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AN UNUSUAL OXIDATIVE DEMETHYLATION REACTION OF CONESSINE WITH N-BROMOSUCCINIMIDE[1]

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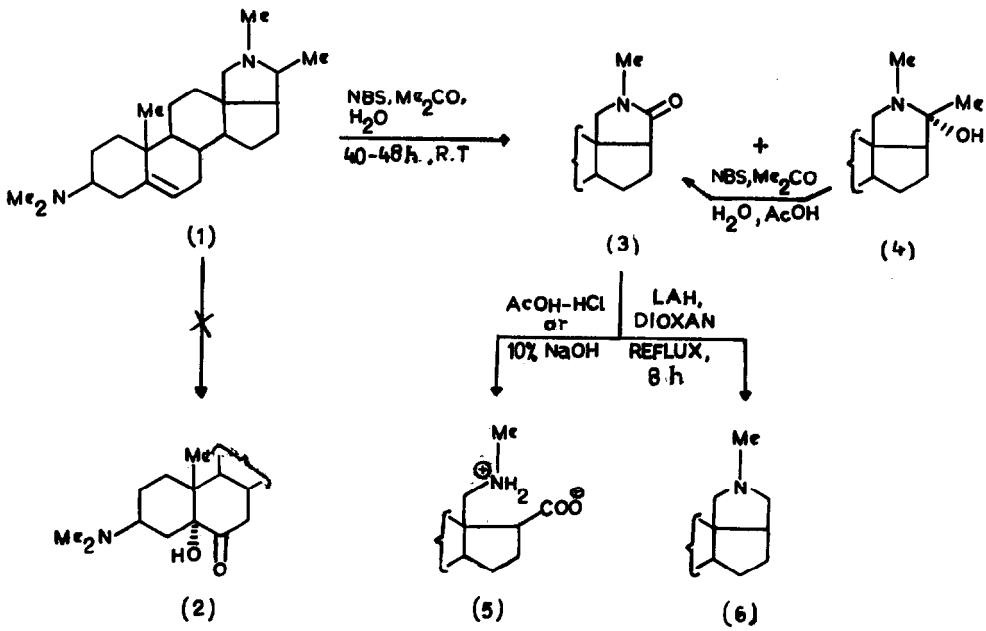
Abstract: Oxidation of conessine (1) with NBS gave lactam (3) in an almost quantitative yield. An intermediate (4) isolated in minor amount was demonstrated to react further with NBS to give (3). Acid or base hydrolysis of (3) resulted in an amino acid (5). 21-Norconessine (6) was obtained from LAH reduction of (3).

The use of N-bromo succinimide (NBS) as a versatile oxidizing agent is well known[2]. In steroid chemistry, this reagent has been used for the selective oxidation of cholesterol into a 5α-hydroxy-6-ketone[3]. While trying to oxidize conessine (1) to ketol (2)[1] with NBS in aqueous acetone containing a little of acetic acid, we were surprised to find that the desired product (2) was not formed. Instead, a lactam (3β-dimethylamino-21-nor-con-5-enine-20-one, 3) was exceptionally isolated from the reaction mixture in an almost quantitative yield. The formation of (3) is entirely different from the known reactions of this reagent with respect to the double bond [3],allylic position[4] or amino functions [2,5]. We now report the results of this unusual reaction [6].

The reaction began as soon as conessine, 1, dissolved in aqueous acetone was treated with NBS with or without acetic acid. Two to two and a half molar ratio of NBS to (1) was required for completion of the reaction in 40-48 h at room temperature. However, the reaction proceeded at a much slower pace and completed in 4 days when acetone was replaced with dioxan. No reaction occurred in aqueous chloroform or methanol. At the end of the reaction, the mixture was diluted with water, neutralized with ammonia solution and extracted with chloroform to give (3): yield 85%; m.p. 168-170°C; M^+ 356 (99%, $C_{23}H_{36}N_2O$); UV (MeOH) λmax 285 nm; IR (KBr, cm^{-1}) 1690 (lactam C=O); PMR ($CDCl_3$, δ) 0.99 (3H, s, 19-Me), 2.36 (6H, s, $N(Me)_2$), 2.82 (3H, s, >N-Me), 2.98 (1H, d, J=10 Hz, 3α-CH), 3.08 (2H, s, 18-CH_2) and 5.36 (1H, br s, 6-vinylic H). The mother liquor of (3) after column chromatography gave 3β-dimethylamino-con-5-enine-20α-ol (4): yield (< 1%); m.p. 140-142 °C; IR (KBr, cm^{-1}) 3400 (OH st.), 1380 (OH bending); PMR ($CDCl_3$, δ) 0.99 (3H, s, 19-Me), 1.28 (3H, s, 21-Me), 2.18 (6H, s, $-N(Me)_2$), 2.44 (2H, d, J=14 Hz, 18-CH_2), 2.80 (1H, s, D_2O exchangeable OH), 2.84 (3H, s, >N-Me) and 5.36 (1H, br s, 6-vinylic H). When NBS reaction was repeated in aqueous acetone in the presence of acetic acid, the product (4) got converted into (3) suggesting (4) to be an intermediate in the reaction.

The structure of the lactam (3) was established by acid [7,8] and alkaline [9,10] hydrolysis which gave amino acid (5): m.p. 278-280 °C; IR (KBr , cm $^{-1}$) 3450 (NH st.), 2600 (Carboxylic OH st.), 1680 (C= O st.); PMR ($CDCl_3$, δ) 3.46 (2H, m, D_2O exchangeable, NH_2). However, the hydrolysis of the lactam (3) with alkali was more facile and occurred instantaneously whereas it was slow under acidic conditions. Lithium aluminium hydride reduction [7] of lactam (3) in dioxan gave 21-norconessine (6): m.p. 98-100 °C; M^+342 (50%, $C_{23}H_{38}N_2$); PMR ($CDCl_3$, δ) 2.55 (4H, m, 18 & 20-CH_2), which fully corroborated the structure of lactam (3).



Work is currently underway to explore the mechanism and generality of this reaction.

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References and notes

1. This work forms part 4 in the series, "Plant-based antiamoebic drugs". For part 3 see K.K.Bhutani and R.M.Vaid, J. Chem. Research, in press.
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10. (5) was formed by shaking (3) in $CHCl_3$ with 10% NaOH solution.

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