Piperidine Derivatives: Synthesis of Potential Analgesics in 3-Substituted 4-Phenylpiperidine Series

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Abstract □ The syntheses of 1-methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-piperidinol and 1-methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-propanoyloxypiperidine are described. Preliminary pharmacological testing showed these compounds to be weakly active in the writhing test.

Keyphrases □ Piperidine derivatives—synthesized, pharmacological activity evaluated □ Analgesic activity, potential—piperidine derivatives synthesized and evaluated □ Structure–activity relationships—piperidine derivatives, pharmacological activity evaluated

Various compounds based on the morphinan nucleus and its fragments were synthesized, and several correlations of structure–analgesic activity relationships were made (1, 2). However, relatively few, if any, definitive studies were reported on remote peripheral areas that are not in the proximity of the active or essential binding area of the molecule, *e.g.*, the polycyclic moiety of the benzomorphans. A series of morphine derivatives (I) was synthesized (3) with remarkably high analgesic activities (in some cases 10,000 times morphine), and additional binding sites believed to be located away from the periphery of the polycyclic nucleus were postulated (4).

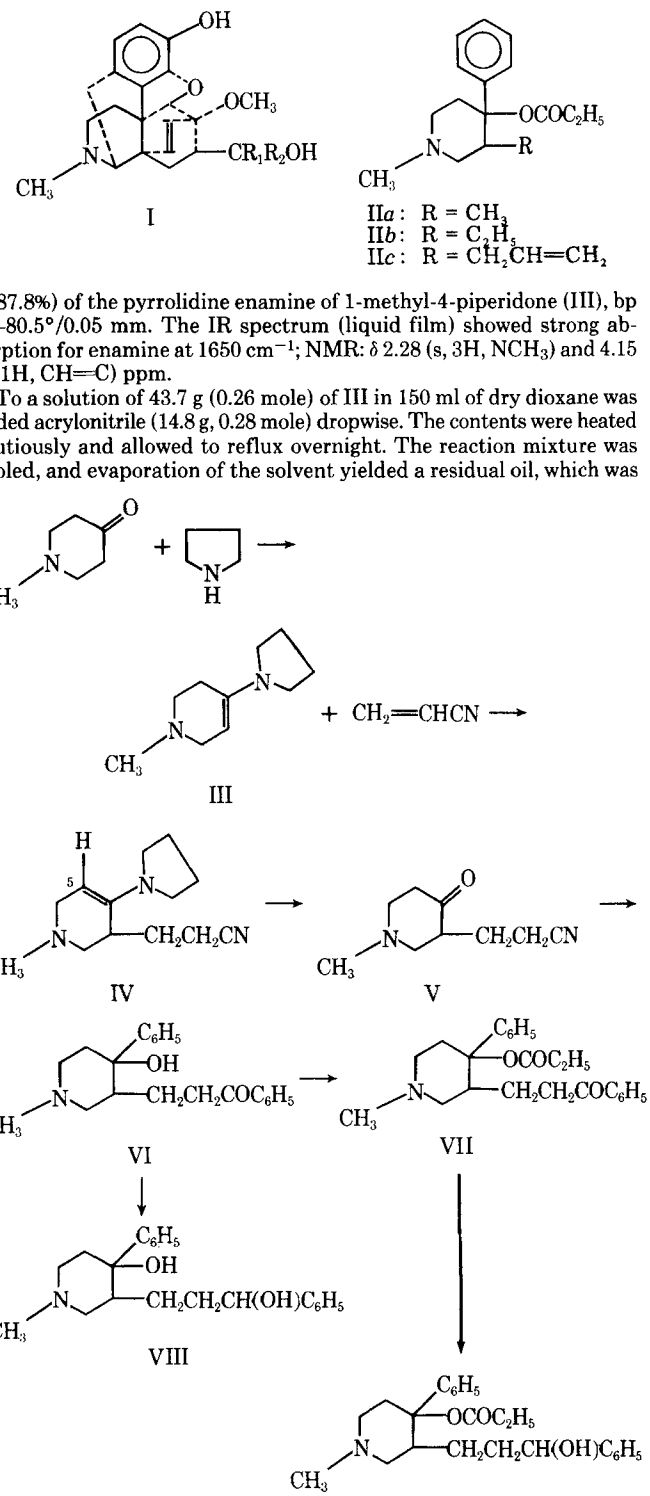
Substitutions at the 3-position in the 4-phenylpiperidines produced compounds with significant analgesic activity, *e.g.*, the 3-methyl (II*a*), 3-ethyl (II*b*), and 3-allyl (II*c*) analogs in the "reversed ester" series of the 4-phenylpiperidines (1).

The purpose of this investigation was to synthesize compounds based on the 4-phenylpiperidine unit of the morphine derivative (shown by solid lines in Structure I) in an attempt to illustrate the significance of the alcoholic group and to determine a possible site of attachment in the periphery of the analgesic receptor. This report discusses the synthetic work involved in the preparation of 1-methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-piperidinol (VIII) and 1-methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-propanoyloxypiperidine (IX).

EXPERIMENTAL[1]

1-Methyl-3-cyanoethyl-4-piperidone (V)—A solution of 1-methyl-4-piperidone (33.9 g, 0.3 mole), pyrrolidine (42.6 g, 0.6 mole), and *p*-toluenesulfonic acid (10 mg) in 250 ml of dry toluene was refluxed overnight (~10 hr), and the water formed (7 ml) was removed using a Dean–Stark trap (Scheme I). The solvent and excess pyrrolidine were removed under reduced pressure; the residue, upon distillation, gave 43.7 g (87.8%) of the pyrrolidine enamine of 1-methyl-4-piperidone (III), bp 80–80.5°/0.05 mm. The IR spectrum (liquid film) showed strong absorption for enamine at 1650 cm^{-1}; NMR: δ 2.28 (s, 3H, NCH_3) and 4.15 (t, 1H, CH=C) ppm.

To a solution of 43.7 g (0.26 mole) of III in 150 ml of dry dioxane was added acrylonitrile (14.8 g, 0.28 mole) dropwise. The contents were heated cautiously and allowed to reflux overnight. The reaction mixture was cooled, and evaporation of the solvent yielded a residual oil, which was



Scheme I

[1] Melting points were determined in a Thomas-Hoover melting-point apparatus and are uncorrected. IR spectra were determined on a Beckman Acculab 3. NMR spectra were determined on a Hitachi Perkin-Elmer R-24. If not otherwise stated, the spectra were recorded in chloroform-*d* using tetramethylsilane as the internal standard. Mass spectra were obtained on an A.E.I. MS-902 spectrometer. Elemental analyses were performed by Baron Consulting Co., Orange, Conn. TLC was carried out on silica gel GF_{254} plates. The solvent systems used were: A, ammonium hydroxide-saturated benzene–methanol (4:1); and B, ammonium hydroxide-saturated chloroform–acetone (2:1). Dragendorff spray reagent was used to visualize products on TLC plates.

subjected to fractional distillation *in vacuo*. The fractions boiling between 130 and 141°/0.32–0.33 mm were combined to give 18.2 g (31.6%) of IV; IR (liquid film): 1645 (strong, enamine) and 2250 (medium, nitrile) cm^{-1}; NMR: δ 2.28 (s, 3H, NCH_3), 4.27, and 4.35 (dd, 1H, CH=C, J = ~3 Hz) ppm.

To 18.2 g of IV were added 60 ml of water and 80 ml of dioxane, and the mixture was heated at reflux temperature for 1.75 hr. Excess pyrrolidine and water were removed under reduced pressure; the residue was dissolved in chloroform, dried over anhydrous potassium carbonate, and filtered. Evaporation of solvent gave a residual oil which, upon distillation, yielded 10.4 g (75%) of 1-methyl-3-cyanoethyl-4-piperidone (V), bp 100–108°/0.20–0.27 mm; IR (liquid film): 1710 (strong, carbonyl) and 2245 (medium, nitrile) cm^{-1}; NMR: δ 2.28 (s, 3H, NCH_3) ppm.

An analytical sample of V was obtained by column chromatography (silica gel, 60–200 mesh, 80 g). Five grams of V was dissolved in a minimum amount of petroleum ether and chromatographed. Fractions of 15 ml were collected, and the column was eluted with solvents of increasing polarity [petroleum ether (bp 30–60°)–benzene (3:2), 1.5 liters, and (2:3) 1.5 liters; benzene, 2 liters; and benzene–ethanol (19:1), 1.5 liters]. Fractions 371–652 gave the desired product V (4.2 g, 84%), R_f 0.51 (System A). An analytical sample of V was obtained from fractions 643–650.

Anal.—Calc. for $C_9H_{14}N_2O$: C, 65.02; H, 8.49; N, 16.86. Found: C, 64.93; H, 8.46; N, 16.70.

1-Methyl -3- (3-phenyl-3-oxopropyl) -4- phenyl-4-piperidinol (VI)—Under a nitrogen atmosphere, a solution of phenyllithium was freshly prepared by allowing 23.5 g of bromobenzene and 2.13 g of lithium wire to react in 200 ml of anhydrous ether (Scheme I). The flask and its contents were immersed in an ice bath during the addition of 5 g (0.03 mole) of V. After the reaction mixture was stirred at 0–5° for 45 min and for 5 additional hr at room temperature, it was hydrolyzed by the slow addition of 100 ml of 10% sulfuric acid solution, during which time the flask and its contents were kept cool in an ice bath.

After stirring at room temperature for 14 hr, 50 ml of water was added and the contents were refluxed for 45 min. The flask was cooled, and the insoluble solid (13.5 g) was obtained by filtration. The solid was dissolved in water (with gentle warming), made basic with ammonium hydroxide solution, and extracted with chloroform (7 × 100 ml). The combined chloroform extracts were dried over anhydrous potassium carbonate and filtered. Evaporation of solvent gave an oil, 8.9 g (91.5%) of VI.

The oil was crystallized with 20 ml of ether to yield 6.5 g (66.8%) of piperidinol VI, mp 110–112° (with previous softening) after recrystallization from benzene. TLC showed VI to be a mixture, R_f 0.51 and 0.57 (System A). Attempts to separate the two compounds by repeated crystallizations were not successful; IR (potassium bromide): 3470 (OH) and 1675 (carbonyl) cm^{-1}; NMR: δ 7.09–7.80 (m, 10H, ArH) and 2.29 (s, 3H, NCH_3) ppm. The mass spectrum showed M^+ at m/e 323.

Anal.—Calc. for $C_{21}H_{25}NO_2$: C, 77.97; H, 7.79; N, 4.33. Found: C, 76.31, 75.99, 76.40; H, 7.94, 8.01, 7.70; N, 4.25, 4.22, 4.26.

Repeated recrystallizations did not improve the analysis. The picrate had a melting point of 207–211° after recrystallization from benzene–ethanol.

Anal.—Calc. for $C_{21}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 58.67; H, 5.11; N, 10.14. Found: C, 58.66; H, 5.13; N, 10.26.

1-Methyl-3-(3-phenyl-3-oxopropyl)-4-phenyl-4-propanoyloxypiperidine (VII)—To a solution of 2 g (0.006 mole) of VI and 2 ml of triethylamine (redistilled) in 25 ml of dry toluene was added 3.5 g of propanoyl chloride in 5 ml of dry toluene dropwise, with refluxing, over 15 min (Scheme I). The reaction mixture was heated under reflux temperature for an additional 1.5 hr. The flask was cooled, the contents were transferred with chloroform (50 ml) and water (20 ml) to a separator, and the layers separated.

The aqueous layer was extracted once with a 25-ml portion of chloroform. The combined chloroform extracts were dried over anhydrous potassium carbonate and filtered. Evaporation of the solvent gave a residue characterized as a hydrochloride by its IR spectrum (broad, 2500 cm^{-1}). The residue was made basic with 100 ml of saturated solution of sodium bicarbonate and then extracted with five 50-ml portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate and filtered.

Evaporation of the solvent gave an oil, 2.2 g (93.6%) of ester VII; IR (liquid film): 1735 (strong, ester), 1680 (strong, carbonyl), 760, and 700 (aromatic hydrogens) cm^{-1}. Unsuccessful attempts were made to effect crystallization of this oil using common solvents. The hydrochloride was prepared by passing anhydrous hydrogen chloride through an ethereal solution of the oil, mp 167–169° (after recrystallization from ethyl acetate–petroleum ether); NMR [deuterium oxide with sodium 3-(trimethylsilyl)propanesulfonate as internal standard]: 7.3–8.05 (m, 10H, ArH), 3.26 (s, 3H, NCH_3), and 1.25 (t, 3H, $OCOCH_2CH_3$, J = ~7 Hz) ppm. The hydrochloride was converted into a free base, and TLC showed it to be a mixture, R_f 0.73 and 0.84 (System A); the mass spectrum showed M^+ at m/e 379. An analytical sample of the hydrochloride was obtained after recrystallization from ethyl acetate–ethanol, mp 183–185°.

Anal.—Calc. for $C_{24}H_{30}ClNO_3$: C, 69.28; H, 7.27; N, 3.36. Found: C, 69.30; H, 6.98; N, 3.61.

The picrate had a melting point of 209.5–211° after recrystallization from benzene–ethanol.

Anal.—Calc. for $C_{24}H_{29}NO_3 \cdot C_6H_3N_3O_7$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.49; H, 5.34; N, 9.10.

1-Methyl-3-(3-hydroxy-3-phenylpropyl) -4-phenyl-4-propanoyloxypiperidine (IX)—To a solution of 5.07 g (0.013 mole) of VII and sodium hydroxide (0.25 g) in 10 ml of methanol was added a solution of sodium borohydride (1.28 g) and sodium hydroxide (0.25 g) in 15 ml of methanol dropwise, with stirring, at 0° (Scheme I). The funnel was washed with 5 ml of methanol, and the contents were allowed to stir at 0° for 6 hr and at room temperature for an additional 18 hr. At this point, 10 ml of water was added and stirring was continued for 15 min.

Most of the methanol was evaporated under reduced pressure, and the residue was extracted with chloroform (4 × 25 ml). The combined chloroform extracts were dried over anhydrous potassium carbonate and filtered. Evaporation of solvent gave 4.4 g of an oil. This material was dissolved in a minimum amount of benzene and was subjected to column chromatography (silica gel, 60–200 mesh, 80 g). The column was eluted with 6.1 liters of benzene–ethanol (16:1), and 15-ml fractions were collected.

Fractions 116–230, on evaporation, gave a solid, 0.70 g (13.8%) of IX, mp 153–155° (after recrystallization from benzene–heptane), R_f 0.45 (System A) and 0.77 and 0.66 (System B). The mass spectrum showed M^+ at m/e 381; IR (potassium bromide): 3400 (broad, not clear, OH), 1735 (strong, ester), 754, and 700 (aromatic hydrogens) cm^{-1}; NMR: δ 6.95–7.39 (m, 10H, ArH), 2.19 (s, 3H, NCH_3), 1.16 (t, 3H, $OCOCH_2CH_3$, J = ~7 Hz), and 4.34 (t, 1H, $CHOH$, J = ~6 Hz) ppm.

Anal.—Calc. for $C_{24}H_{31}NO_3$: C, 75.55; H, 8.19; N, 3.67; O, 12.59. Found: C, 75.31; H, 8.09; N, 3.89; O, 12.97.

1-Methyl-3-(3-hydroxy-3-phenylpropyl)-4-phenyl-4-piperidinol (VIII)—A solution of 2 g (0.006 mole) of VI, 2.56 g of sodium hydroxide, and 2.84 g of sodium borohydride in 160 ml of methanol was stirred for 48 hr at room temperature (Scheme I). At this point, 50 ml of water was added and the contents were allowed to stir for an additional 75 min at room temperature. Most of the methanol was removed under reduced pressure, and the aqueous phase was extracted with chloroform (5 × 50 ml). The combined chloroform extracts were dried over anhydrous potassium carbonate and filtered.

Evaporation of solvent yielded 1.6 g (79.5%) of VIII, mp 61–64° (after sublimation at 0.15 mm), R_f 0.49 and 0.55 (System A). The mass spectrum showed M^+ at m/e 325; IR (potassium bromide): 3390 (broad, OH), 754, and 700 (aromatic hydrogens) cm^{-1}; NMR: δ 7.22, 7.34 (two s, 10H, ArH), 2.22 (s, 3H, NCH_3), and 4.36 (t, 1H, $CHOH$, J = ~6 Hz) ppm.

Anal.—Calc. for $C_{21}H_{27}NO_2$: C, 77.49; H, 8.37; N, 4.31. Found: C, 77.67; H, 8.37; N, 4.59.

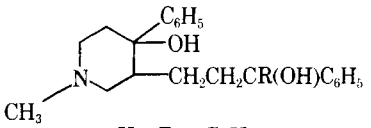
1-Methyl-3-(3-hydroxy-3,3-diphenylpropyl)-4-phenyl-4-piperidinol (X)—In a 500-ml flask, a solution of phenyllithium was freshly prepared by allowing 31.5 g of bromobenzene and 3.24 g of lithium wire to react in 90 ml of anhydrous ether under nitrogen for 2 hr at room temperature. The flask and its contents were immersed in an ice bath, and a solution of 2 g (0.006 mole) of VI in 10 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to stir at room temperature for 15 hr and was subsequently hydrolyzed by the slow addition of water (20 ml), during which time the flask and its contents were kept cool in an ice bath. After stirring for 1.5 hr at room temperature, the contents were poured into a separator and the layers separated.

The aqueous phase was extracted with ether (4 × 50 ml). The combined ether extracts were dried over anhydrous potassium carbonate and filtered. Removal of ether under reduced pressure gave 1.5 g (60.5%) of X, mp 171–172° (after two recrystallizations from heptane–carbon tetrachloride). The mass spectrum showed M^+ at m/e 401; IR (potassium bromide): 3425 (broad, OH), 758, and 700 (aromatic hydrogens) cm^{-1}; NMR: δ 7.14–7.32 (m, 15H, ArH) and 2.3 (s, 3H, NCH_3) ppm.

Anal.—Calc. for $C_{27}H_{31}NO_2$: C, 80.75; H, 7.79; N, 3.49. Found: C, 80.54; H, 7.95; N, 3.38.

RESULTS AND DISCUSSION

Chemistry—Reaction of the enamine III with acrylonitrile in dry dioxane gave IV. The conclusion that the product consisted of the tri-



X: R = C_6H_5
XI: R = CH_3

substituted isomer IV was based on NMR spectral evidence. The olefinic proton at C-5 appeared as two doublets centered at δ 4.27 and 4.35 ppm. The formation of the tetrasubstituted isomer was not expected on steric grounds, but analogous results were reported previously for the pyrrolidine enamines of 2-methylcyclohexanone and 2-phenylcyclohexanone (5). The presence of absorption bands at 1645 (enamine) and 2250 (nitrile) cm^{-1} in the IR spectrum further confirmed the structure. Hydrolysis of IV afforded the monoalkylated ketonitrile V.

The ketoalcohol VI was obtained by the reaction of V with phenyllithium. TLC indicated VI to be a mixture. Attempts to obtain the major diastereomer in high purity by repeated crystallizations proved unsuccessful. Satisfactory elemental analysis[2] for VI could not be obtained. Treatment of VI with propanoyl chloride in the presence of triethylamine in refluxing toluene afforded the desired compound VII as an oil. Compound VII was further characterized as a hydrochloride and picrate.

Selective reduction of ketones and aldehydes in the presence of other functional groups such as esters, amides, and alkylhalides is generally possible using sodium borohydride as a reducing agent (6). Thus, IX was prepared by the reaction of VII with sodium borohydride. Isolation of IX was achieved by column chromatography. Similarly, VIII was obtained in 79.5% yield by the treatment of VI with sodium borohydride.

Reaction of VI and VII with methylmagnesium bromide or iodide failed to give the desired compound XI. Treatment of VI with methyllithium or ethyllithium also failed. Enolization of VI possibly may hinder the desired addition by these reagents. However, addition at the aryl carbonyl was successfully achieved using phenyllithium. Compound X was obtained using this reagent.

The reaction of 3-substituted 4-piperidiones with aryl lithium could give a mixture of diastereomeric alcohols [XII (β-*cis*-R_1–R_3) and XIII (α-*trans*-R_1–R_3)]. Based upon the stereochemical course of addition to ketones (6), the formation of the *trans*-diastereomer (XIII) should be favored. Thus, by analogy with the results previously reported for the prodinols XII*b* and XIII*b* and the 3-allyl derivatives XII*c* and XIII*c* in which XIII*b* and XIII*c* were 60 and 91%, respectively, of the diastereomeric mixture (7, 8), it could be assumed that the major diastereomer would correspond to XIII*a* in the treatment of V with phenyllithium.

In the NMR spectrum (chloroform-*d*) of VI[3], a complex aromatic pattern was observed at δ 7.09–7.80 ppm (W_H = 15 Hz; Fig. 1A). Comparatively broader and more complex NMR signals were reported for the aromatic protons of *trans*-XIII*b* than for the corresponding *cis*-compound (9); furthermore, the band width at half-weight of the aromatic proton signals appeared to be considerably greater for the α-diastereomer (14 Hz) than for the β-diastereomer (5 Hz). Similar differences also were observed in the spectra of the 3-allyl derivatives XIII*c* (14 Hz) and XII*c* (4.5 Hz) (8). The *N*-methyl signal of VI appeared as a singlet (with the

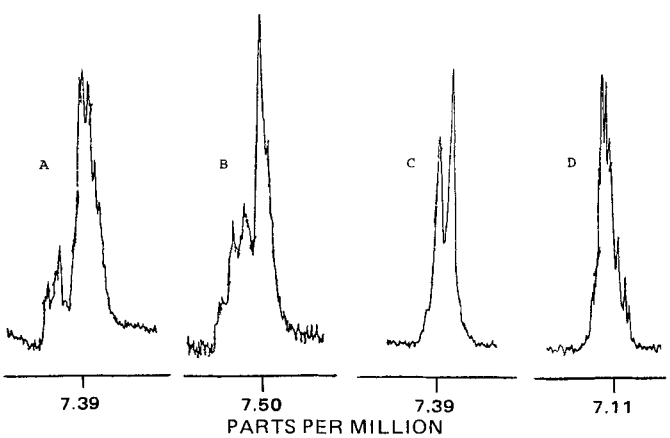
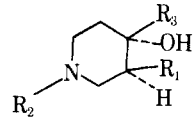
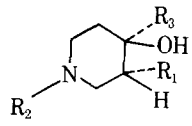


Figure 1—*Aromatic NMR signals of VI (A), VII (B), VIII (C), and IX (D).*



XII*a*–XII*e*



XIII*a*–XIII*e*

XII*a* and XIII*a*: R_1 = $CH_2CH_2COC_6H_5$, R_2 = CH_3, R_3 = C_6H_5
XII*b* and XIII*b*: R_1 = R_2 = CH_3, R_3 = C_6H_5
XII*c* and XIII*c*: R_1 = $CH_2CH{=}CH_2$, R_2 = CH_3, R_3 = C_6H_5
XII*d* and XIII*d*: R_1 = CH_3, R_2 = C_2H_5, R_3 = *o*-$CH_3C_6H_4$
XII*e* and XIII*e*: R_1 = CH_3, R_2 = $CH_2C_6H_5$, R_3 = *o*-$CH_3C_6H_4$

slight trace of the *N*-methyl signal of the other diastereomer) at δ 2.29 ppm.

A complex aromatic absorption was also seen in the NMR spectrum of VII[4] at δ 7.3–8.05 ppm (W_H = ~8 Hz; Fig. 1B). The *N*-methyl protons appeared as a 3H singlet at δ 3.26 ppm, and the methyl of the propanoyloxy ester was a triplet at δ 1.25 (J = ~7 Hz) ppm. However, the aromatic pattern of VIII[5] appeared as two sharp singlets at δ 7.22 and 7.34 ppm. The *N*-methyl signal appeared as a 3H singlet (W_H = ~6 Hz) at δ 2.22, and the benzylic proton appeared as a near 1:2:1 triplet at δ 4.36 (J = ~6 Hz) ppm.

In the NMR spectrum of IX[5], the aromatic pattern did not show a hump downfield and appeared less complex compared to the patterns of VI and VII. Perhaps the aromatic signal patterns of VIII and IX were being obscured to a greater extent by the C_6H_5CHOH signal than the VI and VII patterns were being obscured by the C_6H_5CO signal, assuming of course that the compound with the α-configuration in these diastereomeric mixtures was the predominant diastereomer. A similar example, in which the presence of another aromatic group in the molecule influences the aromatic pattern, is seen with XIII*d* and XIII*e* (10). The methyl signal of the propanoyloxy ester group in the NMR spectrum of IX was a triplet at δ 1.16 (J = ~7 Hz) ppm, and the benzylic proton appeared as a near 1:2:1 triplet (J = ~6 Hz) at δ 4.34 ppm.

Pharmacology—In preliminary pharmacological testing, VIII (NIH 9082) showed no activity in the hot-plate test (inactive up to 100 mg/kg) and in the tail-flick test (inactive up to 30 mg/kg); however, in the writhing test it had an ED_{50} value of 80.5 mg/kg in mice. Similarly, IX (NIH 9083) appeared inactive in the hot-plate test (inactive up to 50 mg/kg) and in the tail-flick test (inactive up to 30 mg/kg) but had an ED_{50} value of 32 mg/kg in the writhing test.

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[2] Microanalyses of the picrate of VI were, however, within 0.3% of theory.

[3] Assumed to be a diastereomeric mixture based upon stereochemical grounds and as indicated by its TLC (see *Experimental*).

[4] Hydrochloride salt in deuterium oxide with sodium 3-(trimethylsilyl)propanesulfonate as the internal standard. TLC indicated it to be a mixture.

[5] In chloroform-*d*. TLC indicated it to be a mixture.