PREPARATION OF INDOLOQUINOLIZIDINE DERIVATIVES THROUGH PYRIDINE PSEUDOBASES

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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).

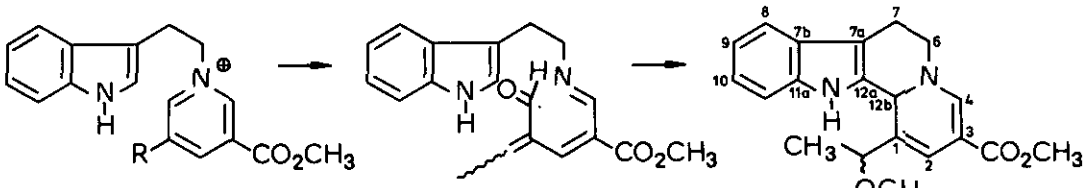
1 2

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 3a[7] was stirred in aqueous KOH-solution, the glutaconaldehyde analoque 4 was obtained.[8] Treatment of 4 with MeOH/HCl led to the tetrahydroindoloquinolizidine derivative 5.[9,10]



3a R = CH_3-CH(OCOCH$_3$)-

4

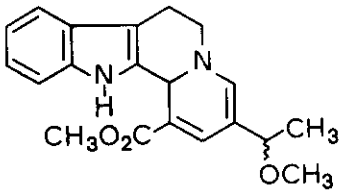
5

3b R = H

3c R = CH_3-CH_2-

3d R = CH_3-CH(OH)-

The strong absorption maximum in the UV spectrum of 5 (vide infra) at 293 nm ($\geq$N-CH=$\overset{|}{C}$-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.



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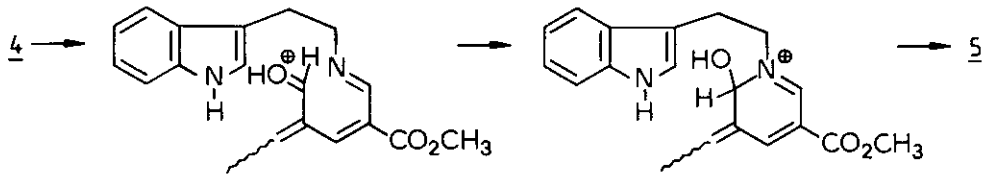
The formation of 5 can be visualized by the formation of a carbinolamine derivative, followed by acid-induced cyclization and addition of the MeO^- ion (Scheme 2).



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 procedure[5] 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, =CH-C<u>H</u>$_3$), 2.8-3.8 (4H, m, -CH_2-CH_2-), 3.70 (3H, s, -OCH_3), 4.76 (1H, q, J = 7 Hz, =C<u>H</u>-CH_3), 5.29 (1H, s, -C<u>H</u>=C(-CO_2CH_3)-), 6.92 (1H, d, J = 2 Hz, indolyl α-H), 7.1-7.5 (5H, m, aromatic protons and -N=CH-), 8.20 (1H, br s, NH), 9.30 (1H, s, -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 analoque 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}. ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, d, J = 7 Hz, $-CH_3$), 2.8-3.7 (4H, m, $-CH_2-CH_2-$), 3.74 (3H, s, $-OCH_3$), 3.78 (3H, s, $-OCH_3$), 4.05 (1H, q, J = 7 Hz, $-CH-CH_3$), 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; $-CH-CH_3$ 18.2, $-CO_2CH_3$ 51.6, $-CH-OCH_3$ 53.2, $-CH-OCH_3$ 60.9, $-CO_2CH_3$ 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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