Synthesis and Analgesic Properties of N-Substituted *trans*-4a-Aryldecahydroisoquinolines

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A respresentative series of N-substituted derivatives of the morphine-based *trans*-4a-aryldecahydroisoquinoline were synthesized and evaluated for opioid analgesic activities. Compounds with potent analgesic activity and high affinities for the μ and κ opioid receptors were discovered. The effect of varying the N-substituent in the *trans*-4a-aryldecahydroisoquinoline paralleled, to a certain extent, previous findings with other morphine part structures. Replacement of the *N*-methyl with a phenethyl group significantly increased analgesic potency. The *N*-cyclopropylmethyl analogue was found in rodents to have mixed agonist–antagonist properties; however, its antagonist activity was far weaker than those reported for the *N*-(cyclopropylmethyl)morphinan and -benzomorphan derivatives. Resolution of the stereoisomers and determination of their absolute configuration by X-ray crystallography showed that the opioid receptor effects were predominantly found with the 4a*R*,8a*R* isomer, the same relative absolute configuration of morphine. Unexpectedly, the 4a*R*,8a*R* *N*-cyclopropylmethyl analogue (compound **30**), which in rodents had mixed agonist–antagonist properties similar to those of pentazocine, was found in rhesus monkeys to behave as a full morphine-like agonist.

One approach for the discovery of new analgesics has been to synthesize portions of the morphine molecule and undertake structure–activity relationship studies with these part structures. In general this strategy has been quite successful, leading to the discovery, for example, of the morphinan[1] and benzomorphan[2] series. While it is believed that the new morphine-based structures will retain significant analgesic activity, often the overall analgesic properties of the new series vary especially in regard to their relative agonist and antagonist activities and their receptor selectivities. These differences have led to the discovery of opioid analgesics with improved clinical usefulness.

One morphine part structure that has received little attention is the *trans*-4a-aryldecahydroisoquinoline,[3] which, as seen in Figure 1, has a close relationship to both the morphinan and the benzomorphan structures. Previously we have described a direct approach for the synthesis of the decahydroisoquinoline structure and analogues of it.[4,5] We now report the synthesis and pharmacological activity of a number of N-substituted *trans*-4a-aryldecahydroisoquinolines. The opioid receptor affinities are discussed, and the structure–activity relationships observed with this new series are compared to those already reported for the morphinan and the benzomorphan series.

Chemistry. We have recently described a high-yield five-step synthesis to the *trans*-aryldecahydroisoquinoline **1** from the *N*-ethyltetrahydropyridine **3** (Scheme I).[6] The synthetic sequence involved the use of the metalated enamine **4** to generate the bicyclic enamine **5**. Compound **5** was selectively reduced to the *trans*-isoquinoline **6**, which was N-dealkylated by using vinyl chloroformate[7] via the vinyl formamide **7**. Use of the *N*-ethyltetrahydropyridine **3** in this sequence over the *N*-methyl analogue **2** is urged because compound **2**, which is the 3-methoxy derivative of the parkinsonism-causing agent MPTP,[8] was found, like MPTP, to be highly neurotoxic.[6] However, the *N*-ethyl MPTP derivative **3** was not neurotoxic in mice even at doses 8 times those of MPTP.[6]

The methylisoquinoline **8** was synthesized by reduction of the vinyl formamide **7**, and the enantiomers of **8** were separated by fractional recrystallization of their mandelic acid salts. An X-ray crystal structure determination of **9** as its D-mandelic salt revealed that compound **9**, the (+) isomer, has the 4a*R*,8a*R* absolute configuration. Treatment of the *trans*-(3-methoxyphenyl)isoquinolines (**1** and **8–12**) with HBr in acetic acid gives the 3-hydroxy derivatives in high yield. The N-substituted decahydroisoquinoline derivatives **19** were prepared either by alkylation with an appropriate halide or by acylation with an acid chloride followed by reduction of the resulting amide. The compounds obtained from **18** all had the (–) optical rotation and the 4a*R*,8a*R* configuration, which is the same relative absolute configuration found in morphine.

X-ray Analysis of Compound 9. Compound **9** crystallized from 2-propanol/acetone/water as colorless prisms in the space group $P222$, $Z = 4$, with unit cell dimensions of $a = 6.831$ (5) Å, $b = 17.681$ (12) Å, $c = 20.456$ (14) Å. The calculated density was 1.203 g cm^{-3}. A total of 1973 unique reflections with 2θ less than 116.0 were measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved by using the Random Tangent method (RANT) of the SHELXTL program library (G. M. Sheldrick, 1981) and was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen. Hydrogen atoms were included with isotropic temperature factors at calculated positions. The final R factor was 0.0747 for 1571 observed reflections. Figure 2 shows an ORTEP plot of the molecule.

Pharmacological Results

The analgesic activity of these compounds in the mouse writhing and the rat tail heat tests is given in Table I. The procedures for these tests have been previously described.[9]

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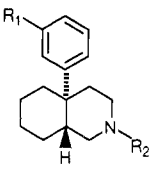
(2) Eddy, N. B.; May, E. L. *Synthetic Analgesics, Part IIb, 6,7-Benzomorphans*; Barton, D. H. R., von Doering, W., Eds; Pergamon: New York, 1966.
(3) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650–6657 and references cited therein.
(4) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955–5956.
(5) Zimmerman, D. M.; Robey, R. L. U.S. Patent 4 236 009, 1980; *Chem. Abstr.* **1981**, *94*, 121345*t*.
(6) Zimmerman, D. M.; Cantrell, B. E.; Reel, J. K.; Hemrick-Luecke, S. K.; Fuller, R. W. *J. Med. Chem.* **1986**, *29*, 1517–1520.
(7) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.
(8) Markey, S. P.; Schmuff, N. R. *Med. Res. Rev.* **1986**, *6*, 389–429.

0022-2623/88/1831-0555$01.50/0

Table I. Structures of the 2-Substituted *trans*-4a-Aryldecahydroisoquinolines and Their Activity in the Mouse Writhing and the Rat Tail Heat Analgesia Tests



compd	isomer	R_1	R_2	mouse writhing: ED_{50},[a] mg/kg, sc	rat tail heat: $ED_{2_{sec}}$,[b] mg/kg, sc
19	(±)	H	CH_3	3.5 (2.1–5.8)	8.8 (3.0–15.6)
8	(±)	OCH_3	CH_3	1.2 (0.9–1.5)	3.3 (3.0–4.0)
13	(±)	OH	CH_3	0.5 (0.5–0.6)	0.4 (0.3–0.5)
15	(–)	OH	CH_3	2.1 (1.1–3.1)	1.6 (1.1–2.1)
14	(+)	OH	CH_3	0.4 (0.3–0.5)	0.3 (0.2–0.3)
20	(±)	OH	$CH_2CH{=}CH_2$	1.0 (1.0–1.3)	1.4 (0.9–1.8)
21	(–)	OH	$CH_2CH{=}CH_2$		
22	(+)	OH	$CH_2CH{=}CH_2$		
23	(±)	OH	CH_2CH_3	18.2 (15.8–20.9)	>100
25	(+)	OH	CH_2CH_3		
26	(±)	OH	$CH_2CH_2CH_3$	1.5 (1.1–1.9)	1.3 (0.8–1.7)
27	(–)	OH	$CH_2CH_2CH_3$		
28	(+)	OH	$CH_2CH_2CH_3$		
29	(±)	OH	CH_2-c-C_3H_5	3.3 (2.4–4.5)	5.6 (3.9–7.4)
30	(–)	OH	CH_2-c-C_3H_5	2.2 (1.8–2.8)	3.0 (1.9–4.3)
31	(+)	OH	CH_2-c-C_3H_5	>50	>50
32	(±)	OH	$CH_2CH{=}C(CH_3)_2$	1.0 (0.8–1.3)	1.5 (0.9–1.9)
33	(±)	OH	CH_2CH_2Ph	0.3 (0.2–0.3)	0.08 (0.03–0.19)
34	(–)	OH	CH_2CH_2Ph		
35	(+)	OH	CH_2CH_2Ph		
36	(±)	OH	CH_2-c-C_4H_7	0.6 (0.2–1.1)	–
morphine				0.9 (0.7–1.1)	0.7 (0.5–0.9)
cyclazocine				0.07 (0.02–0.2)	–
nalorphine				0.7 (0.4–1.1)	>100
pentazocine				2.0 (1.4–2.9)	2.6 (1.8–3.7)

[a] The ED_{50} value (95% confidence limits) is defined as the dose required for 50% reduction in frequency of writhing. [b] The $ED_{2_{sec}}$ value (95% confidence limits) is defined as the dose required for a 2-s increase in reaction time.

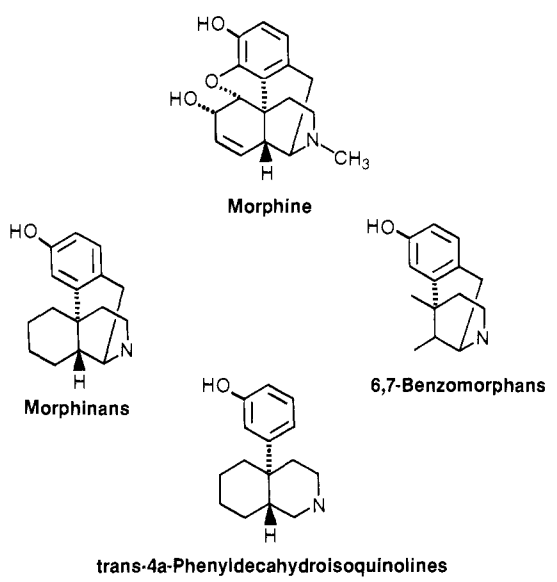


Figure 1.

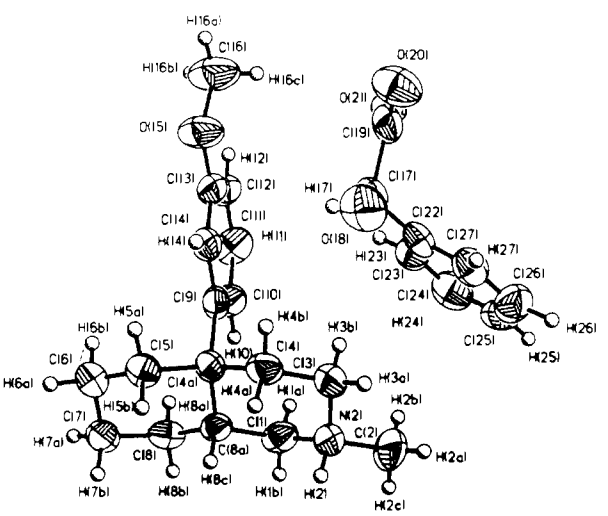
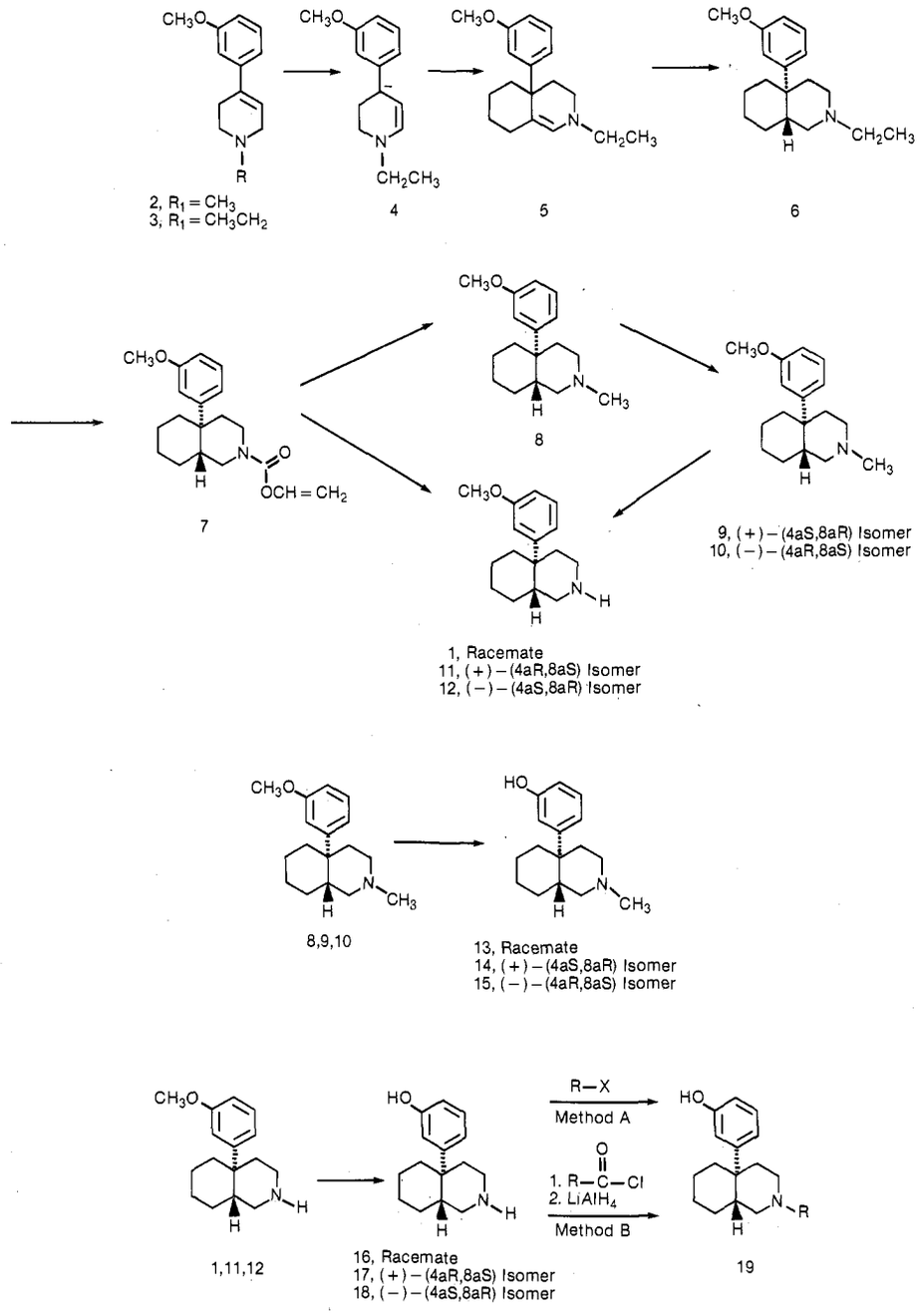


Figure 2.

In the mouse writhing test, compound **13**, the racemic *N*-methyl-3-hydroxy derivative, has an analgesic potency comparable to that of morphine. There was a stepwise increase in activity by altering the substitution at the 3-phenyl position from hydrogen to methoxy to hydroxy. Replacement of the *N*-methyl with a phenethyl group, compound **33**, increased analgesic potency twofold. Both compounds **13** and **33** produced a pattern of behavioral effects similar to those observed with morphine, including Straub tail and increased locomotor activity. Compounds substituted at the nitrogen with allyl, propyl, cyclopropylmethyl, cyclobutylmethyl, and dimethylallyl groups were also potent analgesics. Comparison of the individual enantiomers (**14** and **15**) of compound **13** in the writhing test showed that with this *N*-methyl derivative the analgesic activity resided predominantly in the 4a*R*,8a*R* enantiomer **14**; however, the other stereoisomer (**15**) still produced significant analgesia. With the *N*-cyclopropylmethyl derivative **29** the analgesic activity was selectively in the 4a*R*,8a*R* isomer, compound **30**.

(9) Zimmerman, D. M.; Smits, S. E.; Hynes, M. D.; Cantrell, B. E.; Leander, J. D.; Mendelsohn, L. G.; Nickander, R. *Drug Alcohol Depend.* **1985** *14*, 381–402.

Scheme I[a]



[a] For the sake of clarity, only one enantiomer is depicted.

In general the relative analgesic potencies of the *trans*-decahydroisoquinolines in the rat tail heat test parallel those observed in the mouse writhing test. The (3-hydroxyphenyl)-*N*-phenethyl derivative again was the most potent, having activity as the racemate approximately 3–4 times that of morphine. The *N*-allyl and *N*-cyclopropylmethyl derivatives had analgesic potencies similar to that of pentazocine, whereas nalorphine fails to increase reaction time by 2 s in this test even at a dose of 100 mg/kg.

All racemic mixtures of the *trans*-decahydroisoquinolines were evaluated for their ability to antagonize the analgesic response of morphine (5 mg/kg, sc) in the rat tail heat test. The procedure has been previously described.[9] Among the racemates, only the *N*-cyclopropylmethyl derivative **29** showed significant antagonist activity, and this activity was found selectively in its 4a*R*,8a*R* stereoisomer, compound **30**. Figure 3 shows the morphine antagonist activity of compound **30** compared with the antagonist activities of pentazocine and nalorphine. Compound **30** antagonized the analgesic effects of morphine in the rat tail heat test with doses as low as 1 mg/kg, sc. Under similar conditions, it required 10 mg/kg of pentazocine and 1 mg/kg of nalorphine. Attempts to determine a dose that would reduce the analgesic response of morphine by 50% (AD_{50}) with compound **30** were unsuccessful because, as the dose of **30** was increased, its agonist effects became increasingly apparent.

Compound **30** was also able to antagonize the morphine-induced Straub tail reaction and increased locomotor activity in mice. The experimental details of this test have been previously described.[9] The dose that caused a 50% reduction of the effects of 40 mg/kg, sc, of morphine (AD_{50}) was 10.5 mg/kg, sc. In this test, the AD_{50}'s for pentazocine and nalorphine were 16.9 and 0.45 mg/kg, sc, respectively. Compounds **31** (the opposite enantiomer of compound **30**) and **20** (the *N*-allyl racemic mixture) were inactive in this test.

Table II. Affinity of the 2-Substituted *trans*-4a-Aryldecahydroisoquinolines for the μ and κ Opioid Receptors

	[^{3}H]NAL binding assay (μ receptor)			[^{3}H]EKC binding assay (κ receptor)		
		% displacement[a]			% displacement[a]	
compd	K_i, nM	100 nM	1000 nM	K_i, nM	100 nM	1000 nM
15	8.9			433		
14	0.96			61		
22		15	42		2	16
21	7.3			22.8		
28		43	83		4	
27	473				12	46
25		34	70		0	15
24	29			529		
31		4	35		5	32
30	4.2			2.5		
34	0.23			89		
35		19	74		8	53
cyclazocine	1.2			1.3		
pentazocine	6.9			75		
nalorphine	6.5			15		
morphine	5.7			167		

[a] Percent stereospecific displacement of either [^{3}H]NAL or [^{3}H]EKC run in triplicate at the concentration indicated.

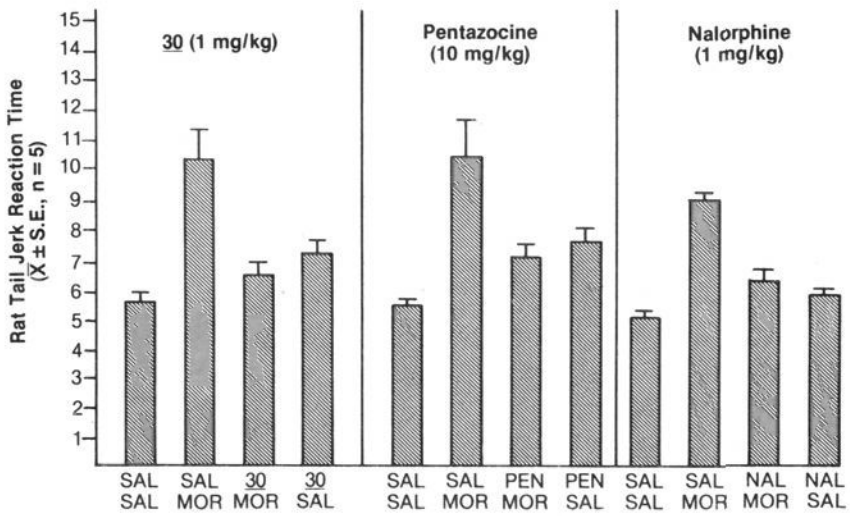


Figure 3. Antagonism of morphine analgesia by **30**, pentazocine, and nalorphine in the rat tail jerk test. The analgesic effect of morphine sulfate (MOR) 10 min after the sc administration of 5 mg/kg was determined in combination with either saline (SAL), compound **30**, pentazocine (PEN), or nalorphine (NAL). The test antagonists were administered at the sc doses indicated 60 min before test.

The affinities of the individual enantiomers of several of the *trans*-4a-aryldecahydroisoquinolines for the μ and κ opioid receptors are given in Table II. μ receptors were labeled by using [^{3}H]naloxone (Nal) with rat brain homogenates. κ receptors were labeled by using [^{3}H]ethylketocyclazocine (EKC) and homogenates from guinea pig cortex in the presence of fentanyl and D-Ala^2-D-Leu^5-enkephalin to block the μ and δ receptor binding of EKC. The details of both procedures have been previously described.[9] Several of the isoquinolines with the 4a*R*,8a*R* absolute configuration have high affinity for the μ receptor, and except for the cyclopropylmethyl derivative **30**, all had substantially lower affinity for the κ receptor. The *N*-methyl derivative **14** has an affinity for the μ receptor 6 times that of morphine while the affinity of the *N*-phenethyl analogue **34** is 25 times that of morphine. There appeared to be a good correlation of the relative affinities of these compounds for the μ receptor and their analgesic potencies in both the mouse writhing and rat tail heat analgesic tests. Both *N*-methyl stereoisomers (compounds **14** and **15**) have significant affinity for the μ receptor. The affinity of the 4a*R*,8a*R* (compound **14**) isomer is 8–10-fold higher than that of the 4a*S*,8a*S* isomer (compound **15**). With the *N*-allyl and *N*-cyclopropylmethyl derivatives, the affinities of the 4a*R*,8a*R* isomers (**21** and **30**) for the μ receptor were substantially greater than those of their opposite stereoisomers (**22** and **31**). Of all the N-substituted isoquinolines, only compound **30** had high affinity for the κ receptor.

Discussion

In general, the changes in analgesic activity that occur with modification of the *trans*-4a-phenylisoquinoline molecule paralleled those previously reported with the morphinan[1] and benzomorphan[2] series. At the 3-phenyl position, activity increased from hydrogen to methoxy to hydroxy. Substitution of phenethyl for the *N*-methyl group increases potency, and analgesic activity was retained with the *N*-cyclopropylmethyl and the *N*-allyl derivatives. As is the case in the morphinan and benzomorphan series, the *N*-(cyclopropylmethyl)isoquinoline analogue has antagonist activity; however, its antagonist activity is weak compared to the antagonist activities of the *N*-(cyclopropylmethylmorphinan (cyclorphan) and -benzomorphan (cyclazocine) derivatives. Furthermore the *N*-allylisoquinoline derivative does not have morphine antagonist properties, whereas the *N*-allyl derivatives in the morphinan and benzomorphan series are potent antagonists. Resolution of the *trans*-4a-phenylisoquinolines showed that the analgesic activity and affinity for opioid receptors resided predominately in the 4a*R*,8a*R* isomer, the same absolute configuration found for the active isomers of the morphinans, benzomorphans, and morphine;[1,2] however, unlike *N*-methylmorphinan and -benzomorphan derivatives, the (4a*S*,8a*S*)-*N*-methylisoquinoline isomer (compound **15**) has significant analgesic activity and affinity for the μ receptor.

Compound **30** was found to have mixed agonist–antagonist properties similar in potency to those of pentazocine in both rats and mice. Such a profile of activity is normally indicative of a reduced dependence liability not only in rodents but also in other species. Compound **30** was evaluated for its physical dependence and abuse liabilities under the auspices of the Committee on Problems of Drug Dependence at the University of Michigan and the Medical College of Virginia.[10] Surprisingly, in single dose suppression studies in morphine-dependent rhesus monkeys undergoing spontaneous withdrawal, compound **30** suppressed withdrawal and was more potent and longer lasting than morphine. Furthermore, primary physical dependence studies showed that chronic administration of compound **30** produced a marked physical dependence more

(10) Personal communication as reported in the *Proceedings of the 39th Annual Scientific Meeting, Committee on Problems of Drug Dependence*, Cambridge, MA, July 6–9, 1977.

severe than that of morphine. Therefore, in rhesus monkeys compound **30** produced effects that would be expected of a potent, long-lasting, morphine-like agonist.

On the basis of its rodent pharmacology, this profile of activity with compound **30** in rhesus monkeys was clearly unexpected. The opioid antagonist properties identified in rodents were absent in rhesus monkeys. Furthermore, in rhesus monkeys, **30** was estimated to be 3–6 times more potent than morphine, which was significantly greater than its potencies in the rodent analgesic tests. The reason for the apparent difference in opioid properties with compound **30** between these species is unexplained.

Experimental Section

Melting points were determined for all solids on a Thomas–Hoover apparatus and are uncorrected. Mass spectra were recorded on a CEC 21-110 mass spectrometer for all compounds and were consistent with assigned structures. NMR spectra were recorded on either a Varian T-60 or Brucker WM-270 spectrometer and were consistent with assigned structures. Optical rotations were determined on a Perkin-Elmer Model 241 automatic polarimeter and were run as a 1% solution in methanol. All compounds had elemental analysis within 0.3% of theoretical value unless otherwise indicated. Where melting points are not indicated, the substance is a liquid at room temperature.

2-Methyl-4aβ-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydroisoquinoline (8). A solution of **7**[6] (1.55 g, 0.005 mol) in 25 mL of anhydrous toluene was added dropwise to 2 mL of Red-Al at room temperature under nitrogen. The reaction mixture was then heated at 90 °C for 1 h, then cooled to room temperature, and poured into 1 N HCl. The acidic layer was washed one time with ether and then made strongly basic with 50% NaOH with ice cooling. The desired product was extracted into ether, and the ether layer was washed two times with water, dried over K_2CO_3, and concentrated under reduced pressure to yield 1.21 g (95%). The hydrobromide salt was prepared and recrystallized from isopropyl ether/ethanol (1:1): mp 168–170 °C. Anal. ($C_{17}H_{26}NOBr$) C, H, N.

(+)-(4a*R*,8a*R*)-2-Methyl-4aβ-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydroisoquinoline (9). Into 200 mL of 2-propanol were dissolved 39.3 g (0.15 mol) of **8** and 26.1 g (0.17 mol) of (−)-D-mandelic acid. The solvent was removed by evaporation under reduced pressure, and the resulting solid was recrystallized from 1900 mL of hot water. The precipitate (26.1 g) was recrystallized from 260 mL of acetone and 626 mL of isopropyl ether, giving 17.9 g of the resolved mandelate salt: mp 97–101 °C. Treatment of the salt with excess 1 N NaOH and subsequent ether extraction and evaporation yielded 10.25 g of **9** as a viscous oil (52%): $[\alpha]_{365}$ +41.9°; $[\alpha]_D$ +6.8°. Anal. ($C_{17}H_{26}NO$) C, H, N.

(−)-(4a*S*,8a*S*)-2-Methyl-4aβ-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydroisoquinoline (10). The resulting filtrate from the above water recrystallization step was evaporated to dryness under reduced pressure to yield 39.0 g. The free amine was liberated with base and distilled at 109–112 °C (0.1 mm) to yield 21.0 g of a clear viscous oil: $[\alpha]_{365}$ 27.7°. This 21.0 g (0.08 mol) and 13.9 g (0.09 mol) of (+)-L-mandelic acid were dissolved into 100 mL of 2-propanol. The solvent was removed by evaporation, and the resulting solid was recrystallized from 245 mL of acetone and 578 mL of isopropyl ether to yield 23.0 g of the resolved mandelate salt: mp 98–101 °C. Treatment with excess 1 N NaOH and subsequent ether extraction and evaporation afforded 13.0 g of a viscous oil (66%): $[\alpha]_{365}$ −41.4°; $[\alpha]_D$ −6.8°. Anal. ($C_{17}H_{26}NO$) C, H, N.

(+)-(4a*S*,8a*S*)-4aβ-(3-Methoxyphenyl)-1,2,3,4,4a,5,6,7,-8,8aα-decahydroisoquinoline (11). A solution of 8.9 g (0.056 mol) of phenyl chloroformate in 40 mL of dichloromethane was added dropwise to 13.0 g (0.051 mol) of **10** at room temperature under a nitrogen atmosphere. Following a 4-h reflux, the mixture was cooled to room temperature and concentrated under reduced pressure. The resulting oil was treated with 100 mL of 1 N NaOH and stirred with slight warming for 15 min. The desired carbamate was then extracted into ether, and the ether layer was washed with 1 N HCl and water. The ether layer was dried over K_2CO_3 and the solvent evaporated under reduced pressure, giving 20.6 g of colorless oil. This oil was then treated with 470 mL of ethanol and 118 mL of 50% aqueous KOH at reflux for 66 h. The mixture was cooled and concentrated under reduced pressure. The resulting alkaline concentrate was extracted two times with ether, and the ether extracts were concentrated under vacuum. The resulting oil was dissolved into 200 mL of 1 N HCl and washed with ether. The aqueous layer was then made strongly basic (pH >12) with 50% NaOH with ice cooling. The desired amine **11** was extracted into ether, and the ether layer was washed, dried over K_2CO_3, and concentrated under reduced pressure to yield 10 g of crude **11**. Vacuum distillation at 121–125 °C (0.1 mm) afforded 9.1 g of **11** as a clear viscous oil (74%): $[\alpha]_{385}$ +29.0°; $[\alpha]_D$ +9.2°.

(−)-(4a*R*,8a*R*)-4aβ-(3-Methoxyphenyl)-1,2,3,4,4a,5,6,7,8,-8aα-decahydroisoquinoline (12). This compound was prepared as above from **9**. Vacuum distillation at 119–123 °C (0.1 mm) afforded 7.3 g of **12** (67%): $[\alpha]_{365}$ −29.4°; $[\alpha]_D$ −9.0°.

General Procedure for the Synthesis of the 3-Hydroxyphenyl Analogues. The *O*-demethylation of all 3-methoxyphenyl compounds followed the procedure described below for **16**.

3-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-4aβ-isoquinolinyl)phenol (16). Freshly distilled **1** (5.2 g, 0.02 mol) was treated with 40 mL of glacial acetic acid and 40 mL of 50% aqueous hydrobromic acid at reflux temperature for 18 h. The reaction mixture was cooled to room temperature and diluted with 200 mL of water. The pH was adjusted to 10 by using 50% NaOH with ice cooling. The desired product was extracted into a 3:1 1-butanol/toluene mixture, dried over K_2CO_3, and concentrated under reduced pressure toyield 4.2 g (90%). The solid was recrystallized from dimethylformamide: mp 212–214 °C. Anal. ($C_{15}H_{21}NO$) C, H, N.

Compounds **17**, **18**, and **13–15** were prepared in the same manner as **16**.

(+)-(4a*S*,8a*S*)-3-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-4aβ-isoquinolinyl)phenol (17): prepared from **11** and recrystallized from hexane/ethyl acetate (1:3) in 89% yield; mp 234–237 °C; $[\alpha]_{365}$ +26.8°; $[\alpha]_D$ 8.4°.

(−)-(4a*R*,8a*R*)-3-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-4aβ-isoquinolinyl)phenol (18): prepared from **12** and recrystallized from hexane/ethyl acetate (1:3) in 91% yield; mp 235–238 °C; $[\alpha]_{365}$ −25.6°; $[\alpha]_D$ −8.2°.

3-(2-Methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (13): prepared from **8** and recrystallized from acetonitrile/ethanol (4:1) in 55% yield; mp 202–204 °C. Anal. ($C_{16}H_{23}NO$) C, H, N.

(+)-(4a*R*,8a*R*)-3-(2-Methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (14): prepared from **9**; recrystallized from ethyl acetate in 68% yield; mp 213–215 °C. Anal. ($C_{16}H_{23}NO$) C, H, N. It was converted to the hydrobromide salt and recrystallized from ethyl acetate/methanol (9:1): $[\alpha]_{365}$ +22.95°; $[\alpha]_D$ +5.53°; mp 240–241 °C. Anal. ($C_{16}H_{24}NOBr$) C, H, N.

(−)-(4a*S*,8a*S*)-3-(2-Methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (15): prepared from **10** and recrystallized from ethyl acetate in 71% yield; mp 213–215 °C. Anal. ($C_{16}H_{23}NO$) C, H, N. The hydrobromide salt was prepared and recrystallized from ethyl acetate/methanol (9:1): mp 240–241 °C; $[\alpha]_{365}$ −23.84°; $[\alpha]_D$ −5.85°. Anal. ($C_{16}H_{24}NOBr$) C, H, N.

General Alkylation Procedure for Preparing N-Substituted *trans*-4a-(3-Hydroxyphenyl)decahydroisoquinolines (Method A). Either **16**, **17**, or **18** (1.0 g, 0.004 mol) was heated with 0.005 mol of the appropriate alkyl halide and 0.55 g of $NaHCO_3$ in 30 mL of DMF. After refluxing for 1 h, the mixture was cooled and poured into 100 mL of water. The product was extracted into 300 mL of ether. The ether layer was washed two times with water, dried over K_2CO_3, and concentrated under vacuum. The products were purified by recrystallization either as a free base or a salt form.

Compounds **20–28** and **32** were prepared by this procedure and exhibited the following properties.

3-(2-Allyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (20): prepared from **16** and allyl bromide and recrystallized from ethyl acetate (64%); mp 146–148 °C. Anal. ($C_{18}H_{25}NO$) C, H, N.

(−)-(4a*R*,8a*R*)-3-(2-Allyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (21): prepared from **18** and allyl

bromide and recrystallized from ethyl acetate (65%); mp 170–171.5 °C; $[\alpha]_{365}$ −45.8°; $[\alpha]_D$ −14.8°. Anal. ($C_{18}H_{25}NO$) C, H, N.

(+)-(4a*S*,8a*S*)-3-(2-Allyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (22): prepared from **17** and allyl bromide and recrystallized from ethyl acetate (72%); mp 172–172 °C; $[\alpha]_{365}$ +45.2°; $[\alpha]_D$ +14.6°. Anal. ($C_{18}H_{25}NO$) C, H, N.

3-(2-Ethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (23): prepared from **16** and ethyl iodide. The maleate salt was recrystallized from ethyl acetate/ethanol (6:1) (61%): mp 138–140 °C. Anal. ($C_{21}H_{29}NO_5$) C, H, N.

(−)-(4a*R*,8a*R*)-3-(2-Ethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (24): prepared from **18** and ethyl iodide and recrystallized from ethyl acetate (73%); mp 166–169 °C; $[\alpha]_{365}$ −0.4°; $[\alpha]_D$ −4.8°. Anal. ($C_{17}H_{25}NO$) C, H, N.

(+)-(4a*S*,8a*S*)-3-(2-Ethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (25): prepared from **17** and ethyl iodide and recrystallized from ethyl acetate (78%); mp 167–169 °C; $[\alpha]_{365}$ 0°; $[\alpha]_D$ +4.4°. Anal. ($C_{17}H_{25}NO$) C, H,N.

3-(2-*n*-Propyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (26): prepared from **16** by employing *n*-propyl iodide. The maleate salt was recrystallized from ethyl acetate (50%): mp 150–151 °C. Anal. ($C_{22}H_{31}NO_5$) C, H, N.

(−)-(4a*R*,8a*R*)-3-(2-*n*-Propyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (27): prepared from **18** and *n*-propyl iodide and recrystallized from hexane/ethyl acetate (2:1) (61%); mp 124–125 °C; $[\alpha]_{365}$ −15.6°; $[\alpha]_D$ −8.7°. Anal. ($C_{18}H_{27}NO$) C, H, N.

(+)-(4a*S*,8a*S*)-3-(2-*n*-Propyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl)phenol (28): prepared from **17** and *n*-propyl iodide and recrystallized from ethyl acetate (49%); mp 123–124.5 °C; $[\alpha]_{365}$ +14.8°; $[\alpha]_D$ +8.1°. Anal. ($C_{18}H_{27}NO$) C, H, N.

3-[2-(3-Methyl-2-butenyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (32): prepared from **16** and 4-bromo-2-methyl-2-methyl-2-butene and recrystallized from chloroform (64%); mp 113–115 °C. Anal. ($C_{20}H_{29}NO$) C, H, N.

General Acylation/Reduction Procedure for Preparing N-Substituted *trans*-4a-(3-Hydroxyphenyl)decahydroisoquinolines (Method B). To 1.0 g (0.004 mol) of either **16**, **17**, or **18** and 1.0 g of triethylamine in 30 mL of DMF was added dropwise 0.01 mol of the appropriate acid chloride at room temperature under nitrogen. After the reaction mixture was heated for 2 h at 90 °C, the solution was cooled and poured into 100 mL of water. The desired amide was extracted into 300 mL of ether. The ether layer was washed two times with water, dried over K_2CO_3, and concentrated under vacuum. The resulting amide was dissolved into 75 mL of anhydrous THF and added dropwise to 0.75 g of $LiAlH_4$ dispersed in 50 mL of anhydrous THF. After a 4-h reflux, the reaction mixture was cooled, and the excess $LiAlH_4$ was neutralized by the careful addition of 10 mL of ethyl acetate with ice cooling. Saturated NH_4Cl solution was then added to precipitate the lithium salts. The solution containing the desired product was separated, evaporated to dryness, and worked up in the standard manner. The products were recrystallized either as a free base or a salt.

Compounds **29–31** and **33–36** were prepared by this procedure and exhibited the following properties.

3-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (29): prepared from **16** and cyclopropanecarboxylic acid chloride. The maleate salt was recrystallized from ethyl acetate/ethanol (9:1) (61%): mp 135–138 °C. Anal. ($C_{23}H_{31}NO_5$) C, H, N.

(+)-(4a*S*,8a*S*)-3-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (31): prepared from **17** and cyclopropanecarboxylic acid chloride. The succinate salt was recrystallized from 2-propanol (56%): mp 161–162 °C; $[\alpha]_{365}$ +13.9°; $[\alpha]_D$ +5.3°. Anal. ($C_{23}H_{33}NO_5$) C, H, N.

(−)-(4a*R*,8a*R*)-3-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (30): prepared from **18** and cyclopropanecarboxylic acid chloride. The succinate salt was recrystallized from acetonitrile (61°): mp 157–159 °C; $[\alpha]_{365}$ −14.9°; $[\alpha]_D$ −5.8°. Anal. ($C_{23}H_{33}NO_5$) C, H, N.

3-[2-(Phenylethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (33): prepared from **16** and phenylacetyl chloride. The maleate salt was recrystallized from ethyl acetate (51%): mp 56.5–59 °C. Anal. ($C_{27}H_{33}NO_5$) C, H, N.

(−)-(4a*R*,8a*R*)-3-[2-(Phenylethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (34): prepared from **18** and phenylacetyl chloride and recrystallized from ethyl acetate (63%); mp 210–213 °C; $[\alpha]_{365}$ −81.7°; $[\alpha]_D$ −26.6°. Anal. ($C_{23}H_{29}NO$) C, H, N.

(+)-(4a*S*,8a*S*)-3-[2-(Phenylethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (35): prepared from **17** and phenylacetyl chloride and recrystallized from ethyl acetate (54%); mp 210–212 °C; $[\alpha]_{365}$ +78.8°; $[\alpha]_D$ +25.6°. Anal. ($C_{23}H_{29}NO$) C, H. N.

3-[2-(Cyclobutylmethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aβ-isoquinolinyl]phenol (36): prepared from **16** and cyclobutanecarboxylic acid chloride. The maleate salt was recrystallized from ethyl acetate/ethanol (9:1) (20%): mp 136–138 °C. Anal. ($C_{24}H_{33}NO_5$) C, H, N.

Registry No. (±)-**1**, 58637-24-4; (±)-**7**, 111635-65-5; (±)-**8**, 51605-17-5; (±)-**8**·HBr, 111635-66-6; **9**, 59908-28-0; **10**, 59889-34-8; **11**, 111765-98-1; **12**, 111765-99-2; (±)-**13**, 51605-18-6; **14**, 111819-33-1; **14**·HBr, 83502-25-4; **15**, 111819-34-2; **15**·HBr, 83502-24-3; (±)-**16**, 58637-26-6; **17**, 111766-00-8; **18**, 111766-01-9; (±)-**20**, 58637-29-9; **21**, 111766-02-0; **22**, 111766-03-1; (±)-**23**, 111635-67-7; (±)-**23**·maleate, 111635-68-8; **24**, 111766-04-2; **25**, 111766-05-3; (±)-**26**, 58974-76-8; (±)-**26**·maleate, 58974-77-9; **27**, 111766-06-4; **28**, 111766-07-5; (±)-**29**, 63843-35-6; (±)-**29**·maleate, 63843-36-7; **30**, 59889-36-0; **30**·succinate, 60719-85-9; **31**, 59889-38-2; **31**·succinate, 111819-35-3; (±)-**32**, 58670-09-0; (±)-**33**, 51605-27-7; (±)-**33**·maleate, 111635-69-9; **34**, 111766-08-6; **35**, 111766-09-7; (±)-**36**, 63843-31-2; (±)-**36**·maleate, 63843-32-3; $PhCH_2COCl$, 103-80-0; c-C_3H_5COCl, 4023-34-1; c-C_4H_7COCl, 5006-22-4.

Supplementary Material Available: Tables giving the atomic coordinates, bond lengths, bond angles, and anisotropic temperature factors (5 pages). Ordering information is given on any current masthead page.