graphed on a silica gel (Merck 7734) column, and the active component, 12-carboxyeudesma-3,11(13)-diene, was eluted with $CHCl_3$–pet ether (1.5:1). I (*ca.* 500 mg) was obtained as a colorless, low melting point compound which migrated as a single spot on tlc, and could not be crystallized: ν_{max} ($CHCl_3$) 2,900, 2,830(v.s), 1.690 (v.s), 1,615 (s) (>C=C<CO_2H), 1,435(s), 1,365(m), 968 (v.s) cm^{-1}; λ_{max} 210 mμ (ε 5,500); $[\alpha]^{25}D$ +10° (*c* 0.8, $CHCl_3$); nmr, δ 0.82 s (3 H) (C_{10}-CH_3), 1.62 broadened singlet due to allylic coupling (3 H) (C_4-CH_3), δ 5.31 m (1 H) (C_3-H), 5.66 s (1 H) and 6.32 s (1 H) (>C=CH_2) and 8.25 (1 H) (—CO_2H).

Anal. ($C_{15}H_{22}O_2$) C, 76.88; H, 9.46; mol wt, 234; found, C, 76.80; H, 9.34; M^+ 234.

The cyclohexylamine salt of I was prepared by treating I (500 mg) dissolved in butanone (10 ml), with cyclohexylamine (250 mg). The cyclohexylamine salt which separated at room temperature as a crystalline mass was crystallized once from butanone and once from Me_2CO to give colorless needles, mp 152–154°.

Anal. ($C_{21}H_{35}NO_2$) C, 75.63; H, 10.58; N, 4.20; found, C, 75.63; H, 10.65; N, 4.17.

Tetrahydro Derivative of I: 12-Carboxyeudesmane (III).—I (200 mg) was dissolved in EtOH (10 ml) and hydrogenated in the presence of Adams catalyst (PtO_2) at room temperature and atmospheric pressure. The product (III) was isolated in the usual manner, as a colorless, low-melting point compound: ν_{max} (CCl_4) 3,600 (w), 2,960, 2,910, 2,855 (s), 1,710 (s), 1,460 (m), 1,390 (m) cm^{-1}.

The Me ester, obtained as an oily colorless compound, by treating III with excess CH_2N_2, showed identical data with those reported for the Me ester of tetrahydrocostic acid[3,4]: ν_{max} (neat) 2,900 (s), 1,730 (s), 1,453, 1,380 (m), 750 (s) cm^{-1}; $[\alpha]^{25}D$ + 20° (*c* 1.0, $CHCl_3$); bp 130° (0.4 mm).

Se Dehydrogenation of I.—The acid (300 mg) was heated with Se (500 mg) at 260° under N_2 for 15 hr. The product, 1-methyl-7-ethyl naphthalene, was chromatographed on alumina column (grade I) and eluted with pet ether. The uv, the ir, and the nmr spectra of 1-methyl-7-ethyl naphthalene were identical with those obtained from the dehydrogenation product of isoalantolactone: nmr, δ 1.34 t, J = 7 cps, (3 H) due to the Me group of 7-Et, δ 2.66 s (3 H), due to 1-Me, 2.83 q, J = 7 cps, (2 H) due to the two protons of CH_2 of 7-Et.

Acknowledgment.—The authors wish to thank Mr. Gabriel Spitz for his technical assistance.

Notes

Acyl Derivatives of 5-Hydroxy-6,7-benzomorphans. Prodine Congeners

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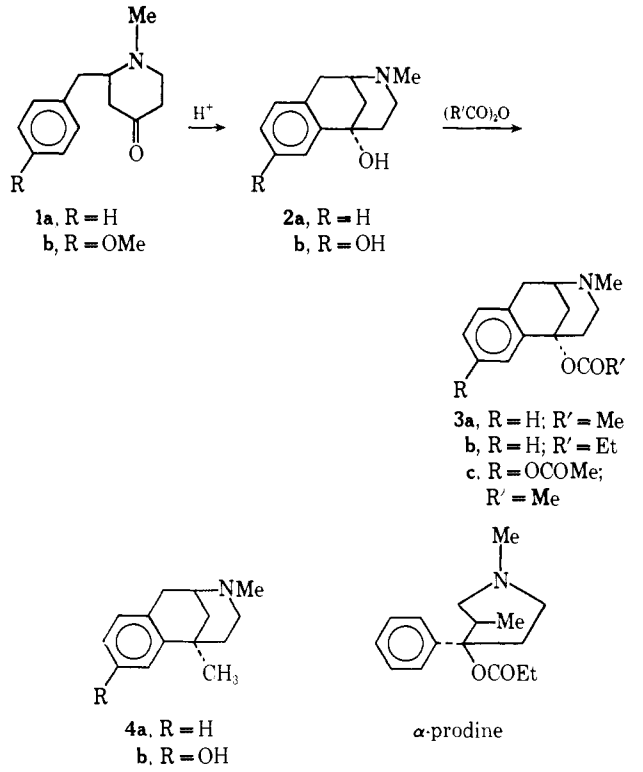
Received June 22, 1970

The synthesis of 4-piperidones (**1a,b**) from 4-methoxypyridine[2a,b] made available possible precursors of 5-hydroxy-6,7-benzomorphans (**2a,b**) acyl derivatives of which may be considered "hybrids" of the prodines[3] and 5-alkyl-6,7-benzomorphans (**4**).[4a,b] In this note are described the acid cyclization of **1a,b** to **2a,b** and some pharmacologic actions of **2a,b** and a few acyl derivatives thereof.

2-Benzyl-1-methyl-4-piperidone (**1a**)[2a] and boiling 48% HBr gave 5-hydroxy-2-methyl-6,7-benzomorphan (**2a**) in 84% yield. No 5-bromide was detected in the reaction mixture. The OH group of **2a** could not be tosylated or replaced by Cl ($SOCl_2$) or H (HI-P). In cyclizing the *p*-methoxy analog **1b** to 2′,5-dihydroxy-2-methyl-6,7-benzomorphan (**2b**), polyphosphoric acid[5] was superior to 48% HBr. Acyl derivatives **3a,b,c** were prepared from **2a,b** and the appropriate anhydride in the presence of pyridine at reflux temperature.



Pharmacology.—In Table I it is seen that the 5-OH compound **2a** has low-grade analgetic activity, and the 2′-OH relative **2b** is without effect to 100 mg/kg. Both acetylation and propionylation improve activity (compare **2a,b** with **3a,b,c**), but the degree of potency of the α-prodine or benzomorphan parents was attained only with the 5-AcO compound **3a** which is twice as potent as

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(2) (a) M. Takeda, A. E. Jacobson, K. Kanematsu, and E. L. May, *J. Org. Chem.*, **34**, 4154 (1969); (b) M. Takeda, A. E. Jacobson, and E. L. May, *ibid.*, 4158.

(3) 1,3-Dimethyl-4-phenyl-4-propionoxypiperidines; *cf.* R. A. Hardy, and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press, New York, N. Y., 1965, p 196 ff.

(4) (a) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963); (b) see H. Kugita, S. Saito, and E. L. May, *J. Med. Pharm. Chem.*, **5**, 357 (1962), for a "pethidine–benzomorphan hybrid."

(5) Boiling 48% HBr in this instance gave only 11% of **2b** and much tar.

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)[5,6] 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; *m/e* 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[5a] 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; *m/e* 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 0.56 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; *m/e* 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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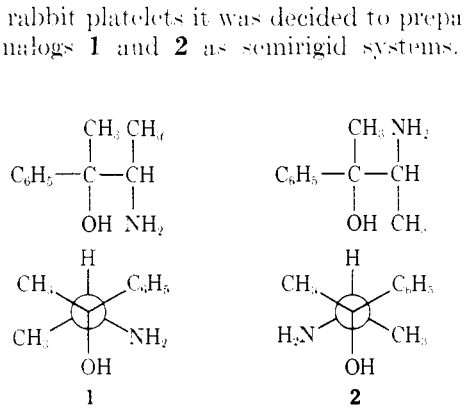
Received June 5, 1970

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).