160. Conversion of Natural (*S*)-Bulbocapnine into Two (Ring A)-Substituted Derivatives of (*R*)-Apomorphine[1])

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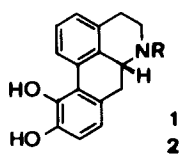
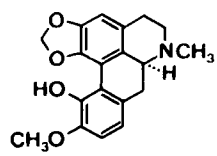
Summary

(6a*R*)-1,2-(Methylenedioxy)aporphine-10,11-diol (**8**) and (6a*R*)-aporphine-1,2,10,11-tetrol (**16**) have been prepared from natural (*S*)-bulbocapnine (**4**). For both compounds, the partial synthesis included racemic intermediates which have been resolved into their enantiomers. Both compounds **8** and **16** showed dopaminergic activity in rats, although to a lower extent than (*R*)-apomorphine (**1**) itself.

Following the initial reports of a possible use of (*R*)-apomorphine (**1**) for treating *Parkinson*'s disease in man [1] [2], structure-activity relationship studies related to this compound have been done by different groups. For the aporphines, the following structural elements have been found to be of importance: the presence of an *N*-alkyl group and its size plays a role, since (*R*)-*N*-norapomorphine (**2**) is only slightly active [3], whereas the corresponding *N*-methyl and *N*-propyl compounds **1** and **3** are highly active in a variety of animal tests [4] [5]. The *S*-enantiomer of **1** is inactive in these tests, showing that the *R*-configuration is necessary at C(6a) [6]. The position of the two hydroxy groups seems to be optimal at C(10) and C(11): catechol isomers [5] as well as two monomethyl ethers of apomorphine [7] [8] were found to be considerably less active.



1 R = CH_3
2 R = H
3 R = n-C_3H_7



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[1]) Presented by *A.B.* at the 10th European Symposium on Bio-Organic Chemistry, Gregynog Hall, Wales (U.K.), May 14th to 17th, 1976, and during a lecture tour in Japan (autumn 1976).

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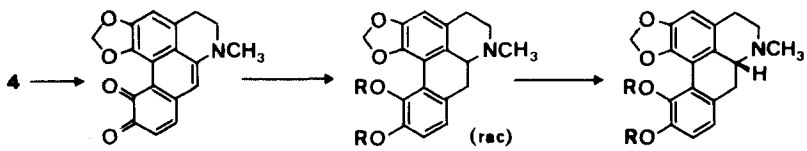
In order to study the effect of the substitution in ring A relatively to apomorphine, the two analogs **8** and **16** with *R*-configuration were prepared from natural bulbocapnine (**4**). This alkaloid with *S*-configuration is known to be contained in *Corydalis cava;* we could easily isolate it in 1.5% yield from the dry bulbs.

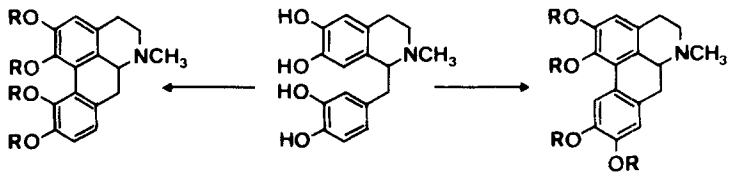
The preparation of **8** is outlined in *Scheme 1.* Mercury(II) chloride oxidation of **4** afforded, as described by *Cava et al.* [9], the quinone **5**, which was reduced to the racemic diol **6**. This compound is very sensitive to oxygen and was therefore directly converted to the diacetyl derivative **7a**. The latter could easily be resolved with (+)-tartaric acid[4]). The less soluble tartrate was converted to the free base **7b** and treated with methanolic hydrogen chloride to afford the hydrochloride of **8**. The *R*-configuration of **8** was proven by methylation with diazomethane, which gave the known (*R*)-bulbocapnine methyl ether [10].

Scheme 1



Aporphines of type **10** and **11** occur in plants in various *O*-methylated forms [11] [12]. Tetrahydropapaveroline (THP), the nor-analog of **9**, has been found to be a urinary metabolite in parkinsonian patients treated with L-dopa [13] [14]. A biosynthetic conversion of THP into the aporphine **10** (R=H) *via* its *N*-methyl derivative **9** by *o,o*-coupling, although highly speculative, suggested the preparation of the hitherto unknown aporphine-1,2,10,11-tetrol (**16**)[5]).

Scheme 2

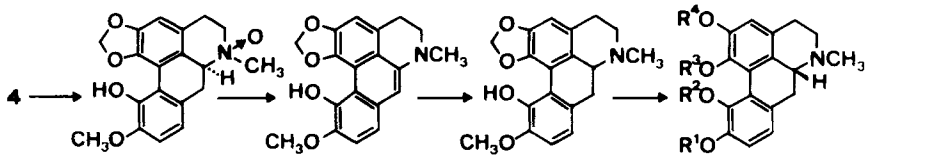


[4]) (*S*)-Apomorphine was prepared in 1972 by *R. Joos* and *B. Hennessy* at *Hoffmann-La Roche Inc.*, Nutley N.J., U.S.A., by a procedure similar to that described in the present paper for the synthesis of **8** (unpublished results). We thank Dr. *R. Joos* for his personal communication.

[5]) The correlations mentioned here are shown without indication of the absolute configuration. All 1,2,10,11- and most of the 1,2,9,10-tetraoxygenated plant aporphines are known to belong to the *S*-series [12], whereas apomorphine has *R*-configuration. It is unknown whether THP detected in the urine of patients is optically active or not.

(6a*R*)-Aporphine-1,2,10,11-tetrol (**16**) was synthesized from (*S*)-bulbocapnine (**4**) as shown in *Scheme 3. Cava & Srinivasan,* in a publication dealing with the *Polonovski* rearrangement of aporphine-*N*-oxides to nor-aporphines, have mentioned that on successive treatment of nuciferine-*N*-oxides with sulfur dioxide and aqueous sodium hydroxide, 6a,7-didehydronuciferine was obtained in moderate yield [15]. We found that by treating the mixture of *N*-oxides **12** (obtained from **4** by treatment with *m*-chloroperbenzoic acid) with acetic anhydride at 0°, 6a,7-didehydrobulbocapnine (**13**) was obtained in fair yield. This hitherto unknown compound could not be prepared by conventional oxidation procedures from bulbocapnine[6]). Reduction of **13** with zinc and acid afforded *rac*-bulbocapnine (**14a**), which was resolved with (+)-tartaric acid. The complete ether cleavage of (*R*)-bulbocapnine (**14b**) to **16** was not possible by a direct method: treatment with mineral acids resulted in formation of tars, whereas direct treatment with boron tribromide in dichloromethane is known to give 1,11-(methylenedioxy)aporphine-2,10-diol [16]. Therefore, the methylenedioxy and the methoxy groups were sequentially cleaved by treatment with boron trichloride to the monomethyl ether **15**, followed by boron tribromide to give (6a*R*)-aporphine-1,2,10,11-tetrol hydrobromide (**16**) in good yield.

Scheme 3



12 **13** **14a** (rac)

14b $R^1=CH_3, R^2=H, R^3+R^4=CH_2$

15 $R^1=CH_3, R^2=R^3=R^4=H$

16 $R^1=R^2=R^3=R^4=H$

Pharmacological evaluation. **8** · HCl and **16** · HBr were compared with (*R*)-apomorphine hydrochloride (**1** · HCl) in the following tests. Turning behavior: unilateral lesions of the nigro-striatal dopamine system were made with 6-hydroxydopamine in the medial forebrain bundle (MFB) in female rats (5 animals per dose), and the contralateral turning behavior after application of the compounds was recorded according to *Ungerstedt et al.* [17]. Homovanillic acid (HVA): this main metabolite of dopamine was determined fluorometrically in the whole rat brain [18]. Each value represents the mean of four determinations. Changes of the concentration of HVA reflect alterations of the turnover or metabolism of central dopamine. Acute toxicity: the lethal dose was determined tentatively, using one animal for each dose.

The table shows that both **8** · HCl and **16** · HBr have some apomorphine-like dopaminergic activity, but the latter is clearly less active and less toxic. It is not known if this lower activity *in vivo* is due to a lower uptake into the central nervous system, to a faster elimination or still to other factors.

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[6]) We have applied this method with success, and often with higher yields, to some other aporphines (unpublished results). We thank our colleague, Dr. *R. Joos,* for having drawn our attention to this method.

Table

Compound	**1** · HCl	**8** · HCl	**16** · HBr
Contralateral turning (rats)			
Minimal active dose (mg/kg *i.p.*)	0.25	1.0	30
Homovanillic acid in whole rat brain (1 h after application)			
Dose (mg/kg *i.p.*)	5	50	50
HVA content (% of controls)	23.1 ± 1.0	25.5 ± 4.2	82.5 ± 4.0
Acute toxicity (mice, mg/kg)			
I.v.	15–30	31–62	250–500
S.c.	60–120	62–125	2000–4000

We are indebted to Dr. *M. Pieri,* Dr. *E.P. Bonetti,* and Dr. *H.H. Keller* of our pharmaceutical research department for the biological evaluation of the compounds reported. We are also grateful to the colleagues of our Central Research Units, in particular to Dr. *M. Grosjean,* Dr. *W. Arnold,* Dr. *A. Dirscherl,* Dr. *G. Englert,* Mr. *M. Meister* and Dr. *W. Vetter* for the analytical and spectral data and their interpretation.

Experimental Part

General remarks. Melting points (m.p.) were taken on a *Tottoli* apparatus using open capillaries and are not corrected. Reactions were routinely monitored by TLC. (silica gel plates F 254 *Merck;* solvent system: chloroform/2-propanol/acetic acid/water 20:20:6:4). ^{1}H-NMR. spectra were recorded on a *Varian* HA 100 or a *Bruker-Spectrospin* HX 90 E (*Fourier* transform mode) spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Abbreviations: s = singlet, d = doublet, m = multiplet, br. = broad, J = coupling constant (Hz). Mass spectra were recorded on an *AEI* MS 902 spectrometer; mass numbers are given in *m/e*, relative intensity in % in parentheses. Abbreviations: i.V. = in vacuum, i.HV. = in high vacuum, RT. = room temperature.

(6aR)-1,2-(Methylenedioxy)aporphine-10,11-diol diacetate (**7b**). A suspension of the quinone **5** (5.9 g, 19.2 mmol) [9] in 2N HCl (500 ml) and ethanol (250 ml) was treated with zinc powder (12 g) and heated without stirring to 80° for 1 h. The mixture was filtered, the residue washed with ethanol, and the solution treated with fresh zinc powder (12 g) and heated again for 3 h at 80°. More zinc powder (6 g) was added, and after another hour at 80°, the mixture was cooled to RT., excess zinc filtered off and washed with ethanol. The ethanol was evaporated i.V. and the remaining aqueous solution was adjusted to pH 6.5 with 5N NaOH. The mixture was then treated simultaneously with acetic anhydride (48 ml) and 5N NaOH, keeping the pH between 6.5 and 7.0. A small precipitate was filtered off and washed several times with chloroform. The chloroform extract was washed (brine), dried (Na_2SO_4), filtered and evaporated to give 5.49 g of a brown oil. The acetylation was completed by dissolving this oil in acetic anhydride (17 ml) and heating to 65° for 45 min. After evaporation i.HV., the residue was dissolved in benzene, washed ($NaHCO_3$-solution and brine), dried (Na_2SO_4), filtered and evaporated to give 5.2 g of crude **7a** as a foam. For the optical resolution, this material was dissolved in ethanol (100 ml) and treated with a solution of (+)-tartaric acid (1.18 g) in ethanol (60 ml). The precipitate was filtered off (3.7 g) and recrystallized once from ethanol and once from methanol to give **7b** (1.42 g) as its tartrate. This material was used without further purification for the next step.

(6aR)-1,2-(Methylenedioxy)aporphine-10,11-diol (**8**). From the tartrate of **7b**, the free base was prepared by partition between benzene and $NaHCO_3$-solution. Removal of benzene left 1.0 g of **7b** as a yellow oil, which was dissolved in methanol (50 ml), treated with 5.0 ml of 2.3N HCl in methanol and refluxed under argon for 4 h. The solution was concentrated to 20 ml, ether was added and the resulting crystals were filtered off to give the hydrochloride of **8** as white crystals (0.7 g). Recrystallization from methanol gave the analytical sample: m.p. 210° (dec.), $[\alpha]_D^{22°} = -204°$ ($c = 0.08$, methanol). –

^{1}H-NMR. (90 MHz, d-DMSO): 3.01 (*s*, 3 H, NCH_3); 5.97 and 6.09 (2 *d*, *J* = 6, 2 H, OCH_2O); 6.68 and 6.78 (2 *d*, *J* = 8, 2 H, H–C(8) and H–C(9)); 6.79 (*s*, 1 H, H–C(3)); 8.48 and 9.27 (2 *s*, 2 H, 2 OH). – MS.: 311 (100, M^+), 310 (79), 294 (23), 281 (24), 268 (19), 210 (7).

$C_{18}H_{17}NO_4 \cdot HCl \cdot 2H_2O$ (283.8) Calc. C 56.28 H 5.77 N 3.64% Found C 56.13 H 5.47 N 3.52%

(6aR)-Bulbocapnine methyl ether. **8** · HCl (70 mg) was dissolved in methanol (3 ml) and treated with 40 ml of CH_2N_2-solution. The mixture was allowed to stand at RT. for several days, after which it was evaporated to dryness. The residue was chromatographed on aluminium oxide (activity grade III) and the evaporated fractions crystallized from ether/hexane to give (6a*R*)-bulbocapnine methyl ether (48 mg) as crystals, m.p. 128–130°, $[\alpha]_D^{22°} = -251°$ (*c* = 1.0, $CHCl_3$).

6a,7-Didehydrobulbocapnine (**13**). A solution of (*S*)-bulbocapnine (**4**; 6.5 g, 20 mmol) in $CHCl_3$ (160 ml) was stirred at 0° under argon and treated with *m*-chloroperbenzoic acid (5.2 g, purity about 90%). The mixture was stirred at 0° for 1 h and then poured onto a column of 300 g of aluminum oxide (activity grade I, basic) in chloroform. Fractions were eluted with chloroform and chloroform/methanol mixtures 4:1 and 1:1. Evaporation afforded the crude mixture of two *N*-oxides **12** as a brown oil (7.0 g). A solution of this crude material in chloroform (160 ml) was stirred at 0° under argon and treated dropwise with acetic anhydride (10 ml). After 1.5 h at 0°, additional 2 ml of acetic anhydride were added. The mixture was again stirred for 1 h, treated with methanol (10 ml) and then stirred for 2 h at RT. The reaction mixture was then washed with saturated $NaHCO_3$-solution, dried (Na_2SO_4), filtered and evaporated to give 7,1 g of a brown oil. This was chromatographed on aluminum oxide (300 g, activity grade III, neutral). Elution with benzene afforded, after evaporation, 2.5 g (38%) of pure **13** as greenish crystals. Recrystallization from benzene/hexane afforded the analytical sample: m.p. 118.5–120°. – UV. (ethanol, λ_{max} nm (logε)): 244 (4.51), 266 (4.56), 310*s* (3.91), 339 (4.11), 402 (3.57). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 3.01 (*s*, 3 H, NCH_3); 3.24 (*m*, 4 H, CH_2CH_2); 3.96 (*s*, 3 H, OCH_3); 6.12 (*s*, 2 H, OCH_2O); 6.45 and 6.93 (2 *s*, 2 H, H–C(3) and H–C(7)); 7.13 and 7.22 (2 *d*, *J* = 8, 2 H, H–C(8) and H–C(9)). – MS.: 323 (100, M^+), 308 (90), 280 (23), 222 (18).

$C_{19}H_{17}NO_4$ (323.3) Calc. C 70.58 H 5.30 N 4.33% Found C 70.86 H 5.37 N 4.06%

rac-*Bulbocapnine* (**14a**) *and (6aR)-bulbocapnine* (**14b**). A suspension of **13** (10.5 g, 32.3 mmol) in 1N H_2SO_4 (700 ml) was treated with zinc powder (20 g) and heated without stirring to 75°. Additional portions of zinc powder (4 g each) were added after 2 h and 5 h. After the reaction was complete, the mixture was cooled to RT. and the zinc was filtered off and washed with water and chloroform. The filtrate was neutralized with $NaHCO_3$ and transferred to an extraction funnel. The chloroform layer was separated, washed (brine), dried (Na_2SO_4), filtered and evaporated to dryness to give 10.2 g (96%) of crystalline **14a**, m.p. 205–208°. This material was, without further purification, resolved with (+)-tartaric acid as described by *Kikkawa* [19] to afford **14b**, $[\alpha]_D^{22°} = -241°$ (*c* = 0.5, $CHCl_3$).

(6aR)-Aporphine-1,2,10,11-tetrol (**16**). A suspension of **14b** · HCl (1.6 g, 4.43 mmol) in CH_2Cl_2 (160 ml, filtered over aluminium oxide, activity grade I, basic) was stirred at RT. under argon and then treated with 2.8 ml (6.5 mmol) of a 2.3M BCl_3-solution in CH_2Cl_2. The mixture was stirred at RT. for 18 h, after which further 1.9 ml (4.4 mmol) of the same BCl_3-solution was added. The mixture was stirred at RT. for additional 48 h, carefully treated with methanol and evaporated to dryness. The residue was dissolved in methanol and this solution heated under reflux for 5 min and again evaporated to dryness. This operation was repeated twice to give crude **15** as the hydrochloride (A 100 MHz ^{1}H-NMR. spectrum taken in d-DMSO showed one methoxy group at δ 3.83 and no methylenedioxy group). A suspension of this crude hydrochloride in CH_2Cl_2 (155 ml) was stirred under argon and then treated with a solution of BBr_3 (4.2 ml, 44 mmol) in CH_2Cl_2 (11 ml). This mixture was stirred at RT. for 18 h, carefully treated with methanol as described above and then crystallized from methanol/ether to give pure **16** as the hydrobromide (1.65 g, 94%). Recrystallization from methanol/ether gave the analytical sample as beige crystals: m.p. 259–260°, $[\alpha]_D^{22°} = -178°$ (*c* = 1.0, methanol). – ^{1}H-NMR. (90 MHz, d-DMSO): 3.05 (*s*, 3 H, NCH_3); 6.72 (*s*, 1 H, H–C(3)); 6.82 (*s*, 2 H, H–C(8) and H–C(9)); 9.7 (br., 5 H, 4 OH and HBr).

$C_{17}H_{17}NO_4 \cdot HBr \cdot \frac{1}{2} CH_3OH$	Calc.	C 53.09	H 5.09	N 3.53	Br 20.16%
(396.3)	Found	„ 52.81	„ 5.19	„ 3.19	„ 20.32%

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