Synthesis and Analgetic Activity of the Diastereomeric 8-Hydroxy-6,7-benzomorphans†

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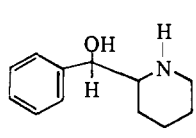
The observed activity of the recently synthesized[1] stereoisomers of phenyl-2-piperidylcarbinol (**1**) as both inhibitors of synaptosomal uptake of norepinephrine[2] and potentiators of norepinephrine effects on the rat vas deferens,‡ coupled with the recent success in the employment of conformationally rigid compounds as probes of the adrenergic receptor,[3-7] suggests that conformationally rigid analogs of **1** could prove biologically active and further define receptor requirements. The diastereomerically related 8α-hydroxy-6,7-benzomorphan (**2**) and 8β-hydroxy-6,7-benzomorphan



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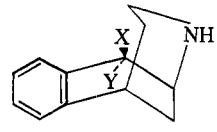


2, X = H; Y = OH
3, X = OH; Y = H

(**3**) are doubly attractive compounds since they are not only conformationally rigid analogs of **1** but also are chemically related to known analgetic agents.[8]

We wish to report the synthesis of **2** and **3** and a preliminary study of the analgetic activity of these compounds. The evaluation of the compounds as adrenergic agents will be reported later.

The synthesis of the diastereomeric 8-hydroxy-6,7-benzomorphans utilized 2-methyl-6,7-benzomorphan (**4**), prepared according to the method of Kanematsu, *et al.*,[9] as the starting material and is outlined in Scheme I.

Thus, **4** was oxidized[10] to the corresponding 3-methyl-8-oxo-6,7-benzomorphan (**5**) using Thiele's reagent. The resultant **5** upon reduction with sodium borohydride yielded only the 2-methyl-8β-hydroxy diastereomer **11** as demonstrated by nuclear magnetic resonance spectroscopy ($J_{H_{8\alpha},H_1}$ = 6.5 Hz).§ N-Demethylation of **5** was accomplished by a Von Braun reaction[11] to afford 8-oxo-6,7-benzomorphan (**6**) which was converted to the 2-tosyl derivative **7**.[12] Reduction of **7** with sodium borohydride[13] gave exclusively 2-tosyl-8β-hydroxy-6,7-benzomorphan (**8**) ($J_{H_{8\alpha},H_1}$ = 6.0 Hz) which was N-detosylated with lithium aluminum hydride[14] to the desired **3** ($J_{H_{8\alpha},H_1}$ = 6.0 Hz). Conversion of **8** to the 8β-tosyloxy derivative **9** was accomplished with tosyl chloride–pyridine and the tosyloxy group was displaced with refluxing water–acetone affording 2-tosyl-8α-hydroxy-6,7-benzomorphan (**10**, $J_{H_{8\beta},H_1}$ = 1.0 Hz). The *N*-tosyl group was again removed with lithium aluminum hydride[14] giving the desired **2** ($J_{H_{8\beta},H_1}$ = 1.0 Hz).

Experimental Section#

2-Methyl-6,7-benzomorphan (4) was prepared according to the method of Kanematsu, *et al.*[9] **4**·HCl had mp 222–223.5° (lit.[15] 224–225°).

2-Methyl-8-oxo-6,7-benzomorphan (5) was prepared according to the method of Nishimura.[10] **5**·picrate had mp 194–194.5° (lit.[15] 194°). The free amine was regenerated by chromatographing **5**·picrate over Al_2O_3 (60 g, 26 × 2 cm, Woelm neutral), yield 3.46 g (72%).

2-Methyl-8β-hydroxy-6,7-benzomorphan (11). With ice cooling a solution of $NaBH_4$ (0.450 g, 12 mmol) in H_2O (9 ml) and MeOH (36 ml) was added to a stirred solution of **5** (0.47 g, 2.3 mmol) in MeOH (30 ml). The reaction mixture was allowed to come to room temperature and stirred for 24 hr. The solution was made basic with 1 *N* NaOH, the solvent was removed, and H_2O (20 ml) was added. This solution was extracted with $CHCl_3$ and dried ($MgSO_4$) and the solvent was removed. The residue was treated with HCl gas in ether. The resultant **11**·HCl was recrystallized from EtOH–ether: yield 0.315 g (56.2%); mp 219–220°.

8-Oxo-6,7-benzomorphan (6).[11] **2-Cyano-8-oxo-6,7-benzomorphan (12).** To a solution of **5** (1.07 g, 5 mmol) in $CHCl_3$ (10 ml) was added with stirring over a 20-min period a solution of BrCN (0.841 g, 8 mmol) in $CHCl_3$ (5 ml). The resultant solution was refluxed for 2.5 hr, cooled, extracted with 15% HCl (4 × 20 ml), washed with H_2O (2 × 25 ml), and dried ($MgSO_4$). The solvent was removed under vacuum leaving an orange oil: yield 0.86 g; ir (neat) 2250 cm^{-1} (CN). **8-Oxo-6,7-benzomorphan (6).** The cyano intermediate was refluxed in 6% HCl (15 ml) for 12 hr, cooled, basified with concentrated NH_4OH, extracted with $CHCl_3$ (4 × 15 ml), and dried ($MgSO_4$). The solvent was removed under vacuum leaving a brown oily residue, yield 0.695 g, which showed two major peaks in the vpc. Two compounds could be distinguished *via* tlc using silica gel GF_{254} as the adsorbent, Me_2CO as the solvent, and I_2 as the developer. The reaction mixture (0.695 g) was chromatographed on a dry-packed[16] silica gel G column (110 g) eluting with Me_2CO and collecting 15-ml fractions. The front running yellow fraction was identical with **5**, yield 0.31 g. The second, orange fraction was identified as **6** plus a minor impurity (vpc ratio about 30:1), yield 0.36 g (51% based on recovered starting material).

2-Tosyl-8-oxo-6,7-benzomorphan (7). A solution of **6** (1.48 g, 8 mmol)** in H_2O (100 ml) was tosylated according to the method of Scheifele and Deter[12] and recrystallized from MeOH: yield first crop 1.36 g, mp 159.5–160.5°; yield second crop 0.33 g, mp 157.5–159° (overall 63.3%).

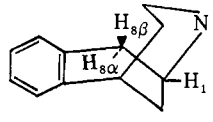
2-Tosyl-8β-hydroxy-6,7-benzomorphan (8). $NaBH_4$ (0.100 g, 2.6 mmol) was added portionwise to a suspension of **7** (0.836 g, 2.5 mmol) in 95% ETOH (5 ml).[13] The stirred mixture was warmed to 50° on a water bath for 30 min, allowed to stir 12 hr at room temperature, and poured into crushed ice (about 20 g). The mixture was made acidic with HCl, extracted with $CHCl_3$ (4 × 20 ml), washed with 5% Na_2CO_3, and dried ($MgSO_4$). The solvent was removed under vacuum leaving a white solid which was recrystallized from benzene–petroleum ether (bp 30–60°): yield 0.736 g (84%); mp 137.5–138.5°. *Anal.* ($C_{19}H_{21}O_3NS$) C, H, N, S.

8-β-Hydroxy-6,7-benzomorphan (3).[16] A mixture of **8** (0.500 g, 1.5 mmol), $LiAlH_4$ (0.370 g), and THF (12 ml) was heated under reflux for 40 hr, cooled, and decomposed by adding wet ether followed by H_2O. The solid was removed *via* filtration and re-

†Taken in part from the dissertation presented by J. J. Fauley, Sept 1971, to the Graduate School of the Ohio State University, Columbus, Ohio, in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

‡C. Buckner and P. N. Patil, unpublished results, The Ohio State University, 1971.

§The relative configuration of 8-hydroxy-6,7-benzomorphan derivatives was assigned on the basis of nuclear magnetic resonance analysis. The Karplus equation suggests that the coupling constant between vicinal protons is dependent on the dihedral angle and reaches maxima at dihedral angles of 0 and 180° and a minimum at 90°. In 8α-substituted 6,7-benzomorphans the dihedral angle between the 8β proton ($H_{8\beta}$) and the vicinal proton (H_1) is about 90°, whereas in 8β-substituted 6,7-benzomorphans the dihedral angle between the 8α proton ($H_{8\alpha}$) and the vicinal proton (H_1) is about 30°. Therefore $J_{8\alpha,1}$ would be expected to be larger than $J_{8\beta,1}$.



#Melting points were determined in open capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 257 or Model 237 grating spectrophotometer. The nmr spectra were recorded with a Varian A-60A nmr spectrometer at 60 MHz. Vapor-phase chromatographs were taken using an F & M Model 402 gas chromatograph equipped with flame ionizing detector and glass columns. Elemental analyses were determined by Alfred Bernhardt Micranalytical Laboratory, Fritz-Pregl-Strasse 14-16, West Germany.

**Contained the impurity which could not be removed.

Scheme I

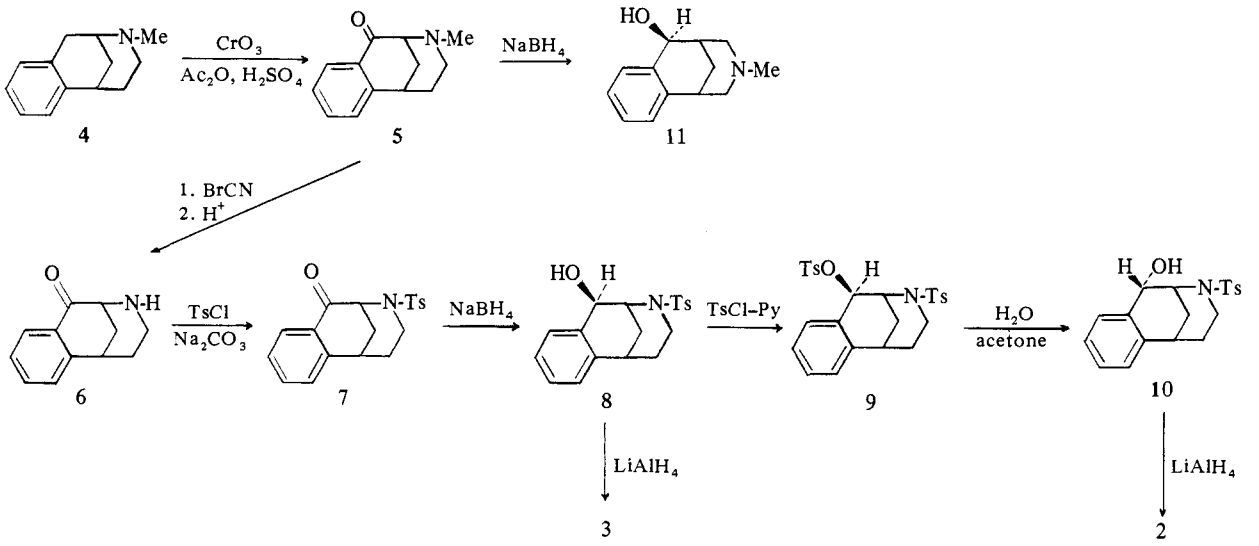


Table I. Analgetic ED_{50} Values in the Mouse Hot Plate Assay

Compound	ED_{50}, mg/kg sc
(±)-8α-Hydroxy-6,7-benzomorphan·HCl (2)	56.5 (42.2–75.8)
(±)-8β-Hydroxy-6,7-benzomorphan·HCl (3)	13.7 (10.6–17.5)
(±)-2-Methyl-8β-hydroxy-6,7-benzomorphan·HCl (11)	Inactive
Codeine·HCl	7.5

peatedly washed with ether. The ether phase was dried ($MgSO_4$). The solvent was colncentrated to about 20 ml and acidified with a saturated solution of HCl–ether. The resultant **3**·HCl was recrystallized from Me_2CO (2)–MEOH (1)–ether: yield 0.101 g (36.3%); mp 284–286° dec; free base mp 114–115°; nmr ($CDCl_3$) δ 4.76 (d, 1, $H_{8\alpha}$, J_{H_8,H_1} = 6.0 Hz). *Anal.* ($C_{12}H_{16}NOCl$) C, H, N.

2-Tosyl-8β-tosyloxy-6,7-benzomorphan (9).[17,18] To a solution of 8 (0.300 g, 0.9 mmol) in pyridine (3 ml), TsCl (0.330 g, 1.7 mmol) was added. The solution was allowed to stand at room temperature for 48 hr and then poured into ice–H_2O (60 ml) and stirred for 1 hr. The resultant white 9 was removed by filtration and dried over P_2O_5: yield 0.410 g (94.3%); mp 136–140°.

2-Tosyl-8α-hydroxy-6,7-benzomorphan (10).[19] A mixture of 9 (0.704 g, 1.4 mmol) and H_2O (1)–acetone (1) (350 ml) was heated to effect solution. The solution was refluxed for 6 hr, cooled, concentrated under vacuum, extracted with $CHCl_3$ (4 × 100 ml), washed with 5% Na_2CO_3 (200 ml), and dried ($MgSO_4$). The solvent was removed under vacuum leaving an oily residue which was crystallized by dissolving in benzene, adding petroleum ether (bp 30–60°) to the cloud point, and seeding: yield 0.434 g (98.5%); mp 132.5–135.5°.

8α-Hydroxy-6,7-benzomorphan (2).[14] The conditions were identical with those used for 3 above. The **2**·HCl was recrystallized from acetone (2)–MeOH (1)–ether: yield 0.108 g (32%); mp 218–220° dec; nmr (D_2O) δ 4.45 (d, 1, $H_{8\beta}$, $J_{H_{8\beta},H_1}$ = 1.0 Hz). *Anal.* ($C_{12}H_{16}NOCl$) C, H, N.

Biological. The analgetic activities of compounds 2, 3, and 11 were determined in the laboratories of Dr. Everette L. May, using the hot plate method[20] as modified by Jacobson and May,[21] and are given in Table I.

We found these activities to be quite interesting since they are not what one would expect on the basis of classical structure–action relationships in this area. As pointed out in the introduction, these compounds were originally made as rigid analogs of compounds affecting the autonomic nervous systems. We were, therefore, primarily interested in the secondary amines. While we were not surprised to find a difference in analgetic activity between the α and β racemates, we expected that the tertiary amine would be a more potent analgetic than the secondary amine. As indicated by the data, this was not the case.

We are pursuing this line of investigation in order to determine whether the *N*-methyl compound or its derivatives possesses analgetic antagonist activity. All compounds are also being resolved so that testing can be done on the enantiomers rather than the racemates.

References

(1) J. J. Fauley and J. B. LaPidus, *J. Org. Chem.*, 36, 3065 (1971).
(2) E. D. Hendley, S. H. Snyder, J. J. Fauley, and J. B. LaPidus, *Pharmacologist*, 13, 203 (1971).
(3) E. E. Smissman and W. H. Gastrock, *J. Med. Chem.*, 11, 860 (1968).
(4) E. E. Smissman and G. S. Chappell, *ibid.*, 12, 429 (1969).
(5) E. E. Smissman and R. T. Borchardt, *ibid.*, 14, 377 (1961).
(6) E. E. Smissman and R. T. Borchardt, *ibid.*, 14, 383 (1971).
(7) W. L. Nelson and D. D. Miller, *ibid.*, 13, 807 (1970).
(8) E. L. May and L. T. Sargent, "Analgetics," deStevens, Ed., Academic Press, New York, N. Y., 1965, p 145.
(9) K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, 12, 405 (1969).
(10) T. Nishimura, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 713.
(11) A. Pohland and H. R. Sullivan, U. S. Patent 3,342,824 (1967).
(12) H. J. Scheifele and D. F. Deter, ref 10, p 34.
(13) M. A. Rehman and G. R. Proctor, *J. Chem. Soc.*, 58 (1967).
(14) M. Kulka and R. H. Manske, *J. Org. Chem.*, 17, 1561 (1952).
(15) K. Kanematsu, R. T. Parfitt, A. E. Jacobson, J. H. Ager, and E. L. May, *J. Amer. Chem. Soc.*, 90, 1064 (1968).
(16) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).
(17) E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, 86, 485 (1964).
(18) R. B. Bates, G. Buchi, T. Matsuura, and R. R. Shaffer, *ibid.*, 82, 2327 (1960).
(19) J. Kochi and G. Hammond, *ibid.*, 75, 3443 (1953).
(20) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, 107, 385 (1953).
(21) A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965).