SODIUM DITHIONITE REDUCTION OF 1-[2-(3-INDOLYL)ETHYL]PYRIDINIUM SALTS: FORMATION OF A 1,2-DIHYDROPYRIDINE DERIVATIVE VIA THE CORRESPONDING 1,4-DIHYDROPYRIDINE DERIVATIVE

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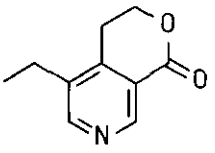
Abstract - The 1,2-dihydropyridine derivative (3) was prepared by the sodium dithionite reduction of 1-[2-(3-indolyl)ethyl]pyridinium bromide (2). It is shown that the isolated 1,2-dihydropyridine derivative (3) is a rearrangement product of the initially formed unstable 1,4-dihydropyridine derivative (4).

The sodium dithionite reduction of alkylpyridinium salts possessing an electron-withdrawing group at the 3-position of the pyridinium ring to the corresponding 1,4-dihydropyridine derivatives, followed by acid-induced cyclization of the appropriate derivatives to indoloquinolizidine systems, has proven to be very useful in the preparation of indole alkaloid models of the vallesiachotamine type.[1-4]

It has also been shown that sodium dithionite reductions of certain alkylpyridinium salts can lead to 1,2- and/or 1,6-dihydropyridine derivatives.[5-8] We have exploited the 1,2-dihydropyridine formation in our syntheses of desmethylhexahydrovallasiachotaminelactones[9] and gambirtannine derivatives.[10]

The mechanism of the dithionite - reduction of pyridinium salts was long a matter of controversy,[11-20] but it is nowadays generally accepted that the reaction proceeds through a sulfinate intermediate, which looses SO_2.[21] However, the formation of the 1,2- and/or 1,6-dihydropyridine derivatives, as direct reduction products or through rearrangement taking place in the primarily formed 1,4-dihydropyridine derivatives, still remains open.

We recently used dithionite - treatment followed by catalytic reduction of the formed 1,4-dihydropyridine in the preparation of 1,4,5,6-tetrahydropyridine, where the C(4)H and C(5)H are trans to each other (cf. ref. 22, compound 1g).



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With the above information in mind we reasoned that the alkylpyridinium salt (2), prepared from the pyridine lactone (1) and tryptophyl bromide,[23] would be ideally suited for an examination of the structure(s) of dihydropyridine(s) prepared by dithionite reduction, and, in the case of 1,4-dihydropyridine formation, for the preparation of 1,4,5,6-tetrahydropyridine (7) [C(4)H-C(5)H trans], useful for syntheses of indole alkaloids of 18,19-dihydrocorynantheol type.[24]

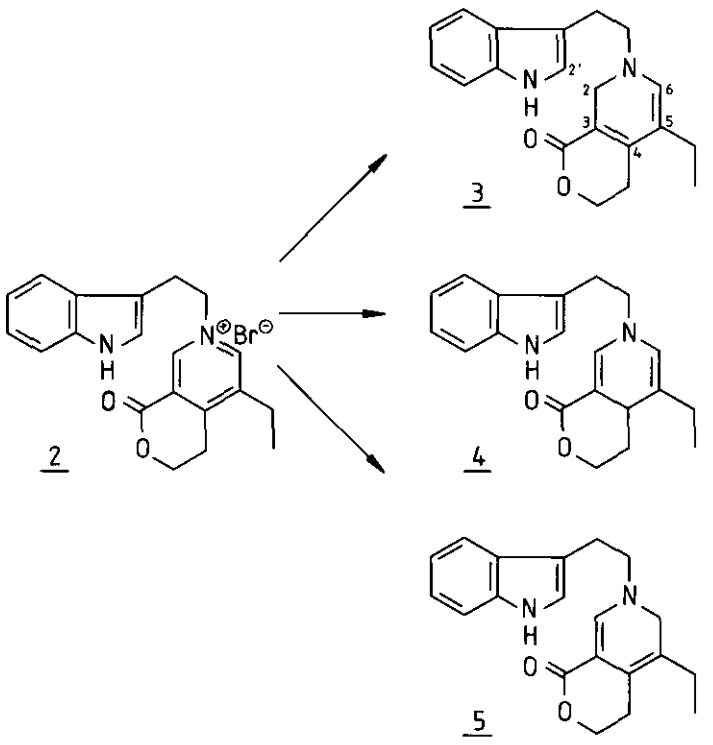
RESULTS AND DISCUSSION

Sodium dithionite reduction of the pyridinium salt (2), using a relatively long reaction time (~ 5 h) and $NaHCO_3$ buffer, afforded a dihydropyridine derivative with the 1,2-dihydropyridine structure (3). The isolation of this derivative is in good agreement with our earlier results when we

prepared desmethylhexahydrovallesiachotaminelactones via appropriate 1,2-dihydropyridine derivatives [cf. ref. 9, compound(8)].

However, we discovered that when the sodium dithionite reduction of the pyridinium salt (2) (vide supra) was interrupted after 1 to 1.5 h reaction time, the reaction mixture contained mainly another unstable dihydropyridine derivative [tlc; m/z 322 (M^+)].

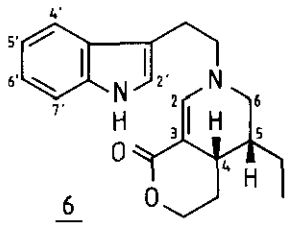
In theory, the sodium dithionite reduction of the pyridinium salt (2) to the dihydropyridine stage can lead to three products [compounds (3), (4) and (5) (Scheme 1)]. Of these, the 1,2-dihydropyridine derivative (3),



Scheme 1

exclusively isolated after the 5 h sodium dithionite reduction of the pyridinium salt (2) (vide supra), was not present in appreciable amount after the 1 - 1.5 h reaction time. The non-identity of the isolated product with the 1,2-dihydropyridine derivative (3), limited our choice between structures (4) (1,4-dihydropyridine derivative) and (5) (1,6-dihydropyridine derivative).

To resolve the problem, complicated by the instability of the formed dihydropyridine derivative, we decided to reduce catalytically (Pd/C) the crude dithionite reduction product without further purification. We expected that structure (4) would lead relatively easily to the 1,4,5,6-tetrahydropyridine structure (6) [C(4)H-C(5)H cis] and in lesser amount to the highly desired 1,4,5,6-tetrahydropyridine structure (7) [C(4)H-C(5)H trans] [cf. ref. 14, compound 1g)], whereas structure (5) would lead exclusively to the 1,4,5,6-tetrahydropyridine structure (6) [C(4)H-C(5)H cis], but only with great difficulty, if at all (tetrasubstituted double bond).



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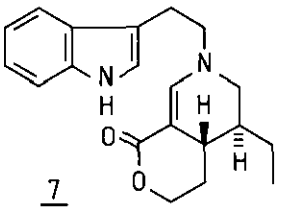

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The catalytic reduction (Pd/C) of the unpurified reaction mixture obtained after 1 - 1.5 h sodium dithionite reduction (vide supra), led relatively easily (cf. Experimental) to the 1,4,5,6-tetrahydropyridine derivative (6) [C(4)H-C(5) H cis], which was also prepared directly from the pyridinium salt (2) by catalytic reduction (cf. Experimental). However, the expected

and highly desired isomeric 1,4,5,6-tetrahydropyridine derivative (7) [C(4)H-C(5)H trans] was not detected in the reaction mixture.

Although the ease of the catalytic reduction (Pd/C) supported the presence of the 1,4-dihydropyridine derivative (4) in the reaction mixture after the short time sodium dithionite reduction (vide supra), the absence of the expected isomeric 1,4,5,6-tetrahydropyridine derivative (7) did not permit categorical exclusion of the alternative 1,6-dihydropyridine structure (5).

To decide between the alternative structures (4) and (5), we repeated the catalytic reduction (Pd/C) of the unpurified reaction mixture from the short time sodium dithionite reduction (vide supra) but now using D_2 instead of H_2. The compound obtained this time was the C(5)D-C(6)D analogue of the 1,4,5,6-tetrahydropyridine derivative (6) (^{13}C Nmr; cf. Figure 1). This unequivocally proved that the dihydropyridine derivative primarily formed in the sodium dithionite reduction of the pyridinium salt (2) was the 1,4-dihydropyridine derivative (4) and not the 1,6-dihydropyridine derivative (5).

The present results show that the 1,2-dihydropyridine derivative (3), obtained by sodium dithionite reduction of the pyridinium salt (2) using a relatively long reaction time (~ 5 h) (vide supra), is a rearrangement product of the primarily formed 1,4-dihydropyridine derivative (4) (Scheme 2). As far as we know, this is the first time it has been unequivocally shown that the formation of a 1,2-dihydropyridine derivative by sodium dithionite reduction of a pyridinium salt passes through the 1,4-dihydropyridine derivative.

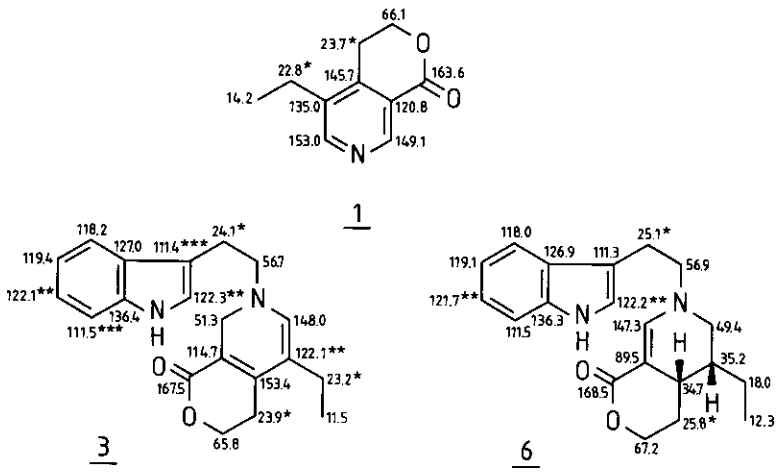
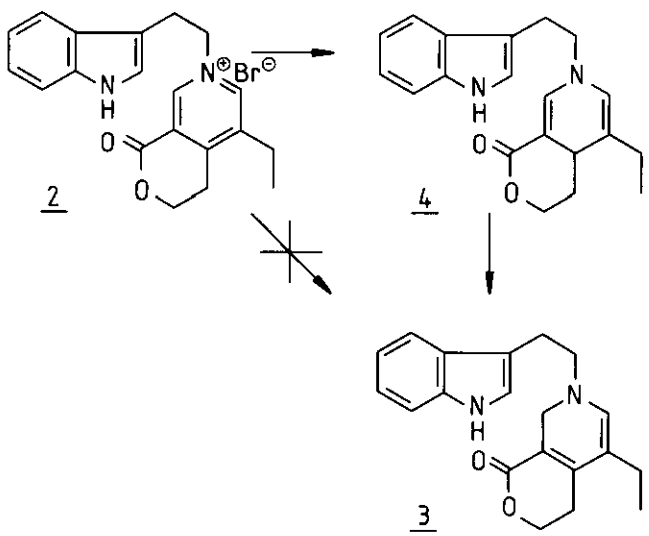


Figure 1



Scheme 2

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer. Absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. ^{1}H and ^{13}C Nmr spectra were recorded in $CDCl_3$ with a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^{1}H Nmr) and 15.04 MHz (^{13}C Nmr). Chemical shift data are given downfield from TMS. Abbreviations s, d, t, m, br, and def are used to designate singlet, doublet, triplet, multiplet, broad, and deformed, respectively. For ^{13}C Nmr data see Figure 1. Mass spectrometry was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound (1)

3-Ethyl-4-methyl-5-methoxycarbonylpyridine[22,25] (483 mg, 2.70 mmol), NaOH (130 mg, 3.25 mmol), methanol (10 ml), and water (0.25 ml) were refluxed for 16 h. About 2/3 of the solvent was evaporated and diethyl ether (35 ml) was added. The precipitate that formed was filtered and dried. To the formed Na-salt (500 mg, 2.67 mmol), formaldehyde (35%, 0.5 ml), water (40 ml), and toluene (40 ml), were added, and the mixture was stirred for 24 h (autoclave, 130°C). The cooled solution was extracted several times with toluene, and the combined extracts were washed with water and dried (Na_2SO_4). The crude product was purified by column chromatography (silica gel, CH_2Cl_2). Two lactonic products were isolated: lactone (1) and, as a minor component, a compound formed from the reaction of two units of formaldehyde with the Na-salt (vide supra), followed by the cleavage of water (M^+ at m/z 189). The water phase contained considerable amounts of the unreacted Na-salt.

Lactone (1). Yield: 202 mg (40%) (after repeated recycling of the unreacted Na-salt). Mp 75-77°C (n-hexane) (lit., 76-78°C,[25] 74-76°C[26]). Ir 1720 (C=O). ^{1}H Nmr 1.27 (3H, t, J = 7.5 Hz, $-CH_2-\underline{CH_3}$), 2.74 (2H, q, J = 7.5 Hz, $-\underline{CH_2}-CH_3$), 3.06 (2H, t, J = 6.0 Hz, $-O-CH_2-\underline{CH_2}-$), 4.58 (2H, t, J = 6.0 Hz, $-O-\underline{CH_2}-CH_2-$), 8.60 and 9.08 (2H, 2 x s, arom. H), m/z 177 (M^+, 100%), 162,

147, 119.

Preparation of compound (2)

Alkylation of compound (1) (100 mg, 0.56 mmol) with tryptophyl bromide[23] (127 mg, 0.57 mmol) afforded salt (2). Yield: 215 mg (96%).

Preparation of compound (3)

$Na_2S_2O_4$ (180 mg, 1.03 mmol) was added during 30 min to a stirred mixture of salt (2) (60 mg, 0.15 mmol), $NaHCO_3$ (120 mg, 1.43 mmol), MeOH (8 ml), and H_2O (16 ml). Stirring was continued (N_2-atm., room temperature) for 5 h. Water was added and the mixture was extracted several times with CH_2Cl_2. The combined extracts were washed with water and dried (Na_2SO_4). The unstable product was immediately analyzed without further purification. Yield: 28 mg (58%). Amorphous material. Ir 3300 (NH), 1720 (C=O). ^1H Nmr 0.94 (3H, t, J = 7.0 Hz, $-CH_2-\underline{CH_3}$), 4.05-4.30 (4H, m, $-CH_2-O-$ and 2 x H-2), 6.98 (1H, d, J = 2.5 Hz, H-2'), 7.10-7.40 (4H, m, H-4', 5', 6', 7'), 7.45 (1H, d, J = 1 Hz, H-6), 8.58 (1H, br s, NH), m/z 322 (M^+), 192, 144 (100%), 130; exact mass: 322.1695 (calcd for $C_{20}H_{22}N_2O_2$: 322.1681).

Preparation of compound (6) by successive sodium dithionite and catalytic (H_2/Pd/C) reductions

$Na_2S_2O_4$ (450 mg, 2.58 mmol) was added to a stirred mixture of salt (2) (150 mg, 0.37 mmol), $NaHCO_3$ (450 mg, 5.36 mmol), MeOH (10 ml), and H_2O (20 ml). Stirring was continued for 1.5 h (N_2-atm., room temperature). Water was added and the mixture was extracted several times with CH_2Cl_2. The combined extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated in vacuo. The crude product was immediately dissolved in MeOH (40 ml) and hydrogenated [Pd/C (10%), 16 h)] and purified by chromatography (silica gel, CH_2Cl_2/MeOH; 9/1). Yield: 42 mg (35 %). mp 152-154°C (benzene) (lit.,[25] 155-156°C). Ir 3280 (NH), 1660 (C=O). ^1H Nmr 0.92 (3H, def, $-CH_2-\underline{CH_3}$), 6.92 (1H, d, J = 2.5 Hz, H-2'), 7.15-7.50 (4H,

m, H-4', 5', 6', 7'), 7.54 (1H, d, J = 1 Hz, H-2), 8.60 (1H, br s, NH), m/z 324 (M^+), 194 (100%), 144, 143, 130; exact mass: 324.1845 (calcd for $C_{20}H_{24}N_2O_2$: 324.1838). (cf. ref. 25).

Preparation of compound (6) by catalytic hydrogenation

Salt (2) (120 mg, 0.30 mmol) was dissolved in MeOH (30 ml) buffered with Na_2HPO_4 x 2 H_2O (514 mg) and NaH_2PO_4 x 2 H_2O (208 mg). Catalytic hydrogenation [Pd/C (10%), 15 h] afforded compound (6). Yield: 57 mg (59%). Analytical data were identical with those of compound (6) prepared by successive sodium dithionite and catalytic reductions (vide supra).

Preparation of compound (6-d_2) by successive sodium dithionite and catalytic (D_2/Pd/C) reductions

Compound (6-d_2) was prepared similarly to compound (6) (successive reductions) described above. Yield: 30%. Ir 3280 (NH), 1660 (C=O). ^{1}H Nmr 0.92 (3H, def, $-CH_2-\underline{CH_3}$), 6.94 (1H, d, J = 2.5 Hz, H-2'), 7.10-7.50 (4H, m, H-4', 5', 6', 7'), 7.52 (1H, d, J = 1 Hz, H-2), 8.58 (1H, br s, NH), m/z 326 (M^+)/325, 196 (100%)/195, 144, 143, 130.

REFERENCES

1. J. H. Supple, D. A. Nelson, and R. E. Lyle, Tetrahedron Lett., 1963, 1645.
2. M. Lounasmaa, P. Juutinen, and P. Kairisalo, Tetrahedron, 1978, 34, 2529.
3. M. Lounasmaa and R. Jokela, Tetrahedron Lett., 1978, 3609.
4. M. Lounasmaa and H.-P. Husson, Acta Chem. Scand., 1979, B33, 466.
5. K. Wallenfels and H. Schuly, Liebigs Ann. Chem., 1959, 621, 178.
6. J.-F. Biellmann and H. Callot, Tetrahedron Lett., 1966, 3991.
7. J.-F. Biellmann and H. J. Callot, Bull. Soc. Chim. Fr., 1968, 1154.
8. J.-F. Biellmann and H. J. Callot, Bull. Soc. Chim. Fr., 1968, 1159.

9. R. Jokela and M. Lounasmaa, Tetrahedron, 1982, 38, 1015.
10. E. Frostell, R. Jokela, and M. Lounasmaa, Acta Chem. Scand., 1981, B35, 671.
11. D. Mauzerall and F. H. Westheimer, J. Am. Chem. Soc., 1955, 77, 2261.
12. R. F. Hutton and F. H. Westheimer, Tetrahedron, 1958, 3, 73.
13. E. M. Kosower and S. W. Bauer, J. Am. Chem. Soc., 1960, 82 , 2191.
14. M. B. Yarmolinsky and S. P. Colowikc, Biochim. Biophys. Acta, 1956, 20, 177.
15. W. S. Caughey and K. A. Schellenberg, J. Org. Chem., 1966, 31, 1978.
16. J.-F. Biellmann and H. J. Callot, Bull. Soc. Chim. Fr., 1968, 1299.
17. A. C. Lovesey and W. C. J. Ross, J. Chem. Soc. (B), 1969, 192.
18. T. J. van Bergen, T. Mulder, R. A. van der Veen, and R. M. Kellogg, Tetrahedron, 1978, 34, 2377.
19. G. Blankenhorn and E. G. Moore, J. Am. Chem. Soc., 1980, 102, 1092.
20. R. M. G. Roberts, D. Ostović, and M. M. Kreevoy, J. Org. Chem., 1983, 48, 2053.
21. O. Louis-André and G. Gelbard, Bull. Soc. Chim. Fr., 1986, 565.
22. M. Lounasmaa, R. Jokela, P. Mäkimattila, and B. Tirkkonen, Tetrahedron, 1990, 46, 2633.
23. T. Hoshino and K. Shimodaira, Liebigs Ann. Chem., 1935, 520, 19.
24. C. Szántay, G. Blasko, K. Honty, and G. Dörnyei, "The Alkaloids", Vol. 27, ed. by A. Brossi, Academic Press, San Diego, 1986, p. 174.
25. E. Wenkert, K. G. Dave, and F. Haglid, J. Am. Chem. Soc., 1965, 87, 5461.
26. T. R. Govindachari, K. Nagarajan, and S. Rajappa, J. Chem. Soc., 1957, 551.

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