Interesting Pharmacological Properties of the Optical Isomers of α-5,9-Diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan

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Optical resolution of α-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (II) has been effected with *d*-mandelic or (+)-3-bromo-8-camphorsulfonic acid. The (−) isomer, almost twice as potent (equivalent to morphine) analgetically as the racemate as expected, is, surprisingly, also a mild antagonist to some of morphine's effects. Equally unexpected was the codeine-like analgetic activity and physical dependence capacity observed for the (+) isomer. As racemate II has been found to have little or no physical dependence capacity, there must be some antagonism between the two antipodes.

In 1959,[1] we reported that α-(−)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan contains all of the analgetic activity of, and is much less toxic than, the parent racemate (I). Since then (−)-I has been tested extensively. Although it is nearly equivalent to morphine in relieving postoperative pain, it has little capacity to support a morphine dependence in rhesus monkeys or man and generally shows an unusual separation of morphine-like effects.[2] These results have prompted us to prepare the enantiomers of α-(±)-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (II),[3] a clinically effective[2] analgesic of low physical dependence capacity in monkeys.[2]

Racemate II could be separated into its antipodes with *d*-mandelic acid (ethanol–acetone medium) in which case the *d*-mandelate salt of (+)-II crystallizes first. When the less satisfactory (+)-3-bromo-8-camphorsulfonic acid in water was used, the salt of (−)-II was isolated first.

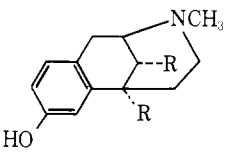
Pharmacology.—As shown in Table I, (−)-II is equivalent to morphine and nearly twice as effective as the racemate, (±)-II,[4] in analgetic atcivity.[4] The *dextro* isomer, (+)-II, proved to be codeine-like, not only as an analgetic (mice) but also in its (intermediate) capacity to support a morphine dependence in monkeys, in contrast to (+)-I and (+) isomers in the morphinan series which are inert in animals in these respects. Furthermore, administration of 0.5–32 mg/kg of (−)-II to morphine-dependent monkeys withdrawn for 12–14 hr failed completely to suppress abstinence; doses of 3 mg/kg and 32 mg/kg to nonwithdrawn, morphine-dependent monkeys actually precipitated abstinence signs of intermediate intensity (nalorphine-like antagonism). The dose–response curve is flat, and it is estimated that (−)-II is about one-twentieth as potent as nalorphine.[5] Apparently, too, (−)-II is antagonizing some of the effects of (+)-II, since (±)-II, like (−)-II, has no physical dependence capacity.[2,5] Further studies with (−)-II are in progress.

TABLE I

ANALGETIC ACTIVITY, ACUTE TOXICITY, AND PHYSICAL DEPENDENCE CAPACITY (PDC)[2,5] OF α-5,9-DIETHYL-2-METHYL-6,7-BENZOMORPHAN AND ITS ANTIPODES

Compd	ED_{50}[a]	LD_{50}[a]	PDC[b]
(±)-II·HCl	2.1	423	No[c]
(−)-II·HCl	1.2		No[d]
(+)-II·HCl	7.9	273	Intermediate[e]
Morphine sulfate	1.2	576	High[f]
Codeine·HCl	7.5	270	Intermediate[g]

[a] Expressed in milligrams per kilogram (mice, subcutaneous administration); *cf.* N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953), and A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965). [b] See ref 2. [c] No suppression of morphine abstinence symptoms from 0.5–16 mg/kg and only partial suppression at 24–40 mg/kg. A dose of 60 mg/kg caused convulsions. [d] No suppression from 0.5–32 mg/kg. Intermediate abstinence signs were precipitated in dependent, nonwithdrawn monkeys. [e] No suppression at 2–4 mg/kg, very slight suppression at 8–16, and almost complete suppression for 5 hr at 32 mg/kg. [f] Stabilizing (complete suppression) dose, 3.0 mg/kg. [g] Similar to (+)-II·HCl.



I, R = Me
II, R = Et

Experimental Section

Melting points (capillary) were taken with total-immersion thermometers.

Resolution of α-(±)-5,9-Diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (II). A. With *d*-Mandelic Acid.—*d*-Mandelic acid (0.7 g),[6] 1.0 g of (±)-II,[3] 3 ml of absolute ethanol, and 3 ml of acetone were heated to solution. On cooling, finally at 0° for 7–15 hr, 0.7 g (90%) of needles or slim rods (**d-mandelate salt of (+)-II**), mp 194–197°, was collected and washed with 5–10 ml of acetone. The analytical sample (from methanol–acetone) melted at 198–200°.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.6; H, 8.0. Found: C, 72.7; H, 8.1.

The **base of (+)-II** was prepared by dissolving the *d*-mandelate salt in a little hot methanol and adding an equal volume of 5% NH_4OH. This base crystallized from acetone or acetone–alcohol in thin prisms, mp 217–219°, $[\alpha]^{24}D$ + 59.0° (*c* 1.07, 95% EtOH).

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7; H, 9.7. Found: C, 78.9; H, 9.7.

The **hydrochloride of (+)-II**, prepared by passing HCl into an acetone solution (containing a little ethanol) of (+)-II base, crystallized from absolute ethanol–ether in needles, mp 165–168° (froth), $[\alpha]^{21}D$ +36.8° (*c* 1.09, H_2O). Carbon, hydrogen, and

(1) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

(2) N. B. Eddy and E. L. May, "Synthetic Analgesics, Part II(B), 6,7-Benzomorphans," Pergamon Press, London, 1966, p 138 ff.

(3) J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962).

(4) In postoperative pain, 20 mg of (±)-II is slightly superior to 10 mg of morphine.[2]

(5) We are indebted to Drs. M. H. Seevers and J. Villareal of the Department of Pharmacology, University of Michigan, for these dependence studies (private communication).

(6) Aldrich Chemical Co., Inc.

chlorine analyses were indicative of 0.5 mole of solvate ethanol which was lost on melting as shown by the following data.

Anal. Calcd for $C_{17}H_{26}ClNO$: C, 69.0; H, 8.9. Found: C, 68.8; H, 8.8.

The filtrate and acetone washings (combined) from the 0.7 g of needles (above), left at 0° overnight, gave 0.5–0.6 g (64–78%) of prisms (**d-mandelate salt of (−)-II**), mp 190–193°[7] which, recrystallized from methanol–acetone, melted at 193–194°.

Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.6; H, 8.0. Found: C, 72.8; H, 8.2.

Base (−)-II, prepared as (+)-II, melted at 217–219°, $[\alpha]^{25}D$ −61.5° (*c* 0.55, 95% EtOH).[8]

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7, H, 9.7. Found: C, 78.7; H, 9.8.

The **hydrochloride of (−)-II** melted at 167–170° (froth), $[\alpha]^{22}D$ −37.4° (*c* 0.52, H_2O). It showed a correct analysis for the anhydrous material after melting.

(7) Occasionally, especially if the cooling time is 5 hr or less, the yield of (+)-II *d*-mandelate is only 0.5 g. If so, 0.9 g of a mixture, mp 170–190°, crystallizes from the filtrate and acetone washings. This mixture is dissolved in 2 ml of hot methanol and treated with 10 ml of acetone. Concentration of the solution to about half-volume and cooling at −5° for 1.5 hr gives 0.7 g (90%) of pure *d*-mandelate salt of (−)-II, mp 191–193°.

(8) Y. K. Sawa and J. Irisawa, *Tetrahedron*, **21**, 1129 (1965), prepared (+)-II from sinomenine and (−)-II from thebaine. We thank Dr. Sawa for sending us specimens of his bases for direct comparison.

Anal. Calcd for $C_{17}H_{26}ClNO$: C, 69.0; H, 8.9. Found: C, 68.8; H, 8.8.

B. With (+)-3-Bromo-8-camphorsulfonic Acid.[9] A mixture of 2.5 g of (±)-II, 2.7 g of the ammonium salt of (+)-3-bromo-8-camphorsulfonic acid,[10] 0.85 ml of concentrated HCl, and 75–100 ml of water was heated to solution, which was treated with Norit. The filtrate was cooled slowly to room temperature where it was kept for 24 hr giving 1.9 g (71%) of heavy prisms, mp 238–241°. These were converted to 0.85 g of pure (−)-**II base** essentially as described above.

The filtrate from the 1.9 g of prisms was made basic with NH_4OH to give 1.3 g of solid. It was digested with 50–60 ml of boiling acetone. Filtration gave 0.3 g of (±)-II. On concentration of the filtrate to 10–15 ml. and cooling, 0.6 g of (+)-II, mp 212–216°, was obtained.

Acknowledgment.—Mrs. Louise Atwell of this laboratory performed the analgesic tests. Rotations were performed by Mrs. Evelyn Peake and microanalyses by Miss Paula Parisius both also of this laboratory.

(9) Initial experiments with this agent were performed by Dr. S. E. Fullerton; see S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(10) Sold by the Aldrich Chemical Co. as *d*-α-bromocamphor-π-sulfonic acid ammonium salt.

Central Nervous System Depressants. I. 1-Aminoalkyl-3-aryl Derivatives of 2-Imidazolidinone,[1a-c] 2-Imidazolidinethione, and Tetrahydro-2(1H)-pyrimidinone[1d]

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1-Aminoalkyl-3-aryl-2-imidazolidinones exhibit potent central nervous system depressant activity when tested in laboratory animals. Representative 1-aminoalkyl-3-aryl-2-imidazolidinethiones were less active and 1-aminoalkyl-3-aryltetrahydro-2(1H)-pyrimidinones were inactive in these tests. Several *m*-halo derivatives have been of particular interest and the compound, 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone hydrochloride (imidoline), has been chosen for evaluation in man.

In an earlier publication,[2] we described the preparation of a series of 1-aryl-3-methyl-2-imidazolidinones. The observation that some of these compounds exhibited low-potency CNS-depressant activity prompted us to extend this research to other 2-imidazolidinone derivatives and led to the discovery that many 1-aminoalkyl-3-aryl-2-imidazolidinones are potent CNS depressants.

The preparation of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone (I) and 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinethione (II) is illustrated in Chart I. The reaction of 2-bromoethylamine with *m*-chloroaniline gave N-(*m*-chlorophenyl)ethylenediamine (III), and further reaction with potassium cyanate resulted in a 55% overall yield of [2-(*m*-chloroanilino)ethyl]urea (IV). Cyclization to 1-(*m*-chlorophenyl)-2-imidazolidinone (V) was effected by heating IV in an oil bath at 220°. Compound V could also be prepared directly from III by reaction with N,N′-carbonyldiimidazole. Alkylation to I was accomplished by treating V in diglyme with sodium hydride and 2-chloroethyl-N,N-dimethylamine. Compound I was also prepared by reaction of 7-(*m*-chlorophenyl)-1,1-dimethyldiethylenetriamine (VI) with N,N′-carbonyldiimidazole. Compound VI was prepared from N,N-dimethylethylenediamine and N-(2-bromoethyl)-*m*-chloroaniline. When I was heated with phosphorus pentasulfide in xylene, II was obtained in 60% yield.

Other 2-imidazolidinone, 2-imidazolidinethione, and tetrahydro-2(1H)-pyrimidinone derivatives were similarly prepared. Details are given in the Tables I–VII and in the Experimental Section.

Pharmacological Methods.—The compounds described in this paper were screened by the following tests in an effort to select agents having an interesting or unique action on the central nervous system.

A. Ataxia (reduced rod-walking ability).—The agents studied were administered intraperitoneally in a 2% starch vehicle to groups of six mice at three or more graded dose levels. At 15- and 30-min intervals after treatment, each animal was placed on the midpoint of a horizontal steel rod (1.55 cm in diameter and about 6 dm in length), positioned 45.7 cm above the surface of the table, and forced to walk toward a platform at either end of the rod. The criterion of inability to perform this act was consistent slipping

(1) (a) American Cyanamid Co., Belgian Patent 623,942 (March 27, 1963); (b) Farbenfabriken Bayer, French Patent 2288M (Feb 17, 1964); (c) W. B. Wright and H. J. Brabander, U. S. Patent 3,196,152 (July 20, 1965); (d) presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4051 (1961).