

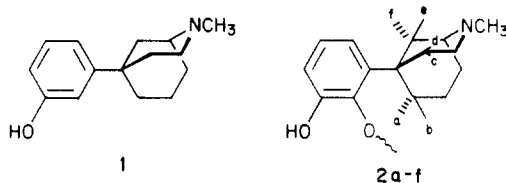
Probes for Narcotic Receptor Mediated Phenomena. 9.¹ Synthesis of (±)-(3 α ,6 α ,11 α)-1,3,4,5,6,11a-Hexahydro-2-methyl-2H-3,6a-methanobenzofuro[2,3-c]azocin-10-ol, an Oxide-Bridged 5-(*m*-Hydroxyphenyl)morphan[†]

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The synthesis of racemic (3 α ,6 α ,11 α)-1,3,4,5,6,11a-hexahydro-2-methyl-2H-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (**2d**) is described. The route used acid-catalyzed ring closure of enamine **5** to yield the unsaturated phenylmorphan **6**. Conversion of **6** to oxide-bridged **2d** was accomplished in a multistep fashion that utilized the introduction of a bromine atom, followed by O-demethylation of the phenolic methyl ethers and base-catalyzed intramolecular phenoxide displacement of the bromine. Compound (±)-**2d** represents an oxide-bridged derivative of the potent 5-(*m*-hydroxyphenyl)morphan class of opioid analgesics **1**. Unlike the 5-(*m*-hydroxyphenyl)morphans that have a freely rotating phenyl group, **2d** has the phenyl ring conformationally restricted at an angle of 49° relative to atoms 1, 3, 11a, and 12 of **2d**. The low binding of (±)-**2d** to rat brain homogenate receptor preparations [IC₅₀ = 1000 nM] may indicate that the phenyl angle of 49° is not suitable for binding to opioid receptors.

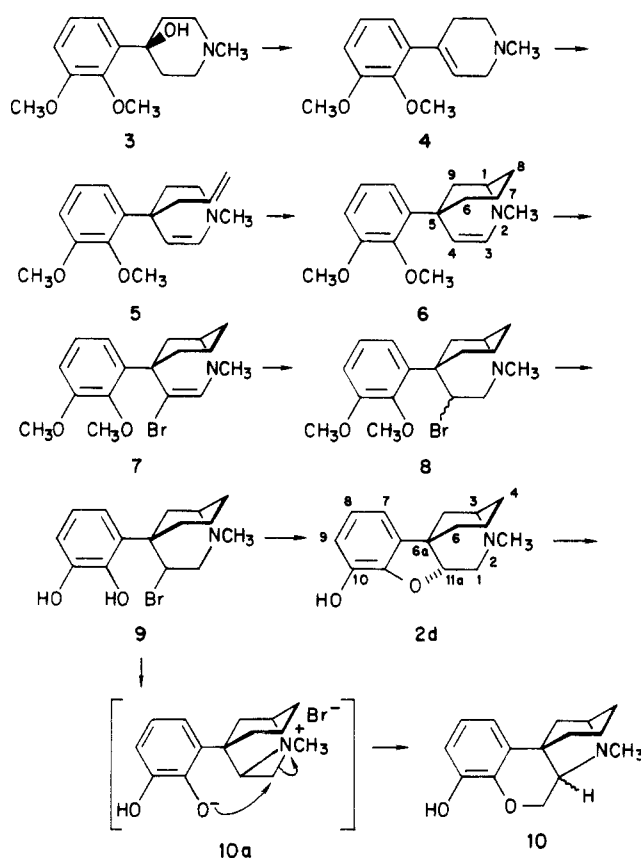
As one aspect of our program to study the structure and function of the opioid receptor system,¹ we are pursuing a synthetic study of the 2-methyl-5-(*m*-hydroxyphenyl)morphan nucleus (**1**) to define the conformational requirements for optimum binding of this class of compounds to opioid receptors. Since the phenylmorphan skeleton is rigid, conformational flexibility resides predominantly in the rotation of the phenyl ring about a single bond. As such, an initial goal of this study is to determine the phenyl ring torsion orientation that results in greatest receptor affinity. As outlined more fully in two previous reports on this work,^{2,3} our approach has been to freeze the conformation of the phenyl ring by means of an oxide bridge. Six unique isomeric oxide-bridged phenylmorphan-like compounds are possible with the phenyl ring held close to a 60° angle relative to the previous isomer in the series (**2a-f**).



The first isomer synthesized,² **2a**, had essentially no opioid receptor affinity⁴ (IC₅₀ = 1766 nM), while the second isomer³ **2f** had an 18-fold greater binding affinity⁴ (IC₅₀ = 96 nM). Encouraged by the latter result, we set out to prepare further members of the series **2a-f**. In this paper, we report the synthesis and X-ray structure determination of **2d**. This synthesis represents a new entry into the hexahydro-2H-3,6a-methanobenzofuro[2,3-c]azocine ring system.

Synthesis. The synthetic approach to **2d**, shown in Scheme I, contains two crucial features: the synthesis of the phenylmorphan skeleton **6** and subsequent closure of the oxide bridge to form the desired 3,6a-methanobenzofuro[2,3-c]azocine structure (**6** → **2d**). The acid-catalyzed

Scheme I



ring closure of **5** to form **6** was anticipated on the basis of the work of Evans in a similar system.⁵ A valuable feature of this procedure is the accompanying introduction of a

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Services and Instrumentation, NIADDK.

1-Methyl-4-hydroxy-4-(2,3-dimethoxyphenyl)piperidine (3). A solution of veratrole (69.0 g, 0.5 mol) in anhydrous ether (450 mL) was cooled in an ice bath and stirred under argon while 1.6 M *n*-butyllithium (250 mL, 0.4 mol) was added. The reaction mixture was then stirred under argon at 20 °C for 18 h. The resulting white suspension was cooled on ice water while a solution of 1-methyl-4-piperidone (45.2 g, 0.4 mol) in ether (75 mL) was slowly added over 5 min. The solid dissolved, giving a cloudy yellow solution which was washed with aqueous NaHCO₃ (3 × 100 mL), filtered to remove some white crystalline solid, and evaporated, yielding a yellow oil (99.0 g). The oil was distilled (110 °C bath, 56 °C head, 0.2 mm) to remove unreacted amine along with a volatile side product (34.0 g). The reddish undistilled oil (58.0 g, 58%) remaining was product 3, sufficiently pure for further work.

A sample was crystallized from acetone as the oxalate salt and recrystallized from MeOH-acetone for analysis: mp 196–198 °C (loss of solvent above 180 °C); CIMS (NH₃), *m/e* 252 (M⁺H). Anal. (C₁₄H₂₁NO₃·C₂H₂O₄·1/2 C₃H₆O·1/2 H₂O) C, H, N.

1-Methyl-4-(2,3-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine (4). Addition of 3 (105.0 g, 0.42 mol) and H₂SO₄ (60 mL) to H₂O (100 mL) gave a red solution, which was stirred at 115 °C. After 1 h the mixture was cooled on ice water and made alkaline (pH 10) by addition of concentrated aqueous NaOH. Extraction with CHCl₃ (2 × 200 mL), washing with H₂O (2 × 300 mL), and evaporation gave a clear brown oil (93.0 g). Flash chromatography (500 g of silica gel, CH₂Cl₂-MeOH-NH₄OH, 9:1.5:0.1) gave product 4 as a brown oil (73.0 g). The brown color was removed by distillation (111 °C head, 165 °C bath, 3 mm), giving pure 4 [CAUTION]⁸ as a viscous yellow oil (46.0 g, 47%). A sample of 4·HCl was prepared by treatment of a methanolic solution of 4 with 37% HCl followed by evaporation to dryness and crystallization from MeOH: mp 235–236 °C; CIMS (NH₃), *m/e* 234 (M⁺H). Anal. (C₁₄H₁₉NO₂·HCl) C, H, N.

(±)-1-Methyl-4-(2,3-dimethoxyphenyl)-4-(3-propenyl)-1,4,5,6-tetrahydropyridine (5). A solution of 4 (46.0 g, 197 mmol) in dry THF (30 mL) was stirred under argon at –78 °C. A solution of *n*-butyllithium, 1.6 M in hexane (210 mL, 336 mmol), was added to the reaction, producing a deep red color. The mixture was stirred at –15 °C for 75 min and then cooled to –78 °C. Allyl bromide (41.0 g, 336 mmol) was added, producing a yellow solution, which was then brought to 20 °C and mixed with H₂O (20 mL). The reaction mixture was evaporated, and the residue was partitioned between CHCl₃ (2 × 200 mL) and H₂O (200 mL), evaporated to an oil, and distilled (172 °C head, 235 °C bath, 5 mm), giving the desired product 5 as a light yellow oil (41.0 g, 76%): CIMS (NH₃), *m/e* 290 (M⁺ + NH₄).

(±)-2-Methyl-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]non-3-ene Oxalate (6-oxalate). A solution of 5 (41.0 g, 0.15 mol) in 85% H₃PO₄ (40 mL) and 88% formic acid (40 mL) was left at 20 °C for 4 days. The resulting dark brown mixture was diluted with H₂O (100 mL) and cooled in ice while aqueous NaOH (100 g in 300 mL H₂O) was added. Extraction with CHCl₃ (2 × 250 mL), washing the CHCl₃ extract with aqueous NaHCO₃ (300 mL), and evaporation gave an oil (46.0 g). A solution of this oil in acetone (200 mL) was treated with oxalic acid (15.3 g) in acetone (100 mL) to yield 6 as a white oxalate salt (12.6 g, 23%): mp 148–151 °C; CIMS (CH₄), *m/e* 274 (M⁺H). Anal. (C₁₇H₂₃NO₂·C₂H₂O₄) C, H, N.

(±)-2-Methyl-4-bromo-5-(2,5-dimethoxyphenyl)-2-azabicyclo[3.3.1]non-3-ene (7). Neutralization of the oxalate salt of 6 (2.54 g, 7.0 mmol) (partitioned between saturated aqueous NaHCO₃ and CHCl₃) gave the free base as a light orange oil (1.82 g, 6.67 mmol). To a solution of the free base in dry THF (20 mL) at –78 °C was added *N*-bromoacetamide (1.01 g, 7.3 mmol) in dry THF (4 mL). The mixture was stirred at 20 °C for 20 min and then evaporated to an orange, crystalline solid. Partitioning between aqueous saturated NaHCO₃ (10 mL) and CHCl₃ (2 × 20 mL) and evaporation of solvent gave a crystalline orange solid (3.51 g), which was purified by flash chromatography (CH₂Cl₂-MeOH, 99:1) to yield 7 as a white crystalline solid (1.45 g, 62%): mp 152–155 °C; CIMS (CH₄), *m/e* 352, 354 (M⁺H). Anal. (C₁₇H₂₂BrNO₂) C, H, N.

(±)-2-Methyl-4-bromo-5-(2,3-dimethoxyphenyl)-2-azabicyclo[3.3.1]nonane Hydrobromide (8-HBr). Addition of 37%

HCl (1.0 mL) to a suspension of 7 (1.00 g, 2.8 mmol) in MeOH (20 mL) gave a light brown solution to which was added NaCN-BH₃ (215 mg, 3.4 mmol). The resulting milky mixture was stirred 20 min at 20 °C and then diluted with saturated aqueous NaHCO₃ (30 mL), extracted (3 × 60 mL CHCl₃), and evaporated to a light brown oil. The oil was dissolved in MeOH, acidified with 37% HBr, evaporated to a foam, and triturated with 2-propanol to yield 8-HBr as white crystals (870 mg, 72%): mp 190–192 °C; CIMS (CH₄), *m/e* 354, 356 (M⁺H); NMR (CDCl₃, free base) δ 3.17 (dd, 1 H, C(3)-H, *J* = 7, 13 Hz), 3.38 (t, 1 H, C(3)-H, *J* = 13 Hz), 5.31 (dd, 1 H, C(4)-H, *J* = 7, 13 Hz). Anal. (C₁₇H₂₄BrNO₂·HBr) C, H, N.

(±)-2-Methyl-4-bromo-5-(2,3-dihydroxyphenyl)-2-azabicyclo[3.3.1]nonane Hydrobromide (9-HBr). A solution of crude 8-HBr (1.64 g, 4.6 mmol) in CHCl₃ (50 mL) was stirred at 20 °C while BBr₃ (10 mL, 15.1 mmol) was added, giving an emulsion. After 45 min the reaction was terminated by cautious addition of MeOH (20 mL). Solvent was evaporated, leaving a foam, which was redissolved in MeOH (20 mL) and reevaporated to yield 9-HBr as a foam (1.87 g, 100%). Treatment with 2-propanol gave crystalline 9-HBr: mp 219–223 °C; CIMS (NH₃), *m/e* 326, 328 (M⁺H). Anal. (C₁₅H₂₀BrNO₂·HBr) C, H, N.

Reaction of 9-HBr in Hot Pyridine. A solution of 9-HBr (1.87 g, 5.7 mmol) in pyridine (25 mL) was heated at 90 °C under argon for 5 1/2 h. At the end of this time TLC (CHCl₃-MeOH-NH₄OH, 90:10:1) showed 10 as the major spot, *R*_f = 0.54 with a secondary spot at *R*_f 0.43, and a slower spot, *R*_f 0.07. Pyridine was evaporated and the residue partitioned between aqueous Na₂CO₃ and CHCl₃. Evaporation of solvent gave a brown oil, which was purified by silica gel flash chromatography (CHCl₃-MeOH, 9:1) to yield pure 10, which was crystallized from MeOH as the hydrochloride salt, 10·HCl:¹⁰ mp 268–273 °C; CIMS (CH₄), *m/e* 246 (M⁺H); NMR (10 base, CDCl₃) δ 1.18–2.07 (m, 8 H), 2.45 (s, 3 H), 2.48 (dd, 1 H, *J* = 6, 11 Hz), 3.18 (t, 1 H, *J* = 6 Hz), 4.32–4.45 (m, 2 H), 6.50 (dd, 1 H, *J* = 3, 7 Hz), 6.66–6.77 (m, 2 H); high-resolution MS (C₁₅H₁₉NO₂) calcd 245.1416, found 245.1410.

(±)-(3α,6α,11α)-1,3,4,5,6,11a-Hexahydro-2-methyl-2H-3,6a-methanobenzo[2,3-*c*]azocin-10-ol Hydrochloride (2d·HCl). To a suspension of 9-HBr (600 mg, 1.47 mmol) in dry THF (50 mL) was added potassium *tert*-butoxide (495 mg, 4.42 mmol). The resulting grey suspension was stirred at 20 °C under argon for 30 min and then acidified with 37% HCl (500 μL), evaporated to an off-white solid, and partitioned between dilute aqueous NH₄OH (10 mL) and CHCl₃ (2 × 30 mL). Evaporation of solvent gave a syrup, which was acidified with methanolic HCl and crystallized from MeOH to afford 2d·HCl as a white salt (350 mg, 85%): mp 299–300 °C (dec); CIMS (NH₃), *m/e* 246 (M⁺H); NMR (2d base, CDCl₃) δ 1.20–1.39 (m, 1 H), 1.48 (d, 1 H, *J* = 14 Hz), 1.59–1.93 (m, 6 H), 2.00–2.16 (m, 1 H), 2.45 (s, 3 H), 2.80 (br s, 1 H), 2.92 (dd, 1 H, *J* = 7, 11 Hz), 3.11 (dd, 1 H, *J* = 6, 12 Hz), 4.66 (t, 1 H, *J* = 7 Hz), 6.59 (dd, 1 H, *J* = 2, 6 Hz), 6.70–6.75 (m, 2 H). Anal. (C₁₅H₁₉NO₂·HCl·1/2 CH₃OH) C, H, N.

X-ray. Recrystallization from methanol afforded prismatic crystals, space group *P*2₁/*c*, dimensions *a* = 7.130 (1) Å, *b* = 15.786 (1) Å, *c* = 12.818 (1) Å, β = 103.58°, *Z* = 4, *V* = 1402.4 Å³, *D*_x = 1.334 g cm^{–3}, formula C₁₅H₂₀NO₂Cl, *M* = 281.77. The X-ray intensity data were collected by standard methods by using an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å; max (sin θ)/λ = 0.6228 Å^{–1}). There were 2841 independent reflections (1110 with *I* < σ(*I*)). The phase problem was solved with programs of MULTAN 78,¹³ and all heavier atoms were found in an *E* map. Standard refinement techniques allowed the detection of all H atoms and the structure was refined, with the programs of XRAY72¹⁴ to an *R* factor of 0.054 (*R*_w = 0.052). The function minimized in the refinement was ΣωΔ² with weights as in Peterson and Levy.¹⁵ A table of the heavier atom parameters and full refinement parameters are deposited as supplemental

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material. A table of observed and calculated structure factors was submitted to the referees and may be obtained from J.V.S.

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Registry No. (\pm)-**2d**, 100448-10-0; **3**, 82359-62-4; **3-oxalate**, 100430-71-5; **4**, 82359-63-5; **4-HCl**, 100430-72-6; (\pm)-**5**, 100430-70-4; (\pm)-**6**, 100448-03-1; (\pm)-**6-oxalate**, 100448-11-1; (\pm)-**7**, 100448-04-2; (\pm)-**7-HCl**, 100448-05-3; **8**, 100448-06-4; **8-HBr**, 100448-07-5; **9-HBr**, 100448-08-6; **10**, 100448-09-7; **10-HCl**, 100448-12-2; veratrole, 91-16-7; 1-methyl-4-piperidone, 1445-73-4; allyl bromide, 106-95-6.

Supplementary Material Available: Tables of atomic parameters for all atoms, bond angles, and torsion angles (4 pages). Ordering information is given on any current masthead page.

¹H NMR Configurational Correlation for Retro-Inverso Dipeptides: Application to the Determination of the Absolute Configuration of "Enkephalinase" Inhibitors. Relationships between Stereochemistry and Enzyme Recognition

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A stereospecific synthesis of thiorphan [*N*-[2(*RS*)-(mercaptomethyl)-1-oxo-3-phenylpropyl]glycine] and *retro*-thiorphan [3-[[1(*RS*)-(mercaptomethyl)-2-phenylethyl]amino]-3-oxopropanoic acid], two highly potent inhibitors of enkephalinase, a neutral endopeptidase involved in enkephalin metabolism, is reported. Due to a rapid isomerization process, derivatives of *retro*-thiorphan, which contains a 2-substituted malonyl moiety, cannot be separated by classical methods. However, a separation of the diastereoisomeric mixtures of these *retro*-thiorphan derivatives was achieved by HPLC. The absolute configuration of each isomer was determined by using an NMR configurational correlation. The inhibitory potency of the various inhibitors indicates that, in the thiorphan series, the affinity for enkephalinase is independent of the stereochemistry of the 2-(mercaptomethyl)-1-oxo-3-phenylpropyl moiety. In contrast, in the *retro*-thiorphan series a 100-fold difference in the inhibitory activity of the two enantiomers is observed. This indicates that there are large differences in the conformational behavior of the two series of inhibitors at the active site of the enzyme.

The neutral endopeptidase (EC 3.4.24.11)¹ designated enkephalinase² is involved in the metabolism of the endogenous opioid peptides Met-enkephalin (Tyr-Gly-Gly-Phe-Met) and Leu-enkephalin (Tyr-Gly-Gly-Phe-Leu). Inhibition of this enzyme has been shown to be a useful method for investigating the physiological functions of opioid peptides.³⁻⁶ Moreover, inhibition of enkephalin metabolism represents a new approach in the search for analgesics.^{3,7} The design of potent and specific inhibitors of a given peptidase requires the knowledge of both its mechanism of action and its substrate specificity. Crystallographic studies of various zinc metallopeptidases such as carboxypeptidase A⁸ and thermolysin⁹ have shown that they have a common mechanism of catalysis and that their specificity is related to well-defined interactions (ionic, hydrophobic, H bonds, etc.) between the side chains of the substrate and the enzyme subsites surrounding the catalytic site.

On the basis of these findings, highly potent inhibitors of metallopeptidases such as angiotensin converting enzyme, ACE (EC 3.4.15.1),¹⁰ a metallopeptidase involved

in blood pressure regulation, and enkephalinase^{3,7,11,12} have been rationally designed after a careful characterization of their subsite specificity. The specificity of enkephalinase is essentially insured by the preferential interactions of the S₁' subsite with aromatic or large hydrophobic residues and of the S₂' subsite with small lipophilic moieties^{13,14} (the nomenclature used for the individual subsites of the enzyme, S₁', S₂', ..., is that of Schechter and Berger¹⁵).

Taking these features into account, two highly potent enkephalinase inhibitors have been designed that are able to interact with the catalytic site by a thiol group and to recognize the S₁'-S₂' subsites. However, these two compounds, designated thiorphan [*N*-[2(*RS*)-(mercaptomethyl)-1-oxo-3-phenylpropyl]glycine]³ and *retro*-thiorphan [3-[[1(*RS*)-(mercaptomethyl)-2-phenylethyl]amino]-3-oxopropanoic acid]⁷ were synthesized as racemic mixtures. The retro-inversion of the amide bond in thiorphan and derivatives was shown to induce a complete differentiation between enkephalinase and ACE inhibition.⁷ Generally, enzymes bind preferentially to compounds that mimic the configuration of the natural substrate, and studies on enkephalinase inhibition, by various

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