224. Note on Attempts to Prepare Ring-B Homomorphinan-6-ones by *Grewe* Cyclization from Octahydro-1-phenethylisoquinolines

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Grewe cyclization of the *N*-formyl-protected octahydroisoquinolin-6-one **1** prepared by conventional chemistry did not afford the expected homomorphinanone. The exclusive reaction product obtained in good yield was the α,β-unsaturated *N*-formyloctahydroisoquinolin-6-one **2**, further converted by acid hydrolysis into the crystalline octahydroisoquinolin-6-one **8**.

Grewe cyclization of 1-benzyl-octahydroisoquinolines in strong acid is a well established route to morphinans [1–3] and a key reaction in the total synthesis of opium alkaloids by *Rice* [4] [5]. We now report that similar treatment of 1-phenethyloctahydroisoquinolines failed to give ring closure to ring-B homorphinan-6-ones related to the alkaloid androcymbine [6]. The novel *N*-protected octahydro-1-phenethylisoquinoline **1** with a β,γ-unsaturated keto group, in principle ideally suited for *Grewe* cyclization, was prepared by conventional chemistry, and afforded by treatment with 80% H_2SO_4 [7] or triflic acid (= trifluoromethanesulfonic acid) [4] [5] α,β-unsaturated isoquinolinone **2** instead of a tetracyclic ketone[2]). Removal of the aromatic proton from C(6') required for cyclization is obviously disfavored in the 1-phenethyl series of octahydroisoquinolines where the aromatic ring is further removed from the double bond than in the 1-benzyl series, disfavored over abstraction of a proton from C(5) resulting in the formation of the α,β-unsaturated ketone **2**.

The synthesis of the required isoquinolines **1** and **7** was accomplished by conventional methods as follows: Amide **3**, prepared by heating 3-methoxyphenethylamine and 3-(3-methoxyphenyl)propionic acid [8] afforded, with $POCl_3$ in MeCN, the 3,4-dihydroisoquinoline **4**, and by selective *O*-demethylation in refluxing 48% HBr [7] the phenolic compound **5**. *Birch* reduction of **5** in liq. NH_3 with Li, and *t*-BuOH as a proton donor [9], gave the hexahydroisoquinoline **6**, converted with ethyl formate into the *N*-formyl compound **7** with an electron-withdrawing group on the amine N-atom, reducing its basic properties [10] and making **7** an ideal compound to study *Grewe* cyclization. Treatment of **6** with HCl [11] afforded directly the octahydroisoquinolin-6-one **8**, isolated

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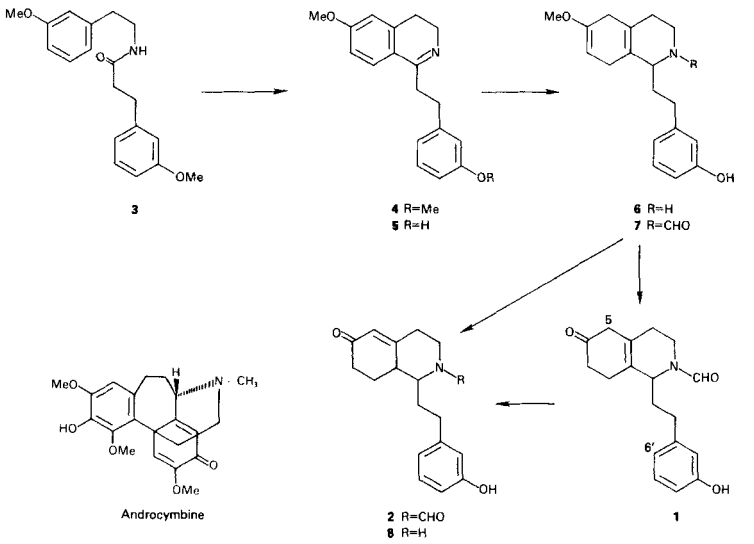
[2]) The chemical reactions reported here were accomplished with racemic materials, and structures shown, therefore, represent racemates.



in 64% yield as hydrochloride salt, whereas from **7** with anh. triflic acid, **2** was obtained in 67% yield. Treatment of **7** with HCOOH, a procedure used by *Rice* in his total synthesis of opium alkaloids [4], afforded the octahydroisoquinolin-6-one **1**, showing in the IR spectrum the unconjugated carbonyl group at 1715 cm^{-1} and the amide group at 1647 cm^{-1}. In the α,β-unsaturated ketone **2**, obtained from **1** by treatment with 80% H_2SO_4 or anh. triflic acid (yield 75%), the carbonyl group at 1715 cm^{-1} was missing. The ^{1}H-NMR spectrum of **2** showed a vinylic H–C(5) at 5.89 ppm absent in **1**. TLC analysis of crude reaction products and mother liquors obtained after removal of **2** did not show material which could be associated with morphinan structures. Acid hydrolysis of **2** afforded the octahydroisoquinolin-6-one **8** obtained after usual workup as a crystalline base. The spectral data of **8** (see *Exper. Part*) are in full agreement with its structure.

Experimental Part

General. M.p. are corrected. Elemental analyses and IR spectra were performed by *Hoffmann-La Roche & Co. AG*, Basel. NMR: *Bruker AM 400* spectrometer with TMS as internal reference. EI-MS: *Varian-Mat CH-7 (70 eV)*. The 3-(3-methoxyphenyl)propionic acid was obtained by hydrogenation of the corresponding cinnamic acid, and 3-methoxyphenethylamine was purchased from *Aldrich*.

N-(3'-Methoxyphenethyl)-3-(3"-methoxyphenyl)propionamide (**3**). A flask containing 29.8 g (165.5 mmol) of 3-(3-methoxyphenyl)propionic acid and 25.0 g (165.5 mmol) of 3-methoxyphenethylamine was evacuated, refilled with Ar, and placed in an oil bath at 195–200° while passing a continuous stream of Ar over the solid to sweep out the H_2O formed. After 2 h at 195–200°, the mixture was cooled r.t. and dissolved in 200 ml of $CHCl_3$. Washings with 2N HCl and 10% Na_2CO_3, drying with Na_2SO_4, and evaporation gave 46.04 g (89%) of **3**. An anal. sample was obtained by flash chromatography (SiO_2, CH_2Cl_2/EtOH 100:3): Colorless liquid which solidified in the refrigerator, m.p. 49–50°. IR (KBr): 3364*m*, 3299*m*, 2945*w*, 1636*s*, 1595*s*, 1536*s*, 1491*s*, 1469*m*, 1453*m*, 1434*m*, 1318*m*, 1259*s*, 1167*s*, 1039*s*, 856*m*, 795*s*, 698*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.41 (*t*, J = 8, CH_2(2)); 2.72, 2.91 (2 *t*, J = 7,8, both 2 H, CH_2(3), CH_2–C(1')); 3.48 (*dd*, CH_2NH); 3.78 (*s*, 2 CH_3O); 5.37 (*s*, NH); 6.68–6.80 (*m*, H–C(2'), H–C(4'), H–C(6'), H–C(2"), H–C(4"), H–C(6")); 7.16–7.21 (*m*, H–C(5'), H–C(5")). MS: 313 (M^+). Anal. calc. for $C_{19}H_{23}NO_3$ (313.397): C 72.82, H 7.40, N 4.47; found: C 72.39, H 7.55, N 4.52.

*3,4-Dihydro-6-methoxy-1-(3'-methoxyphenethyl)isoquinoline Hydrogen Bromide (**4**·HBr).* To a soln. of 45.6 g (145.6 mmol) of **3** in 200 ml of MeCN were added 25 ml (265.0 mmol) of $POCl_3$. At r.t., Ar was passed through this mixture for 30 min. Then the mixture was refluxed (bath temp. 110°) for 1 h under Ar, evaporated, cooled (0–5°), and basified with 20% NaOH. Extraction with Et_2O, followed by washings with brine, drying, and evaporation gave 41.05 g of a clear brown viscous liquid, which was dissolved in 30 ml of MeOH. To this soln., 20 ml of 48% HBr were added to give a pH of 1. Addition of Et_2O and cooling to 4° overnight yielded 44.83 g (82%) of **4**·HBr. An anal. sample was provided by recrystallization from MeOH/Et_2O: fine white needles, m.p. 157–158°. IR (KBr): 2952*w*, 2833*m*, 2704*m*, 1786*w*, 1644*s*, 1598*s*, 1560*m*, 1491*m*, 1449*m*, 1324*s*, 1292*m*, 1255*s*, 1172*m*, 1135*m*, 1037*m*, 1008*m*, 937*w*, 899*m*, 783*w*, 704*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.93, 3.08 (2 *t*, J = 7.5, both 2 H, CH_2–C(1'), CH_2(4)); 3.55, 3.77 (2 *m*, both 2 H, CH_2–C(1), CH_2(3)); 3.77, 3.91 (2 *s*, both 3 H, CH_3O); 6.70 (*dd*, J = 8, 2.5, H–C(4')); 6.74 (*d*, J = 7.5, H–C(6')); 6.83 (*m*, H–C(5), H–C(2')); 6.92 (*dd*, J = 8, 2.5, H–C(7)); 7.11 (*dd*, J = 8, 7.5, H–C(5')); 7.71 (*d*, J = 8.5, H–C(8)). MS (free base **4**): 296 (M^+ + 1), 295 (M^+). Anal. calc. for $C_{19}H_{21}NO_2$·HBr (376.294): C 60.65, H 5.89, Br 21.23, N 3.72; found: C 60.62, H 5.93, Br 21.48, N 3.68.

3,4-Dihydro-1-(3'-hydroxyphenethyl)-6-methoxyisoquinoline (**5**). A soln. of 16.0 g (42.6 mmol) of **4**·HBr in 40 ml of 48% HBr was refluxed (bath temp. 110°) for 1 h, evaporated, the residue dissolved in H_2O, rendered alkaline with conc. aq. NH_3, and extracted with $CHCl_3$/i-PrOH 2:1 (3 × 100 ml). The org. layer was washed with brine, dried with Na_2SO_4, and evaporated to give **5** as a brown viscous liquid. Crystallization from EtOH gave 10.1 g (84%) of **5**. An anal. sample was provided by recrystallization from EtOH: fine white sticks, m.p. 147–148°. IR (KBr): 3418*w*, 2909*m*, 2827*w*, 1604*s*, 1584*s*, 1570*m*, 1484*m*, 1455*m*, 1417*w*, 1371*m*, 1314*s*, 1282*s*, 1254*s*, 1229*m*, 1165*m*, 1132*m*, 1076*w*, 1026*m*, 856*m*, 794*w*, 697*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.68 (*t*, J = 7, CH_2–C(1)); 2.85–2.89, 2.99–3.01 (2 *m*, both 2 H, CH_2–C(1'), CH_2(4)); 3.60 (*t*, J = 7.5, CH_2(3)); 3.85 (*s*, CH_3O); 6.51 (*dd*, J = 2, H–C(2')); 6.59 (*d*, J = 7.5, H–C(6')); 6.66 (*ddd*, J = 7.5, 2.5, 2, H–C(4')); 6.74 (*d*, J = 2.5, H–C(5)); 6.83 (*dd*, J = 8.5, 2.5, H–C(7)); 7.06 (*t*, J = 7.5, H–C(5')); 7.51 (*d*, J = 8.5, H–C(8)). MS: 281 (M^+), 280 (M^+ –1). Anal. calc. for $C_{18}H_{19}NO_2$ (281.355): C 76.84, H 6.81, N 4.98; found: C 76.50, H 6.70, N 5.14.

1,2,3,4,5,8-Hexahydro-1-(3'hydroxyphenethyl)-6-methoxyisoquinoline (**6**). To 350 ml of dist. NH_3 were added 3.9 g (557 mmol) of Li and 200 ml of dry *t*-BuOH/Et_2O 1:1 at – 70°. To this well stirred mixture, 10.0 g (35.6 mmol) of powdered **5** were added at once. The stirring at – 70° was continued for 50 min, then 75 ml of abs. MeOH were added dropwise. The mixture was allowed to warm up and was kept at r.t. overnight. After evaporation of the remaining *t*-BuOH, the residue was dissolved in H_2O, and a soln. of 32 g (600 mmol) of NH_4Cl in 160 ml of H_2O was added dropwise. The precipitate was collected, washed with H_2O, MeOH, and petroleum ether to yield 8.44 g (83%) of **6**. Two crystallization from MeOH afforded an anal. sample: white crystals, m.p. 172–173°. IR (KBr): 3419*m*, 3302*m*, 2952*s*, 2824*s*, 2701*m*, 2602*m*, 2491*w*, 1700*s*, 1670*m*, 1595*s*, 1529*w*, 1509*w*, 1445*s*, 1397*m*, 1282*s*, 1256*w*, 1219*s*, 1162*s*, 1010*m*, 998*m*, 881*m*, 791*s*, 704*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.50–2.20, 2.54–2.89, 3.05–3.10 (3 *m*, 3 H, 8 H, 1 H, resp. CH_2–C(1), CH_2–C(1'), CH_2(3), CH_2(4), CH_2(5), CH_2(8)); 3.24 (*m*, H–C(1)); 3.55 (*s*, CH_3O); 4.63 (*dd*, J = 3, H–C(7)); 6.63 (*dd*, J = 2, H–C(2')); 6.64 (*ddd*, J = 7.5, 2.5, 2, H–C(4')); 6.73 (*d*, J = 7.5, H–C(6')); 7.13 (*m*, H–C(5')). MS: 285 (M^+). Anal. calc. for $C_{18}H_{23}NO_2$ (285.387): C 75.76, H 8.12, N 4.91; found: C 75.50, H 8.20, N 4.90.

N-Formyl-1,2,3,4,5,8-hexahydro-1-(3'-hydroxyphenethyl)-6-methoxyisoquinoline (**7**). A soln. of 3.0 g (10.5 mmol) of **6** and freshly distilled ethyl formate (300 ml) was refluxed for 72 h under Ar. Filtration and evaporation yielded 3.5 g of a solid. Flash chromatography (SiO_2, AcOEt) gave 2.55 g (77%) of **7** as a mixture of rotamers: white powder, m.p. 77–78°. IR (KBr): 3394*m*, 3282*m*, 2937*m*, 2834*m*, 1702*m*, 1649*s*, 1614*s*, 1586*s*, 1503*m*, 1485*m*, 1453*s*, 1399*m*, 1277*m*, 1248*m*, 1223*m*, 1157*m*, 1040*w*, 1011*w*, 880*w*, 784*m*, 698*m*. ^{1}H-NMR (400 MHz, $CDCl_3$, selected signals of mixture of rotamers (complicated ^{1}H-NMR for *N*-formylderivatives [12])): 3.55 (*s*, CH_3O); 4.63 (*dd*, J = 3, H–C(7)); 6.63–6.73 (*m*, H–C(2'), H–C(4'), H–C(6')); 7.07–7.13 (*m*, H–C(5')); 7.70–8.20 (*m*, OH, CHO). MS: 312 (M^+ –1). Anal. calc. for $C_{19}H_{23}NO_3$ (313.397): C 72.82, H 7.40, N 4.47; found: C 72.53, H 7.47, N 4.24.

N-Formyl-1,2,3,4,5,6,7,8-octahydro-1-(3'-hydroxyphenethyl)-6-oxoisoquinoline (**1**). A soln. of 500 mg (1.6 mmol) of **7** in 5 ml of abs. THF and 30 ml of 88% HCOOH/H_2O 5:1 was stirred at r.t. for 1 h. Extraction with $CHCl_3$, followed by washings with sat. $NaHCO_3$ and brine, drying with Na_2SO_4, and evaporation gave **1** as a yellow foam. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 100:7) gave 400 mg (84%) of **1** as a mixture of rotamers; white powder, m.p. 51–52°[3]). IR (KBr): 3274*m*, 2908*m*, 2853*m*, 1715*s*, 1647*s*, 1595*s*, 1585*s*, 1484*m*,

[3]) Although anal. samples were dried at 50–80° under high vacuum, it was impossible to get correct combustion analysis. These *N*-formyl derivatives seem to hold solvents of crystallization which can not be removed without decomposition.

1453*m*, 1399*m*, 1278*m*, 1242*w*, 1211*w*, 869*w*, 785*m*, 698*m*. ^{1}H-NMR (400 MHz, $CDCl_3$; selected data [12]): 4.44–4.70 (*m*, *d*, *J* = 10, H–C(1)); 6.69–6.73 (*m*, H–C(4'), H–C(2'), H–C(6')); 7.09–7.16 (*m*, H–C(5')); 7.6–7.9 (br. *s*, OH); 8.04, 8.14 (2 *s*, CHO). MS: 299 (M^+).

N-*Formyl-1,2,3,4,6,7,8,8a-octahydro-1-(3'-hydroxyphenethyl)-6-oxoisoquinoline* (**2**). A mixture of 80 mg (0.27 mmol) of **1** and 0.5 ml of freshly distilled CF_3SO_3H was kept at r.t. under Ar for 5 days. On TLC, no significant impurities could be detected. After addition of H_2O (5 ml), the soln. turned from red to light yellow. Extraction with $CHCl_3$ (4 × 10 ml), washing with H_2O, drying with Na_2SO_4, and evaporation gave 60 mg (75%) of **2** as a light yellow foam. An anal. sample was provided by flash chromatography (SiO_2, CH_2Cl_2/MeOH 100:8): white powder, mixture of rotamers, m.p. 84–85°[3]). IR (KBr): 3409*m*, 3291*m*, 3048*w*, 2947*w*, 2869*w*, 1650*s*, 1599, 1586*m*, 1484*w*, 1452*m*, 1403*w*, 1356*w*, 1334*w*, 1278*w*, 1257*w*, 1228*w*, 1187*w*, 1157*w*, 1131*w*, 878*w*, 785*w*, 698*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; selected data [12]): 5.89 (*s*, H–C(5)); 6.65–6.80 (*m*, H–C(4'), H–C(2'), H–C()6')); 7.11–7.16 (*m*, H–C(5')); 7.27 (*s*, CHO). MS: 299 (M^+).

The same treatment as described above also gave **2** in a 67% yield when starting from **7**. Again no cyclization product could be detected on TLC.

1,2,3,4,6,7,8,8a-Octahydro-1-(3'-hydroxyphenethyl)-6-oxoisoquinoline (**8**). A mixture of 99 mg (0.33 mmol) of **2**, 4 ml of abs. MeOH, and 1 ml of 4.2M HCl/MeOH was refluxed under Ar for 16 h. After evaporation, the residue was purified by flash chromatography (SiO_2, AcOEt/MeOH/conc. aq. NH_3 100:15:0.5) and crystallized from MeOH/Et_2O: 65 mg (64%) of **8**·HCl as white crystals, m.p. 218–219°. This compound was identical with a sample derived from **6** by treatment with HCl/MeOH at r.t. for 7 h. IR (KBr): 3386*m*, 3236*m*, 2756*m*, 2710*m*, 2604*m*, 2510*m*, 2439*m*, 1653*s*, 1587*s*, 1531*s*, 1486*m*, 1275*m*, 1218*m*, 883*w*, 788*w*, 701*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.59–1.67, 1.95–2.05, 2.16–2.25, 2.29–2.36, 2.41–2.49, 2.63–2.88, 3.07–3.20 (7 *m*, 1 H, 1 H, 1 H, 1 H, 2 H, 5 H, 2 H, resp., CH_2(3), CH_2(4), CH_2(7), CH_2(8), H–C(9), CH_2–C(1), CH_2–C(1')); 3.56–3.61 (*m*, H–C(1)); 6.00 (*dd*, *J* = 2, H–C(5)); 6.65 (*ddd*, *J* = 7.5, 2, 1.5, H–C(4')); 6.70 (*dd*, *J* = 2, 1.5, H–C(2')); 6.73 (*d*, *J* = 7.5, H–C(6')); 7.11 (*t*, *J* = 7.5, H–C(5')). Anal. calc. for $C_{17}H_{22}ClNO_2$ (307.821): C 66.33, H 7.20, N 4.55, Cl 11.52; found: C 65.98, H 6.96, N 4.45, Cl 11.49.

A portion of this material was converted to the free base **8**; m.p. 154–155° (MeOH). IR (KBr): 3420*m*, 3304*m*, 2923*m*, 2857*m*, 1630*s*, 1600*s*, 1587*m*, 1526*w*, 1456*m*, 1423*m*, 1377*s*, 1280*m*, 1263*m*, 1215*w*, 1194*m*, 1155*w*, 824*w*, 767*w*, 698*w*. ^{1}H-NMR (400 MHz, CD_3OD): 1.42–1.54, 1.65–1.78, 1.98–2.10, 2.22–2.83, 3.14–3.28 (5 *m*, 1 H, 1 H, 1 H, 8 H, 3 H, resp., CH_2(3), CH_2(4), CH_2(7), CH_2(8), H–C(9), CH_2–C(1), H–C(1), CH_2–C(1')); 5.85 (*dd*, *J* = 2, H–C(5)); 6.58 (*ddd*, *J* = 7.5, 2, 1.5, H–C(4)); 6.67 (*dd*, *J* = 2, 1.5, H–C(2')); 6.69 (*d*, *J* = 7.5, H–C(6')); 7.06 (*t*, *J* = 7.5, H–C(5')). MS: 271 (M^+). Anal. calc. for $C_{17}H_{21}NO_2$ (271.360): C 75.25, H 7.80, N 5.16; found: C 75.14, H 7.85, N 5.15.

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