Separation of Morphine-like Effects by Optical Resolution. Levo Isomers as Strong Analgetics and Narcotic Antagonists

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l- and *d*-mandelic acids have been used in combination to separate enantiomers of α-(±)-5-methyl- (Ic) and -5-ethyl-2′-hydroxy-2-methyl-6,7-benzomorphans (Id); *d*-10-camphorsulfonic and *d*-mandelic acids were employed for the α-(±)-2,9-dimethyl-2′-hydroxy-5-propyl analog (Ie). In every instance, the levo isomers were twice as potent, analgetically, as the racemates but would not suppress abstinence symptoms in morphine-dependent rhesus monkeys; in fact, they were nalorphine-like. The dextro isomers were weak analgetics (codeine-like or less active), but, curiously, had low, intermediate, or high physical dependence capacity in monkeys, similar to the pattern seen with the dimethyl and diethyl homologs reported.[1b,2]

During the last several years, it has been shown that α-(−)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan [(−)-Ia][1] is practically the equivalent of morphine in postoperative pain and in producing morphine-like effects in postaddicts but is little better than a placebo in supporting a morphine dependence in monkey or man.[2] More recently, (−)-Ia and the analgetically equipotent diethyl homolog, (−)-Ib, both of low toxicity, have been found to elicit negligible physical dependence properties in rhesus monkeys by either chronic administration or in single-dose experiments;[2,3] in fact they will precipitate or exacerbate abstinence signs in monkeys physically dependent on morphine.[4] Equally intriguing is that the much less potent (codeine-like) (+)-Ib will actually substitute for morphine to an intermediate degree, although (±)-Ib will not. All these findings suggested a nalorphine-like antagonism for the levo isomers of Ia and Ib, the possibility of complete separation of analgetic activity and dependence liability of the morphine type, and thus the hope of discovering the near-ideal analgetic agent. Consequently, we have resolved three other compounds of this series, the 5-methyl (Ic), 5-ethyl (Id), and α-5-propyl-9-methyl (Ie) analogs, and have subjected these optical pairs to similar pharmacological studies. The results are reported below.

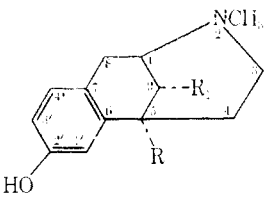
Racemates Ic and Id were each optically resolved with a combination of *d*- and *l*-mandelic acids using methanol, acetone, or methanol–acetone as solvent media. Compound Ie could best be separated into its antipodes by first utilizing *d*-10-camphorsulfonic acid [for (+)-Ic], then *d*-mandelic acid for the (−) isomer. The yields were 50–60% calculated from pure base obtained.

Pharmacology.—In Table I are presented analgetic activities, physical dependence capacities,[2-4] and antagonistic potencies for Ia–e optical isomers along with similar data for morphine and codeine. Like α-(−)-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan [(−)Ib], α-levo isomers Ia (5,9-dimethyl), Ic (5-methyl), Id (5-ethyl), and Ie (5-propyl-9-methyl), all morphine-like or stronger in analgetic potency, uniformly have no capacity to substitute for morphine in dependent monkeys and show varying degrees of antagonistic activity. That is, they will precipitate abstinence symptoms in nonwithdrawn, morphine-dependent monkeys and will intensify these symptoms in dependent monkeys deprived of their regular doses of morphine. This property of antagonism is nalorphine-like in all respects and ranges from one-fifth (for Ie) to one-fiftieth (for Ic) the potency of nalorphine. This is in sharp contrast to (−)-morphine and (−)-codeine which are rated high and intermediate, respectively, in physical dependence capacity and evince only agonist properties in this test.

The dextro isomers of Ia–e, of much lower analgetic activity (codeine-like or weaker), with one exception (Ia), *will* relieve signs of abstinence in dependent, withdrawn monkeys. In one instance [(+)-Ie] almost complete substitution is seen; this *dextro* compound, of lower analgetic potency than codeine, is therefore rated high in physical dependence capacity.[2-4]

The racemates corresponding to Ia–e have shown low or no physical dependence capacity[2] suggesting antagonism between dextro and levo isomers in this series. Optical resolution has, therefore, consistently resulted in a favorable separation of morphine-like effects in certain animal species.

Compounds (−)-Ib, (−)-Id, and (−)-Ie are worthy candidates for human trials.



Ia, R = R_1 = Me
b, R = R_1 = Et
c, R = Me; R_1 = H
d, R = Et; R_1 = H
e, R = Pr; R_1 = Me

Experimental Section

Analytical values were within ±0.3% of the theoretical values. Rotations in 95% EtOH (free bases and mandelate salts) and H_2O (HCl salts) were taken on a Perkin-Elmer 141 polarimeter, concentrations 1.0–1.4 g/100 ml of solution. Melting points (capillary) are corrected.

(1) (a) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959); (b) *J. Med. Chem.*, **9**, 851 (1966).

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

(3) G. A. Deneau, J. E. Villarreal, and M. H. Seevers, Addendum 2, Minutes of the 28th and 30th Meetings of the Committee on Problems of Drug Dependence, 1966, 1968; and J. E. Villarreal, personal communication.

(4) J. E. Villarreal, *Advan. Mental Sci.*, in press.

Resolutions. A. Ic.—(±)-Ic[5] (2.2 g), 1.8 g (1.15 equiv) of *l*-mandelic acid (Aldrich Chemical Co., Inc.), 10 ml of Me_2CO, and 1 ml of MeOH were heated to solution and left at 25° for 3 hr and at −5° for 18 hr; yield 1.7 g, mp 175–185°. This white solid, recrystallized from MeOH, gave 1.2 g of (−)-**Ic** ***l*-mandelate,** mp 190–192°, which in MeOH–aqueous NH_3 yielded 0.65 g (60%) of (−)-Ic, mp 211–212°, $[\alpha]^{20}D$ −72.5°, after a recrystallization from Me_2CO or MeOH [*Anal.* ($C_{14}H_{19}NO$) C, H]; **hydrochloride** (from absolute EtOH–HCl then recrystallization from absolute EtOH), mp 262–265°, $[\alpha]^{20}D$ −49.6°. *Anal.* ($C_{14}H_{20}ClNO$) C, H.

The combined filtrates (from the 1.7 g of *l*-mandelate and from recrystallization of this 1.7 g) were concentrated to 2–3 ml and treated with excess aqueous NH_3 to give 1.5 g of base mixture. This material, 1.2 g of *d*-mandelic acid (Aldrich), 6 ml of Me_2CO, and 2 ml of MeOH were warmed to solution, cooled, and kept at 5° for 1 hr to give 1.7 g of white solid, mp 184–188°. One recrystallization from 5–6 ml of MeOH gave 1.3 g of (+)-**Ic** ***d*-mandelate,** mp 191–192.5°, in turn converted to 0.7 g (63%) of (+)-**Ic,** mp 209–210.5°, $[\alpha]^{20}D$ +74.5°, after a recrystallization from Me_2CO [*Anal.* ($C_{14}H_{19}NO$) C, H]; **hydrochloride** (from MeOH–Me_2CO), mp 262–265°, $[\alpha]^{20}D$ +49.1°.

B. Id.—Racemate Id[6] (5.0 g), 3.3 g of *d*-mandelic acid, 13 ml of absolute EtOH, and 5 ml of Me_2CO were heated to solution, filtered, and left at 25° overnight to give 1.7 g (41%) of white solid which was recrystallized from MeOH–Me_2CO (4:15 ml). Cooling to 0° gave 0.9 g of (−)-**Id** ***d*-mandelate,** mp 170.5–172°, $[\alpha]^{20}D$ +25.1°. *Anal.* ($C_{23}H_{29}NO_4$) C, H. It gave 0.5 g of (−)-Id from aqueous NH_3; mp 208–210°, $[\alpha]^{20}D$ −49.7°. *Anal.* ($C_{15}H_{21}NO$) C, H. The hygroscopic **hydrochloride** (from ethereal HCl) was recrystallized from MeOH–Me_2CO and carefully dried for 3 hr at 100° *in vacuo* just prior to analysis; mp 186.5–188.5°, sealed capillary. *Anal.* ($C_{15}H_{22}ClNO$) C, H.

The combined filtrates (from isolation and recrystallization of (−)-Id *d*-mandelate) were concentrated to 7–10 ml, made basic with dilute NH_4OH, diluted with H_2O, and cooled to give 4.3 g of a mixture of (±)- and (+)-Id. This mixture, 2.8 g of *l*-mandelic acid, 8 ml of MeOH, and 35 ml of Me_2CO, was warmed to solution and filtered and the filter was washed with Me_2CO. The combined filtrate and washings were distilled to half-volume, diluted (Me_2CO), and again distilled to half-volume. Addition of Me_2CO to 75 ml and refrigeration gave a white solid which was recrystallized from absolute EtOH–Me_2CO (11:25 ml) giving 1.3 g (31%) of (+)-**Id** ***l*-mandelate,** mp 170.5–171.5°, $[\alpha]^{20}D$ −21.3°. *Anal.* ($C_{23}H_{29}NO_4$) C, H. The (+)-**Id base** melted at 209.5–211.5° and had $[\alpha]^{24}D$ +51°. *Anal.* ($C_{15}H_{21}NO$) C, H. The **hydrochloride** had mp 188–189° and was hygroscopic like the enantiomer. *Anal.* ($C_{15}H_{22}ClNO$) C, H. (±)-Id was recovered as in the case of Ic.

C. Ie.—Absolute EtOH (20 ml), 2.0 g of (±)-Ie,[7] and 2.0 g of *d*-10-camphorsulfonic acid (Eastman) were heated to solution and left at room temperature for 6 hr to give 1.3 g of square plates, mp 245–247° after filtration and washing with cold EtOH. This salt yielded 0.65 g (65%) of (+)-Ie (from aqueous MeOH–NH_3), mp 235–237°, $[\alpha]^{20}D$ +69.8°, after a recrystallization from MeOH. *Anal.* ($C_{17}H_{25}NO$) C, H, N. The **hydrochloride** (from *i*-PrOH–Et_2O) had mp 166–169°, $[\alpha]^{20}D$ +50.8°. *Anal.* ($C_{17}H_{26}ClNO$) C, H, Cl.

The filtrate and washings from the 1.3 g of square plates above were made basic with NH_4OH and diluted with an equal volume of H_2O. Cooling gave 1.2 g of (−)- and (±)-Ie which, with 0.8 g of *d*-mandelic acid, was heated to solution in 5 ml of Me_2CO. After 6 hr at 25°, 1.1 g of (−)-**Ie mandelate,** mp 209–211°, was filtered and converted to 0.65 g (65%) of (−)-**Ie,** mp 236–238°, $[\alpha]^{20}D$ −70.0°, with MeOH–dilute NH_4OH. *Anal.* ($C_{17}H_{25}NO$) C, H, N. The **hydrochloride** melted at 166–169°, $[\alpha]^{20}D$ −49.3°. *Anal.* ($C_{17}H_{26}ClNO$) C, H.

TABLE I

PHARMACOLOGIC PROPERTIES OF 6,7-BENZOMORPHAN OPTICAL ISOMERS

Compd[a]	ED_{50}[b] (mice), mg/kg sc	Physical dependence capacity[c]	Antagonistic act.[c]
(−)-Ia	0.9	No[d]	0.02–0.033 nalorphine
(+)-Ia	Inactive	No	No
(−)-Ib	1.2	No[e]	0.1 nalorphine
(+)-Ib	7.9	Intermediate	No
(−)-Ic	1.8	No[f]	0.02 nalorphine
(+)-Ic	22.9	Very low	No
(−)-Id	0.6	No[g]	0.025–0.05 nalorphine
(+)-Id	21.8	Low	No
(−)-Ie	0.8	No[h]	0.2 nalorphine
(+)-Ie	12.3	High	No
Morphine	1.2	High	No
Codeine	7.5	Intermediate	No

[a] Administered as HCl salts in water except for morphine (as sulfate). [b] *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). [c] *Cf.* ref 2–4. [d] From 0.5–8 mg/kg. [e] From 0.5–32 mg/kg. [f] From 1.0–20 mg/kg. [g] From 2–16 mg/kg. [h] From 0.5–2 mg/kg.

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(7) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963); C. F. Chignell, J. H. Ager, and E. L. May, *ibid.*, **8**, 235 (1965).