

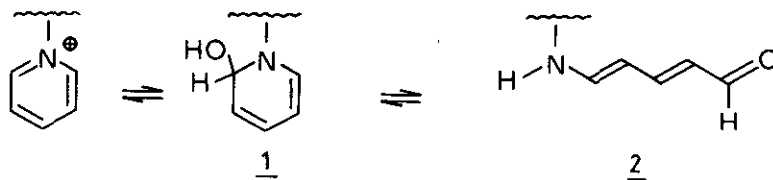
PREPARATION OF INDOLOQUINOLIZIDINE DERIVATIVES THROUGH
PYRIDINE PSEUDOBASES

Mauri Lounasmaa* and Tarja Ranta

Laboratory for Organic and Bioorganic Chemistry, Department of Chemistry,
Technical University of Helsinki, SF-02150 Espoo 15, Finland

Abstract - The pseudobase formation from appropriate pyridinium salts with a convenient leaving group on the C-3 side-chain can be exploited for the preparation of indoloquinolizidine derivatives.

Nucleophilic attack of OH^- ions at the C-2 position of pyridinium salts, leading to pseudobases (e.g. 1), is a well-known reaction.^{1,2} Very often it is followed by ring opening and the formation of glutaconaldehyde derivatives (e.g. 2).^{3,4} In either case, the acid treatment generally conducts back to pyridinium salts (Scheme 1).



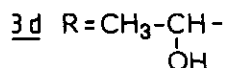
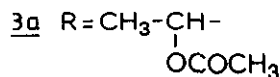
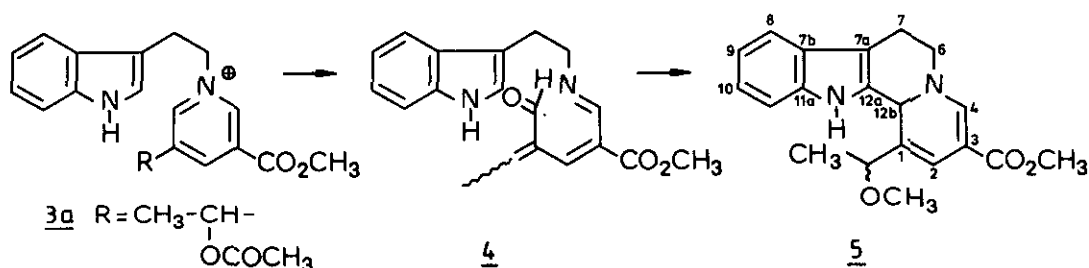
Scheme 1

In the course of attempts to prepare indole alkaloid models of indoloquinolizidine type,^{5,6} we became interested in the applicability of the pseudobase/glutaconaldehyde derivative route to the synthesis of indoloquinolizidine derivatives from appropriate 1-[2-(3-indolyl)ethyl]-pyridinium salts.

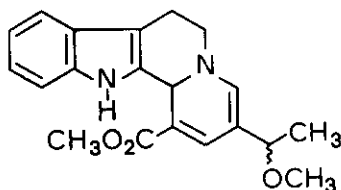
Considering the above reaction course we reasoned that if the procedure could be modified, for example by eliminating an appropriate leaving group from the C-3

side-chain of the intermediate pseudobase, the reversible acid-induced conversion back to pyridinium salt could be avoided and the method would gain much in its synthetic utility. In the present communication we describe the first results obtained with a model compound, which clearly indicate the feasibility of the reasoned method.

When the pyridinium salt 3a⁷ was stirred in aqueous KOH-solution, the glutaconaldehyde analogue 4 was obtained.⁸ Treatment of 4 with MeOH/HCl led to the tetrahydroindoloquinolizidine derivative 5.^{9,10}

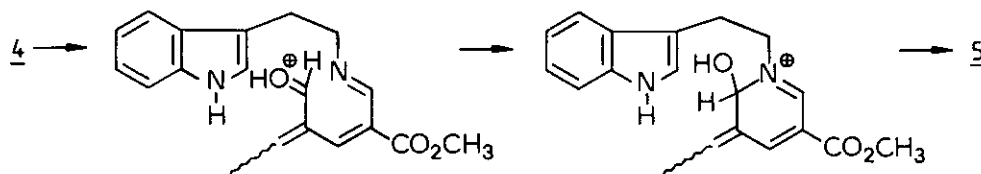


The strong absorption maximum in the UV spectrum of 5 (*vide infra*) at 293 nm ($>N-CH=C-CO_2CH_3$ chromophoric system)¹¹ is in good agreement with the proposed structure and clearly excludes the alternative tetrahydroindoloquinolizidine structure 6 which would be expected to show a UV absorption maximum over 320 nm. As a corollary, it is confirmed that the initial nucleophilic attack of the OH⁻ ion has taken place at C-2 position of the unsymmetrical pyridinium salt.



6

The formation of 5 can be visualized by the formation of a carbinolamine derivative, followed by acid-induced cyclization and addition of the MeO^- ion (Scheme 2).



Scheme 2

The essential contribution of the leaving group on the C-3 side-chain to the success of the present method was shown by the failure to find indoloquinolizidine derivatives when compounds 3b, 3c and 3d (an OH group is a less good leaving group than an acyloxy group) were subjected to similar reaction conditions (*vide supra*).⁷

REFERENCES AND NOTES

1. J. Becher, *Synthesis*, 1980, 589 and references therein.
2. A.N. Kost, S.P. Gromow and R.S. Sagitullin, *Tetrahedron*, 1981, 37, 3423 and references therein.
3. J. Becher, L. Finsen and I. Winckelmann, *Tetrahedron*, 1981, 37, 2375.
4. This includes *cis-trans* isomerization.¹
5. M. Lounasmaa and C.-J. Johansson, *Tetrahedron*, 1977, 33, 113.
6. M. Lounasmaa and A. Koskinen, *Tetrahedron Letters*, 1982, 1489 and earlier references.
7. Compounds 3a-d were prepared by the standard procedure⁵ from tryptophyl bromide and corresponding pyridine derivative.
8. Compound 4 (A *cis-trans* isomerization is possible). Yield 11 %. Amorphous.
 UV (EtOH) λ_{max} 292 (4.3), 411 (3.8) nm. IR (film) 1680, 1640, 1630, 1540 cm^{-1} .
¹H NMR (CDCl_3) δ 1.16 (3H, d, $J = 7$ Hz, $=\text{CH}-\text{CH}_3$), 2.8-3.8 (4H, m, $-\text{CH}_2-\text{CH}_2-$), 3.70 (3H, s, $-\text{OCH}_3$), 4.76 (1H, q, $J = 7$ Hz, $=\text{CH}-\text{CH}_3$), 5.29 (1H, s, $-\text{CH}=\text{C}^1-\text{CO}_2\text{CH}_3$), 6.92 (1H, d, $J = 2$ Hz, indolyl α -H), 7.1-7.5 (5H, m, aromatic protons and $-\text{N}=\text{CH}-$), 8.20 (1H, br s, NH), 9.30 (1H, s, $-\text{CHO}$). MS m/z 324 (M^+ , 16 %), 309 (30%), 144 (82 %), 143 (100 %), 130 (82 %).

9. The healthy influence of the 5-methoxycarbonyl group of the pyridinium salt 3a in the successful execution of the reactions needs to be underlined. When the 5-desmethoxycarbonyl analogue of 3a was subjected to similar reaction conditions, just a trace of the corresponding tetrahydroindoloquinolizidine derivative was detected.
10. Compound 5. Yield 32 %. Amorphous. UV (EtOH) λ_{\max} 227 (4.3), 293 (4.1) nm. IR (film) 1698, 1645 cm^{-1} . ^1H NMR (CDCl_3) δ 1.27 (3H, d, $J = 7$ Hz, $-\text{CH}_3$), 2.8-3.7 (4H, m, $-\text{CH}_2-\text{CH}_2-$), 3.74 (3H, s, $-\text{OCH}_3$), 3.78 (3H, s, $-\text{OCH}_3$), 4.05 (1H, q, $J = 7$ Hz, $-\text{CH}-\text{CH}_3$), 5.19 (1H, d, $J = 2$ Hz, H-12b), 6.43 (1H, s, H-2), 7.13 (1H, d, $J = 2$ Hz, H-4), 7.30-7.60 (4H, m, aromatic protons), 9.31 (1H, br s, NH). ^{13}C NMR (CDCl_3) C(1) 115.2, C(2) 134.4, C(3) 121.4, C(4) 151.7, C(6) 48.4, C(7) 21.9, C(7a) 109.9, C(7b) 126.5, C(8) 118.0, C(9) 118.7, C(10) 121.4, C(11) 110.9, C(11a) 132.4, C(12a) 136.1, C(12b) 49.5; $-\text{CH}-\text{CH}_3$ 18.2, $-\text{CO}_2\text{CH}_3$ 51.6, $-\text{CH}-\text{OCH}_3$ 53.2, $-\text{CH}-\text{OCH}_3$ 60.9, $-\text{CO}_2\text{CH}_3$ 168.8. MS m/z 338 (M^+ , 100 %), 337 (20 %), 323 (94 %), 307 (21 %), 291 (24 %), 279 (42 %).
11. C. Djerassi, H.J. Monteiro, A. Walser and L.J. Durham, J. Am. Chem. Soc., 1966, 88, 1792.

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