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A NEW SYNTHESIS OF SPIROBENZYLISOQUINOLINES. ANALOGUES OF SIBIRICINE AND CORYDAINE

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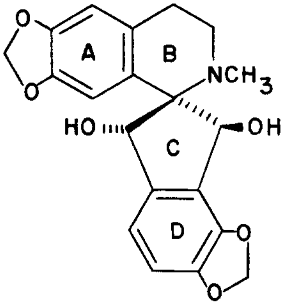
Abstract: The reduction product of dehydrocordrastine, 6, with di-isobutylaluminum hydride spontaneously rearranged to the spirobenzylisoquinolines 7a and 7b, analogous to the alkaloids sibiricine (5a), corydaine (5b), and yenhusomidine (5c).

Previous syntheses (1) of spirobenzylisoquinline alkaloids (2) have led to compounds with symmetrical substitution in ring C, such as ochrobirine (1), compounds with only a single carbon substituent in that ring, such as ochotensine (2a) and ochotensimine (2b), or to mono-oxygenated compounds such as fumaricine (3a), fumaritine (3b), and fumariline (4) (2).



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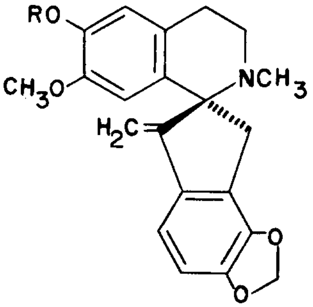
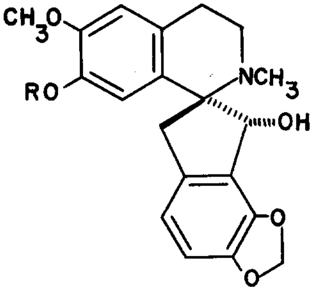
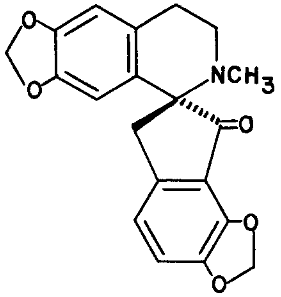


2 a: R = H
b: R = CH_3

Such syntheses are not easily adaptable to the preparation of alkaloids with two different substituents in ring C, and consequently neither sibiricine (5a) (3), corydaine (5b) (4), or yenhusomidine (5c) (5) have been synthesized.



3 a: R = CH_3
b: R = H



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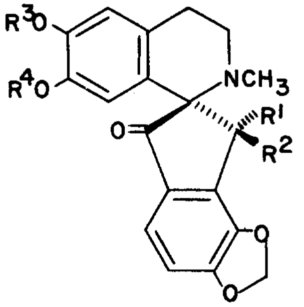
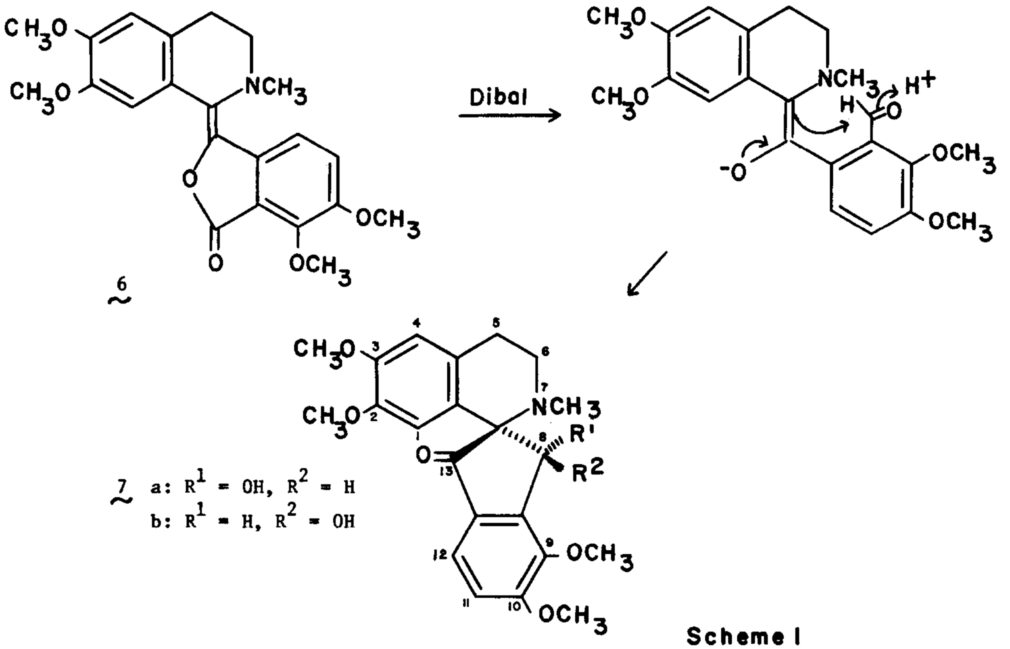


5 a: R^1 = OH, R^2 = H, $R^3 + R^4 = CH_2$
b: R^1 = H, R^2 = OH, $R^3 + R^4 = CH_2$
c: R^1 = H, R^2 = OH, $R^3 = R^4 = CH_3$

We report here a new route to the spirobenzylisoquinoline skeleton which provides both the sibiricine and corydaine stereochemical types by a one-step, high-yield rearrangement of a dehydrophthalideisoquinoline.

Treatment of the known dehydrocordrastine (6) with di-isobutylaluminum hydride at -78° led to the equimolar formation of the diasteromeric spirobenzylisoquinolines, 7a, m.p. 149-151° and 7b, m.p. 118-120°, in 76% total yield. The reaction presumably proceeds by reductive opening of the oxygen ring and reclosure of the resulting enolate as shown in Scheme 1. Spectral data for the two compounds are: i.r. (ν_{max} KBr), 7b; 3430, 3200, 1705 cm^{-1}, 7a; 3460, 3120, 1710 cm^{-1}): p.m.r. (100 MHz, $CDCl_3$ solution, δ) 7b; 2.31 (3H, s, N-CH_3), 3.0-3.25, 3.65-3.95 (each 2H, m, C-5 and C-6 H's), 3.57, 3.82, 3.98 and 4.04 (each 3H, s, OCH_3), 5.10 (1H, s, C-8H), 6.02 (1H, s, C-1H), 6.58 (1H, s, C-4H), 7.08 and 7.60 (2H, ABq, J = 8Hz, C-11 and C-12 H's), 7a; 2.31 (3H, s, NCH_3), 2.6-3.2 (4H, m, C-5 and C-6 H's), 3.47, 3.78, 3.95 and 3.98 (each 3H, s, OCH_3), 5.59 (1H, s, C-8H), 6.05 (1H, s, C-1H), 6.60 (1H, s, C-4H), 7.06 and 7.62 (2H, ABq, J = 8Hz, C-11 and C-12 H's). These data are consistent with the proposed structures. The mass spectral fragmentations are entirely analogous with the fragmentation pattern observed for sibiricine (5a) (7). Both 7a and 7b show intense ions (8) at m/e 399 ($C_{22}H_{25}NO_6$), 384 ($C_{21}H_{22}NO_6$), 370 ($C_{21}H_{24}NO_5$), 368 ($C_{21}H_{22}NO_5$), 354 ($C_{21}H_{24}NO_4$), 220 ($C_{12}H_{14}NO_3$), and 206 ($C_{12}H_{16}NO_2$). The isomers 7a and 7b were differentiated by the observation of a 19% nuclear

Overhauser enhancement of the signal of the hydrogen geminal to hydroxyl at C-8 in 7a at δ 5.59 upon irradiation at the N-methyl frequency at δ 2.31; similar irradiation of 7b at δ 2.31 caused no appreciable enhancement of the signal at δ 5.10.



7 a: R^1 = OH, R^2 = H
b: R^1 = H, R^2 = OH

Scheme I

The shapes and positions of the signals of the hydrogens at C-8 also allow differentiation of 7a and 7b. Thus the C-8 hydrogen signal in 5a (3) and 7a is broad ($W_{1/2} \simeq$ 4Hz), sharpening on addition of D_2O to $W_{1/2} \simeq$ 2Hz, and is located close to δ 5.60. On the other hand, the corresponding signal in yenhusomidine (5c) (5) and 7b is a sharp singlet ($W_{1/2} \simeq$ 2Hz) near δ 5.10 and is unaffected by the addition of D_2O.

It is anticipated that rearrangement of appropriately substituted dehydrophthalides will lead to sibiricine (5a), corydaine (5b), and yenhusomidine (5c). Synthesis of these compounds by this method is at present under way.

Acknowledgments:

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8. Ion compositions were determined by high resolution mass spectrometry and the molecular formulas of 7a and 7b confirmed by elemental analysis.
9. Absolute stereochemistry is not necessarily implied in the structural formulas.