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A ONE-STEP CONVERSION OF ISOQUINOLINIUM SALTS INTO NAPHTHALENE DERIVATIVES[1]

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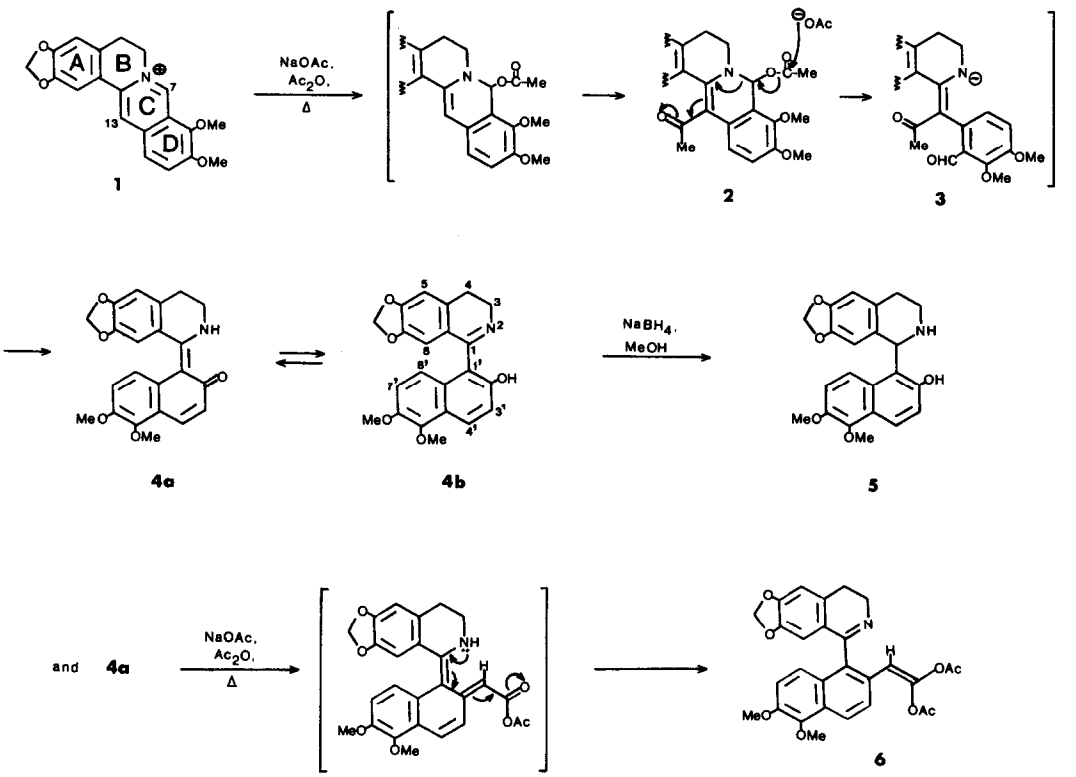
Isoquinolinium salts are known to undergo ring opening when strong electron withdrawing groups are directly bonded to the nitrogen atom.[3a-d] We now wish to report a new and unusual ring opening of alkyl isoquinolinium salts. Treatment of such salts with sodium acetate and acetic anhydride produces naphthalene derivatives.

Heating berberine chloride (1) with sodium acetate and acetic anhydride at 110° under nitrogen for 48 hrs generated the nearly white naphthyl derivative 4, $C_{22}H_{19}NO_4$, mp 219° (EtOH), in 39% yield, as well as the yellow vinyl diacetate 6, $C_{28}H_{25}NO_8$, mp 206-208° (MeOH), in 24% yield. Product 4, which can exist in solution as tautomers 4a and 4b, may be formed through the steps indicated in Scheme I.

The opening of ring C of the berberine system proceeds because of the electronegativity of the C-13 acetyl group in intermediate 2 which provides resonance stabilization to anion 3. Subsequent intramolecular aldol condensation then furnishes compound 4 which dissolves in chloroform to give a red solution due to predominance of the tautomeric form 4a. Recrystallization from ethanol yields nearly colorless crystals in which form 4b must prevail.[4]

Compound 4 shows m/e 377 (M^+) (base); λ_{max}^{EtOH} 233, 270, 278, 291sh, 320 and 362sh (log ε 5.06, 4.09, 4.17, 4.06, 4.11 and 3.82); $\nu_{max}^{CHCl_3}$ 1600 cm^{-1} (arom.) and 1625 cm^{-1} (C=O). Nmr ($CDCl_3$, 60 MHz) δ2.50-3.80 (4H, m, CH_2-CH_2), 3.90 and 4.00 (2 x 3H, 2s, 2 OCH_3), 5.90 (2H, q, J = 1 Hz, O-CH_2-O), 6.37 (1H, s, H-5 or H-8), 6.77 (1H, s, H-5 or H-8), 6.98 (2H, s, H-7' and H-8'), 7.66 (2H, q, J = 10 Hz, ics = 52 Hz, H-3' and H-4'), 8.85 (1H, broad s, NH).

Scheme I



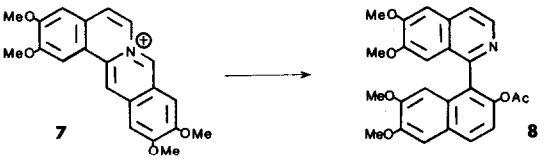
Reduction of 4 with $NaBH_4$ in MeOH led in quantitative yield to the colorless 1-(α-naphthyl)tetrahydroisoquinoline derivative 5, $C_{22}H_{21}NO_5.C_2H_5OH$, mp 150° (EtOH); m/e 379 (M^+), 364, 362, 335, 204 (base), 189 and 185; λ_{max}^{EtOH} 236, 272, 283, 293 and 348 nm (log ε 4.92, 4.03, 4.14, 4.11 and 3.87), with a bathochromic shift in base due to the presence of the phenolic function. Nmr ($CDCl_3$) δ4.00 and 4.03 (2 x 3H, 2s, 2 OCH_3), 5.77 (2H, q, J = 1 Hz, OCH_2O), 5.87 (1H, s, H-1), 6.10 (1H, s, H-8), 6.58 (1H, s, H-5), 7.00-8.20 (4H, 2 superimposed q, H-3' and H-4', and H-7' and H-8').

The vinyl diacetate 6 exhibits m/e 503 (M^+), 374 (base); λ_{max}^{EtOH} 236, 260sh, 267, 297sh, 324 and 382 nm (log ε 4.87, 4.45, 4.49, 4.18, 4.05 and 4.03); $\nu_{max}^{CHCl_3}$ 1723 cm^{-1} (broad, C=O). Nmr ($CDCl_3$, 60 MHz) δ2.02 (6H, s, 2 CH_3CO), 2.22-3.75 (4H, m, CH_2-CH_2), 3.88 and 3.97 (2 x 3H, 2s, 2 OCH_3), 6.07 (2H, broad d, J = 3 Hz, O-CH_2-O), 6.30 (1H, s, H-5 or H-8), 6.74

(1H, s, HC=C), 6.95 (1H, s, H-5 or H-8), 7.05 (2H, s, H-7' or H-8'), 7.87 (2H, q, J = 9 Hz, ics = 55 Hz). Compound 6 must be formed by further reaction of 4 since treatment of 4 with acetic anhydride and sodium acetate at 110° generated 6 (Scheme I).

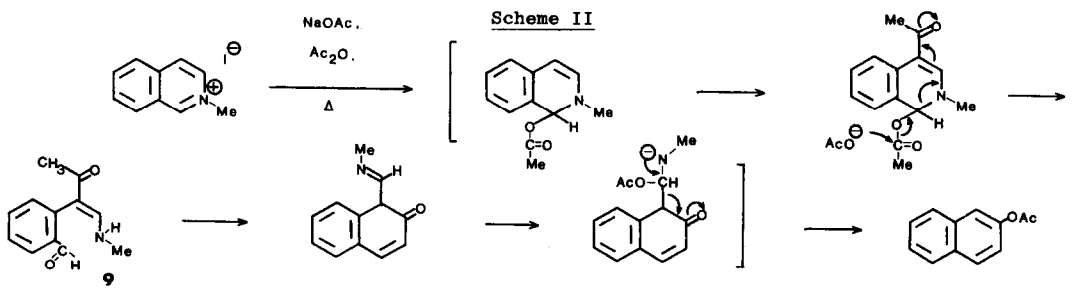
Although berberine has been known since 1826[5] and various efforts have been made to open ring C of this alkaloid,[3b,c] the present report represents the first successful cleavage of the N-7 to C-8 bond of a berberine derivative.

In a related experiment, 2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium chloride (7)[6] was heated at 110° with sodium acetate and acetic anhydride for 48 hrs to generate predominantly one product, the 1-(α-naphthyl)isoquinoline acetate 8, $C_{25}H_{23}NO_6$, mp 102-104° (ether), m/e 433 (M^+), 418, 391 (base) and 376; λ_{max}^{EtOH} 234, 313sh and 326 nm (log ε 5.14, 4.00 and 4.07) in 70% yield. In this case, the presence of the additional double bond in ring B induces immediate aromatization of the product.



To test the generality of this transformation of isoquinolinium salts into naphthalene derivatives, isoquinoline methiodide was treated with sodium acetate and acetic anhydride for 48 hrs at 110°. Several components were detected by tlc in the resulting mixture. The main product, obtained in 15% yield based on the weight of unreacted methiodide salt, proved to be β-naphthyl acetate whose formation is rationalized in Scheme II.[7]

Scheme II



The transformation of isoquinolinium salts into naphthalene derivatives can, therefore, be achieved using sodium acetate and acetic anhydride. The yields will vary depending upon the nature of the starting isoquinolinium salt.

References

1. This project was supported by NIH research grant CA-11450 awarded by the National Cancer Institute, PHS/DHEW. The authors are grateful to Professor C.K. Bradsher for a sample of authentic 7, and to Dr. B.B. Brown of S.B. Penick and Co. for a gift of berberine chloride. Satisfactory elemental analyses were obtained for all new compounds.
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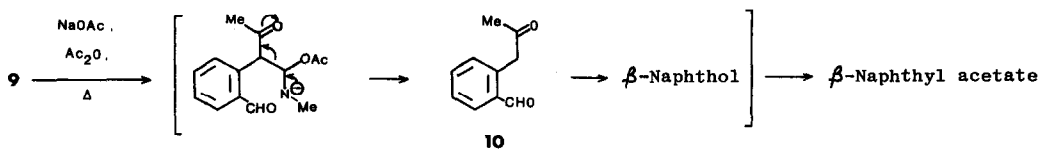
3. (a) W.J. Gensler in Heterocyclic Compounds, Vol. 4, ed. by R.C. Elderfield, J. Wiley and Sons, Inc., New York (1952), pp. 454-490; (b) D. Beke, Adv. Heterocycl. Chem., 1, 167 (1963); (c) V. Šimanek, V. Preininger, S. Hegerová and F. Šantavy, Coll. Czech. Chem. Commun., 37, 2746 (1972); and (d) M. Shamma and L. Tőke, Chem. Commun., 740 (1973).
4. Tautomer 4a can exist as two geometric isomers which may be interconvertible. No specific preferred geometry is herewith indicated. For related examples see L. Tőke, G. Blaskó, L. Szabó, G. Tóth and Cs. Szántay, Acta Chim. Acad. Sci. Hung., 81, 97 (1974).
5. For a review of the early chemistry of berberine see R.H.F. Manske and W.R. Ashford in The Alkaloids, Vol. 4, ed. by R.H.F. Manske and H.L. Holmes, Academic Press, New York (1954), pp. 84-91.
6. C.K. Bradsher and N.L. Dutta, J. Org. Chem., 26, 2231 (1961); and T. Kametani, M. Takeshita, F. Satoh and K. Nyu, J. Pharm. Soc. Japan, 94, 478 (1974).
7. The direct yield of β-naphthyl acetate was 8%. An alternate but related mechanism for the formation of this product would involve conversion of 9 to the ketoaldehyde 10 which could then aldolize to β-naphthol:



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