Synthetic Studies in the Alkaloid Field. Part VI.*Preparation of the Diastereoisomeric Mixtures of 1,4,6,7,12,12b-Hexahydro-3-(1-hydroxyethyl)-indolo[2,3-*a*]quinolizines

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Some years ago Ziegler and Sweeny elegantly synthesized dihydrocorynantheol *1* and its C(3) epimer, 3-epidihydrocorynantheol *2* employing the diastereoisomeric mixtures of 1,4,6,7,12,12b-hexahydro-3-(1-hydroxyethyl)-indolo[2,3-*a*]quinolizines *3a* and *3b* in the Claisen rearrangement with dimethylacetamide dimethylacetal.[1] More recently, indolo[2,3-*a*]-quinolizines *3a* and *3b* have been used to check the applicability of the Claisen rearrangement for the preparation of geissoschizine *4* analogues.[2] The indolo[2,3-*a*]quinolizines *3a* and *3b* are thus of proven interest as synthetic intermediates in the alkaloid field but in both cases described [1,2] they have been prepared in a relatively cumbersome way.

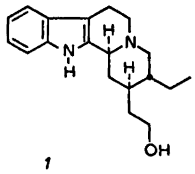
In connection with our investigation [3,4] of the sodium dithionite reduction of appropriate 1-[2-(3-indolyl)ethyl]pyridinium salts we found that the diastereoisomeric mixtures of *3a* and *3b* can be easily prepared in about 30 % total yield. This preparation is the subject of the present communication.

* Part V. Lounasmaa, M. and Hämeilä, M. *Tetrahedron. In press.*

Tryptophyl bromide [5] was treated with 3-acetylpyridine to yield 1-[2-(3-indolyl)ethyl]-3-acetylpyridinium bromide *5*, which was reduced by sodium dithionite. Owing to the sufficient acidity of the reaction medium, this led directly to the indoloquinolizine derivative *7*. Alternatively, buffering of the sodium dithionite reaction medium with sodium hydrogencarbonate yielded the intermediate 1,4-dihydro derivative *6*, which was converted into the tetracycle *7* by acid treatment. Dehydrogenation of compound *7* with palladium in aqueous maleic acid solution [4] yielded a tetradehydro compound, isolated as the perchlorate *8*. Sodium borohydride reduction of the latter yielded the diastereoisomeric mixtures of 1,4,6,7,12,12b-hexahydro-3-(1-hydroxyethyl)indolo[2,3-*a*]-quinolizines *3a* and *3b*.

Experimental. The IR spectra were measured on a Perkin-Elmer 457 apparatus and the UV spectra on a Beckmann ACTA M IV apparatus. The ^{1}H NMR spectra were taken with either a Varian T-60 instrument or a Jeol JNM FX-100 instrument. TMS was used as internal standard. The mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6E Mass Spectrometer at 70 eV using direct sample insertion into the ion source, whose temp. was 150–160 °C. The melting points were determined on a Kofler micro hot stage and are uncorrected.

1-[2-(3-Indolyl)ethyl]-3-acetylpyridinium bromide 5. A mixture of 3-acetylpyridine (9 ml) and tryptophyl bromide [5] (5 g) was heated under nitrogen at 100 °C for 3 h. The mixture was allowed to cool, crushed to grains, and stirred in dry ether. The mixture was filtered. Yield 7.3 g (95 %), m.p. 215–216 °C (MeOH) (lit. 214–216 °C,[6] 216–217 °C [7]). IR (KBr): NH 3440 (m), 3380 (m), 3220 (m), C=O 1705 (s), C=C 1630 (m), 1580 (w) cm^{-1}. ^{1}H NMR (60 MHz, DMSO-d_6): δ 2.67 (3 H, s, CH_3CO), 3.45 (2 H, t, J 7 Hz, $-CH_2-CH_2-N$), 5.05 (2 H, t, J 7 Hz, $-CH_2-CH_2-N$), 6.8–7.7



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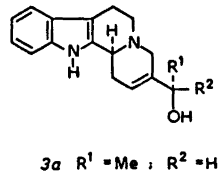
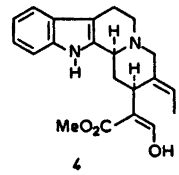
2 H-3β



3a R^1 = Me ; R^2 = H

3b R^1 = H ; R^2 = Me



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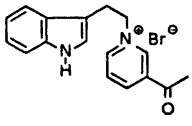

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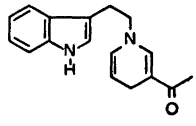

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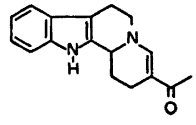

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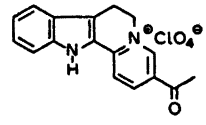

8

(5 H, m, ind.), 8.22 (1 H, dd, *J* 8 and 6 Hz, H-5), 8.95 (1 H, dt, *J* 8 and 1.5 Hz, H-4), 9.21 (1 H, dt, *J* 6 and 1.5 Hz, H-6), 9.55 (1 H, br s, H-2), 11.05 (1 H, br s, NH) (*cf.* Ref. 7).

1-[2-(3-Indolyl)ethyl]-3-acetyl-1,4-dihydropyridine 6. Sodium dithionite (1.6 g) was added in small portions during 1 h to a magnetically stirred solution of pyridinium bromide *5* (500 mg) and $NaHCO_3$ (2 g) in 120 ml of aqueous MeOH (1:2, H_2O:MeOH) under nitrogen. The mixture was stirred for 20 h, filtered, and the filtrate evaporated under vacuum. The residue was extracted several times with dichloromethane. The extracts were washed with water, dried over Na_2SO_4, and evaporated under vacuum. The residue was chromatographed on alumina (act. IV). Yield 250 mg (65 %). Amorphous mass. IR(KBr): C=O 1665 (s), C=C 1600 (s) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ 1.79 (3 H, s, CH_3CO), 4.94 (1 H, m, H-5), 5.74 (1 H, dd, *J* 8 and 1 Hz, H-6), 6.52 (1 H, d, *J* 1 Hz, H-2), 6.98 (1 H, d, *J* 2 Hz, α-indolyl). MS (IP 70 eV; *m/e*): 266 (M), 144, 136, 130.

1,2,6,7,12,12b - Hexahydro - 3-acetylindolo[2,3-a]quinolizine 7. A solution of 1,4-dihydropyridine derivative *6* (250 mg) in anhydrous MeOH was saturated with dry HCl gas during a 2 h period. The solution was left standing for 1 h at room temperature and then poured slowly into a suspension of $NaHCO_3$ in dichloromethane. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV). Yield 232 mg (93 %), m.p. 130–134/170–180 °C (MeOH). IR (KBr): NH 3340 (m), C=O, C=C 1620 (m) and 1580 (s) cm^{-1}. UV [EtOH 94 % (log ε)]: λ_{max} 221 (4.60), 310 (4.61) nm. λ_{min} 255 nm. ^1H NMR (100 MHz, $CDCl_3$): δ 2.22 (3 H, s, CH_3CO), 4.52 (1 H, br d, *J* 10 Hz, H-12b), 7.44 (1 H, s, H-4), 8.56 (1 H, br s, NH). MS (IP 70 eV; *m/e*): 266 (M), 265, 251, 223, 156.

The alternative preparation of *7*, without buffering the reaction medium (*vide supra*), afforded *7* in 45 % yield.

Perchlorate 8. A mixture of 65 mg of *7*, 70 mg of maleic acid and 60 mg of palladium-charcoal (10 %) in 8 ml of water was refluxed for 20 h under nitrogen. The solution was filtered and the filtrate evaporated under vacuum. A saturated solution of sodium perchlorate was added and the salt *8* separated. Yield 53 mg (60 %), m.p. 284–286 °C (dec.) (MeOH). IR (KBr): NH 3440 (m), C=O 1700 (s), C=C 1630 (s), 1620 (s) cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ 2.70 (3 H, s, CH_3CO), 3.45 (2 H, t, *J* 7 Hz, $-CH_2-CH_2-N$), 5.00 (2 H, t, *J* 7 Hz, $-CH_2-CH_2-N$), 7.2–7.7 (4 H, m, ind.), 8.30 (1 H, d, *J*8 Hz, H-1), 8.96 (1 H, d, *J* 8 Hz, H-2), 9.49 (1 H, s, H-4), 12.50 (1 H, br s, NH).

1,4,6,7,12,12b-Hexahydro-3-(1-hydroxyethyl)-indolo[2,3-a]quinolizines 3a *and* 3b. Sodium borohydride (300 mg) was added to a magnetically stirred solution of perchlorate *8* (70 mg) in 15 ml of aqueous MeOH (2:5, H_2O:MeOH) under nitrogen at room temperature. The mixture was stirred for 2 h, water added, and the MeOH evaporated under vacuum. The mixture was extracted several times with dichloromethane. The extracts were washed with water, dried over Na_2SO_4 and evaporated under vacuum. Yield 48 mg (93 %), m.p. 210–215 °C (MeOH) (lit. 205–212 °C,[1] 212 °C [2]). IR (KBr): NH 3400 (m), OH 3280 (m), Bohlmann bands 2815 (w), 2755 (w) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ 1.32/1.34 (3 H, 2 × d, *J* 6 Hz, CH_3), 4.24 [1 H, br q, $-CH(OH)CH_3$], 5.76 (1 H, m, H-2), 7.84 (1 H, br s, NH) (*cf.* Ref. 2). MS (IP 70 eV; *m/e*): 268 (M), 267, 170, 169.

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