(9) C. Kaiser, A. M. Pavloff, E. Garvey, P. J. Fowler, D. H. Tedeschi, C. L. Zirkle, E. A. Nodiff, and A. J. Saggiomo, *ibid.*, **15**, 665 (1972).
(10) J. R. Campbell, *Aldrichimica Acta*, **4**, 55 (1971).
(11) D. C. Remy and W. A. Van Saun, Jr., *Tetrahedron Lett.*, **27**, 2463 (1971).
(12) I. Møller Nielsen, W. Hougs, N. Lassen, T. Holm, and P. V. Petersen, *Acta Pharmacol. Toxicol.*, **19**, 87 (1962).

Phenylmorphan Agonists-Antagonists

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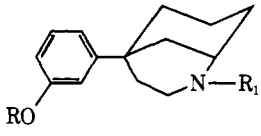
In 1953[1] Clark, *et al.*, reported that substitution of allyl, methallyl, *n*-propyl, or isobutyl for methyl in morphine-type structures containing a free phenolic group at C-3 "invariably produced compounds capable of counteracting the analgesic effect of morphine." Since that time, similar modifications 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	(+) series
1, R = H; R_1 = Me	**8**, R = H; R_1 = Me
2, R = R_1 = Me	**9**, R = R_1 = Me
3, R = Me; R_1 = H	**10**, R = Me; R_1 = H
4, R = R_1 = H	**11**, R = R_1 = H
5, R = H; R_1 = Pr	**12**, R = H; R_1 = Pr
6, R = H; R_1 = $CH_2CH{=}CH_2$	**13**, R = H; R_1 = $CH_2CH{=}CH_2$
7, R = H; R_1 = CH_2—◁	**14**, R = H; R_1 = CH_2—◁

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 $LiAlH_4$ 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-demethylation[7] of **2** and **9**. Compound **9** was produced by diazomethane methylation of **8**.[6]

Pharmacology. As seen in Table I and as reported before,[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 H_2O in a Perkin-Elmer 141 polarimeter.

(+)-5-*m*-Methoxyphenyl-2-methylmorphan (9) Hydrobromide. MeOH (50 ml), 3 g of **8**,[6b] and 200 ml of ethereal CH_2N_2 (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 H_2O. Drying ($MgSO_4$) and distillation [bp 130° (0.2 mm)] gave 2.8 g (88%) of **9**. The HBr salt (from Me_2CO–EtOH, 9:1) melted at 199–201°. *Anal.* ($C_{16}H_{24}BrNO$) C, H, N.

(+)-5-*m*-Methoxyphenylmorphan (10) Hydrobromide. This compound, mp 154–155° (from Me_2CO–Et_2O), was obtained (43% yield) in the von Braun reaction on **9** as described before[7] (recovery of **9**, 19%). *Anal.* ($C_{15}H_{22}BrNO$) C, H, N.

(±)-5-*m*-Hydroxyphenylmorphan (4). Compound **3**·HBr[7] (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 H_2O was made basic with 12 *M* NH_4OH to give 1.8 g (93%) of **4**, mp 216–223°. Sublimation [160–180° (0.01 mm)] and recrystallization from Me_2CO gave pure **4**, mp 232–234° dec. *Anal.* ($C_{14}H_{19}NO$) 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*-Hydroxyphenylmorphan (11). As described for **4**, compound **11** was obtained from **10** in 83% yield, mp 233–234° dec. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

(±)-5-*m*-Hydroxyphenyl-2-propylmorphan (5) Hydrobromide. Propyl iodide (0.5 g), 0.6 g of **4**, 0.8 g of K_2CO_3, and 17 ml of

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§ H. Blumberg, personal communication.

‡ 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

[a]Subcutaneous 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). [b]Data 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. [c]Relative value; nalorphine = 1. [d]Somewhat longer acting than nalorphine. [e]Only a hint of antagonistic activity at 4 and 8 mg/kg; 16 mg/kg induced convulsions. [f]Short acting. [g]No apparent effect at 4, 8, and 18 mg/kg. [h]Same duration of action as nalorphine. [i]Stabilizing 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 $CHCl_3$ and H_2O. Drying (Na_2SO_4) and evaporation of the $CHCl_3$ 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.* ($C_{17}H_{26}BrNO$) 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°; $[\alpha]^{20}D$ +7.55°. *Anal.* ($C_{17}H_{26}BrNO$) C, H, N.

(±)-2-Allyl-5-*m*-hydroxyphenylmorphan (6) Hydrobromide. Allyl bromide (0.45 g), 0.7 g of **4**, 0.9 g of K_2CO_3, 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 $CHCl_3$ and H_2O. Drying (Na_2SO_4) and evaporation of the $CHCl_3$ 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.* ($C_{17}H_{24}BrNO$) C, H, N, Br.

(+) isomer 13 was similarly obtained from **11** as the HBr salt in 72% yield: mp 176–178°; $[\alpha]^{20}D$ +10.6°. *Anal.* ($C_{17}H_{24}BrNO$) C, H, N.

(±)-2-Cyclopropylmethyl-5-*m*-hydroxyphenylmorphan (7) Hydrobromide. To a stirred suspension of 0.25 g of **4**, 3 ml of Et_3N, and 10 ml of CH_2Cl_2 was added (cooling) 0.36 g of cyclopropylcarbonyl chloride in 2 ml of CH_2Cl_2. The resulting clear solution was refluxed overnight, washed with 10% HCl and then H_2O, dried (Na_2SO_4), 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 $LiAlH_4$ 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.* ($C_{17}H_{26}BrNO$) C, H, N, Br.

(+) isomer 14 was prepared from **11** in a similar manner: yield of hydrobromide 62%; mp 226–226.5°; $[\alpha]^{20}D$ +117.8°. *Anal.* ($C_{17}H_{26}BrNO$) C, H, N.

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References

(1) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, 3rd, *J. Amer. Chem. Soc.*, **75**, 4963 (1953).
(2) M. J. Lewenstein and J. Fishman, U. S. Patent 3,254,088 (1966).
(3) (a) J. Hellerbach, O. Schnider, H. Besendorf, and B. Pellmonts, "Synthetic Analgesics," Part II (A), Pergamon Press, London, 1966; (b) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).
(4) (a) M. Gordon, J. J. Lafferly, D. H. Tedeschi, N. B. Eddy, and E. L. May, *Nature (London)*, **192**, 4807, 1089 (1961); (b) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).
(5) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, **11**, 241 (1971).
(6) (a) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955); (b) E. L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970).
(7) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).
(8) J. E. Villarreal, "Advances in Mental Science, Drug Dependence," Vol. II, R. T. Harris, W. McIsaac, and C. R. Schuste, Ed., University of Texas Press, Houston, Texas, 1970, pp 83–116.

Alkaloids in Mammalian Tissues. 4. Synthesis of (+)- and (−)-Salsoline and Isosalsoline[1]

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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-dopa[2] 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.