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PHOTO-OXYGENATION OF 8-METHOXYBERBERINEPHENOLBETAINE. A NOVEL SYNTHESIS OF SPIROBENZYLISOQUINOLINE SYSTEM FROM BERBERINE

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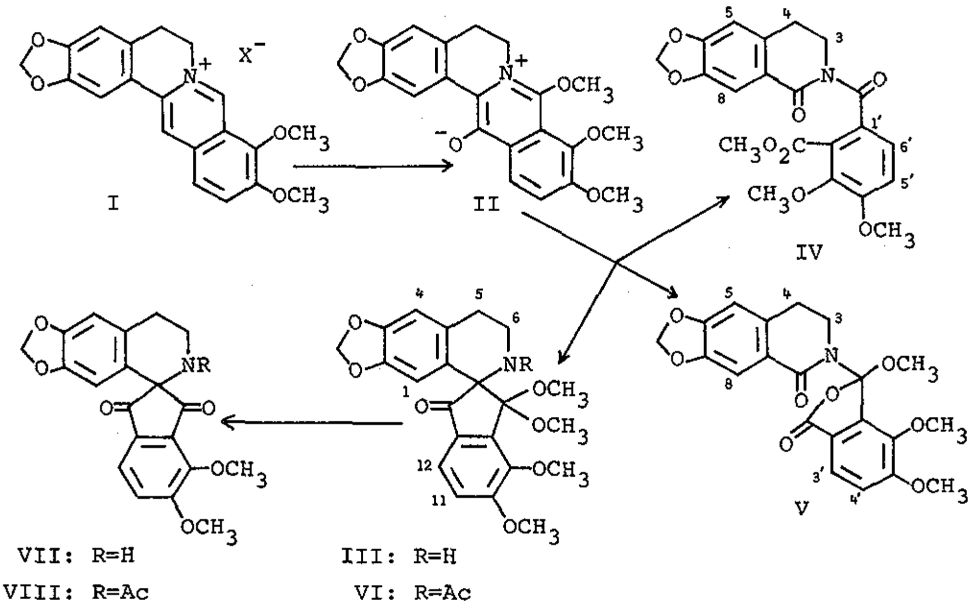
Photo-oxygenation of 8-methoxyberberinephenolbetaine(II) afforded the spirobenzylisoquinoline(III), the imide-ester(IV), and methoxyberberal(V). Acidic hydrolysis of III yielded the diketospirobenzylisoquinoline(VII).

Several elegant rearrangements of protoberberine metho salts to spirobenzylisoquinolines have been reported.[1-5] In the previous paper,[6] we described the efficient conversion of berberine(I) to 8-methoxyberberinephenolbetaine(II).[7] The present communication deals with a novel and convenient synthesis of the spirobenzylisoquinoline(III) from II by photo-oxygenation.

Irradiation(100W high-pressure Hg lamp, with Pyrex filter) of II in methanol in a stream of oxygen for 45 min afforded the spirobenzylisoquinoline(III)[40%, mp 194-196°, m/e:413(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708, λ_{max}^{MeOH} nm(log ε):230(4.33), 289(4.29), δ:2.72-4.00m(4H, H_2-5,6), 3.24s, 3.35s, 3.92s, 4.00s(each 3H, OCH_3 x 4), 5.82q(2H, OCH_2O), 6.26s(1H, H-1), 6.59s(1H, H-4), 7.10, 7.60 AB-q(2H, J=8 Hz, H-11, 12)], the imide-ester(IV)[10%, mp 147-148°(lit.[8] mp 143-144°), m/e: 413(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}:1730, 1678, λ_{max}^{MeOH} nm(log ε):233(4.55), 277 (4.05), 319(4.17), δ:3.03t(2H, J=6 Hz, H_2-4), 3.76s(3H, OCH_3),

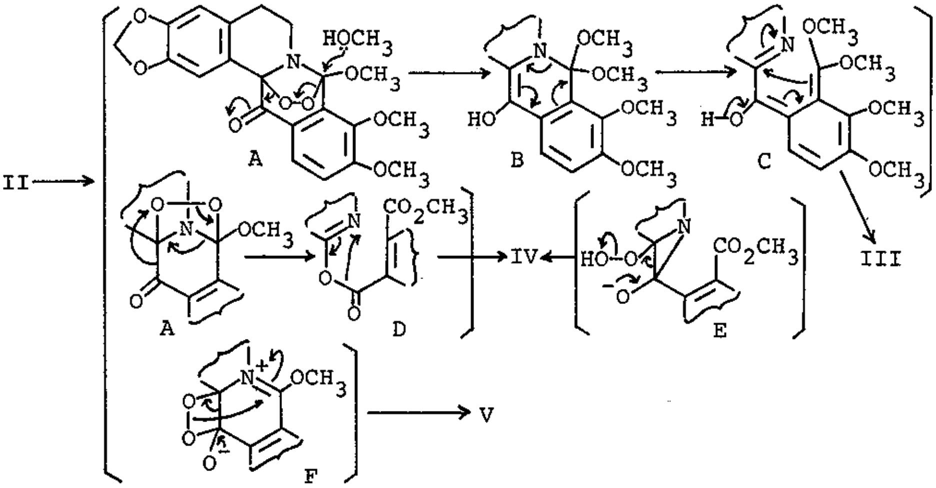


3.92s(6H, OCH_3 x 2), 4.06t(2H, J=6 Hz, H_2-3), 6.03s(2H, OCH_2O), 6.70s(1H, H-5), 6.95, 7.22 AB-q(2H, J=8 Hz, H-5',6'), 7.48s(1H, H-8)], and methoxyberberal(V)[1%, mp 200-202.5°, m/e:413(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}:1770, 1662, λ_{max}^{MeOH} nm(log ε):223(4.66), 267(4.31), 307 (4.04), δ:2.74-3.12m(2H, H_2-4), 3.32s, 3.79s, 3.96s(each 3H, OCH_3 x 3), 4.04-4.42m(2H, H_2-3), 5.96s(2H, OCH_2O), 6.64s(1H, H-5), 7.10, 7.68 AB-q(2H, J=8 Hz, H-4',3'), 7.34s(1H, H-8)]. The same reaction in the presence of rose bengal gave III, IV, and V in 12, 57, and 16% yield, respectively.

The presence of a secondary amino group in III was proved by its conversion to the N-acetyl derivative(VI)[mp 283-284°, m/e: 455(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}:1711, 1643, δ:2.15s(3H, N-$COCH_3$)]. Hydrolysis of III with 10% hydrochloric acid yielded the diketospirobenzylisoquinoline(VII)[77%, mp 178-179°, m/e:367(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}:1739, 1707, ν_{max}^{MeOH} nm(log ε):247.5(4.63), 291.5(4.13), 334(3.73), δ:2.82t (2H, J=6 Hz, H_2-5), 3.48t(2H, J=6 Hz, H_2-6), 4.05s, 4.10s(each 3H, OCH_3 x 2), 5.81s(2H, OCH_2O), 6.01s(1H, H-1), 6.64s(1H, H-4), 7.41, 7.82 AB-q(2H, J=8 Hz, H-11,12)], which was acetylated to give the N-acetyl derivative(VIII)[mp 282-283°, m/e:409(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742, 1711, 1638, δ:2.14s(3H, N-$COCH_3$)].

Since the spiro-compound(III) has a carbonyl and a ketal group in its molecule, it is possible to transform III into any particular type of the spirobenzylisoquinoline alkaloids,[9] including those with two different substituents on the five-membered ring such as sibiricine.

A possible reaction pathway from II to III, IV, and V could be shown as follows. Photo-oxygenation of II would give the epidioxy compound(A)[10] via zwitterionic peroxide. Methanolysis of A accompanied with deoxygenation might afford the enol(B), which would rearrange to III via the o-quinodimethide(C) similar to that proposed by Nalliah et al.[2] On the other hand, Baeyer-Villiger type



rearrangement of A followed by acyl migration,[11] or rearrangement *via* the aziridine(E)[8] would give IV. The lactone(V) would be derived through the dioxetane(F).[10]

The present one-step transformation of 8-methoxyberberine-phenolbetaine(II) to the spiro-compound(III), coupled with the efficient synthesis[6] of II from berberine(I), provides a simple and general method for the synthesis of the spirobenzylisoquinoline alkaloids.

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