FORMATION OF EXOCYLIC TERMINAL METHYLENE GROUPS IN PIPERIDINE DERIVATIVES

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Abstract - The preparation of exocyclic terminal methylene groups in piperidine derivatives by $LiAlH_4$ reduction of appropriate vinylogous urethanes, is described.

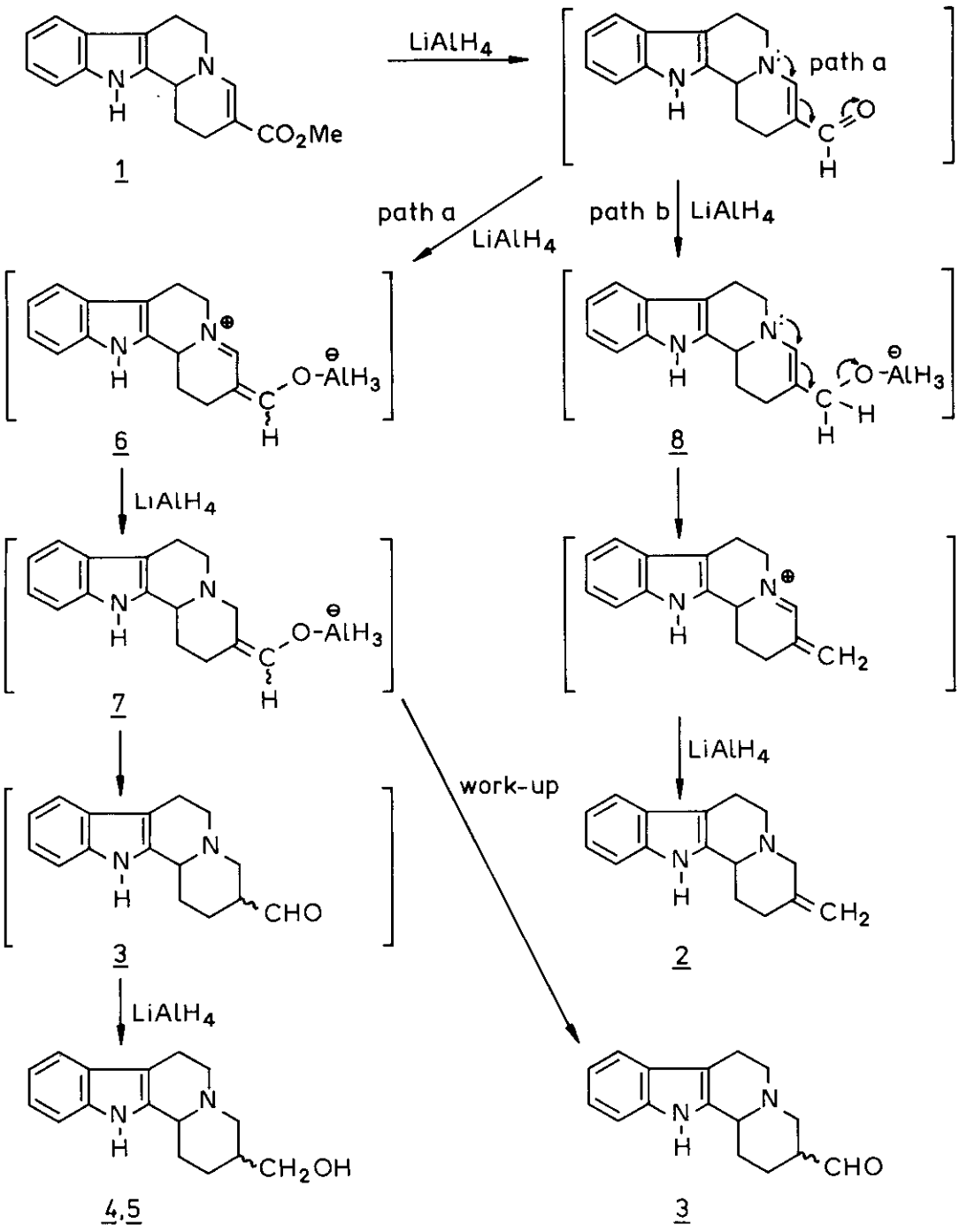
The reduction of urethanes to amines with $LiAlH_4$ is a useful synthetic method.[1-5] In the course of our studies on vallesiachotamine derivatives[6-8] we became interested in vinylogous urethanes. Our recent preparation of (±)-deplancheine[9] by $LiAlH_4$ reduction of 1,2,6,7,12,12b-hexahydro-3-acetylindolo[2,3-a]quinolizine, which is a vinylogous amide, led us to examine in detail the behaviour of some vinylogous urethanes under analogous reduction conditions.

We found four products when 1,2,6,7,12,12b-hexahydro-3-methoxycarbonylindolo-[2,3-a]quinolizine 1[6] was treated with $LiAlH_4$ in THF. The formation of the four compounds, 2, 3, 4, and 5, is portrayed in Scheme 1. After the initial reduction of the methoxycarbonyl group of the urethane to the corresponding aldehyde group, two paths are possible.

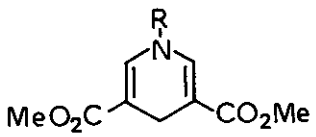
Path a. The iminium salt derivative 6 is reduced to 7 and then transformed to the alcohols 4 and 5 via 3. However, the isolation of 3 from the reaction mixture indicates that the intermediate 7 is sufficiently stable in the used reaction conditions (vide infra) partly to resist further reduction.

Path b. Reduction of the aldehyde function to the amino alcohol derivative 8 is followed by elimination and subsequent reduction of the resulting iminium salt, leading to 2 [(±)-18-nor deplancheine; biogenetic numbering[10]].

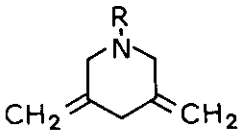
Two further vinylogous urethanes 9[7] and 10[11,12] were examined. The mechanism for the formation of compounds 11, 12, 13 and 14, and, 15, 16, 17 and 18, respectively, is similar to that depicted in Scheme 1.


LiAlH4
path a
path b
work-up
CO2Me
CHO
CH2OH
CH2
O-AlH3
1
2
3
4,5
6
7
8

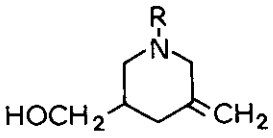
SCHEME 1.



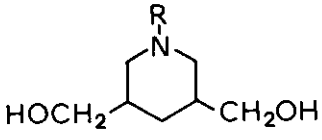
9, 10



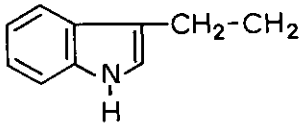
11, 15



12, 16



13, 14, 17, 18

9, 11, 12, 13, 14 R = 

10, 15, 16, 17, 18 R = CH_3

EXPERIMENTAL

The IR spectra were measured on either a Perkin-Elmer 700 spectrophotometer or a Perkin-Elmer 125 spectrophotometer. The ^1H NMR spectra were recorded with either a JEOL JNM FX-100 or a JEOL JNM FX-60 instrument, and the mass spectra with a JEOL JMS-D-100 or a Varian MAT 112S mass spectrometer, at 75 eV, using direct sample insertion into the ion source. The melting points were determined with Fisher-Johns melting point apparatus and are uncorrected.

SYNTHESES OF COMPOUNDS 2, 3, 4 and 5

To a suspension of 400 mg of $LiAlH_4$ in dry THF under nitrogen was added 97 mg of 1,2,6,7,12,12b-hexahydro-3-methoxycarbonyl[2,3-a]quinolizine 1[6] and the reaction mixture was stirred for 5 h at room temperature. Thereafter the mixture was refluxed for 15 min. Saturated Na_2SO_4 solution and ether were added, the inorganic precipitate was filtered. The ether fraction was dried over Na_2SO_4 and evaporated under vacuum. The crude yield was fractionated by TLC (on silica gel (EtOH/EtOAc/toluene; 1 : 2 : 2)) yielding the following compounds:

3-Methylene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine 2. Yield 16 mg (20 %). Mp 106-110°C (MeOH). IR (KBr) $>C=CH_2$ 3090 (w), 1645 (m), 895 (m) cm^{-1}.

^{1}H NMR (100 MHz, C_2D_6CO) δ 4.75 (2H, na m, $\geq C=CH_2$), 3.45 (1H, d, H-12b). 6.93-7.43 (4H, m, arom.), 9.90 (1H, br s, NH). MS (IP 75 eV, 110°C) m/e 238 (42 %) (M^+), 237 (56 %), 169 (14%), 156 (11 %), 85 (86 %), 83 (100 %).

3-Formyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3a]quinolizine 3. Yield 7 mg (8 %). Amorphous. IR (KBr) C=O, 1725 (m) cm^{-1}. ^{1}H NMR (60 MHz, DMSO-d_6) δ 10.20 (1H, s, -CHO). MS (IP 75 eV, 100°C) m/e 254 (100 %) (M^+), 253 (88 %), 225 (45 %), 170 (86 %), 169 (74 %), 156 (29 %).

3-Hydroxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3a]quinolizines 4 and 5.[13] Compound 4. Yield 14 mg (16 %). MS (IP 75 eV, 110°C) m/e 256 (37 %) (M^+), 255 (48 %), 170 (14 %), 169 (16 %), 85 (91 %), 83 (100 %). Compound 5. Yield 15 mg (17 %). MS (IP 75 eV, 110°C) m/e 256 (78 %) (M^+), 255 (100 %), 170 (26 %), 169 (31 %).

SYNTHESES OF COMPOUNDS 11, 12, 13 and 14

1-[2(3-Indolyl)ethyl]-3,5-dimethoxycarbonyl-1,4-dihydropyridine 9[7] (266 mg) was reduced with $LiAlH_4$ (720 mg) as described above. The crude yield was fractionated by TLC on silica gel (EtOH/EtOAc/toluene; 1 : 2 : 2) yielding the following compounds:

1-[2-(3-Indolyl)ethyl]-3,5-dimethylenepiperidine 11. Yield 45 mg (23 %). Mp 118-122°C (MeOH). IR (KBr) $\geq C=CH_2$ 3085 (w), 1650 (m), 895 (m) cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.28 (2H, s, H-4C), 4.83 (4H, na m, 2 x $\geq C=CH_2$), 7.03 (1H, indolyl-αH), 7.00-7.50 (4H, aromatic protons), 8.22 (1H, NH). MS (IP 75 eV, 100°C) m/e 252 (60 %) (M^+), 144 (30 %), 130 (60 %), 122 (100 %).

1-[2-(3-Indolyl)ethyl]-3-methylene-5-hydroxymethylpiperidine 12. Yield 30 mg (14 %). Amorphous. IR (film) $C=CH_2$ 3090 (w), 1640 (m), 885 (m) cm^{-1}. ^{1}H NMR (60 MHz, DMSO-d_6) δ 4.77 (2H, na m, $\geq C=CH_2$), 6.96 (1H, indolyl-αH). MS (IP 75 eV, 100°C) m/e 270 (15 %) (M^+), 252 (8 %), 144 (30 %), 140 (45 %), 130 (45 %).

1-[2-(3-Indolyl)ethyl]-3,5-dihydroxymethylpiperidines 13 and 14.[14] Compound 13. Yield 5 mg (2 %). MS (IP 75 eV, 120°C) m/e 288 (2 %) (M^+), 270 (5 %), 158 (100 %), 144 (60 %), 130 (70 %). Compound 14. Yield 18 mg (8 %). MS (IP 75 eV, 120°C) m/e 288 (2 %) (M^+), 270 (5 %), 158 (100 %), 144 (70 %), 130 (60 %).

SYNTHESIS OF COMPOUND 10.

3,5-Dimethoxycarbonylpyridine (5 g) and CH_3I (4 ml) in methanol were refluxed 35 h under nitrogen. The mixture was allowed to cool, and the yellow salt was crushed

to grains and washed with ether. Yield 8.5 g (98 %). Mp 192-194°C. IR (KBr) C=O 1720, 1730 (s) cm^{-1}. Sodium dithionite (3 g) was added in small portions over a period of 1 h to a magnetically stirred solution of the obtained salt (1 g) and $NaHCO_3$ (5 g) in 140 ml of H_2O/MeOH (1:2) under nitrogen. The mixture was stirred for 22 h. Methanol was evaporated under vacuum and the water fraction was extracted several times with $CHCl_3$. The extract was washed with H_2O and dried over Na_2SO_4. The product was purified on alumina (act. II-III).

N-Methyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine 10. Yield 0.5 g (74 %). Mp 139-142°C. IR (KBr) C=O 1700 (s), C=C 1610 (s) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$) δ 6.91 (2H, s, >CH-N-CH<), 3.72 (6H, s, 2 x $COOCH_3$), 3.07 (3H, s, >N-CH_3). MS (IP 75 eV, 70°C) m/e 211 (35 %) (M^+), 210 (60 %), 196 (100 %), 180 (35 %), 152 (10 %).

SYNTHESES OF COMPOUNDS 15, 16, 17 and 18.

N-Methyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine 10 (117 mg) was reduced with $LiAlH_4$ (700 mg) as described above. The crude yield was fractionated by TLC [silica gel (MeOH/$CHCl_3$, 20:80; or $(C_2H_5)_2NH$/$CHCl_3$, 5:95)] yielding the following compounds:

N-Methyl-3,5-dimethylenepiperidine 15. Yield 2 mg (2%). Amorphous. IR (KBr) >C=CH_2 3090 (w), 1645 (m), 885 (m) cm^{-1}. MS (IP 75 eV, 100°C) m/e 123 (45 %) (M^+), 122 (100 %).

N-Methyl-3-methylene-5-hydroxymethylpiperidine 16. Yield 11.5 mg (15 %). Amorphous. IR (KBr) >C=CH_2 3090 (w), 1645 (m), 885 (m) cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6) δ 2.35 (3H, s, >N-CH_3), 4.83 (2H, na m, >C=CH_2). MS (IP 75 eV, 40°C) m/e 141 (80 %)(M^+), 140 (90 %), 126 (40 %), 111 (85 %), 109 (50 %), 84 (40 %), 82 (65 %), 58 (50 %), 57 (35 %), 44 (80 %), 42 (100 %).

N-Methyl-3,5-dihydroxymethylpiperidines 17 and 18.[14] Compound 17. Yield 6 mg (7 %). MS (IP 75 eV, 120°C) m/e 159 (10 %) (M^+), 158 (8 %), 144 (5 %), 143 (20 %), 142 (40 %), 128 (13 %), 58 (100 %), 57 (90 %), 44 (90 %), 43 (60 %), 42 (45 %).

Compound 18. Yield 12 mg (13 %). MS (IP 75 eV, 120°C) m/e 159 (40 %) (M^+), 158 (35 %), 144 (10 %), 143 (25 %), 142 (40 %), 128 (35 %), 58 (100 %), 57 (55 %), 44 (90 %), 43 (60 %), 42 (45 %).

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Received, 14th April, 1982