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6-Demethoxythebaine and Its Conversion to Analgesics of the 6,14-Ethenomorphinan Type

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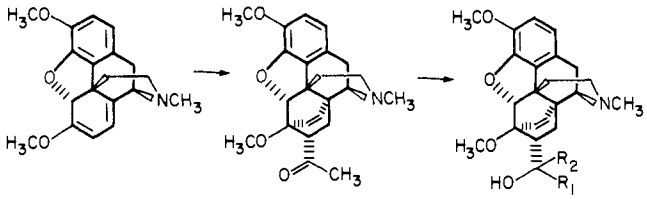
The 6-demethoxy analogue of thebaine has been easily prepared from codeine via isocodeine and its sulfenate ester. This diene, **7**, readily undergoes reaction with vinyl ketones to afford Diels–Alder adducts of the 6,14-ethenomorphinan type. Further reactions afford the epimeric 19(*R*)- and 19(*S*)-butyl-6-demethoxy-7α-orvinols (**16**). Pharmacological testing shows the *R* diastereomer to be highly analgesic and the *S* diastereomer to be a much less potent agonist, with similar potencies and relationships as found in the corresponding oripavine series. Thus, any hydrogen bonding between the 6-methoxyl group and the tertiary alcohol can be eliminated as contributory to either the activity of, or difference between, the epimeric orvinols.

In the search for more potent analgesics, a particularly interesting group has been the variety of bicyclic analogues of morphine derived from the Diels–Alder adducts of a number of dienophiles with thebaine (**1**).[2] Addition of

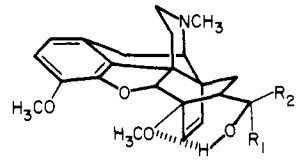


1 **2** **3**

organometallic reagents to thevinone (**2**), the bicyclic ketone prepared by Diels–Alder reaction of methyl vinyl ketone with thebaine, affords the alkylthevinols **3**. Some of the corresponding phenols, the alkylorvinols, have analgesic activities over 1000 times greater than morphine.[3] The activity differs between epimers (at C-19, orvinol nomenclature, or at the 7α-methanol, morphinan nomenclature), with the *R* epimer having much greater agonist activity.

Recently, Loew and Berkowitz have carried out quantum mechanical calculations for conformational differences between the C-19 epimers for various alkyl chain lengths.[4] Their calculations show that conformations with a hydrogen bond between the C-6 methoxyl and the C-19 hydroxyl are lowest in energy for both epimers, consistent with NMR and crystallographic results. With the hydroxyl group thus fixed, the larger substituent will occupy one of two different areas, depending on whether the absolute stereochemistry is *R* or *S*. The increased binding of the alkyl chain with a lipophilic site on the receptor might then account for an increase in the activity of one diastereomer relative to the other.

To examine this hypothesis, we have prepared the epimeric alcohols (*R*)- and (*S*)-**4** where the C-6 methoxyl



4

S, $R_1 > R_2$
R, $R_2 > R_1$

has been replaced by a hydrogen, namely, (*R*)- and (*S*)-**16**. In this way, intramolecular H bonding will be eliminated as a factor in determining the active conformation of the alkyl chain.

Chemistry. The preparation of 6-demethoxythebaine was first attempted starting from codeine (**5**) and using 1,4-elimination reactions. Codeinone dimethyl ketal can be converted to thebaine by treatment of the ketal with either phosphorous oxychloride in pyridine or with alkoxides.[5] Analogously, we considered that treatment of codeine or isocodeine methyl ethers with one of these reagents might result in elimination and give the diene. However, both methyl ethers decomposed on treatment with alkoxides in refluxing toluene. Codeine methyl ether returned only starting material upon reaction with phosphorous oxychloride, and isocodeine methyl ether gave a chlorocodide under the same conditions.

Preparation of the mesylates of codeine and isocodeine and the acetate and pivalate of isocodeine, followed by reaction with a variety of bases, gave decomposition products, alcoholysis products, or recovered starting material.

An effective procedure for the preparation of dienes from allylic alcohols has been recently developed using an arylsulfenyl chloride.[6] With this work as a model, codeine (**5**) was treated with 2,4-dinitrobenzenesulfenyl chloride, and the allylic sulfoxide, resulting from rearrangement of the sulfenate ester, was the product. Presumably, the trans relationship of the C-14 hydrogen and the sulfoxide prevented elimination. Attempted isomerization to the *cis*-

(1) Postdoctoral Fellow of the Schweizerischer Nationalfonds zur Forderung der Wissenschaftlichen Forschung.
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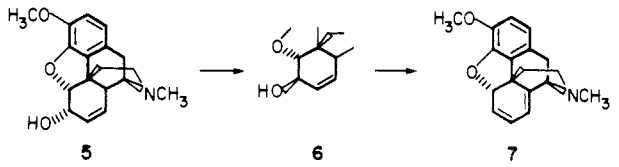


sulfoxide with lithium diisopropylamide or potassium *tert*-butoxide proved unsuccessful.

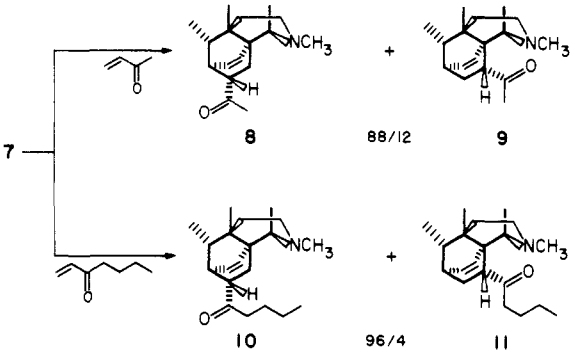
Isocodeine (**6**), however, on reaction with the sulfenyl chloride underwent rearrangement to the *cis*-sulfoxide which readily eliminated. Thus, codeine was converted to isocodeine (**6**) using *N*,*N*-dimethylformamide dineopentyl acetal and acetic acid in toluene, followed by methanolysis of the resulting isocodeine acetate, in an overall yield of 90%.[7] Treatment of isocodeine (**6**) with 2,4-dinitrobenzenesulfenyl chloride in dichloromethane afforded 6-demethoxythebaine (**7**) in 61% yield.[8]

Thebaine forms a 6,14-etheno adduct **2** with methyl vinyl ketone, which is a 98:2 mixture of C-7α/7β stereoisomers.[2] The absence of the regioisomeric ketone adduct is presumably a result of a combination of steric and electronic effects. The electronic effect is due to the polarization of the diene by the methoxyl group; thus, the dipolar Diels–Alder reaction gives only the observed regiochemistry. Since diene **7** has no polarizing functionality, only the steric effects will control the regiochemistry.

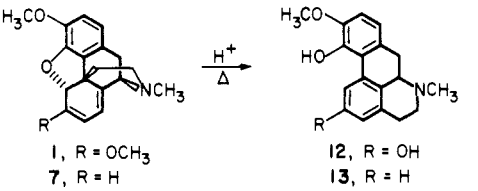
Reaction of 6-demethoxythebaine (**7**) with methyl vinyl ketone afforded the adduct in 50% yield. HPLC analysis showed that the ketone was an 88:12 mixture of 6-demethoxy-7α-thevinone (**8**) and a slightly less polar compound **9**. The preparative separation of **8** and **9** was very difficult; however, partial purification gave a sample of **8** which was enriched in **9**. Computer subtraction of the NMR spectrum of pure 6-demethoxy-7α-thevinone (**8**) from the NMR spectrum of **8** enriched in compound **9** gave a spectrum which indicates that ketone **9** is the 8α-regioisomeric adduct.

The chemical shift of the proton at C-5 appears to be diagnostic of the stereochemistry of the C-7 substituent in the 6-methoxy series.[9] A C-7α substituent has a signal at δ 4.5 for the C-5 proton; a C-7β substituent would give a shift to near δ 4.9 due to the anisotropy of the acetyl group. The chemical shift of δ 4.4 found for the proton on C-5 of compound **9** indicates it is not the **7** stereoisomer. The assignment of **9** as the 8α-acetyl compound rests on the chemical shift of the C-8 proton at δ 3.9, since now it is α to the ketone and in the deshielding region of the tertiary amine. The proton on C-9 also is shifted downfield due to the deshielding effect of the carbonyl group.

Reaction of 6-demethoxythebaine with butyl vinyl ketone, prepared from valeryl chloride,[10] gave the adduct 7α-valeryl-6-demethoxythevinone **10** in 72% yield. Again, a small amount, 4% by HPLC, of a less polar compound was isolated by chromatography and identified, by similar NMR analysis, as the regioisomer **11**. Apparently, the smaller amount of regioisomer produced with the butyl vinyl ketone than with the methyl vinyl ketone reflects the greater steric demand of the butyl group.

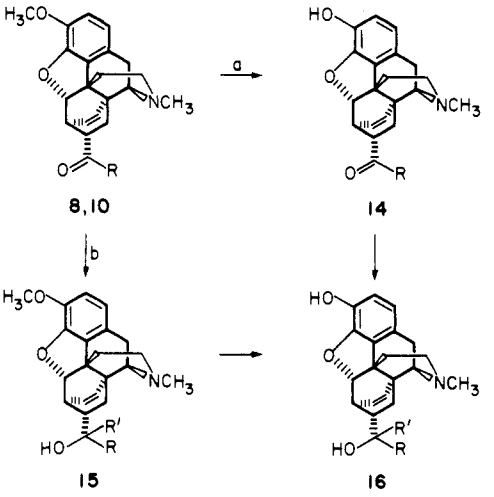


Since 6-demethoxythebaine (**7**) can be prepared easily,



it was of interest to observe whether **7** would undergo acid-catalyzed rearrangement in a manner analogous to thebaine. Thebaine, when heated in strong acid, rearranges to the aporphine **12**.[11] Recently, a detailed, convenient procedure for this rearrangement has been developed.[12] Following this protocol, diene **7** was treated with methanesulfonic acid at 95 °C and, as is the case with thebaine, rearrangement occurs readily, affording apocodeine hydrochloride (**13**·HCl) in 64% yield.

For the synthesis of the desired alcohols **16** from the Diels–Alder adducts there are two possible routes. Path a involves demethylation of the aryl ethers **8** or **10**, followed



by formation of tertiary alcohol **16**. Since the adduct contains a ketone, the demethylation would best be carried out under neutral or acidic conditions. The second route, path b, consists of alcohol formation and then phenolic demethylation, **15** → **16**.

Treatment of ketone **8** with boron tribromide[13] gave phenol **14a** in 82% yield. The demethylation of the butyl adduct **10** by boron tribromide proceeded in similar fashion and gave **14b** as a crystalline solid in 54% yield.

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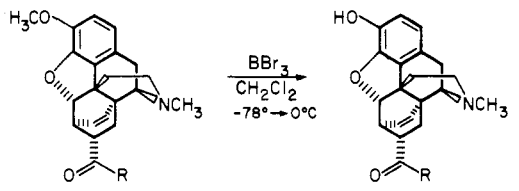
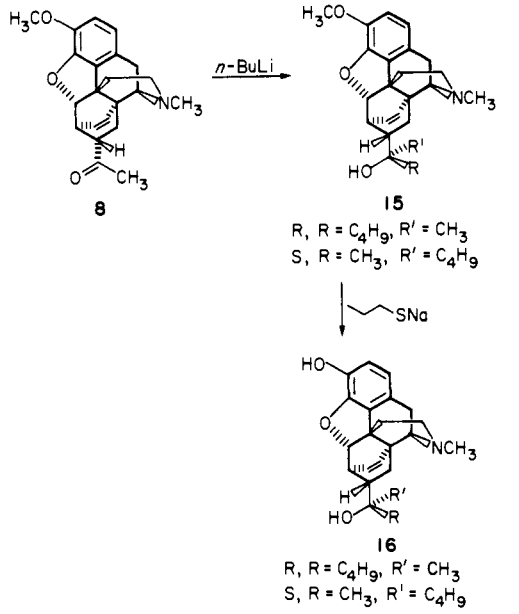


8, R = CH_3
10, R = n-C_4H_9

14a, R = CH_3, 82%
14b, R = n-C_4H_9, 54%

Formation of the tertiary alcohols by the addition of n-butyllithium to the carbonyl group of **14a** afforded a mixture of the diastereomeric alcohols and recovered ketone. The separation of the alcohols proved to be extremely difficult due to the susceptibility of the phenols to oxidation during the protracted separation of the ketone. The same problems occurred after the addition of methyllithium to phenol **14b**. Therefore, this route was set aside in favor of formation of tertiary alcohol first, to be followed by ether cleavage.

6-Demethoxythevinone (**8**) was treated with n-butyllithium to afford a mixture of tertiary alcohols and recovered ketone. HPLC analysis showed the mixture of alcohols had an R/S ratio of 1.2:1 and was obtained in 86% yield along with 14% recovered ketone. The crude product mixture was then treated with sodium borohydride in order to facilitate separation by forming the more polar secondary alcohol. Reduction gave a mixture of secondary and tertiary alcohols, from which chromatography on silica gel afforded the diastereomerically pure alcohol (R)-**15** in



8

15
R, R = C_4H_9, R' = CH_3
S, R = CH_3, R' = C_4H_9

16
R, R = C_4H_9, R' = CH_3
S, R = CH_3, R' = C_4H_9

40% yield and the alcohol (S)-**15** in 33% yield. Assignment of the stereochemistry is based on the correspondence of the NMR signal of the carbinol methyl group of one diastereomer with that of (R)-propylthevinol at δ 0.97.[9] The other diastereomer has a methyl signal at δ 1.07. Alternatively, methyllithium could be added to butyl ketone **10** to give a mixture of (R)- and (S)-**15** in which (S)-**15** predominated slightly.

Demethylation of the alcohols **15** was attempted with potassium hydroxide in diethylene glycol[14] and with diphenylphosphide anion in tetrahydrofuran;[15] in each case there was extensive decomposition. The best method for demethylation was sodium propanethiolate in dimethylformamide.[16] By this procedure, the alcohol (R)-**15** was demethylated in 69% yield and the alcohol (S)-**15** was demethylated in 52% yield to 19(R)- [(R)-**16**] and 19-(S)-n-butyl-6-demethoxy-7α-orvinol [(S)-**16**], respectively.

Pharmacology. The pharmacological activity of the diastereomeric tertiary alcohols (R)- and (S)-**16** and of the (R)-methyl ether (R)-**15** was determined using the tail-flick method in Sprague–Dawley rats.[17] The standard compound used for control and comparison was 19(R)-n-propylorvinol (etorphine) which has been established to have >1000 times the analgesic effect of morphine.[3]

The dose–response curve of the (R)-phenol (R)-**16** corresponded to that of etorphine fairly well with a 50% response value (3.5×10^{-3} μmol/kg) approximately equal to that of the standard (4.5×10^{-3} μmol/kg). The (R)-methyl ether (R)-**15** and the (S)-phenol (S)-**16** gave 50% response values [2×10^{-1} μmol/kg for (R)-**15** and 1.5×10^{-1} μmol/kg for (S)-**16**] only 20–40 times that of morphine.

An examination of the time–response data showed that peak activity occurred around 40 min after injection.

Conclusion

The pharmacological activity of (R)-**16**, the (R)-phenol, shows the hydrogen bond between the methoxy group and the tertiary alcohol is not necessary for the potent analgesic activity. Based on the activities of the (S)-phenol (S)-**16** and the (R)-alcohol (R)-**15**, both the R configuration and the 3-hydroxy group are necessary for maximum activity. The requirement of the 3-hydroxy group for maximum activity, of course, has been shown many times.[3] However, the specificity for the R configuration in the 6-demethoxy series is quite interesting. Since there are no intramolecular hydrogen-bonding constraints nor any apparent intramolecular steric interactions in either (R)- or (S)-**16**, there must be relatively free conformational mobility about the C7–C19 bond in both. Thus, the alkyl side chain of each carbinol is free to interact with a potential lipophilic binding site in the receptor. The fact that the R absolute configuration leads to much greater activity than the S supports a second binding site hypothesis for this region of the receptor.

Experimental Section

^{1}H NMR spectra were obtained on a Varian T60, EM390, or 250-MHz spectrometer; ^{13}C NMR spectra were obtained on a TT-23 instrument; both were measured in $CDCl_3$. UV spectra in methanol were obtained on a Varian 219 spectrophotometer; IR spectra were obtained neat, unless otherwise specified, on a Perkin-Elmer 137 spectrophotometer. Analytical TLC was conducted on precoated aluminum plates (silica gel 60 F-254) and were developed with 9:1 chloroform/methanol. Alumina for column chromatography was activity III supplied by Waters Associates. All chemicals were reagent grade. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl immediately before reaction. Evaporations were performed at reduced pressure using a Berkeley rotary evaporator. MS spectra and microanalyses were conducted by the Analytical Laboratory, Chemistry Department, University of California, Berkeley.

6-Demethoxythebaine (7). A mixture of 7.51 g (25 mmol) of isocodeine (**6**),[7] 5.8 g (57 mmol) of triethylamine, and 15.01 g (64 mmol) of 2,4-dinitrobenzenesulfenyl chloride in 125 mL of dichloromethane was heated at reflux temperature for 1.5 h. The mixture was allowed to cool to room temperature, sodium carbonate was added, and the reaction mixture was filtered after being stirred vigorously. The filter cake wa washed well with chloroform, and the combined organic phases were extracted with 1 M aqueous phosphoric acid. The combined aqueous layers were

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washed twice with chloroform, adjusted to pH 11 with 2 M aqueous sodium hydroxide, and extracted with 6 × 70 mL of chloroform. The combined organic extracts were washed with water, dried over potassium carbonate, filtered, and evaporated. Chromatography of the residue on silica gel using 5% methanol/chloroform as eluent gave 4.34 g (61%) of the diene **7** as a yellow oil, which could be crystallized from ethyl acetate: mp 70–71 °C (lit.[8] mp 68–70 °C); $[\alpha]^{23}_D$ −194° (*c* 1.5, C_2H_5OH) [lit.[15] $[\alpha]^{23}_D$ −194° (*c* 0.5, $CHCl_3$)]; ^1H NMR δ 2.4 (s, 3 H, NCH_3), 3.18 (d, *J* = 18 Hz, 1 H, 10β H), 3.44 (d, *J* = 6 Hz, 1 H, C-9 H), 3.71 (s, 3 H, OCH_3), 5.28 (d, *J* = 3 Hz, 1 H, C-5 H), 5.4–5.85 (m, 3 H, C-6, C-7, C-8 H), 6.4 (d, *J* = 8 Hz, 1 H, Ar H), 6.5 (d, *J* = 8 Hz, 1 H, Ar H); IR 1675, 1635, 1600 cm^{-1}; UV λ_{max} (log ε) 230 nm (3.99), 264 (3.58), 278 (3.57); ^{13}C NMR δ 29.12, 37.20, 41.97, 43.51, 45.78, 56.08, 60.87, 88.85, 111.18, 112.81, 118.49, 121.30, 125.39, 127.21, 133.05, 139.96, 142.53, 144.64. Anal. ($C_{18}H_{19}NO_2$) C, H, N.

Apocodeine (13). A solution of 0.35 g (1.3 mmol) of diene **7** in 5 mL of methanesulfonic acid was heated at 95 °C for 1 h and then slowly poured into 75 mL of 1.86 M aqueous potassium bicarbonate. After stirring for 1 h, the mixture was extracted with ether. The combined ethereal layers were washed with water and brine and dried over sodium sulfate. Addition of ethereal anhydrous hydrochloric acid and evaporation at reduced pressure gave apocodeine hydrochloride as a colorless solid, which was recrystallized from ethanol–ether: yield 0.25 g (64%); mp 258–261 °C (lit.[12] mp 260–263 °C).

6-Demethoxy-7α-thevinone (4,5α-Epoxy-3-methoxy-7α-acetyl-17-methyl-6,14-ethenomorphinan; 8). A solution of 3.03 g (10.8 mmol) of the 6-demethoxythebaine (**7**) and 38.0 g (540 mmol) of methyl vinyl ketone was heated at reflux for 24 h, then allowed to cool to room temperature, and evaporated, and the residue was dissolved in chloroform and extracted with 1 M aqueous phosphoric acid. The aqueous phase was washed with chloroform and then 2 M aqueous sodium hydroxide was added to pH 11 and the aqueous suspension was extracted with chloroform. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated. Chromatography of the residue on silica gel using 5% methanol/chloroform as eluent gave an oil which crystallized on addition of ether: yield of **8**, 1.75 g (46%); mp 159–161 °C; ^1H NMR δ 2.07 (s, 3 H, $COCH_3$), 2.32 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 4.40 (d, *J* = 3 Hz, C-5 H), 5.36 (d, *J* = 8 Hz, 1 H, C-19 H), 5.60 (dd, *J* = 6 and 9 Hz, 1 H, C-18 H); ^{13}C NMR δ 22.31, 26.63, 28.10, 33.13, 37.52, 43.13, 43.31, 45.53, 47.52, 56.35, 60.28, 93.96, 113.14, 119.04, 124.50, 128.30, 134.32, 137.58, 141.69, 148.30, 206.91; IR ($CDCl_3$) 1707 cm^{-1}; $[\alpha]_D$ −143° (*c* 2, C_2H_5OH). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

4,5α-Epoxy-3-methoxy-8α-acetyl-17-methyl-6,14-ethenomorphinan (9). A sample of ketone **8** was enriched with the slightly less polar compound **9** from the column chromatography of noncrystalline ketone **8**. Using the 250-MHz spectrometer, the ^1H NMR spectrum of the enriched sample was taken and stored in the memory. A spectrum of pure crystalline ketone **8** was then taken and subtracted from the first spectrum: ^1H NMR δ 1.65 (dd, 1 H, C-7 H), 2.15 (s, 3 H, $COCH_3$), 2.4 (s, 3 H, NCH_3), 3.24 (d, *J* = 18 Hz, 1 H, C-10β H), 3.6 (d, *J* = 7 Hz, 1 H, C-9 H), 3.80 (s, 3 H, OCH_3), 3.92 (dd, 1 H, C-8β H), 4.5 (d, *J* = 3 Hz, 1 H, C-5 H), 5.55 (d, *J* = 9 Hz, 1 H, C-19 H), 5.95 (dd, *J* = 9 Hz, 1 H, C-18 H).

4,5α-Epoxy-3-methoxy-7α-pentanoyl-17-methyl-6,14-ethenomorphinan (10). A solution of 0.91 g (3.24 mmol) of 6-demethoxythebaine (**7**) and 1.91 g (17.0 mmol) of butyl vinyl ketone[10] in 5 mL of benzene, heated at reflux for 27 h, was allowed to cool to room temperature and evaporated. The residue was dissolved in chloroform and extracted with 1 M aqueous phosphoric acid, and the aqueous layers were washed with chloroform and adjusted to pH 11 with 2 M aqueous sodium hydroxide. The suspension was extracted with chloroform, and the combined organic layers were washed with water and brine and then dried over magnesium sulfate. Evaporation gave a yellow oil, which was purified by medium-pressure LC on 200 g of silica gel using 10% methanol/chloroform as eluent to give butyl ketone **10** as a yellow oil: yield 0.92 g (72%); ^1H NMR δ 2.31 (s, 3 H, NCH_3), 3.68 (s, 3 H, OCH_3), 4.40 (d, *J* = 3 Hz, 1 H, C-5 H), 5.35 (d, *J* = 9 Hz, 1 H, C-19 H), 5.62 (dd, *J* = 6 and 9 Hz, 1 H, C-18 H); IR 1710, 1630, 1600 cm^{-1}; UV λ_{max} (log ε) 239 nm (3.74), 287 (3.16); MS, *m/e* (relative intensity) 83 (100), 132 (51), 144 (45), 281 (40), 308 (52), 393 (M^+, 76); $[\alpha]^{23}_D$ −116° (*c* 0.24, CH_3OH). Anal. ($C_{25}H_{31}NO_3$) C, H, N.

The second component eluted from the column was the starting diene **7**: yield 0.12 g (13%).

4,5α-Epoxy-3-methoxy-8α-pentanoyl-17-methyl-6,14-ethenomorphinan (11). Preparative TLC (3% methanol/chloroform) on silica gel of the first fraction of ketone **10** from the column chromatography gave a slightly less polar compound. NMR analysis showed the compound to be the regioisomer **11**: ^1H NMR 2.25 (s, 3 H, NCH_3), 3.06 (d, *J* = 18 Hz, 1 H, C-10β H), 3.30 (d, *J* = 6 Hz, 1 H, C-9 H), 3.68 (s, 3 H, OCH_3), 3.8 (m, 1 H, C-8β H), 4.33 (d, *J* = 3 Hz, 1 H, C-5 H), 5.35 (d, *J* = 9 Hz, 1 H, C-19 H), 5.69 (dd, *J* = 6 and 9 Hz, 1 H, C-18 H); IR 1710, 1635, 1605 cm^{-1}; MS, *m/e* (relative intensity) 57 (46), 144 (84), 149 (49), 225 (50), 256 (28), 280 (64), 281 (100), 308 (23), 393 (M^+, 99).

6-Demethoxy-7α-orvinone (4,5α-Epoxy-3-hydroxy-7α-acetyl-17-methyl-6,14-ethenomorphinan; 14a). A solution of 1.90 g (5.4 mmol) of 6-demethoxy-7α-thevinone (**8**) in 45 mL of dichloromethane was added dropwise over 15 min to a stirred solution of 7.4 g (29 mmol) of boron tribromide in 10 mL of dichloromethane cooled to −78 °C. The white suspension was kept at −78 °C for 30 min and then allowed to warm to 0 °C over 1 h. After 10 min at 0 °C, the mixture was poured into a mixture of ice and 50 mL of aqueous ammonium hydroxide. After the mixture stirred for 30 min, the layers were separated, the aqueous layer was extracted with chloroform, and the chloroform was washed with water and brine and dried over sodium sulfate. Evaporation gave a solid residue which was recrystallized from ether/hexane: yield 1.50 g (82%) of orvinone **14a**; mp 105–110 °C; ^1H NMR δ 2.06 (s, 3 H, $COCH_3$), 2.32 (s, 3 H, NCH_3), 4.40 (d, *J* = 3 Hz, 1 H, C-5 H); MS, *m/e* (relative intensity) 266 (22), 267 (39), 294 (33), 337 (M^+, 100); calcd for $C_{21}H_{23}NO_3$, *m/e* 337.1678; found, *m/e* 337.1682.

4,5α-Epoxy-3-hydroxy-7α-pentanoyl-17-methyl-6,14-ethenomorphinan (14b). A solution of 0.94 g (2.4 mmol) of ketone **10** in 20 mL of dichloromethane was added over 5 min to a stirred solution of 3.17 g (13 mmol) of boron tribromide in 5 mL of dichloromethane at −78 °C. The reaction was kept at −78 °C for 30 min, allowed to warm to 0 °C over 30 min, kept at 0 °C for 10 min, and then poured into a mixture of ice and concentrated ammonium hydroxide. After the mixture stirred for 30 min, the layers were separated, the aqueous fraction was saturated with sodium chloride and extracted with 300 mL of dichloromethane, and the combined organic extracts were washed with brine. Drying over sodium sulfate, evaporating, and chromatographing of the residue on silica gel using 5% methanol/chloroform as eluent afforded 0.49 g (54%) of phenol **14b** as a solid: mp 60–64 °C; ^1H NMR δ 2.32 (s, 3 H, NCH_3), 4.39 (d, *J* = 3 Hz, 1 H, C-5 H); MS, *m/e* (relative intensity) 266 (25), 267 (48), 294 (47), 379 (M^+, 100). Anal. ($C_{24}H_{29}NO_3$) C, H, N.

19(*R*)- and 19(*S*)-Butyl-6-demethoxy-7α-thevinol [4,5α-Epoxy-3-methoxy-α-*n*-butyl-α,17-dimethyl-6,14-ethenomorphinan-7α(*R*)- and -(*S*)-methanol; (*R*)- and (*S*)-15]. A solution of 1.66 g (4.7 mmol) of ketone **8** in 12 mL of tetrahydrofuran was cooled at −78 °C, and then 6.0 mL (9.3 mmol) of 1.55 M *n*-butyllithium in hexane was added over 5 min. The solution was stirred at −78 °C for 2 h and then allowed to warm to room temperature. Water was added, the mixture was stirred for 10 min, ether was added, and the layers were separated. The aqueous layer was extracted with chloroform, and the combined organic layers were washed with water and brine and dried over sodium sulfate. Evaporation gave an oil, which was dissolved in 10 mL of absolute ethanol, 1.5 g (39 mmol) of sodium borohydride was added, the mixture stirred for 2 h, water was slowly added, and the mixture was extracted with chloroform. The combined organic layers were washed with water and brine, dried over sodium sulfate, and evaporated to give an oil, which was chromatographed on silica gel using chloroform/methanol/diethylamine (89:10:1) as eluent. The appropriate fractions for each diastereomer were combined and evaporated to afford crystals. If further chromatography was necessary, preparative TLC was used with ethyl acetate/hexane/concentrated ammonium hydroxide (100:10:0.5) as eluent.

(*R*)-**15**: yield 0.79 g (41%); mp 53–55 °C; ^1H NMR δ 0.89 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 0.97 (s, 3 H, CCH_3), 2.33 (s, 3 H, NCH_3),

3.71 (s, 3 H, OCH_3), 4.36 (d, J = 3 Hz, 1 H, C-5 H), 5.35 (d, J = 8 Hz, 1 H, C-19 H), 5.64 (dd, J = 6 and 10 Hz, 1 H, C-18 H); UV λ_{max} (log ϵ) 240 nm (3.69), 288 (3.15); IR ($CHCl_3$) 2950, 1640, 1605 cm^{-1}; $[\alpha]^{23}_D$ −160° (c 0.40, $CHCl_3$). Anal. ($C_{26}H_{35}NO_3$) C, H, N.

(**S**)-15: yield 0.64 g (33%); mp 48–51 °C; ^1H NMR δ 0.87 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.07 (s, 3 H, CCH_3), 2.32 (s, 3 H, NCH_3), 3.70 (s, 3 H, OCH_3), 4.35 (d, J = 3 Hz, 1 H, C-5 H); UV λ_{max} (log ϵ) 240 nm (3.72), 288 (3.17); $[\alpha]^{23}_D$ −119° (c 0.50, $CHCl_3$). Anal. ($C_{26}H_{35}NO_3$) C, H, N.

19(*R*)-Butyl-6-demethoxy-7α-orvinol [4,5α-Epoxy-3-hydroxy-α-*n*-butyl-α,17-dimethyl-6,14-ethenomorphinan-7α-(*R*)-methanol; (*R*)-16]. A solution of 0.42 g (1.0 mmol) of (*R*)-15 in 10 mL of dimethylformamide was stirred as 0.1 g (4.2 mmol) of degreased sodium hydride was added in small portions, followed by 0.25 g (3.3 mmol) of propanethiol. The mixture was heated at reflux for 1 h, then allowed to cool to room temperature, and poured into 1 M aqueous phosphoric acid. The aqueous solution was extracted with ether, adjusted to pH 11 with aqueous ammonium hydroxide, and extracted with chloroform. The combined organic extracts were washed with water and brine and dried over sodium sulfate. Evaporation gave a solid residue and chromatography on alumina with 1% methanol/chloroform gave (*R*)-16 as colorless crystals: yield 0.28 g (69%); mp 93–95 °C; ^1H NMR δ 0.96 (s, 3 H, CCH_3), 2.40 (s, 3 H, NCH_3), 4.50 (d, J = 3 Hz, 1 H, C-5 H), 5.30 (s, 1 H, OH), 5.45 (d, J = 8 Hz, 1 H, C-19 H), 5.74 (t, J = 8 Hz, 1 H, C-18 H); UV λ_{max} (log ϵ) 240 nm sh (3.36), 290 (2.84).

19(*S*)-Butyl-6-demethoxy-7α-orvinol [(*S*)-16]. Demethylation of (*S*)-15 by the above procedure gave phenol (*S*)-16 in 52% yield: mp 87–90 °C; ^1H NMR δ 1.07 (s, 3 H, CCH_3), 2.40 (s, 3 H, NCH_3), 4.50 (d, J = 3 Hz, 1 H, C-5 H), 5.30 (s, 1 H, OH).

Pharmacological Methods. Sprague–Dawley rats weighing 180–210 g restrained in cages in the dark were used in the tail-flick test.[17] Test compounds were prepared in 0.01 N aqueous hydrochloric acid and were administered in this solution at 1 mL/kg, subcutaneously. Hot water (54–55 °C) provided the stimulus and reaction times were measured 10 min after injection for a maximum of 15 s. Seven rats at seven different dose levels were used for each compound. Percent response is defined as the reaction time minus the control time (1.5 s) as a percent of the maximum response time minus the control time (15–1.5 s).

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Opiate Receptor Interaction of Compounds Derived from or Structurally Related to Fentanyl

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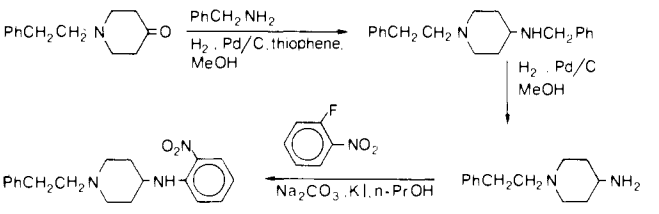
The opiate receptor affinity of compounds derived from or structurally related to fentanyl (1) was determined by in vitro receptor binding assays. The relatively high affinity of fentanyl (3 times morphine) was hardly influenced by the introduction of a 2-CH_3, 2-OCH_3, or a 2-Cl substituent into the anilino phenyl and was moderately reduced by 2-C_2H_5, 2-OC_2H_5, and 2,6-$(CH_3)_2$ substitution in this ring. Removal of the *N*-propionyl group of the 2-OCH_3 derivative, fixation of the anilino phenyl in fentanyl to the propionyl group or the piperidine ring, and replacement of the amide N by C all caused a sharp decline of receptor affinity. Examination of molecular models seemed to indicate that optimal opiate receptor interaction of fentanyl and its derivatives requires a virtually perpendicular position of the anilino phenyl with respect to the amide function.

Fentanyl (1) is a highly potent narcotic analgesic agent[1,2] which is widely used in anesthesiology. Structurally it belongs to the 4-anilinopiperidines. The analgesic potency of fentanyl (300 times morphine in the tail withdrawal test in rats[1]) could be further enhanced (up to 10 000 times morphine) by the introduction of an appropriate substituent (e.g., 3-CH_3, 4-$COOCH_3$, or 4-CH_2OCH_3) into the piperidine ring.[3-5] In vitro receptor binding studies have shown that these derivatives possess a very high opiate receptor affinity (ORA) with K_1 values in the subnanomolar range.[6,7]

Scheme I



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In a previous paper[8] we described the synthesis and in vitro opiate receptor affinity of a series of phenolic hydroxy derivatives of fentanyl and the corresponding methoxy derivatives. Since the ORA did not increase after the introduction of a phenolic OH, we concluded that it is very unlikely that, with respect to drug–receptor interaction,

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