REACTIONS WITH INDOLE DERIVATIVES, XLIX

THE STEREOSELECTIVE TOTAL SYNTHESIS OF D-NORVINCAMINE

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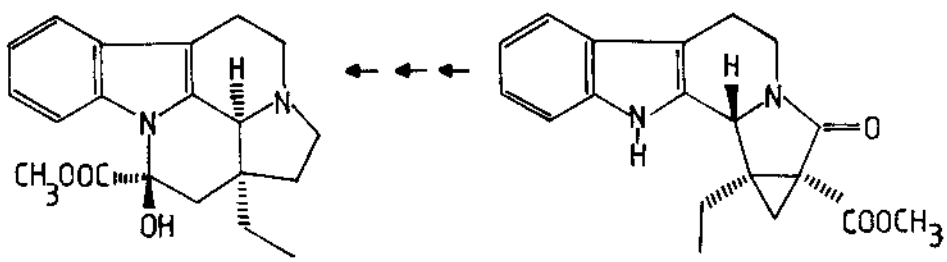
Abstract —— A stereoselective synthesis of D-norvincamine (1) is described starting from cyclopropane derivative (2), via isoeburnamonine (6).

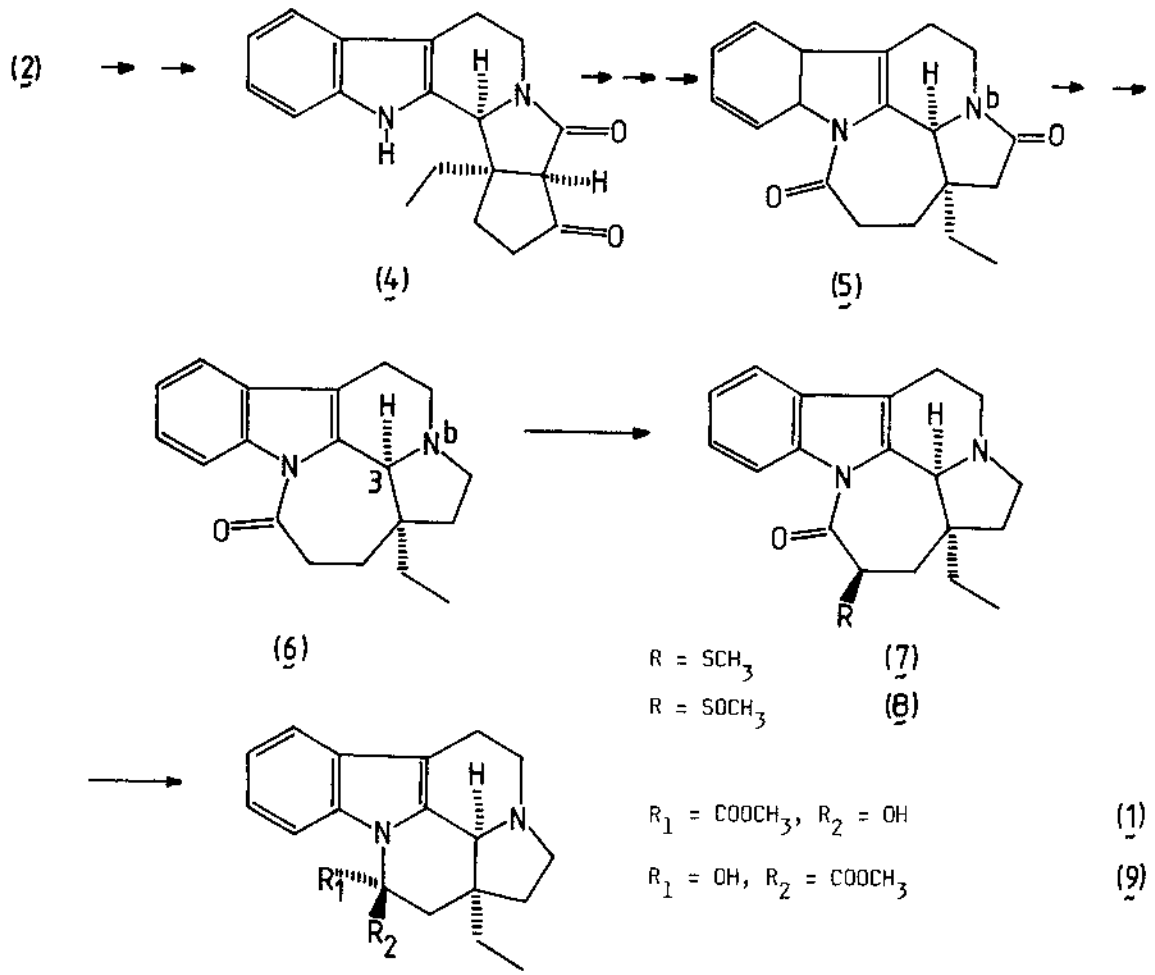
In the course of our synthetic studies on eburnamonine-vincamine type indole alkaloids we now have developed a stereoselective total synthesis of D-norvincamine (1). This was achieved via cyclopropane derivative 2, which was easily and stereoselectively prepared from tryptamine. Vincamine (3) has very important physiological activities[4], and thus D-norvincamine (1) is also an attractive compound from the pharmacological point of view and additionally this compound is expected to yield interesting information on the configurational stability of the α-hydroxyester moiety in relation to ring-size.



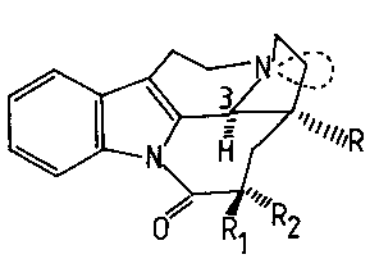
(1) (2)

The regioselective reduction of the five membered lactam in compound (5), which was derived from lactam (2) via the important intermediate (4)[2], was achieved by Borch's method.[5] Meerwein-reagent ($Et_3O^+ \cdot PF_6^-$) reacted only with the oxygen of the five membered lactam, which is in accord with the higher donor capacity of N_b, and subsequent treatment with tetraethylammonium tetrahydroborate afforded the desired amine (6) in 89% yield. Isoeburnamonine (6) did not show Bohlmann bands[6] in the IR spectrum, this implies that the hydrogen at C_3 is cis in relation to the lone pair of N_b. This spectral behaviour is analogous with homo-eburnamonine.

The sulfenylation of the acylindole (6) was carried out by quenching the enolate with dimethyl disulfide.[8] The TLC of the reaction mixture showed the presence of two products (epimers?). However, after the usual work up (see experimental section) and chromatographic separation we only obtained



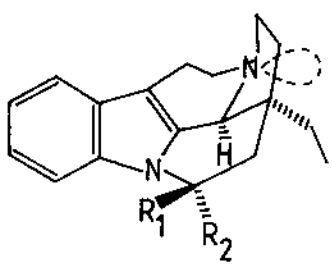
one sulfenylated product in 76% yield, together with the 17% of starting material. In the case of the des-ethyl compound (11), we were able to separate the two isomers (12) and (13) obtained in a similar sulfenylation reaction.

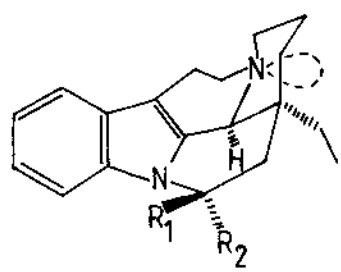


R = Et, R_1 = R_2 = H (6)
R = Et, R_1 = SCH_3, R_2 = H (7)
R = Et, R_1 = H, R_2 = SCH_3 (10)
R = R_1 = R_2 = H (11)
R = H, R_1 = SCH_3, R_2 = H (12)
R = H, R_1 = H, R_2 = SCH_3 (13)

From this observation we concluded that during the work up and isolation the isomer 10 epimerized to the more stable isomer (7) owing to steric repulsion between the ethyl group and SCH_3 group. (See Scheme 3). The oxidation of the sulfide (7) using 1 equiv m-chloroperbenzoic acid in methylene chloride at -65°C gave rise to the sulfoxide (8) in 88% yield after purification by Al_2O_3 column chromatography. A positive reaction to Schlittler reagent on TLC excluded the possibility of N_b-oxide formation. The conversion of the sulfoxide (8) to norvincamine (1) was performed by the

procedure of Schlessinger et al.[9] Thus compound (8) was treated with 2.5 equiv of trifluoroacetic anhydride followed by addition of 8 equiv sodium methoxide in methanol. The NMR spectrum of the crude products showed the presence of two isomers in the ratio 3 : 2. The major isomer a (mp 152-153°C) and the other isomer b (mp 170-173°C) exhibited satisfactory analytical and spectral properties, which corresponded to those expected for norvincamine (1) and epi-norvincamine respectively (9). The correlation of the R_f values on TLC (major product a was less polar than b) corresponded to the behaviour of vincamine (3) and epi-vincamine (14). (Vincamine (3) is less polar than epi-vincamine (14)[10]). In the NMR spectrum the chemical shift of the methyl ester group of (1) was observed at lower field than that of isomer 9. A similar relation can be seen in the NMR spectra of vincamine - epi-vincamine.[10] Further, in analogy with epi-vincamine (14)[10], (9) epimerized gradually to (1) in THF and tert-butanol solution in the presence of Hünig-Base.





R_1 = OH, R_2 = $COOCH_3$, norvincamine (1)
R_1 = $COOCH_3$, R_2 = OH, epi-norvincamine (9)

R_1 = OH, R_2 = $COOCH_3$, vincamine (3)
R_1 = $COOCH_3$, R_2 = OH, epi-vincamine (14)

In contrast to the six-membered ring compounds the nor-series does not favor the ester group in α-position. The fact that pure epi-norvincamine on equilibration does yield the same ratio of diastereomers as obtained in this synthesis proves that one is dealing with the thermodynamically controlled reaction product.

EXPERIMENTAL

Borch reduction of dilactam (5): 100 mg of dilactam (5), dissolved in 5 ml of dry methylene chloride, was treated with 100 mg of triethyloxonium hexafluorophosphate for 15 h at room temperature. At 0°C 71 mg of tetraethylammonium tetrahydroborate was added slowly to this solution and the resulting reaction mixture was stirred at 0°C for 5 min and then at room temperature for 10 min. After the addition of 2 ml acetone, the reaction mixture was poured into a saturated sodium bicarbonate solution and extracted five times with methylene chloride. The combined extract was washed with brine, dried over magnesium sulfate and then evaporated to dryness at reduced pressure. To destroy the amine-borane complex the resulting residue was dissolved in 5 ml of dry methylene chloride and treated with 1 ml of trifluoroacetic acid at room temperature for 3 h. The reaction

mixture was evaporated under reduced pressure and after the addition of ice-cooled sodium bicarbonate solution was extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography to afford 85 mg (89%) of isoeburnamonine (6). mp 150-151°C; UV (CH_3OH), acylindole spectrum λ_{max} 204, 242, 267, 292, 300 nm; IR (KBr) ν_{max} 1697 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) τ 1.44-1.63 (1H,m), 2.49-2.83 (3H,m), 5.85 (1H,s), 9.03 (3H,t,J=7 Hz); MS (40°C) M^+ 294 ME (100%), 293 (82), 266 (16), 263 (8), 238 (30), 237 (16), 223 (16); $C_{19}H_{22}N_2O$ calc. 294.1732, found 294.1728 (MS).

Sulfenylation of isoeburnamonine (6): To a solution of 98 µl of dry diisopropylamine in 4 ml of dry THF at -70°C under nitrogen 0.44 ml of 1.6 M n-BuLi in hexane was added dropwise. The resulting solution was stirred for 45 min at -70°C, after which a solution of 100 mg of isoeburnamonine (6) in 3 ml of dry THF and 0.4 ml of dry HMPA was added in a dropwise manner. This solution was stirred for 10 min at -70°C, warmed to -30°C over 20 min, and then stirred at 0°C for 30 min. 61 µl of dimethyldisulfide was then added dropwise at 0°C. The resulting solution was stirred at 0°C for 10 min and was then allowed to warm to room temperature over 2 h. The reaction mixture was poured into a mixture of saturated ammonium chloride solution and ice and extracted five times with methylene chloride. The organic layers were washed with brine, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography to afford 88 mg (76%) of (7) and 17 mg (17%) of starting material (6). (7): mp 164.5-166°C; UV (CH_3OH), acylindole spectrum λ_{max} 203, 240, 267, 292, 302 nm; IR (KBr) ν_{max} 1693, 1610 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) 1.38-1.60 (1H,m), 2.48-2.83 (3H,m), 5.87 (1H,s), 6.18 (1H,dd,J_1=1 Hz, J_2=9 Hz), 7.70 (3H,s), 8.93 (3H,t,J=7 Hz); MS (90°C) M^+ 340 ME (100%), 339 (53), 294 (21), 293 (36), 279 (11), 266 (17), 265 (26), 256 (11), 251 (19), 233 (26), 223 (13), 162 (15); $C_{20}H_{24}N_2OS$ calc. C 70.55, H 7.11, N 8.23, found C 70.26, H 7.11, N 8.19.

Sulfenylation of (11): To a stirred solution of lithium diisopropylamide (0.41 mmol) in 2 ml of dry THF under N_2 at -70°C was added a solution of 55 mg of (11) in 1.5 ml of dry THF and 0.5 ml of dry HMPA. This solution was stirred for 10 min at -70°C, then warmed to -25°C over 30 min. After the addition of 22 µl of dimethyldisulfide at 0°C, the resultant mixture was stirred at 0°C for 30 min and was then allowed to warm to room temperature over 30 min. The reaction mixture was poured into a mixture of saturated ammonium chloride solution and ice and extracted with methylene chloride. The organic layers were washed with brine, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography to afford 23 mg (36%) of (12) and 19 mg (29%) of (13). (R_f; (13) > (12). (12): UV (CH_3OH), acylindole spectrum λ_{max} 205, 242, 267 (s), 290, 302 nm; IR ($CHCl_3$) ν_{max} 1692, 1455 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) τ 1.39-1.53 (1H,m), 2.47-2.78 (3H,m), 5.35 (1H,d,J=7.5 Hz), 6.16 (1H,d,J=9.5 Hz), 7.70 (3H,s); MS (70°C) M^+ 312 ME

(100%), 311 (72), 265 (89), 237 (33), 210 (44), 149 (56); $C_{18}H_{20}N_2OS$ calc. 312.1296, found 312.1297 (MS). (13): UV (CH_3OH), acylindole spectrum λ_{max} 205, 245, 270 (s), 302 nm; IR ($CHCl_3$) ν_{max} 1680, 1458 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) τ 1.44-1.62 (1H,m), 2.46-2.89 (3H,m), 4.99 (1H,d,J= 7.5 Hz), 6.13 (1H,dd,J_1=1.5 Hz, J_2=7.5 Hz), 7.61 (3H,s); MS (80°C) M^+ 312 ME (31%), 311 (35), 265 (100), 264 (67), 237 (26), 236 (32), 210 (26), 209 (21); $C_{18}H_{20}N_2OS$ calc. 312.1296, found 312.1297 (MS).

Oxidation of sulfide (7): A solution of 25 mg of m-chloroperbenzoic acid (85% pure) in 1 ml of dry methylene chloride was added dropwise to a stirred mixture of 40 mg of sulfide (7) in 3 ml dry methylene chloride and 12 mg of anhydrous sodium carbonate at -65°C under N_2. After 10 min the reaction mixture was chromatographed directly over 5 g of Al_2O_3 (neutral, grade IV, ethyl acetate) to afford 37 mg (88%) of sulfoxide (8). UV (CH_3OH) λ_{max} 203, 246, 302 nm; IR ($CHCl_3$) ν_{max} 1677, 1610 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) τ 1.51-1.76 (1H,m), 2.47-2.79 (3H,m), 5.71 (0.5H,d,J=10.5 Hz), 6.21 (0.5H,d,J=11 Hz), 5.87 (0.5H,s), 5.90 (0.5H,s), 6.99 (1.5H,s), 7.48 (1.5H,s), 8.93 (1.5H,t,J= 7 Hz), 8.95 (1.5H,t,J=7 Hz); MS (110°C) M^+ 356 ME (62%), 339 (12), 294 (25), 293 (100), 292 (31), 291 (22), 265 (15), 264 (17), 263 (17), 239 (12), 238 (11), 237 (14), 223 (14); $C_{20}H_{24}N_2O_2S$ calc. 356.1559, found 356.1550 (MS).

Norvincamine (1) and epi-norvincamine (9): Trifluoroacetic anhydride (51 µl) was added to a solution of 52 mg sulfoxide (8) in 2 ml dry methylene chloride at 0°C under N_2. The reaction mixture was stirred at 0°C for 10 min and then allowed to warm to room temperature during 20 min. Sodium methoxide prepared from 27 mg sodium metal and 1 ml of dry methanol was added to this solution. After 22 h at room temperature the reaction mixture was poured into a mixture of saturated ammonium chloride solution and ice and then extracted with methylene chloride. The combined extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure, giving a mixture of norvincamine (1) and epi-norvincamine (9) in the ratio 3 : 2, as determined by NMR spectrum. The mixture was separated by Al_2O_3 (neutral, grade IV, benzene/methyl tert-butyl ether) to give 23 mg (46%) of norvincamine (1) and 14 mg (28%) of epi-norvincamine (9). (1): mp 152-153°C (from benzene); UV (CH_3OH) λ_{max} 225, 272 nm; IR ($CHCl_3$) ν_{max} 3520, 1735 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) τ 2.44-2.60 (1H,m), 2.78-2.99 (3H,m), 6.06 (3H,s), 6.12 (1H,s), 9.02 (3H,t,J=7 Hz); MS (50°C) M^+ 340 ME (100%), 293 (25), 281 (29), 266 (15), 253 (25), 238 (25), 219 (63), 184 (92), 149 (33); $C_{20}H_{24}N_2O_3$ calc. C 70.56, H 7.11, N 8.23, found C 70.58, H 7.11, N 8.23. (9): mp 170-173°C (from methanol); UV (CH_3OH) λ_{max} 225, 270 nm; IR ($CHCl_3$) ν_{max} 3520, 1740 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) τ 2.46-2.62 (1H,m), 2.83-3.03 (3H,m), 5.90 (1H,s), 6.21 (3H,s), 9.01 (3H,t,J=7 Hz); MS (60°C) M^+ 340 ME (100%), 293 (18), 281 (35), 279 (24), 266 (8), 253 (21), 238 (20), 219 (46), 184 (97), 167 (21), 149 (42); $C_{20}H_{24}N_2O_3$ calc. C 70.56, H 7.11, N 8.23, found C 70.57, H 7.14, N 8.14.

Epimerization of epi-norvincamine (9): 10 mg of (9) was heated at 70°C for 3 days with 6 µl of diisopropylethylamine in 0.9 ml of dry THF and 0.1 ml of dry tert-butanol under N_2. The reaction mixture was evaporated to dryness under reduced pressure to give a mixture of norvincamine (1) and epi-norvincamine (9) in the ratio 3 : 4, as determined by NMR spectrum.

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