# Notes

Novel Opiates and Antagonists. 4.[1] 7-Alkanoylhydromorphones

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A series of 7-alkanoyl-substituted hydromorphone derivatives were prepared by acylation of the morpholine enamines. The most potent compound (6i) of the series was found to have agonist activity of the same order of magnitude as that of buprenorphine. The N-cyclopropylmethyl-substituted series was found to exhibit structure–activity relationships for analgesia and narcotic antagonism similar to those of the *endo*-ethanotetrahydrooripavines.

The *endo*-ethanotetrahydrooripavines [e.g., buprenorphine (1)] are potent narcotic analgesics and antagonists.[2]

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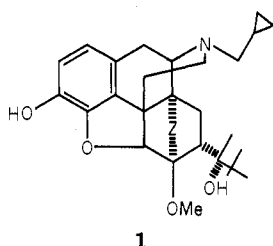
Extensive SAR studies of this series indicate that, in general, the most important factor for enhanced activity is the alkyl group at C-7.[3] The hydroxy and bridging groups contribute to the activity, possibly, by stabilizing a more active conformation. Since these bridged systems are conformationally very rigid, we were interested in determining the effect of 7-substitution on the analgesic activity of less rigid, nonbridged compounds. Recently, the syntheses of 7-alkylhydromorphones have been described.[4] We report here on the preparation, the chemistry, and the analgesic and narcotic antagonist activities of 7-acyldihydromorphinones.

Chemistry. The morpholine enamines of cyclic ketones are readily acylated by treatment with carboxylic acid chlorides to afford, after hydrolytic workup, β-diketones.[5] Enamines of dihydrocodeinone have been prepared previously, but very few reactions have been carried out with them. Seki prepared a series of 6-aminocodeine derivatives by reduction of the corresponding enamines.[6] Kovar and Schielein alkylated the pyrrolidine enamine with 1-fluoro-2,4-dinitrobenzene.[7]

The morpholine enamine 3a was prepared from di-

2a, R = Me; R' = Me
b, R = Me; R' = CH₂-c-C₃H₅
c, R = H; R' = CH₂-c-C₃H₅

3a, R = Me
b, R = CH₂-c-C₃H₅

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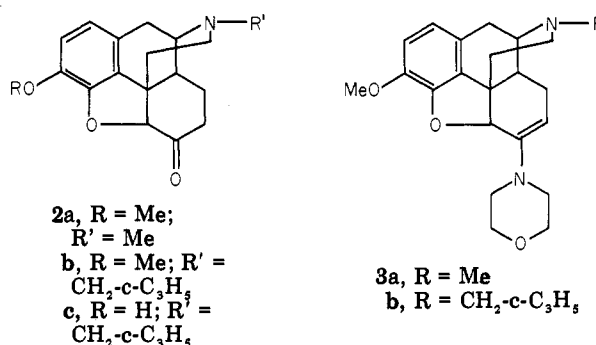
hydrocodeinone (2a) by the usual procedures.[5,6] Treatment of 3a with acetyl chloride and triethylamine in CHCl₃ at room temperature overnight afforded only 2a upon workup. However, heating these reagents at the reflux temperatures of chloroform, benzene, or trichloroethylene solutions afforded 7-acetyldihydrocodeinone (4a) in varying yields, the best being a trichloroethylene solution which afforded a 54% yield of 4a with a recovery of 27% of 2a. The use of a higher boiling solvent, tetrachloroethane, resulted in a complex mixture containing very little 4a. The structure of 4a was established from its NMR and mass spectra. Thus, the NMR spectrum showed a new singlet at δ 2.10 due to the acetyl group. The singlet due to H-5 was at δ 4.93 compared with δ 4.67 in 2a and δ 5.07 in the enamine 3a. The mass spectrum gave a parent ion at m/e 341 with a major daughter ion at m/e 298 due to loss of acetyl.

All of the β-diketones listed in Table I were prepared in a similar manner from either enamine 3a or its cyclopropylmethyl analogue 3b.[8] In some cases, repeated chromatographic separations were required to completely

(1) Part 1: R. K. Razdan, D. E. Portlock, H. C. Dalzell, and C. Malmberg, *J. Org. Chem.*, 43, 3604 (1978). Part 2: R. K. Razdan, P. Herlihy, H. C. Dalzell, and D. E. Portlock, *ibid.*, 44, 3730 (1979). Part 3: J. O. Polazzi, R. N. Schut, M. P. Kotick, J. F. Howes, P. F. Osgood, R. K. Razdan, and J. E. Villarreal, *J. Med. Chem.*, 23, 174 (1980).

(2) K. W. Bentley and D. C. Hardy, *J. Am. Chem. Soc.*, 89, 3267 and 3282 (1967); K. W. Bentley, D. C. Hardy, and B. Meek, *ibid.*, 89, 3273 (1967).

(3) (a) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, 11, 241 (1971). (b) J. W. Lewis, *Adv. Biochem. Psychopharmacol.*, 8, 123 (1974).

(4) M. P. Kotick, D. L. Leland, J. O. Polazzi, J. F. Howes, and A. R. Bousquet, *J. Med. Chem.*, 24, 1445 (1981).

(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, 85, 207 (1963).

(6) I. Seki, *Yagugaku Zasshi*, 84, 626 (1964); *Chem. Abstr.*, 61, 9545 (1964).

(7) K. A. Kovar and F. Schielein, *Arch. Pharm. (Weinheim, Ger.)*, 311, 73 (1978); see also ref 4.

(8) The precursor 2b and N-(cyclopropylmethyl)dihydronormorphinone (2c) have previously been reported by M. Gates and T. A. Montzka, *J. Med. Chem.*, 7, 127 (1964). See also M. P. Kotick, D. L. Leland, J. O. Polazzi, and R. N. Schut, *J. Med. Chem.*, 23, 166 (1980).

separate the diketone 4 from the morpholine amide of the carboxylic acid utilized. In addition, in several cases the presence of a second product was observed and successfully isolated in example 4g. On the basis of IR, NMR, and mass spectral data, we have tentatively assigned it structure 5[9] (see Experimental Section). However, acceptable

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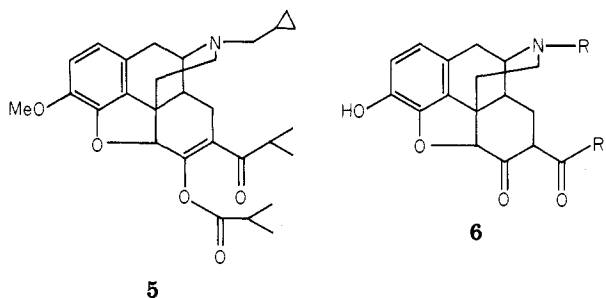
elemental analysis could not be obtained for this compound. Supportive evidence for 5 as an enol acylate was provided by the fact that treatment with K_2CO_3/CH_3OH formed the diketone 4g. Accordingly, base treatment prior to extraction was incorporated in the general isolation procedure. Although we have been unable to determine all of the factors suppressing the side reactions, it appears that heating the mixture for an extended period during the acylation step is detrimental to the formation of the diketones 4. In most cases, heating at reflux for 6–8 h was found to be optimal. The attempted acylation of 3b with pivaloyl chloride was unsuccessful, affording only 2b.

Demethylation of 4 by treatment with BBr_3 in $CHCl_3$[10] afforded moderate to good yields of the 7-acylhydromorphones, 6. Those which have been prepared are listed in Table II.

Various other reactions of 4 were investigated in an attempt to alter the diketone functionality; e.g., enol–ether formation was tried, but the reaction resulted in a complex mixture. The addition of excess methyllithium to 4a was also examined. It formed a product which was assigned structure 7 on the basis of NMR and mass spectral data. However, these studies were not pursued further, as these alcohols proved to be unstable and no well-characterized derivatives could be successfully prepared.

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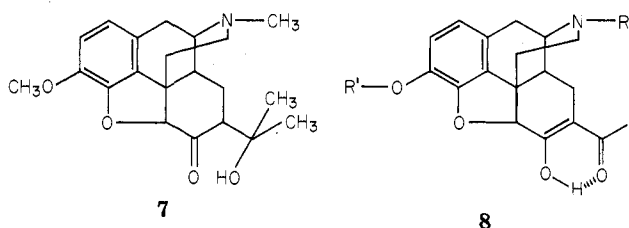
Pharmacology. These compounds were tested for analgesic activity in the acetic acid mouse writhing assay. Narcotic antagonist activity was determined against an ED_{80} dose of morphine using the rat tail-flick assay. These procedures have been described previously.[11]

As expected, the agonist activities of the hydrocodone derivatives, 4 (Table I), were less than the corresponding hydromorphone derivatives, 6 (Table II). In general, the compounds of the methyl ether series, 4, showed only

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(9) The enamines of 2-acetylcyclohexanone have been acetylated under milder conditions than we have used, to give the corresponding enol acylate: R. Jacquier and G. Maury, *Bull. Soc. Chim. Fr.*, 320 (1967).

(10) K. C. Rice, *J. Med. Chem.*, 20, 164 (1977).

(11) J. F. Howes, P. F. Osgood, R. K. Razdan, F. Moreno, A. Castro, and J. E. Villarreal, Committee on Problems of Drug Dependence, Proceedings of the Meeting, 41st, 1979, U.S. Government Printing Office, Washington, DC, 1980, p 99.

Table I

compd	R	R'	yield, %	mp, °C	formula	anal.[a]	agonist[b] ED_{50}, mg/kg	antagonist[c] AD_{50}, mg/kg
2a (hydrocodone)							1.06 (0.7–1.6)	
4a	CH_3	CH_3	55	195–196	$C_{20}H_{23}NO_4$	C, H, N (MS)	23.5 (7.1–78)	
4b	CH_3	C_3H_7	15	160–161	$C_{22}H_{27}NO_4 \cdot 0.25H_2O$	C, H, N (MS)	Ia[d]	
4c	CH_3	C_5H_{11}	50	155–156	$C_{24}H_{31}NO_4$	C, H, N (MS)	4.0 (1.7–28)	
2b	CH_2-c-C_3H_5						17 (11–26.3)	3.4 (1.1–10.8)
4d	CH_2-c-C_3H_5	CH_3	50	164–165	$C_{23}H_{27}NO_4$	C, H, N	>10	>10
4e	CH_2-c-C_3H_5	C_2H_5	30	160 (soft)[e]	$C_{24}H_{29}NO_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl (MS)	>10	6.5 (1.7–25.1)
4f	CH_2-c-C_3H_5	C_3H_7	72	155 (soft)[e]	$C_{25}H_{31}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl	2.8 (1.8–4.4)	8.1 (5.5–12)
4g	CH_2-c-C_3H_5	i-C_3H_7	26	190 (dec)[e]	$C_{25}H_{31}NO_4 \cdot HCl \cdot 0.5H_2O$[f]	H, N, Cl (MS)	7.5 (4.4–13)	2.8 (0.8–9.4)
4h	CH_2-c-C_3H_5	C_4H_9	52	foam[e]	$C_{26}H_{33}NO_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	>10	Ia[d]
4i	CH_2-c-C_3H_5	C_5H_{11}	50	135 (soft)[e]	$C_{27}H_{35}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl	5.7 (2–16)	Ia[d]
4k	CH_2-c-C_3H_5	C_6H_{13}	26	foam[e]	$C_{27}H_{35}NO_4 \cdot HCl$	C, H, N, Cl	>10	>10
4l	CH_2-c-C_3H_5	C_6H_5	48	foam[e]	$C_{28}H_{29}NO_4 \cdot HCl \cdot H_2O \cdot 0.5C_7H_7NO$[g]	C, H, N, Cl (MS)	11.3 (6.2–21)	8.0 (2.4–27)
4m	CH_2-c-C_3H_5	p-F-C_6H_4	28	178–180[e]	$C_{28}H_{28}FNO_4 \cdot HCl \cdot H_2O$	H, N, Cl (MS)	Ia[d]	>10

[a] Analyses listed agree with those calculated from the formula within ±0.4%. MS indicates that the molecular weight of the free base has been confirmed by low-resolution mass spectrometry. These compounds have a strong tendency to retain solvents. [b] Mouse acetic acid writhing test: ref 12; cf. B. A. Whittle, *Br. J. Pharmacol.*, 22, 246 (1964); 95% confidence limits. [c] Rat tail-flick morphine antagonist procedure: ref 12; cf. L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, 143, 141 (1964). [d] Inactive at the highest dose tested (10 mg/kg). [e] The HCl salt. [f] C: calcd, 65.98; found, 65.42. [g] This sample contains about 20% benzamide (by weight), which could not be removed.

moderate activity, and no meaningful SAR could be developed. In the phenolic series, 6, there was an increase in agonist potency with an increase in the chain length at C-7. Narcotic antagonist potency, however, decreased with the increase in chain length. The propionyl derivative, 6e was an exception. The peak agonist potency was present when the substituent was hexanoyl, 6i, or heptanoyl, 6k. In the limited cases studied, the agonist activities of the branched derivatives were reduced, as were the potencies of the aromatic acyl derivatives, 6l and 6m. On the other hand, the antagonist potency of the isopropyl analogue, 6g, was greater than that of the corresponding n-propyl analogue, 6f, and that of the benzoyl derivative, 6l, was equal to that of the unsubstituted compound, 2c.

The pharmacological activities of the tertiary alcohol 7 could not be properly studied because of the lack of stability described earlier.

Discussion

It is interesting that the agonist and antagonist activities of the 7-acyl derivatives 6 follow a pattern that is similar to the one observed for the oripavine tertiary alcohols of the buprenorphine type (1),[3] except that the agonist activity in the present series, 6, peaks at a longer chain length (six carbons as in 6i compared to four carbons in the unbranched series in buprenorphine type 1 compounds[3]). The agonist activity of the most potent of these compounds (6i) is of the same order of magnitude as that of buprenorphine, as determined in these laboratories. On the other hand, in the 7-alkyl series corresponding to 4, there is a decrease in potency as the alkyl size is increased.[4]

It has been postulated that the opiate analgesic receptor contains a lipophilic site with which the alkyl groups of the oripavines have a strong, specific interaction.[3a,12] In view of the similarities in the SAR of these compounds and that of 6, it is tempting to suggest that they interact with the same lipophilic site. A comparison of Drieding models of 6, in the enol form 8, and 1 in the hydrogen-bonded conformation (the more stable under nonsolvating conditions)[12] indicates that the aliphatic groups occupy positions 3–4 Å away from each other. This may indicate that the lipophilic site is rather large. On the other hand, comparison with the non-hydrogen-bonded conformation of 1 indicates that in this case the alkyl groups are in a similar position. This latter conformation may be made relatively more stable by solvation. Further studies of the specificity of the interaction of 6 with the receptor and of the effect of solvation on the stabilities of the conformations of the oripavines may aid in distinguishing between these possibilities.

Experimental Section

Melting points were determined on a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard and in $CDCl_3$ solution unless otherwise stated. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. HPLC analyses were performed on a Waters Associates A202 chromatograph (μ-Porasil column). Precoated TLC plates (silica gel 60F; EM Reagent) were used for thin-layer chromatographic analysis. Column chromatographic separations used EM Reagent silica gel 60 (0.063–0.200 mm) and gradient elution with chloroform–methanol. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Mass spectra were obtained by the Mass Spectrometry Laboratory, Cornell University, Ithaca, NY, and are reported as m/e (relative in-

(12) G. H. Loew and D. S. Berkowitz, J. Med. Chem., 22, 603 (1979), and referneces therein.

(13) A. Cowan, J. W. Lewis, and I. R. MacFarlane, Br. J. Pharmacol., 60, 537 (1977).

Table II

compd	R	R'	yield, %	mp, °C	formula	anal.[a]	agonist[b] ED_{50}, mg/kg	antagonist[c] AD_{50}, mg/kg
morphine							0.79 (0.42–1.5)	
1 (buprenorphine)							0.13[f] (0.076–0.22)	
hydromorphone							0.08 (0.04–0.14)	
6b	CH_3	C_3H_7	61	175 (dec)[e]	$C_{21}H_{25}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl (MS)	5.2 (1.9–14)	
6c	CH_3	C_5H_{11}	47	160 (dec)[e]	$C_{23}H_{29}NO_4 \cdot HCl \cdot 3H_2O$	C, H, N, Cl (MS)	0.76 (0.41–1.41)	g
2c							1.3 (0.27–6.5)	0.19 (0.10–0.34)
6d	$CH_2\text{-}c\text{-}C_3H_5$	CH_3	84	135	$C_{22}H_{25}NO_4 \cdot 0.5CH_3OH$[h]	C, H, N (MS)	4.0 (2.5–6.5)	1.3 (0.49–3.5)
6e	$CH_2\text{-}c\text{-}C_3H_5$	C_2H_5	66	foam[e]	$C_{23}H_{27}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl (MS)	Ia[d]	0.52 (0.32–0.81)
6f	$CH_2\text{-}c\text{-}C_3H_5$	C_3H_7	60	220 (dec)[e]	$C_{24}H_{29}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl	4.6 (1.5–15)	2.6 (1.2–5.5)
6g	$CH_2\text{-}c\text{-}C_3H_5$	$i\text{-}C_3H_7$	75	210 (soft)[e]	$C_{24}H_{29}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl (MS)	10 (0.4–2.52)	0.81 (0.4–1.5)
6h	$CH_2\text{-}c\text{-}C_3H_5$	C_4H_9	59	240 (dec)[e]	$C_{25}H_{31}NO_4 \cdot HCl$	C, H, N, Cl	1.59 (0.90–2.80)	3.3 (1.5–7.3)
6i	$CH_2\text{-}c\text{-}C_3H_5$	C_5H_{11}	30	190 (dec)[e]	$C_{26}H_{33}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl	0.29 (0.18–0.47)	22 (8–60)
6j	$CH_2\text{-}c\text{-}C_3H_5$	$CH_2\text{-}t\text{-}C_4H_9$	85	213–215[e]	$C_{26}H_{33}NO_4 \cdot HCl \cdot H_2O$	C, H, N, Cl	Ia[d]	>10
6k	$CH_2\text{-}c\text{-}C_3H_5$	C_6H_{13}	37	175 (soft)[e]	$C_{27}H_{35}NO_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl (MS)	0.4 (0.11–1.4)	Ia[d]
6l	$CH_2\text{-}c\text{-}C_3H_5$	C_6H_5	69	foam[e]	$C_{27}H_{27}NO_4 \cdot HCl \cdot H_2O$[i]	C, H, N, Cl	4.35 (1.3–15)	0.24 (0.03–1.9)
6m	$CH_2\text{-}c\text{-}C_3H_5$	$p\text{-}F\text{-}C_6H_4$	78	155–157	$C_{27}H_{26}FNO_4$	C, H, N	>10	~10

[a–e] See corresponding footnotes in Table I. [f] Reported:[13] mouse writhing, ED_{50} = 0.033 mg/kg; mouse tail-flick antagonism, AD_{50} = 0.22 mg/kg. [g] Unable to obtain a satisfactory dose-response. [h] C: calcd, 70.46; found, 70.92. [i] C: calcd, 67.00; found, 66.33. Cl: calcd, 7.32; found, 7.94.

tensity). All organic layers after extractions were dried with Na₂SO₄. Except as noted, all reagents and solvents were used as obtained from the supplier. Tetrahydrofuran was distilled from sodium ketyl.

7-Acetyldihydrocodeinone (4a). A solution of dihydrocodeinone (2a; 996 mg, 3.3 mmol), morpholine (2.5 mL, 28 mmol), and p-toluenesulfonic acid monohydrate (5 mg) in benzene (50 mL) was heated at reflux through 3 Å molecular sieves for 3 days. The mixture was then concentrated in vacuo to afford crude **3a** as a solid.

To a stirred, cooled (ice bath) solution of this crude enamine (600 mg, 1.6 mmol) in trichloroethylene (50 mL) was added sequentially triethylamine (0.35 mL, 2.5 mmol) and acetyl chloride (0.6 mL, 8 mmol). A fine white solid precipitated from the solution, and after 15 min, the solution was removed from the ice bath and heated at reflux for 6 h. During this time, the color changed to orange and then to red. Water (25 mL) was added, and the mixture was heated at reflux for 1 h. After cooling, the mixture was made basic with 50% NH₄OH, extracted with chloroform, dried, and concentrated. The resulting oil was column chromatographed to afford **4a** (300 mg, 55% yield) and recovered **2a** (170 mg, 27% yield). Recrystallization (MeOH) afforded pure **4a**: mp 195–196 °C; NMR δ 2.10 [s, 3 H, C(O)CH₃], 2.45 (s, 3 H, NCH₃), 3.88 (s, 3 H, OCH₃), 4.93 (s, 1 H, H-5), 6.73 (AB q, J = 8 Hz, 2 H, aryl); IR (KBr) 1620 (br) cm⁻¹; MS, m/e 341 (100, M⁺), 326 (13, M⁺ - CH₃), 298 [18, M⁺ - C(O)CH₃]. Anal. (C₂₀H₂₃NO₄) C, H, N.

The other diketones of structure **4** were prepared by essentially the same procedure, starting with either **2a** or **2b**.[8] One change which was made was to stir a methanol solution of the crude product (i.e., prior to chromatography) with 1 g of K₂CO₃ for 3–5 h. This solution was then concentrated, diluted with water,

extracted with CHCl₃, dried, concentrated, and then chromatographed.

Isolation of the Enol Isobutyrate, 5. A trichloroethylene solution of **3b** (2.95 mmol), triethylamine (0.5 mL, 3.6 mmol), and isobutyryl chloride (1.3 mL, 12 mmol), prepared as above, was heated at reflux for 9 h. After hydrolysis and the usual workup, an oil was obtained which contained a substantial amount of **5**. After several chromatographs, 100 mg (7% yield) of **5** was obtained: NMR δ 0.2 and 0.6 (m, 5 H, c-C₃H₅), 0.93 [d, J = 7 Hz, 6 H C(CH₃)₂], 1.22 and 1.25 [doublets, J = 7 Hz, 6 H, C(CH₃)₂], 3.88 (s, 3 H, OCH₃), 5.20 (s, 1 H, H-5), 6.72, 6.75 (AB q, 2 H, aryl); IR (film) 1755 (s), 1700–1610 (several) cm⁻¹; MS, m/e 479 (9, M⁺), 408 [8, M⁺ - C(O)C₃H₇], 392 [1, M⁺ - OC(O)C₃H₇], 43 (100). Treatment of a methanol solution of a mixture of **4g** and **5** with K₂CO₃ (as above) for 2 h afforded only **4g**.

N-(Cyclopropylmethyl)-7-acetyldihydronormorphinone (6d). To a stirred solution of distilled BBr₃ (0.3 mL, 3 mmol) in CHCl₃ (6 mL) was added, dropwise, **4d** (100 mg, 0.26 mmol) in CHCl₃ (1 mL). After 0.5 h, the mixture was poured onto a 1:1 ice–NH₄OH mixture and stirred for 1 h. The layers were then separated, and the aqueous layer was extracted with CHCl₃. The CHCl₃ layers were combined, dried, and concentrated. Column chromatography afforded **6d** (80 mg, 84% yield): mp 135 °C (MeOH); NMR δ 0.2 and 0.6 (m, 5 H, c-C₃H₅), 2.17 (s, 3 H, Ac), 4.4 (br s, OH), 4.88 (s, 1 H, H-5), 6.67, 6.65 (AB q, J = 8 Hz, aryl); MS, m/e 367 (30, M⁺), 55 (100). Anal. (C₂₂H₂₅NO₄·0.5CH₃OH) C, H, N. The other compounds of structure **6** were prepared in a similar fashion.

Novel Opiates and Antagonists. 5.[1]
7-Carbethoxy-N-(cycloalkylmethyl)-3-hydroxymorphinan-6-ones and -isomorphinan-6-ones

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A direct conversion of deoxydihydrothebaine-φ (1) to 3-methoxymorphinan-6-one (3Ca) and its trans isomer **3Ta** was achieved in excellent yield by the catalytic reduction of 1 in AcOH containing CF₃COOH. Treatment of **3Ca** or **3Ta** with NaH and diethyl carbonate formed the corresponding 7-carbethoxy derivatives **4a** which, on O-demethylation, furnished the 3-hydroxy compounds **4b**. The analgesic N-methyl compounds **3** were converted to the 17-(cyclopropylmethyl) or 17-(cyclobutylmethyl) derivatives **6–8**. Two of these compounds, one in the cis (**7Ca**) and the other in the trans (**7Ta**) series, showed mixed agonist/antagonist activity in the pentazocine range.

The search for opioid analgesics of the mixed agonist/antagonist type continues to be of intense interest to medicinal chemists. Pentazocine, a benzomorphan derivative, was the first analgesic belonging to this class of compounds to be introduced to the market. Since then, others, such as nalbuphine, butorphanol, and buprenorphine, have followed with the main clinical objective of decreasing the incidence of undesirable side effects and increasing the efficacy.[2]

As part of our program directed toward this goal, we have studied 7-acyldihydromorphinones.[1] These compounds were prepared on the basis of our interest in determining the effect of 7-substitution on the analgesic activity of less rigid nonbridged compounds. To extend these studies, we prepared the 7-carbethoxy derivatives of morphinan-6-ones. During the course of this work it became apparent that the corresponding isomorphinan-6-ones were also easily accessible. This provided us an opportunity to study the effect of 7-carbethoxy substitution on analgesia in both the cis- and the trans-morphinan-6-ones. Recently, the influence of 7-alkyl substitution on analgesia in cis- and trans-morphinanones has been reported.[3] Further chemical elaboration of the carbethoxy group to give novel compounds was attempted; however, except for a few limited cases, the chemistry proved to be unrewarding and was not pursued. Our findings in this area are described in this paper.

(1) For paper 4, see Quick, J.; Herlihy, P.; Razdan, R. K.; Howes, J. F. *J. Med. Chem.*, preceding paper in this issue.

(2) See, for example, "Narcotic Antagonists"; Braude, M.; Harris, L. S.; May, E. L.; Smith, J. P.; Villarreal, J. E., Eds.; Raven Press: New York, 1973. Jaffe, J. H.; Martin, W. R. In "The Pharmacological Basis of Therapeutics"; Goodman, L. S.; Gilman, A., Eds.; Macmillan: London, 1980; p 521.

(3) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* 1980, 23, 1427.