

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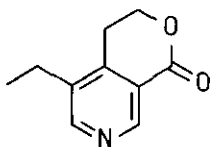
Abstract - The 1,2-dihydropyridine derivative (3) was prepared by the sodium dithionite reduction of 1-[2-(3-indolyl)ethyl]pyridinium bromide (2). It is shown that the isolated 1,2-dihydropyridine derivative (3) is a rearrangement product of the initially formed unstable 1,4-dihydropyridine derivative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

The sodium dithionite reduction of alkyipyridinium 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 alkyipyridinium 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 desmethylhexahydrovallasiachotaminelactones⁹ 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 loses SO₂.²¹ 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

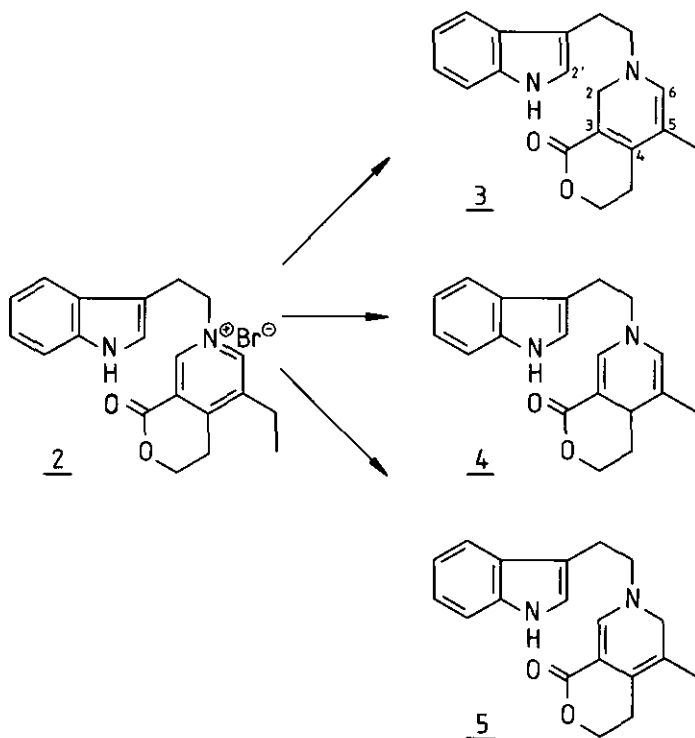
RESULTS AND DISCUSSION

Sodium dithionite reduction of the pyridinium salt (2), using a relatively long reaction time (~ 5 h) and NaHCO₃ 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^+)].

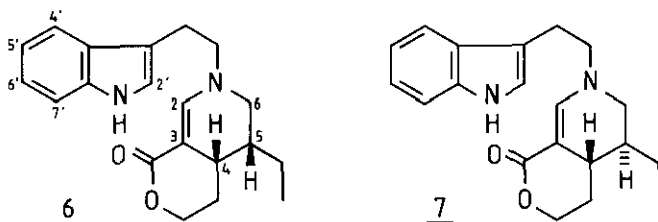
In theory, the sodium dithionite reduction of the pyridinium salt (2) to the dihydropyridine stage can lead to three products [compounds (3), (4) and (5) (Scheme 1)]. Of these, the 1,2-dihydropyridine derivative (3),



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).



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 D₂ instead of H₂. The compound obtained this time was the C(5)D-C(6)D analogue of the 1,4,5,6-tetrahydropyridine derivative (6) (¹³C 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.

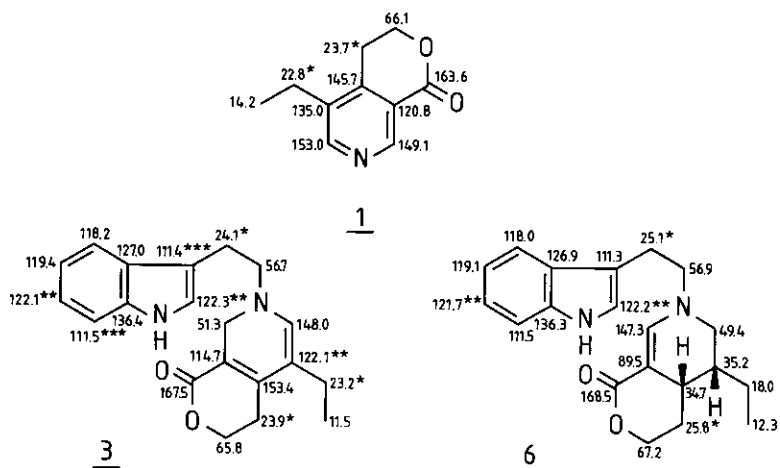
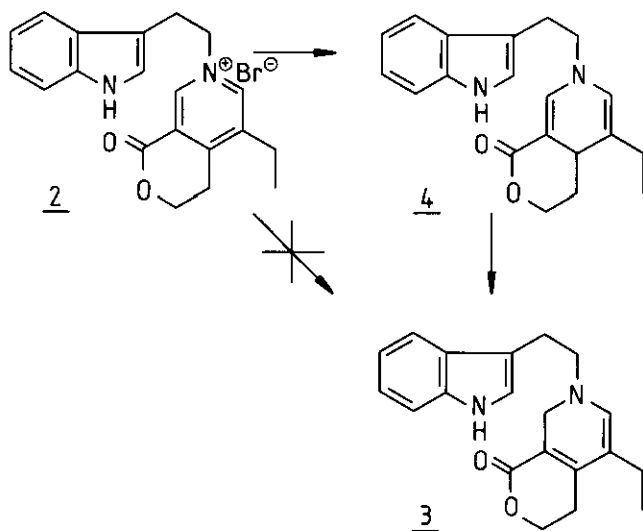


Figure 1



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. ^1H and ^{13}C Nmr spectra were recorded in CDCl_3 with a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H 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 $75-77^\circ\text{C}$ (n-hexane) (lit., $76-78^\circ\text{C}$,²⁵ $74-76^\circ\text{C}$ ²⁶). Ir 1720 ($\text{C}=\text{O}$). ^1H Nmr 1.27 (3H, t, $J = 7.5$ Hz, $-\text{CH}_2-\text{CH}_3$), 2.74 (2H, q, $J = 7.5$ Hz, $-\text{CH}_2-\text{CH}_3$), 3.06 (2H, t, $J = 6.0$ Hz, $-\text{O}-\text{CH}_2-\text{CH}_2-$), 4.58 (2H, t, $J = 6.0$ Hz, $-\text{O}-\text{CH}_2-\text{CH}_2-$), 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 bromide²³ (127 mg, 0.57 mmol) afforded salt (2). Yield: 215 mg (96%).

Preparation of compound (3)

Na₂S₂O₄ (180 mg, 1.03 mmol) was added during 30 min to a stirred mixture of salt (2) (60 mg, 0.15 mmol), NaHCO₃ (120 mg, 1.43 mmol), MeOH (8 ml), and H₂O (16 ml). Stirring was continued (N₂-atm., room temperature) for 5 h. Water was added and the mixture was extracted several times with CH₂Cl₂. The combined extracts were washed with water and dried (Na₂SO₄). 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, -CH₂-CH₃), 4.05-4.30 (4H, m, -CH₂-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 C₂₀H₂₂N₂O₂: 322.1681).

Preparation of compound (6) by successive sodium dithionite and catalytic (H₂/Pd/C) reductions

Na₂S₂O₄ (450 mg, 2.58 mmol) was added to a stirred mixture of salt (2) (150 mg, 0.37 mmol), NaHCO₃ (450 mg, 5.36 mmol), MeOH (10 ml), and H₂O (20 ml). Stirring was continued for 1.5 h (N₂-atm., room temperature). Water was added and the mixture was extracted several times with CH₂Cl₂. The combined extracts were washed with water and dried (Na₂SO₄). 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, CH₂Cl₂/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, -CH₂-CH₃), 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 $Na_2HPO_4 \times 2 H_2O$ (514 mg) and $NaH_2PO_4 \times 2 H_2O$ (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-d₂) by successive sodium dithionite and catalytic (D₂/Pd/C) reductions

Compound (6-d₂) was prepared similarly to compound (6) (successive reductions) described above. Yield: 30%. Ir 3280 (NH), 1660 (C=O). ¹H Nmr 0.92 (3H, def, -CH₂-CH₃), 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.

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