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.

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

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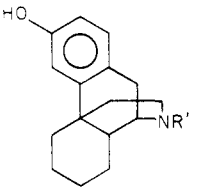
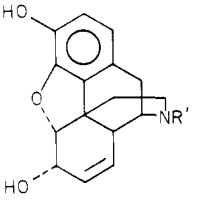
A series of 8-alkyl-3-methoxy-17-methylmorphinan-6-ones (**3C**) and -isomorphinan-6-ones (**3T**) were prepared by conjugate addition of lithium dialkylcuprates to the corresponding 7,8-didehydro-6-ones **2C** and **2T**. These 17-methyl compounds were potent analgesics and were converted to mixed narcotic 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

(1) M. P. Kotick, D. L. Leland, J. O. Polazzi, and R. N. Schut, *J. Med. Chem.*, **23**, preceding paper in this issue.
(2) J. F. Howes, P. F. Osgood, R. K. Razdan, and J. E. Villarreal, manuscript in preparation.
(3) E. L. May in "Agonist and Antagonist Actions of Narcotic Drugs", H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, Eds., University Park Press, Baltimore, MD., 1973, p 17. L. H. Harris in "Narcotic Antagonists", M. Braude, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villarreal, Eds., Raven Press, New York, 1973, p 13.
(4) Y. K. Sawa and S. Maeda, *Tetrahedron*, **20**, 2247 (1964).
(5) K. W. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

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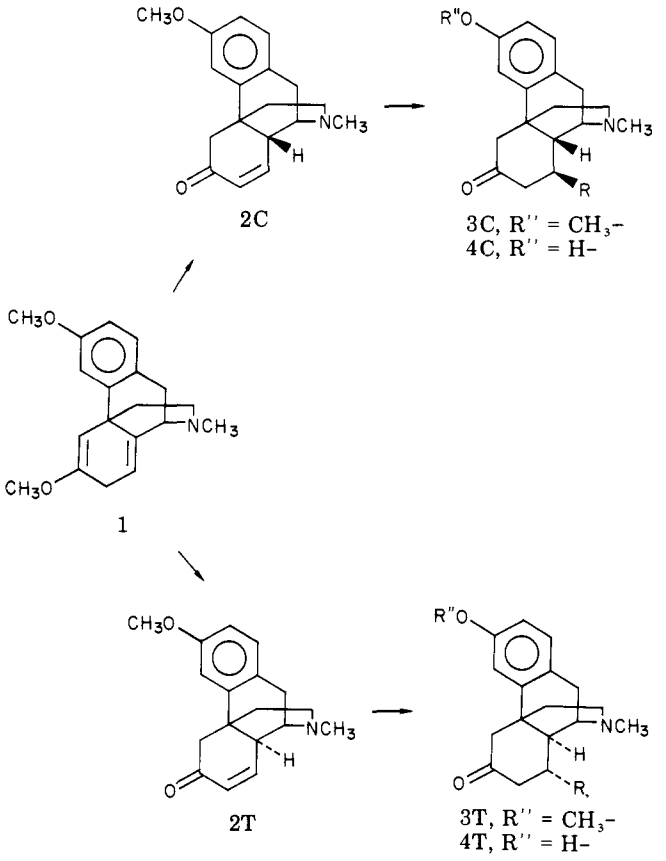
Scheme I[a]



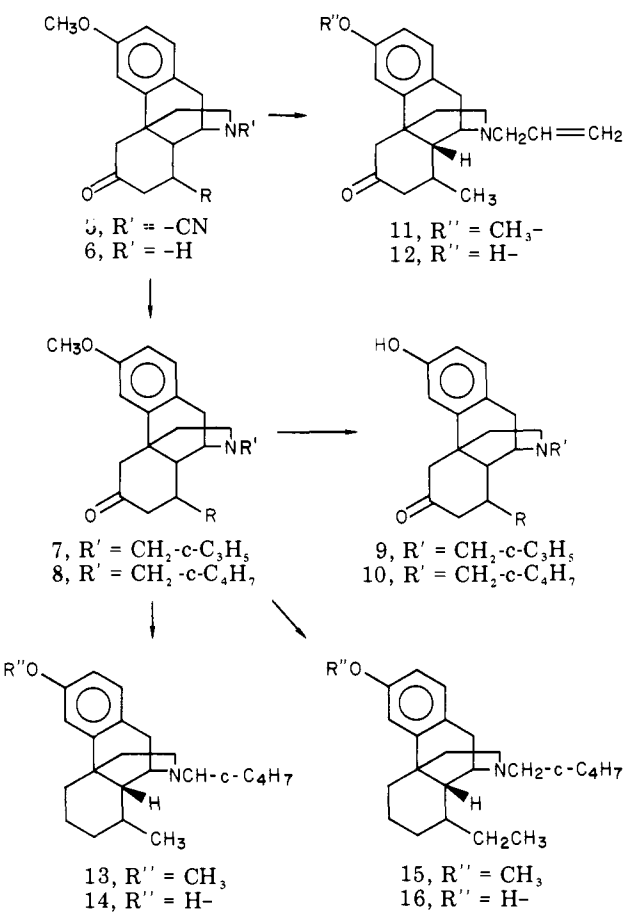
[a] For a, R = $-CH_3$; b, $-CH_2CH_3$; c, $-(CH_2)_2CH_3$; d, -H.

3Ta–c in good yield. We originally assigned the configuration of the 8-alkyl group as β in the **3C** series by analogy with the stereochemistry of this reaction in the codeinone series.[1] This assignment has been confirmed by chemical studies.[7] Only a single product was obtained in these reactions, with no indication for the formation of an α isomer or a 1,2-addition product. In the B/C-trans series, **3T**, the 8-alkyl group is tentatively assigned the thermodynamically more stable 8α configuration.

The 8-alkyl-3-methoxy-17-methylmorphinan-6-ones **3C** and **3T** were converted to the 3-hydroxy compounds **4** by treatment with refluxing 48% HBr for 10–20 min. Conversion of **3** to the *N*-(cycloalkylmethyl) compounds **7** and **8** was carried out as previously described[1] via the intermediacy of the *N*-cyano compound **5** and the nor compound **6**, followed by alkylation with cyclopropylmethyl or cyclobutylmethyl bromide (Scheme II). The 3-hydroxy-*N*-(cycloalkylmethyl) compounds were prepared by methoxy group cleavage with HBr. The *N*-allyl compounds **11** and **12** were similarly prepared. For reference purposes, the 7,8-saturated compounds (R = H, series **d**) were prepared by catalytic reduction of **2C** or **2T**. These were converted to the *N*-(cycloalkylmethyl) derivatives as described above.

The 6-deoxy compounds **13** and **14** were prepared in order to study the effect on activity of the 6-oxo group. Levorphan and levallorphan are not substituted in this position. Likewise, the mixed narcotic agonist–antagonist

Scheme II[a]



[a] For **C**, B/C ring junction cis; for **T**, B/C ring junction trans. For a, R = $-CH_3$; b, $-CH_2CH_3$; c, $-(CH_2)_3CH_3$; d, -H.

Table I. Analgesic Activity

compd	ED_{50}, μmol/kg, sc injectn (95% CL)	
	mouse writhing	rat tail flick
3Cd	1.72 (0.91-3.23)	2.32 (1.89-2.84)
a	1.34 (0.65-2.71)	3.57 (1.37-9.38)
b	3.23 (2.51-4.14)	10.6 (5.4-20)
c	15.4 (9.1-26.1)	>28
3Td	5.54 (4.0-7.68)	>70
a	2.65 (1.93-3.60)	*a*
b	37 (27-49)	>28
c	55 (40-75)	IA/28
4Cd	0.52 (0.35-0.76)	70
a	2.55 (1.74-3.76)	>30
b	2.29 (1.79-2.96)	33 (13-81)
c	IA[b]/27	IA/27
4Td	0.75 (0.49-1.14)	1.33 (0.97-1.82)
a	1.18 (0.81-1.71)	0.93 (0.43-1.96)
b	2.11 (1.14-3.91)	2.31 (1.20-4.41)
c	1.37 (0.70-2.72)	2.46 (1.60-3.77)
codeine	10.3 (2.7-40)	75 (19-293)
morphine	2.1 (1.1-4.0)	19.3 (9.2-40.6)
dihydrocodeinone	2.36 (1.56-3.60)	5.2 (3.6-7.5)
dihydromorphinone	0.25 (0.12-0.44)	1.34 (1.18-1.52)

[a] Lethal at 9 μmol/kg. Animals convulsed and died. [b] Inactive at dose indicated.

(6) Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, 15, 154 (1961).

(7) Compound **7Ca** was alkylated with phenylselenyl chloride in CH_2Cl_2–EtOAc in the presence of HCl to give a 35% yield of the 7β-phenylselenyl derivative.[8] This was oxidized with $NaIO_4$ in THF–H_2O–MeOH, and elimination was completed by refluxing in toluene to give the 7,8-unsaturated 8-methyl compound. Catalytic hydrogenation from the β face gave 8α-methyl **7Ca**. The methyl group of 8α-methyl **7Ca** was observed as a symmetrical doublet in the NMR ($CDCl_3$) at δ 0.60 (J = 7 Hz). The methyl group of **7Ca** occurs as an unsymmetrical doublet at δ 0.80. This anisotropic effect of the aromatic A ring on the 8-alkyl group thus parallels our earlier observation (ref 1).

Table II. Analgesic and Narcotic Antagonist Activity

compd	ED_{50}, μmol/kg (95% CL) analgesic: mouse writhing, sc injn	antagonist: rat tail flick, ip injn	agonist/antagonist
7Cd	0.66 (0.19-2.37)	14.9	0.04
a	0.71 (0.38-1.33)	4.27 (1.44-12.7)	0.17
b	4.1 (1.44-14.5)	>50	
c	12.4	IA[a]/25	
7Td	>25	3.6 (1.6-8.2)	
a	>80	9.0 (4.3-19.9)	
b	IA/25	1.64 (0.44-6.31)	
c	IA/22	6.4 (0.17-250)	
8Cd	0.58 (0.21-1.57)	IA/25	
a	1.38 (0.92-2.05)	16.4 (5.6-47)	0.08
b	14.2 (5.6-36.1)	IA/50	
c	34 (24-50)	IA/50	
8Td	20.3 (10.7-38.4)	IA/30	
a	47 (12-187)	IA/25	
b	IA/75	>25	
c	IA/24	>24	
9Cd	3.28 (1.29-8.39)	7.4 (4.1-13.2)	0.44
a	10.2	1.8	5.7
b	IA/50	4.7 (3.1-6.8)	
c	IA/25	24.3	
9Td	8.9[b]	2.24 (1.06-4.71)	4.0[c]
a	IA/25	0.89 (0.39-2.02)	
b	IA/25	0.88 (0.15-5.15)	
c	IA/24	3.34	
10Cd	0.047 (0.006-0.342)	IA/25	
a	0.29 (0.027-2.85)	2.79 (0.98-8.0)	0.10
b	0.54[b] (0.33-0.77)	0.82 (0.49-1.36)	0.65[c]
c	1.06 (0.30-3.79)	7.67 (3.69-15.9)	
10Td	2.6 (0.97-6.88)	13.8 (5.0-38)	
a	5.98 (0.85-42.2)	12.8 (6.9-23)	
b	>24	11.6	
c	>24	4.5 (1.36-14.5)	
11	3.47 (2.16-5.56)	>24	
12	>25	0.65 (0.19-2.27)	
13	19.8 (12.0-32.6)	IA/10	
14	14.5 (9.14-23.0)	3.73	
15	>25	IA/7.7	
16	>25	IA/9	
butorphanol	0.34 (0.13-0.90)	2.0 (0.96-9.4)	0.17
cyclazocine	0.41 (0.11-1.66)	0.81 (0.48-1.44)	0.50
pentazocine	12.9 (8.68-19.3)	36.4 (13.6-100)	0.36
nalorphine	3.51 (0.58-21.4)	2.47 (0.46-13.5)	1.42
naloxone	IA	0.11 (0.03-0.30)	

[a] Inactive at dose indicated. [b] Short-duration, ED_{50} at 5 min. [c] Based on analgesic ED_{50} at 5 min.

butorphanol[9] has no functionality at the 6 position but does have a 14-hydroxy group. Treatment of **8Ca** under Huang-Minlon conditions[10] gave a mixture of the 6-deoxy-3-methoxy (**13**) and 6-deoxy-3-hydroxy (**14**) compounds, which were resolved by chromatography. The 6-deoxy-8-ethyl compounds **15** and **16** were prepared in a similar manner.

Pharmacological Results. Compounds were tested for analgesia in the acetic acid mouse writhing and heat stimulus rat tail-flick assays. Narcotic antagonist activity was measured against an ED_{80} dose of morphine using the rat tail-flick method. These procedures have previously been described.[1,2] The compounds in Table I are listed with increasing size of the 8 substituent (**d**, **a**, **b**, **c**) in order to show the affect of this group on activity.

In the agonist assays, compound **3C** and **3T** were, in general, less potent than the reference compounds **3d**. Potency decreases with increasing chain length at the 8 position when R is longer than methyl.[11] The same general trend was observed within the series of 8-alkyldihydrocodeinones. For phenolic compounds **4C**, activity drops off precipitously when R is increased from ethyl to *n*-propyl (**4Cc**). In the **4T** series, the compounds are potent agonists in both the mouse writhing and rat tail-flick procedures. This potency is maintained even with R = *n*-propyl (**4Tc**). As a class, compounds **3** and **4** are of about the same potency as the previously reported 8β-alkyldihydrocodeinones.

The results obtained with N-antagonist derivatives are recorded in Table II. In the cyclopropylmethyl cis **7C** series, a methyl group (**7Ca**) does not influence the agonist potency but does enhance the antagonist potency about threefold. When R = Et (**7Cb**), the analgesia decreases and antagonism is lost. In the cyclopropylmethyl trans series, **7Ta-d**, the 8 substituent somewhat modifies the antagonist potency.

The structure-activity relationships in the 3-hydroxy series **9** and **10**, in general, parallel the results obtained with the 3-methoxy compounds **7** and **8**. For compounds in the **9C** and **9T** series which have agonist and antagonist

(8) I. Iijima, K. C. Rice, and J. V. Silverton, *Heterocycles*, **6**, 1157 (1977).
(9) I. Monković, H. Wong, A. C. Pircio, Y. G. Perron, I. J. Pachter, and B. Belleau, *Can. J. Chem.*, **53**, 3094 (1975).
(10) Y. K. Sawa and H. Tada, *Tetrahedron*, **24**, 6185 (1968).
(11) The 8-*n*-butyl analogues of 3C and 3T had mouse writhing ED_{50} values of 35 and <50 μmol/kg, respectively.

Table III. Rat Physical Dependence Liability Study, Weight Changes

drug	infusion schedule	N	% change in wt from day 0[a] on day: +1	+2	+3	+4
10Ca tartrate	40 (mg/kg)/day for 6 days	6	+1.2[b] ± 1.1	+2.00[c] ± 2.9	+6.1 ± 3.2	+9.6 ± 2.9
10Ca tartrate	80 (mg/kg)/day for 6 days	4	+1.7 ± 1.9	+3.1 ± 2.0	+5.3 ± 2.3	+9.5 ± 2.7
butorphanol tartrate	40 (mg/kg)/day for 6 days	4	−6.6[c] ± 2.1	−3.1[b] ± 1.5	+0.9 ± 2.0	+2.2 ± 2.3
control	saline for 6 days	4	+6.8[b] ± 1.00	+10.2 ± 1.5	+14.5 ± 2.7	+15.7 ± 4.2

[a] Cessation of infusion. [b] $p < 0.05$. [c] $p < 0.10$.

ED_{50} values below ~25 μmol/kg, the antagonist properties are enhanced by the introduction of a short 8 substituent while agonist properties are reduced. Compounds **9Td** and **10Cb** were short-acting analgesics; the ED_{50} in this case was determined after 5 min. The 8-alkyl substituent in the **10C** series decreases analgesia but does introduce an antagonist component of action into the parent molecule. In the **10T** series, the 8-alkyl group maintains antagonist potency with a corresponding decrease in agonism.

In general, the conversion of the 3-methoxy compounds **7** and 8 to the 3-hydroxy analogues **9** and **10** increases the antagonist properties. In the cyclopropylmethyl series **7**, conversion to **9** decreases analgesic potency, while it somewhat enhances the analgesic activity in the cyclobutylmethyl series (**8** → **10**). For the entire series in Table II, the 8-alkyl substituent tends to modify the narcotic antagonist component of action. No definitive statement can be made on the relative potencies of this class of compounds as compared with their 4,5-epoxy counterparts.

The dilemma of choosing an appropriate N-antagonist group is illustrated by the *N*-allyl compounds **11** and **12**. The 3-methoxy-*N*-allyl compound **11** is a good analgesic with an antagonist ED_{50} >25 μmol/kg. The corresponding 3-hydroxy compound **12** is inactive as an analgesic while possessing good antagonist properties. Data such as these do not allow one to draw predictable structure–activity relationships in the narcotic analgesic area.[12] The 6-deoxy compounds **13** thru **16** were less active in both agonist and antagonist assays than the corresponding 6-oxo compounds. Other work has shown that a trigonal carbon atom at C6 is essential for maintenance of potency in this series.[13]

Compound **10Ca** was chosen for further study in other pharmacological models. This compound had an agonist–antagonist ratio of 0.1, in contrast to that of our previously studied *N*-(cyclopropylmethyl)-8β-ethyl-4,5α-epoxy-3-methoxymorphinan-6-one (agonist/antagonist = 2.7).[1] The tartrate salt of **10Ca**, prepared as a more suitable crystalline form, had an ED_{50} in the mouse writhing agonist assay of 0.29 μmol/kg and an antagonist ED_{50} of 2.5 μmol/kg. In the rat tail-flick model, antagonism never approached 100%, but tended to level off at ca. 50%. The compound proved to be morphine-like in the rat intestine model[14] (ID_{50} = 0.2 μmol/kg) with a maximum inhibition of 67% at 2 μmol/kg. In rat infusion studies[15] with **10Ca**, no significant weight loss was noted after withdrawal, indicating that **10Ca** did not cause primary dependence (see Table III). Furthermore, **10Ca** did not substitute for morphine in dependent rats. No significant suppression of withdrawal signs were seen in morphine-dependent rats when given 50 (mg/kg)/day of **10Ca**.

Monkey studies, on the other hand, showed that **10Ca** was able to substitute completely for morphine in drug-dependent animals. In single dose suppression studies, **10Ca** in the dose range of 0.125–2.0 mg/kg sustained morphine dependence. At 1.0 and 2.0 mg/kg, signs designated as drowsiness, ptosis, salivation, and body sag were quite evident.

Based on the above results in monkeys, further development of **10Ca** was not pursued. The compound remains of interest because it did not show up as a typical morphine-like drug in rat studies. These results raise the question as to what the ideal ratio of agonist to antagonist properties should be for a useful agent. Chemical and pharmacological studies directed toward answering this question continue in our laboratories.

Experimental Section

Methods have been previously described.[1] Processing in the usual manner implies that the organic phases were washed with dilute NH_4OH, dried ($MgSO_4$), and evaporated at 40 °C. The residue was further dried at 50 °C under high vacuum. Samples for analysis were dried overnight under high vacuum usually at 100 °C. For pharmacological testing, salts of the compounds were administered in distilled H_2O; free bases were dissolved by the dropwise addition of 1 N HCl and then further diluted.

8β,17-Dimethyl-3-methoxymorphinan-6-one (3Ca). To a solution of Me_2CuLi, prepared from CuI (15.1 g, 79.4 mmol) and MeLi (158.8 mmol), in Et_2O (600 mL) at 0 °C under argon was added quickly dropwise a solution of **2C** (18.0 g, 63.5 mmol) in warm C_6H_6 (250 mL). The mixture was stirred at 0 °C for 1 h and quenched by pouring into saturated NH_4Cl solution (1 L), followed by stirring for 30 min. The organic layer was separated and the aqueous phase adjusted to pH ≃12. The basic aqueous phase was extracted with three portions of $CHCl_3$, and the combined organic phases were processed in the usual fashion. The residue obtained on evaporation was coevaporated with EtOAc to give a crystalline solid, which was recrystallized from EtOAc with charcoal treatment to give **3Ca**, 10.0 g, mp 126–127 °C. Concentration of the mother liquor gave additional **3Ca**: mp 125.5–126.5 °C; overall yield 68%. Recrystallization from EtOH gave pure **3Ca**, mp 131–132 °C. Anal. ($C_{19}H_{25}NO_2$) C, H, N.

8β-Ethyl-3-methoxy-17-methylmorphinan-6-one (3Cb). EtLi was prepared by the addition of EtCl (3.1 mL, 42 mmol) in Et_2O (20 mL) under argon to a suspension of Li (86 mmol) in Et_2O (30 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 suspension of CuI (4.00 g, 21 mmol) in Et_2O (200 mL) stirred at −78 °C. The suspension was allowed to warm to −40 °C, kept for 10 min at this temperature, and then treated with a solution of **2C** (4.77 g, 16.8 mmol) in warm C_6H_6 (50 mL) rapidly dropwise while keeping the temperature at about −40 °C. Stirring was continued at −40 °C for 10 min, then the mixture was allowed to warm to 0 °C, and the reaction was quenched by pouring into saturated NH_4Cl solution (300 mL). Processing in the usual fashion gave **3Cb** (5.5 g) as a syrup. The syrup was converted to the HCl salt and crystallized from MeOH–EtOAc to give 4.22 g (71%) of **3Cb**·HCl, mp 257 °C dec. Recrystallization from the same solvent pair gave pure **3Cb**·HCl, mp 263–265 °C. Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

3-Methoxy-17-methyl-8β-*n*-propylmorphinan-6-one (3Cc). *n*-PrLi was prepared from *n*-PrCl (42 mmol) and Li (86 mmol) and added to CuI (21 mmol) in Et_2O at −78 °C. Further reaction

(12) The same conclusion has been reached by other workers. See, for example, Y. Lambert, J. P. Davis, I. Monkovič, and A. W. Pircio, *J. Med. Chem.*, 21, 423 (1978).
(13) The isomeric C6 alcohols derived from **7Ca** had the following ED_{50} values: 6β, 6.7; 6α, 7.7 μmol/kg. Both compounds were inactive as antagonists at 3.0 mg/kg.
(14) R. Rodriguez and J. C. Villarreal, Proceedings of the Committee on Problems of Drug Dependence, 1974, p 453.
(15) D. J. Teiger, *J. Pharmacol. Exp. Ther.*, **190**, 408 (1974).

Table IV. 8-Alkyl-17-(cycloalkylmethyl)-3-methoxymorphinan-6-ones 7 and 8

no.	R	R'	yield, %, of free base[a]	yield, %, of HCl salt	recrystn solvent[b]	mp, °C	formula[c]
7Ca	$-CH_3$	$-CH_2$-c-C_3H_5	72		B-H	114-115	$C_{22}H_{29}NO_2$
b	$-CH_2CH_3$	$-CH_2$-c-C_3H_5	95	64	EA	246-248	$C_{23}H_{31}NO_2 \cdot HCl$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_3H_5	95	67	H	>120[f]	$C_{24}H_{33}NO_2 \cdot HCl$
d	-H	$-CH_2$-c-C_3H_5	77	58	EA	265-267	$C_{21}H_{27}NO_2 \cdot HCl$
7Ta	$-CH_3$	$-CH_2$-c-C_3H_5	63	53	M-EA	268-270	$C_{22}H_{29}NO_2 \cdot HCl \cdot 0.5MeO$
b	$-CH_2CH_3$	$-CH_2$-c-C_3H_5	70	50	E	268-271[g]	$C_{23}H_{31}NO_2 \cdot HCl$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_3H_5		89[d]	M-EA	233-235[g]	$C_{24}H_{33}NO_2 \cdot HCl$
d	-H	$-CH_2$-c-C_3H_5	70	53	M-EA	255-256[e,g]	$C_{21}H_{27}NO_2 \cdot HCl \cdot H_2O$
8Ca	$-CH_3$	$-CH_2$-c-C_4H_7	83	34	M-EA	217-220	$C_{23}H_{31}NO_2 \cdot HCl$
b	$-CH_2CH_3$	$-CH_2$-c-C_4H_7	85	77	M-EA	252-254	$C_{24}H_{33}NO_2 \cdot HCl$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_4H_7	70	46	M-EA	192-193	$C_{25}H_{35}NO_2 \cdot HCl$
d	-H	$-CH_2$-c-C_4H_7	62	33	M-EA	272-274[g]	$C_{22}H_{29}NO_2 \cdot HCl$
8Ta	$-CH_3$	$-CH_2$-c-C_4H_7	76	50	M-EA	233-236[g]	$C_{23}H_{31}NO_2 \cdot HCl$
b	$-CH_2CH_3$	$-CH_2$-c-C_4H_7	30	18	E	235-238	$C_{24}H_{33}NO_2 \cdot HCl$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_4H_7		47[d]	M-EA	244-247	$C_{25}H_{35}NO_2 \cdot HCl$
d	-H	$-CH_2$-c-C_4H_7	50		E	96.5-97.5	$C_{22}H_{29}NO_2$

[a] Yield of purified free base after chromatography. [b] B = benzene; E = ethanol; EA = ethyl acetate; EE = ethyl ether; H = hexane; M = methanol; W = water. [c] All compounds had C, H, and N analysis within ±0.40% of the calculated value. [d] Not chromatographed; crystallized directly as HCl salt. [e] Hygroscopic. [f] Foams. [g] Decomposition.

with **2C** (16.8 mmol) as above gave, after workup, **3Cc** as a syrup, which crystallized on standing. The crystalline residue was converted to the HCl salt and crystallized from MeOH–EtOAc to give 4.28 g (70%) of **3Cc**·HCl, mp 234–235 °C. Recrystallization gave pure **3Cc**·HCl, mp 235–237 °C. Anal. ($C_{21}H_{29}NO_2 \cdot HCl$) C, H, N.

8α,17-Dimethyl-3-methoxyisomorphinan-6-one (3Ta). Me_2CuLi was prepared in Et_2O (25 mL) at 0 °C under argon from CuI (4.38 mmol) and MeLi (8.76 mmol). To this was added **2T** (3.5 mmol) dissolved in warm C_6H_6 (15 mL), and the mixture was kept at 0 °C for 1 h. Workup and processing in the usual fashion gave a syrup, which was chromatographed (15:1 $CHCl_3$–MeOH). Pure fractions were combined to give 960 mg (92%) of **3Ta**. This was converted to **3Ta**·HCl, which crystallized from EtOAc and was recrystallized from EtOH to give pure **3Ta**·HCl, mp >265 °C. Anal. ($C_{19}H_{25}NO_2 \cdot HCl$) C, H, N.

8α-Ethyl-3-methoxy-17-methylisomorphinan-6-one (3Tb). Et_2LiCu was prepared as described above from EtCl (84 mmol), Li (168 mL), and CuI (42 mmol) in Et_2O (400 mL) below −40 °C. To this was added **2T** (9.54 g, 34 mmol) in warm C_6H_6 (100 mL). Reaction and workup as previously described gave 10.6 g of crude **3Tb**. A 2.1-g sample of this material was chromatographed (10:1 $CHCl_3$–MeOH) to yield 2.0 g of pure **3Tb**, which was converted to the HCl salt. Crystallization from MeOH–EtOAc gave 1.2 g of **3Tb**·HCl, mp >215 °C dec, in two crops. Anal. ($C_{20}H_{24}NO_2 \cdot HCl$) C, H, N.

3-Methoxy-17-methyl-8α-*n*-propylisomorphinan-6-one (3Tc). *n*-Pr_2CuLi (42 mmol) was reacted with **2T** (34 mmol) in the usual manner and processed to give crude **3Td** (12.3 g). A portion of this material (2.0 g) was converted to the HCl salt, which crystallized from MeOH–EtOAc to give 1.7 g of beige-colored crystals, mp 240–245 °C dec. Anal. ($C_{21}H_{29}NO_2 \cdot HCl$) C, H, N.

8-Alkyl-3-hydroxy-17-methylmorphinan-6-ones (4). A mixture of **3** (free base or HCl salt) and concentrated HBr (1.0 g/15 mL) was immersed in a preheated oil bath (≃140 °C) and refluxed for 10 to 20 min. The reaction mixture was cooled, diluted with H_2O, and adjusted to pH 10–11 by the addition of concentrated NH_4OH. The basic solution was extracted with three portions of $CHCl_3$, and the extracts were processed in the usual manner.

4Ca: 169.5–171.5 °C; crystallized from benzene. The HCl salt, mp >265 °C, was obtained in 68% yield from **3Ca** and crystallized from EtOH. Anal. ($C_{18}H_{23}NO_2 \cdot HCl \cdot 0.5EtOH$) C, H, N. **4Cb** was purified by chromatography using 10:1 $CHCl_3$–MeOH with 1% NH_4OH. **4Cb**·HCl, mp 220–224 °C, was obtained in 87% yield after crystallization from EtOAc. Anal. ($C_{19}H_{25}NO_2 \cdot HCl$) C, H, N. 4Cc was purified by chromatography and crystallized as the HCl salt, mp 254–357 °C, in 79% yield from MeOH–EtOAc. Anal. ($C_{20}H_{27}NO_2 \cdot HCl$) C, H, N. **4Cd** was obtained as the crystalline free base, mp 218–221 °C, after chromatography and crystalization from MeOH. Anal. ($C_{17}H_{21}NO_2 \cdot 0.5CH_3OH$) C, H, N.

4Ta directly gave an HCl salt, mp >265 °C, in 95% yield on crystallization from EtOH. Anal. ($C_{18}H_{23}NO_2 \cdot HCl$) C, H, N. **4Tb** was obtained crystalline from EtOAc in 42% yield as the free base, mp 166–168 °C. Anal. ($C_{19}H_{25}NO_2$) C, H, N. **4Tc** was obtained as the free base, mp 185–186 °C, in 66% yield from EtOAc. Anal. ($C_{20}H_{27}NO_2$) C, H, N. **4Td** was purified by chromatography to give an 89% yield of the free base as a foam. The HCl salt, mp >260 °C dec, was obtained in 32% yield by crystallization from MeOH–EtOAc. Anal. ($C_{17}H_{21}NO_2 \cdot HCl$) C, H, N.

8-Alkyl-17-cyano-3-methoxymorphinan-6-ones (5). A rapidly stirred mixture of the free base of **3** in $CHCl_3$ (1.0 g/10 mL) containing finely powdered K_2CO_3 (1.5 equiv) was treated dropwise with a solution of BrCN (1.2 equiv) in $CHCl_3$ (1.0 g/20 mL). The mixture was rapidly stirred for 30 min and then heated at reflux for 2 h. The cooled solution was filtered from insolubles, and the filtrate was evaporated to dryness and azeotroped with EtOH. In cases where crystallization occurred, the crystals were collected and used in the next step without further purification. If crystallization did not occur, syrupy **5** was hydrolyzed directly.

5Ca: 81% yield; mp 202–205 °C. **5Cb**: 73% yield; mp 141–145 °C. **5Cc**: 97% yield; syrup. **5Cd**: 80% yield; mp 211–214 °C. **5Ta**: 47% yield; mp 132–134 °C. **5Tb**: syrup. **5Tc**: syrup. **5Td**: 66% yield; mp 178–180 °C.

8-Alkyl-3-methoxymorphinan-6-one Hydrochlorides (6). Hydrolysis was effected by refluxing a suspension of **5** in 2 N HCl (1 g/30 mL) for 5 to 15 h. The resulting solution was evaporated to dryness and azeotroped several times with EtOH and the crystalline residue suspended in EtOH. The crystals were collected, air-dried, and used for the preparation of **7** and **8** without further characterization.

6Ca: 90% yield; mp 204–208 °C. **6Cb**: 72% yield; mp >280 °C. **6Cc**: 57% yield; mp >280 °C. **6Cd**: 73% yield; mp 190–200 °C. **6Ta**: 70% yield; mp 271–273 °C. **6Tb**: 79% from **4Tb**; mp 273–275 °C. **6Tc**: 56% from **4Tc** as the syrupy free base obtained pure by chromatography. **6Td**: 66% yield; mp 265–267 °C.

8-Alkyl-17-(cycloalkylmethyl)-3-methoxymorphinan-6-ones (7 and 8). A mixture of **6** (free base or HCl salt) in DMF (1 g/10 mL) containing $NaHCO_3$ (2.2 equiv) and cycloalkylmethyl bromide (1.5 equiv) was heated at 100 °C under argon for 16–22 h. The cooled mixture was filtered to remove insolubles and the filtrate evaporated using an oil pump at 50 °C. The residue was dissolved in H_2O, adjusted to pH 10–11 with concentrated NH_4OH, and extracted with three portions of C_6H_6 or toluene. The organic layer was processed in the usual fashion and the residue chromatographed. Pure fractions were combined and the product crystallized as the free base or HCl salt. See Table IV.

8-Alkyl-17-(cycloalkylmethyl)-3-hydroxymorphinan-6-ones (9 and 10). The 3-methoxy compound **7** or **8** (salt or free base) in concentrated HBr (1.0 g/15 mL) was refluxed in a pre-

Table V. 8-Alkyl-17-(cycloalkylmethyl)-3-hydroxymorphinan-6-ones 9 and 10

no.	R	R′	yield, %, of free base[a]	recrystn solvent[k]	mp, °C	formula[e]
9Ca	$-CH_3$	$-CH_2$-c-C_3H_5	69	E	195-196	$C_{21}H_{27}NO_2$
b	$-CH_2CH_3$	$-CH_2$-c-C_3H_5	64	M-EA	>190[i]	$C_{22}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_3H_5	57	M-EE	162-164	$C_{23}H_{31}NO_2$[f]
d[b]	-H	$-CH_2$-c-C_3H_5	64	W	125-127	$C_{20}H_{25}NO_2$
9Ta	$-CH_3$	$-CH_2$-c-C_3H_5	72[c]	M	>300	$C_{21}H_{27}NO_2 \cdot HBr$
b	$-CH_2CH_3$	$-CH_2$-c-C_3H_5	29	M-EA	287-291	$C_{22}H_{29}NO_2 \cdot HCl \cdot H_2O$[g]
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_3H_5	46	E	273-276[j]	$C_{23}H_{31}NO_2 \cdot HCl \cdot 0.5EtOH$
d	-H	$-CH_2$-c-C_3H_5	48	EA	>265[j]	$C_{20}H_{25}NO_2 \cdot HCl \cdot H_2O$
10Ca	$-CH_3$	$-CH_2$-c-C_4H_7	84	M-EA	>150[i]	$C_{22}H_{29}NO_2 \cdot HCl$[h]
b	$-CH_2CH_3$	$-CH_2$-c-C_4H_7	98	E	>190[i]	$C_{23}H_{31}NO_2 \cdot HCl \cdot 0.5EtOH$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_4H_7	99	M-EA	210-212	$C_{24}H_{33}NO_2 \cdot HCl$
d	-H	$-CH_2$-c-C_4H_7	90	M-EA	262-264	$C_{21}H_{27}NO_2 \cdot HCl$
10Ta	$-CH_3$	$-CH_2$-c-C_4H_7	93[d]	M-EA	>200[j]	$C_{22}H_{29}NO_2 \cdot HCl$
b	$-CH_2CH_3$	$-CH_2$-c-C_4H_7	69[d]	E	>290	$C_{23}H_{31}NO_2 \cdot HCl \cdot 0.5EtOH$
c	$-(CH_2)_2CH_3$	$-CH_2$-c-C_4H_7	68[d]	W-E	>295	$C_{24}H_{31}NO_2 \cdot HCl$
d	-H	$-CH_2$-c-C_4H_7	87	M-EA	>265[j]	$C_{21}H_{27}NO_2 \cdot HCl$

[a] Yield of purified free base after chromatography. [b] Y. Sawa, R. Maeda, and N. Tada report this compound as the monohydrate, mp 127-128 °C. U.S. Patent 3 654 280 (1972). [c] Crystallized directly from reaction mixture in 72% yield. [d] Obtained directly as crystalline HCl salt without chromatography. Yield of HCl salt given in this column. [e] All compounds had C, H, and N analysis within ±0.4% of the calculated value, except as indicated in footnotes *f* and *g*. [f] C: calcd, 78.15; found, 77.61. [g] C: calcd, 67.07; found 66.48. [h] Tartrate salt, mp 204-212 °C, from E. [i] Foams. [j] Decomposition. [k] For definition of abbreviations, see Table IV, footnote *b*.

heated oil bath (≃140 °C) for 10 to 20 min. The mixture was cooled in ice and diluted with H_2O (30–40 mL), and the solution was adjusted to pH 10–11 by the addition of concentrated NH_4OH. The basic mixture was extracted with three portions of $CHCl_3$ or EtOAc, and the organic extracts were processed in the usual fashion. The residue was chromatographed ($CHCl_3$–MeOH, 8:1 to 15:1 with up to 0.5% NH_4OH), and the purified material was crystallized as the free base or HCl salt. See Table V.

17-Allyl-3-methoxy-8β-methylmorphinan-6-one (11) was prepared from **6Ca**·HCl (3.22 g, 10 mmol), $NaHCO_3$ (1.26 g, 15 mmol), and allyl bromide (1 mL, 11 mmol) in DMF (50 mL) at 100 °C for 18 h. Workup gave a syrup (2.60 g), which was chromatographed (15:1 $CHCl_3$–MeOH) to give 2.06 (64%) g of **11**. The HCl salt, **11**·HCl, mp 129–130 °C, was recrystallized from EtOH. Anal. ($C_{21}H_{27}NO_2 \cdot HCl \cdot 0.5EtOH$) C, H, N.

17-Allyl-3-hydroxy-8β-methylmorphinan-6-one (12). Compound **11**·HCl (1.50 g) was refluxed for 15 min with 48% HBr (15 mL) and then processed in the usual fashion. Evaporation of the organic extracts gave 1.29 g of **12** as a foam, which formed crystals, mp 187–190 °C, on warming with H_2O. Anal. ($C_{20}H_{25}NO_2$) C, H, N.

8β-Alkyl-17-(cyclobutylmethyl)-3-methoxy- and -3-hydroxymorphinans (13–16). A mixture of **8Ca** or **8Cb** (7 mmol), NaOH (4.67 g, 83 mmol), and $NH_2NH_2 \cdot H_2O$ (4.67 mL, 93 mmol) in triethylene glycol (25 mL) was heated for 1 h at 150 °C, then from 150 to 170 °C with azeotropic distillation for 3 h, and finally at 190–200° for 3 h. The cooled mixture was diluted with H_2O and extracted three times with EtOAc. The EtOAc extracts were washed with H_2O, dried, and evaporated to a syrup, which consisted of two major products. The syrup was chromatographed (15:1 $CHCl_3$–MeOH with 0.2% concentrated NH_4OH), and the faster migrating 3-methoxy compounds (**13** or **15**) eluted, followed by the 3-hydroxy compounds (**14** or **16**).

8β-Methyl-3-methoxy (13): 58% yield. HCl salt, mp 230–233 °C, crystallized and recrystallized from MeOH–EtOAc. Anal. ($C_{23}H_{33}NO \cdot HCl$) C, H, N.

8β-Methyl-3-hydroxy (14): 25% yield. HCl salt, mp 190–195 °C, recrystallized from EtOAc. Anal. ($C_{22}H_{31}NO \cdot HCl$) C, H, N.

8β-Ethyl-3-methoxy (15): 28% yield. HCl salt, mp 231–234 °C, recrystallized from MeOH–EtOAc. Anal. ($C_{24}H_{35}NO \cdot HCl$) C, H, N.

8β-Ethyl-3-hydroxy (16): 36% yield. Free base, mp 151–153 °C, crystallized from $CHCl_3$. Anal. ($C_{23}H_{33}NO$) C, H, N.

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