5-Aryl-3-azabicyclo[3.2.0]heptan-6-one Ketals, Compounds with Morphine-Like Analgesic Activity

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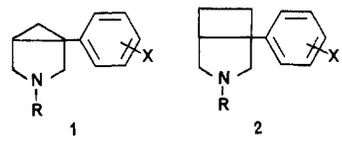
A series of 5-aryl-3-azabicyclo[3.2.0]heptan-6-one ketals **6** were synthesized by hydride reduction of 1-aryl-4,4-dimethoxy-1,2-cyclobutanedicarboximides **5**. Imides **5** were obtained as the sole, regioselective products of the [2 + 2] photocycloaddition of 1,1-dimethoxyethylene to 2-arylmaleimides. The *m*-methoxyphenyl-*N*-methyl analogue **6a** was demethylated to phenol **7** with EtSNa–DMF. Both **6a** and **7** were similar to morphine in analgesic potency in rats and mice and showed physiological effects that were identical with those of morphine and that were completely reversed by naloxone. Compound **7** was identical with morphine in its ability to displace [^{3}H]naloxone from homogenates of rat brain minus cerebellum. A molecular mechanics analysis of the *m*-methoxyphenyl analogue **6a** showed that the nitrogen atom, the methoxyphenyl group, and the methoxyl oxygen *cis* to the phenyl group can be superimposed on the corresponding features of the morphine molecule, and perhaps this accounts for the observed opiate–receptor binding properties of **7**.

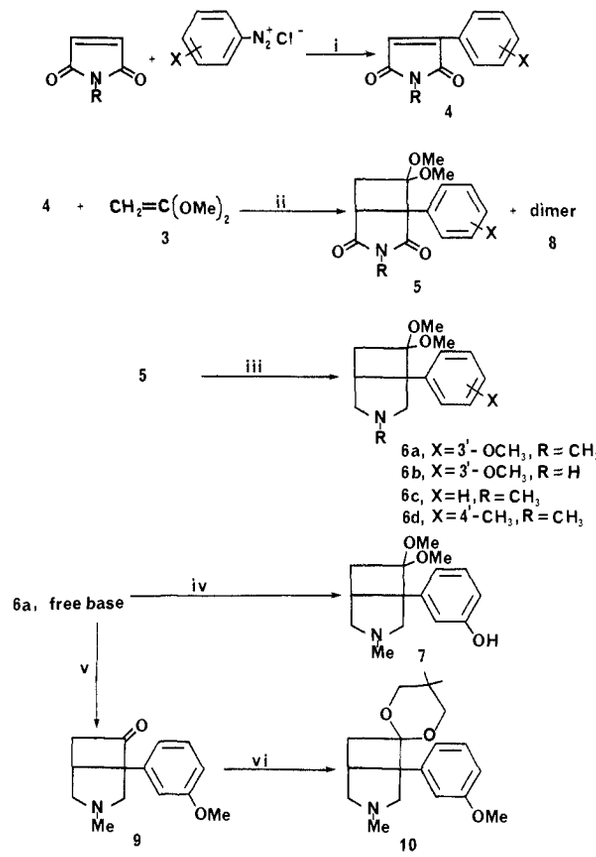
We have previously[1] reported on the nonnarcotic analgesic activity of 1-aryl-3-azabicyclo[3.1.0]hexanes, **1**, and



we wished to explore the pharmacological effects of homologation of this system to 1-aryl-3-azabicyclo[3.2.0]-heptanes, **2**. The route that was employed gave 5-aryl-3-azabicyclo[3.2.0]heptan-6-one dimethyl ketals **6**[2] as intermediates. These, and most notably phenol **7**, showed unexpected morphine-like activity. Thus, the present study is concerned with the chemical synthesis and pharmacology of the ketals **6a–d** and **7**. Elaboration of these compounds to the originally desired **2** will be the subject of a future paper.

Chemistry. Phenylmaleimides **4** (Table II) were prepared by the Rondestvedt[3] modification of the Meerwein reaction, as reported by Izzo.[4] In a previous communication[5] we reported the formation of an unusual Diels–Alder type dimer obtained in the synthesis of *N*-methyl-2-*p*-tolylmaleimide, as a result of excessive heating during the 2,6-lutidine dehydrohalogenation of the intermediate chlorosuccinimide. This side reaction was suppressed by dilution of the lutidine with isopropyl alcohol and by reduction of the heating time. Irradiation of the maleimides **4**, with Pyrex-filtered UV light, in neat 1,1-dimethoxyethylene (**3**) or in a solution of **3** in dichloromethane and in the presence of sodium carbonate gave the 1-aryl-4-oxo-1,2-cyclobutanedicarboximide dimethyl ketals **5** (Table III) as the sole, regioselective products in good yields, along with some dimer **8**, which was characterized only in the preparation of **5a**. The synthesis of cyclobutanone ketals by a [2 + 2] photocycloaddition of ketene acetals to α,β-unsaturated enones has been reported by Corey[6] and Boeckman,[7] wherein reactions were, likewise, regiospecific. The expected regiospecificity was observed for the formation of **5**, as confirmed by ^{1}H NMR spectroscopy. For **5a** the bridgehead methine proton at δ 3.32 is coupled to the adjacent cis and trans cyclobutane methylene protons, with a coupling constant of 4.4 and 10.5 Hz, respectively. Reduction of the imides **5** with sodium bis(2-methoxyethoxy)aluminum hydride in toluene gave the desired 5-aryl-3-azabicyclo[3.2.0]heptan-6-one dimethyl ketals, which were then converted to the corresponding fumarate salts **6a–d** (Table I). The aromatic methoxyl group of **6a** was efficiently demethylated[1,8] with sodium ethyl mer-

Scheme I[a]



[a] Reagents: i = (1) $CuCl_2$/acetone, (2) 2,6-lutidine/*i*-PrOH; ii = UV (Pyrex filter), neat or CH_2Cl_2; iii = (1) $NaAlH_2(OCH_2CH_2OCH_3)_2$/toluene, (2) fumaric acid; iv = (1) NaSEt/DMF, (2) HOAc; v = HCl/H_2O; vi = $HOCH_2C(CH_3)_2CH_2OH$/*p*-TosOH.

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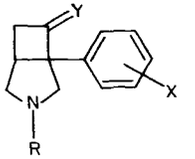
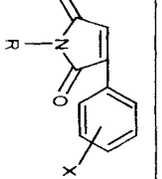
Table I. Physical Properties and Biological Activity of 5-Aryl-3-azabicyclo[3.2.0]heptan-6-one Ketals



compd	X	Y	R	mp, °C	yield, %	salt	formula[a]	3-legged gait (rat):[b] ED_{50} (95% CL), mg/kg ip	[^{3}H]naloxone binding: concn, μM	[^{3}H]naloxone binding: inhibn,[f] %
6a	*m*-OCH_3	$(OCH_3)_2$	CH_3	158-159	77[c]	fumarate	$C_{16}H_{23}NO_3 \cdot C_4H_4O_4$	4.0 (2.8-5.6), po	25	61 (±0.9)
									0.78	7 (±5.6)
6b	*m*-OCH_3	$(OCH_3)_2$	H	135-139	70[c]	fumarate	$C_{15}H_{21}NO_3 \cdot 1.5C_4H_4O_4$	>25	NT[e]	
6c	H	$(OCH_3)_2$	CH_3	167-169	86[c]	fumarate	$C_{15}H_{21}NO_2 \cdot C_4H_4O_4$	<25 (4/4A)	25	62 (±4.9)
									0.78	13 (±8.9)
6d	*p*-CH_3	$(OCH_3)_2$	CH_3	177-178	40[c]	fumarate	$C_{16}H_{23}NO_2 \cdot C_4H_4O_4$	R (25)[d]	25	62 (±2.6)
									0.78	11 (±3.8)
7	*m*-OH	$(OCH_3)_2$	CH_3	188-191	54	free base	$C_{15}H_{21}NO_3$	~3	25	99 (±8.5)
									0.78	85 (±7.3)
9	*m*-OCH_3	O	CH_3	128-131	81	fumarate	$C_{14}H_{17}NO_2 \cdot C_4H_4O_4$	R (25)[d]	25	22 (±5.7)
									0.78	12 (±4.9)
10	*m*-OCH_3	$OCH_2CMe_2CH_2O$	CH_3	166-167	82	fumarate	$C_{19}H_{27}NO_3 \cdot C_4H_4O_4$	<25 (8/10A)	NT[e]	
morphine sulfate								35 (5-233), po	25	100 (±3.3)
								0.4 (0.06-2.0), sc	0.78	97 (±3.2)

[a] The analyses of all new compounds were within 0.4% of the theoretical value for C, H, and N. [b] Inflammed rat-paw reversal of abnormal (three-legged) gait. Less than 95% of vehicle-treated rats exhibited any reversal of abnormal gait. A (active): a ≥50% reduction of abnormal gait was considered a positive analgesic response. [c] Procedure C. [d] R (reject): highest dose tested, inactive. [e] NT, not tested. [f] Standard deviation was determined from triplicate binding experiments.

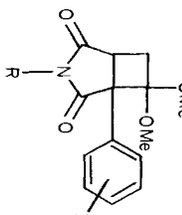
Table II. Physical Properties of 2-Arylmaleimides 4. Procedure A



compd	X	R	mp, °C	yield, %	formula[a]
4a	*m*-OCH_3	CH_3	146-148	39	$C_{12}H_{11}NO_3$
4b	*m*-OCH_3	H	157-158	29	$C_{11}H_9NO_3$
4c[b]	H	CH_3	147-148	71	$C_{11}H_9NO_2$
4d	*p*-CH_3	CH_3	124-126	30	$C_{12}H_{11}NO_2$

[a] The analyses of all new compounds were within 0.4% of the theoretical value for C, H, and N. [b] Described in ref 21.

Table III. Physical Properties of 1-Aryl-4,4-dimethoxy-1,2-cyclobutanedicarboximides. Procedure B



compd	X	R	mp, °C	yield, %	formula[a]
5a	*m*-OCH_3	CH_3	113-115	66	$C_{16}H_{19}NO_5$
5b	*m*-OCH_3	H	125-130	30	$C_{15}H_{17}NO_5$
5c	H	CH_3	144-144.5	93	$C_{15}H_{17}NO_4$
5d	*p*-CH_3	CH_3	138-144	30	$C_{16}H_{19}NO_4$

[a] The analyses of all new compounds were within 0.4% of the theoretical value for C, H, and N.

captide in dimethylformamide to give phenol **7** with no alterations in the ketal group. Hydrolysis of **6a** to the ketone **9** (Table I) was accomplished with hot, aqueous hydrochloric acid, and this was reketalized to **10** (Table I) with 2,2-dimethyl-1,3-propanediol and 1.1 equiv of *p*-toluenesulfonic acid.

Pharmacology. The results of analgesic testing using the reversal of the abnormal (three-legged) gait in rats,[1,9] along with the inhibition of [^{3}H]naloxone binding,[10,11] is shown in Table I. The interesting fact about these compounds is that they adhere to the same constraints that govern analgesic activity and opiate binding properties for the morphine family of compounds. Thus, the most potent members of the series in the three-legged gait test are the *m*-hydroxyphenyl (**7**) and the *m*-methoxyphenyl-*N*-methyl (**6a**) analogues. Like morphine, **7** shows limited oral (po) activity but is quite potent by a parenteral route, ED_{50} = 3 mg/kg, intraperitoneally (ip). If compound **6a**, then, is to be considered the codeine analogue by virtue of its aromatic methoxy group, it is noteworthy that the oral

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Table IV. IC_{50} Values in Competition Binding with [^{3}H]Naloxone in the Presence and Absence of Na^+ Ions[a]

compd	IC_{50}, nM −NaCl	IC_{50}, nM +NaCl (100 mM)	Na index
codeine	2600	22 000	8.5
naloxone	46	42	0.91
morphine sulfate	74	380	5.1
levallorphan	9	34	3.7
6a	9924	62 531	6.3
7	61	579	9.4

[a] IC_{50} is defined by the concentration of drug required to inhibit by 50% the stereospecific binding of [^{3}H]naloxone (5 nM) to homogenates of rat brain minus cerebellum in the presence or absence of 100 mM NaCl. The sodium index [IC_{50} ($+Na^+$)/IC_{50} ($-Na^+$)] is the ratio of the IC_{50} values for inhibition by drugs of [^{3}H]naloxone binding in the presence of 100 mM NaCl to the IC_{50} values in the absence of added NaCl. Each analysis involved eight displacing concentrations of ligand, and was carried out in triplicate.

potency (ED_{50} = 4 mg/kg) is equivalent to that of the morphine congener **7**, while codeine has a lower potency (ED_{50} = 51 mg/kg, po[1]) in this procedure. As expected,[12] the secondary amine **6b** showed significantly diminished potency. The deoxy analogue **6c** paralleled 3-deoxydihydromorphine,[13] showing a retention of analgesic activity. The *p*-tolyl compound (**6**), which was prepared as an intermediate for the bicifadine (**1**, X = *p*-CH_3; R = H) homologue, was devoid of analgesic activity. The lack of activity for the ketone **9** suggests that the ketal remains intact in vivo and is required for the observed narcotic analgesic activity in these compounds. The spiroketal **10** shows analgesic activity; however, narcotic-type activity was not assessed. The compounds that were active in this analgesic screen (**6a,c** and **7**) also showed overt morphine effects, such as catatonia, exophthalmus, decreased respiration, and decreased motor activity in rats and Straub tail in rats and mice. These effects were completely inhibited by naloxone. Due to the oral potency of **6a**, it was evaluated further. It was active in the rat tail flick–high-intensity radiant heat stimulus[14] (ED_{50} = 5.7 mg/kg, po) and the mouse hot plate test[15] (55 °C), showing a significant increase in threshold response at 20 mg/kg, subcutaneously (sc) or po. The LD_{50} of **6a** in rats was 20 mg/kg, po, however, indicating a low therapeutic ratio. Table I also compares the inhibition of [^{3}H]naloxone binding by compounds at 25 and 0.78 μM concentrations, and it is interesting that compound **6a** shows inhibition in a range that is comparable to the less active and inactive compounds **9c** and **9d**, respectively. However, phenol **7** shows binding characteristics that parallel those of morphine. Table IV compares the IC_{50} values of **6a** and **7** in [^{3}H]naloxone binding, as well as the sodium index values, which are indicative of the agonist/antagonist characteristics of opiate–receptor binding compounds. Compound **6a** has an IC_{50} value of around 1×10^4 nM, with a sodium index (6.3) equivalent to that of morphine (5.1), a pure agonist, while the phenol **7** has an IC_{50} value (61 nM)

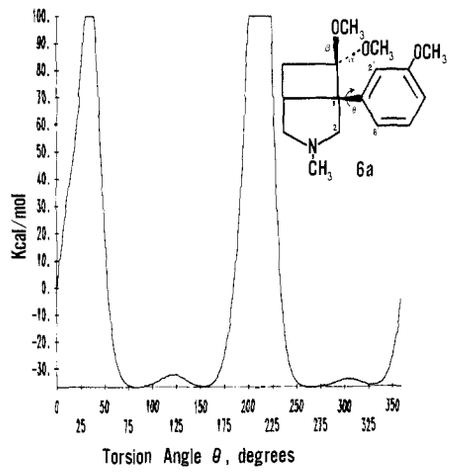

Figure 1. Energy barrier for rotation of the phenyl group about torsion angle θ in compound **6a**.

equivalent to morphine (74 nM). In addition, the sodium index of **7** (9.4) defines it as a pure agonist that binds to the μ-receptor. The potent narcotic analgesic activity of **6a**, in relationship to its moderate displacement of [^{3}H]-naloxone, is perhaps due to metabolism to **7**.

Discussion

On simple inspection, phenol **7** contains some of the features of the "morphine pharmacophore",[12] which include a basic, tertiary, methyl-substituted nitrogen atom that is attached by a two-carbon bridge to a quaternary carbon atom, which, in turn, is disposed meta to a hydroxyphenyl group. Molecular mechanics analysis of **6a** was used to compare nonbonded interatomic distances for comparison with the morphine molecule, as well as to study the energy barriers for rotation of the phenyl group. The calculated nonbonded interatomic distance from N to the β-methoxyl oxygen for **6a** is 4.50 Å, while the distance to the α-methoxyl oxygen is 3.26 Å. For morphine, the N to ether-oxygen distance is 5.25 Å, and the distance to the allylic oxygen is 6.74 Å. These data, along with a comparison of molecular models, suggest that the nitrogen, β-methoxyl oxygen, and phenoxyl portion of **6a**/**7** can be superimposed on the nitrogen, ether oxygen, and phenoxyl portion of the morphine molecule, thereby possibly accounting for the morphine-like behavior of these compounds. For the best overlap of the phenyl group of **6a**/**7** and that of morphine, the torsional angle described by the phenyl plane and the C-1 to C-2 bond of **6a**/**7** is 1.3°, with N to phenoxyl-oxygen distances of 7.15 and 7.14 Å for **6a**/**7** and morphine, respectively. If the morphine-like opiate receptor binding properties of **2** require the above conformation for the phenyl ring, then a calculated energy of 39 kcal would be required, relative to an energy minimum with a rotation of −31° at a torsional angle of 330°. Receptor binding is probably occurring with the phenyl ring oriented within this range of torsional angles. The high energy barriers to rotation of the phenyl ring (Figure 1) are primarily due to interactions between the 2′/6′ (ortho) hydrogens and the β-methoxyl oxygen.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses are within ±0.4% of theory. ^{1}H NMR spectra were obtained on a Varian Associates HA-100A spectrometer, and chemical shifts are reported in δ units downfield from tetramethylsilane as the internal standard. ^{1}H NMR spectra were obtained for all intermediates and final products, and were consistent with the assigned structures. IR spectra were measured on a FT Nicolet 7199 (50 scans) spectrometer. UV spectra were run on a Varian Cary 219 spectrophotometer. Mass spectra were

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obtained on a Varian CH-7 spectrometer at 70 eV. Where noted, specific synthetic procedures are representative of general methods used for the preparation of the compounds in Tables I–III. Vitride-T is a trade name for sodium bis(2-methoxyethoxy)aluminum hydride in toluene.

2-(3-Methoxyphenyl)-*N*-methylmaleimide (4a). Procedure A (Table II). A 126 g (1.02 mol) portion of *m*-anisidine was dissolved in a mixture of 300 mL of 12 N hydrochloric acid and 100 mL of water and cooled in an ice–salt bath, and this was then diazotized by the dropwise addition of a solution of $NaNO_2$ in 160 mL of H_2O, at 0–5 °C with vigorous stirring. To this mixture was then added a solution of 113.5 g (1.02 mol) of *N*-methylmaleimide in 800 mL of acetone at 0 °C, the pH was adjusted to 3 with solid NaOAc, and then 25 g of $CuCl_2 \cdot 2H_2O$ was added in one portion with stirring. The mixture was stirred for 3 h as it slowly warmed to room temperature, with the pH being adjusted to 2.9 periodically. There were sporadic evolutions of gas. After 18 h at room temperature, the mixture was filtered to give 47 g of brown solid. This was combined with 25 g of 2,6-lutidine in 125 mL of *i*-PrOH, the mixture was heated on a stream bath for 15 min, and then 100 mL of H_2O was added. The mixture was filtered, and the dark brown solid was washed with *i*-PrOH and then ether to give 86.5 g (39%) of product as yellow crystals, mp 138–146 °C. Recrystallization from EtOH gave yellow crystals: mp 146–148 °C; ^1H NMR (Me_2SO-d_6) δ 2.93 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 7.24 (s, 1, vinyl H); IR (KBr) 1695 (C=O) cm^{-1}; UV (MeOH) λ_{max} 222 nm (ϵ 1200), 255 (10900), 275 (5600), 345 (3300). Anal. ($C_{12}H_{11}NO_3$) C, H, N.

4,4-Dimethoxy-1-(3-methoxyphenyl)-*N*-methyl-1,2-cyclobutanedicarboximide (5a). Procedure B (Table III). Bis(3-methoxyphenyl)-*N*,*N*′-dimethyl-1,2,3,4-cyclobutanetetracarboxylic 1,2:3,4-Diimide (8). A mixture of 5 g (23 mmol) of **4a**, 49 g (0.5 mol) of 1,1-dimethoxyethylene, and 0.5 g of K_2CO_3 in 250 mL of CH_2Cl_2 was irradiated in a photochemical reactor fitted with a Pyrex well and a 400-W Hanovia, medium-pressure, ultraviolet lamp. After 1 h, all **4a** had been consumed (TLC, silica gel, 30% EtOAc–hexane). An additional 5 g of 4a was added, and irradiation was continued. This process was repeated until 30 g (0.138 mol) of **4a** was reacted. The solution was evaporated to a volume of 200 mL and filtered to give 3.11 g (10% yield) of dimer **8** as a tan solid. Recrystallization from CH_2Cl_2 gave colorless crystals: mp 207–208 °C; ^1H NMR (Me_2SO-d_6) δ 2.94 (s, 6, NCH_3), 3.73 (s, 6, OCH_3), 4.68 (s, 2, CHCO), 6.66–6.99 (m, 2, *p*-H), 6.99–7.41 (m, 6, aromatic H); UV λ_{max} (MeOH) 270 nm (ϵ 3800); IR (KBr) 1723 (imide C=O) cm^{-1}; mass spectrum, *m*/*z* (relative intensity) 434 (2.1), 349 (1.4), 264 (1.0), 217 (100). Anal. ($C_{24}H_{22}N_2O_6$) C, H, N.

The filtrate from the above reaction mixture was evaporated to 100 mL, cooled, and filtered to give 23.4 g (56% yield) of **5a** as colorless crystals: mp 113–115 °C; ^1H NMR ($CDCl_3$) δ 2.41 (dd, J = 18.5 and 5.5 Hz, 1, cis H), 2.97 (s, 3, NCH_3), 3.03 (s, 3, OCH_3), 3.32 (s, 3, OCH_3), 3.82 (s, 3, phenyl OCH_3), 6.71–7.04 (m, 1, *p*-H), 7.04–7.51 (m, 3, phenyl H); UV λ_{max} (MeOH) 282 nm (ϵ 2570), 275 (2750); IR (KBr) 1765 (C=O) cm^{-1}; mass spectrum, *m*/*z* (relative intensity) 305 (1.9), 217 (6.0), 132 (60), 88 (100). Anal. ($C_{16}H_{19}NO_5$) C, H, N.

6,6-Dimethoxy-5-(3-methoxyphenyl)-3-methyl-3-azabicyclo[3.2.0]heptane (6a) Fumarate. Procedure C (Table I). A mixture of 5.00 g (16.4 mmol) of imide **5a**, 50 mL of Vitride-T, and 50 mL of toluene was stirred at room temperature for 0.5 h and then refluxed for 18 h. The cooled reaction mixture was carefully quenched with 30 mL of 10 N NaOH, and the precipitated oil was extracted with ether and dried over Na_2SO_4. Evaporation of the solvent gave 3.75 g of red oil, which was distilled on a Kugelrohr apparatus at 145 °C (0.04 mm) to give 3.50 g (77%) of a colorless oil. This was combined with an equimolar amount of fumaric acid in boiling acetone to give **6a** fumarate as colorless crystals: mp 158–159 °C; ^1H NMR (Me_2SO-d_6) δ 2.57 (s, 3, NCH_3), 2.70 (s, 3, OCH_3), 3.18 (s, 3, OCH_3), 3.78 (s, 3, phenyl OCH_3), 6.59 (s, 2, CH=CH), 6.70–7.00 (m, 3, phenyl H), 7.04–7.40 (m, 1, 5′-H), mass spectrum (free base), *m*/*z* (relative intensity) 277 (1.7), 246 (1.9), 189 (46.1), 188 (100). Anal. ($C_{16}H_{23}NO_3 \cdot C_4H_4O_4$) C, H, N.

6,6-Dimethoxy-5-(3-hydroxyphenyl)-3-methyl-3-azabicyclo[3.2.0]heptane (7). To 2.4 g of 50% NaH–mineral oil (0.05 mol) in 15 mL of DMF at 0 °C was added a solution of 4.4 mL (3.7 g, 0.06 mol) of ethanethiol (stench!) in 10 mL of DMF over 0.5 h (foaming occurred). Then, a solution of 2.77 g (0.010 mol) of the free base of **6a** in 10 mL of DMF was added in one portion, and this mixture was refluxed for 3 h, during which the evolved MeSEt was trapped with a scrubbing tower containing coarse, activated charcoal. The DMF was removed in vacuo, 25 mL of H_2O was added to the residue, and the mineral oil was extracted with ether. The aqueous solution was decolorized with charcoal, and glacial AcOH was added to the filtered solution to pH 8. The precipitated tan crystals were collected and air-dried to give 1.30 g (49%) of **7**. Recrystallization from EtOAc–MeOH gave 1.00 g of colorless crystals: mp 188–191 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3, NCH_3) 2.87 (s, 3, OCH_3) 2.26 (s, 3, OCH_3), 6.70 (m, 3, phenyl H), 7.04 (t, 1, 5′-H), 8.88 (br s, 1, OH); IR (KBr) 2950 (OH), 1560 cm^{-1}. Anal. ($C_{15}H_{21}NO_3$) C, H, N.

5-(3-Methoxyphenyl)-3-azabicyclo[3.2.0]heptan-6-one (9) Fumarate. A mixture of 4.99 g (18 mmol) of **6a** and 50 mL of 10% HCl was refluxed for 15 min, cooled, and then diluted with 50 mL of 10% NaOH. The resultant oil was extracted with CH_2Cl_2, dried over Na_2SO_4, and then evaporated to give 3.91 g of red oil. Kugelrohr distillation at 140 °C (0.15 mm) gave 3.39 g (81% yield) of the free base of **9** as a yellow liquid. A 2.18-g portion of the oil was combined with 1.20 g of fumaric acid in 100 mL of hot acetone to give 2.25 g of **9** fumarate as colorless crystals: mp 130–134 °C; ^1H NMR (Me_2SO-d_6) δ 2.36 (s, 3, NCH_3), 3.78 (s, 3, OCH_3), 6.64 (s, 2, CH=CH), 6.70–7.00 (m, 3, phenyl H), 7.16–7.42 (m, 1, 5′-H); IR (KBr) 3427 (br, OH), 2479 (br, NH^+), 1786 (cyclobutanone), 1707 (acid) cm^{-1}; mass spectrum (free base), *m*/*z* (relative intensity) 231 (100), 216 (47), 188 (91). Anal. ($C_{14}H_{17}NO_2 \cdot C_4H_4O_4$) C, H, N.

5-(3-Methoxyphenyl)-3,5′,5′-trimethylspiro[3-azabicyclo[3.2.0]heptane-6,2′-[1,3]dioxane] (10) Fumarate. A solution of 1.18 g (5.10 mmol) of **9** (free base), 0.78 g (7.49 mmol) of 2,2-dimethyl-1,3-propanediol, and 1.05 g (5.52 mol) *p*-toluenesulfonic acid monohydrate in 25 mL of toluene was refluxed for 29 h with a Dean–Stark separator. The reaction mixture was diluted with ether, washed with 10% NaOH and then H_2O, and then evaporated to give 1.64 g of a brown oil. Kugelrohr distillation gave 1.33 g (82%) of the free base of **10** as a colorless oil, bp 175 °C (0.1 mm).

A 1.02-g portion of the oil in 10 mL of acetone was added to 0.400 g of fumaric acid in 30 mL of acetone. The solution was evaporated to 35 mL and cooled to give 1.31 g of **10** fumarate as colorless crystals: mp 166–167 °C dec. Anal. ($C_{23}H_{31}NO_7$) C, H, N.

Pharmacological Methods. Inflamed Rat-Paw Reversal of Abnormal Gait. A modification[1] of the procedure of Atkinson and Cowan[9] was used as the primary assay.

Inhibition of [^{3}H]Naloxone Binding. Inhibition of [^{3}H]-naloxone binding was conducted employing the procedure originally described by Pert and Snyder[9,10] and modified by Ong et al.[11]

Mouse Hot-Plate Method. An adaptation of the method of Eddy et al.[15] was employed. Individual mice were confined on a heated surface (Techni Lab Instruments, Model 475) maintained at 55.0 ± 0.5 °C, and the time required to elicit a response (licking of paws or an attempt to jump from plate) was recorded. A maximum (cut-off) time of 30 s was used. Compounds were prepared in a 2% starch suspension containing 5% polyethylene glycol and a drop of Tween 80 and administered orally or subcutaneously in a constant volume of 10 mL/kg. The criterion for analgesia is a 100% increase in response time over that of vehicle-treated mice.

Rat Tail Flick–Radiant Heat Method. A modification of the method of D'Amour and Smith[14] was used. The tail of each rat was exposed to high-intensity radiant heat stimulus 90 min after oral administration of the compound, and the time required to elicit a threshold response (characteristic tail flick) was recorded. A maximum exposure (cut-off time) of 15 s was employed for the high-intensity stimulus. Compounds were prepared in a 2% starch suspension containing 5% polyethylene glycol 400 and a drop of Tween 80 and administered in a constant volume of 5 mL/kg. The criterion for analgesia is a 100% increase in response time over that of vehicle-treated rats.

Statistics. ED_{50}'s and 95% confidence limits were calculated according to the linear arc sine transformation method of Finney.[16]

Molecular Mechanics and Computer Graphics. The coordinates for the atoms in **6a** were calculated with the program MMII,[17] These data were used with the Lederle molecular modeling system VAX 11/780 with an Evans and Sutherland Multi Picture System to graphically superimpose **6a** with the morphine crystal structure[18] so that the root mean square deviations in the nonbonded distances between the N, 1′-phenyl C, 1-C, and 7-β-methoxyl oxygen atoms of **6a** and the N, C-12, C-13, and the ether oxygen of morphine were minimized.[19,20] The phenyl ring of **6a** was then rotated around the C-1–C-1′ bond to align the ring and its oxygen atom with the corresponding features of morphine. The degree of superimposition of the molecules was then studied by rotating the structures around the various axes.

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Registry No. **3**, 922-69-0; **4a**, 66504-57-2; **4b**, 64643-37-4; **4c**, 54433-49-7; **4d**, 716-00-7; **5a**, 88905-19-5; **5b**, 88905-20-8; **5c**, 88905-21-9; **5d**, 88905-22-0; **6a**, 88905-31-1; **6a** (base), 88905-23-1; **6b**, 88905-32-2; **6b** (base), 88905-24-2; **6c**, 88905-33-3; **6c** (base), 88905-25-3; **6d**, 88905-34-4; **6d** (base), 88905-26-4; **7**, 88905-27-5; **8**, 88905-28-6; **9**, 88905-35-5; **9** (base), 88905-29-7; **10**, 88905-36-6; **10** (base), 88905-30-0; 3-$CH_3OC_6H_4NH_2$, 536-90-3; 3-$CH_3OC_6H_4N_2^+Cl^-$, 19183-05-2; $C_6H_5NH_2$, 62-53-3; $C_6H_5N_2^+Cl^-$, 100-34-5; 4-CH_3NH_2, 106-49-0; 4-$CH_3C_6H_4N_2^+Cl^-$, 2028-84-4; $HOCH_2C(CH_3)_2CH_2OH$, 126-30-7; maleimide, 541-59-3; *N*-methylmaleimide, 930-88-1.

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Novel Opiates and Antagonists. 6.[1] 7-Alkyl-6,7-didehydromorphinans

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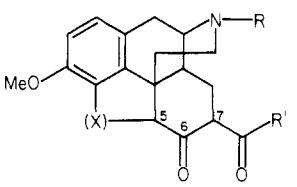
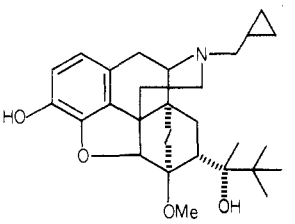
A method for preparing a variety of 7-alkyl-6,7-didehydromorphinans from the corresponding 6-morphinanones is described. The key intermediates in this sequence are the 7-formyl derivatives. The two epimeric *B/C-trans*-7-(1-hydroxypentyl)morphinans (**16a,b**) are stereochemically similar to the *endo*-ethanotetrahydrooripavines and are extremely potent in the mouse writhing test. The corresponding *B/C-cis*-7-(1-hydroxypentyl)morphinans are inactive in this test.

Recently, it was demonstrated that acyl group substitution at position 7 of hydromorphone afforded a series of compounds (**1a**) whose narcotic analgesic agonist and



1a, X = -O-
b, X = -H, H-



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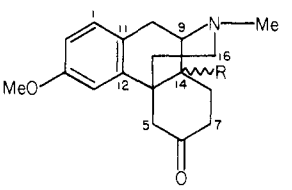
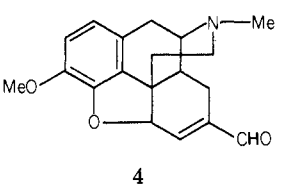
antagonist activities paralleled those of the *endo*-ethanotetrahydrooripavines, e.g., buprenorphine (**2**).[3] In order to further enhance the structural similarity of these 7-acyl derivatives to **2**, we desired to make two further modifications on **1a**. Removal of the furano ring would allow the preparation of *B/C-trans*-morphinans and, thus, yield compounds with the same stereochemistry as **2** at C-14. Secondly, removal of the carbonyl at position 6 would stabilize the desired α-hydroxyl group on the alkyl side chain.

Accomplishment of the first goal was initially attempted by preparation of diketone **1b** from the morphinan enamine or enol. There have been no reports of enamine formation from the morphinanones **3**; likewise, all our attempts failed.[4] Our efforts were then turned to the development of a new methodology that might accomplish both goals simultaneously. We report here the details of



3a, R = H
b, R = ||||H



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that method, which requires the 7-formyl derivatives **4** or **14** as key intermediates. The effects of such modifications on the analgesic activity are also reported.

Chemistry. The reduction of, or alkyllithium addition to, (alkylthio)methylene ketones, followed by acid hydrolysis, affords α,β-unsaturated aldehydes.[5] The (alkylthio)methylene ketones may be prepared by treatment of either the α-formyl ketones[5] or the (dimethylamino)-methylene ketones[6] with an alkanethiol. The latter route was attractive for the preparation of the key intermediates,

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