241. Apomorphinans from Isoquinolines: *Grewe* Cyclization of 1-(2-Hydroxybenzyl)-*N*-methyloctahydroisoquinoline and its *O*-Methyl Ether

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Summary

Wolff-Kishner reduction of the optically active ketomorphinan **5** afforded the optically active morphinan **6** differing chromatographically and spectroscopically from the material obtained in a *Grewe*-cyclization of the isoquinoline **1**. A single crystal X-ray analysis of a hydrobromide salt of a phenolic amine obtained from **1** and **2** with refluxing hydrobromic acid showed this compound to be the *N*-methylapomorphinan **4**.

It was reported that the isoquinoline **1** afforded with refluxing hydrobromic acid the cyclic ether **3**, converted on further treatment into a phenolic base of m.p. 232–236° for which a 1-hydroxymorphinan structure was proposed [1]. The same phenolic compound was later prepared elsewhere by a somewhat modified procedure [2]. This phenolic base was, however, not identical by TLC and ^{1}H-NMR with (–)-1-hydroxy-*N*-methylmorphinan (**6**), prepared from the ketomorphinan **5** [3] by a *Wolff-Kishner* reduction *(Scheme 1)*[2]). Whereas the structure of the cyclic ether **3** was supported by a chemical degradation, that of the 'so-called' 1-hydroxy-*N*-methylmorphinan was not secured with additional data (s. [1]), and required in the light of our findings a reexamination of its structure.

We now report that the *Grewe*-cyclization, when repeated with the isoquinoline **2** prepared by the route shown in *Scheme 2*, afforded compounds **3** and **4** identical with the materials obtained elsewhere [1] from **1**. A single crystal X-ray analysis of the

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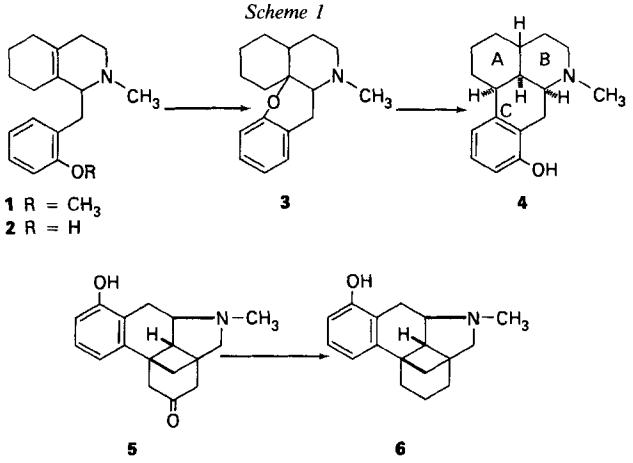
[2]) We would like to thank Dr. *E. Mohacsi* from *Hoffmann-La Roche Inc.*, Nutley, New Jersey, for having given us a sample (±)-**4** prepared with a modified procedure (see p. 13 in [8]).

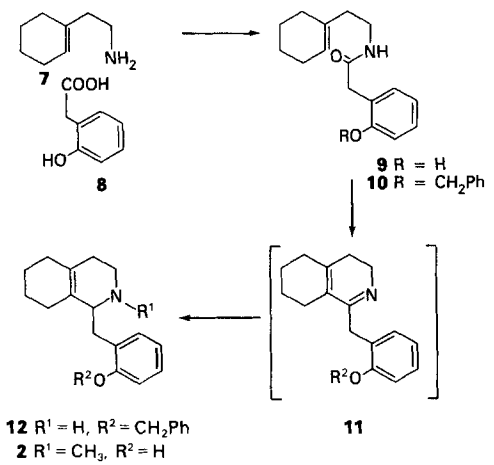
hydrobromide salt of the phenolic base of m.p. 232–234° proved that this compound had the structure of the 8-hydroxylated *N*-methylapomorphinan **4**[3]).

The X-ray presentation reveals that this material has the H-atoms at the three neighboring chiral C-atoms connecting rings A and B with C *cis*- and *trans*-positioned to the fourth H-atom. This is shown in formula **4** in an arbitrarily chosen absolute configuration. The finding of apomorphinans among by-products of the *Grewe*-morphinan synthesis is well-documented [4], and probably proceeds here from the cyclic

Scheme 1



Scheme 2



[3]) It seems reasonable to delineate for the parent structure of compound **4** the name apomorphinan, in line with the term morphinan, thus **4** is (±)-*N*-methylapomorphinan-8-ol. The complicated generic nomenclature of **4** as (±)-10,11-dideoxy-1,2,3,3a,11b,11c-hexahydroapomorphin-8-ol can thus be avoided. Systematic name of **4**: (±)-6-methyl-2,3,3a,4,5,6,6a,7,11b,11c-decahydro-1*H*-dibenzo[*de*,*g*]quinolin-8-ol.

ether **3** *via* carbenium ion intermediates and cyclization, possibly involving a dienone-phenol rearrangement [5]. The apomorphinan **4** should be an interesting compound for further transformation [6] since the overall yield of **4** from **1** and **2** is quite remarkable.

Single crystal X-ray analysis was also performed with the hydrobromides of **2** and **3**, confirming the structures assigned to these compounds based on chemical and spectroscopic data.

It is unfortunate that the apomorphinan **4** was used by other investigators in a structure-activity study of aromatic substituted morphinans, comparing aromatic substitution with analgesic potency and binding to the opiate receptors [7]. A similar study has recently been carried out in the ketomorphinan series, where **5** of established structure served in the comparison [8].

X-Ray Crystallographic Data[4]). – *For* **2**: $C_{17}H_{23}NO \cdot HBr$, mol. wt. 338.3, monoclinic, space group $P2_1/c$, $a = 7.368$ (4) Å, $b = 8.798$ (5) Å, $c = 25.247$ (8) Å, $\beta = 91.8$ (1)° $V = 1635.9$ (8) Å^3, $Z = 4$, $d_{calc} = 1.37$ g · cm^{-3}. The 2155 independent reflections were measured out to $2\theta_{max} = 45°$ with a computer-controlled diffractometer *(Nicolet P3F)* using Mo$K\alpha$ radiation with a graphite monochromator on the incident beam. The structure was solved using direct methods [9]. Full-matrix least-squares refinement [10] using 1560 reflections for which $|F_0| > 3\delta_F$ gave a final R-factor of 6.6% ($R_w = 5.7\%$).

For **3** *(s. Fig. 1)*: $C_{17}H_{24}NO \cdot HBr$, mol. wt. 339.3, orthorhombic, space group $P2_12_12_1$, $a = 7.503$ (4) Å, $b = 13.648$ (6) Å, $c = 15.729$ (9) Å, $V = 1610.6$ (9) Å^3, $Z = 4$, $d_{calc} = 1.38$ g · cm^{-3}. The 1195 independent reflections were measured out to $2\theta_{max} = 45°$ as above using Cu$K\alpha$ radiation. The structure was solved by direct methods [9] and refined by full-matrix least-squares methods [11] using 1113 reflections for which $|F_0| > 3\sigma_F$. The final R-factor for this set of data was 4.1% ($R_w = 4.8\%$).

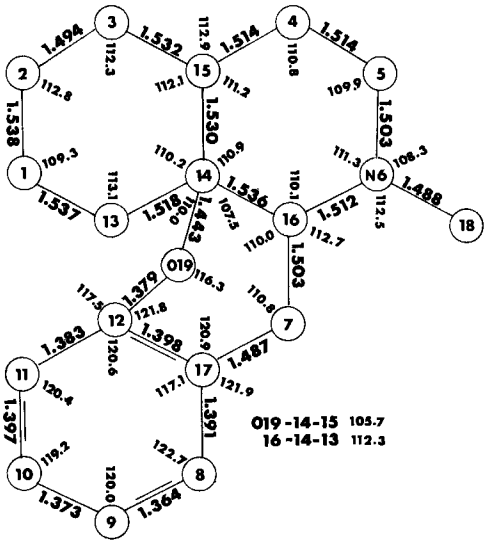


Fig. 1. *The X-Ray Diffraction Structure of* **3** *Showing the Atomic Numbering (arbitrary), Bond Lengths and Angles*

[4]) Coordinates and thermal parameters for all three molecules have been deposited with the Crystallographic Data Centre, Cambridge University, University Chemical Lab, Cambridge CB2 1EW, England.

For **4** *(s. Fig. 2 and 3):* $C_{17}H_{23}NO \cdot HBr$, mol.wt. 338.3, monoclinic, space group $P2_1/n$, $a = 10.938$ (4) Å, $b = 8.996$ (4) Å, $c = 15.941$ (5) Å, $\beta = 101.9$ (1)°, $V = 1534.9$ (9) Å^3, $Z = 4$, $d_{calc} = 1.46$ g · cm^{-3}. The 1894 independent reflections were measured out to $2\theta_{max} = 45°$, under the same experimental conditions as for **2**. The structure was solved by direct methods and refined in the same manner as for **2** using 1446 reflections for which $|F_0| > 3\delta_F$. The final R-factor for this set of data was 6.6% ($R_w = 5.8\%$).

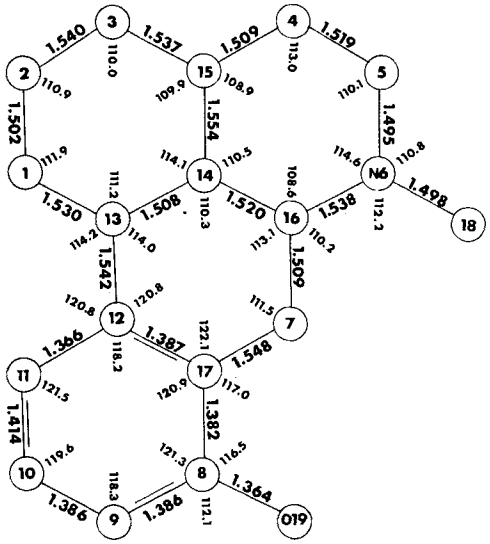


Fig. 2. *The X-Ray Diffraction Structure of* **4** *Showing the Atomic Numbering (arbitrary), Bond Lengths and Angles*

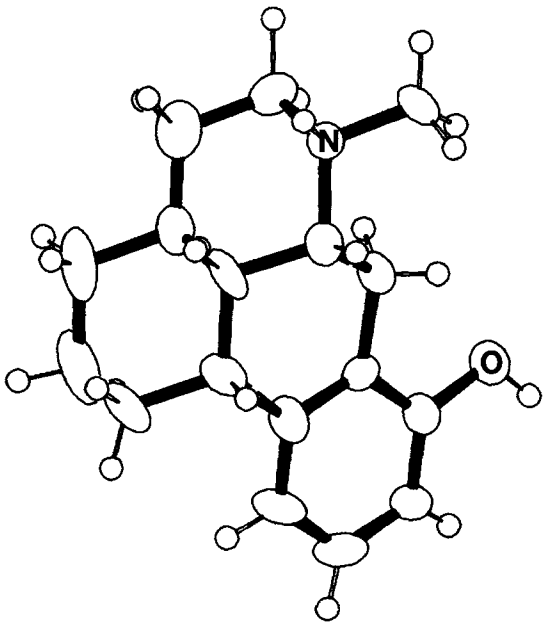


Fig. 3. *A Diagram Showing the Structure and Conformation of the Apomorphinan* **4**

Discussion of X-Ray Results. – Molecules **3** and **4** have similar conformations in that the aromatic ring is planar and the six-membered ring fused to it has a half-chair conformation. The remaining six-membered rings have normal chair conformations. Bond lengths and angles for both molecules, shown in *Fig. 1* and *2*, are well within expected ranges. The only intermolecular approaches less than *Van der Waal's* distances are H-bonds. In **3** the bromide ion forms one H-bond to the protonated N-atom of a neighboring molecule. The Br · · · · N distance is 3.25 Å. In **4** the bromide ion forms two H-bonds; one to the hydroxy O-atom and the other to the protonated N-atom of a symmetry-related molecule. The Br · · · · O distance is 3.22 Å, and the Br · · · · N distance is 3.21 Å.

Experimental Part

General Remarks. Physical constants and spectra were determined using the instrumentation indicated. Melting points (m.p.): *Reichert Thermovar* melting point microscope (uncorrected). IR (cm^{-1}): *Infrascan H 900* from *Hilger & Watts*. ^{1}H-NMR: in ppm relative to TMS (= 0 ppm) as internal standard; *s* = singlet, *d* = doublet, *dd* = doublet of doublets, *m* = multiplet, *J* [Hz] = apparent coupling constant; *Jeol-LNM-FX-100* spectrometer (100 MHz) and *Jeol C-60 HL* high resolution NMR instrument (60 MHz). MS (*m/z*): *Finnigan MAT 44S* for chemical ionization (CI). Optical rotations (concentration (g/100 ml), solvent): *Perkin-Elmer*, polarimeter model *241 MC*.

*1-(2-Hydroxybenzyl)-*N*-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline Hydrobromide (***2*** · HBr).* A mixture of 2.0 g (4.8 mmol) of **12** · HBr (s. below), 2.0 g (24.4 mmol) of NaOAc, 6 ml of 37% formalin, 1.2 g of 10% Pd/C and 60 ml of 2N AcOH was hydrogenated at r.t. at 30 psi for 16 h. The catalyst was filtered off, washed with H_2O, the filtrate was rendered alkaline with 30% NH_4OH, and extracted with CH_2Cl_2. The org. layer was washed with brine, dried, and evaporated to give 1.1 g of an oil which was converted into the hydrobromide salt in the usual way to yield 1.25 g (77%) of **2** · HBr. A portion of this material was recrystallized from MeOH/Et_2O to give an anal. sample, m.p. 185–187°. IR (KBr): 3150 (OH, $^+$NH). ^{1}H-NMR (100 MHz, (D_6)DMSO): 7.22–6.64 (*m*, 4 H, arom. H), 2.76 (*s*, 3 H, NCH_3). MS (CI): 258 ($M^+ + 1$).

$C_{17}H_{23}NO \cdot HBr$ (338.28) Calc. C 60.36 H 7.13 N 4.26% Found C 60.23 H 7.40 N 4.02%

7-Methyl-2,3,4,4a,5,6,7,7a,8,13a-decahydro-1 H*-[1]benzopyrano[2,3-*j*]isoquinoline Hydrobromide (***3*** · HBr) and Apomorphinan*[3] ***4*** *from* **2**. A solution of 1.3 g (3.84 mmol) of **2** · HBr and 10 ml of 48% HBr was refluxed for 16 h under N_2. The mixture was cooled, basified with NaOH, and extracted with CH_2Cl_2. The org. layer was washed with H_2O, dried, and evaporated to give 540 mg of a foam which was converted into the hydrobromide salt of **3** in the usual way (260 mg, 20%). Two recrystallization from EtOH/Et_2O gave a sample of **3** · HBr with m.p. 278–280° (dec.; [1]: 277–278° (dec.). This material was identical by TLC, IR and mixed m.p. with the material prepared from **1** [1].

The aq. layer from above was cooled, acidified with conc. HCl, basified with 30% NH_4OH, and extracted with CH_2Cl_2. The org. layer was dried and evaporated to give 210 mg of a crystalline residue which was treated with acetone to yield 145 mg (15%) of **4**. This product was purified *via* its hydrobromide salt which was reconverted into the free base **4**: m.p. 232–236° (dec.; [1]: 234–235° (dec.). This material was found to be identical by TLC and mixed m.p. with material prepared from **1** by analogous treatment [1], and with material prepared by a modified procedure [2]. The hydrochloride salts **4** · HCl of all 3 materials prepared from different isoquinoline precursors proved to be identical by IR.

*(−)-1-Hydroxy-*N*-methylmorphinan* (**6**). A mixture of 20 mg (0.074 mmol) of **5**, 2 ml of triethylene glycol and 1 ml of 64% hydrazine hydrate was stirred under Ar at 125° (bath temp.) for 1.5 h. After cooling to r.t., 300 mg of KOH pellets were added, the mixture was heated up gradually to 205° (bath temp.) and kept at 205° for 3 h. Then it was poured on ice, acidified with 2N HCl, washed with Et_2O, rendered alkaline with 30% NH_4OH, and extracted with $CHCl_3$. The org. layer was washed with H_2O, dried, and evaporated to give 16 mg of an oil, which was crystallized with MeOH to afford pure **6**, m.p. 223–226°, $[\alpha]_D^{26} = -43.6°$ ($c = 0.11$, $CHCl_3$). IR

($CHCl_3$): 3605 (OH). ^{1}H-NMR (100 MHz, $CDCl_3$): 7.02 (*dd*, J = 8, 1 H, arom. H); 6.80 (*d*, J = 8, 1 H, arom. H); 6.55 (*d*, J = 8, 1 H, arom. H); 2.38 (*s*, 3 H, NCH_3). MS (CI): 258 ($M^+ + 1$).

$C_{17}H_{23}NO$ (257.36) Calc. C 79.33 H 9.01 N 5.44% Found C 78.95 H 9.16 N 5.44%

N-[2-(1-Cyclohexen-1-yl)ethyl]-2-(2-hydroxyphenyl)acetamide (**9**). A solution of 12.5 g (0.1 mol) of 2-(1-cyclohexen-1-yl)ethylamine (**7**), 15.2 g (0.1 mol) of (2-hydroxyphenyl)acetic acid (**8**) and 100 ml of xylene was heated under reflux with azeotropic H_2O separation for 6 h. After evaporation, the oily residue was crystallized with isopropyl ether to yield 22.3 g (86%) of **9**. An anal. sample was prepared by recrystallization from isopropyl ether, m.p. 74–76°. ^{1}H-NMR (60 MHz, (D_6)DMSO): 9.64 (*s*, 1 H, OH); 7.67 (*m*, 1 H, NH); 7.15–6.50 (*m*, 4 H, arom. H); 5.26 (*m*, 1 H, olef. H); 3.34 (*s*, 2 H, CH_2CO). MS (CI): 260 ($M^+ + 1$).

$C_{16}H_{21}NO_2$ (259.34) Calc. C 74.10 H 8.16 N 5.40% Found C 73.82 H 8.38 N 5.48%

2-(2-Benzyloxyphenyl)-N-[2-(1-cyclohexen-1-yl)ethyl]acetamide (**10**). At r.t. and under N_2, 7.6 ml (66 mmol) of benzyl chloride were added dropwise within 10 min to a mixture of 17.0 g (65.6 mmol) of **9**, 12.0 g (86.9 mmol) of anh. K_2CO_3, and 120 ml of anh. DMF. This mixture was stirred at 85° (bath temp.) for 3 h, cooled to r.t., filtered, and the filtrate was evaporated. The oily residue was crystallized with Et_2O to give 20.2 g (88%) of **10**. An analytical sample was recrystallized from MeOH, m.p. 91–92°. ^{1}H-NMR (60 MHz, (D_6)DMSO): 7.60–6.80 (*m*, 9 H, arom. H); 5.26 (*m*, 1 H, olef. H); 5.02 (*s*, 2 H, PhCH_2O); 3.36 (*s*, 2 H, CH_2CO). MS (CI): 350 ($M^+ + 1$).

$C_{23}H_{27}NO_2$ (349.46) Calc. C 79.04 H 7.79 N 4.01% Found C 79.44 H 7.89 N 3.99%

1-(2-Benzyloxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline Hydrobromide (**12** · *HBr*). A solution of 12 g (34.3 mmol) of **10**, 7 ml (74.2 mmol) of $POCl_3$ and 100 ml of MeCN was refluxed for 2 h under N_2, evaporated, and the oily residue was basified with conc. NaOH while cooling with ice. Extraction with CH_2Cl_2, followed by washings with H_2O and brine, drying, and evaporation gave 11.5 g of **11** as an oil which was not further characterized. In portions, 2.0 g (52.8 mmol) of $NaBH_4$ were added to a solution of **11** in 200 ml of EtOH while a temp. of 10° was maintained. The mixture was allowed to warm up to r.t. and was then again cooled (5–10°) and acidified (pH 5) with 30% AcOH. Evaporation gave an oily residue which was basified with conc. NaOH while cooling with ice. Extraction with CH_2Cl_2, washings with H_2O and brine, drying, and evaporation afforded 10.3 g of an oil which was converted into the hydrobromide salt in the usual manner to yield 7.2 g (51%) of **12** · HBr. A sample was recrystallized from MeOH/Et_2O to give analytically pure **12** · HBr, m.p. 183–185°. ^{1}H-NMR (60 MHz, $CDCl_3$): 9.15 (br. *s*, 1 H, $^+$NH); 7.55–6.70 (*m*, 9 H, arom. H); 5.12 (*s*, 2 H, PhCH_2O). MS (CI): 334 ($M^+ + 1$).

$C_{23}H_{27}NO \cdot HBr$ (414.38) Calc. C 66.66 H 6.81 N 3.38% Found C 66.92 H 6.63 N 3.31%

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