9α- and 9β-Hydroxyphenylmorphans

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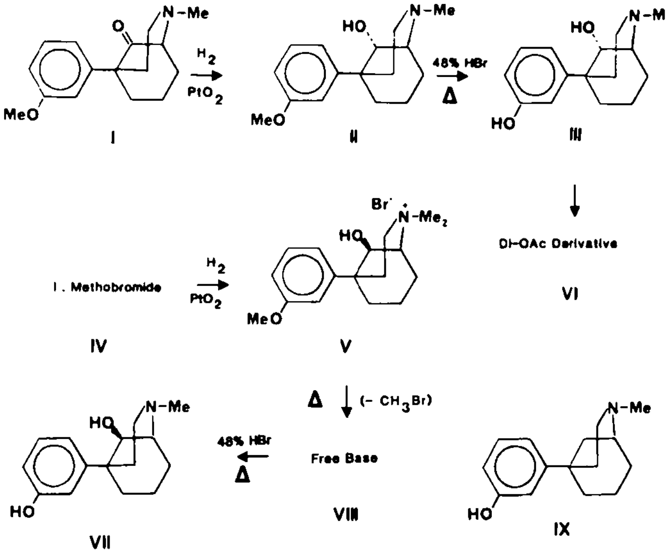
Abstract ☐ Platinum-oxide hydrogenation of 5-*m*-methoxyphenyl-2-methyl-9-oxomorphan (I) gave the 9α-hydroxy racemate (II) whose phenolic analogue (III) is a strong antinociceptive agent, fully supportive of morphine dependence in rhesus monkeys. The di-*O*-acetyl derivative (VI) of III was similar to III in its profile of activity. The diastereoisomer of III (VII), obtained by hydrogenation of the methobromide of I (IV), extrusion of methyl bromide, and *O*-demethylation of the resultant free base (VIII), was almost inactive antinociceptively and did not suppress withdrawal symptoms in morphine-dependent monkeys. The orientation of the C-9 hydroxyl groups was deduced from spectral data and by analogy.

Keyphrases ☐ 9α- and 9β-Hydroxyphenylmorphans—hydrogenation, diastereoisomer spectral data, synthesis ☐ Antinociceptive activity—9α- and 9β-hydroxyphenylmorphans, potency, withdrawal symptoms, substitution for morphine, antagonism

The introduction of a 9α-methyl group (1) into 5-*m*-hydroxyphenyl-2-methylmorphan (IX) (2), whose antipodes are strong antinociceptive agents showing a separation of morphine-like effects (1, 3), gives low-potency antagonists without appreciable pain-relieving properties. It was desired to determine the effect of hydroxyl substitution in the 9-position of IX. One of the two possible diastereoisomers (VII) resulting from such substitution would be similar to the very potent (10 times morphine) oxymorphone (4) with respect to 9-OH—N geometry. The synthesis of VII and its diastereoisomer (III) and some pharmacological findings are presented herein.



Scheme I

RESULTS AND DISCUSSION

Chemistry—When bicyclic ketone I (free base of hydrochloride salt) was hydrogenated in ethanol (platinum oxide), addition of hydrogen was stereoselective; the 9α-alcohol (II) was isolated in 98% yield. To obtain the 9β-alcohol (VIII), the methobromide of I (IV) was similarly hydrogenated, giving V which was converted to free base VIII pyrolytically (Scheme I).

Hydroxyl assignments are based principally on IR spectral data, which indicated strong 9-OH N bonding for VIII. Only free hydroxyl absorption and 9-OH-π bonding were seen for II. The ^{1}H-NMR data also appeared to support these assignments (see C-9 H values for ^{1}H-NMR and IR maxima in the *Experimental Section*). Finally, this stereochemical pattern of addition of hydrogen to the carbonyl group of I would be similar to that observed in the benzomorphan series (5) and for 5-*m*-methoxyphenyl-2-methyl-9-methylenemorphan (1).

Phenols III and VII were prepared from II and VIII, respectively, with boiling 48% hydrobromic acid or with boron tribromide in methylene chloride (6). Diacetate VI resulted from treatment of III with acetic anhydride containing a little pyridine.

Pharmacology—As recorded in Table I, the 9α-hydroxy racemate (III) is comparable to morphine in antinociceptive activity in mice by the tail-flick (TF) (7), *p*-phenylquinone-writhing (PPQ) (7), hot-plate (HP) (8), and Nilsen (9) tests, while the 9β-isomer (VII) had low-order potency in the PPQ test only. Compound III fully supported morphine dependence in rhesus monkeys at 1–16 mg/g, but VII, as expected, did not substitute for morphine at 3–18 mg/kg (10). The antinociceptive potency of the di-*O*-acetyl derivative of III (VI) was similar to that of the parent III in the TF, PPQ, and HP tests. In opiate-dependent monkeys, VI completely suppressed abrupt withdrawal at 10.0 mg/kg[1]. It was reported earlier (11) that VI did not suppress withdrawal at 1–10 mg/kg, results that seem inconsistent with the antinociceptive profiles of activity of VI and its precursor III. None of the three racemates (III, VI, and VII) elicited properties of antagonism in the opiate-dependent monkey (10, 11) or in the TF *versus* morphine test (10).

It seems noteworthy that VII, with 9-OH—N geometry similar to that of oxymorphone (4) is relatively inactive. It would therefore be of interest to synthesize the 14α-hydroxy epimer of oxymorphone which would correspond to the very active III.

EXPERIMENTAL SECTION[2]

9α-Hydroxy-5-*m*-methoxyphenyl-2-methylmorphan (II) Hydrochloride—Compound I (1.0 g, 3.9 mmol) in 60 mL of methanol was hydrogenated (Parr apparatus, 30 psig, 25°C) with 0.15 g of platinum oxide during 2 h. The filtered solution was evaporated to dryness under reduced pressure giving 0.98 g of II, mp 98–100°C (from ether-petroleum ether). IR ($CHCl_3$): 3650 w (free OH) and 3570 m cm^{-1} (OH-π bonding); ^{1}H-NMR ($CDCl_3$): δ 2.52 (3, s, N—CH_3), 3.81 (3, s, O—CH_3), and 4.32 ppm (1, d, J = 3 Hz, C-9). The hydrochloride salt (from acetone-hydrogen chloride) crystallized from methanol-ether in prisms, mp 225–227°C. ^{1}H-NMR (Me_2SO-d_6): δ 2.80 (3, s, N—CH_3), 3.75 (3, s, O—CH_3) and 5.51 ppm (1, d, J = 3 Hz, C-9); EI-MS: m/z 261 (M^+ − HCl).

Anal.—Calc. for $C_{16}H_{24}ClNO_2 \cdot 0.25\ H_2O$: C, 63.6; H, 8.2; N, 4.6. Found: C, 63.6; H, 8.4; N, 4.4.

9α-Hydroxy-5-*m*-hydroxyphenyl-2-methylmorphan (III)—The hydrochloride salt of II (0.5 g, 2.0 mmol) was added to 5 mL of nearly boiling 48% hydrobromic acid. The solution was refluxed for 12–15 min, cooled, and made alkaline with ammonium hydroxide. The liberated base was dissolved in chloroform (6–8 mL, three extractions). On standing for 30 min, the combined extracts deposited 200 mg of III, mp 193–196°C. From the filtrate and chloroform washings of the precipitate, an additional 140 mg of III separated after cooling to 0°C, total yield 80%. It was nearly pure [TLC: R_f 0.25, silica gel, chloroform-methanol-ammonium hydroxide (90:9:1)] and was recrystallized by dissolving 200 mg in 200 mL of boiling acetone, filtering the hot

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[1] Unpublished results.

[2] Melting points (uncorrected) were taken in a Thomas-Hoover capillary apparatus. IR and NMR spectra were obtained with a Beckman Aculab 8 and a 60-MHz Hitachi-Perkin Elmer Model R-24, respectively. Mass and analytical data are from the Section on Microanalytical Services and Instrumentation (Dr. David Johnson, Chief), National Institutes of Health.

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Table I—Antinociceptive Data for 9-Hydroxyphenylmorphans and Morphine

Compound	Antinociceptive Activity (ED_{50}), mg/kg sc			
	Tail-Flick Test	*p*-Phenylquinone Test	Hot Plate Test	Nilsen Test
III[a]	3.5 (2.5–5.0)	0.2 (0.07–0.4)	1.9 (1.5–2.6)	2.7 (2.2–3.2)
VI[b]	7.3 (3.6–14.7)	1.0 (0.3–3.1)	2.0 (1.4–2.8)	—
VII[c]	Inactive[d]	8.6 (4.2–17.6)	Inactive[e]	—
Morphine[f]	5.8 (5.7–5.9)	0.23 (0.20–0.26)	1.0 (0.8–1.1)	1.3 (1.0–1.7)

[a] Hydrochloride salt. [b] Hydrobromide salt. [c] *dl*-Mandelate salt. [d] Essentially inactive; 46% of mice affected at 60 mg/kg. [e] Essentially inactive; 30% of mice affected at 100 mg/kg. [f] Sulfate salt.

solution, concentrating the filtrate to 4 mL, and cooling to 5°C. The yield was 140 mg, mp 197–198°C.

Anal.—Calc. for $C_{15}H_{21}NO_2 \cdot 0.5\ H_2O$: C, 72.8; H, 8.5; N, 5.7. Found: C, 72.8; H, 8.4; N, 5.7.

The hydrochloride salt of III (acetone-hydrogen chloride) was recrystallized from methanol-acetone, mp 225.5–227.0°C. EI-MS: *m/z* 247 (M^+ − HCl).

Anal.—Calc. for $C_{15}H_{22}ClNO_2$: Cl, 12.5. Found: Cl, 12.2.

By the method of Rice (5), III could be obtained equally well from II, using boron tribromide.

9α-Acetoxy-5-*m*-acetoxyphenyl-2-methylmorphan (VI) Hydrobromide—Acetic anhydride (20 mL), 0.7 g (2.8 mmol) of III (hydrochloride salt) and a drop of pyridine were refluxed for 1 h. The cooled mixture was poured into 50 mL of ice water, made alkaline by careful addition of potassium carbonate (stirring), and extracted with chloroform-ethanol (10:1, 4 × 25 mL). The combined extracts were washed twice with water, dried (sodium sulfate), and evaporated under reduced pressure to afford 0.62 g (68%) of oily VI which, in acetone, was converted to 0.63 g of the hydrobromide salt with 32% hydrogen bromide-acetic acid. It was recrystallized from acetone methylene chloride, mp 220–223°C. IR (Nujol): 1760 and 1750 cm^{-1}; EI-MS: *m/z* 331 (M^+ − HBr).

Anal.—Calc. for $C_{19}H_{26}BrNO_4$: C, 55.4; N, 6.4; N, 3.4. Found: C, 55.4; H, 6.6; N, 3.3.

9β-Hydroxy-5-*m*-hydroxyphenyl-2-methylmorphan (VII) *dl*-Mandelate—The methobromide (IV) (2) of I (0.5 g, 1.4 mmol) in 30 mL of methanol was hydrogenated (0.15 g of platinum oxide, 23–25°C, 30 psig) for 42 h. The filtered solution was evaporated to dryness under reduced pressure to afford 0.56 g of hygroscopic solid, which was dissolved in 5 mL of 1-nonanol. The solution was refluxed for 5 min under nitrogen, cooled, diluted with 20 mL of ether, and extracted with 20 mL of 10% hydrochloric acid in four portions. The combined extracts were made basic with ammonium hydroxide and extracted with 50 mL of ether in four portions. The ether was washed twice with water, dried (sodium sulfate), and evaporated to dryness under reduced pressure (0.3 mm, 18 h) giving 0.23 g (55% yield) of VIII, mp 68–70°C. IR ($CHCl_3$): 3640 w (free OH), 3560 w (OH–π bonding), and 3400 s cm^{-1} (OH—N bonding); ^{1}H-NMR ($CDCl_3$): δ 2.40 (3, s, N—CH_3), 3.80 (3, s, O—CH_3), and 4.14 ppm (1, d, J = 4 Hz, C-9); EI-MS: *m/z* 261 (M^+), 244, 232, and 218.

To this base was added 5 mL of hot 48% hydrobromic acid. The solution was refluxed for 10 min, cooled, poured into 20 mL of saturated saline, made alkaline with ammonium hydroxide, and extracted with 50 mL of ether in four portions. The extracts were washed twice with saturated saline, dried (sodium sulfate), and evaporated giving 0.18 g of VII. Treatment of VII with 0.11 g (1 equivalent) of *dl*-mandelic acid in acetone furnished 0.25 g (14% based on starting IV) of the *dl*-mandelate salt of VII, which crystallized from methanol-acetone as a hemihydrate, mp 93–94°C; EI-MS: *m/z* 247 (M^+ − mandelic acid).

Anal.—Calc. for $C_{23}H_{29}NO_5 \cdot 0.5\ H_2O$: C, 67.6; H, 7.4; N, 3.5. Found: C, 67.2; H, 7.2; N, 3.3.

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