

A PHOTOLYTIC PROTOBERBERINE→SPIROBENZYLISOQUINOLINE REARRANGEMENT

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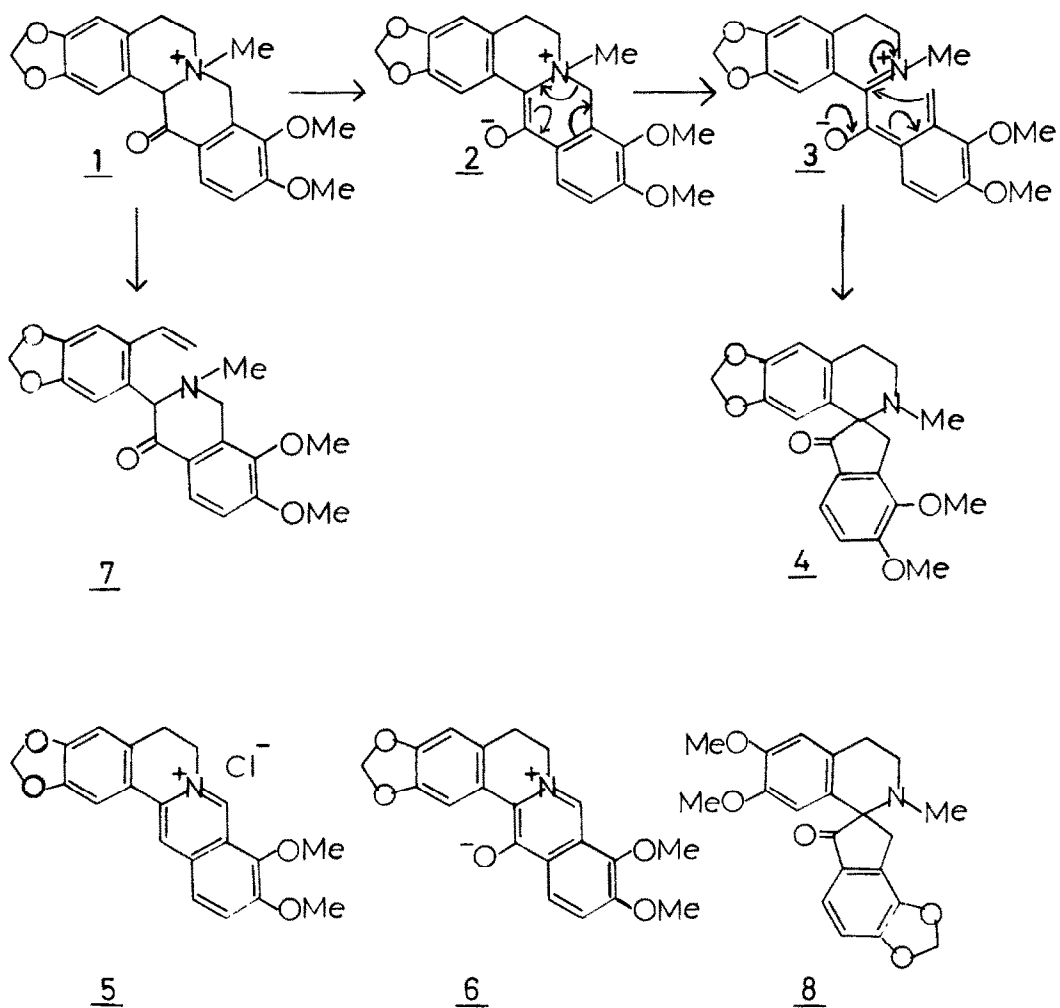
(Received in USA 25 May 1973; received in UK for publication 11 June 1973)

It has been recently demonstrated that thermal base catalysed rearrangements of 13-methyldihydroprotoberberine metho salts containing two phenolic hydroxyl groups proceeded via a quinonemethide intermediate to spirobenzylisoquinolines of the ochotensine type ^{1,2}. This elegant rearrangement was further developed to yield a dibenzocyclopent(b)azepine as the final product when only a single phenolic hydroxyl group was present in the starting protoberberine ³.

The structural relationship between the protoberberines and spirobenzylisoquinolines has also prompted us to seek a similar interconversion. We directed our efforts towards the synthesis of the hitherto unknown 13-ketotetrahydroprotoberberine system, 1 which appeared admirably suited to such a rearrangement by two possible pathways. Electrocyclic bond reorganisation of this system in the enolate form, 2 could result in an o-quinodimethide, 3 which could undergo intramolecular nucleophilic addition of the methylene group to the immonium double bond to yield the spiroketone 4 as shown. (Scheme 1). The negatively charged oxygen atom is placed precisely to promote such addition. Alternatively, there was the possibility that a base catalysed intramolecular Stevens Rearrangement could result in the same product.

The synthesis of 1 from the readily available berberinium chloride, 5 was achieved by reduction of the phenol betaine 6 ⁴ with lithium aluminium hydride in tetrahydrofuran followed directly by methylation of the product with dimethyl sulfate under nitrogen to 1 in 60% overall yield [m.p. 274-6°; $\nu_{\max}^{\text{nujol}}$ 1680 cm^{-1} ; (d_6 -DMSO) 7.87 and 7.41 (AB q, 2H), J_{AB} = 9.0Hz; 6.93(s, 1H); 6.87(s, 1H), 6.10(s, 2H), 5.77(s, 1H), 5.23(br. s, 2H); 4.00(s, 3H); 3.90(s, 3H); 3.88(m, 2H); 3.27(m, 2H) and 3.40(s, 3H). $\lambda_{\max}^{\text{MeOH}}$ 230 and 287 nm, $\log \epsilon_{\max}$ 4.29 and 4.30 resp. shifted to 270 and 362 nm, $\log \epsilon_{\max}$ 4.10 and 4.35 resp. in base].

Scheme 1



This compound formed a remarkably stable enolate in the presence of base and all efforts to induce the desired Stevens rearrangement with a variety of bases and in various solvents resulted either, in the recovery of starting material or, when dipolar aprotic solvents were used (e.g. HMPT), in the formation of the styrene 7 by a Hofmann degradation. It is possible that steric constraints prevent the recombination of the radical pair ⁵ to produce the spiro compound.

Upon photolysis of 1 in a basic medium (NaH, ethanol) i.e. as the enolate 2, under nitrogen, at 3500 Å, for 24 hours, the desired rearrangement to 4 was achieved. [45% yield; m.p. 163-4°; $\nu_{\max}^{\text{CHCl}_3}$ 1706 cm^{-1} ; $\delta(\text{CDCl}_3)$ ⁶ 7.58 and 7.03 (AB q, 2H), $J_{\text{AB}} = 8.2\text{Hz}$; 6.56(s, 1H) C₄-H; 6.09 (s, 1H) C₁-H; 5.81(q, 2H), O-CH₂-O; 3.98(s, 3H), and 3.92(s, 3H) 2xOCH₃; 3.57 and 3.28 (AB q, 2H) $J_{\text{AB}} = 18.0\text{Hz}$, C₉-2H; 2.70-3.10(m, 4H); 2.28(s, 3H) N-CH₃. $\lambda_{\max}^{\text{EtOH}}$ 237 and 292 nm, $\log \epsilon_{\max}$ 4.38 and 4.33 resp. m/e 367·1398; C₂₁H₂₁N₂O₅ requires 367·1420]. All spectral properties of the spiroketone, 4 are virtually identical with those of an isomeric compound 8, synthesised earlier ⁷ by standard methods.

Experiments designed to confirm the proposed mechanism are now underway; in particular it is envisaged that the o-quinodimethide intermediate could be trapped as a Diels-Alder adduct ⁸ in the photolysis of this or a related system. Furthermore, the addition step of the mechanism is strikingly similar to the recently reported ⁹ intramolecular cycloaddition of an o-quinodimethide to an olefinic double bond. Moreover, in a subsequent adaptation of this reaction, a thermal rearrangement of a benzocyclobutenyl precursor via such an o-quinodimethide was claimed ¹⁰ to produce the spirobenzylisoquinoline system in low yield.

The present method constitutes the first application of photochemistry to the synthesis of a spirobenzylisoquinoline and has certain practical advantages. A carbonyl group of the five-membered ring is readily amenable to modification, as desired, for the synthesis of any particular alkaloid of the spirobenzylisoquinoline group ¹¹ possessing a single substituent on the five-membered ring. It also holds promise of being adaptable to the synthesis of alkaloids of the sibiricine ¹² type which carry two substituents on the five membered ring. Studies to realise this goal are being actively pursued. ¹³

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Acknowledgements

Financial support of this work from the National Research Council of Canada is gratefully acknowledged.