analyses are indicated only by symbols of the elements, analytical results obtained by those elements were within ±0.4% of the theoretical values.

DL-α,1-**Dichloro-2-naphthalenepropanoic Acid.** To a mixture containing 9.41 g (0.05 mol) of 1-nitro-2-naphthylamine in 150 ml of acetone and 50 ml of concentrated HCl was added slowly a solution of 3.45 g (0.05 mol) of $NaNO_2$ in 20 ml of H_2O with stirring at 0°. Glacial acrylic acid (50 ml) was then introduced to the reaction mixture followed by careful addition of 600 mg of CuCl in small increments so as not to exceed a reaction temperature of 5°. When the N_2 evolution had ceased, the mixture was reduced in vacuo and then treated with 200 ml of aqueous 5% $KHCO_3$ to effect solution. The aqueous solution was then extracted with 100 ml of Et_2O and 100 ml of $CHCl_3$. The aqueous layer was separated, treated with activated charcoal, and filtered. The filtrate was acidified by the addition of concentrated HCl and the precipitate which formed was collected on a filter to give 9.21 g (68%) of crude product. Recrystallization from formic acid gave an analytical sample, mp 157–158°. Anal. ($C_{13}H_{10}Cl_2O_2$) C, H, Cl.

DL-α,1-**Dibromo-2-naphthalenepropanoic Acid.** Following the same procedure as that described above, 9.41 g (0.05 mol) of 1-nitro-2-naphthylamine in 150 ml of acetone and 60 ml of concentrated HBr were treated with 50 ml of glacial acrylic and 1.5 g of CuBr to yield 5.73 g (32%) of crude product, mp 171–178°. Recrystallization from HOAc–H_2O gave an analytical sample, mp 177–178°. Anal. ($C_{13}H_{10}Br_2O_2$) C, H, Br.

β-(1-**Chloro-2-naphthyl**)-DL-**alanine** (1). A 1.25-g (0.00464 mol) sample of DL-α,1-dichloro-2-naphthalenepropanoic acid was treated with 40 ml of concentrated NH_4OH at 70° for 60 h. The reaction mixture was evaporated to dryness in vacuo, and the resulting residue was washed with H_2O, acetone, ether, and hot benzene to yield 0.72 g (62%) of crude product, mp 249–251°. Recrystallization from acetic acid–ether gave an analytical sample, mp 256–257° dec. Anal. ($C_{13}H_{12}ClNO_2$) C, H, Cl.

β-(1-**Bromo-2-naphthyl**)-DL-**alanine** (2). A 1.00-g (0.00279 mol) sample of DL-α,1-dibromo-2-naphthalenepropanoic acid was treated with 100 ml of concentrated NH_4OH for 48 h at 0° and then for 48 h at 25°. The reaction mixture was evaporated to dryness in vacuo and the residual material was washed with H_2O, filtered, and air-dried to give 0.60 g (73%) of crude solid, mp 235–237° dec. The solid was washed with boiling acetone to obtain the desired product, mp 248–249° dec. Anal. ($C_{13}H_{12}BrNO_2$) C, H, N.

Microbiological Assays. The assay procedure[6] and inorganic salts–glucose medium[7] for *E. coli* (ATCC 9723) were the same as previously reported. For the lactic acid bacteria a previously described procedure and basal medium[8] were used except that 0.2 μg/ml of calcium pantothenate and 0.02 μg/ml of pantethine were included in the vitamin supplement, phenylalanine and tyrosine were omitted from the amino acid medium, and the concentration of tryptophan was decreased to 3 μg/ml. Additional modifications are noted for each organism. For *L. dextranicum* (ATCC 8086), the phosphate concentration was increased fourfold and the medium further supplemented with 100 μg/ml of glutamine. For *L. plantarum* (ATCC 8014), the concentrations of phenylalanine and tyrosine were reduced to 1 μg/ml.

The naphthylalanines (10 mg) were dissolved in sterile H_2O (10 ml) with slight warming. From these solutions, serial dilutions were made to the desired concentration and added aseptically to the previously autoclaved tubes. After inoculation, the assay tubes with *E. coli* were incubated at 37° for 16 h, and those with *L. dextranicum* and *L. plantarum* were incubated at 30° for 18 h.

In all assays the amount of growth was determined spectrophotometrically at 625 nm with a Bausch & Lomb Spectronic 20 in terms of absorbance readings of the turbid culture medium against a blank of uninoculated medium set at zero absorbance. Appropriate controls were run in all assays and the results of the minimum inhibitory concentrations of the various compounds and the standard (2-chlorotyrosine) were shown to be reproducible on repeating the assays at least six times.

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Optical Resolution of (±)-2,5-Dimethyl-2'-hydroxy-9α- and -9β-propyl-6,7-benzomorphans and Their Pharmacological Properties

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The levo and dextro isomers of 2,5-dimethyl-2'-hydroxy-9α- and -9β-propyl-6,7-benzomorphans have been prepared. The analgesic potency and physical dependence capacity of the optical isomers and their racemic parents were determined. The 9α-propyl levo isomer was analgesically equipotent with morphine; the 9β-propyl levo isomer was considerably more potent subcutaneously and equipotent orally. None of the optical isomers suppressed the withdrawal syndrome; the 9β-propyl levo isomer exacerbated the withdrawal syndrome.

The separation of desired analgesia from physical dependence, one of the more serious side effects of morphine-like drugs, has been achieved with the benzomorphan molecule in at least two ways. (1) Substitution of certain saturated and unsaturated side chains for the methyl group on the nitrogen atom of this molecule has produced agonist–antagonists, as observed in both monkey species and in man.[1] (2) More recently, it has been shown that optical resolution produces one isomer (levo) that is without physical dependence capacity in rhesus monkeys and which may actually induce or exacerbate the abstinence syndrome.[2-4]

Only very occasionally have we observed antagonistic effects to narcotic analgesics in racemic *N*-methylbenzomorphans.[5-7] (These *N*-methyl racemic compounds are generally found in the 9α-alkylbenzomorphan series.)

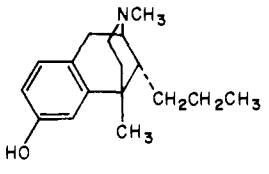
Table I. Analgesic Activity and Physical Dependence Capacity (PDC) of *dl*-2,5-Dimethyl-2'-hydroxy-9α- and -9β-propyl-6,7-benzomorphans and Their Antipodes

Compound	ED_{50},[a] mg/kg	ED_{50},[b] mg/kg	PDC[c]
1[d]	1.61 (1.03–2.52)	1.8 (1.3–2.6)	Low[e,f]
2·HCl·2H₂O	0.64 (0.45–0.90)	0.35 (0.26–0.49)	None[g–i]
3 (+)-mandelate	*j*		None[k,l]
4 (−)-mandelate	1.1 (0.69–1.7)	1.2 (0.75–1.8)	None[h,k,m]
5·HCl·H₂O	*n*		None[g,o]
6·HCl·H₂O	0.30 (0.20–0.43)	0.35 (0.23–0.52)	None[g,p,q]
Morphine hydrochloride	1.2 (0.9–1.3)	0.8 (0.6–1.2)	High
Nalorphine hydrochloride	36.4 (27.2–48.7)	4.8 (2.1–11.0)	None

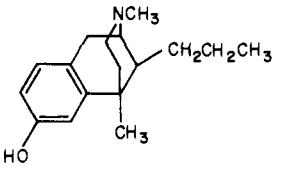
[a] Eddy hot-plate assay (95% SE limits), sc injection, mice (ref 14 and 15). [b] Nilsen assay (95% SE limits), sc injection, mice (ref 16). [c] Physical dependence capacity, monkeys, single dose suppression (ref 12). [d] Titrated with dilute HCl for solution. [e] Reference 13. [f] Did not completely substitute for morphine at 1.5–6 mg/kg. [g] Reference 11. [h] At 0.5–16 mg/kg. [i] Did not substitute for morphine in the dose range tested. [j] No marked effect at 20–40 mg/kg (slightly toxic at 40 mg/kg). [k] Reference 10. [l] Neither suppressed not precipitated abstinence at 5 or 10 mg/kg. Abstinence signs were not precipitated in nonwithdrawn, morphine-dependent monkeys at 10 mg/kg. [m] No apparent effect (neither suppressed or precipitated abstinence). [n] Only 3/10 effected at 20 mg/kg (toxic at 50 mg/kg). [o] At 2.5–10 mg/kg. [p] The oral ED_{50} (Nilsen test[17]) was 7.26 mg/kg (4.5–11.6) as compared with codeine (ED_{50} 21.4) and oxycodone (ED_{50} 1.3). [q] May exacerbate withdrawal. Severe depression noted at 1–16 mg/kg.

However, some 9α- and 9β-alkylbenzomorphans have recently been synthesized which have either an antagonistic effect or which do not suppress the withdrawal syndrome in monkeys; these were nonquaternary carbon compounds (at C-5).[6,7] Generally, the 9β-alkylbenzomorphans, which have been observed to have considerably greater analgesic potency than the comparable 9α compounds, also display increased toxicity.[8]

We have optically resolved the recently synthesized 2,5-dimethyl-2'-hydroxy-9α- and -9β-propyl-6,7-benzomorphans (**1**, **2**)[9] and have examined their analgesic potencies and their ability to suppress the withdrawal syndrome in physically dependent monkeys, as compared with their parent racemic compounds.



1, (±) base
3, (+) isomer
4, (−) isomer



2, (±) base
5, (+) isomer
6, (−) isomer

The (+)- and (−)-α-methoxy-α-trifluoromethylphenylacetic acids have not previously been used to resolve amines. Generally, this reagent has been utilized for the determination of the optical purity of compounds by NMR. We found that we could get reasonable yields of pure enantiomeric salts of the (+)- and (−)-9α-substituted benzomorphans after one recrystallization of the (+)- or (−)-α-methoxy-α-trifluorophenyl acetates. Other resolving agents (e.g., mandelic acid) which were tried were ineffective in separating the enantiomers of the 9α-substituted benzomorphan.

Pharmacology. None of the optical isomers of **1** and **2** suppressed the withdrawal syndrome of morphine[10–12] (Table I).

The racemic 9α-propylbenzomorphan **1** suppressed only slightly the withdrawal syndrome and could be said to have a low physical dependence capacity.[13] It caused non-dose-related reduction in withdrawal signs on single-dose suppression (SDS) tests in monkeys. Myoclonic jerks were noted in all of the animals receiving the high dose (6.0 mg/kg sc), in one animal (out of three) receiving a 3.0 mg/kg dose, and in one animal (out of three) receiving the 1.5 mg/kg dose.[13]

Most remarkedly, the racemic 9β-propylbenzomorphan **2**, a potent analgesic, neither suppressed nor precipitated abstinence,[11] one of the very few analgesically potent 9β-alkylbenzomorphans which appear to have no untoward side effects in mice or monkey species at any of the tested dose levels (maximum of 16 mg/kg).

The 9α-propyl levo isomer **4**, comparable with morphine in analgesic potency, did not show any antagonistic effect; it neither suppressed nor precipitated abstinence.[10] In fact, it had no apparent effect whatever in the monkey. No toxic effects were noted at all between 0.5 and 16 mg/kg.

The 9α-propyl dextro isomer **3** had little obvious effect at 2.0 or 10.0 mg/kg in SDS monkey studies. At the upper dose there was an impression of increased severity of abstinence signs. In nonwithdrawn monkeys, however, abstinence signs were not precipitated at 10.0 mg/kg. At this dose level in normal monkeys, the animals became apprehensive and irritable, showing signs of restlessness, increased spontaneous movement, tremors and muscle rigidity, piloerection, and pupil dilation. These effects lasted for 1–2 h.[10]

The 9β-propyl levo isomer **6**, a more potent analgesic than morphine, both on subcutaneous (hot-plate[14,15] and Nilsen[16] test) and oral administration (in the Nilsen test[17]), appeared to have some narcotic antagonist activity.[11] It did not substitute for morphine but exacerbated the withdrawal syndrome. One monkey at 16.0 and one at 8.0 mg/kg (out of two and three animals, respectively) had clonic convulsions within 0.5 h after drug administration. Pentobarbital and morphine were administered to terminate convulsions. At the 4.0, 2.0, and 1.0 mg/kg doses severe retching and some vomiting were noted. Some animals were depressed for 24 h.[11]

The 9β-propyl dextro isomer **5** did not substitute for morphine. At the highest dose tested (10.0 mg/kg), all the monkeys showed head tremor and were gazing; one was uncoordinated. At the 5.0 mg/kg dose, two (out of three) animals showed head tremor and three (out of three) were gazing.[11]

Conclusion

The racemic 9β-propylbenzomorphan **2** and the levo isomer of the 9α-propyl compound **4** appear to warrant further examination for their potential as nondependence liable, potent analgesics and the levo 9β-propyl compound **6** for its possible utility as an orally effective agonist–antagonist.

Experimental Section

Melting points were determined in open capillary tubes and are corrected. Optical rotations were measured with a Cary 60 recording spectropolarimeter at 589 nm, using the solvents and concentrations specified. Microanalyses were performed by the Laboratory's Section on Microanalytical Services and Instrumentation and are within 0.4% of the calculated values.

(+)-2,5-Dimethyl-2'-hydroxy-9α-propyl-6,7-benzomorphan (3). To a solution of (+)-α-methoxy-α-trifluoromethylphenylacetic acid (4.60 g, 19.6 mmol) in Me_2CO (100 ml) was added **1** (free base, 4.62 g, 17.81 mmol). The mixture was heated to solution,

distilled at atmospheric pressure to 40 ml, and allowed to stand at room temperature until crystallization was complete (2 h). The solid was filtered, washed with cold Me_2CO, and dried to give 2.55 g of **3-(+)-α-methoxy-α-trifluoromethylphenyl acetate**, mp 198.5–200° dec. Recrystallization from *i*-PrOH gave 2.2 g (50%) of prisms: mp 203.5–204.5° dec; $[\alpha]^{24}D$ +64.3° (*c* 0.60, EtOH). Anal. ($C_{27}H_{34}F_3NO_4$) C, H, N. This salt (2.20 g, 4.46 mmol) was dissolved in hot MeOH (10 ml), made alkaline with NH_4OH, and slowly diluted to 25 ml with H_2O. After cooling, the material was filtered, washed with H_2O, and dried to give 1.12 g (97%) of **3**, mp 200–202.5°. Two recrystallizations (EtOH–H_2O) gave prisms: mp 201–202.5°; $[\alpha]^{24}D$ +56.9° (*c* 0.60, EtOH). Anal. ($C_{17}H_{25}NO$) C, H, N. The mandelate salt of **3** was prepared by treating a solution of **3** (742 mg, 2.86 mmol) in Me_2CO with (+)-mandelic acid (455 mg, 2.98 mmol). When crystallization was complete at 5°, the solid was filtered, washed with Me_2CO, and dried to give **3** (+)-mandelate (1.00 g, 85%). Recrystallization gave irregular plates (EtOH–H_2O, 1:9): mp 181–182.5°; $[\alpha]^{24}D$ +66.8° (*c* 0.60, EtOH). Anal. ($C_{25}H_{33}NO_4$) C, H, N.

(−)-2,5-Dimethyl-2'-hydroxy-9α-propyl-6,7-benzomorphan (4). The combined filtrates and washings from 2.2 g of **3-(+)-α-methoxy-α-trifluoromethylphenyl acetate** were evaporated to a syrup which was dissolved in warm MeOH (40 ml), made alkaline with NH_4OH, and slowly diluted with H_2O (40 ml). The crystalline mixture of the (±) and (−) bases (3.2 g) was filtered, washed, and dried. To this mixture (3.20 g, 12.34 mmol), dissolved in Me_2CO (40 ml), was added (−)-α-methoxy-α-trifluoromethylphenylacetic acid (3.20 g, 13.66 mmol). The mixture was concentrated to 20 ml by distillation at atmospheric pressure and allowed to stand at room temperature until crystallization was complete (1 h). The solid was filtered, washed with Me_2CO and then Et_2O, and dried to give 3.05 g of material, mp 198–200° dec. This solid was dissolved in hot *i*-PrOH (60 ml), centrifuged, concentrated to 25 ml by distillation at atmospheric pressure, and allowed to stand at room temperature for 1 h. The resulting prisms were filtered, washed with *i*-PrOH, and dried to give **4-(−)-α-methoxy-α-trifluoromethylphenyl acetate** (2.60 g, 59%): mp 203–204.5° dec; $[\alpha]^{24}D$ −64.5° (*c* 0.57, EtOH). Anal. ($C_{27}H_{34}F_3NO_4$) C, H, N. A solution of this salt (2.60 g, 5.27 mmol) in warm MeOH (10 ml) was treated with NH_4OH, as described for its antipode, to give **4** (1.36 g, 99%), mp 199.5–202.5° dec. Recrystallization from EtOH–H_2O gave prisms: mp 201–202.5° dec; $[\alpha]^{24}D$ −56.6° (*c* 0.59, EtOH). Anal. ($C_{17}H_{25}NO$) C, H, N. The (−)-mandelate salt was prepared from **4** (967 mg, 3.72 mmol) and (−)-mandelic acid (576 mg, 3.78 mmol) in Me_2CO (50 ml) as described above for its enantiomer. In this manner, 1.35 g (88.1%) of **4** (−)-mandelate was obtained: mp 181–182.5°. Recrystallization from EtOH–H_2O (1:9) gave irregular plates: $[\alpha]^{24}D$ −66.3° (*c* 0.59, EtOH). Anal. ($C_{25}H_{33}NO_4$) C, H, N.

(+)-2,5-Dimethyl-2'-hydroxy-9β-propyl-6,7-benzomorphan (5). To a solution of (−)-tartaric acid (3.15 g, 20.87 mmol) in H_2O (10 ml) was added 100% EtOH (40 ml) and **2** (5.0 g, 19.3 mmol). The mixture was heated to solution and cooled slowly to 25° during which time crystalline material separated. Ethanol–H_2O (8:2, 20 ml) was added and the batch cooled to 5° for 0.5 h. The solid was filtered, washed with 80% EtOH, and dried to give 3.70 g. Two recrystallizations from 80% EtOH and drying in high vacuum at 80° gave optically pure, hydrated **5** (−)-acid tartrate (2.65 g, 67%): needles; no definite melting point (shrinks and decomposes at 135–160°); $[\alpha]^{24}D$ +31.6° (*c* 0.53, 80% MeOH). Elemental analyses on several samples of material which had been exhaustively dried indicated that varying amounts of water still retained. One sample which gave satisfactory analytical data for **5** (−)-acid tartrate hydrate showed $[\alpha]^{24}D$ +31.0° (*c* 0.52, 80% MeOH). Anal. ($C_{21}H_{31}NO_7 \cdot H_2O$) C, H, N. Brief boiling of hydrated **5** (−)-acid tartrate in absolute EtOH or MeOH gave the neutral tartrate: small prisms; mp 259–261° dec; $[\alpha]^{24}D$ +41.5° (*c* 0.51, 70% MeOH). Anal. ($C_{38}H_{56}N_2O_8$) C, H, N.

5 (−)-acid tartrate (2.65 g) was dissolved in hot MeOH (15 ml), made alkaline with NH_4OH, and slowly diluted to 50 ml with H_2O. The crystalline material was filtered, washed with H_2O, and dried to give 1.57 g of **5** (94%), mp 169–170.5°. Recrystallization gave prisms from MeOH: $[\alpha]^{24}D$ +85.2° (*c* 0.55, EtOH). Anal. ($C_{17}H_{25}NO$) C, H, N. The hydrochloride of **5** was prepared in EtOH using a slight excess of 37% HCl. Recrystallization from H_2O followed by air drying gave **5**·HCl·H_2O: rectangular plates; mp 264.5–266.5° dec; $[\alpha]^{24}D$ +60.2° (*c* 0.52, EtOH). Anal. ($C_{17}H_{26}ClNO \cdot H_2O$) C, H, N.

(−)-2,5-Dimethyl-2'-hydroxy-9β-propyl-6,7-benzomorphan (6). The combined filtrates and washings from 2.65 g of **5** (−)-acid tartrate were evaporated to a syrup and dissolved in warm MeOH (20 ml), made alkaline with NH_4OH, and slowly diluted to 100 ml with H_2O. The solid was filtered, washed with H_2O, and dried to give 3.10 g of a solid mixture of (±) and (−) bases. The mixed bases (3.10 g, 11.95 mmol) were heated to solution with (+)-tartaric acid (1.90 g, 12 mmol) in 80% EtOH (50 ml). The solution was cooled to 5° for 1 h and the resulting crystals were filtered, washed with cold 80% EtOH, and dried to give 3.60 g. One recrystallization from 80% EtOH gave 3.0 g (76%) of optically pure **6** (+)-acid tartrate which after drying in high vacuum showed $[\alpha]^{24}D$ −31.2° (*c* 0.58, 80% MeOH) and, like its antipode, had no definite melting point. Elemental analysis of this sample was satisfactory for a hemihydrate. Anal. ($C_{21}H_{31}NO_7 \cdot 0.5H_2O$) C, H, N. The neutral tartrate was obtained as previously described for its enantiomer: prisms; mp 259–261.5° dec; $[\alpha]^{24}D$ −39.9° (*c* 0.52, 70% MeOH). Anal. ($C_{38}H_{56}N_2O_8$) C, H, N.

The **6** (+)-acid tartrate was converted to the (−)-base **6** as described above for its enantiomer **5**. Recrystallization from MeOH gave **6**: prisms; mp 168.5–170°; $[\alpha]^{24}D$ −84.5° (*c* 0.56, EtOH). Anal. ($C_{17}H_{25}NO$) C, H, N. The **6** hydrochloride monohydrate, prepared as described for **5**·HCl·H_2O, was obtained as rectangular plates, mp 264–266° dec, and showed $[\alpha]^{24}D$ −60.9° (*c* 0.56, EtOH). Anal. ($C_{17}H_{26}ClNO \cdot H_2O$) C, H, N.

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