

THE ORIGIN OF THE METHYLENOXY BRIDGE IN SOME ISOQUINOLINE ALKALOIDS<sup>1</sup>

Maurice Shamma and Jerome L. Moniot

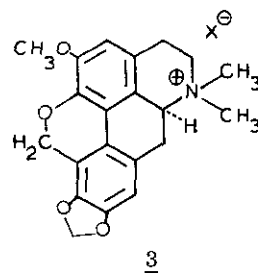
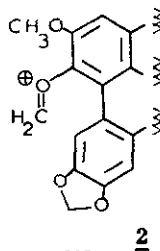
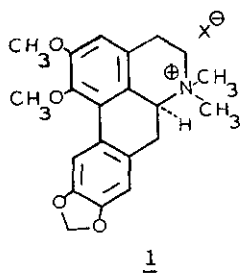
Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

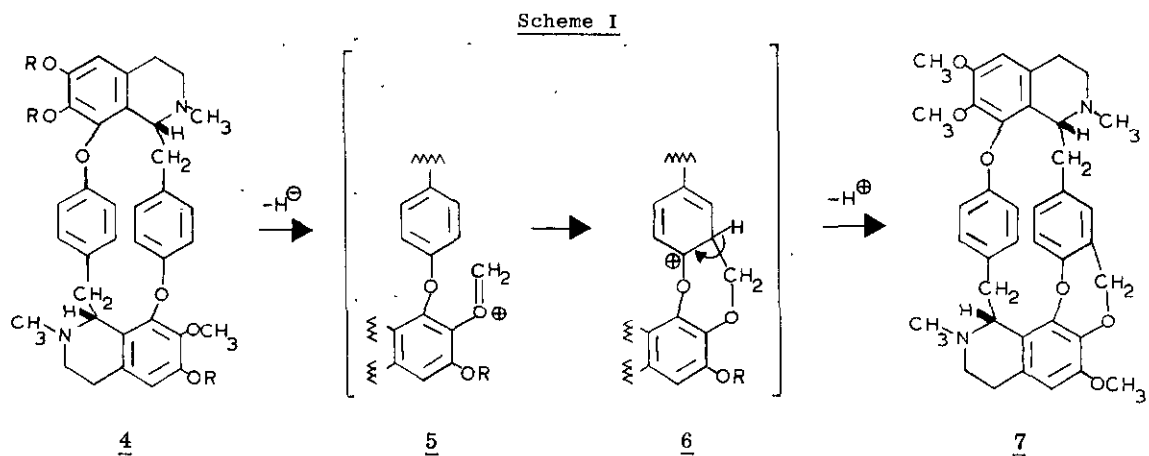
The isolation of nantenine methochloride (1) from T. polygamum points to an oxonium ion being involved in the biogenesis of the methylenoxy bridge of thalphenine (3). Oxonium ions are also implicated in the formation of insularine (7), cissampareine (9), and repanduline (12).

As part of a continuing investigation of the alkaloids of Thalictrum polygamum Muhl. (Ranunculaceae), we have isolated and characterized the new aporphine (+)-nantenine methochloride (1), C<sub>21</sub>H<sub>24</sub>O<sub>4</sub>NCl, mp 213-214<sup>0</sup> (CHCl<sub>3</sub>), [α]<sub>D</sub><sup>20</sup> +39<sup>0</sup> (EtOH), λ<sub>max</sub><sup>EtOH</sup> 225, 278sh, 285, 310 and 320sh nm (log ε 4.24, 3.65, 3.79, 3.94 and 3.84), nmr CDCl<sub>3</sub> δ 3.15s and 3.72s (2x3H, NCH<sub>3</sub>), 3.65s and 3.85s (2x3H, OCH<sub>3</sub>), 5.83 broad s (2H, OCH<sub>2</sub>O), 6.70s and 6.95s (2x1H, arom. H) and 7.70s (1H, H-11); spectrally identical with a sample of (+)-nantenine methochloride prepared from synthetic nantenine. The importance of this new alkaloid resides in its pivotal role in the probable biogenetic scheme for the unusual aporphine (+)-thalphenine (3), also found in the same plant.<sup>2</sup>

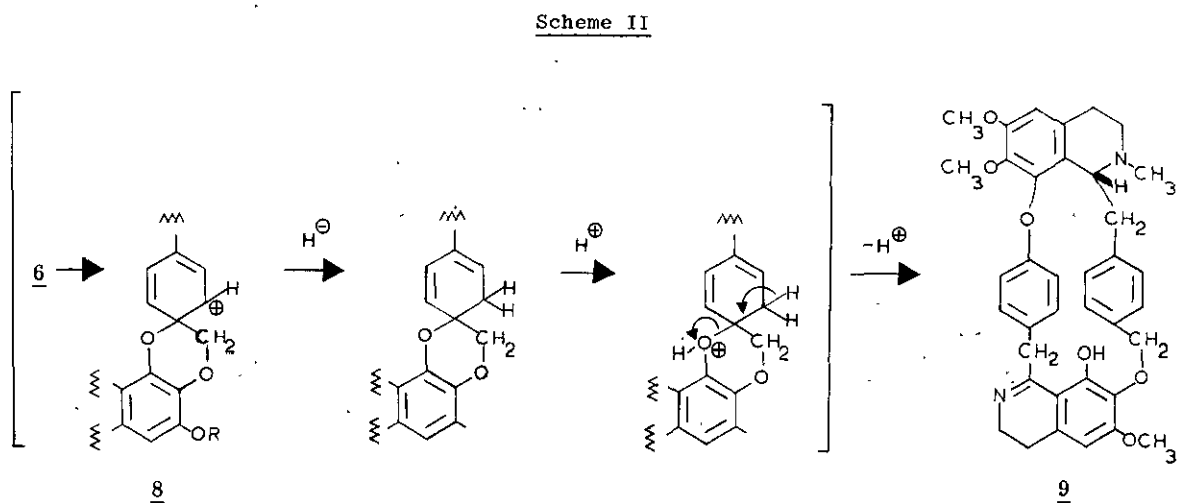
Assuming an ionic mechanism, the most likely biogenetic mode of formation for the methylenoxy bridge in thalphenine (3) appears to be through the intermediacy of an oxonium ion of type 2 derived from nantenine, or its N-metho salt (1), by the net loss of a hydride ion.<sup>3</sup>



The oxonium ion theme can also be extended to the biogenesis of the bisbenzyl-isoquinoline alkaloid insularine (7)<sup>4</sup> which must be formed via the oxonium ion 5 derived from the cycleanine type dimer 4 (Scheme I).

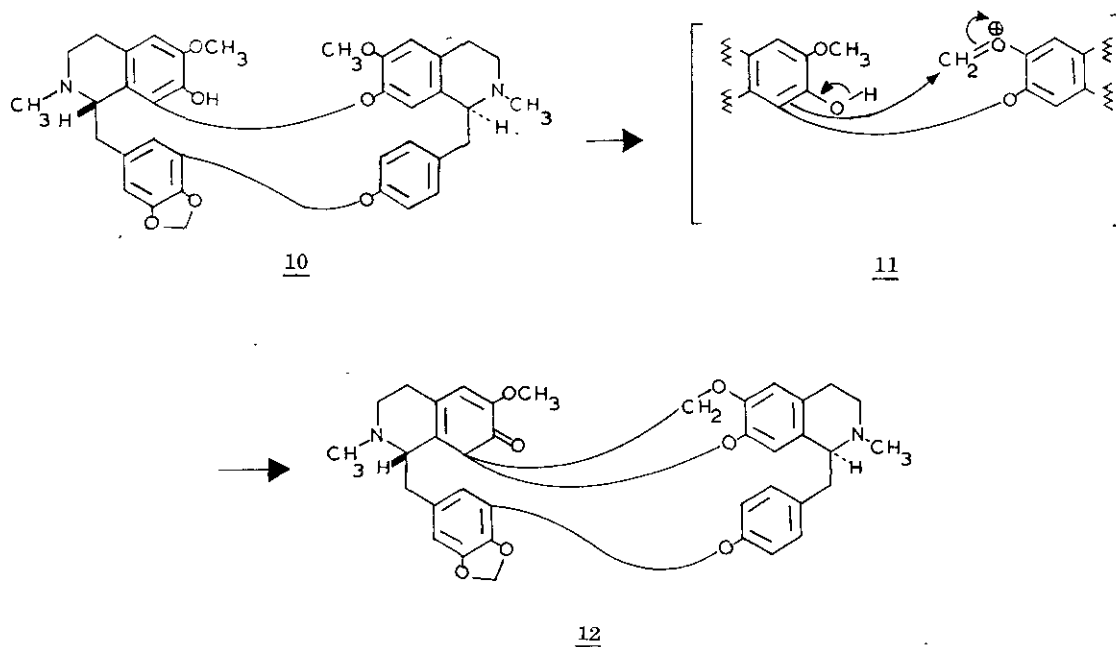


Furthermore, the identical intermediate 6, or one of its close analogs, could undergo a 1,2-alkyl shift to afford 8. Subsequent hydride addition and bond cleavage, as shown in Scheme II, would result in eventual formation of the alkaloid cissampareine (9) found in *Cissampelos pareira* L. (Menispermaceae).<sup>5</sup>



A further bisbenzylisoquinoline with a methylenoxy bridge is repanduline (12) which also incorporates an  $\alpha$ -ketol function. Its probable biogenetic precursors have been judiciously represented in the past by structures 10 and 11, where 10 corresponds to the accompanying alkaloid nortenuipine<sup>6</sup> (Scheme III).

Scheme III



The methylenoxy bridge is not limited to isoquinoline alkaloids, but is also found in other groups of natural products such as the mopanol and the peltogynols. There again it has been observed that the probable precursors of these bridged dihydroflavonols are the accompanying and unbridged *o*-methyl analogs.<sup>7</sup> The biogenesis of the methylenoxy bridge in nature, as proposed, should be viewed as part of a larger context which includes "onium" salts in the formation of the much more common methylenedioxy bridge from an *o*-hydroxyanisole, and the related cyclization of an *N*-methyltetrahydrobenzylisoquinoline to a tetrahydroprotoberberine base.<sup>8,9,6</sup>

### References

1. This project was supported by grant HL-12971 from the National Institutes of Health.
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