Table I

Analgetic Activities of 5-Hydroxy- and 5-Acyloxy-2-methyl-6,7-benzomorphans

Compd	ED_{50} mg/kg, sc[a]
2a	42
2b	Inactive
3a	5.1
3b	11.1
3c	25
4a[b]	11.0
4b[b]	3.0
α-Prodine	1.0

[a] 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] See ref **7**.

4a and is pethidine-like.[6] In general, **2** and **3**, with a "quasi"-quaternary C, are less active than corresponding benzomorphans with H at position 5 (tertiary C congeners).[7] Compound **3a** has no capacity to support morphine dependence in Rhesus monkeys at 5.0 mg/kg but gives partial to almost complete suppression of abstinence at 10 and 20 mg/kg.[8] Thus, hybrid **3a** is more like α-prodine than benzomorphan types in pharmacologic actions.[4a] The reverse is true for a previously reported[4b] benzomorphan–pethidine hybrid which is comparable to pethidine in analgetic activity[4b] but will not suppress abstinence in morphine-dependent monkeys to 48 mg/kg.[9]

Experimental Section

Melting points (capillary) were taken in a Hershberg apparatus, total-immersion thermometers. Ir spectra were recorded with a Perkin-Elmer Infracord, nmr with a Varian A-60. Found C, H, and N values are all within ±0.3% of theory.

5-Hydroxy-2-methyl-6,7-benzomorphan (2a).—Ketone **1a** (1.2 g)[2c,6] and 20 ml of 48% HBr were refluxed gently for 18 hr, cooled, made basic (NH_4OH), and extracted with $CHCl_3$. Evaporation of the dried (Na_2SO_4) extracts left 1.0 g (84%) of **2a**: mp 186–188° (from AcOEt); λ_{max}^{Nujol} 3.05 μ; δ_{TMS}^{DMSO} 2.28 (s, 3, NCH_3), 3.23 (s, 1, OH, disappeared on addition of D_2O), 7.0–7.6 (m, 4, C_6H_4) ppm; $p_{K'}$ 7.203. *Anal.* ($C_{13}H_{17}NO$) C, H, N. The **hydrochloride** crystallized from Me_2CO–MeOH–Et_2O in plates, mp 236–238°. *Anal.* ($C_{13}H_{18}ClNO$) C, H, N.

Similar treatment of 2-benzyl-4,4-dimethoxy-1-methylpiperidine[2a] gave **2a** in comparable yield.

2′,5-Dihydroxy-2-methyl-6,7-benzomorphan (2b) Hydrochloride.—Polyphosphoric acid (7 g)[5] and 1 g of **1b** were kept at 140–145° (bath temperature) for 1.5 hr. After cooling, 9 ml of H_2O and 9 ml of 12 *M* HCl were added and the mixture was refluxed for 23 hr to hydrolyze phosphate ester, made basic (NH_4OH), and washed with $CHCl_3$.[10] The aq layer was continuously extracted with boiling $CHCl_3$ for 2 days. Evaporation of the $CHCl_3$ left 423 mg of residue which, in Me_2CO, was acidified with dry HCl to give 412 mg (40%) of **2b**·HCl: mp 267–270° (plates from MeOH, mp 269–271, dec); λ_{max}^{Nujol} 3.02, 3.05 μ; $p_{K'}$ 7.219. *Anal.* ($C_{13}H_{18}ClNO_2$) C, H, N.

5-Acetoxy-2-methyl-6,7-benzomorphan (3a).—Pyridine (3 ml), 0.45 g of **2a**, and 15 ml of Ac_2O were refluxed for 4 hr, evaporated to dryness *in vacuo*, treated with ice, made basic with NH_4OH, and extracted with ether. Evaporation of the dried (Na_2SO_4) ether gave 0.52 g (94%) of **3a**: mp 95–96° after recrystallization from hexane; λ_{max}^{Nujol} 5.76 μ, $\delta_{TMS}^{CDCl_3}$ 2.09 (s, 3, CH_3CO), 2.40 (s, 3, CH_3N), 7.15 (s, 4, C_6H_4) ppm. *Anal.* ($C_{15}H_{19}NO_2$) C, H, N. The **hydrochloride** crystallized from MeCO–AcOEt: mp 123–126° (turbid melt, bubbling); λ_{max}^{Nujol} 2.80 (hydrate H_2O), 5.75 μ. *Anal.* ($C_{15}H_{20}ClNO_2 \cdot H_2O$) C, H, N.

2-Methyl-5-propionoxy-6,7-benzomorphan (3b) Hydrochloride. Propionic anhydride (15 ml), 4 ml of pyridine, and 0.36 g of **2a** kept at 145–150° (bath temperature) for 4 hr, gave, after work-up as described in the previous experiment, 0.38 g (73%) of **3b**·HCl (from Et_2O)–dry HCl): mp 125–127° (after recrystn from Me_2CO–AcOEt); λ_{max}^{Nujol} 2.80 (hydrate H_2O), 5.75 μ. *Anal.* ($C_{16}H_{22}ClNO_2 \cdot H_2O$) C, H, N.

2′,5-Diacetoxy-2-methyl-6,7-benzomorphan (3c) Hydrochloride.—The hydrochloride of **2b** (310 mg), 8 ml of Ac_2O, and 0.8 ml of pyridine were refluxed for 4.5 hr, evaporated to dryness *in vacuo*, treated with 30 ml of Et_2O, and filtered. Recrystallization of the precipitate from Me_2CO–AcOEt gave 370 mg (90%) of **3c**·HCl: mp 129–138°, unchanged by further recrystn; λ_{max}^{Nujol} 2.95 (hydrate H_2O), 5.67, 5.71 μ; $p_{K'}$ 7.303. *Anal.* ($C_{17}H_{22}ClNO_4 \cdot H_2O$) C, H, N.

(6) The phenyl nucleus is equatorial and trans to Me in α-prodine but rigidly held in axial position in the benzomorphans.

(7) K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 405 (1969).

(8) Private communication from Dr. J. E. Villarreal, Department of Pharmacology, University of Michigan, Ann Arbor, Mich.

(9) G. A. Deneau and M. H. Seevers, Minutes of the 1963 Meeting of the Committee on Drug Addiction and Narcotics, National Academy of Science, National Research Council, Addendum 1, p 10.

(10) Evaporation of these washings gave 250 mg of an intractable residue which did not include **2b**.

A Conformational Study of β-Phenethanolamine Receptor Sites. IV. Synthesis of *erythro*- and *threo*-3-Amino-2-phenyl-2-butanols

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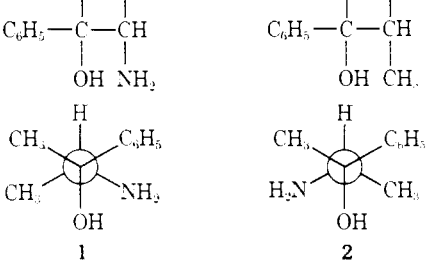
In an earlier paper[1] the synthesis and preliminary testing of the decalin analogs of ephedrine and ψ-ephedrine were reported. Since these rigid analogs were active as α-adrenergic stimulants and showed marked differences in their inhibition of histamine uptake into rabbit platelets it was decided to prepare the butane analogs **1** and **2** as semirigid systems. The

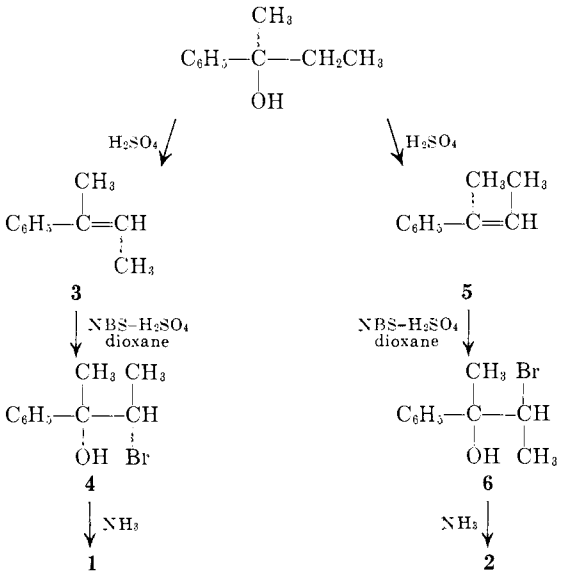


erythro analog **1** was prepared from *trans*-2-phenyl-2-butene (**3**) by formation of *erythro*-3-bromo-2-phenyl-2-butanol (**4**) followed by amination with NH_3. Since the erythro isomer was obtained from this reaction it is apparent that neighboring group participation occurs to give an intermediate epoxide which then opens with NH_3 to give an overall retention of configuration.

The threo analog **2** was prepared from *cis*-2-phenyl-2-butene (**5**) *via* the bromohydrin **6** followed by amination as with the erythro system.

* To whom correspondence should be addressed.

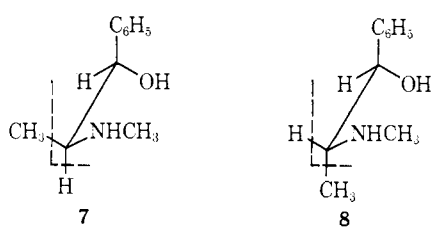
(1) E. E. Smissman and W. H. Gastrock, *J. Med. Chem.*, **11**, 860 (1968).



Biological Data.—The *dl*-erythro isomer **1** (10^{-4} *M*) showed direct agonist effect in that it was equally effective on the normal and reserpinized rat vas deferens. This compound increased the pD_2 of D-(−)-norepinephrine (NE) from 6.4 to 7.0 while it increased the maximal response in the rat vas deferens by 25%. It increased the effect of NE on the rabbit aortic strip at 10^{-4} *M*. At 10^{-3} *M* it inhibited the spontaneous movement of the rabbit jejunum. At a dose of 1–10 mg/kg, the dog and rat blood pressures were increased by 30–80 mm for 4–8 min. Tachyphylaxis was observed with repeated administration while phenoxybenzamine blocked and reversed this effect.

The *dl*-threo isomer **2** was identical in qualitative responses with the erythro compound but much less effective. The pD_2 of NE on the rat vas deferens increased from 6.4 to 6.7 while the maximum response continued to increase by 25%. The blood pressure increase in both the dog and rat was much less than with the erythro isomer but was also blocked and reversed by phenoxybenzamine.

These results are similar to those observed with ephedrine (erythro, **7**) and ψ-ephedrine (threo, **8**) in which the relative pressor activity is 26:4 for the corresponding racemates. These observations support the findings of LaPidus[2] and coworkers who proposed that both ephedrine and ψ-ephedrine can occupy the same three sites on a receptor surface (Ph, OH, NH_2) with the inference that their agonist response differs due to the configuration of the Me group α to the amino function.



In photocell activity cages, mice treated with ephedrine showed a slight depression of activity at 25 mg/kg with no change at lower doses. With the erythro isomer **1**, greatly increased activity at doses as low as 50 mg/kg was observed. With the threo isomer **2**, activity was depressed in doses up to 150 mg/kg.

The LD_{50} (mice) for ephedrine was 200 mg/kg; for erythro isomer **1**, 300 mg/kg; for threo isomer **2**, 300 mg/kg.

(2) J. B. LaPidus, A. Tye, P. Patil, and B. A. Modi, *J. Med. Chem.*, **6**, 76 (1963).

Experimental Section[3]

cis- and *trans*-**2-Phenyl-2-butene (5 and 3).**—Dehydration of methylethylphenylcarbinol was performed according to Klages[4] to give a mixture of *cis*- and *trans*-2-phenyl-2-butene. The olefins were separated into pure cis and trans components utilizing an annular still and proved to be identical with the compounds previously prepared and characterized by Cram.[5]

erythro-**3-Bromo-2-phenyl-2-butanol (4).**—*trans*-2-Phenyl-2-butene (650 mg, 0.0049 mole) was suspended in a mixture of dioxane (15 ml), H_2O (10 ml), and H_2SO_4 (800 mg). To this mixture was added *N*-bromosuccinimide (925 mg, 0.0052 mole) in several portions. The mixture was stirred for 12 hr and the solvent removed. The residue was extracted with Et_2O, washed with H_2O, and dried ($MgSO_4$); yield 850 mg, 76%. Spectral data were consistent with the assigned structure. *Anal.* ($C_{10}H_{13}BrO$) C, H, Br.

erythro-**3-Amino-2-phenyl-2-butanol (1).**—The bromohydrin **4** (850 mg, 0.0037 mole) was placed in a steel reaction vessel and 50 ml of liquid NH_3 was added. The vessel was sealed and maintained at a temperature of 170° for 15 hr, then cooled, and opened, the NH_3 allowed to evaporate, and the residue dissolved in $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and concentrated to give an oil. The oil was dissolved in 25 ml of Et_2O and HCl gas was added to form the HCl salt. The salt was recrystallized from EtOH, mp 155°. It could also be recrystallized from H_2O as the monohydrate. Spectral data were consistent with the assigned structure. *Anal.* ($C_{10}H_{16}ClNO \cdot H_2O$) C, H, N.

threo-**3-Bromo-2-phenyl-2-butanol (6).**—*cis*-2-Phenyl-2-butene (**5**) (15 g, 0.114 mole) was suspended in a mixture of dioxane (100 ml) and H_2SO_4 (20 g). To this mixture was added NBS (21.4 g, 0.12 mole) in several portions. The mixture was stirred at 25° for 12 hr and the solvent removed. The residue was extracted (Et_2O), the extract washed (H_2O) and dried ($MgSO_4$); yield 24.6 g, 94%. Spectral data were consistent with the assigned structure. *Anal.* ($C_{10}H_{13}BrO$) C, H, Br.

threo-**3-Amino-2-phenyl-2-butanol (2).**—The bromohydrin **6** (4.5 g, 0.019 mole) was placed in a steel reaction vessel and treated in the same manner as described for the preparation of **1**. An oil (1.25 g) was obtained and its HCl salt was prepared: mp 253°; ir (KBr) 2.95 (OH); 3.31 (NH_3^+, superimposed on CH); 6.25 (Ph) 6.33 (NH_4^+); 6.69, 9.39 (doublet); 1342, 14.49 μ; nmr (D_2O) δ 7.7 (5 protons), 3.82 (1 H, quartet) 1.82 (3 H, singlet) 1.22 (3 H, doublet). *Anal.* ($C_{10}H_{16}ClNO$) C, H, N. The free amine was liberated from its HCl salt: ir (liquid) 2.97 (broad), 3.48, 6.24, 6.69, 6.92, 11.11 (doublet), 13.33, 14.49 μ; nmr ($CDCl_3$) δ 7.35 (5 H), 3.0 (1 H), 1.95 (3 H broad), 1.45 (3 H singlet) 0.75 (3 H doublet.).

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(3) Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and are corrected. Ir data were recorded on a Beckman IR-5 spectrophotometer, and nmr data on a Varian Associates Model A-60 spectrophotometer (TMS). Microanalysis were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F and M Model 185, The University of Kansas. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ± 0.4% of the theoretical values.

(4) A. Klages, *Ber.*, **35**, 3507 (1902).

(5) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1949).