(5) T. Jen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, 38, 2857 (1973).
(6) The material found in ref 3 as well as in the following publications [(a) A. D. Russell and R. H. Fountain, *J. Bacteriol.*, 106, 65 (1971), and (b) C. H. O'Callaghan, R. B. Sykes, and S. E. Staniforth, *Antimicrob. Agents Chemother.*, 10, 245 (1976)] indicates that the substituent at C-3′ is actually expelled concomitant with opening of the β-lactam ring.
(7) The thermal addition of glyoxylates to β-lactams is described by R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 55, 408 (1972).
(8) All new compounds were characterized by spectroscopic methods. Satisfactory elemental analyses were obtained for compounds 4, 6, 8, and 11.
(9) See the paper cited in ref 7.
(10) Although one of the carboxylate epimers of 4 could be purified by fractional crystallization to give a single diastereoisomer [mp 165–169 °C dec; NMR ($CDCl_3$–Me_2SO-d_6) δ 5.14 (s, CO_2CH_2Ph), 5.25 (dd, J = 5, 9 Hz, C-3′ β-lactam H), 5.99 (s, $CHCO_2CH_2Ph$)], its stereochemical integrity was lost during ester cleavage (see ref 12).
(11) Compounds were tested in a disk assay against *B. subtilis*.
(12) Acid 5 was a 1:1 mixture of carboxylic acid epimers. Hydrolysis of the crystalline diastereoisomer of 4 (ref 10) under a variety of conditions always resulted in epimerization to give the same 1:1 epimeric ratio of carboxylic acids.
(13) Thioacetate esters are known to hydrolyze rapidly when treated with mild base according to T. C. Bruice in "Organic Sulfur Compounds", Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N.Y., 1961, Chapter 35.
(14) The facile cleavage of thioesters by amines is described by J. J. Godfrey, U.S. Patent 3 086 049 (1963), and G. Fuchs, *Acta Chem. Scand.*, 19, 1490 (1965), as well as by T. C. Bruice as cited in ref 13.
(15) Substantial decomposition of 9 took place in a matter of minutes and thus made extremely difficult any isolation or purification techniques which required the intermediacy of 9.
(16) Although 5 and 6 could be converted to the bisnorisopenicillin 11, for our large-scale work we chose to use the bromo derivative 7 which was prepared in a manner similar to that for iodide 6 (C. D. Perchonock, unpublished results).
(17) It is our belief that the monocycle 6 exhibits antibacterial activity due to its in situ conversion to bisnorisopenicillin (10). Evidence for this theory will be the subject of a forthcoming publication.

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Articles

Analgesics. 1. Synthesis and Analgesic Properties of *N-sec*-Alkyl- and *N-tert*-Alkylnormorphines

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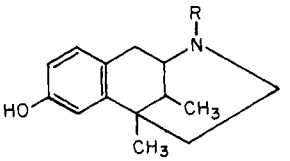
A series of *N-sec*- and *N-tert*-alkylnormorphines was synthesized and evaluated for analgesic potency, antagonist activity, and opiate receptor binding. Computer-assisted conformational analysis profiles were utilized to assist in the selection of compounds for synthesis and correlation of receptor events with in vivo observations. *N-tert*-Alkylnormorphines **5a–c** were devoid of agonist activity; however, some *sec*-alkyl analogues showed interesting mixed agonist–antagonist actions. *N-sec*-Butyl- and *N*-(α-methylallyl)normorphine were separated into *R* and *S* isomers, which exhibited quantitative pharmacological differences. The *N-sec*-butyl *S* isomer **10a** showed analgesia approximating morphine with nalorphine-like antagonist activity. Preliminary testing indicates only slight evidence for physical dependence with this compound.

It is generally acknowledged that compounds possessing potent analgesic activity yet having some degree of antagonist properties are good candidates for clinically useful analgesics with low addition potential. N-Substituents of fused ring opiates play a central role in determining the relative analgesic agonist/antagonist potencies of these molecules and in a given compound, this ratio is directly related to drug–receptor events. The success achieved with the drug pentazocine (Id),[1] a mixed agonist–antagonist, suggested that the nitrogen substituent of appropriate opiate bases should be investigated further. Archer and co-workers[2] have compared the antagonist protencies of a number of N-substituted 5,9-dimethylbenzazocines I. It was found that the *N*-propyl (Ia, AD_{50} = 0.019) and *N*-cyclopropylmethyl (Ib, AD_{50} = 0.019) analogues were more antagonistic than the *N*-allyl compound (Ic, 0.047). The AD_{50} values for dimethylallyl (Id) and dichloroallyl (Ie)



Ia, R = n-C_3H_7
b, R = c-C_3H_5-CH_2-
c, R = CH_2=$CHCH_2$-
d, R = $(CH_3)_2C$=$CHCH_2$-
e, R = Cl_2C=$CHCH_2$-
f, R = *cis*-ClCH=$CHCH_2$-

compounds were 3.9 and 5.1, respectively, whereas the *cis*-3-chloroallyl analogue If was also a strong antagonist, AD_{50} = 0.018. Since the compounds with saturated N-substituents were equal to or more antagonistic than the vinyl analogues, it would appear that the spatial ar-

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rangement was more significant than the electronic effects of the double bond.

One factor influencing interaction at the receptor site could be the presence of a number of different N-substituent conformers. Restriction of conformational freedom of the N-substituent could cause the molecule to adopt binding modes favoring either agonism or antagonism. Indeed, by placement of substituents at appropriate locations on the alkyl side chain, it should be possible to obtain such conformational restrictions.

Choosing the morphinoid system as a suitable opiate substrate because of the expected potency of its derivatives and the naturally established chirality, we prepared a number of new N-substituted analogues. Our primary interest was to study the effect of substituting methyl groups at the α position of *N*-propyl- and *N*-allylnormorphine, both strong antagonists, and *N*-phenethylnormorphine, a potent agonist. Accordingly, the three *N-tert*-alkylnormorphines, *N-tert*-amyl- (**5a**), *N*-(α,α-dimethylallyl)- (**5b**), and *N*-(α,α-dimethylphenethyl)normorphine (**5c**), were synthesized along with the *N-sec*-alkyl analogues, *N-sec*-butyl (**10a,b**), *N*-(α-methylallyl) (**10c,d**), and *N*-(α-methylphenethyl) (**10k**) compounds. Initial pharmacological evaluation indicated a lack of activity in the *N-tert*-alkyl series. However, the *N-sec*-alkylnormorphines were of considerable interest and prompted synthesis of a number of related analogues as part of a structure–activity investigation. In addition to the standard pharmacological assays, this study was aided by the use of a computer-assisted calculation of conformational profiles.

Chemistry. The synthetic routes for the *N-tert*- and *N-sec*-alkylnormorphines are outlined in Chart I. N-Demethylation of codeine (**1**) was readily effected via treatment with trichloroethyl chloroformate,[3] followed by reduction of the resulting trichloroethylurethane with zinc dust in buffered aqueous THF[4] to afford norcodeine (**2**) in 65% yield.

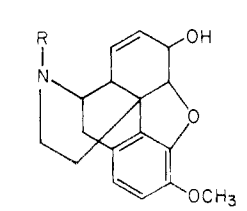
Reaction of **2** with acetone–cyanohydrin at 60 °C, without solvent, gave the dimethylcyanomethyl intermediate **3** as a gum identified by its NMR spectrum. When **3** was allowed to react with appropriate Grignard reagents[5] in Et_2O–THF, the cyano group was rapidly displaced to yield (36–60%) the *N-tert*-alkylnorcodeines (**4**). Subsequent O-demethylation by sodium propylmercaptide[6,7] in dimethylformamide (DMF) at 110 °C afforded the normorphines **5**.

Some of the *N-sec*-alkyl compounds could also be prepared by this general route. Treatment of norcodeine (**2**) or diacetylnormorphine (**6**) with lactonitrile gave the *N*-methylcyanomethyl compounds **7** and **8** as mixtures of diastereomers. The mixtures were reacted directly with Grignard reagents to yield the *N-sec*-alkylnorcodeines **9** or -normorphines **10**. O-Demethylations of the codeines **9** were accomplished in high yield via treatment with lithium diphenylphosphide[8] at room temperature. This reagent was found to offer distinct advantages over mercaptide–DMF[6] or BBr_3–$CHCl_3$[9] for O-demethylation.

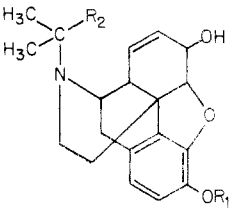
The crude normorphines **10** containing asymmetric *N-sec*-alkyl groups were obtained as diasteromeric mixtures; however, separation could be accomplished by fractional crystallization of the hydrochloride salts. In the case of the *N-sec*-butyl compound this process gave a major isomer (**10a**) in a 36% yield, while the minor isomer (**10b**) was obtained in 10% yield. In order to establish the absolute configuration for **10a,b**, the mesylate esters of levo (*R*) and dextro (*S*) 2-butanol were prepared and used to alkylate norcodeine via the general procedure of Von Braun et al.[10] Based on the expected Walden inversion during displacement, we were able to assign the major isomer as the *S* configuration, $[\alpha]_D$ −112°, and the minor isomer as the *R* form, $[\alpha]_D$ −102°. The differences in optical rotation were not of sufficient magnitude to allow assessment of purification in an isomeric mixture nor to permit routine assignment of configuration in the general series.

The ^{13}C NMR spectra showed small, but distinct differences in chemical shifts for the carbon atoms about the chiral center. The spectra were relied upon as a primary standard of purity for these compounds. ^{13}C NMR examination of a crude reaction mixture containing the *R* and *S* isomers of the *N*-(α-methylvinyl) compound showed both epimers to be present in a 1:1 ratio. Surprisingly, when the bases were converted to the HCl salts and recrystallized, only one diastereomer (**10c**) was recovered. The other isomer (**10d**) could be obtained by recrystal-

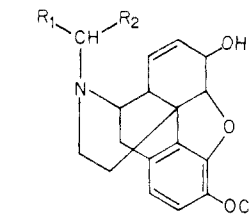
Chart I



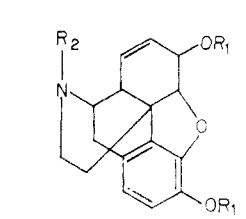
1, R = CH_3
2, R = H
3, R = $(CH_3)_2C(CN)$
7, R = $CH_3CH(CN)$



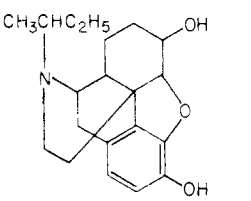
4a, R_1 = CH_3; R_2 = C_2H_5
b, R_1 = CH_3; R_2 = $-CH=CH_2$
c, R_1 = CH_3; R_2 = $-CH_2C_6H_5$
5a, R_1 = H; R_2 = C_2H_5
b, R_1 = H; R_2 = $-CH=CH_2$
c, R_1 = H; R_2 = $-CH_2C_6H_5$



9a, R_1 = CH_3; R_2 = C_2H_5
b, R_1 = CH_3; R_2 = $-CH=CH_2$
c, R_1 = CH_3; R_2 = $CH_2C_6H_5$
d, R_1 = CH_3; R_2 = n-C_3H_7
e, R_1 = R_2 = C_2H_5
f, R_1, R_2 = $-(CH_2)_5-$
g, R_1, R_2 = $-(CH_2)_6-$



6, R_1 = Ac; R_2 = H
8, R_1 = Ac; R_2 = $CH_3CH(CN)$
11, R_1 = R_2 = H



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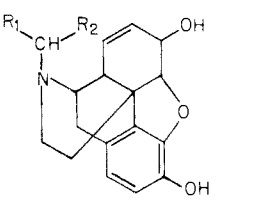
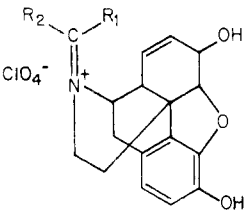
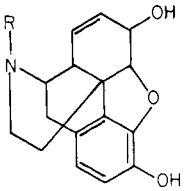


10a, R_1 = CH_3; R_2 = C_2H_5 (*S*)
b, R_1 = CH_3; R_2 = C_2H_5 (*R*)
c, R_1 = CH_3; R_2 = $-CH=CH_2$ (*R*)
d, R_1 = CH_3; R_2 = $-CH=CH_2$ (*S*)
e, R_1 = CH_3; R_2 = n-C_3H_7
f, R_1 = R_2 = C_2H_5
g, R_1, R_2 = $-(CH_2)_3-$
h, R_1, R_2 = $-(CH_2)_4-$
i, R_1, R_2 = $-CH_2CH_2CH=CH-$
j, R_1, R_2 = $-(CH_2)_5-$
k, R_1 = CH_3; R_2 = $-CH_2C_6H_5$



12a, R_1 = R_2 = C_2H_5
b, R_1, R_2 = $-(CH_2)_3-$
c, R_1, R_2 = $-(CH_2)_5-$

Table I. Physical Data for *N*-Alkylnormorphines



Compd no.	R	Method[f]	Mp, °C	Yield, %	Formula[g]
5a	$-C(CH_3)_2C_2H_5$		155-157	41	$C_{21}H_{27}NO_3 \cdot 0.5H_2O$
5b	$-C(CH_3)_2CH=CH_2$		220-225	36	$C_{21}H_{25}NO_3 \cdot HCl \cdot 0.25H_2O$
5c	$-C(CH_3)_2CH_2C_6H_5$		170	67	$C_{26}H_{29}NO_3 \cdot 1.5HBr \cdot H_2O$
10a	$-CH(CH_3)C_2H_5$ (*S*)	C	338	89	$C_{20}H_{25}NO_3 \cdot HCl$
10b	$-CH(CH_3)C_2H_5$ (*R*)	C	213-215	89[e]	$C_{20}H_{25}NO_3 \cdot HCl$
10c	$-CH(CH_3)CH=CH_2$ (*R*)	C	303-304	21	$C_{20}H_{23}NO_3 \cdot HCl$
10d	$-CH(CH_3)CH=CH_2$ (*S*)[d]	C	215	7	
10e	$-CH(CH_3)C_3H_7$[c]	C	290	25	$C_{21}H_{27}NO_3 \cdot HCl$[a]
10f	$-CH(C_2H_5)_2$	C, F	288-290	38, 63	$C_{21}H_{27}NO_3 \cdot HCl$
10g	Cyclopentyl	F, E	277	38, 40	$C_{21}H_{25}NO_3 \cdot HCl \cdot 0.5H_2O$
10h	Cyclohexyl	C	297	60	$C_{22}H_{27}NO_3 \cdot HCl \cdot 1.5H_2O$
10i	1-(2-Cyclohexenyl)[c]	E	251-253	37	$C_{22}H_{25}NO_3 \cdot HCl \cdot 0.75H_2O$
10j	Cycloheptyl	C, E	230-235	19, 79	$C_{23}H_{29}NO_3 \cdot HCl \cdot H_2O$[b]
10k	$-CH(CH_3)CH_2C_6H_5$[c]	C, D	200-205	65, 66	$C_{25}H_{27}NO_3 \cdot 0.5H_2SO_4 \cdot 2H_2O$

[a] C: calcd, 66.7; found, 66.1. [b] C: calcd, 65.5; found, 66.2. [c] Configuration (*R* or *S*) not determined. [d] Free base; best preparation contained 15% 10c. [e] Yield based on O-demethylation of pure *R* or *S* isomer. [f] Methods are described in the Experimental Section. [g] All compounds with empirical formulas were analyzed for C, H, and N with values within ±0.4% of theoretical values except as indicated.

lization of the crude free base, however. It was subsequently discovered that the HCl salt of **10d** was readily epimerized during the recrystallization process. The configuration of **10c** was determined as the *R* form by hydrogenation of the material over a PtO_2 catalyst to afford a tetrahydro derivative **13** whose ^{13}C NMR spectrum was in agreement with the dihydro derivative similarly obtained from hydrogenation of the (*R*)-*sec*-butyl compound **10a**. We were able to isolate one diastereomer for the *N*-(α-methylphenethyl) compound **10k**, characterized as the hemisulfate salt.

Other *N*-*sec*-alkylnormorphines (**10e,f,h,j**) were prepared by the direct displacement of appropriate halides by norcodeine, followed by O-demethylation as above. Two *N*-cycloalkylnormorphines (**10g,i**) were synthesized by similar N-alkylation of normorphine (**11**). This procedure obviated the need for O-demethylation of the norcodeine intermediates but suffered yieldwise, presumably from the expected competition between O- and N-alkylation. Finally another useful route was developed where an appropriate ketone, such as cyclopentanone, cycloheptanone, or diethyl ketone, was condensed with normorphine perchlorate to form the iminium perchlorates **12a-c**.[11] Reduction of **12a-c** with sodium borohydride[12] yielded the N-substituted normorphines **10f,g,j**. Physical properties are recorded in Table I.

Pharmacology. Opiate receptor binding was measured by the method of Pert and Snyder.[13] Rats (150-250 g) were decapitated and their whole brains with cerebella removed were homogenized in 110 vol of ice-cold Tris-HCl buffer (pH 7.4 at 25 °C). After centrifugation at 10000g, the supernatant fluid was discarded and the brain membranes were reconstituted in the original volume of Tris buffer with or without NaCl (100 mM). Aliquots (1.9 mL) of this freshly prepared homogenate were incubated with [^3H]-naloxone (2.6 nM, 65000 cpm), obtained from New England Nuclear Corp. (20 Ci/mmol), for 30 min at 25 °C. Samples were placed on ice for 15 min, rapidly filtered individually by low pressure over Whatman glass fiber filters (GFB), and washed with two 5-mL portions of cold Tris buffer. Membrane-laden filters were transferred to counting vials containing 10 mL of scintillation cocktail [BioSolv, 10% (Beckman Instruments, Inc.), in toluene containing Liquifluor (New England Nuclear Corp.)] and counted by liquid scintillation spectrometry at 50% efficiency. The concentration of nonradioactive drug required for 50% inhibition (IC_{50}) of stereospecific [^3H]-naloxone binding (binding occurring in the presence of 100 nM levallorphan subtracted from radioactivity bound in the presence of 100 nM dextrallorphan) was determined by plotting the percent inhibition of the mean of triplicate incubations of five to six concentrations of drug on log probit paper. IC_{50} values represent the mean from three to four separate determinations in which values varied less than 25%.

Antagonist activity was assessed as potency in inhibiting the morphine-induced Straub-tail response. The method used was a modification of that developed by Blumberg and Dayton.[14] Male Swiss-Webster mice (18-22 g, Simonsen Laboratories, Gilroy, Calif.) were injected subcutaneously with 30 mg/kg of morphine sulfate (10 mL/kg) and placed individually in open-top glass cylinders (30 cm high and 20 cm in diameter). They were observed for 20 min and the Straub-tail reaction was scored according to the criteria of Blumberg and Dayton. Animals that failed to demonstrate the response continuously during the 30 min were discarded. Thirty minutes after the morphine administration the mice were injected subcutaneously at the nape with a test compound, nalorphine (a reference drug), or diluent only, i.e., 0.005 N HCl or 0.9% saline solution. Three dose levels (ten mice per level) of each compound were evaluated. Immediately after the treatment, the observation of the Straub-tail state was continued for 30 min and the responses were scored in the manner described previously. An animal was considered to have shown an inhibition, if its total score was 50% or less of the average score of the diluent-injected control group.

At each dose level of each compound the percentage of animals that showed an inhibition of Straub-tail reaction

was computed. The percentages were plotted against dose (expressed in micromoles per kilogram of the free base) on logarithmic probability paper. The median effective doses (ED_{50}) and the 95% confidence limits were computed according to the graphic method of Litchfield and Wilcoxon.[15]

Analgesic potency was determined by both the tail flick[16,17] and phenylquinone writhing methods.[18] In tests utilizing the tail-flick method, male, Swiss–Webster mice, weighing 18–22 g, were used. A beam of light was focused on the tail of the mouse. The intensity of the light was adjusted to give a control reaction time of 2–4 s. Animals responding outside this range were rejected. Two control readings taken 30 min apart were averaged. The drugs were dissolved in 0.9% saline and injected ip into groups of ten mice. Measurements were made 20 min after injection. A 10-s cutoff time was used.

The response was calculated as the percent maximum possible inhibition.[19] The following formula was used.

$$\frac{\text{test time} - \text{control time}}{10\text{ s} - \text{control time}} \times 100 = \%\text{ max inhibn}$$

The results were plotted vs. log dose and the ED_{50} values determined. The 95% confidence limits were calculated by the method of Litchfield and Wilcoxon.[15] Data are reported in Table II.

Conformational Analysis. Energy–conformation calculations of N-substituents were performed for the series of *N-sec-* and *N-tert*-alkylnormorphine derivatives whose synthesis and testing are described above. These included the three *N-tert*-alkylnormorphines, *N-tert*-amyl- (**5a**), *N*-(α,α-dimethylallyl)- (**5b**), and *N*-(α,α-dimethylphenethyl)normorphine (**5c**), and the diastereoisomers of the *N-sec*-alkyl analogues, *N-sec*-butyl- (**10a,b**), *N*-(α-methylallyl)- (**10c,d**), and *N*-(α-methylphenethyl)normorphine (**10k**). In addition, two N-primary alkyl derivatives, *N*-ethyl- and *N-n*-propylnormorphine, and the α-methyl derivative of the *N*-ethyl compound (*n*-isopropylnormorphine) were also studied. The *N*-allyl and *N*-phenethyl primary compounds have been previously characterized.

The purpose of these calculations was to determine the effect of α-methyl substitution on the conformational behavior of the parent primary alkyl substituent and to correlate this effect with possible alterations of relative agonist and antagonist potency in the parent compounds.

The method used to calculate the energy of each compound as a function of N-substituent conformation is called perturbative configuration interaction using localized orbitals (PCILO) which is embodied in a well-documented computer program.[20] It has been used to study a number of similar systems in the past.[21,22] In initial calculations, all methyl groups were assumed to be staggered, nested rotations about the two main torsion angles of the N-substituents $\tau_1(C_9N\text{–}C_\alpha C_\beta)$ and $\tau_2(NC_\alpha\text{–}C_\beta C_\gamma)$ made at 30° intervals. Local minima found in the energy–conformation maps were then optimized using a parabolic fit of energy to all rotational angles in increments of 6°. This local minimization allowed a more precise determination of energy differences between local minima and a verification of the assumed staggered conformations of methyl groups. In the tabulation and discussion of results, twist angles are listed using a right-handed convention as in previous work.[23] Tables III–XI give the energy–conformation results for all compounds studied (see paragraph at end of paper regarding supplementary material). Low-energy conformers obtained for each compound are illustrated in Figures 1–3.

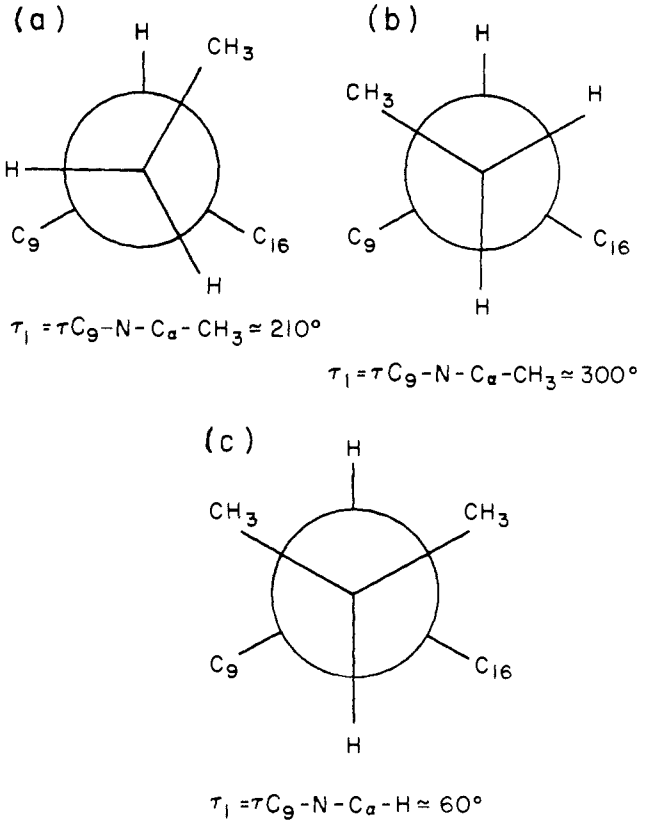


Figure 1. (a, b) Low-energy conformers of *N*-ethylnormorphine with CH_3 groups staggered and (c) of *N*-isopropylnormorphine with CH_3 groups staggered.

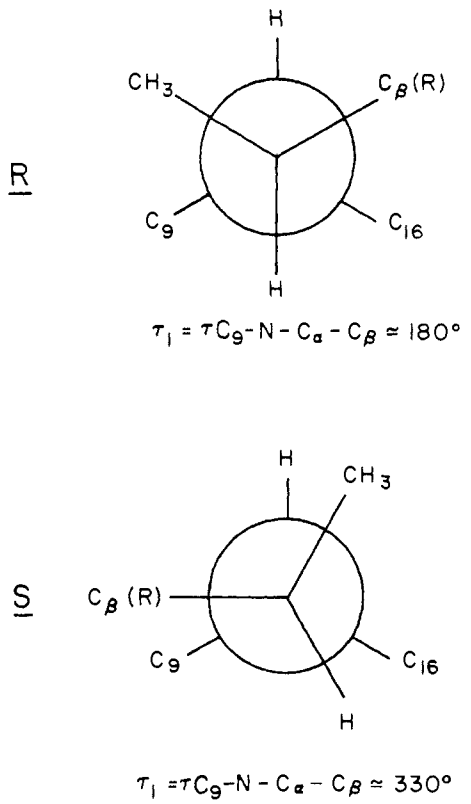


Figure 2. Low-energy values of τ_1 for (*R*)- and (*S*)-*N-sec*-alkylnormorphines.

Energy–conformational results for the primary alkyl substituents *N*-ethyl and *N-n*-propyl followed the same pattern as previously obtained for the *N*-allyl group of nalorphine. As shown in Figure 1a,b for the *N*-ethyl

Table II. Opiate Receptor Affinities and Analgesic and Antagonist Potencies

Compd no.	N-Substituent	Opiate receptor inhibn,[a] IC_{50}, nM		Sodium response ratio[b]	Analgesia, ED_{50}, μmol/kg (95% CL)[c]		Analgesic antag,[d] ED_{50}, μmol/kg (95% CL)
		−NaCl	+NaCl		Tail flick	Writhing	
5a	$C(CH_3)_2C_2H_5$	~1000	~1000		>580	>290	
5b	$C(CH_3)_2CH=CH_2$	>1000	>1000		>295	~74	
5c	$C(CH_3)_2CH_2C_6H_5$	~1000	~1000		>310	~176	
10a	$CH(CH_3)C_2H_5$ (S)	28	62	2.2	13.4 (10.4–16.7)	11.0 (7.0–17.4)	7.4 (4.9–11.1)
10b	$CH(CH_3)C_2H_5$ (R)	60	110	1.8	19.0 (12.2–29.3)	6.4 (3.7–11.2)	16.2 (11.6–22.7)
10c	$CH(CH_3)CH=CH_2$ (R)	27	80	3.0	44.5 (32.0–62.1)	13.0 (8.1–20.2)	11.0 (6.8–16.2)
10d	$CH(CH_3)CH=CH_2$ (S)	16	25	1.6	104.6 (72.0–151.6)		
10e	$CH(CH_3)C_3H_7$	37	340	9.2	>439	9.0 (6.6–12.3)	80.8 (51.8–126.0)
10f	$CH(C_2H_5)_2$	78	175	2.2	19.9 (12.9–27.8)	2.3 (1.4–3.9)	17.2 (11.3–26.3)
10g	Cyclopentyl	34	45	1.3	124 (96.2–160)	15.5 (9.5–25.3)	15.5 (11.0–21.9)
10h	Cyclohexyl	38	92	2.4	>212	15.7 (9.0–27.4)	
10i	1-(2-Cyclohexenyl)	51	130	2.5	79.7 (53.8–118)		23.8 (14.3–39.7)
10j	Cycloheptyl	19	150	8.0	>136	9.9 (5.0–19.8)	60.8 (36.6–100.9)
10k	$CH(CH_3)CH_2C_6H_5$	3.4	125	37.0	4.3 (2.4–7.8)	0.13 (0.07–0.23)	No inhibn
N-*n*-Propylnormorphine		14	14	1.0	51.0 (41.8–62.2)	29.0 (18.0–46.4)	0.6 (0.3–1.6)
N-Allylnormorphine		2.0	6.0	3.0		3.2 (1.8–5.4)	1.0 (0.8–1.4)
Morphine		10	250	25.0	10.5 (8.4–13.3)	1.5 (1.1–2.1)	No inhibn
N-Phenethylnormorphine		4.2	133	31.3	1.7 (1.4–2.0)	0.27 (0.17–0.43)	No inhibn

[a] Inhibition of opiate receptor binding is presented as the concentration of drug which reduced specific [^{3}H]naloxone binding by 50%; the means of three to four determinations varied by less than 25%. [b] The ratio of IC_{50} values for incubations in the presence of 100 mM NaCl to those for incubations in its absence. [c] See ref 15–18. [d] Inhibition of Straub tail response (ref 14); CL = confidence limits. All affinity and potency values are expressed as micromoles of the free base.

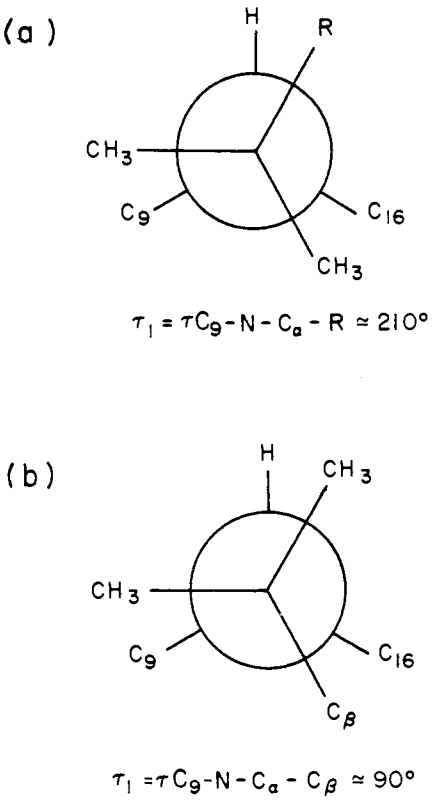


Figure 3. Low-energy values of τ_1 for *N*-*tert*-alkylnormorphines.

derivative, two isoenergetic global minima were found with relatively low-energy barriers to rotation between them (Table III) and similar behavior was found for the *N*-*n*-propyl derivative (Table IV).

Results for all the *N*-*sec*-alkyl derivatives indicate that the presence of a single methyl group on the C_α position leaves only one of the two global minima of the primary compounds intact, and a different one, depending on the chirality (*R* or *S*) of the optically active C_α center. For example, in contrast to the *N*-ethyl compound, *N*-isopropylnormorphine has only one low-energy conformer (Figure 1c) with a relatively high barrier to rotation to other local minima (Table V). For the optically active *N*-*sec*-alkyl derivatives studied, *N*-*sec*-butyl-, *N*-(α-methylallyl)-, and *N*-(α-methylphenethyl)normorphine, the *R* and *S* epimers of each had a different low-energy conformer of the parent primary compound as a global minimum, as shown in Tables VI–IX for the *N*-*sec*-butyl and α-methyl-*N*-allyl compounds. All low-energy local minima ($\Delta E \leq 3$ kcal/mol) have trans configurations (Figure 2) with respect to the H atoms on the nitrogen and the adjacent C_α hydrogen atom.

Substitution of two methyl groups in the C_α position to form *N*-*tert*-alkylnormorphines causes an even greater loss of N-substituent flexibility in all three compounds studied (**5a–c**) as shown in Tables X and XI. As summarized below (τ_1, ΔE) these compounds have the same two local minima as the primary compound and an additional one at $\tau_1(C_9\text{–}N\text{–}C_\alpha\text{–}C_\beta) = 90°$. For compound **5a**, τ_1 = 90°,210°,330° (ΔE = 0.9, 0.0, and 0.5 kcal/mol); for **5b**, τ_1 = 90°,210°,330° (ΔE = 0.0, 2.7, and 1.4 kcal/mol); and for **5c**, τ_1 = 90°,180°,330° (ΔE = 2.3, 0.5, and 0.0 kcal/mol). However, there are high-energy barriers between these minima which were obtained by local optimizations for energy intervals <30°.

Compounds with the tertiary carbon substituted on the normorphine nitrogen clearly displayed low analgesic potency in both the tail-flick and writhing tests, and their

affinities for the opiate receptor were correspondingly quite low (Table II, compounds **5a–c**). In contrast, compounds with secondary, but otherwise similar, substituents (**10a–d,k**) exhibited affinities and potencies at least an order of magnitude greater than those of the tertiary compounds, with some potencies approximating that of morphine. The introduction of secondary substituents of higher molecular weight (**10e,g–i**) generally resulted in substantially reduced potency in the tail-flick test but not in the writhing test. The *N*-(3-pentyl) compound **10f** was a notable exception in that its tail-flick potency was very similar to that of the 2-butyl compounds **10a,b**.

In the sense that opiate affinities varied relatively little among compounds with secondary substituents (Table II), writhing data appeared to parallel opiate receptor binding better than did the tail-flick results. Neither test, however, gave results which closely paralleled receptor binding IC_{50} values either in the presence or absence of 100 mM sodium chloride. On the other hand, although the correlation was not perfect, binding in the presence of 100 mM NaCl appeared to correlate with antagonist potency as measured by inhibition of the Straub tail response.

None of the compounds examined was as potent an antagonist as *N*-allylnormorphine or *N*-propylnormorphine. All of those examined, with the exception of **10k**, proved to be mixed agonist/antagonist and exhibited sodium response ratios less than 10. Only the weakest measured antagonist (**10e**) exhibited a sodium response ratio greater than 3.0.

With respect to the agonist *N*-phenethylnormorphine, the introduction of a single α-methyl group (**10k**) had insignificant effects on receptor affinity and slightly reduced agonist potency. However, in the case of *N*-allylnormorphine and *N*-*n*-propylnormorphine, both mixed agonist/antagonists, the introduction of an α-methyl group in the N-substituent decreased receptor affinity and decreased antagonist potency (**10a–c**). By both of the in vivo test methods employed, agonist potency was increased in the case of the propyl derivatives **10a,b** but appeared to be decreased in the allyl derivative **10c** (writhing assay).

The effects of chirality on the α carbon in this series were not as pronounced as the effects noted for β-carbon chirality in benzomorphan and oxymorphone analogues with *N*-tetrahydrofurfuryl substituents.[24] In those cases where both diastereoisomers could be examined (**10a–d**), the *S* diastereomer exhibited the higher affinity for the opiate receptor. In the case of **10a,b**, the *S* diastereomer was also the more potent with respect to both agonist and antagonist activity. However, the *R* diastereomer of the allyl derivative **10b** was the more potent agonist.

Discussion

Several studies have demonstrated a general parallelism between the analgesic potencies of a wide range of narcotic analgesics and their binding affinities to the stereospecific opiate receptor in brain homogenates. In addition, such binding has been characterized biochemically in terms of several factors including a differential effect of sodium ion on the affinities of agonists and antagonists; opiates exhibiting a sodium response ratio above 12 are "pure agonists" while antagonists and mixed agonist/antagonists generally exhibit much lower ratios.[25] The results obtained in the present study are consistent with these observations and support the concept that binding assays are of predictive value with respect to the type and potency of activity to be expected.

Characterization of opiate drugs in terms of in vitro receptor affinities is also fundamental to an understanding of structure–activity relationships at the macromolecular level, especially in terms of stereochemical and conformational considerations. It has previously been hypothesized, based on results of molecular orbital (MO) calculations,[23] that the dual agonist/antagonist activity of certain N derivatives of morphine, such as nalorphine or *N*-*n*-propylnormorphine, could be due to the existence of two types of N-substituent conformations at the receptor. It was further inferred that, if this were true, the extent of agonism and antagonism in a given opiate could be modulated by a selective interference with the conformational freedom of the N-substituent which could separate "agonist" and "antagonist" conformations. Specifically, the suggestion was made that methyl substitution at the C_α position[26] could have this effect and that *R* and *S* isomers of *N*-*sec*-alkylnormorphines formed would behave differently than their parent primary *N*-alkyl compound. The conformational effect of the α-methyl substitution has been verified by preliminary quantum mechanical calculations,[26] the full results of which have been described here, together with synthesis and pharmacological activity.

It is now of interest to examine the relationship between the pharmacological results and the conformational data in light of the original hypothesis and to examine other more direct effects of the methyl group which could not be predicted.

Low-energy conformations of the tertiary α,α-dimethyl *N*-alkyl substituents were relatively unchanged from those of the parent molecules, but barriers to rotation were much higher, making these substituents more rigid. In the low-energy conformer of these molecules (Figure 3) there is at least a C_α-methyl group in the position trans to the axial nitrogen proton, whereas in both secondary and primary *N*-alkyl compounds this position is occupied by a hydrogen atom in all of the low-energy conformers (Figure 2). Since the α,α-dimethyl *N*-alkyl substituents dramatically decreased in vitro binding and in vivo potency, it can be deduced that there is a relatively rigid receptor site blocking accommodation at this position. If this conclusion is correct, all *N*-*tert*-alkyl derivatives of fused ring opiates should be relatively inactive both as agonists and antagonists.

In neither the *N*-propyl- nor *N*-allyl-α-methyl derivatives did there appear to be a complete separation of agonism and antagonism in their optical isomers, and it is interesting to try to understand their binding and agonist and antagonist potencies relative to the parent primary compounds in light of their conformational behavior and the specific effect of the added methyl groups.

Both of these *N*-*sec*-alkyl compounds have similar conformational behavior. The *R* isomer has a global minimum $\tau_1 \simeq 180°$ while the *S* isomer a minimum at $\tau_1 \simeq 330°$ (as shown schematically in Figure 2). Thus, the calculations confirm the idea that specific N-substituent conformations would be favored, depending on the chirality of the C_α center. The α-methyl group, however, confers a certain inflexibility to the resultant structures.

An examination of the effect of the α-methyl group on binding and potency for all compounds studied allows an assessment of its role in receptor-site interactions. For the pure agonist, *N*-phenethylnormorphine, addition of an α-methyl group has very little effect on binding and potency. The conformational result for this compound indicates that the protons on the N and C_α atoms are in a trans position. From these results it appears that the α-methyl group can be accommodated in this compound but does not have significant direct interaction with the receptor site.

For the mixed agonist–antagonists, *N*-allyl- and *N*-*n*-propylnormorphine, the addition of an α-methyl group diminishes binding and antagonism. Agonism is increased for the *N*-*n*-propyl derivatives. Accommodation of the α-methyl group at the receptor site then seems less facile than in the pure agonists and its induced accommodation could make the low-energy agonist and antagonist forms of the N-substituent less suitable for binding. If they bind in higher energy conformations, the tendency of an α-methyl group to preferentially stabilize agonist and antagonist conformations would be lessened and incomplete separation of agonism and antagonism obtained, as observed.

Thus, it appears that the direct effect of the α-methyl group at the receptor allows the retention of mixed agonist/antagonist properties in *N*-*sec*-alkylnormorphines. This result renders the compounds which were synthesized and tested promising candidates for clinical evaluation. This is particularly true for *N*-*sec*-butyl compounds which have a tail-flick agonist potency in the same range as morphine and retain significant antagonism. Preliminary studies indicate these compounds (**10a,b**) to have a low addiction potential. These and other studies are under way to verify their usefulness and will be reported elsewhere.

Experimental Section

Norcodeine (2). Norcodeine was prepared by a modification of the procedure of Montzka et al.[3] A mixture of 79.80 g (0.267 mol) of codeine (1) in 500 mL of 1,1,2,2-tetrachloroethane was treated with 100 g (0.47 mol) of 2,2,2-trichloroethyl chloroformate, and the stirred solution was heated to reflux (147 °C) for 2 h. Then, the excess solvent was evaporated and the residue dissolved in 500 mL of THF. On standing, unreacted codeine hydrochloride separated and was collected (11.9 g). Then, the filtrate was treated with 150 g of zinc powder and 150 mL of 1 N NaH_2PO_4. After 30 min of vigorous stirring at reflux, the mixture was cooled and diluted with 200 mL of Et_2O. The gray precipitate was collected by filtration and stirred 10 min with 200 mL of H_2O, 300 mL of 2-PrOH, 900 mL of $CHCl_3$, and 40 mL of concentrated NH_4OH. Then the organic layer was separated, dried ($MgSO_4$), and concentrated by evaporation to a pale yellow oil. Dilution with 200 mL of ethyl acetate produced a white crystalline precipitate: yield 42.8 g (65%); mp 186–187 °C (lit.[27] mp 185 °C).

Preparation of *N*-*tert*-Alkylnorcodeines 4a–c. *N*-(2-Methyl-2-butyl)norcodeine (4a). A mixture of 10.0 g (0.035 mol) of norcodeine (**2**) and 60 g (0.70 mol) of acetone–cyanohydrin was heated at 60 °C for 90 min. Then, the reaction mixture was evaporated under vacuum to remove excess acetone–cyanohydrin and H_2O. The residue was dissolved in 100 mL of dichloromethane and treated with 100 mL of hexane, which caused the precipitation of unreacted **2**. The mixture was filtered and evaporated to give 10.5 g of *N*-(2-cyano-2-propyl)norcodeine (3) (85%) as a gum: NMR ($CDCl_3$) δ 6.7 (d, 1 H, C_2-H), 6.6 (d, 1 H, C_1-H), 4.9 (d, 1 H, C_5-H), 3.8 (s, 3 H, OCH_3), 1.60 [d, 6 H, $-C(CH_3)_2CN$].

A solution of 3.17 g (0.009 mol) of 3 in 75 mL of dry THF was added dropwise to excess ethylmagnesium bromide in ether. After 10 min, the reaction mixture was poured over ice (500 g) and the ether–THF layer was separated, dried, and evaporated to yield 1.17 g (36%) of *N*-(2-methyl-2-butyl)norcodeine (**4a**) as a gum: purified by chromatography on silica gel (EtOAc–EtOH–Et_3N, 85:14:1); NMR ($CDCl_3$) δ 0.80 (t, 3 H, J = 7 Hz, $-CH_2CH_3$), 1.1 [d, 6 H, $-C(CH_3)_2Et$].

Similar reaction of 3 with vinylmagnesium bromide and benzylmagnesium chloride afforded **4b** (60%) and **4c** (60%) both as gums: NMR (**4b**) δ 1.30 [s, 6 H, $-C(CH_3)_2-$], 4.8–6.2 (m, 5 H, vinyl); NMR (**4c**) δ 1.20 [d, 6 H, $-C(CH_3)_2-$].

Preparation of *N*-*tert*-Alkylnormorphines 5a–c. Compound **4a** was O-demethylated by our previously described method.[6] Thus, 0.55 g (0.0015 mol) of **4a** in 25 mL of DMF under N_2 was treated with 0.60 g (0.0053 mol) of KO-*t*-Bu and 0.60 g (0.0079 mol) of PrSH, and the mixture was heated (110 °C) for 3 h. After workup 0.28 g (53%) of **5a** was obtained as a crystalline solid. Recrystallization from hexane–Et_2O gave an analytical sample: NMR ($CDCl_3$) δ 0.85 (t, 3 H, $-CH_2CH_3$), 1.15 [s, 6 H, $-C(CH_3)_2Et$]. Compounds **5b** and **5c** were similarly obtained; physical data for **5a–c** appear in Table I.

Diacetylnormorphine (Norheroin, 6). Morphine sulfate (53.8 g, 0.189 mol) was acetylated in 500 mL of toluene by treatment with 55 g (0.70 mol) of acetyl chloride and 50 g (0.78 mol) of pyridine. The crude 3,6-diacetylmorphine (62 g, 89%) was immediately dissolved in 600 mL of 1,1,2,2-tetrachloroethane, treated with 100 g (0.47 mol) of 2,2,2-trichloroethyl chloroformate, and heated at reflux (~147 °C) for 2 h. After the volatiles were removed in vacuo, the residue was dissolved in 700 mL of THF. After the addition of 150 g (2.3 mol) of zinc powder and 150 mL of 1 N NaH_2PO_4 solution the mixture was stirred at reflux for 30 min. The gray precipitate was collected, treated with 400 mL of H_2O, 900 mL of $CHCl_3$, and 300 mL of 2-propanol, and neutralized with concentrated NH_4OH. The organic layer was separated and evaporated to leave **6** as a gum (52.1 g, 77%): NMR δ 6.90 (d, 1 H, C_1-H), 6.75 (d, 1 H, C_2-H), 5.70 (m, 2 H, olefin), 5.30 (m, 2 H, C_5,C_6-H), 2.20 (s, 3 H, 3-OAc), 2.10 (s, 3 H, 6-OAc). Compound **6** was unstable and suffered transacetylation to give *N*-(6-diacetyl)normorphine if heated during evaporation. An alternate synthesis was reported by Rice and Jacobson.[28]

***N*-(1-Cyano)-1-ethylnorcodeine (7).** A mixture of 20.2 g (0.071 mol) of norcodeine, 10.0 g (0.14 mol) of lactonitrile, and 9.3 mL of toluene was heated at 60 °C for 5 min and the solvent removed in vacuo to leave 25.3 g (92%) of crude solid product shown to be a 3:1 epimeric mixture by NMR and TLC. Repeated crystallization from benzene gave white crystals, mp 140.5–141.5 °C. However, the NMR spectrum showed a 9:1 epimeric mixture, unchanged by further recrystallization: NMR (major isomer) δ 1.50 [d, 3 H, $-CH(CH_3)CN$] and (minor isomer) 1.55 [d, 3 H, $-CH(CH_3)CN$].

***N*-*sec*-Alkylnorcodeines 9a–g. Method A.** A solution of 16.0 g (0.047 mol) of the cyano intermediate **7** in 100 mL of dry THF was added dropwise to an excess of C_2H_5MgBr in Et_2O. After 10 min the reaction mixture was quenched with ice and worked up as described for the *tert*-alkylnorcodeines **4**. Removal of solvent afforded *N*-*sec*-butylnorcodeine (**9a**) as a gum (6.0 g, 99%): NMR ($CDCl_3$) δ 0.90 (t, 3 H, CH_2CH_3), 1.10 (d, 3 H, CH_3CH-), 3.80 (s, 3 H, OCH_3); TLC (silica; CH_2Cl_2–hexane–Et_3N, 2:2:1) single spot, R_f 0.6. The codeine series intermediates **9b** and **9c** were similarly prepared by reaction of **7** with vinylmagnesium bromide and benzylmagnesium chloride, respectively.

Method B. A neat mixture of 3.2 g (0.011 mol) of norcodeine (**2**), 8.5 g (0.056 mol) of (*R*)-2-mesyloxybutane [derived from (–)-2-butanol and mesyl chloride], and 9.0 g (0.085 mol) of Na_2CO_3 was stirred at 75 °C for 15 h. The mixture was cooled and partitioned between 50 mL of 1 N HCl and 50 mL of $CHCl_3$. The aqueous solution was alkalized with concentrated NH_4OH and extracted with 50 mL of $CHCl_3$. After drying over $MgSO_4$ and evaporation in vacuo, 1.17 g (30%) of **9a** (*S* epimer) was obtained as a gum, indistinguishable by TLC and NMR from **9a** prepared by method A. The intermediates **9d–g** were similarly prepared by N-alkylation of norcodeine with 2-bromopentane, 3-bromopentane, bromocyclohexane, and bromocycloheptane, respectively. Each compound was obtained as a chromatographically pure gum and identified by the NMR spectrum.

***N*-*sec*-Alkylnormorphines 10a–k.** Physical data appear in Table I.

Method C. O-Demethylation of *N*-*sec*-Alkylnorcodeines. A solution of 16.0 g (0.046 mol) of the codeine intermediate **9a** (method A) in 500 mL of THF, under N_2, was treated sequentially with 14.4 g (0.077 mol) of diphenylphosphine and 100 mL (0.06 mol) of 1.6 M Buli in hexane. The mixture was stirred at reflux for 30 min, poured into 300 mL of ice–H_2O, and extracted with 1 L of ether. The aqueous solution was adjusted to pH 8–9 with HOAc and the precipitated product extracted into $CHCl_3$ (200 mL). The solution was dried ($MgSO_4$) and evaporated to leave 13.3 g (83%) of **10a**,b as a solid. ^{13}C NMR indicated an approximate 50:50 mixture of diastereomers.

A solution of 3.2 g of crude **10a**,b in 100 mL of 2-PrOH was treated with 15 mL of 3% HCl in MeOH and evaporated in vacuo. The residual HCl salt was thrice recrystallized from 2-PrOH–Et_2O to afford 1.51 g of the *S* isomer **10a**: mp 338 °C; $[\alpha]^{21}_D$ –112° (MeOH); NMR (free base, $CDCl_3$) δ 0.92 (t, 3 H, CH_2CH_3), 1.10

(d, 3 H, CH_3CH–). Repeated recrystallization of material from the mother liquor afforded the *R* isomer (0.41 g): mp 213–215 °C; $[\alpha]^{21}_D$ –102° (MeOH); NMR (free base, $CDCl_3$) 0.90 (t, 3 H, CH_2CH_3), 1.10 (d, 3 H, CH_3CH–).

The codeine intermediate **9a** was separately prepared in *S* and *R* forms by N-alkylation of norcodeine with (*R*)- and (*S*)-2-mesyloxybutane (method B). O-Demethylation as above gave the pure (*S*)- and (*R*)-*N*-(2-butyl)normorphine with physical data for the HCl salts in agreement with the above **10a** and **10b**, respectively.

The decoupled ^{13}C NMR spectra of the free bases **10a,b** in $CDCl_3$ showed narrowly separated, but distinct doublets for the aliphatic carbon atoms about the new chiral center (C_9 58.23, 57.94), ($C_{2'}$ 55.19, 53.53), ($C_{1'}$ 23.84, 23.08); the pure *S* isomer **10a** showed 57.94 (C_9), 55.19 ($C_{2'}$), 23.84 ($C_{1'}$); the pure *R* isomer **10b** showed 58.23 (C_9), 53.53 ($C_{2'}$), 23.08 ($C_{1'}$) (all values in ppm).

The *N*-(α-methylallyl)normorphines **10c,d** were similarly prepared from **9b**, again showing a 50:50 mixture of *R* and *S* forms by ^{13}C NMR. The *R* isomer **10c** was obtained as the HCl salt by recrystallization of the crude mixture; $[\alpha]^{21}_D$ –121° (MeOH). The *S* isomer **10d** could not be obtained as the HCl salt from recrystallization of the crude residue from the mother liquor. Repeated recrystallization of the crude free base from EtOAc afforded **10d** in low yield, however, contaminated by 15% of **10c**. Conversion to the HCl salt, followed by recrystallization, promoted epimerization, affording **10c** as the only isolable product. As for **10a,b** the *R* and *S* isomers (**10c,d**) showed nearly identical ^1H NMR and ^{13}C NMR spectra, except for doubled signals exhibited for carbons around the new chiral center.

Hydrogenation of **10c** as the free base in EtOH over PtO_2 afforded a tetrahydro derivative **13**. This product was identical by ^1H and ^{13}C NMR with the product obtained by similar saturation of the (*R*)-*N*-(2-butyl)normorphine (**10b**) and distinctly different from the reduction product from **10a**, thus establishing the configuration of the new chiral center in **10c** as the *R* epimer and **10d** as the *S* epimer.

Method D. Grignard Reaction on *N*-(1-Cyano)-1-ethylnorheroin. A mixture of 6.5 g (0.018 mol) of norheroin (**6**) and 3.0 g (0.042 mol) of lactonitrile was heated briefly to 60 °C to produce the 3,6-diacetoxycyanoamine derivative **8**. Addition and evaporation in vacuo of 50 mL of toluene served to remove H_2O. The crude gum **8** (8.1 g) was directly added to excess benzylmagnesium chloride in Et_2O and the resulting product (6.3 g) isolated as in method A. The material was dissolved in 100 mL of 2-PrOH and treated with a solution of 0.75 g of 98% sulfuric acid in 5 mL of 2-PrOH. A tan crystalline precipitate (**10k**) was collected which weighed 4.19 g. NMR and TLC comparison confirmed that this material and that produced by method A were the same.

Method E. N-Alkylation of Normorphine. Normorphine (**11**) was prepared by saponification of norheroin (**6**) with 5% NaOH in MeOH (room temperature for 2 h): mp 276–277 °C (lit.[27,29] mp 276–277 °C). A mixture of 1.00 g (0.037 mol) of **11**, 4.0 g (0.037 mol) of Na_2CO_3, 3.2 g (0.019 mol) of 3-bromocyclohexene, and 60 mL of dry DMF was stirred at 60 °C for 15 min. The mixture was filtered and evaporated in vacuo, and the residue was partitioned between $CHCl_3$ and 3 N HCl. The aqueous portion was adjusted to pH 8–9 with concentrated NH_4OH and the gummy precipitate extracted into $CHCl_3$. Drying ($MgSO_4$) and evaporation afforded 0.52 g of **10i**: TLC (silica gel; $CHCl_3$–MeOH–Et_3N, 9:1:1) single spot, R_f 0.55. The material was characterized as the HCl salt.

Method F. Reduction of Iminium Salts of Normorphine. A mixture of 0.372 g of **11** (as the $HClO_4$ salt), 0.2 mL of Et_3N, and 10 mL of cyclopentanone was stirred at reflux for 30 min as the reactants dissolved and pink salts crystallized. Then the cooled mixture was diluted with 15 mL of Et_2O and filtered to give 0.38 g of the iminium salt **12b** (86%), mp 285–290 °C dec. Anal. ($C_{21}H_{24}ClNO_7 \cdot 2H_2O$) C, H, N (C, 53.8).

A mixture of 0.32 g (0.0007 mol) of **12b** and 0.05 g (0.004 mol) of $NaBH_4$ in 5 mL of THF was stirred until the mixture became colorless and clear. The reaction was quenched in 50 mL of H_2O, and the product (0.21 g) was recovered after adjustment of the pH to 8–9 with HOAc and extraction into CH_2Cl_2. The NMR of the free base and HCl salt were identical with that of **10g** produced by method E. Similarly, compounds **10f** and **10j** were prepared by this route, but without characterization of the imminium salts **12a** and **12c**.

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Supplementary Material Available: Tables III–XI listing conformational energies of substituted normorphine and nalorphine compounds (8 pages). Ordering information is given on any current masthead page.

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