before, and the product of evaporation was purified as in Table IV.

Acknowledgment. We thank Mr. C. H. Cashin, Miss A. Kitchen, and colleagues of the Pharmacology Department for the biological results. We are grateful to Dr. D. M. Rackham, Mr. R. C. Harden, and Mr. R. M. Roberts for the spectral determinations and Mr. D. N. B. Mallen and colleagues for mass spectra.

References and Notes

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Optical Resolution of Some Homobenzomorphan Derivatives and Their Pharmacological Properties

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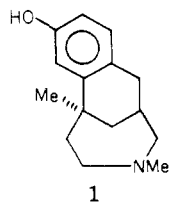
Racemic 1,4-dimethyl- (1), 1,4,12α-trimethyl- (2), and 1,4,12β-trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (3) have been optically resolved. The analgesic potency and physical-dependence capacity of the optical isomers and their racemic parents were determined. The levo isomers of compounds 2 and 3 were analgesically much more potent than the dextro isomers and were equipotent with morphine. Optical resolution gave no effect on the analgesic activity of compound 1. None of the optical isomers and the racemates suppressed the morphine-withdrawal syndrome in the monkey.

In the previous paper,[1] we described the synthesis and analgesic activity of derivatives of 10-hydroxy-4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (homobenzomorphan), including compounds which had the potency of morphine. Since it has been shown that in the 6,7-benzomorphan analgesics optical resolution produces one isomer (levo) that is analgesically potent and without physical-dependence capacity in rhesus monkeys,[2] it appeared interesting to resolve the racemic homobenzomorphans and to evaluate their pharmacological properties. We have resolved 1,4-dimethyl- (1), 1,4,12α-trimethyl- (2), and 1,4,12β-trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (3)



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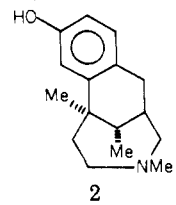

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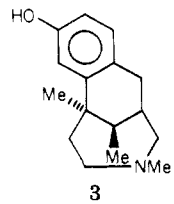

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and have examined their analgesic potency and their ability to suppress the withdrawal syndrome in physically dependent monkeys, as compared with their parent racemic compounds.

The racemates 1 and 2 were resolved by treatment with *d*- and *l*-mandelic acids and fractional crystallization of the mandelate salts from methanol–acetone to constant rotation. Resolution of compound 3 was achieved by treatment with *d*- and *l*-tartaric acids and fractional crystallization of the tartrate salts from methanol to constant rotation. In all cases, both (+) and (−) rotamers were obtained.

Pharmacology. The resolved compounds were tested for analgesic activity by the method of pressure stimuli on the mouse tail[3,4] and the Eddy hot-plate test.[5,6] Table I shows the analgesic ED_{50} values of these compounds and the parent racemates when administered sc. In the case of compounds 2 and 3, virtually all of the analgesic activity is exhibited by levo isomers. These results are similar to those of the 6,7-benzomorphan series.[2] Compound (−)-3 was found to be the most potent of the group, being about two times as potent as morphine. On the contrary, it was observed that in compound 1 there was no effect of resolution on analgesic activity. In the precipitated withdrawal test in monkey, compounds 1, (+)-1 and (−)-1 appeared to be strong depressants.[7] Their depressant properties may be suggested as a possible reason for the peculiar results observed in the analgesic tests. Perhaps, when a compound has both analgesic and depressant properties, odd results are obtained in the analgesic test in mice. The racemic compound 1 and the levo isomer (−)-1, potent analgesics comparable with morphine, appeared to have some narcotic antagonist activity (mouse tail-flick test).[7]

Table I also indicates the acute toxicities of compounds 1–3, (+)-1, and (−)-1.[4] The racemates showed toxicity at 30 mg/kg iv in mice. It is interesting that the levo isomer (−)-1 is much less toxic than the dextro isomer (+)-1.

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Table I. Analgesic Activity, Acute Toxicity, and Physical Dependence Capacity of Resolved Homobenzomorphan

compd	ED_{50}, mg/kg sc (95% SE limits)		LD_{50}, mg/kg iv (95% SE limits)	PDC,[a] mg/kg (dose range)
	pressure stimuli	hot plate		
1[b]	1.6 (1.3-1.9)	0.49 (0.35-0.65)	30.3 (26.8-34.2)	no (3.0-12.0)[d]
(+)-1[b]	1.2 (1.0-1.6)	2.6 (2.1-3.4)	7.8 (6.5-9.2)	no (1.5-6.0)[e]
(-)-1[b]	2.3 (1.7-3.1)	1.8 (1.3-2.4)	101.0 (86.4-118.1)	no (1.5-6.0)[f]
2[c]	1.3 (1.0-1.6)	1.5 (1.1-2.0)	30.8 (27.2-34.8)	no (1.0-4.0)[g]
(+)-2[c]	26.5 (22.7-30.9)	8.2 (5.4-12.4)		no (0.5-4.0)[h]
(-)-2[c]	1.2 (0.7-2.1)	1.3 (1.0-1.7)		no (0.7-5.6)[i]
3[c]	1.0 (0.9-1.2)	1.2 (0.9-1.6)	27.7 (24.3-31.4)	no (0.6-2.4)[j]
(+)-3[c]	inactive	17.9 (13.3-26.0)		no (5.0-10.0)[k]
(-)-3[c]	0.7 (0.5-1.0)	0.57 (0.42-0.78)		no (0.3-2.4)[l]
morphine	1.24 (1.02-1.50)	1.2 (0.9-1.3)		high
pentazocine	8.5 (4.7-15.3)	9.0 (6.5-12.4)	33.0 (28.8-37.8)	

[a] Physical-dependence capacity, monkey, single dose suppression (ref 7 and 8). [b] Administered as hydrobromide. [c] Titrated with dilute HCl for solution. [d] Did not substitute for morphine at the doses tested. Ataxia was noted at all doses and salivation was seen at 6 and 12 mg/kg. [e] Did not substitute for morphine at the doses tested. Appeared to exacerbate withdrawal at the highest dose. Ataxia was seen in all animals (3/3) receiving the highest dose. [f] Did not substitute for morphine at the doses tested. May have exacerbated withdrawal at the highest dose. Ataxia was noted in all animals (3/3) receiving the highest dose. [g] No clear effect upon progression of morphine abstinence signs. Caused CNS depression with motor incoordination at 2 and 4 mg/kg. [h] Neither suppressed nor precipitated the abstinence syndrome at doses tested. Ataxia and/or motor incoordination were seen at doses tested. [i] Neither suppressed nor precipitated morphine abstinence signs at doses tested. Caused prominent confusion and ataxia at 2.8 and 5.6 mg/kg. [j] Caused motor incoordination and confusion at 1.2 and 2.4 mg/kg. [k] Caused CNS depression without suppressing the signs of morphine abstinence at the doses tested. [l] Caused marked motor incoordination at 0.6 to 2.4 mg/kg. No clear effect upon the progression of morphine abstinence signs at the doses tested.

As for physical-dependence capacity in the rhesus monkey, none of the compounds suppressed the morphine abstinence syndrome; they were unlike morphine in the single dose suppression and precipitated withdrawal tests.[7,8] However, in self-administration tests in monkeys, some were self-administered at rates comparable to or below that of codeine.[8] These results suggest that enlargement of the C ring in 6,7-benzomorphan by introducing an extra methylene group between the nitrogen and the bridgehead carbon may diminish physical-dependence capacity. Motor incoordination or ataxia were noted in the animals receiving higher doses of these compounds.

These compounds represent a new type of molecule which possess interesting pharmacological properties—good analgesic activity and lowered physical-dependence capacity of the morphine type. Further examinations of the racemic compounds **1–3** and the levo isomers (-)-**1**, (-)-**2**, and (-)-**3** for their potential as nondependence-liable, potent analgesics are in progress.

Experimental Section

Melting points were determined with a micromelting point apparatus (Yanagimoto) and are uncorrected. Optical rotations were measured with JASCO DIP-4 digital polarimeter at 589 nm, using the solvents and concentrations specified. Microanalyses were performed by the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, and were within ±0.4% of the calculated values.

(-)-1,4-Dimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine [(-)-1]. To a solution of *d*-mandelic acid (15.2 g, 0.1 mol) in MeOH (50 mL) was added 1 (23.1 g, 0.1 mol). The mixture was heated to solution, 40 mL of MeOH was distilled at atmospheric pressure, and the mixture was diluted with 40 mL of Me_2CO and allowed to stand at 0 °C for 2 days. The solid was filtered and washed with cold MeOH–Me_2CO (1:9) to give 13.0 g of crude (-)-1-*d*-mandelate. Recrystallization from MeOH–Me_2CO (1:9) gave 11.5 g (60%) of the pure salt, mp 177–180 °C. Anal. ($C_{15}H_{21}NO{\cdot}C_8H_8O_3$) C, H, N. This salt (11.5 g) was dissolved in H_2O, make alkaline with NH_4OH, filtered, washed with H_2O, and dried to give 6.7 g (97%) of (-)-1: mp 249–252 °C; $[\alpha]^{20}_D$ -21.8° (*c* 2.0, 1 N HCl). (-)-1·HBr: mp 266–270 °C (from MeOH), $[\alpha]^{20}_D$ -15.0° (*c* 5.0, H_2O). Anal. ($C_{15}H_{21}NO{\cdot}$HBr) C, H, N.

(+)-1,4-Dimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine [(+)-1]. The combined filtrates and washings from 11.5 g of (-)-*d*-mandelate were evaporated to a syrup, which was dissolved in H_2O (50 mL), made alkaline with NH_4OH, filtered, and dried to give a crystalline mixture of (±) and (+) bases (15.4 g). This mixture (15.4 g, 0.067 mol) was added to a solution of *l*-mandelic acid (10.1 g, 0.067 mol) in MeOH (40 mL). The mixture was heated to solution, 30 mL of MeOH was removed by distillation at atmospheric pressure, and the residual mixture was diluted with Me_2CO (40 mL) and allowed to stand at 0 °C for 2 days. The solid was filtered and washed with MeOH–Me_2CO (1:9) to give 13.5 g of crude (+)-1-*l*-mandelate. Recrystallization from MeOH–Me_2CO (1:9) gave 12.4 g (65%) of the pure salt, mp 177–180 °C. Anal. ($C_{15}H_{21}NO{\cdot}C_8H_8O_3$) C, H, N. A solution of this salt (12.4 g) in H_2O was treated with NH_4OH, as described for its antipode, to give (+)-1: yield 7.4 g (99%); mp 246–251 °C; $[\alpha]^{20}_D$ +21.5° (*c* 2.0, 1 N HCl). (+)-1·HBr: mp 266–270 °C (from MeOH); $[\alpha]^{20}_D$ +15.0° (*c* 5.0, H_2O). Anal. ($C_{15}H_{21}NO{\cdot}$HBr) C, H, N.

(-)-1,4,12α-Trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine [(-)-2]. To a solution of *d*-mandelic acid (1.91 g, 12.56 mmol) in Me_2CO (25 mL) was added **2** (2.94 g, 12.0 mmol). The mixture was heated to solution and allowed to stand at room temperature for 15 h. The crystals were filtered, washed with cold Me_2CO, and dried at room temperature to give 2.0 g of crude (-)-2-*d*-mandelate. Five recrystallizations from MeOH–Me_2CO (1:9) gave 1.7 g of the optically pure salt as prisms, which gave no definite melting point (shrinks at 85–115 °C). Drying under high vacuum at 75–80 °C for 20 h gave 1.54 g (63%) of fine plates of mp 169–172 °C, which gave satisfactory analytical data for (-)-2-*d*-mandelate. Anal. ($C_{16}H_{23}NO{\cdot}C_8H_8O_3$) C, H, N. This salt was dissolved in H_2O, treated with NH_4OH, filtered, washed with H_2O, and dried to give 0.88 g (95%) of (-)-2, mp 219–222 °C. Recrystallization from EtOH gave a 0.8 g of fine needles: mp 222–224 °C; $[\alpha]^{27}_D$ -29.0° (*c* 1.02, 1 N HCl). Anal. ($C_{16}H_{23}NO$) C, H, N.

(+)-1,4,12α-Trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine [(+)-2]. The combined filtrates and washings from 1.7 g of (-)-2-*d*-mandelate were evaporated to a solid mass, which was dissolved in H_2O (30 mL), made alkaline with NH_4OH, filtered, washed with H_2O, and dried to give 1.95 g of a solid mixture of (±) and (+) bases. This mixture (1.95 g, 7.69 mmol) was added to a solution of *l*-mandelic acid (1.28 g, 8.4 mmol) in Me_2CO (40 mL). The mixture was heated to solution and allowed to stand at room temperature for 25 h. The crystals were filtered, washed with cold Me_2CO, and dried at room temperature to give 2.5 g of crude (+)-2-*l*-mandelate. Four recrystallizations from MeOH–Me_2CO (1:9) gave 1.9 g of prisms which had no definite melting point, like its antipode. Drying under high vacuum at 75–80 °C for 25 h gave 1.7 g (70%) of fine plates of mp 167–171 °C. Anal. ($C_{16}H_{23}NO{\cdot}C_8H_8O_3$) C, H, N. The

(+)-2-*d*-mandelate (1.6 g) was converted to the (+)-2 base (0.93 g, 94%) of mp 219–222 °C, as described above for the enantiomer (-)-2. Recrystallization from EtOH gave fine needles of pure (+)-2: mp 225–226 °C; $[\alpha]^{27}_D$ +28.9° (*c* 1.14, 1 N HCl). Anal. ($C_{16}H_{23}NO$) C, H, N.

(-)-1,4,12β-Trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine [(-)-3]. To a suspension of 3 (2.71 g, 11.05 mmol) in MeOH (40 mL) was added *d*-tartaric acid (0.83 g, 5.53 mmol) in MeOH (10 mL). The mixture was heated to solution and allowed to stand at room temperature for 5 h. The solid was filtered, washed with cold MeOH, and dried to give 1.1 g of fine cubes. Three recrystallizations from MeOH gave optically pure (-)-3-*d*-tartrate: yield 0.91 g (50.8%); mp 208–211 °C; $[\alpha]^{27}_D$ -17.7° (*c* 2.0, H_2O). Anal. ($C_{32}H_{46}N_2O_2 \cdot C_4H_6O_6$) C, H, N. The neutral tartrate (0.9 g) was dissolved in H_2O (20 mL), basified with NH_4OH, filtered, washed with H_2O, and dried to give 0.67 g (97%) of (-)-3. Recrystallization from MeOH–Me_2CO (9:1) gave pure (-)-3 as prisms: mp 175–176 °C; $[\alpha]^{29}_D$ -34.3° (*c* 1.53, 1 N HCl). Anal. ($C_{16}H_{23}NO$) C, H, N.

(+)-1,4,12β-Trimethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine [(+)-3]. The combined filtrates and washings from 0.9 g of (-)-3-*d*-tartrate were evaporated to a syrup and dissolved in H_2O (50 mL), made alkaline with NH_4OH, filtered, washed with H_2O, and dried to give 1.8 g of a solid mixture of (±) and (+) bases. The mixed bases (1.8 g, 7.35 mmol) were heated to solution with *l*-tartaric acid (0.56 g, 3.73 mmol) in MeOH (30 mL). The solution was allowed to stand at room temperature for 6 h. The resulting crystals were filtered, washed with cold MeOH, and dried to give 1.1 g of fine cubes. Two recrystallizations from MeOH gave optically pure (+)-3-*l*-tartrate: yield 0.97 g (58%); mp 207–210 °C; $[\alpha]^{27}_D$ +17.4° (*c* 2.0, H_2O). Anal. ($C_{32}H_{46}N_2O_2 \cdot C_4H_6O_6$) C, H, N. The neutral tartrate (0.97 g) was converted to the (+)-3 base (0.69 g, 99%) as described above for its enantiomer (-)-3. Recrystallization from MeOH–Me_2CO (9:1) gave pure (+)-3: prisms; mp 173–175 °C; $[\alpha]^{29}_D$ +36.3° (*c* 1.53, 1 N HCl). Anal. ($C_{16}H_{23}NO$) C, H, N.

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Additions and Corrections

1978, Volume 21

James Z. Ginos,* George C. Cotzias, and David Doroski: New Dopaminergic and Potential Anti-Parkinson Compounds, N,N-Disubstituted β-(3,4-Dihydroxyphenyl)ethylamines..

Page 162. In Table III, the melting point for compound **25** should read as 136.5–137.5 °C, after crystallizing twice from absolute ethanol–ether.

1979, Volume 22

Arthur E. Jacobson,* Kenner C. Rice, Jurgen Reden, Lillian Lupinacci, Arnold Brossi, Richard A. Streaty, and Werner A. Klee: Paradoxical Effects of *N*-Cyanoalkyl Substituents upon the Activities of Several Classes of Opioids.

Page 329. In Table II, footnote *d* should read as follows: Binding constant from rat brain homogenates, in nmol/L.