

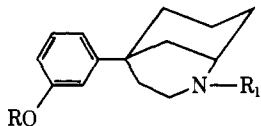
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Phenylmorphans Agonists-Antagonists

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In 1953¹ Clark, *et al.*, reported that substitution of allyl, methallyl, *n*-propyl, or isobutyl for methyl in morphine-type structures containing a free phenolic group at C-3 "invariably produced compounds capable of counteracting the analgesic effect of morphine." Since that time, similar modifications of oxymorphone,^{2,§} like morphine a pentacyclic molecule, 3-hydroxy-*N*-methylmorphinan (tetracyclic),³ 2'-hydroxy-6,7-benzomorphans (tricyclic),⁴ and several hexacyclic structures (etheno- and ethanooripavines)⁵ have given stronger narcotic antagonists, propyl, allyl, and cyclopropylmethyl being the most effective nitrogen substituents. In an extension of research to bicyclic structures, (±)- and (+)-5-*m*-hydroxyphenyl-2-methylmorphans (1 and 8)⁶ have been converted to 2-propyl, allyl, and cyclopropylmethyl congeners (5-7 and 12-14).



(±) series

- 1, R = H; R₁ = Me
- 2, R = R₁ = Me
- 3, R = Me; R₁ = H
- 4, R = R₁ = H
- 5, R = H; R₁ = Pr
- 6, R = H; R₁ = CH₂CH=CH₂
- 7, R = H; R₁ = CH₂-

(+) series

- 8, R = H; R₁ = Me
- 9, R = R₁ = Me
- 10, R = Me; R₁ = H
- 11, R = R₁ = H
- 12, R = H; R₁ = Pr
- 13, R = H; R₁ = CH₂CH=CH₂
- 14, R = H; R₁ = CH₂-

The phenylmorphans contain the phenolic hydroxyl in the same relative position (meta to the quaternary carbon linkage) as the above-mentioned more compact, rigid molecules. And (+) isomer 8 is some three times more potent than morphine with high physical dependence capacity (PDC) in monkeys; the racemate, morphine-like in analgesic potency, has intermediate PDC, but the (-) isomer, also as potent as morphine for analgesia, is a nalorphine-like antagonist in morphine-dependent monkeys.^{6b} It was, therefore, of interest to compare the (+) and the (±) series.

Chemistry. The allyl and propyl substituents were introduced by direct alkylation of 4 and 11 using allyl bromide and propyl iodide, respectively.^{3b,4b} Acylation of 4 and 11 with cyclopropylcarbonyl chloride and subsequent reduction with LiAlH₄ gave 7 and 14.

Phenols 4 and 11 were prepared from methyl ethers 3 and 10 (boiling 48% HBr), in turn prepared by von Braun N-demethylation⁷ of 2 and 9. Compound 9 was produced by diazomethane methylation of 8.⁶

Pharmacology. As seen in Table I and as reported be-

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§ H. Blumberg, personal communication.

fore,⁶ *N*-methyl racemate 1 is a morphine-like analgesic in mice with intermediate capacity to suppress morphine abstinence in monkeys, and the (+) isomer 8 is three times more potent in both respects. The (-) isomer, on the other hand, comparable to morphine as an analgesic, is weakly nalorphine-like in morphine-dependent monkeys.^{6,8}

N-Propyl compound 5 is about half as strong as pentazocine as an analgesic and 0.01 as strong as nalorphine as an antagonist with a greater duration of action; the (+) isomer 12 is comparable to 5 as an antagonist with more than twice the agonistic potency. Cyclopropylmethyl derivatives 7 and 14 are similar in effect to the *N*-propyl relatives with, surprisingly, a shorter duration of action and, as expected, higher analgesic activity in the Nilsen than in the hot-plate test. These four compounds appear similar to pentazocine, with steeper dose-response curves, perhaps longer duration of antagonistic effect, and fewer side actions. Allyl compounds 6 and 13, again pentazocine-like for analgesia, were essentially inactive as antagonists but like 5, 12, 7, and 14 would not substitute for morphine. It seems worthy of note that despite the marked differences in pharmacology between *N*-methyl compound 8 and the (-) isomer,⁶ the (±)- and (+)-*N*-substituted compounds, [5 *vs.* 12, 6 *vs.* 13, 7 *vs.* 14] differ little in substitution behavior in morphine-dependent monkeys. For analgesia, however, the (+) isomers were consistently two to three times more potent than corresponding racemates in the Nilsen test. With the hot plate, only propyl compound 12 was (three times) stronger than its racemic relative.

Thus, it is apparent that *potent* antagonists cannot necessarily be fashioned from corresponding *potent* analgesics with simply a *m*-phenolic group attached to a quaternary carbon. Other structural requisites may be a phenethylamine fragment^{4b} and/or an additional fused ring to hold the *m*-phenolic ring in a fixed axial position.^{4b} The phenylmorphans, like pethidine, have a nonrigid equatorial phenyl group.

Experimental Section

Melting points were taken in a Hershberg apparatus (total-immersion thermometers). Infrared and mass spectral data are compatible with the structures shown. Elemental analyses, as indicated by C, H, N, and Br, were within ±0.4% of theory. Rotations were made at a concentration of 1 g/100 ml of H₂O in a Perkin-Elmer 141 polarimeter.

(+)-5-*m*-Methoxyphenyl-2-methylmorphane (9) **Hydrobromide.** MeOH (50 ml), 3 g of 8,^{6b} and 200 ml of ethereal CH₂N₂ (from 20 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) were left for 24 hr and evaporated to dryness. The residue (in ether) was washed with 5% NaOH and then H₂O. Drying (MgSO₄) and distillation [bp 130° (0.2 mm)] gave 2.8 g (88%) of 9. The HBr salt (from Me₂CO-EtOH, 9:1) melted at 199-201°. *Anal.* (C₁₆H₂₄BrNO) C, H, N.

(+)-5-*m*-Methoxyphenylmorphane (10) **Hydrobromide.** This compound, mp 154-155° (from Me₂CO-Et₂O), was obtained (43% yield) in the von Braun reaction on 9 as described before⁷ (recovery of 9, 19%). *Anal.* (C₁₅H₂₂BrNO) C, H, N.

(±)-5-*m*-Hydroxyphenylmorphane (4). Compound 3·HBr⁷ (2.7 g) and 15 ml of 48% HBr were refluxed together for 45 min and evaporated to dryness *in vacuo*. The crystalline residue in H₂O was made basic with 12 *M* NH₄OH to give 1.8 g (93%) of 4, mp 216-223°. Sublimation [160-180° (0.01 mm)] and recrystallization from Me₂CO gave pure 4, mp 232-234° dec. *Anal.* (C₁₄H₁₉NO) C, H, N.

Von Braun demethylation of the OAc derivative of 3 gave a 26% yield of 4 and a 19% recovery of 3.

(+)-5-*m*-Hydroxyphenylmorphane (11). As described for 4, compound 11 was obtained from 10 in 83% yield, mp 233-234° dec. *Anal.* (C₁₄H₁₉NO) C, H, N.

(±)-5-*m*-Hydroxyphenyl-2-propylmorphane (5) **Hydrobromide.** Propyl iodide (0.5 g), 0.6 g of 4, 0.8 g of K₂CO₃, and 17 ml of *z*-Cyclazocine,^{4b} naltrexone,[§] and similar *N*-cyclopropylmethyl compounds are noted for their long duration of action.

Table I. Pharmacology of N-Substituted Phenylmorphans

Compound	Analgesic activity ^a		PDC ^b	Antagonistic activity ^b
	ED ₅₀ (hot plate)	ED ₅₀ (Nilsen)		
1 · HCl	1.5 (2.4–2.9)		Intermediate	No
8 · HCl	0.4 (0.28–0.45)		High	No
5 · HBr	14.5 (10.5–20.1)	14.1 (9.3–21.5)	No	0.01 ^{c,d}
6 · HBr	6.8 (5.2–8.8)	21.5 (15.4–30.3)	No	Slight ^e
7 · HBr	11.2 (7.9–15.7)	7.5 (3.7–15.3)	No	0.01 ^{c,f}
12 · HBr	4.9 (3.8–6.3)	7.7 (5.6–10.4)	No	0.01 ^{c,d}
13 · HBr	9.9 (7.7–12.8)	5.5 (4.2–7.4)	No	No ^g
14 · HBr	16.9 (11.8–24.1)	5.3 (3.4–8.3)	No	0.01 ^{c,h}
Nalorphine hydrochloride	36.3 (27.1–48.7)	4.8 (2.7–8.5)	No	1.0
Pentazocine hydrochloride	12.3 (9.3–16.3)	4.7 (2.9–5.1)	No	0.02 ^c
Morphine sulfate	1.2 (0.9–1.3)	0.8 (0.6–1.2)	High ⁱ	No

^aSubcutaneous administration, mg/kg; T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson, and E. L. May, *J. Pharm. Sci.*, **61**, 86 (1972); N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965). ^bData from the Department of Pharmacology, University of Michigan, personal communication from H. H. Swain, J. Woods, and J. E. Villarreal; for methodology, see ref 8. ^cRelative value; nalorphine = 1. ^dSomewhat longer acting than nalorphine. ^eOnly a hint of antagonistic activity at 4 and 8 mg/kg; 16 mg/kg induced convulsions. ^fShort acting. ^gNo apparent effect at 4, 8, and 18 mg/kg. ^hSame duration of action as nalorphine. ⁱStabilizing dose 3.0 mg/kg compared with 1.6 mg/kg for 8.

DMF were stirred together at 80° for 6 hr and evaporated to dryness *in vacuo*. The residue was treated with CHCl₃ and H₂O. Drying (Na₂SO₄) and evaporation of the CHCl₃ layer gave an oil which was evaporatively distilled [bp 180–200° (0.4 mm)] giving 0.44 g (62%) of a viscous oil which was treated with HBr–AcOH. Recrystallization of the resultant HBr salt of 5 from EtOH gave 0.5 g of pure needles, mp 205.5–207°. *Anal.* (C₁₇H₂₆BrNO) C, H, N, Br.

The (+) isomer 12, similarly prepared from 11, was converted to the HBr salt with HBr–MeOH: mp (from EtOH) 236.5–238.5°; [α]_D²⁰ +7.55°. *Anal.* (C₁₇H₂₆BrNO) C, H, N.

(±)-2-Allyl-5-*m*-hydroxyphenylmorphane (6) **Hydrobromide**. Allyl bromide (0.45 g), 0.7 g of 4, 0.9 g of K₂CO₃, and 25 ml of DMF were stirred together at 80–90° for 6.5 hr and evaporated to dryness *in vacuo*. The residue was treated with CHCl₃ and H₂O. Drying (Na₂SO₄) and evaporation of the CHCl₃ gave a brown oil (0.8 g) which was treated with HBr–AcOH. The resultant hydrobromide crystallized from EtOH in prisms (0.6 g, 55%), mp 222–223°. *Anal.* (C₁₇H₂₄BrNO) C, H, N, Br.

(+) isomer 13 was similarly obtained from 11 as the HBr salt in 72% yield: mp 176–178°; [α]_D²⁰ +10.6°. *Anal.* (C₁₇H₂₄BrNO) C, H, N.

(±)-2-Cyclopropylmethyl-5-*m*-hydroxyphenylmorphane (7) **Hydrobromide**. To a stirred suspension of 0.25 g of 4, 3 ml of Et₃N, and 10 ml of CH₂Cl₂ was added (cooling) 0.36 g of cyclopropylcarbonyl chloride in 2 ml of CH₂Cl₂. The resulting clear solution was refluxed overnight, washed with 10% HCl and then H₂O, dried (Na₂SO₄), and evaporated to dryness. The residue (0.4 g of *N,O*-dicarbonyl compound, ν_{CO} 1745, 1630 cm⁻¹) was reduced with 0.5 g of LiAlH₄ in refluxing THF (20 ml) for 20 hr to give 0.2 g of an oily base (after the usual work-up) which was converted to the hydrobromide (HBr–AcOH). Recrystallization from EtOH gave 0.2 g (54%) of pure 7-HBr, mp 220–222°. *Anal.* (C₁₇H₂₆BrNO) C, H, N, Br.

(+) isomer 14 was prepared from 11 in a similar manner: yield of hydrobromide 62%; mp 226–226.5°; [α]_D²⁰ +117.8°. *Anal.* (C₁₇H₂₆BrNO) C, H, N.

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Alkaloids in Mammalian Tissues. 4. Synthesis of (+) and (–)-Salsoline and Isosalsoline¹

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Based on the concept that alkaloids may not be exclusively plant products but may be formed in the mammalian system by Pictet-Spengler condensation of amino acids and biogenic amines with carbonyl substrates (for leading references, see ref 1), we have prepared a number of optically active substituted tetrahydroisoquinolines derived from L-dopa² and dopamine.³ Recently, definite support for this speculation was provided by the detection of 6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (salsolinol) and 6,7-dihydroxy-1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaveroline) in the urine of Parkinsonian patients on L-dopa treatment.⁴ While the stereochemistry of these alkaloids has yet to be established, their occurrence indicates the possibility that minor metabolites of L-dopa or dopamine, such as their two mono-*O*-methyl ethers, might also undergo similar transformations. In this connection, we now report the synthesis, characterization, and preliminary pharmacology of the enantiomeric salsolines **1b** and **2b**, the isosalsolines **3b** and **4b**, and the related *N*-methyl derivatives **1d–4d**.

Chemistry. The alkaloid (+)-salsoline (**1b**) and its antipode **2b**, previously obtained in poor yield by Pictet-Spengler condensation of 3-hydroxy-4-methoxyphenethyl-

* This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.