($CDCl_3$) δ 6.98 (d, 1 H, J = 10.5 Hz, 7-H), 6.65 (2 H, aromatic), 5.95 (d, 1 H, J = 10.5 Hz, 8-H), 4.62 (s, 1 H, 5-H), 3.3 (d, J = 6.0 Hz, 9-H), 2.45 (s, 3 H, NCH_3). Anal. ($C_{17}H_{16}NO_3Br$) C, H, N.

Acknowledgment. The authors thank Dr. M. Feigenson of the Sterling Winthrop-Research Institute for the biological evaluation of the compounds. This investigation was supported by a grant from the National Institute on Drug Abuse (DA-01674).

Analgesic Narcotic Antagonists. 1. 8β-Alkyl-, 8β-Acyl-, and 8β-(Tertiary alcohol)dihydrocodeinones and -dihydromorphinones

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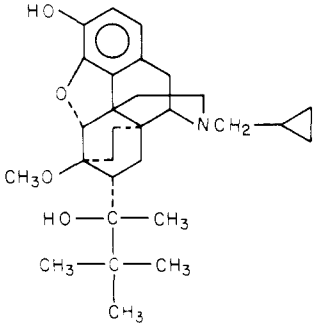
Received June 15, 1979

Conjugate addition of lithium dialkyl cuprates to codeinone (**3**) gave as the major product a series of 8β-alkyldihydrocodeinones 4a-m. A low yield of the 8α-isomer **6** was isolated in several cases. 8β-Acyldihydrocodeinones **10** were prepared by the addition of acyl carbanion equivalents (protected cyanohydrin method or lithium bis(α-ethoxyvinyl)cuprate) to **3** followed by hydrolysis. 8β-Acetyldihydrocodeine (**12**) was reacted with MeLi or *n*-BuLi to give tertiary alcohols **13**, which were oxidized to target dihydrocodeinones **14**. The 8β-substituted compounds with unsaturated (**4c,f,m**), branched (**4d,g,i-k**), or large straight-chain (**4h,l**) alkyl groups, as well as the acyl (**10a-d**) and tertiary alcohol (**14a,b**) derivatives, were less active than dihydrocodeinone (**4n**) in the mouse writhing and rat tail-flick analgesic assays. The analgesically active 8β-methyl (**4a**) and 8β-ethyl (**4b**) compounds were converted to *N*-(cyclopropylmethyl)- and *N*-(cyclobutylmethyl)dihydronorcodeinones (**17** and **18**) and -dihydronormorphinones (**19** and **20**). Some of these compounds had mixed agonist-antagonist profiles of action. One of these compounds, *N*-(cyclopropylmethyl)-8β-ethyldihydronorcodeinone (**17b**), has been selected for further study in man.

The high analgesic potencies of tertiary alcohols derived from Diels-Alder adducts of thebaine[1] have created a target which workers in the strong analgesic area are attempting to emulate. Attempts are being made to dissect out from these analgesics the structural features[2] responsible for their potency and affinity for the opiate receptor.[3] This work is further stimulated by the unique and favorable pharmacological properties of Buprenorphine (**1**), a mixed narcotic agonist-antagonist derived from this series which has been developed as a clinically useful analgesic agent.[4]



1

In an attempt to explain the potent analgesic activity of this series of compounds, Lewis, Bentley, and Cowan[5] hypothesized that a lipophilic site exists on the opiate receptor surface. This proposed site was postulated to interact with the alkyl portion of the tertiary alcohol appendage in the C ring. Examination of this receptor site indicates that the lipophilic area is in the proximity of C7 and C8 of the morphine nucleus. It has more recently been suggested,[6] based on the solid-state conformation of [Leu^5]enkephalin, that a complementary hydrophobic region exists on the C7-C8 face in the C ring of morphine.

To investigate these theories further, we initiated a study to determine the effect of hydrophobic alkyl substitution in this region of the morphine nucleus. We also desired to incorporate a major structural feature of **1**, namely, the tertiary alcohol moiety, into the 8 position of the morphine nucleus. The practical objective of this research was to prepare sufficiently potent compounds with a mixture of analgesic and narcotic antagonist properties. A compound with such a mixed profile of activity has potential for use as a nonaddicting analgesic agent in the treatment of severe pain.

This paper presents the results of our studies on the synthesis of 8-alkyl, 8-acyl and 8-(tertiary alcohol) derivatives of dihydrocodeinone and their preliminary pharmacological profiling. The analgesically active members of this series were converted to potential mixed agonists-antagonists. It is well known that a narcotic antagonist component of action may be incorporated into a morphine-derived narcotic agonist by replacement of the *N*-methyl group with moieties such as allyl, cycloalkylmethyl,[7] or tetrahydrofurfuryl.[8]

Chemistry. It appeared at the onset of our work that carbon-carbon bond formation at C8 could be accomplished by a 1,4 addition to codeinone (**3**). In particular,

(1) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3273 (1967); K. W. Bentley and D. G. Hardy, *ibid.*, **89**, 3281 (1967). This work has been extensively reviewed. See K. W. Bentley, *Alkaloids (N.Y.)*, **13**, 1 (1971).
(2) For an excellent example and review of some of the work in this area, see: W. F. Michne, R. L. Salsbury, and S. J. Michalec, *J. Med. Chem.*, **20**, 682 (1977); W. F. Michne, *ibid.*, **21**, 1322 (1978).
(3) E. J. Simon and R. J. Hiller, *Annu. Rev. Pharmacol. Toxicol.*, **18**, 371 (1978).
(4) A. Cowan, J. W. Lewis, and I. R. Macfarlane, *Br. J. Pharmacol.*, **60**, 537 (1977); A. Cowan, J. C. Doxey, and E. J. R. Harry, *ibid.*, 547 (1977); B. C. Hovell and A. F. Ward, *J. Int. Med. Res.*, **5**, 417 (1977).
(5) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, **11**, 241 (1971).
(6) G. D. Smith and J. F. Griffin, *Science*, **199**, 1214 (1978).
(7) E. L. May in "Agonist and Antagonist Actions of Narcotic Analgesic Drugs", H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, Eds., University Park Press, Baltimore, MD, 1973, p 17.
(8) H. Merz, A. Langbein, K. Stockhaus, G. Walther, and H. Wick *Adv. Biochem. Psychopharmacol.*, **8**, 91 (1973).

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Table I. Analgesic Activity

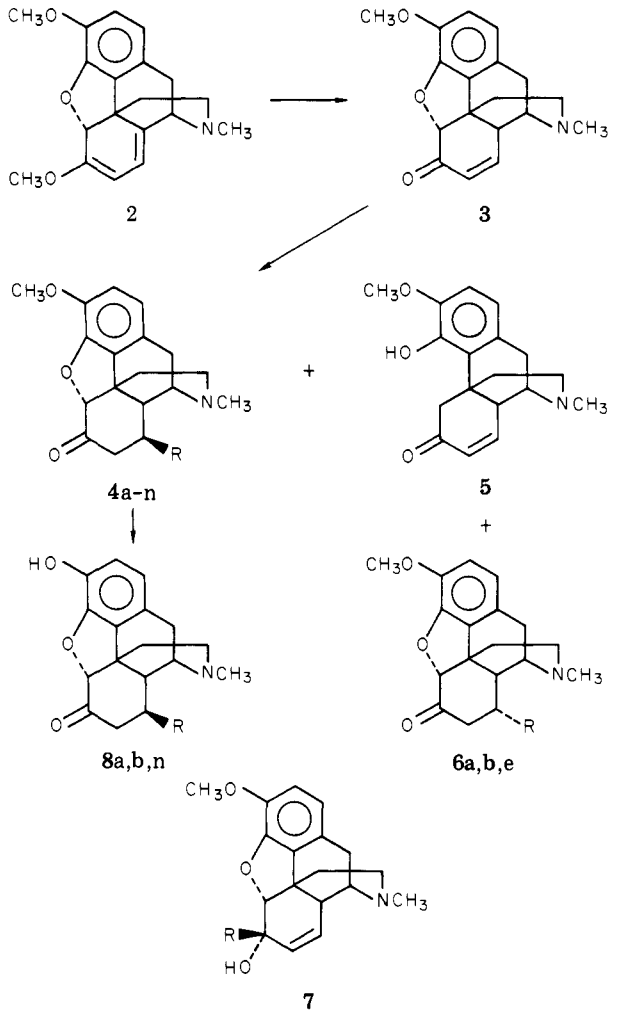
compd	R	ED_{50} subcutaneous injectn, μmol (95% CL) mouse writhing	rat tail flick
4a	Me	4.9 (2.6-9.4)	10.2 (2.9-37.4)
b	Et	1.8 (0.74-4.2)	20.3 (8.5-48.1)
c	vinyl	13.8 (3.9-50.3)	130 (25.7-660)
d	c-Pr	42.0 (18.4-96.2)	>25
e	*n*-Pr	17.5 (11.2-27.2)	
f	*i*-propenyl	>50	
g	*i*-Pr	21.7 (12.2-39.1)	>55
h	*n*-Bu	27.0 (12.5-58.7)	>50
i	*t*-Bu	17.6 (11.5-27.3)	>25
j	*s*-Bu (A)	14.1 (7.6-26.4)	
k	*s*-Bu (B)	>25	
l	*n*-octyl	25.9 (10.3-65.0)	>50
m	Ph	>50	
n[a]	H	2.4 (1.6-3.6)	5.2 (3.6-7.5)
6a	Me	2.0 (1.3-3.2)	3.8 (1.9-7.3)
b	Et	3.0 (1.7-5.0)	>30
e	*n*-Pr	>25	>25
8a	Me	0.24 (0.15-0.42)	1.60 (0.80-3.1)
b	Et	0.41 (0.29-0.64)	1.12 (0.54-2.3)
n[b]	H	0.25 (0.12-0.44)	1.34 (1.18-1.52)

[a] 4n = dihydrocodeinone. [b] 7n = dihydromorphinone.

the use of lithium dialkylcopper reagents[9] represents an effective method for attaching a variety of alkyl groups to the β position of α,β-unsaturated ketones. To incorporate an acyl group at this position, we utilized acyl carbanion equivalents[10] derived from cyanohydrin-protected α,β-unsaturated or aromatic aldehydes. The introduction of an acetyl group at C8 was carried out by the use of the organocopper reagent derived from α-ethoxyvinyllithium.[11] Acyl carbanion equivalents derived from saturated aldehydes added to **3** in a 1,2 manner as expected.[10]

Thebaine (**2**) was converted to codeinone (**3**) in good yield by modification of a reported method.[12] Addition of a benzene solution of **3** to 1.25 equiv of lithium dimethylcuprate in ether at 0 °C gave a mixture of products which were resolved by a combination of crystallization and chromatography. The major product was identified as 8β-methyldihydrocodeinone (**4a**, overall yield 54%) as described below. Chromatography of the mother liquors gave a 4,5-epoxy-cleaved product, thebainone-A (**5**, 6%), identified by comparison with an authentic sample.[13] A

Scheme I[a]



[a] For a, R = -CH_3; b, -CH_2CH_3; c, -CH=CH_2; d, -c-C_3H_5; e, -$(CH_2)_2CH_3$; f, -C(=CH_2)CH_3; g, -$CH(CH_3)_2$; h, -$(CH_2)_3$-CH_3; i, -$C(CH_3)_3$; j, -$CH(CH_3)CH_2CH_3$ (A); k, -$CH(CH_3)$-CH_2CH_3 (B); l, -$(CH_2)_7CH_3$; m, -C_6H_5; n, -H.

small amount (2%) of the 8α-methyl isomer **6a** was obtained as the most polar product by chromatography.

The mass spectral fragmentation pattern of both isomers **4a** and **6a** showed a molecular ion peak at *m/e* 313, followed by loss of a methyl group to give a dihydrocodeinone radical at *m/e* 298. The remainder of the fragmentation pattern was similar to that previously reported for codeinone.[14] Alkylation at the 8 position was indicated by loss of olefinic NMR signals for H7 and H8. The configuration of the methyl group in **4a** and **6a** was definitively proven by NMR. The C8 methyl signal of the major product **4a** was observed as an unsymmetrical doublet at δ 1.0 in $CDCl_3$ solution. The signal for the C8 methyl group of the minor isomer **6a** was found as a more symmetrical doublet at δ 0.40. The upfield shift in **6a** is due to the anisotropic effect of the aromatic A ring which can only occur when the C8 methyl group occupies an axial orientation. The minor axial isomer **6a** is therefore α, while in the major product **4a** the methyl group is β and equatorial. This differs from the expected stereochemistry of conjugate additions of lithium organocuprates where, in the major product, the alkyl group is usually introduced into the axial position.[9]

(9) G. H. Posner, *Org. React.* 19, 1 (1972).
(10) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, 96, 5272 (1974).
(11) R. K. Boeckman, Jr., K. R. Bruza, J. E. Baldwin, and O. W. Lever, Jr., *J. Chem. Soc., Chem. Commun.*, 519 (1975); C. G. Chavdarin and C. H. Heathcock, *J. Am. Chem. Soc.*, 97, 3822 (1975).
(12) J. P. Gavard, F. Krauz, T. Rüll, and M. Delfly, *Bull. Soc. Chim. Fr.*, 486 (1965).
(13) Y. K. Sawa, M. Horiuchi, and K. Tanaka, *Tetrahedron*, 21, 1133 (1965).
(14) D. M. S. Wheeler, T. H. Kinstle, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, 89, 4494 (1967).

Several other differences in the NMR of **4a** and **6a** were noted. The singlet for the H5 proton of the minor α isomer **6a** was observed slightly downfield from that of the major product **4a**. The aromatic region of **4a** was observed as a singlet, whereas this region appears as a sharp doublet in the minor product **6a**. This difference in the aromatic region was also observed in other α,β pairs which we have obtained.

The series of 8-alkyldihydrocodeinones prepared in this work are shown in Scheme I and in Table I. In most cases, only the major 8β-alkylated product **4** was isolated from the reaction mixture and characterized. In the several instances where a low yield of 8-alkylated product was obtained, for example, in the preparation of **4c**, **4i**, and **4m**, the major contaminating product was the 1,2-adduct **7**. Compounds **7** were identified by the presence of olefinic H7 and H8 protons in the NMR and the absence of a ketone band in the IR. These 1,2-adducts **7** result from the addition of the alkyllithium to the C6 ketone of **3**, suggesting that formation of the organocopper reagent was incomplete.

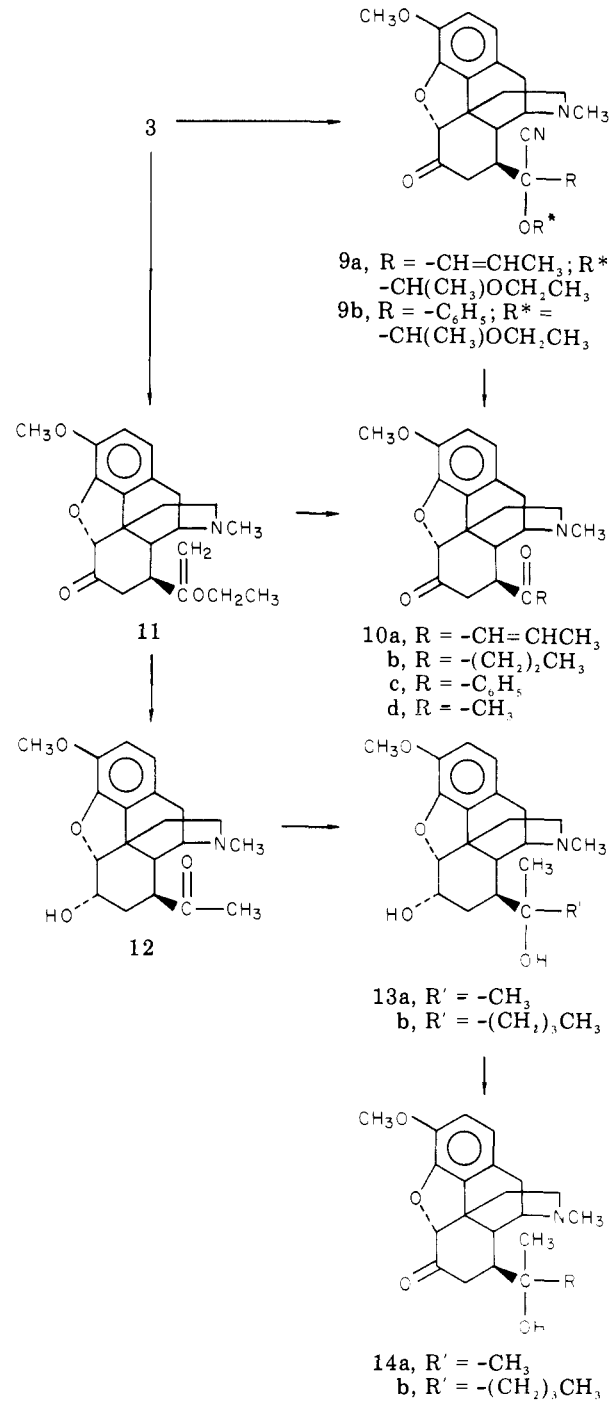
The alkyllithium reagents used for the preparation of the lithium dialkylcuprates were obtained from commercial sources or by *tert*-butyllithium–halogen exchange or by direct preparation from lithium dispersion and the alkyl halide. The stability of the R_2CuLi complexes dictated individual reaction conditions for each conjugate addition to **3**. Details are given under Experimental Section. The yields in most cases were not optimized. The 8β-isopropyl derivative **4g** was prepared by catalytic reduction of the corresponding 8β-isopropenyl adduct **4f** in acidic ethanol. The 8β-ethyl compound **4b** could likewise be prepared by reduction of **4c**. 8β-Alkyldihydromorphinones **8a,b** were prepared by fusion of **4a,b** with pyridine hydrochloride at 180–200 °C for 1 h.[15]

Reaction of **3** with the α-ethoxyethylcyanohydrin of crotonaldehyde gave a good yield of adduct **9a** (Scheme II). Removal of the blocking groups, reported to occur under mild acid–base conditions,[10] gave mixtures of products. Hydrolysis of **9a** to **10a** could readily be affected by treatment with 9:1 CF_3COOH–H_2O,[16] followed by extraction from basic solution. The crude mixture was purified by column chromatography to give **10a** in 56% yield from **3**. Hydrogenation at atmospheric pressure yielded the saturated 8-butyryl compound **10b**. The 8-benzoyl analogue **10c** was obtained directly in crystalline form by hydrolysis of **9b** under similar conditions. Lithium bis(α-ethoxyvinyl)cuprate reacted smoothly with **3** to give a good yield of adduct **11**. Hydrolysis of **11** under mild acid conditions gave the desired **10d** in moderate yields.

On the basis of analogy to our work in the 8-alkyldihydrocodeinones, compounds **10** are shown with the 8-acyl substituent in the β position. No evidence was found in these condensation reactions for the presence of the thermodynamically less stable α isomer. That epoxy bond cleavage did not occur during condensation and hydrolysis was indicated by the presence of a sharp singlet for H5 in the NMR spectra of **10**.

We had orignally planned to treat the 8β-acyldihydrocodeinones **10** with Grignard reagents to obtain the desired tertiary alcohols **14**. Preferrential reaction at the acyl ketone was expected based on the report that codeinone and dihydrocodeinone do not react readily with Grignard reagents.[17] Treatment of **10b** with MeMgI in refluxing

Scheme II

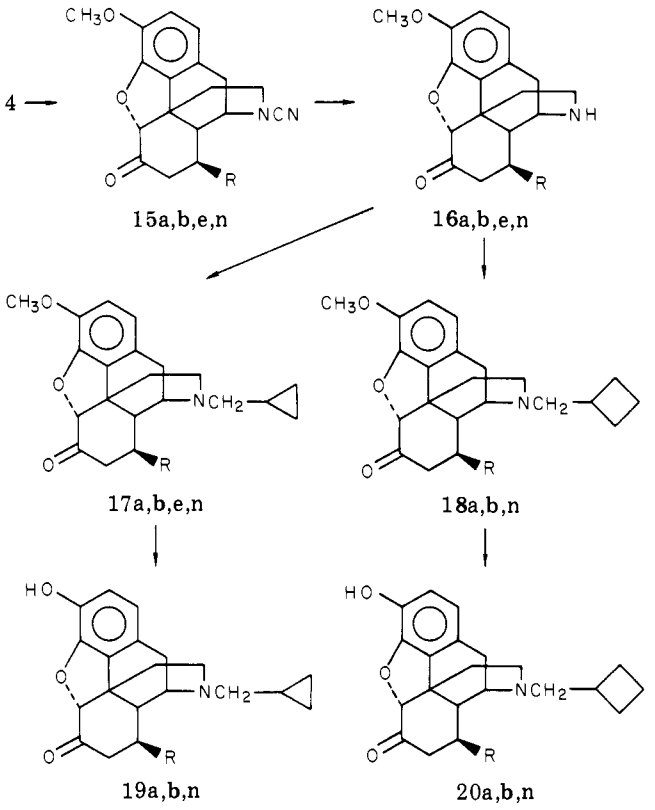


benzene gave only a trace of reaction after 5 h. Forcing the reaction conditions gave a complex mixture of products. Likewise, **10a** reacted only sluggishly with MeMgI. Attempts to selectively block one of the ketone functionalities in **10** for subsequent reaction with alkyllithium compounds was not successful.

Alternatively, intermediate **11** was reduced with $NaBH_4$ and then hydrolyzed to the 8-acyldihydrocodeine derivative **12**. Traces of the 6β-hydroxy isomer of **12** were formed in this reduction. Addition of MeLi or *n*-BuLi to **12** proceeded smoothly at 0 °C to give **13** with no indication for the formation of diastereoisomeric mixtures. The alcohols **13** were oxidized to target compounds **14** by use of Me_2SO–Ac_2O at 65 °C.[18] Only traces of side-chain de-

(15) T. J. Curphey, E. J. Hoffman, and C. McDonald, *Chem. Ind. (London)*, 1138 (1967).
(16) J. E. Cristensen and L. Goodman, *Carbohydr. Res.*, 7, 510 (1968).
(17) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, 72, 3249 (1950).

Scheme III



hydration products were observed in this reaction.

The *N*-methyl compounds **4a,b,e** were transformed to *N*-(cycloalkylmethyl) analogues by a three-step process (Scheme III). Reaction of **4a,b,e** with cyanogen bromide in chloroform solution, with the presence of potassium carbonate, gave the *N*-cyano compounds **15a,b,e** as crystalline solids. Hydrolysis to the 8β-alkyldihydronorcodeinones **16a,b,e** was accomplished by refluxing in 2 N HCl.[19,20] Alkylation on nitrogen was carried out in DMF solution[21] at 100 °C, using sodium bicarbonate as the acid acceptor, to give good conversion to *N*-(cyclopropylmethyl) compounds **17a,b,e** and *N*-(cyclobutylmethy) compounds **18a,b**. The *N*-cycloalkylmethylated derivatives were converted to dihydronormorphinones **19a,b** and **20a,b** by pyridine hydrochloride treatment or by brief refluxing with 48% hydrobromic acid.[22]

For the purposes of comparative pharmacology, dihydrocodeinone (**4n**) was converted by a similar N-dealkylation–alkylation procedure to compounds **17n** and **18n**. Demethylation at C3 gave the *N*-(cycloalkylmethyl)dihydronormorphinones **19n** and **20n** in moderate yields. The cyclopropylmethyl derivatives **17n** and **19n** have previously been reported by Gates.[20]

Results

The *N*-methyl compounds prepared in this study were tested in both the acetic acid induced mouse writhing[23] and heat stimulus rat tail-flick assay for analgesic activity.[24]

Table II. Analgesic and Narcotic Antagonist Activity

compd	ED_{50} subcutaneous injectn, μmol/kg (95% CL): analgesic ED_{50}, mouse writhing	antagonist ED_{50},[a] rat tail flick	agonist/antagonist
17n	39.6 (25.6-61.3)	7.9 (2.5-25.2)	5
a	33.3 (9.5-107)	19.0 (7.9-44.9)	1.8
b	5.2 (0.74-33.7)	1.93 (0.77-4.9)	2.7
e	62.2 (26.8-144)	33.7 (23.9-47.6)	1.8
18n	20.3 (10.8-38.5)	IA[b]/7	
a	11.0 (5.4-22.8)	24	0.46
b	23.0 (8.9-58.9)	IA/7	
19n	4.12 (0.83-19.9)	0.58 (0.31-1.05)	7.1
a	>25	6.12 (2.53-15.0)	
b	20.8 (11.7-37.0)	0.66 (0.21-4.8)	31
20n	0.21 (0.03-1.83)	5.01 (1.03-24.2)	0.04
a	1.72 (0.44-6.62)	4.74 (0.95-24.1)	0.35
b	22.8 (6.2-83.9)	1.29 (0.45-3.79)	17.7
butorphanol	0.34 (0.13-0.90)	2.0 (0.97-9.4)	0.17
cyclazocine	0.41 (0.11-1.7)	0.81 (0.48-1.4	0.50
pentazocine	13.0 (8.5-19)	36.4 (13.6-100)	0.36
nalorphine	3.51 (0.58-21)	2.47 (0.46-13)	1.4

[a] Determined using an intraperitoneal ED_{80} of morphine. [b] IA = inactive at dose shown.

The results of these assays are shown in Table I. The 8-alkyldihydrocodeinones **4a,b** and the 8-alkyldihydromorphinones **8a,b**, in which the substituent at the 8 position is methyl or ethyl, have about the same potency as dihydrocodeinone (**4n**) and dihydromorphinone (**8n**). Introduction of a side chain larger than ethyl, for example, *n*-propyl (**4e**), or of unsaturation (**4c**), or an aromatic group (**4m**) at the C8 position causes a drop in potency. One of the stereoisomers of the *sec*-butyl compounds (**4j**) was active, whereas the other isomer (**4k**) was inactive. This may indicate stereoselectivity in the mode of binding of an 8β substituent to the opiate receptor. The 8α-alkyldihydrocodeinones **6a,b** were also analgesically active. The potency, however, again rapidly falls off when the 8α group is larger than ethyl. The 8-acyl compounds **10** and **12** and the tertiary alcohols **13** and **14**, with the exception of **14b**, had analgesic ED_{50} values greater than 50 μmol/kg. The ED_{50} for **14b** in the mouse writhing assay was 15.5 μmol/kg with no activity demonstrated in the rat tail-flick procedure.

Our work in other series of analgesics based on the morphine ring system has shown that *N*-methyl compounds which are not active analgesics cannot be converted to mixed agonist–antagonists by manipulation of the N substituent. This same opinion has been expressed[25] for

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(19) H. Rapoport and M. Look, U.S. Patent 2890221 (1959); *Chem. Abstr.*, 54, 612*f* (1960).
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(23) B. J. R. Whittle, *Br. J. Pharmacol.*, 22, 246 (1964).
(24) L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, 143, 141 (1964).
(25) S. Archer and L. S. Harris, *Progr. Drug Res.*, 8, 261 (1965); G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, 22, 603 (1979).

other morphine-like structures. We, therefore, limited the preparation of *N*-(cycloalkylmethyl) derivatives to those compounds (**4**) which showed good analgesic activity.

Data for the analgesic and narcotic antagonist potencies of the *N*-(cycloalkylmethyl) compounds **17–20** are presented in Table II. Narcotic antagonism was determined by the rat tail-flick method[24] against an ED_{80} of morphine. Data for the *N*-(cycloalkylmethyl)dihydro compounds, series **n**, are included as a reference base. Also included in Table II are the agonist–antagonist ratios. Numbers in this column greater than 1 indicate that the compound is more antagonistic than analgesic, while ratios less than 1 indicate compounds which are stronger analgesics. In general, *N*-(cyclopropylmethyl) compounds are antagonists, while the *N*-(cyclobutylmethyl) series show more agonist action.

The introduction of a small alkyl substituent into the 8β position of the *N*-(cycloalkylmethyl)dihydro series **n** does affect the analgesic and narcotic antagonist activity of these compounds. This change does not occur in a regular, predictable fashion. The analgesic and antagonist potency of compounds **17–20** is clearly dependent upon both the 8β-alkyl and nitrogen substituents. On the basis of preliminary screening data, mixed agonist–antagonists **17b** and **20a** have been investigated further in other models related to drug dependence and the side effects of narcotic drugs. *N*-(Cyclopropylmethyl)-8β-ethyldihydronorcodeinone (**17b**) is currently undergoing phase I clinical trials. The results of these studies will be reported by others.[26]

Discussion

The data presented in this report indicates that incorporation of a small alkyl group in the 8 position of the codeinone nucleus does not substantially alter the analgesic potency of *N*-methyl compounds **4** and **6**. Larger groups at this position decrease antinociceptive activity, as does the introduction of an acyl or tertiary alcohol moiety. Lack of interaction of the 8β substituent with the lipophilic portion of the receptor is understandable, in that the groups we have introduced in the C ring occupy a different position in space than that of **1**. The ethano C ring bridge in **1** and related compounds forces the tertiary alcohol appendage into a position above the plane of the C and D rings. In our 8β derivatives, the substituent is in the plane of the C–D ring-fused system and extends outward toward a different area on the receptor surface. For the 8α compounds **6**, the alkyl group is forced down into the T shape of the molecule to a position near the aromatic A ring.

The original concept on which this work was based requires more investigation. We have not succeeded in obtaining highly potent compounds; we have, however, found a site close to the C8 region which does modify the narcotic agonist–antagonist ratios of *N*-(cycloalkylmethyl)dihydronorcodeinones and -dihydronormorphinones.

The agonist–antagonist ratio is an attempt to predict substitution and dependence liability from data already available for our series. There should exist, in the continuum between pure narcotic agonists and pure antagonists, an ideal ratio of these activities for a useful analgesic agent. The ability to predict dependence liability from this agonist–antagonist ratio must await further experimental verification.

We are currently exploring other facets of the proposed opiate receptor surface by chemical modification of the morphine structure. This work will form the basis of future communications from these laboratories.[27]

Experimental Section

All organometallic reactions were performed under an inert atmosphere of argon or nitrogen. Processing in the usual fashion implies that the organic extracts were combined, washed with dilute NH_4OH solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under water aspirator pressure on a rotary evaporator. These residues were finally dried at 50–60 °C using a mechanical vacuum pump. Hydrochloride salts usually were prepared by the addition of concentrated HCl to an EtOH solution of the compound, followed by evaporation and azeotropic distillation with EtOH, EtOH–C_6H_6 or toluene mixtures and then C_6H_6 or toluene. Column chromatography was performed by a reported procedure[28] over silica gel G (E. Merck) using the indicated amount of gel and the indicated $CHCl_3$–MeOH mixtures as the eluent. Fractions were combined on the basis of TLC (silica gel 60 F-254, E. Merck) with spots being visualized by UV light and/or by spraying with 20% H_2SO_4–EtOH, followed by charring.

Melting points were taken in open capillary tubes on a Thomas-Hoover apparatus and are not corrected. IR spectra were recorded in KCl disks or $CDCl_3$ solution on a Perkin-Elmer Model 237 spectrophotometer. NMR spectra were determined in $CDCl_3$, unless otherwise indicated, using a Varian T-60A. Chemical shifts are given in parts per million downfield from the internal standard Me_4Si. Coupling constants are first order. Only certain characteristic NMR data are presented. Elemental analyses were determined by Analytical Services, Chemistry Department, Miles Laboratories, Elkhart, Ind., and by Midwest Microlabs, Indianapolis, Ind.

Codeinone (3). A stirred solution of thebaine (**2**; 100 g) in CH_2Cl_2 (1 L) was cooled to below 3 °C in an ice–salt bath and then rapidly saturated with HBr with continued cooling. The temperature of the reaction mixture rose in ≃10 min and was kept below 15 °C by controlling the rate of HBr addition. HBr was added until the solution was saturated (≃35 min) as indicated by a drop in temperature. The mixture was cooled below 5 °C and poured into cold, stirred saturated $NaHCO_3$ solution (2 L). The neutral mixture was adjusted to pH 12 by the addition of 50% NaOH solution. The organic layer was separated and the aqueous phase washed twice with CH_2Cl_2 (400 mL). The organic phases were processed in the usual fashion and evaporated to a semicrystalline brown residue. The residue was triturated with MeOH (100 mL) and chilled. The crystals were collected and washed with three portions of cold MeOH (20 mL). These crystals were suspended in H_2O, and, with warming and stirring, the mixture was adjusted to pH 1–2 by the addition of concentrated HCl. The clear yellow solution was cooled in ice to 30 °C, and 50% NaOH was added to give a thick suspension (pH ≃14). The suspension was cooled below 15 °C, and the crystals were collected, pressed dry, and then washed with cold water. Drying overnight under high vacuum at 65 °C gave 64.5 g (67%) of **2**: mp 183–184 °C with prior sintering (lit.[12] 184 °C); NMR δ 6.67 (s, 2 H, aromatic), 6.68 (2 d, 1 H, H8, $J_{7,8}$ = 10, $J_{8,14}$ = 2 Hz), 6.06 (2 d, 1 H, H7, $J_{7,14}$ = 3 Hz), 4.70 (s, 1 H, H5), 3.85 (s, 3 H, CH_3O–), 2.46 (s, 3 H, CH_3N–).

8β-Methyldihydrocodeinone (4a). A solution of Me_2CuLi was prepared at 0 °C from CuI (20.0 g, 0.105 mol) and MeLi (0.210 mol, 126 mL of a 1.8 M solution containing LiBr in Et_2O) in Et_2O (400 mL). To this was added in a thin stream a warm solution of **3** (25.0 g, 0.084 mol) in dry benzene (500 mL), and the resulting yellow suspension was stirred at 0 °C for 1 h. The mixture was poured into saturated NH_4Cl solution (500 mL) and stirred rapidly for 1 h. The organic phase was separated and the cooled aqueous phase adjusted to pH ≃12 with 50% NaOH. The aqueous phase was extracted with three portions of $CHCl_3$, and the combined organic extracts were processed in the usual manner to give a crystalline residue. The residue was dissolved in a minimal amount of hot EtOH and left overnight in the cold. The tan crystals were collected and dried to give 9.3 g of **4a**. An additional 1.2 g of 4a was obtained on concentration of the mother liquors. Analytically pure **4a**, mp 178–179.5 °C, was prepared by re-

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crystallization from EtOH: NMR δ 6.68 (s, 2 H, aromatic), 4.65 (s, 1 H, H5), 3.57 (s, 3 H, CH_3O–), 2.45 (s, 3 H, CH_3N–), 1.02 (unsymmetrical d, 3 H, J = 6 Hz, 8β-CH_3–). Anal. ($C_{19}H_{23}NO_3$) C, H, N. The hydrochloride of 4a, mp 274–276 °C, was crystallized from EtOH–EtOAc. Anal. ($C_{19}H_{23}NO_3$·HCl) C, H, N.

Thebainone-A (5) and 8α-Methyldihydrocodeinone (6a). The mother liquor obtained above was evaporated to a dry residue (7.2 g) and chromatographed (500 g, 6:1). Elution of 4a (3.7 g, combined yield 54%) was followed by **5** (1.6 g, 6%), identified by comparison (NMR, IR, TLC) with an authentic sample.[13] Continued elution gave **6a** (0.6 g, 2%) as a tan solid: NMR δ 6.68 (narrow d, 2 H, aromatic, $J \simeq 1$ Hz), 4.73 (s, 1 H, H5), 3.93 (s, 3 H, CH_3O–), 2.43 (s, 3 H, CH_3N–), 0.40 (d, 3 H, 8α-CH_3–, J = 7 Hz). The HCl salt of **6a**, mp 284–286 °C, was prepared in the usual fashion and crystallized from EtOH–EtOAc. Anal. ($C_{19}H_{23}NO_3$·HCl) C, H, N.

8β-Ethyl- and 8α-Ethyldihydrocodeinone (4b and 6b). EtLi was prepared by the dropwise addition of EtCl (11.1 g, 0.172 mol) in Et_2O (50 mL) to a suspension of metallic Li [0.345 mol, 2.4 g, 8.0 g of a 30% Li dispersion (containing 2% Na) in mineral oil which was removed by washing three times with hexane] in Et_2O (100 mL) at 0 °C, followed by stirring at 0 °C for 20 min. After cooling to −78 °C, the gray suspension was transferred by use of argon pressure to a stirred suspension of CuI (16.0 g, 0.084 mol) in ether (800 mL) stirred at −78 °C. The suspension was allowed to warm to −40 °C and a warm solution of codeinone (20.0 g, 0.067 mol) in C_6H_6 (400 mL) was added rapidly while keeping the temperature at −40 °C. Stirring was continued at −40 °C for 10 min, and the suspension was allowed to warm to 0 °C. Workup in the usual fashion gave a crystalline residue, which was recrystallized from EtOAc to give 12.2 g of **4b**, mp 146.5–148 °C. Additional **4b** (4.0 g, total yield 73%) was obtained on concentration of the mother liquor. Recrystallization from EtOH gave pure **4b**: mp 147–148 °C; NMR δ 6.70 (s, 2 H, aromatic), 4.70 (s, 1 H, H5), 3.93 (s, 3 H, CH_3O–), 2.46 (s, 3 H, CH_3N–), 1.03–0.73 (unsymmetrical t, 3 H, CH_3CH_2–). The HCl salt of **4b** was crystallized from EtOH–EtOAc. Anal. ($C_{20}H_{25}NO_3$·HCl) C, H, N, Cl.

The mother liquor obtained above was evaporated to a dry residue and chromatographed (600 g, 6:1). After elution of **4b**, **6b** was eluted, followed by a mixture of **6b** and **5**. Fractions containing only **6b** were combined and crystallized from EtOAc to give white crystals: mp 188.5–190 °C; NMR δ 6.68 (narrow d, 2 H, $J \simeq 1$ Hz), 4.72 (s, 1 H, H5), 3.90 (s, CH_3O–), 2.45 (s, CH_3N–), 0.83–0.46 (t, 3 H, CH_3CH_2–). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

8β-Vinyldihydrocodeinone (4c). Vinyllithium was prepared at −78 °C in Et_2O (60 mL) by stirring vinyl bromide (4.5 g, 42 mmol) and *tert*-butyllithium (84 mmol, 52.5 mL of a 1.6 M solution in pentane) for 1 h. The resulting suspension was added to a stirred suspension of CuI (4.0 g, 21 mmol) in Et_2O (200 mL) at −78 °C. Compound **3** (5.0 g, 16.8 mmol) in warm C_6H_6 was added as above at −78 °C, and the mixture was allowed to warm to −5 °C before being poured into NH_4Cl solution. Further processing gave 5.4 g of a syrup, which was chromatographed (500 g, 15:1). Fractions containing the major component were pooled and evaporated to give 3.0 g (55%) of **4c** as white crystals: mp 132–134 °C; NMR δ 6.70 (s), 4.70 (s), 5.8–5.4 (1 H, m, $-CH{=}CH_2$), 5.1–4.8 (2 H, m, $-CH{=}CH_2$), 3.93 (s), 2.43 (s). The HCl salt was recrystallized from EtOH to give pure **4c**·HCl, mp 276–278 °C dec. Anal. ($C_{20}H_{23}NO_3$·HCl) C, H, N.

8β-Cyclopropyldihydrocodeinone (4d). Cyclopropyllithium was prepared by the dropwise addition of cyclopropyl bromide (5.1 g, 42 mmol) in Et_2O (20 mL) to a Li dispersion (84 mmol) in Et_2O (30 mL) at 0 °C, followed by stirring at 0 °C for 1 h. The resulting suspension was cooled to −78 °C and added to CuI (4.0 g) in Et_2O. The mixture was warmed to −40 °C and 5.0 g of **3** was added. Workup in the usual fashion gave 5.9 g of a foam, which was chromatographed (500 g, 10:1) to give 4.4 g (77%) of **4d**, mp 197–198 °C. Recrystallization from EtOH gave a mp of 197–198.5 °C for **4d**: NMR δ 6.63 (s), 4.68 (s), 3.93 (s), 2.16 (s), 0.9–0.3 (5 H, m, cyclopropyl H). The HCl salt of **4d**, mp >265 °C, was crystallized from MeOH–EtOAc. Anal. ($C_{21}H_{25}NO_3$·HCl) H, N; C: calcd, 67.10; found, 66.49.

8β-*n*-Propyl- and 8α-*n*-Propyldihydrocodeinone (4e and 6e). *n*-PrLi was prepared from *n*-PrCl (168 mol) as described above for **4b** and added to CuI (16.0 g) at −78 °C, followed by **3** (20.0 g) in the usual fashion. Workup gave a syrup which crystallized on evaporation with EtOH. Crystalline **4e** (15.8 g), mp 144–146 °C, was collected and an additional portion (3.5 g) was obtained on concentration of the mother liquor: NMR δ 6.68 (s), 4.68 (s), 3.93 (s), 2.46 (s). The HCl salt of **4e**, mp 278–281 °C, was recrystallized from MeOH–EtOAc. Anal. ($C_{21}H_{27}NO_3$·HCl) C, H, N, Cl.

The mother liquor was evaporated to 5.9 g of a dry residue, which was chromatographed (600 g, 6:1) to give additional crystalline **4e** (1.6 g, total yield 91%) followed by **6e** (1.5 g, 6%): NMR δ 6.65 (narrow d), 4.69 (s), 3.93 (s), 2.46 (s). The HCl salt of **6e** crystallized from MeOH–EtOAc as white needles: mp sinters 255 °C, melts 260–263 °C dec. Anal. ($C_{21}H_{27}NO_3$·HCl) C, H, N, Cl.

8β-Isopropenyldihydrocodeinone (4f). Isopropenyllithium was prepared in Et_2O at −78 °C from 2-bromopropene (5.1 g, 42 mmol) and *tert*-butyllithium (84 mmol) as indicated for **4c**. This was added to CuI (4.0 g), followed by **3** (5.0 g) at −78 °C. Stirring was continued at −78 °C for 1 h and then at 0 °C for 1 h. Processing gave a syrup which was chromatographed (600 g, 15:1). Major fractions were pooled to give **4f** (2.5 g, 44%) as a foam: NMR δ 6.70 (2 H), 4.84 (m, 2 H, $=CH_2$), 4.72 (unsymmetrical s, H5), 3.97 (s), 2.43 (s), 1.75 (br s, 3 H, $-CH_2CCH_3$). The HCl salt of **4f**, mp >290 °C dec, was crystallized from EtOH. Anal. ($C_{21}H_{25}NO_3$·HCl) C, H, N.

8β-Isopropyldihydrocodeinone (4g). A solution of **4f** (1.4 g) in 95% EtOH was made acidic by the addition of concentrated HCl, and the mixture was hydrogenated at 50 psi over 10% Pd/C (150 mg) for 5 h. Removal of the catalyst, followed by evaporation of the filtrate, gave a quantitative yield of **4g**·HCl, which was recrystallized from EtOH: NMR (D_2O) δ 7.06 (s), 5.38 (s), 4.06 (CH_3O–), 3.23 (CH_3N–), 1.3–0.8 (m, 7 H, isopropyl H). Anal. ($C_{21}H_{27}NO_3$·HCl) C, H, N, Cl.

8β-*n*-Butyldihydrocodeinone (4h). To a solution of *n*-Bu_2CuLi, prepared at −30 °C from CuI (4.0 g) and *n*-BuLi (17.5 mL of a 2.4 M solution in hexane), in Et_2O (150 mL) was added **3** (5.0 g) in C_6H_6. The mixture was stirred at −30 °C for 1 h and then processed to yield 5.9 g of a foam. The foam was dissolved in Et_2O, and HCl gas was added. Crystals of **4h**·HCl (1.8 g, 27%), mp 239–245 °C, precipitated. Recrystallization from EtOAc gave pure **4h**·HCl, mp 244–246 °C. Anal. ($C_{22}H_{29}NO_3$·HCl) C, H, N.

8β-*tert*-Butyldihydrocodeinone (4i). To the copper cluster prepared from CuI (4.0 g) and *tert*-butyllithium (42 mmol) in Et_2O at −78 °C was added **3** (5.0 g) in C_6H_6, followed by stirring at −78 °C for 1 h. Processing gave 5.2 g of a syrup, which was chromatographed to give 2.4 g (40%) of **4i** as a foam: NMR δ 6.70 (s), 4.64 (s), 3.90, 2.43, 1.00 (s, 9 H). The HCl salt was crystallized from EtOAc to give 2.0 g of pure **4i**·HCl, mp 275–278 °C dec. Anal. ($C_{22}H_{29}NO_3$·HCl) C, H, N.

Diastereoisomeric 8β-*sec*-Butyldihydrocodeinones 4j and 4k. The diastereomeric mixture of di-*sec*-butylcopper lithium was prepared from CuI (4.0 g) and *sec*-butyllithium (42 mmol, 28.8 mL of a 1.46 M solution in cyclohexane) at −78 °C and allowed to warm to −50 °C. Codeinone (**3**; 5.0 g) in C_6H_6 was added at this temperature, and the mixture was allowed to warm to −5 °C. Processing gave 5.9 g of a syrup, which was chromatographed (500 g, 20:1 $CHCl_3$–MeOH) to give 2.3 g (38%) of the faster migrating isomer **4j** as crystals. Recrystallization from EtOH gave pure **4j** as white crystals: mp 188–190 °C; NMR δ 6.70 (s), 4.68 (s), 3.93, 2.44. Anal. ($C_{22}H_{29}NO_3$) C, H, N.

Fractions containing the slower migrating isomer **4k** were evaporated to give 1.5 g (25%) of a foam. The HCl salt of **4k**, mp >290 °C dec, was recrystallized from EtOAc. Anal. ($C_{22}H_{29}NO_3$·HCl) C, H, N.

8β-Octyldihydrocodeinone (4l). Octyllithium was prepared from octyl chloride (6.3 g, 42 mmol) and Li dispersion (84 mmol) and added at −78 °C to CuI (4.0 g) in ether. The suspension was warmed to −40 °C and **3** (5.0 g) was added in C_6H_6. Workup gave a syrup which was chromatographed (500 g, 15:1) to give 6.2 g (82%) of **4l** as a syrup, which was converted to the HCl salt. Recrystallization from MeOH–EtOAc gave pure **4l**·HCl, mp 177–178 °C. Anal. ($C_{26}H_{37}NO_3$·HCl) C, H, N.

8β-Phenyldihydrocodeinone (4m). Ph_2CuLi was prepared at −78 °C in Et_2O and reacted with **3** (5.0 g) at this temperature. Workup gave 6.7 g of a foam which was chromatographed (450

g, 6:1) to give 2.10 g (40%) of 4m as a foam: NMR δ 7.25 (m, 5 H), 6.70 (s, 2 H), 4.18 (s), 3.93, 2.26. The foam was dissolved in Et_2O and treated with HCl gas. The suspension was evaporated to a foam, which crystallized on the addition of C_6H_6. Recrystallization from EtOH–EtOAc gave pure 4m·HCl, mp >270 °C. Anal. ($C_{19}H_{23}NO_3$·HCl) C, H, N, Cl.

8β-Methyldihydromorphinone (8a). A mixture of 4a (2.5 g) and pyridine hydrochloride (8.0 g) was heated under reflux at 180–190 °C for 1 h. The cooled mixture was dissolved in water, adjusted to pH 11 by the addition of concentrated NH_4OH, and extracted five times with CH_2Cl_2. The combined organic phases gave a foam (2.0 g), which was chromatographed (150 g, 4:1) to give 1.3 g (55%) of **8a** as a foam. The foam was dissolved in EtOH, and concentrated HCl was added to give crystals. Recrystallization from EtOH–H_2O gave pure **8a**·HCl, mp >300 °C. Anal. ($C_{18}H_{21}NO_3$·HCl) C, H, N, Cl.

8β-Ethyldihydromorphinone (8b). A mixture of **4b** (1.5 g) and pyridine hydrochloride (5.0 g) was heated at 170–180 °C for 1 h and processed as above. Evaporation of the CH_2Cl_2 extracts gave a semicrystalline residue, which was chromatographed (100 g, 10:1) to give 1.2 g of **8b**. Recrystallization from EtOH gave pure **8b** as white needles, mp 265–267 °C. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

8β-(*trans*-1-Oxo-2-butenyl)dihydrocodeinone (10a). Lithium diisopropylamide was prepared at −78 °C under argon from diisopropylamine (6.1 g, 60 mmol) and *n*-BuLi (60 mmol, 2.4 M in hexane) in THF (100 mL). To this was added α-ethoxyethylcrotonaldehyde cyanohydrin (10.0 g, 60 mmol) in HMPA (20.0 g) dropwise over 15 min. Further stirring at −78 °C for 10 min was followed by the slow dropwise addition of **3** (14.8 g, 50 mmol) in hot THF (200 mL). The reaction was stirred at −78 °C for 20 min and then allowed to warm to room temperature. After pouring into ice water, the mixture was adjusted to pH 4 by the addition of HOAc. The acidic solution was extracted with several portions of Et_2O, which were discarded. The aqueous solution was adjusted to pH 10 with concentrated NH_4OH and extracted with three portions of Et_2O. After backwashing with dilute NH_4OH, the Et_2O layer was dried ($MgSO_4$) and evaporated to give 21.5 g (92%) of **9a** as a foam.

A portion of this foam (5.0 g) was dissolved in 9:1 CF_3COOH–H_2O (50 mL) and stirred at room temperature for 20 min. The solution was evaporated at 40 °C to a thin syrup, which was dissolved in water. The mixture was made basic by the addition of concentrated NH_4OH and extracted with three portions of CH_2Cl_2. Removal of the solvent gave 3.80 g of a foam, which was chromatographed (400 g, 10:1 $CHCl_3$–MeOH) to give 2.32 g (61%) of **10a** as a foam. The foam was converted to the HCl salt, which crystallized from EtOH–Et_2O to give **10a**·HCl, mp 181–182 °C. Recrystallization from EtOH gave **10a**·HCl, mp 182–184 °C, which was shown to be the monoethanolate hemihydrate by elemental analysis and NMR in D_2O. Anal. ($C_{22}H_{25}NO_4$·HCl·EtOH·0.5H_2O) C, H, N.

8β-(1-Oxobutyl)dihydrocodeinone (10b). A solution of the free base **10a** (2.77 g) in EtOH (100 mL)–EtOAc (50 mL) was hydrogentated at atmospheric pressure for 1 h over 5% Pd/C (500 mg), during which time the theoretical amount of hydrogen was consumed. Removal of the catalyst, followed by evaporation of the filtrate, gave 2.09 g (75%) of **10b** as crystals, mp 161–162 °C. Recrystallization from EtOH gave analytically pure **10b**: mp 162–163.5 °C; NMR δ 6.73 (s, 2 H, aromatic), 4.73 (s, 1 H, H5), 3.95 (s, 3 H, CH_3O–), 2.40 (s, CH_3N-), 0.92 (t, 3 H, CH_3-alkyl). Anal. ($C_{22}H_{27}NO_4$) C, H, N.

The HCl salt of **10b** was prepared in EtOH and crystallized from EtOH–Et_2O as white needles, mp 164–165 °C. Recrystallization from the same solvent pair gave **10b**·HCl as the monoethanolate. Anal. ($C_{22}H_{27}NO_4$·HCl·EtOH) C, H, N.

8β-Benzoyldihydrocodeinone (10c). Lithium diisopropylamide (30 mmol) was prepared in THF at −78 °C and to this was added the protected cyanohydrin of benzaldehyde (6.15 g, 30 mmol) in HMPA (7.5 g). Ten minutes later, **3** (7.4 g, 25 mmol) in hot THF (100 mL) was added dropwise. Stirring at −78 °C for 10 min was followed by warming to 0 °C and processing as above. The ether extracts of the basic aqueous solution gave 11.2 g (88%) of **9b** as a foam. A portion of this foam (10.2 g) was dissolved in 9:1 CF_3COOH–H_2O (100 mL) and stirred for 30 min. Evaporation and processing as for **10b** gave 7.9 g (90%) of **10c** as a foam. The foam was converted to the HCl salt and crystallized from EtOH. Two additional crystallizations from EtOH gave **10c**·HCl, mp 192 °C (foams). Anal. ($C_{25}H_{25}NO_4$·HCl) C, H, N, Cl.

8β-(1-Ethoxyvinyl)dihydrocodeinone (11). α-Ethoxyvinyllithium was prepared under argon by the dropwise addition of *t*-BuLi (30 mmol) to ethyl vinyl ether (3.46 g, 48 mmol) in THF (25 mL) at −40 °C. The mixture was warmed to 0 °C while the yellow precipitate which had formed dissolved to give a colorless solution. The solution was recooled to −40 °C and added slowly to a mixture of CuI (2.88 g, 15 mmol) in THF at −40 °C. The mixture was stirred at −40 °C for 30 min, and then **3** (2.97 g, 10 mmol) in warm THF (50 mL) was added dropwise. Stirring was continued at −40 °C for 10 min and then at −5 °C for 45 min. The reaction was quenched by the addition of saturated NH_4Cl solution, made basic with NH_4OH, and extracted with four portions of Et_2O. Evaporation of the Et_2O gave 3.50 g (95%) of a crystalline residue, which crystallized from EtOH to give 11, mp 186–187 °C. Recrystallization (EtOH) gave pure 11: mp 188–189.5 °C; NMR δ 7.10 (s, 2 H, aromatic), 4.76 (s, 1 H, H5), 4.00 (CH_3O–), 2.50 (CH_3N–), 1.30 (t, 3 H, CH_3-alkyl). Anal. ($C_{22}H_{27}NO_4$) C, H, N.

8β-Acetyldihydrocodeinone (10d). Compound 11 (3.50 g, 9.5 mmol) in 1 N HCl (20 mL) and MeOH (20 mL) was stirred at room temperature for 30 min. The mixture was made basic and extracted with CH_2Cl_2. Removal of the solvent gave 2.68 g of a foam, which was chromatographed (300 g, 10:1 $CHCl_3$–MeOH) to give 1.88 g (58%) of **10d** as a foam. The foam crystallized on heating with EtOH to give 1.05 g of crystalline **10**: mp 179–180 °C; NMR δ 6.70 (aromatic), 4.70 (H5), 3.93 (CH_3O–), 2.40 (CH_3N–), 2.16 (CH_3CO–).

The HCl salt of **10d**, mp dec above 240 °C, was crystallized from EtOH. Anal. ($C_{20}H_{23}NO_4$·HCl) C, H, N, Cl.

8β-Acetyldihydrocodeine (12). A solution of 11 (2.19 g, 5.9 mmol) in hot MeOH (100 mL) was cooled to 50 °C in an ice bath and $NaBH_4$ (0.28 g, 9 mmol) was added. Stirring in the ice bath was continued for 30 min, after which 1 N HCl (24 mL) was added and the mixture stirred for 1 h at room temperature. The mixture was made basic with NH_4OH and extracted with CH_2Cl_2. Evaporation and trituration of the residue with EtOH gave 1.10 g (54%) of **12**, mp 128–129 °C. Recrystallization from EtOH gave pure **12**: mp 129.5–130.5 °C; NMR δ 6.73 (aromatic), 4.62 (d, 1 H, J = 6 Hz, H5), 4.90 (CH_3O–), 2.37 (CH_3N–), 2.13 (CH_3CO–). Anal. ($C_{20}H_{25}NO_4$) C, H, N.

8β-(1-Hydroxy-1-methylethyl)dihydrocodeine (13a). A solution of **12** (650 mg, 1.9 mmol) in C_6H_6 (10 mL) was added dropwise to a solution of MeLi (5 mmol) in Et_2O (20 mL) under argon at 0 °C. Stirring was continued at 0 °C for 30 min, and the reaction was quenched with H_2O and extracted with CH_2Cl_2. The organic extracts gave 482 mg (71%) of **13a** as a syrup. The syrup was converted to the HCl salt, which crystallized on the addition of EtOAc. Recrystallization twice from EtOH gave pure **13a**·HCl, mp >265 °C. Anal. ($C_{21}H_{29}NO_4$·HCl) C, H, N, Cl.

8β-(1-Hydroxy-1-methyl-*n*-pentyl)dihydrocodeine (13b). Compound **12** (1.52 g, 4.4 mmol) in THF (25 mL) was added dropwise to a solution of *n*-BuLi (12 mmol) in Et_2O (50 mL) cooled in an ice bath under argon. The mixture was stirred for 1 h at 0 °C, quenched with water, and processed as above to give 1.52 g of a syrup, which was chromatographed (150 g, 6:1 $CHCl_3$–MeOH containing 1% concentrated NH_4OH) to give 982 mg (55%) of **13b** as a foam. The HCl salt of **13b** was obtained as a foam. Anal. ($C_{24}H_{35}NO_4$·HCl) H, N; C: calcd, 65.87; found, 64.54.

8β-(1-Hydroxy-1-methylethyl)dihydrocodeinone (14a). To a mixture of Me_2SO (9 mL) and Ac_2O (6 mL) in an oil bath at 65 °C was added **13a** (900 mg, 2.5 mmol). The mixture was heated at 65 °C for 30 min and then evaporated under high vacuum to a syrup. The syrup was dissolved in CH_2Cl_2 and extracted with five portions of H_2O containing a few drops of NH_4OH. The organic phase was evaporated to a syrup, which was chromatographed (75 g, 10:1 $CHCl_3$–MeOH containing 1% NH_4OH). Pure fractions of **14a** were combined to give 440 mg (49%) of a foam. The foam crystallized from C_6H_6 and recrystallized from C_6H_6–hexane to give pure **14a**, mp 218–220 °C. Anal. ($C_{21}H_{27}NO_4$) C, H, N.

8β-(1-Hydroxy-1-methyl-*n*-pentyl)dihydrocodeinone (14b). Compound **13b** (1.00 g, 2.5 mmol) was oxidized in a mixture of

Me_2SO (9 mL) and Ac_2O (6 mL) at 65 °C for 30 min and processed as above. The crude syrup (861 mg) was chromatographed (75 g, 10:1 CHCl–MeOH with 1% NH_4OH) to give 628 mg (63%) of pure **14b**. Recrystallization from benzene gave an analytical sample of **14b**, mp 116–119 °C, as the hemibenzene solvate. The presence and amount of benzene were established by NMR. Anal. ($C_{24}H_{33}NO_4 \cdot 0.5C_6H_6$) C, H, N.

***N*-Cyano-8β-methyldihydronorcodeinone (15a).** To a rapidly stirred suspension of **4a** (9.39 g, 30 mmol) and powdered anhydrous K_2CO_3 (6.00 g, 47 mmol) in $CHCl_3$ (90 mL) was added a solution of BrCN (3.90 g, 37 mmol) in $CHCl_3$ (60 mL) dropwise over a period of 30 min. Stirring was continued for 30 min at room temperature, after which the mixture was refluxed for 2 h. Cooling was followed by removal of the insolubles by filtration. The filtrate was evaporated to a syrup, which crystallized upon azeotropic distillation with EtOH. The crystals were boiled with EtOH and collected after storage at 5 °C overnight to give 7.93 g (82%) of **15a**, mp 237–241 °C.

***N*-Cyano-8β-ethyldihydronorcodeinone (15b).** Compound **4b**·HCl (5.00 g, 13.7 mmol) was converted to the free base and dissolved in $CHCl_3$ (50 mL). Powdered K_2CO_3 (2.84 g, 20.6 mmol) was added, followed by BrCN (1.95 g, 18.4 mmol) in $CHCl_3$. Reaction and processing as described above gave a crystalline residue, which was boiled with EtOH (30 mL). White crystals of **15b**, 4.3 g (92%), mp 197–198.5 °C, were collected after chilling.

***N*-Cyano-8β-*n*-propyldihydronorcodeinone (15c).** Compound **15c**, prepared as described above for **15a**, was obtained in 75% yield as white crystals, mp 151–153 °C.

8β-Methyldihydronorcodeinone (16a). A mixture of **15a** (7.93 g) and 2 N HCl (200 mL) was heated at reflux for 5 h. Evaporation gave a crystalline residue, which was triturated with EtOH. The crystals were collected and air-dried to give 8.05 g (98%) of **16a**·HCl. Recrystallization from EtOH gave an analytical sample of **16a**·HCl, mp 297–300 °C dec. Anal. ($C_{18}H_{21}NO_3 \cdot HCl$) C, H, N, Cl.

8β-Ethyldihydronorcodeinone (16b). A suspension of **15b** (4.30 g) and 2 N HCl (100 mL) was refluxed for 4 h. The solution was evaporated to a crystalline residue, which was suspended in EtOH, and the crystals were collected to give 3.95 g (89%) of **16b**, mp >260 °C dec.

8β-*n*-Propyldihydronorcodeinone (16c). This compound was prepared as above in 86% yield as white crystals, mp >280 °C dec.

***N*-(Cyclopropylmethyl)-8β-methyldihydronorcodeinone (17a).** To a solution of **16a**·HCl (3.00 g, 9.0 mmol) in DMF (50 mL) containing $NaHCO_3$ (1.80 g, 21.4 mmol) was added cyclopropylmethyl bromide[29] (1.5 g, 11.8 mmol), and the mixture was heated at 100 °C with stirring under argon for 16 h. The cooled mixture was filtered from insolubles and the filtrate evaporated under high vacuum to a semisolid residue. The residue was partitioned between dilute NH_4OH and $CHCl_3$. The aqueous phase was extracted with two additional portions of $CHCl_3$, and the combined organic extracts were evaporated to give a syrup (3.46 g). Chromatography (300 g, 10:1) gave 2.48 g (78%) of **17a** as a syrup. Conversion to the HCl salt gave a foam, which crystallized from EtOH–Et_2O to give **17a**·HCl (1.47 g): mp sinters 198 °C, melts 205–207 °C. Anal. ($C_{22}H_{27}NO_3 \cdot HCl$) C, H, N, Cl.

***N*-(Cyclopropylmethyl)-8β-ethyldihydronorcodeinone (17b)** was prepared as above from **16b**·HCl (2.30 g, 6.6 mmol), $NaHCO_3$ (1.22 g, 14.5 mmol), and CPMBr (1.33 g, 9.9 mmol) in DMF (30 mL). The crude syrup (2.52 g) was chromatographed (200 g, 15:1) to give 1.68 g (69%) of **17b**. The HCl salt crystallized from EtOAc to give pure **17**·HCl, mp 207–209 °C. Anal. ($C_{23}H_{29}NO_3 \cdot HCl$) C, H, N.

***N*-(Cyclopropylmethyl)-8β-*n*-propyldihydronorcodeinone (17c).** Compound **17c** was prepared as above and obtained as a syrup in 75% yield after chromatography. Crystallization from C_6H_6–hexane gave pure **17c**, mp 114–116 °C. Anal. ($C_{24}H_{31}NO_3$) C, H, N.

***N*-(Cyclobutylmethyl)-8β-methyldihydronorcodeinone (18a).** A mixture of **16a**·HCl (6.00 g, 18 mmol), $NaHCO_3$ (3.60 g, 43 mmol), and CBMBr[30] (3.20 g, 21 mmol) in DMF (60 mL) was heated at 100 °C as above. Workup gave a syrup, which was dissolved in EtOH, and an excess of concentrated HCl was added. Repeated evaporation of this mixture with EtOH gave crystals, which were collected to give 4.96 g (68%) of **18a**·HCl, mp 202–205 °C. Anal. ($C_{23}H_{29}NO_3 \cdot HCl$) C, H, N, Cl.

***N*-(Cyclobutylmethyl)-8β-ethyldihydronorcodeinone (18b).** Prepared from **16b**·HCl (8.6 mmol) in the usual fashion and chromatographed (15:1) to give 2.13 g (65%) of **18b** as a foam. The HCl salt was crystallized from EtOAc to give **18b**·HCl as white needles, mp 174–175.5 °C. Anal. ($C_{24}H_{31}NO_3 \cdot HCl$) H, N, Cl; C: calcd, 68.97; found, 67.59.

***N*-(Cyclopropylmethyl)-8β-methyldihydronormorphine (19a).** A mixture of **17a**·HCl (1.00 g) and pyridine hydrochloride (4.0 g) was heated at 190 °C for 2 h. The mixture was cooled, diluted with H_2O (30 mL), and made basic by the addition of concentrated NH_4OH. The dark solution was extracted with three portions of $CHCl_3$. After backwashing, the wet $CHCl_3$ solution was evaporated and azeotroped with EtOH–H_2O, then EtOH–C_6H_6, and finally C_6H_6 to give 982 mg of a dark foam. The foam was dissolved in EtOH, concentrated HCl was added, and the solution was evaporated until crystals formed. The suspension was diluted with EtOAc, and the crystals of **19a**·HCl (635 mg, 66%) were collected. Several recrystallizations from MeOH–EtOAc gave **19a**·HCl, mp 222–225 °C. Anal. ($C_{21}H_{25}NO_3 \cdot HCl$) H, N, Cl; C: calcd, 67.10; found, 64.74.

***N*-(Cyclopropylmethyl)-8β-ethyldihydronormorphinone (19b).** A mixture of **17b** (1.0 g) and pyridine hydrochloride (3.0 g) was heated at 200 °C for 2 h. Workup as above gave a brown foam which was twice chromatographed to give **19b** as a foam. The foam was dissolved in EtOH, and a solution of *d*-tartaric acid (1 equiv) in EtOH was added slowly dropwise. The mixture was evaporated to a crystalline residue, which was twice recrystallized from EtOH–H_2O to give the hemitartrate salt of **19b**, mp 248–250 °C. Anal. ($C_{22}H_{27}NO_3 \cdot 0.5C_4H_6O_6$) C, H, N.

***N*-(Cyclobutylmethyl)-8β-methyldihydronormorphinone (20a).** A solution of **18a**·HCl (600 mg) and 48% HBr (2.5 mL) was heated at reflux for 10 min. The cooled solution was diluted with H_2O and made basic by the addition of concentrated NH_4OH. Extraction with $CHCl_3$ followed by evaporation gave 280 mg of a syrup which was chromatographed (50 g, 10:1) to give 230 mg (40%) of **20a**, which was converted to the HCl salt. Crystallization from EtOH–EtOAc gave pure **20a**·HCl, mp 220–225 °C. Anal. ($C_{22}H_{27}NO_3 \cdot HCl$) C, H, N, Cl.

***N*-(Cyclobutylmethyl)-8β-ethyldihydronormorphinone (20b).** Compound **18b**·HCl (1.30 g) was refluxed with 48% HBr (10 mL) for 15 min. The cooled mixture was diluted with water, made basic with NH_4OH, and extracted six times with CH_2Cl_2. The organic extracts gave 1.18 g of a foam, which was chromatographed (100 g, 15:1) to give 630 mg (50%) of pure material as a foam. The foam was converted to an HCl salt, which crystallized on azeotroping with C_6H_6. The crystals of **20b**·HCl were suspended in EtOAc and collected. Recrystallization from H_2O gave pure **20b**·HCl, mp dec above 200 °C. Anal. ($C_{23}H_{29}NO_3 \cdot HCl$) C, H, N, Cl.

Acetic Acid Writhing Test.[23] Male albino Charles River mice (18–22 g) were used for this study; five mice per dose and at least three doses of drug per ED_{50} were determined. Salts of the test compounds were administered in distilled H_2O; free bases were dissolved by the dropwise addition of dilute HCl and then further diluted with H_2O. The test drug was given by subcutaneous injection 15 min prior to an intraperitoneal injection of 0.5% HOAc (0.4 mL). The number of writhes per group were counted for 20 min starting 5 min after the HOAc injection. Analgesic potency was calculated from the difference between test groups and their controls. ED_{50} values with 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[31]

Rat Tail-Flick Procedure.[24] Male albino rats (100–120 g) were used for this study. Two control reaction times were determined 30 min apart and prior to intraperitoneal injection of test drug. An ED_{80} dose of morphine was administered 10 min later subcutaneously, and reaction times then determined 20 min

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later. The narcotic antagonist activity was determined from the difference between the groups and control groups which received morphine alone. For agonist activity, the drug was administerd subcutaneously, the ED_{80} of morphine was eliminated, and the animals were retested 20 min postdrug.

Acknowledgment. The authors gratefully acknowlege the pharmacological results obtained by Drs. J. F. Howes, P. F. Osgood, and R. K. Razdan, SISA Inc., Cambridge, MA. Thanks are due to these workers and to Dr. J. E. Villarreal, Instituto Miles de Terapeutica Experimental, Mexico City, Mexico, for their continued interest and encouragement. The authors are also indebted to T. J. Leipzig and staff for the large-scale preparation of certain intermediates.

Analgesic Narcotic Antagonists. 2. 8-Alkymorphinan-6-ones

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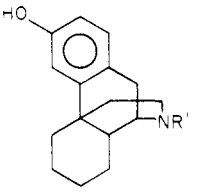
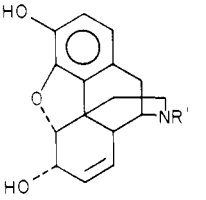
A series of 8-alkyl-3-methoxy-17-methylmorphinan-6-ones (**3C**) and -isomorphinan-6-ones (**3T**) were prepared by conjugate addition of lithium dialkylcuprates to the corresponding 7,8-didehydro-6-ones **2C** and **2T**. These 17-methyl compounds were potent analgesics and were converted to mixed narcotic agonists–antagonists **7–10**, by replacement of the 17-methyl groups with cycloalkylmethyl moieties. The 8 substituent modified the type of activity observed. One of these compounds, 17-(cyclobutylmethyl)-3-hydroxy-8β-methylmorphinan-6-one (**10Ca**), had an agonist–antagonist ratio of 0.1. Compound **10Ca** did not support or cause dependence in rats. This compound, however, appeared to be a typical narcotic agent in morphine-dependent monkeys.

In our previous paper,[1] we reported the conjugate addition of alkyl groups to codeinone by use of lithium dialkylcuprates. The resulting dihydrocodeinones which had a small alkyl group at the 8 position were narcotic agonists. The 8β-methyl- and 8β-ethyldihydrocodeinones were converted into mixed agonist–antagonists by replacement of the *N*-methyl group with *N*-(cycloalkylmethyl) moieties. Further study revealed that some of these 8β-alkyl-*N*-(cycloalkylmethyl) compounds had desirable pharmacological profiles which were dependent upon both the C8 and N substituents. One of these compounds, *N*-(cyclopropylmethyl)-8β-ethyldihydronorcodeinone, was studied further[2] and is currently undergoing clinical trials in man.

It is reported that morphinan compounds which lack the ether oxygen bridge possess increased agonist and antagonist potencies when compared with the corresponding 4,5-epoxymorphinans. For example, levorphan is a more potent analgesic than morphine, and levallorphan is a stronger narcotic antagonist than nalorphine.[3] The novelty of our previously reported 8-alkyldihydronorcodeinones thus led us to further explore conjugate addition reactions to 7,8-didehydro-3-methoxy-17-methylmorphinan-6-ones.[4] We desired to start from naturally derived materials so as to avoid a totally synthetic sequence which would necessitate the resolution of optical isomers.



levorphan, R' = $-CH_3$
levallorphan, R' = $-CH_2CH=CH_2$



morphine, R' = $-CH_3$
nalorphine, R' = $-CH_2CH=CH_2$

Chemistry. Sawa and co-workers some time ago described the preparation of **1** from the readily available morphine alkaloid, thebaine. Reduction of thebaine with Na/liquid NH_3 gives the 4,5-epoxy-cleaved product, dihydrothebaine-ϕ.[5] This is converted to the 4-phenyl ether, which is then cleaved to 4-deoxydihydrothebaine-ϕ (**1**). Hydrolysis[4] of **1** with 25% HCl at 100 °C directly gives a good yield of crystalline **2C** (Scheme I). The B/C-cis ring junction of **2C** is the same as that of morphine. Hydrolysis of **1** under less strenuous conditions allows entry into the isomorphinan-6-one series **2T**, which has a B/C-trans juncture.

Reaction of **2C** or **2T** with lithium dialkylcuprates proceeded smoothly to give the 8-alkyl compounds **3Ca–c** and

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