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A PHOTOCHEMICAL APPROACH TO PROTOBERBERINE ALKALOIDS

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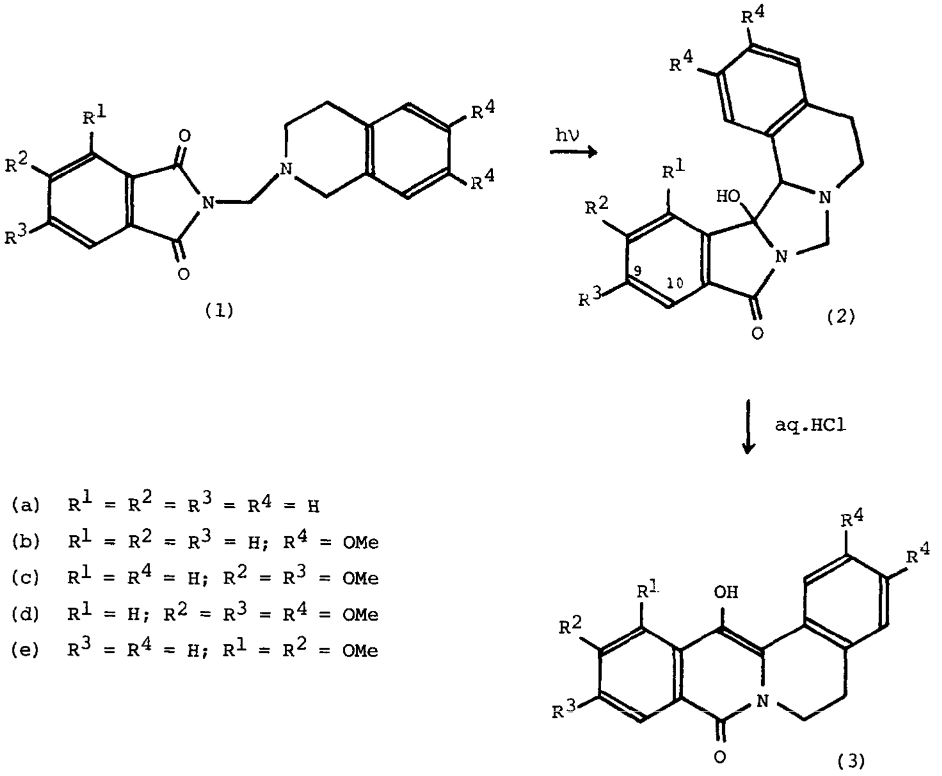
Summary: Photochemical cyclisation of methoxy-substituted N-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)phthalimides and subsequent treatment of the photoproduct with aqueous acid leads to oxygenated compounds with the protoberberine skeleton.

The value of photochemical cyclisations in the synthesis of a variety of alkaloid skeletons has been recognised for some time. One of the most widely used reactions is the photocyclisation of enamides, which has provided a useful route to aporphine, protoberberine, yohimbane and other alkaloid systems.[1,2] We now report a different approach to the synthesis of protoberberines, employing as the key stage the photocyclisation of Mannich bases derived from a phthalimide, formaldehyde, and a tetrahydroisoquinoline.

We have shown previously[3] that irradiation of Mannich bases of phthalimide gives polycyclic compounds with a new imidazolidine ring, and that compound (1a) gives the pentacyclic product (2a).[4] Treatment of (2a) with aqueous HCl produces a dibenzo[a,g]quinolizin-8-one (3a) which has the ring system of the protoberberine alkaloids. The overall yield of (3a) from (1a) has been improved to 74%.

In isoquinoline alkaloids the aromatic rings generally carry hydroxy, methoxy or methylenedioxy substituents, and so to establish the generality of the conversion we prepared and irradiated the Mannich bases (1b-1e).[5] Irradiation (medium-pressure mercury arc, Pyrex filter, benzene solvent) of the symmetrically substituted substrates (1b-1d) leads in each case to the isolation of one product (2b-2d) in yields ranging from 28 to 76% (not optimised). Key features in the assignment of structures for (2) are identification of OH ($\bar{\nu}$ 3300 cm^{-1}), C=O ($\bar{\nu}$ 1710 cm^{-1}; δ_C 174 ppm), quaternary (O)C(N) (δ_C 97 ppm), methine (δ_H 4.5; δ_C 67 ppm) and cyclic (N)CH$_2$(N) (δ_H AB pattern at 4.4 and 4.7 ppm).

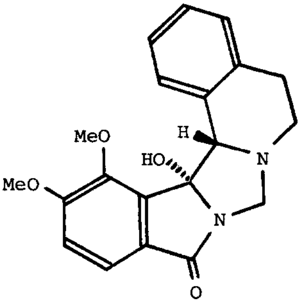


(1) (2) (3)

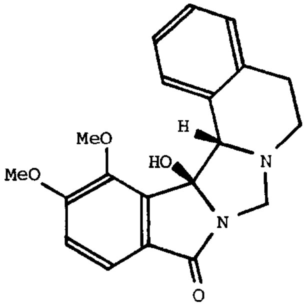
(a) $R^1 = R^2 = R^3 = R^4 = H$
(b) $R^1 = R^2 = R^3 = H$; $R^4 = OMe$
(c) $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
(d) $R^1 = H$; $R^2 = R^3 = R^4 = OMe$
(e) $R^3 = R^4 = H$; $R^1 = R^2 = OMe$

On heating (2b) or (2c) under reflux with aqueous hydrochloric acid (2M), the methoxy-substituted dibenzo[a,g]quinolizin-8-ones (3b,3c) are obtained in yields of 28 and 40% respectively. Of particular interest in the assignment of the enol structure for these 4-hydroxyisoquinolin-1-ones are the infrared absorption at 3100 cm^{-1}, the ready formation of an acetate, and the reversible shift in the ultraviolet absorption brought about by the addition of sodium hydroxide ($\lambda_{max.}$ (EtOH) is 335-340 nm, which on adding NaOH shifts to about 395 nm). This acid-treatment of the photoproduct is also successful in converting (2d) into 13-hydroxy-8-oxoxylopinine (3d) in 35% yield.[6]

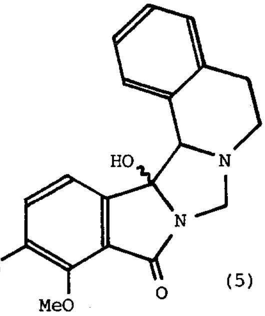
Many of the protoberberine alkaloids have methoxy (or hydroxy) groups at positions C-9 and C-10 rather than at C-10 and C-11 as in xylopinine, and so the orientation of reaction for the unsymmetrically substituted compound (1e) is of considerable interest. Irradiation (medium-pressure mercury arc, Pyrex filter, acetonitrile solvent) gives three compounds which can be separated by silica-gel chromatography (chloroform/methanol eluant). The yields of the three products are 51, 8 and 26%, and the structures assigned are (4a), (4b), and (5) respectively. A fourth product was detected by t.l.c. that might be the stereoisomer of (5).



(4a)



(4b)



(5)

The assignment of orientation is based largely on n.m.r. data. Compounds (4a) and (4b) give rise to doublets (J = 8Hz) in the proton n.m.r. spectra at 6.9/7.25 and 7.05/7.5 ppm respectively, corresponding to two aromatic protons of which one is ortho to carbonyl and para to methoxy; (5) gives rise to an AB pattern centred at 6.7 ppm, which is consistent with neither proton being ortho to carbonyl but both being ortho or para to methoxy. One of the carbon-13 signals for a quaternary aromatic carbon is at 157 ppm for (4a/b) but at 153 ppm for (5) in keeping with this carbon being para to the carbonyl group in (4) but ortho or meta to it in (5); the hydrastines[7] and related compounds provide models for the chemical shift values for the methoxy-bearing carbons in (5).

In general the sequence of reactions (1) → (2) → (3) provides a convenient route to dibenzo[a,g]quinolizines with oxygenated functionality, involving the formal linking of a tetrahydroisoquinoline to a phthalic acid derivative to form a new ring. However, for the unsymmetrical compound (1e) the major orientation of reaction is not that required for making many of the protoberberine alkaloids. Studies are continuing in an attempt to reverse the observed regioselectivity.

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5 All new compounds gave satisfactory elemental microanalysis results and spectral data in accord with the structures assigned.

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