Probes for Narcotic Receptor Mediated Phenomena

Part 30[1])

Synthesis of *rac*-(3*R*,6a*S*,11a*R*)-1,3,4,5,6,11a-Hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol, an Epoxy Isomer of 5-Phenylmorphan

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The synthesis of a series of epoxy 5-phenylmorphans is being explored in order to determine the conformational requirements of the phenolic ring in a phenylmorphan molecule that may be needed both for binding to a specific opioid receptor and for exhibiting opioid agonist or antagonist activity. Of the twelve possible *ortho*- and *para*-bridged isomers (a–f) (*Fig. 1*), we now report the synthesis of the *para*-d isomer, *rac*-(3*R*,6a*S*,11a*R*)-2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol (**3**). Compound **3** was synthesized *via* construction of the 5-phenylazabicyclo[3.3.1]non-3-ene skeleton (*Scheme 1*) and subsequent closure of the epoxy bridge (*Scheme 2*). As determined by an X-ray diffraction study, the epoxy bridge, restricting the phenyl-ring rotation, fixed the dihedral angle between the least-squares planes through the phenyl ring and atoms N(2), C(3), C(11a), and C(6a) of the piperidine ring (*Fig. 2*) at 43.0°, and the torsion angle C(12)–C(6a)–C(6b)–C(10a) at −95.0°.

Introduction. – The initial exploration of 5-phenylmorphans as analgesics was initiated as part of the attempt at simplification of the multi-ring structure of the known opioids at that time (*e.g.*, the 4,5-epoxymorphinans) [2]. In the phenylmorphan series of compounds, the aromatic ring is constrained to the equatorial position relative to the piperidine ring, in contrast to the morphinans where the aromatic ring is in an axial conformation. It was hoped that the removal of appendages from the more-complex molecules might result in compounds with fewer side-effects than those usually attributed to the morphine-type of opioids, such as tolerance, physical dependence liability, and abuse potential, among many others.

Over the past five decades, *May* and co-workers have prepared a number of *N*-substituted phenylmorphans, and some of them have been resolved [3][4]. An interesting effect was noted with the enantiomers of 2-methyl-5-(3-hydroxyphenyl)-morphan (= 3-(2-methyl-2-azabicyclo[3.3.1]non-5-yl)phenol)) [5]. The racemic compound **1a** was a strong morphine-like agonist. The agonist effect is retained by both

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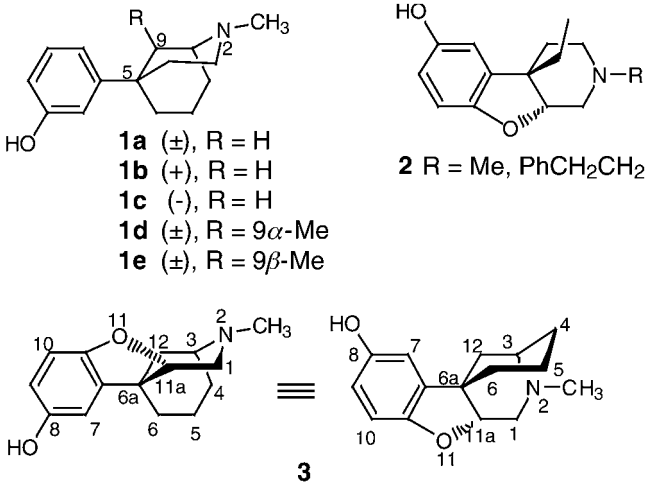
enantiomers, in contrast to the 4,5-epoxymorphinans, such as morphine, where only the natural (−)-morphine absolute configuration has opioid receptor affinity or efficacy. The (+)-phenylmorphan enantiomer **1b**, which is twice as potent as morphine in the mouse hot plate assay, completely substituted for morphine in morphine-dependent monkeys. However, its optical antipode **1c** did not substitute for morphine [6]. The (−)-phenylmorphan enantiomer, with about half of the antinociceptive potency of morphine, had modest opioid antagonist properties. The phenolic OH group *meta*-oriented to the piperidine ring was also noted to be essential for high antinociceptive activity. The 9α-methyl phenylmorphan isomer **1d** showed diminished agonist potency; it displayed a mixed agonist – antagonist profile [4]. Its antagonist activity was found to be half that of nalorphine and was shown to reside only in the (+)-enantiomer (which has the same absolute configuration (1*R*,5*S*,9*R*) as **1c**) [7].



We have, for some time [8–11], been involved in restricting the rotation of the aromatic ring in phenylmorphans by using an epoxy-bridge, in order to study the relationship between the conformation of the *m*-hydroxyphenyl ring and the pharmacological profile of the compound. In theory, our approach allows a more exact determination of the dihedral angle of the aromatic ring to the piperidine ring needed for either opioid agonist or antagonist activity than an unbridged analogue. *Fig. 1* depicts the various epoxy-bridged compounds that can possibly be synthesized, which would have a fixed, determinable angular relationship. There are twelve such

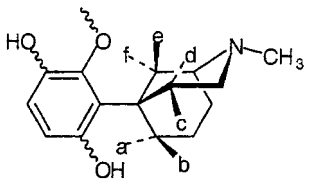


Fig. 1. *Possible epoxy-bridged 5-phenylmorphans* (*ortho* or *para* (a–f) isomers)

racemates that must be prepared, and, thus, 24 enantiomeric compounds with a phenolic OH group *meta* to the piperidine ring.

Our theoretical idea for the determination of the proper angle needed for high receptor affinity and efficacy is, then, dependent on our ability to synthesize these compounds. Further, this determination would become practicable only if we were able to obtain compounds with *in vivo* or *in vitro* opioid agonist or antagonist activity. Although there can be no *a priori* assurance that an epoxy-bridged phenylmorphan would have any opioid-like activity (lesser modifications of opioid structures with potent *in vivo* activity have been known to eliminate such activity), it was reassuring to note that *Hutchinson et al.* found that their epoxy-bridged compounds **2**, with structural similarity to our *para*-d phenylmorphan isomer **3**, were pharmacologically active [12]. Restriction of the rotation of the aromatic ring in their phenylmorphan-like structures led to compounds that were noted to have high affinity (**2**, R = $PhCH_2CH_2$) and were found to be reasonably potent antinociceptive compounds (opioid agonists) [12]. These authors stated that some of their *N*-substituted compounds might have opioid antagonist activity, but that was not examined nor were the racemic compounds resolved.

Recently, we [13] and others [14] re-examined the 5-phenylmorphan structure from a different point of view. *Thomas et al.* noted that pure opioid antagonists had not been obtained in the phenylmorphan series and decided that this was due to unrestricted rotation of the aromatic ring [15]. Restricting its rotation, with a 9β-Me substituent (*i.e.* **1e**), gave ligands that were pure, nonselective, antagonists in the GTPγS assay, especially when an *N*-phenylethyl substituent was present. This approach was based on previous studies by *Zimmerman et al.* in the 4-phenylpiperidine series of analgesics [16]. We have found that restriction of the rotation of the aromatic ring could not be the primary mechanism in determining the opioid antagonist behavior of the compound in the phenylmorphan series [13]. However, conformationally restricted phenylmorphan opioid antagonists were found to have considerably higher receptor affinity [17] than those with freely rotating phenolic rings [13].

Thus far, we have reported the synthesis of *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]azocine-8-ol (**4**) [8][9], the *ortho*-a epoxy-bridged phenylmorphan isomer, *rac*-(1*R*,4a*R*,9a*R*)-1,3,4,9a-tetrahydro-2-methyl-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol (**5**) [8][10], the *ortho*-f epoxy-bridged isomer, *rac*-(3*R*,6a*S*,11a*R*)-1,3,4,5,6,11a-hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocine-10-ol (**6**) [11], the *ortho*-d epoxy-bridged isomer, and *rac*-(4*R*,6a*R*,11b*R*)-2,3,4,5,6,6a-hexahydro-3-methyl-1*H*-4,11b-methanobenzofuro[3,2-*d*]-azocine-10-ol (**7**) [1], the *para*-a epoxy-bridged isomer (*Fig. 2*). We have also reported an improved synthesis of the *ortho*-a epoxy-bridged phenylmorphan isomer [1]. We now report the synthesis of *rac*-(3*R*,6a*S*,11a*R*)-1,3,4,5,6,11a-hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol (**3**), the *para*-d epoxy-bridged phenylmorphan isomer.

Synthesis. – The synthesis of the target compound **3** consisted of two parts: construction of the 5-phenylazabicyclo[3.3.1]nonane skeleton (*Scheme 1*) and subsequent formation of the epoxy bridge [11] (*Scheme 2*). In *Scheme 1*, treatment of alcohol **9** with acid, followed by alkylation and ring closure by the approach of *Evans et al.* [18]

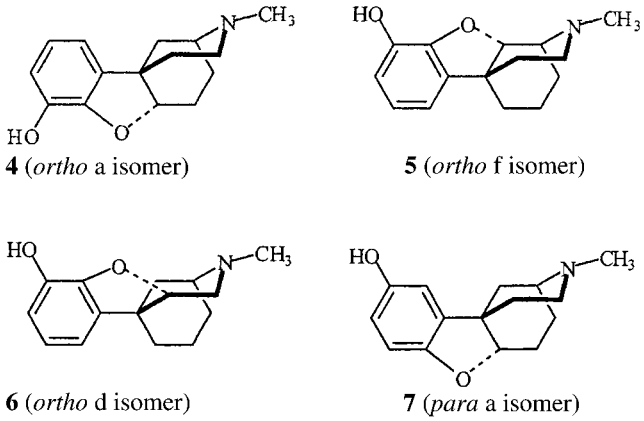
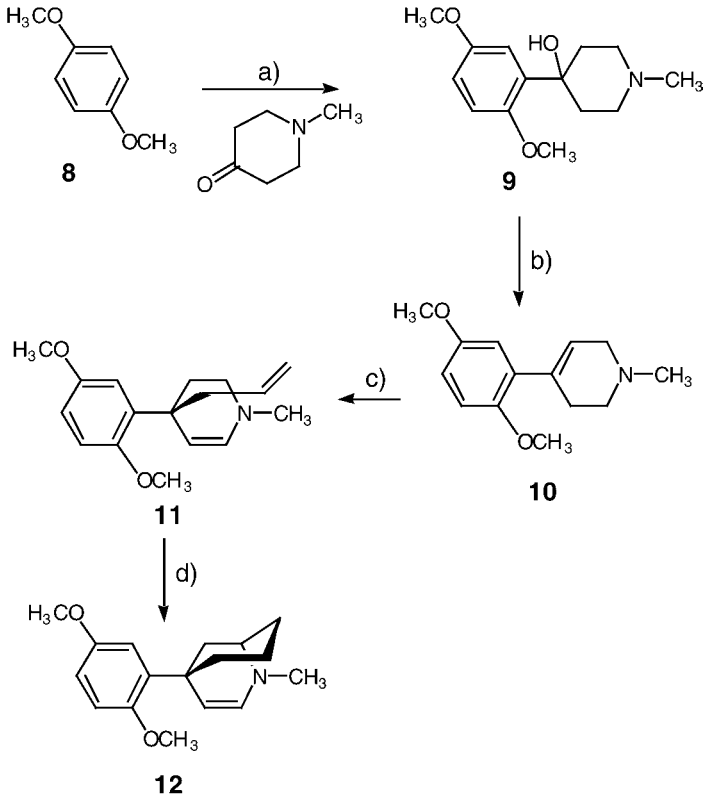


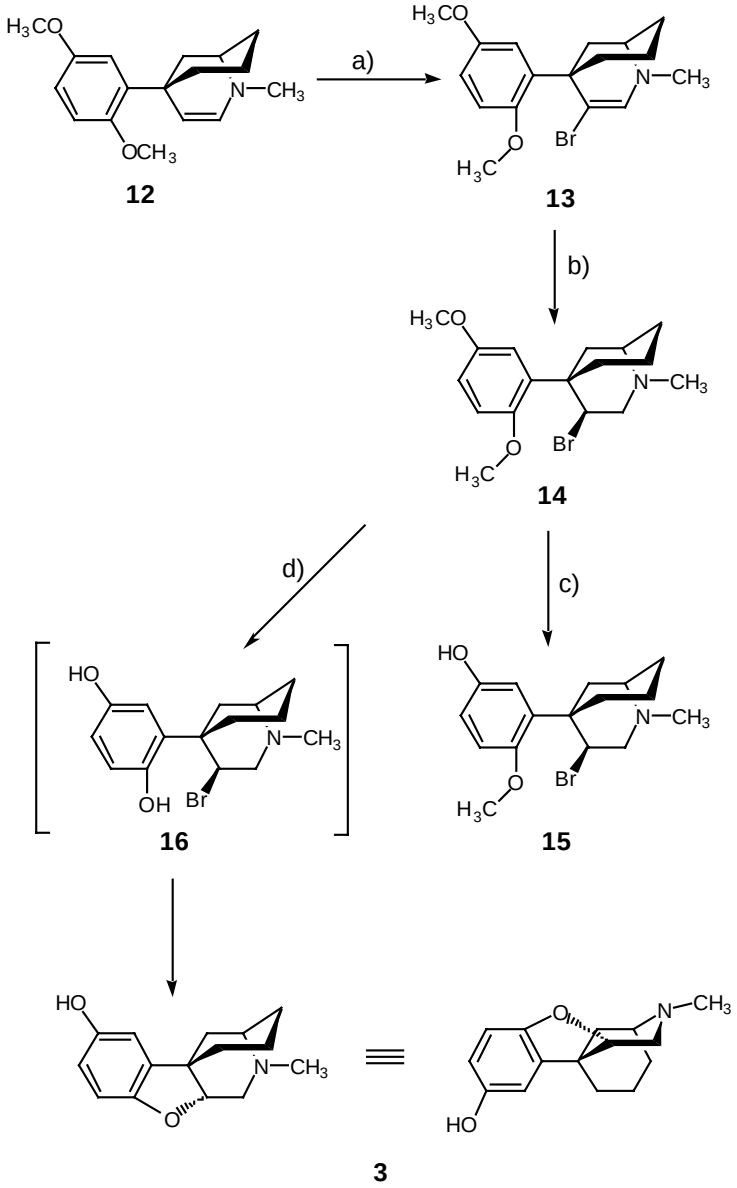
Fig. 2. *Structures of previously synthesized epoxy-bridged isomers*

Scheme 1. *Synthesis of the Key Intermediate, Enamine* **11**



a) BuLi. b) 99% H_2SO_4. c) Allyl bromide. d) *N*-Bromoacetamide.

Scheme 2. *Closure of the Epoxy Bridge*



a) *N*-Bromoacetamide. b) $NaBH_3CN$, HCl. c) Small excess BBr_3. d) 10 equiv. BBr_3, 0.5M KOH.

was envisaged to give the enamine **12**, in which the C=C bond afforded the necessary functionality for the formation of the epoxy bridge.

The synthesis of **9** was straightforward, following the route earlier used for the synthesis of the *ortho*-substituted compound [11]. Arylation of 1-methylpiperidin-4-

one with lithiated 1,4-dimethoxybenzene (**8**) gave, thus, the tertiary alcohol **9**, which afforded tetrahydropyridine **10** upon acid-catalyzed dehydration. A related tetrahydropyridine has shown severe neurotoxic effects [19]. Metallation of **10** with BuLi at $-15°$, followed by alkylation of the anion with allyl bromide at $-78°$, resulted in an 80% yield (by GC) of the terminal olefin **11**. When the crude vinylic compound **11**, without further purification, was treated with $HCOOH/H_3PO_4$ for 50 h at room temperature, **12** could be isolated in 52% yield (based on **10**) as its oxalate salt. Attempted purification of crude **11** by distillation (1–5 mm, head 210–215°, bath 235–250°) gave a complex mixture in which the desired compound **11** could not be detected. However, after subjecting the complex mixture to chromatography and crystallization, a 10% yield of **12** (isolated as the oxalate salt) was obtained, presumably formed *via* thermal rearrangement of **11** during the distillation.

With compound **12** in hand, the stage could be set for the formation of the epoxy bridge. Bromination of the enamine with *N*-bromoacetamide, followed by reduction of the C=C bond with $NaBH_3CN$ under acidic conditions afforded **14** as a single epimeric compound (*Scheme 2*). The configuration could not be determined unambiguously from the NMR spectrum, but from the result of the subsequent ring closure, it may be concluded that the Br-atom was in the β-position. Treatment of **14** with a small excess of Br_3B at room temperature [20] did not bring about the desired didemethylation. Instead, the mono-hydroxy compound **15** was obtained in good yield. From the fact that this compound did not afford a ring-closed product upon treatment with *t*-BuOK in THF [11], we concluded that the less-hindered group had been attacked. Heating a solution of **14** with 10 equiv. of Br_3B at 60° for 3 h gave rise to a more polar product, presumably diphenol **16**, which, upon workup with aqueous KOH, gave the desired epoxy compound **3**. The ^{1}H-NMR spectrum showed a double *doublet* at δ 4.62 ppm ($J = 6.5$ and 8 Hz), typical of a H-atom adjacent to an epoxy bridge. The structure of **3** was established unambiguously by single-crystal X-ray-analysis (*Fig. 3*).

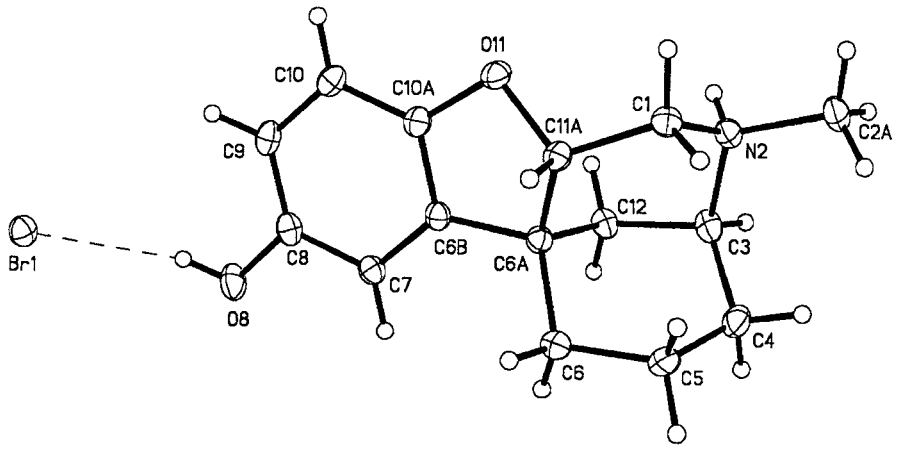


Fig. 3. *X-Ray crystal structure of* rac-*(3*R,*6a*S,*11a*R*)-1,3,4,5,6,11a-hexahydro-2-methyl-2*H*-3,6a-methanobenzo furo[2,3-*c*]azocin-8-ol* (**3**) (drawn from the experimentally determined coordinates with displacement ellipsoids at the 20% probability level)

Results and Discussion. – The *para*-d isomer, *rac*-(3*R*,6a*S*,11a*R*)-1,3,4,5,6,11a-hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol (**3**) was successfully synthesized. As determined by an X-ray crystallographic study, the epoxy bridge, restricting the phenyl-ring rotation, fixes the dihedral angle between the least-squares planes through the phenyl ring and atoms N(2), C(3), C(11a), and C(6a) of the piperidine ring (*Fig. 3*) at 43.0(1)°, and the torsion angle C(12)–C(6a)–C(6b)–C(10a) at –95.0(2)°. A comparison of structural parameters to those in the *ortho*-d isomer [11], which differs by the location of the OH substituent at C(10) *vs.* C(8), shows that only a few of the many shared bond distances and angles differ by as much as three standard deviations, and the comparable dihedral angle between the phenyl and piperidine rings is 49° in the *ortho*-d isomer [11]. The relationship of the dihedral angle noted above and the opioid receptor affinity and pharmacological properties of the epoxy-bridged phenylmorphans will be reported in due course.

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Experimental Part

General. M.p.: *Thomas-Hoover* melting-point apparatus; uncorrected. TLC: 250-μ *Analtech GHLF* silica gel plates with $CHCl_3$/MeOH/conc. NH_4OH 85 : 15 : 0.5 as the solvent system. Column chromatography (CC): 230–400 mesh silica gel *60* (*Fluka 60738*). GC: *Hewlett-Packard 5890* instrument with a flame-ionization detector. IR Spectra: *Beckman 4230 IR* spectrophotometer. ^{1}H-NMR Spectra: *Varian XL-300* instrument, with $CDCl_3$ (TMS as internal standard). Chemical-ionization mass spectra (CIMS) were obtained using a *Finnigan 1015* mass spectrometer. Electron-ionization mass spectra (EI-MS): *VG-Micro Mass 7070F* mass spectrometer. Elemental analyses: *Atlantic Microlabs, Inc.*, Norcross, GA; within ± 0.4% of the theoretical values.

4-(2,5-Dimethoxyphenyl)-1-methylpiperidin-4-ol (**9**). A soln. of *1,4-dimethoxybenzene* (**8**, 207.0 g, 1.50 mol) in 1300 ml of dry Et_2O was cooled in an ice bath and stirred under Ar while a 1.6M soln. of BuLi (775 ml, 1.24 mol) was added over a period of 20 min. The ice bath was removed, and the soln. was stirred for 24 h. The resulting white suspension was cooled to 0°, and a soln. of 1-methylpiperidin-4-one (140.1 g, 1.24 mol) in 150 ml of dry Et_2O was slowly added (20 min). The light yellow, clear soln. was stirred for 45 min. To the mixture was added 400 ml of sat. aq. $NaHCO_3$, the mixture was stirred for 20 min and filtered. The layers were separated, and the org. phase was washed with aq. $NaHCO_3$ (2 × 200 ml) and H_2O (2 × 100 ml). The org. phase was partly evaporated, and crystalline **9** (109.0 g, 0.43 mol, 38% yield based on amine) was obtained. The mother liquor was extracted with 450 ml of 4N HCl. The aq. layer was separated, basified with 28% NH_4OH, and extracted with Et_2O (3 × 100 ml). The combined org. phase was washed with H_2O (50 ml), dried (Na_2SO_4), and evaporated until 50 ml of Et_2O was left. A second crop of **9** (30.0 g, 0.12 mol, total yield 44%) was collected. M.p. 103–104°. ^{1}H-NMR ($CDCl_3$): 2.35 (*s*, MeN); 3.77 (*s*, MeO); 3.87 (*s*, MeO); 6.74–6.91 (*m*, 3 arom. H). CI-MS (NH_3): 252 ($[M+H]^+$), 234 ($[M+H-H_2O]^+$). Anal. calc. for $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.57; found: C 66.69, H 8.44, N 5.53.

4-(2,5-Dimethoxyphenyl)-1,2,3,6-tetrahydro-1-methylpyridine (**10**). Alcohol **9** (109.0 g, 0.43 mol) was suspended in 125 ml of H_2O, and conc. H_2SO_4 (60 ml) was cautiously added while stirring. The mixture was heated to boiling and refluxed for 1 h, at which time complete conversion was observed on TLC. The soln. was cooled to r.t., made alkaline (pH 10) with 40% NaOH, and extracted with Et_2O (2 × 100 ml). The combined org. phase was washed with 0.5M KOH (50 ml) and H_2O (50 ml), dried (Na_2SO_4), and evaporated to give 100.5 g (0.4 mol, 100%) of **10** (***CAUTION***[3]) as a light-yellow oil, pure enough for further use. For analysis, a sample was converted to the HCl salt with ethanolic HCl and recrystallized from EtOH. M.p. 236–237° (dec.) ^{1}H-NMR ($CDCl_3$, free base): 2.38 (*s*, MeN); 3.07 (*m*, 2 H); 2.55 (*m*, 2 H); 2.62 (*m*, 2 H); 3.75 (*s*, MeO–C(2′),

[3]) Studies have indicated that similar 1,2,3,6-tetrahydro-4-phenylpyridines are extremely potent neurotoxins. Care should be taken in handling this material [19].

MeO–C(5′)); 5.77 (*s*, H–C(5)); 6.70–6.82 (*m*, 3 arom. H). CI-MS (NH_3): 234 ($[M+H]^+$). Anal. calc. for $C_{14}H_{19}NO_2 \cdot HCl$: C 62.33, H 7.47, N 5.19; found: C 62.32, H 7.64, N 5.21.

4-(2,5-Dimethoxyphenyl)-1,2,3,4-tetrahydro-1-methyl-4-(prop-2-enyl)pyridine (**11**). Compound **10** (20.3 g, 87 mmol) was dissolved in 150 ml of dry THF and cooled to $-15°$ (ice-salt bath) under Ar. BuLi (80 ml of a 1.6M soln. in hexane) was introduced by syringe, producing a dark-red soln. This was stirred for 20 min, cooled to $-78°$, and allyl bromide (15.5 g, 0.128 mol) in 20 ml of dry THF was added. After the addition, the yellow soln. was warmed to r.t. H_2O (50 ml) was slowly added, and the layers were separated. The aq. soln. was extracted with Et_2O (2 × 100 ml), and the combined org. phase was washed with H_2O (2 × 100 ml). Drying (Na_2SO_4) and evaporation gave 22.1 g of an orange oil, containing 80% of **11** according to GC. This material was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$, free base): 2.56 (*s*, MeN); 3.77 (*s*, MeO); 3.80 (*s*, MeO); 4.61 (*dd*, *J* = 2, 8, H–C(3)); 4.86–4.98 (*m*, CH=C*H*$_2$); 5.46–5.52 (*m*, C*H*=CH$_2$); 5.95 (*d*, *J* = 8, H–C(2)); 6.67–7.00 (*m*, 3 arom. H). CI-MS (NH_3): 274 ($[M+H]^+$).

rac-*5-(2,5-Dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-3-ene Oxalate* (**12** · Oxalate). Crude **11** (20.2 g) was dissolved in a mixture of 20 ml of anh. HCOOH and 20 ml of 85% H_3PO_4 at 0°. The mixture was stirred for 50 h at r.t. The mixture was diluted with 300 ml of H_2O, cooled in ice, and made alkaline with 30% KOH. Extraction with Et_2O (3 × 50 ml), washing with H_2O (50 ml), drying (Na_2SO_4), and evaporation of the solvent gave 18.1 g of a dark-brown oil. To a soln. of this oil in 75 ml of boiling i-PrOH, oxalic acid (6.6 g, 73 mmol) in 150 ml of hot i-PrOH was added. Crystallization began immediately, yielding 14.90 g (41.0 mmol, 52% based on **10**) of **12** · oxalate. An anal. sample was recrystallized from MeOH/acetone, M.p. 193–196° (dec., ending in red melt at 208–210°); ^{1}H-NMR ($CDCl_3$, free base): 2.74 (*s*, MeN); 3.77 (*s*, MeO); 3.80 (*s*, MeO); 4.62 (*dd*, *J* = 7.8, 2, H–C(4)); 6.05 (*d*, *J* = 7.8, H–C(3)), 6.66–6.92 (*m*, 3 arom. H). CI-MS (NH_3): 273 (M^+), 230. Anal. calc. for $C_{17}H_{23}NO_2 \cdot C_2H_2O_4$: C 62.80, H 6.93, N 3.85; found: C 62.54, H 6.85, N 3.80.

rac-*4-Bromo-5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]non-3-ene* (**13**). The oxalate of **12** (6.30 g, 17 mmol) was converted to the free base by partitioning between $CHCl_3$ and 1M KOH to give 4.86 g (17 mmol) of **12**. This material was dissolved in 40 ml of dry THF, cooled to $-78°$, and a soln. of *N*-bromoacetamide (2.76 g, 20 mmol) in 20 ml of dry THF was added. After stirring for 20 min at $-78°$, the mixture was allowed to warm to r.t. The solvents were evaporated, and the oily residue was dissolved in 50 ml of $CHCl_3$ and washed with sat. $NaHCO_3$ (2 × 20 ml) and H_2O (10 ml). The org. fraction was dried (Na_2SO_4) and evaporated. Chromatography of the resulting oil over silica gel (1% MeOH in $CHCl_3$) gave 2.83 g (8.0 mmol, 47%) of **13** as an orange oil, homogeneous in TLC. This material was used directly in the next step. ^{1}H-NMR ($CDCl_3$): 2.75 (*s*, MeN); 3.77 (*s*, MeO); 3.80 (*s*, MeO); 6.38 (*s*, H–C(3)); 6.73–6.87 (*m*, 3 arom. H).

rac-*4-Bromo-5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane Oxalate* (**14** · Oxalate). Compound **13** (2.80 g, 8.0 mmol) was dissolved in 125 ml of MeOH, 3 ml of conc. HCl was added, followed by 0.61 g (9.6 mmol) of $NaBH_3CN$. The soln. was stirred for 20 min at r.t. Sat. $NaHCO_3$ soln. (100 ml) and H_2O (20 ml) were added, and the mixture was extracted with 3 × 50 ml of CH_2Cl_2. The combined org. phase was evaporated to give 2.67 g of a red oily foam. This material was dissolved in 20 ml of MeCN and treated with a soln. of 0.75 g (8.3 mmol) oxalic acid in 5 ml of MeCN. The mixture was heated to boiling and set aside. Crystallization started immediately, giving 1.97 g (4.4 mol, 55%) of **14** · oxalate, M.p. 178–179° (with foaming). ^{1}H-NMR ($CDCl_3$, free base): 2.47 (*s*, MeN); 3.21 (*dd*, *J* = 7.2, 12, H–C(3)); 3.43 (*m*, 2 H); 3.77 (*s*, MeO); 3.83 (*s*, MeO); 5.57 (*dd*, *J* = 7.2, 11.2, H–C(4)); 6.72–6.93 (*m*, 3 arom. H). CI-MS (NH_3): 354, 356 ($[M+H]^+$), 274 ($[M+1-HBr]^+$). Anal. calc. for $C_{17}H_{24}BrNO_2 \cdot C_2H_2O_4$: C 51.36, H 5.90, N 3.15; found: C 51.26, H 5.87, N 3.21.

rac-*3-(4-Bromo-2-methyl-2-azabicyclo[3.3.1]non-5-yl)-4-methoxyphenol* (**15**). Compound **14** (100 mg, 0.28 mmol) was dissolved in 3 ml of pentene-stabilized $CHCl_3$, and 1.6 ml of a 1M soln. of Br_3B in CH_2Cl_2 (1.6 mmol) was added by syringe. After stirring for 20 min at r.t., the mixture was poured into a mixture of ice (10 g) and 3 ml of conc. NH_4OH. The layers were separated, and the aq. layer was extracted with $CHCl_3$ (2 × 10 ml). The combined org. phase was washed with H_2O (10 ml), dried (Na_2SO_4), and evaporated to give 60 mg (0.22 mmol, 77%) of pure **15**. Crystals from EtOH. M.p. 158–159°. ^{1}H-NMR ($CDCl_3$): 2.48 (*s*, MeN); 3.82 (*s*, MeO); 5.55 (*m*, H–C(4)); 6.67–6.85 (*m*, 3 arom. H). CI-MS (NH_3): 340, 342 ($[M+H]^+$), 260 ($[M+H-HBr]^+$). Anal. calc. for $C_{16}H_{22}BrNO_2 \cdot 0.75\ H_2O$: C 54.32, H 6.70, N 3.96; found: C 54.44, H 6.40, N 3.95.

rac-*(3*R*,6a*S*,11a*R*)-1,3,4,5,6,11a-Hexahydro-2-methyl-2*H*-3,6a-methanobenzofuro[2,3-*c*]azocin-8-ol Hydrochloride* (**3** · HCl) *and Hydrobromide* (**3** · HBr). The oxalate salt of compound **14** (1.30 g, 2.97 mmol) was converted to the free base (1M KOH, $CHCl_3$) to give 1.05 g (2.97 mmol, 100%) of an oil. The oil was dissolved in 15 ml of pentene-stabilized $CHCl_3$, and, under N_2, Br_3B (2.8 ml, 30 mmol) was added by syringe over a period of 5 min. The mixture was stirred at r.t. for 30 min, after which TLC showed complete conversion of the starting material (R_f 0.90) to the phenol **15** (R_f 0.62). The soln. was heated to reflux (oil-bath temp. 70°) for 3 h, after which time TLC showed the complete conversion of **15** into a more polar compound (presumably **16**, R_f 0.38).

After cooling to r.t., the mixture was slowly added to a vigorously stirred soln. of KOH (8.0 g, 142 mmol) in a 1:1 mixture of H_2O and MeOH (250 ml), held at 0° under N_2. The mixture was stirred for 20 min, after which TLC showed clean conversion to a less polar material (R_f 0.55). NH_4Cl (5 g) was added, and the layers were separated. The aq. phase was extracted with $CHCl_3$/EtOH 4:1 (2 × 25 ml). The combined org. phase was dried (Na_2SO_4) and evaporated to give 0.6 g of **3** as a light-brown foam. Crude **3** was dissolved in 15 ml of AcOEt, and 5 ml of ethanolic HCl was added. More EtOH (5 ml) was added, and the precipitate was dissolved by heating. Upon cooling to r.t. and scratching, **3**·HCl crystallized (0.50 g, 60%). Recrystallization from EtOH gave irregular hygroscopic crystals. M.p. 234–235°. The HBr salt of **3** was crystallized from MeOH. M.p. 248–250°. ^{1}H-NMR ($CDCl_3$, free base): 1.18–1.36 (*m*, 2 H); 1.42 (*dd*, *J* = 13, 1.9, 1 H); 1.58–2.00 (*m*, 6 H); 2.04 (*d*, *J* = 13, 1 H); 2.2 (br. *s*, OH); 2.43 (*s*, MeN); 2.74 (br. *s*, 1 H); 2.80 (*dd*, *J* = 4.5, 8, H–C(1)); 3.06 (*dd*, *J* = 6.5, 11.3, H–C(1′)); 4.62 (*dd*, *J* = 8, 6.5, 1 H); 6.55 (*dd*, *J* = 6.2, 2.6, 1 H); 6.58 (*m*, 2 H). CI-MS (NH_3): 246 ([*M* + H]$^+$). Anal. calc. for $C_{15}H_{19}NO_2 \cdot HCl \cdot 2\ H_2O$:C 56.69, H 7.61, N 4.41; found: C 56.25, H 7.64, N 4.40. Anal. calc. for $C_{15}H_{19}NO_2 \cdot HBr$: C 55.23, H 6.18, N 4.29; found: C 55.00, H 6.26, N 4.29.

X-Ray Analysis[4]) *of* **3**. For X-ray data, see the *Table*. Data were collected at r.t. with CuK_α radiation on an automated *Bruker P4* diffractometer equipped with a monochromator in the incident beam. The crystal remained stable during data collection. Face-indexed numerical absorption (minimum and maximum transmission 0.040 and 0.56). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 values using the SHELXTL*plus* system of programs [21]. Parameters (179) refined included atomic coordinates and displacement ellipsoids for all non-H atoms. The H atoms on C-atoms were included

Table. *Crystal Data and Strucutre Refinement of* **3**.

Empirical formula	$C_{15}H_{20}NO_2^+ \cdot Br^-$	
Formula weight	326.23	
Temp. [K]	293(2)	
Wavelength	1.54178	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 10.457(2)$ Å	$\alpha = 90°$.
	$b = 10.541(3)$ Å	$\beta = 98.55(2)°$.
	$c = 13.128(2)$ Å	$\gamma = 90°$.
Volume	1431.0(5) Å^3	
Z	4	
Density (calc.)	1.514 Mg/m^3	
Absorption coefficient	3.897 mm^{-1}	
$F(000)$	672	
Crystal size	0.18 × 0.18 × 0.44 mm	
θ Range for data collection	4.28 to 57.34°.	
Index ranges	$-11 \le h \le 11$, $0 \le k \le 11$, $0 \le l \le 14$	
Reflections collected	2131	
Independent reflections	1956 ($R_{int} = 0.0145$)	
Observed reflections ($I > 2\sigma(I)$)	1901	
Completeness to $\theta = 57.34°$	99.9%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1956 / 0 / 179	
Goodness-of-fit on F^2	0.961	
Final *R* indices ($I > 2\sigma(I)$)	$R_1 = 0.0265$, $wR_2 = 0.0781$	
R indices (all data)	$R_1 = 0.0272$, $wR_2 = 0.0788$	
Extinction coefficient	0.0023(2)	
Largest diff. peak and hole	0.251 and −0.395 e.Å^{-3}	

[4]) Coordinates have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC 189625. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (deposit@CCDC.cam.ac.uk).

with a riding model (coordinate shifts of C applied to H-atoms with C–H distance set at 0.96 Å). Coordinates only were refined for OH H-atoms and H-atoms on *N*-atoms.

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