parallels very well with the lipophilic character of the four analgeticis. Of special interest is the good agreement of the slopes of eq 9 and **11**. This reflects a close parallelism between log (C_{brain}/C_{plasma}) and log (C_{iventr}/C_{iv}). This is additional support for the earlier findings that log (C_{iventr}/C_{iv}) is a measure of the different capability of the analgetics to penetrate the blood–brain barrier.

Table II
Radioactively Labeled Analgetics with Physical Constants

Compound	(C_{brain}/C_{plasma})	log (C_{brain}/C_{plasma})	log P
Morphine	0.046	−1.34	−5.00
Dihydromorphine	0.053	−1.28	−5.00
Fentanyl	10.58	1.02	1.29
Etorphine	8.69	0.94	0.15

The parallelism between the intraventricular activity and the receptor activity leads to some qualitative conclusions regarding the drug–receptor interactions. Figure **1** makes possible the comparison of the chemical structures of the analgetics with their relative intrinsic activities. It is interesting to note that the polar compounds like hydromorphine, dihydromorphine, morphine, and normorphine have a greater activity at the receptor than the synthetic derivatives methadone, ketobemidone, and pethidine. Polar functions, like hydroxy, ether, or keto groups seem to be favorable for specific drug–receptor interactions. This is in accord with the findings of Porthogese[9] that the introduction of an OH group in an analgetically active molecule can enhance analgetic activity and simultaneously change the mode of binding. Therefore, the high activity of the nonpolar synthetic analgetics following intravenous application can easily be explained by a good penetration of these compounds through the blood–brain barrier to the reaction site and seems not to be due to especially favorable drug–receptor interactions. In etorphine, the most active compound in this set of analgetics, both favorable properties are combined within one molecule.

The results of this work underline the importance of the passive penetration of drugs through the blood–brain barrier. No criterion was found which would be in accord with a special importance of an active transport[21] through this barrier for the studied analgetics. In addition, the statistical analysis of the pharmacological results has shown, that the efficiencies of the drugs following intraventricular application parallel largely their receptor activities.

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Optical Isomers of Miscellaneous Strong Analgetics

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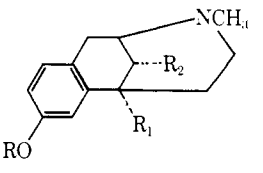
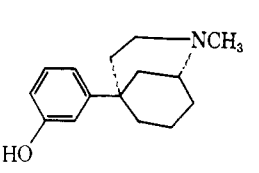
Optical isomers of α-5,9-diethyl-2′-methoxy- (**1a**), α-2,5-dimethyl-9-ethyl-2′-hydroxy- (**1d**), and 2′-hydroxy-2-methyl-6,7-benzomorphans (**1c**) and of 5-(*m*-hydroxyphenyl)-2-methylmorphan (**2**) have been prepared and compared with parent racemates in analgetic activity, physical dependence capacity, and antagonistic behavior. Racemate **1c**, (+)-**1c**, (−)-**1c** and (−)-**2** have morphine-like analgetic and nalorphine-like antagonistic action.

In continuation of our research designed to effect favorable separation of morphine-like effects by optical resolution,[2] the antipodes of α-5,9-diethyl-2′-methoxy- (**1a**), α-2,5-dimethyl-9-ethyl-2′-hydroxy- (**1d**), and 2′-hydroxy- (**1c**) 2-methyl-6,7-benzomorphans and of 5-(*m*-hydroxyphenyl)-2-methylmorphan (**2**) have been prepared. Compounds (+)- and (−)-**1a** were obtained by CH_2N_2 methylation of (+)- and (−)-**1b**. Optical resolution of **1c**, **1d**, and **2** was effected with (+)-3-bromo-8-camphorsulfonic acid ammonium salts,[3] *d*-10-camphorsulfonic acid, and *d*-mandelic acid, respectively.



1a, R = Me; $R_1 = R_2$ = Et
b, R = H; $R_1 = R_2$ = Et
c, R = $R_1 = R_2$ = H
d, R = H; R_1 = Me; R_2 = Et



2

Pharmacology. In Table I are given analgetic activities as determined in the mouse hot plate method,[4] and physical dependence capacities and antagonistic

(1) (a) To whom inquiries should be addressed; (b) Visiting Fellow from Tokyo, 1968–1969.

(2) (a) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969); (b) E. L. May and N. B. Eddy, *ibid.*, **9**, 581 (1966).

(3) From Aldrich Chemical Company as *d*-α-bromocamphor-π-sulfonic acid.

(4) (a) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); (b) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

Table I

Pharmacologic Properties of Benzomorphan and Phenylmorphan Racemates and Optical Isomers

Compd[a]	ED_{50}[b]	PDC[c]	Antagonistic activity[c]
(±)-1a[d]	4.6	No (to 32 mg/kg)[e]	No
(−)-1a	4.2	No (to 8 mg/kg)[f]	No
(+)-1a	6.5	Yes (at 16 mg/kg)	No
(±)-1c[g]	4.4	No	Yes (from 4 to 24 mg/kg)[h]
(−)-1c	4.5	No	Yes (from 2 to 16 mg/kg)[h]
(+)-1c	14.4	No	Yes (at 5 and 10 mg/kg)[i]
(±)-1d[j]	0.8	No (to 12 mg/kg)	No
(−)-1d	0.7	No[k]	No (to 20 mg/kg)
(+)-1d	17.7	No[l]	No[l]
(±)-2[m]	1.4	Intermediate	No
(−)-2	1.5	No	Yes[n]
(+)-2	0.4	Yes[o]	No
Morphine	1.2	High[p]	No
Codeine	7.5	Intermediate	No

[a] Administered subcutaneously as HCl salts in H_2O excepting morphine (as sulfate) and **1a** isomers (as free base in dilute HCl). [b] See ref 4. [c] See ref 5. [d] Prepared by Frank Palopoli, National Drug Company. [e] Very toxic at 16 and 32 mg/kg. [f] Caused severe ataxia and loss of motor control at this dose. [g] See ref 7. [h] Of mild to intermediate severity. [i] Causes moderate to severe abstinence. [j] See ref 8. [k] Causes CNS depression at 0.4 and 0.8 mg/kg and complete loss of motor control at 1.6 mg/kg. [l] To 20 mg/kg. [m] See ref 9. [n] Precipitated abstinence of intermediate severity at 8 mg/kg. [o] Complete suppression at 1.6 mg/kg. [p] Stabilization dose 3 mg/kg.

potencies obtained from the Rhesus monkey.[5] Optical isomers corresponding to **1** and **2** are compared with parent racemates and morphine and codeine. Methyl ethers (±)-**1a** and (−)-**1a** are between morphine and codeine in analgetic potency, will not suppress abstinence in morphine-dependent monkeys and do not exhibit antagonism. The (+)-**1a**, like its phenolic relative (+)-**1b**,[2] is codeine-like as an analgetic and in its ability to substitute for morphine. Neither (±)-**1d**, a very potent analgetic, nor the corresponding optical isomers in which there is a 20-fold difference in analgetic potency have physical dependence capacity or antagonistic behavior. In contrast to (−)-**1a** and (−)-**1d**, α-(−)-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan [(−)-**1b**] and 4 homologs exhibit nalorphine-like antagonism.[2] In the case of **1c** (a structure without a quaternary carbon at position 5), the racemate and *both* optical isomers are good antagonists of morphine; (±)-**1c** and (−)-**1c** showed the same good analgetic potency, but (+)-**1c** was only marginally active. In the phenylmorphan series, (+)-**2**, a 4 times more potent analgetic than the parent racemate or morphine, is also a good suppressor of morphine abstinence phenomena. (−)-**2**, equivalent to morphine in analgetic activity, like (−) isomers of the benzomorphan series heretofore described,[2] is a nalorphine-like antagonist of moderate potency. Racemate **2**, with intermediate physical dependence capacity, no activity as an antagonist, but with morphine-like analgetic activity behaves more like (+)-**2** than (−)-**2**.

Thus, contrary to previous experience,[2] there is little uniformity in the pharmacologic behavior of these miscellaneous racemates and optical isomers. Two observations of especial interest, however, are that: (1) for the first time a racemate, (±)-**1c**, a benzomorphan without a strategically positioned quaternary C possesses a good mixture of agonist (analgetic) and antagonist components and (2) that a *levo* isomer of the phenylmorphan series (a structure more closely related to pethidine than to benzomorphan type analgetics) also induces both morphine-like analgesia and nalorphine-like antagonism.

Experimental Section

Melting points (capillary) were taken with total-immersion thermometers. Rotations were measured on a Perkin-Elmer Model 141 polarimeter; bases in 95% EtOH, hydrochlorides in H_2O (*c ca.* 1) unless otherwise stated. Elemental analyses, performed by the Section on Microanalytical Services and Instrumentation were within ±0.3% of the calculated values.

Preparation of α-(−)- and (+)-5,9-Diethyl-2′-methoxy-2-methyl-6,7-benzomorphan [α-(+)- and (−)-1a].—Ethereal CH_2N_2 (15 ml, 3°), 1.0 g of (+)-**1b**,[2a] and 5 ml of MeOH were stirred for 1–2 hr (clear solution) then treated with 5 ml of the CH_2N_2 solution. The mixture was kept overnight, and a final 5-ml charge of the CH_2N_2 was added. After 3–4 days solvents were evaporated *in vacuo*, and the residue was distilled by evaporation (130°, 0.05 mm) to give 1.0 g of oily α-(+)-**1a** and traces of crystalline α-(+)-**1b** which could be separated readily with ether in which the (+)-**1b** is insoluble. The α-(+)-**1a** crystallized (mp 82–85°) and was recrystallized from MeOH–H_2O; mp 85–86°, $[\alpha]^{20}D$ +51.5°. *Anal.* ($C_{17}H_{27}NO$) C, H. Similarly, α-(−)-**1a** was obtained; mp 85–87°, $[\alpha]^{20}D$ −52.8°. *Anal.* ($C_{18}H_{27}NO$) C, H.

(+)-2′-Hydroxy-2-methyl-6,7-benzomorphan [(+)-1c] and the (−) Isomer [(−)-1c]. A mixture of 3.6 g of (+)-3-bromo-8-camphorsulfonic acid NH_4 salt,[6] 2.4 g of (±)-**1c**·HCl,[7] and 5 ml of H_2O was boiled to solution, kept at room temperature overnight, filtered, and the precipitate washed with 3.5 ml of cold H_2O to give 2.2 g of cottony solid. Two recrystallizations (from 95% EtOH then H_2O) gave 1.5 g of the pure sulfonate salt of (+)-**1c**, mp 213–216° (turbid melt at 151–155°). This was dissolved in 8 ml of hot H_2O, basified with NH_4, and cooled to −5° to give 0.5 g (50% of (+)-**1c**, mp 228–230° dec, $[\alpha]^{20}D$ +88.9 (MeOH); rods from MeOH. *Anal.* ($C_{13}H_{17}NO$) C, H, N. The **hydrochloride** of (+)-**1c** melted at 276–278° dec and had $[\alpha]^{20}D$ +72.1° (MeOH); needles from MeOH–Et_2O). *Anal.* ($C_{13}H_{18}ClNO$) C, H, N.

The filtrate and washings from the 2.2 g obtained as described above deposited 1.6 g of large needles during 2 days. A recrystallization from H_2O gave 1.5 g of the pure sulfonate salt of (−)-**1c**, mp 245–247°. It was converted into the base as described for its enantiomer giving 0.52 g (52%) of (−)-**1c**, mp 227–230° dec, $[\alpha]^{20}D$ −89.5° (MeOH); rods from MeOH. *Anal.* ($C_{13}H_{17}NO$) C, H, N. The **hydrochloride** of (−)-**1c** melted at 276–278° and had $[\alpha]^{20}D$ −72.8° (MeOH); needles from MeOH–Et_2O. *Anal.* ($C_{13}H_{18}ClNO$) C, H, N.

α-(+)-2,5-Dimethyl-9-ethyl-2′-hydroxy-6,7-benzomorphan [α-(+)-1d] and the (−) Isomer [α-(−)-1d]. *d*-10-Camphorsulfonic acid (Eastman, 1.5 g), 1.5 g of α-(±)-**1d**,[8] and 6 ml of absolute EtOH were warmed to solution and filtered and the flask and filter were washed with Me_2CO. Concentration of the combined filtrate and washings (18 ml) to 7 ml, dilution with 10 ml of Et_2O, and slight warming gave, after cooling to −5°, filtering, and washing with Me_2CO, 1.1 g of the *d*-10-camphorsulfonate salt of α-(+)-**1d**, mp 222–224°. It was recrystallized from MeOH–Me_2CO giving 0.9 g, mp 225–227° which was converted into 0.4 g (53% of α-(+)-**1d** with MeOH–NH_4OH. Recrystallization from EtOH–H_2O gave long prisms, mp 204–205.5°, $[\alpha]^{20}D$ +61.0°. *Anal.* ($C_{18}H_{29}NO$) C, H. The hydro-

(5) We are indebted to Dr. J. Villarreal, Department of Pharmacology, University of Michigan for these results (personal communication). See also, J. E. Villarreal and M. H. Seevers, Addendum 2, Minutes of the 30th Meeting of the Committee on Problems of Drug Dependence, National Research Council, National Academy of Sciences, 1968; and J. E. Villarreal, "Recent Advances in the Pharmacology of Morphine-Like Drugs, Advances in Mental Science, Volume II, Drug Dependence," R. T. Harris, W. McIsaac, and C. R. Schuster, Ed., University of Texas Press, Houston, Texas, 1970, pp 83–116.

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(8) J. H. Ager, S. E. Fullerton, and E. L. May, *ibid.*, **6**, 322 (1963).

chloride (from MeOH–Me_2CO) melted at 217–220° and had $[\alpha]^{20}D$, +39.3°. *Anal.* ($C_{16}H_{24}ClNO$) C, H.

The combined filtrate and washings from the 1.1 g of precipitate above were concentrated to 5–6 ml and made basic with NH_4OH–H_2O giving 0.9 g of a mixture of α-(−)- and (±)-**1d**; mp 192–210°. This was digested with 12–15 ml of boiling Me_2CO. Rapid cooling in ice and filtration gave 0.4 g of α-±-**1d**, mp 213–219°. The filtrate was concentrated to 3–5 ml (to the appearance of crystals), cooled to −5°, and filtered giving 0.45 g of α-(−)-**1d**, mp 196–203°. It was suspended in a little MeOH and acidified with HCl gas. Acetone was added, and solvents were distilled with periodic addition of Me_2CO until crystals began separating. Cooling to 0° gave 0.45 g (55%) of α-(−)-**1d**·HCl, mp 218–221°, $[\alpha]^{20}D$ −39.1° after recrystallization from MeOH–Me_2CO. *Anal.* ($C_{16}H_{24}ClNO$) C, H. Treatment of this hydrochloride with MeOH–NH_4OH gave α-(−)-**1d**, prisms from Me_2CO; mp 205–206°, $[\alpha]^{20}D$ −60.8°.

(+)-5-*m*-Hydroxyphenyl-2-methylmorphan [(+)-2] and the (−) Isomer [(−)-2].—*d*-Mandelic acid (0.8 g, Aldrich), 1.1 g of (±)-**2**,[9] and 10 ml of Me_2CO were warmed to disappearance of solid. On cooling, a sirup separated and was dissolved by addition of a few drops of MeOH (slight warming). Crystals separated and the mixture was cooled overnight at −5° to give 1.9 g of *d*-mandelate salts. These were dissolved in 55 ml of boiling MeOH. The solution was concentrated to the appearance of crystals (to 10–15 ml) and left at room temperature for 1 hr to give 0.9 g of the *d*-mandelate salt of (+)-**2**, mp 212–215°. Another similar recrystallization gave 0.8 g, mp 216–218°. It was suspended in boiling H_2O and treated dropwise with NH_4OH to give an oil which crystallized on cooling; yield of (+)-**2** 0.4 g (74%) mp 153–154° before and after recrystallization from MeOH, $[\alpha]^{20}D$ +12.4°. *Anal.* ($C_{15}H_{21}NO$) C, H. The **hydrochloride** (from *i*-PrOH–HCl gas) melted at 233–235° and had $[\alpha]^{20}D$, +4.4° (*c* 1.8). *Anal.* ($C_{15}H_{22}ClNO$) C, H.

The combined filtrates and washings from the 1.9-, 0.9-, and 0.8-g fractions above were concentrated to *ca.* 5 ml and diluted strongly with H_2O and NH_4OH to give 0.5 g of a mixture of (−)- and (±)-**2**. This and 0.4 g of *d*-mandelic acid were heated briefly in 5 ml of MeOH giving crystals immediately. Cooling to −5°, filtering, and washing the precipitate with cold MeOH gave 0.6 g of (−)-**2** *d*-mandelate, mp 212–214° dec. It was converted into 0.35 g (65%) of (−)-**2** as described for (+)-**2**; mp 153–154°, unchanged by recrystallization from EtOH–H_2O or MeOH. It had $[\alpha]^{20}D$ −12.7°. *Anal.* ($C_{15}H_{21}NO$) C, H. The hydrochloride (from *i*-PrOH–HCl gas) melted at 233–235° and had $[\alpha]^{20}D$ −4.8°. *Anal.* ($C_{15}H_{22}ClNO$) C, H.

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Tricyclic Norephedrine Analogs. The Isomeric 9-Hydroxy-10-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrenes[1a]

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The syntheses of the 4 isomeric 9-hydroxy-10-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrenes (**1**, **2**, **3**, and **4**) are described. Spectral and chemical evidence are presented for the structures of the title compounds. Biological data are recorded for α-adrenergic receptor activity and α-adrenergic blocking activity.

A number of studies have been performed to aid in the delineation of the architectural features of adrenergic receptors, each providing some evidence concerning the steric and electronic requirements for analogs of norepinephrine to produce effects in various tissues.[2] More recently studies have been directed at determining the conformational specifications of the agonist drug–receptor complex, with the idea that conformational differences in the drug–receptor interaction of a single drug with different receptors may be at least a partial explanation for different actions of a single drug, and/or different potencies of the same drug, on various tissues. Little has been offered in terms of the architectural features of this complex, although speculation, consistent with the facts, does exist, determined primarily for conformationally mobile agonists.[2c,3] Adrenergic activity of a phenethylamine moiety, and a benzylic hydroxyl group of a given absolute stereochemistry have been defined. In addition stereochemical relationships between the ephedrines and ψ-ephedrines for agonist and antagonist activity have been determined.[4] In this nonrigid system little can be said concerning specific conformational requirements of the drug–receptor complex. Studies by Smissman and coworkers have shown some adrenergic activity in the 2-phenyl-3-amino-*trans*-2-decalols,[5a] although little difference is noted in the isomers and amine depleting activity in the 3-phenyl-3-hydroxy-*trans*-decahydroquinolines.[5b]

In this study we prepared norephedrine analogs **1**, **2**, **3**, **4**, in which 9-(e)-hydroxy-10(e)-amino-1,2,3,4,4a,9,-10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**1**), and the 9(a)-hydroxy-10(a)-amino compound, (**3**) represent *threo* configurations of norephedrine and the 9(a)-hydroxy-10(e)-amino compound (**2**), and the 9(e)-hydroxy-10(a)-amino analog (**4**), represent *erythro* configurations.[6]

(1) (a) Presented to the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 7–12, 1969, MEDI-33; (b) taken in part from the dissertation presented by D. D. Miller, July 1969, to the Graduate School, University of Washington, in partial fulfillment of the Ph.D. degree; (c) U. S. Public Health Service Fellowship, 1-F1-GM-33,942, 1966–1969.

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(6) (a) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (e) and axial (a) substituents at C-9 are in fact *pseudo*-equatorial and *pseudo*-axial respectively; (b) All materials are racemic although only a single isomer is drawn; (c) Consistently throughout nmr discussions of the 9,10-disubstituted compounds, the proton at C-9 will be designated A, the proton at C-10, B, and the C-10a axial proton, C.