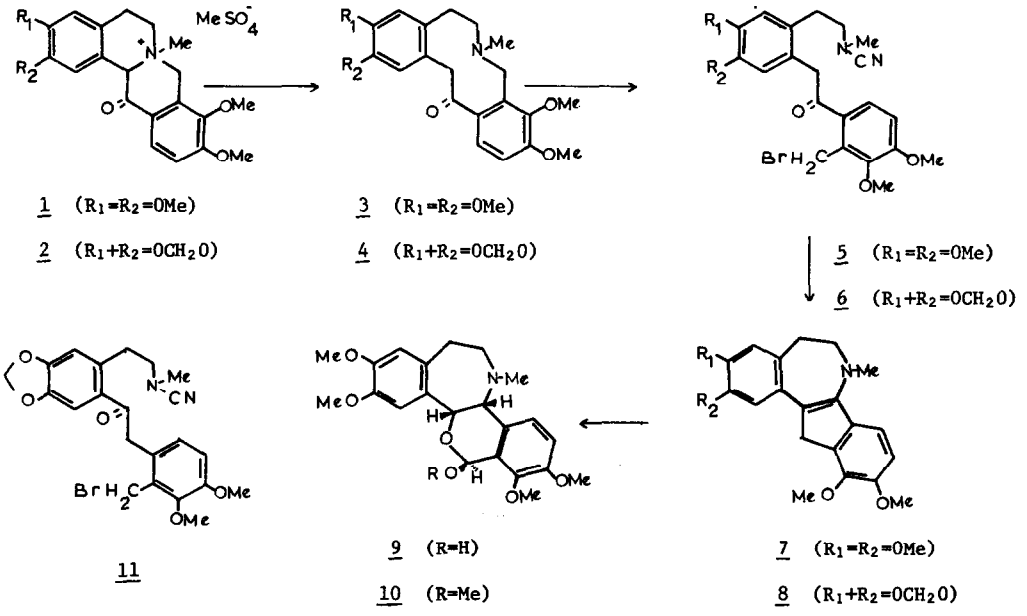
Current views[1] of benzylisoquinoline alkaloid biogenesis assign to the tetrahydroprotoberberines a central position in the biosynthetic chain which progresses from tetrahydrobenzylisoquinolines through the tetrahydroprotoberberines to a variety of alkaloid types. One hitherto speculative link in this sequence recently received experimental support from the observation[2] that doubly labelled tetrahydropalmatine methiodide was incorporated by Papaver bracteatum plants into the rhoeadine alkaloid alpinigenine.

We now report the first in vitro conversion of a tetrahydroprotoberberine to a rhoeadine using the same type of 13-oxoprotoberberinium metho salt which had earlier led to spirobenzylisoquinolines[3] and protopine[4] analogues - two other termini of the biosynthetic chain.

Thus the tetramethoxy-13-oxoprotoberberinium salt 1 was prepared from tetrahydropalmatine in a manner similar to that employed earlier[3] for 2, and in comparable yields. [1; m.p. (of perchlorate) 273-4°; ν_{max}^{nujol} 1690 cm^{-1}; δ(d_6 - DMSO) 3.33 (m, 2H), 3.38 (S, 3H), 3.76 - 3.88 (m, 2H), 3.78 (s, 2 x 3H), 3.88 and 4.00 (s, 2 x 3H), 5.17 (br. s, 2H), 5.65 (s, 1H), 6.87 (s, 1H) 6.97 (s, 1H) 7.41 and 7.90 (q, 2H) J_{AB} = 9.0 Hz.] This compound upon treatment with zinc in 30% aqueous acetic acid produced the tricyclic ketone 3 analogous to 4[4] [3; yield 57%;

m.p. 166-7°; ν_{max}^{nujol} 1682 cm^{-1}; δ($CDCl_3$) 1.80 (s, 3H); 3.77 (s, 3H), 3.83 (s, 2 x 3H), 3.86 (s, 3H) 6.66 (s, 1H) 6.90 (s, 1H), 6.83 and 7.10 (q, 2H) J_{AB} = 8.5 Hz; M^+ = 385.] Both 3 and 4 suffered von Braun ring fission in the 'expected' manner with cyanogen bromide in tetrahydrofuran to yield the bromocyanamides 5 and 6 respectively. [5; yield 47%; m.p. 113-114°; $\nu_{max}^{CHCl_3}$ 2220 and 1682 cm^{-1}; δ($CDCl_3$) 2.83 (s, 3H, N - Me), 2.80 - 3.33 (m, 4H, CH_2-CH_2), 3.86, 3.93, 3.98, 4.00 (s, 4 x 3H, 4 x OMe), 4.30 and 5.08 (s, 2 x 2H, CH_2CO and CH_2Br resp.) 6.76 and 6.85 (s, 2 x 1H, H, and H_4), 7.00 and 7.76 (q, 2H, H_{11} and H_{12} resp.) J_{AB} = 8.5 Hz; M^+ = 490 and 492. Compound 6 had similar spectral properties.] This result is at variance with



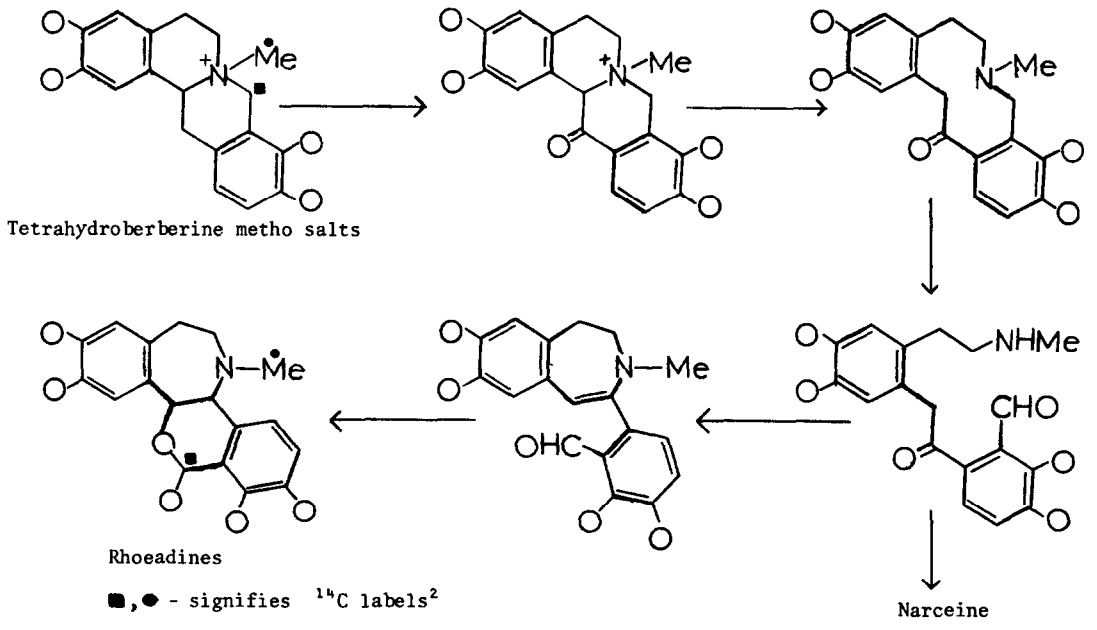
1 (R_1=R_2=OMe)
2 (R_1+R_2=OCH_2O)
3 (R_1=R_2=OMe)
4 (R_1+R_2=OCH_2O)
5 (R_1=R_2=OMe)
6 (R_1+R_2=OCH_2O)
7 (R_1=R_2=OMe)
8 (R_1+R_2=OCH_2O)
9 (R=H)
10 (R=Me)
11

earlier studies in which tetrahydroberberine[5] and cryptopine[6] were found to undergo carbon-nitrogen cleavage with cyanogen bromide in benzene and chloroform solution respectively at different sites; in neither case was any product arising from the expected C_8-N cleavage isolated. The anomalous course of the von Braun reaction in these instances was subsequently rationalised[7] by the postulate that proper access of the bromide ion to C_8 of the intermediate quaternary cyanamide is hindered by the presence of the C_9 oxygen substituent. In view of the present results however, a more complex and solvent dependent mechanism must prevail; we have found for instance that the protopine alkaloid allocryptopine, contrary to the earlier results[6] with

cryptopine, provides mainly the bromocyanamide11 resulting from C_8-N cleavage upon treatment with cyanogen bromide in tetrahydrofuran. [11, 45% yield; m.p. 142-3°; $\nu_{max}^{CHCl_3}$ 2220 and 1680 cm^{-1}; $\delta(CDCl_3)$ 2.80 (s, 3H, N-Me), 3.00-3.33 (m, 4H, CH_2-CH_2), 3.86 and 4.00 (s, 2 x 3H, 2 x OMe), 4.30 (s, 2H, CH_2CO), 4.60 (s, 2H, CH_2Br), 6.10 (s, 2H, $-OCH_2O-$), 6.85 and 7.43 (s, 2 x 1H, C_4-H and C, -H resp.), 6.88 (s, 2H, 2 x aromatic H); M^+ = 474 and 476.]

The bromocyanamides 5 and 6 are "Narceine equivalents" and upon treatment with refluxing ethanolic potassium hydroxide were converted to the indenes 7 and 8 respectively in accordance with previous experience[8,9] with compounds of this type. The indene 7 was found to be identical with a sample previously synthesised[8] in this laboratory and the properties of 8 were very similar to it[10]. Since 7 had previously been converted[8] into the rhoeadine alkaloids (+) cis-alpinigenine, 9 and (+) cis-alpinine, 10 the reactions described here constitute an in vitro duplication[11] of the results of the labelling experiments[2].

In view of the foregoing results the following biogenetic proposal may be made (Scheme 1). It differs from the earlier suggestions[1,2,12] in the recognition of oxidation at C_{13} of the protoberberine as the initial step of the oxidative progression that culminates in the rhoeadines.



SCHEME I

The penultimate enamine-aldehyde is reminiscent of an intermediate proposed[13] for biogenesis of the benzophenanthridine alkaloids. Feeding experiments designed to test the validity of our hypothesis are now being planned.

Acknowledgements

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