Synthesis and Stereochemical Assignment of 7-Arylidene and 7-Heteroarylidene Morphinan-6-ones

Yang Nan, Subhash P. Upadhyaya, Wei Xu, Kathrine E. Hughes, William J. Dunn III and Ludwig Bauer

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 833 S.Wood, Chicago, Illinois 60612-723

Hemendra N. Bhargava

Department of Pharmaceutics and Pharmacodynamics, College of Pharmacy, University of Illinois at Chicago, 833 S. Wood, Chicago, Illinois 60612-7231

George A. Doss

Merck Research Laboratories P.O. Box 2000, Rahway, New Jersey, 07065-0900
Received October 25, 1995

A number of (*E*)-7-arylidenenaltrexones were synthesized by azeotropic distillation of water from a benzene solution of naltrexone and an aromatic aldehyde (benzaldehyde, 4-chloro- and 4-fluorobenzaldehyde, 3-and 4-pyridinecarboxaldehyde and 1-methyl-2-imidazolecarboxaldehyde) using piperidine as a catalyst. In addition, (*E*)-7-benzylidenenaloxone was prepared by the previously published Claisen-Schmidt condensation using sodium hydroxide in methanol. The stereochemistry of these arylidene derivatives **3-9** was determined to be (*E*) by means of nuclear Overhauser enhancement experiments. The ^{13}C nmr spectra of (*E*)-**3-9** are recorded in deuteriochloroform and those of the hydrochlorides in deuteriodimethyl sulfoxide.

J. Heterocyclic Chem., **33**, 399 (1996).

Introduction.

Naltrexone (**1**) and naloxone (**2**) are prototypical, nonselective, opiate receptor antagonists [1]. Structural alterations of their 6 and/or 7-positions can introduce receptor subtype (μ-, δ- and κ) specificity into the ligands, as first suggested by Portoghese [2], Bertha *et al.* [3] and Nelson and coworkers [4]. Numerous modifications of **1** and **2** at C-6 and C-7 have been undertaken, from changing the ketone to other functional groups, introducing substituents α to the ketone on the active methylene group at C-7, to totally changing the landscape by fusing rings to positions 6 and 7. Concomitant with such structural modifications are changes in biological activities [5,6].

Some of the Reactions of the 6,7-Ketomethylene System of **1** and **2**.

The 6,7-keto-methylene system of **1** and **2** exhibits unusually high chemical reactivity in functional conversions of the C-6 ketone or substitution of the C-7 active methylene group. Indeed, both groups are frequently involved when a carbocyclic (e.g., phenyl, cycloalkyl) or heterocyclic ring (furan, pyrrole, quinoline, indole, etc.) is attached to C-6 and/or C-7 [7-17]. Seemingly straightforward and standard reactions were fraught with problems and unexpected products were isolated. For example, when the standard acid-catalyzed Mannich reaction of ketones with formaldehyde and a secondary amine to furnish a β-dialkylamino ketone was applied to 14-hydroxydihydrocodeinone, an extremely complex product (72%) was obtained whose structure was determined by X-ray crystallography [18,19]. The formation of this product is rationalized if the intermediate Mannich base spontaneously eliminates the secondary amine and the resultant α,β-unsaturated ketone undergoes a Diels-Alder reaction with itself. Also, when 14-hydroxydihydrocodeinone reacts with *o*-nitrobenzaldehyde in boiling aqueous alcoholic sodium hydroxide solution, the complex product so obtained is explained only, if after the expected Claisen-Schmidt, the cyclohexanone ring opens subsequently [20]. Whether this enhanced reactivity is due to the stereochemical make-up of the rather rigid 6-morphinanone system, or its inherent electronic make-up, is subject to debate. It is conceivable that the presence of a number of nucleophilic groups in close proximity of C-6 and C-7 (*e.g.*, the alcohol on C-14, the ether at C-5) might assist in attracting and coordinating with electrophilic reagents (including cations accompanying organometallic reagents), thereby facilitating these reactions.

Synthesis of 7-Benzylidene- and 7-[(Heteroaryl)methylene] Naltrexones and Naloxones.

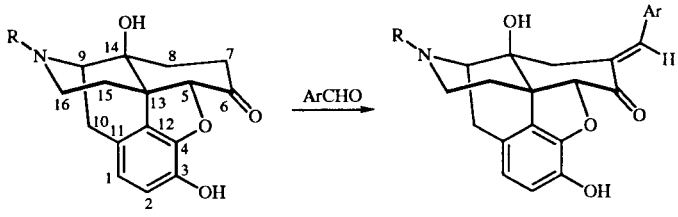
This paper addresses the synthesis and stereochemical assignments of 7-benzylidenenaltrexone (**3**) and analogs **4-9**. The Claisen-Schmidt reaction of **1** with benzaldehyde in methanol containing sodium hydroxide at 0-5° (14 hours) has been reported to yield 7-benzylidenenaltrexone (**3**) in 50% yield. There is no reference to the stereochemistry of **3** [21,22]. When the same reaction was conducted at slightly higher temperature (24°, 18 hours), the major product was a complex hemiacetal (65%),

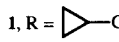
formed by a Michael addition of **1** to **3** to yield a 1,4-diketone, which cyclizes to a six-membered hemiacetal, *via* one of the enols of that diketone [21]. In a separate step, the hemiacetal was converted by methanesulfonic acid in anhydrous dimethylformamide and toluene (with azeotropic removal of water) to a pyran (78%) [21].

We repeated the condensation of **1** with benzaldehyde at 0-5° and found a very complex reaction mixture and the isolation of **3** very tedious, yielding pure material only after extensive chromatography. It was essential to establish the stereochemistry associated with the alkene. Only one α,β-unsaturated ketone of **3** could be detected, after scrutinizing numerous fractions containing the free base or its hydrochloride by proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (nmr) spectroscopy in deuteriochloroform and/or deuteriodimethyl sulfoxide. The vinyl (CH=) system of **3** revealed only one set of ^{1}H and ^{13}C resonances, at δ 7.50 and 140.6 (deuteriochloroform) and δ 7.66 and 138.9 (deuteriodimethyl sulfoxide), respectively. For the corresponding hydrochloride, the ^{1}H and ^{13}C chemical shifts for the vinyl (CH=) system in deuteriodimethyl sulfoxide were at δ 7.64 and 140.7, respectively. In the original paper, there was no mention of any ^{1}H nmr signals of **3** between δ 6.85 and 9.85 [21].

In an effort to improve the yield of the product from the Claisen-Schmidt condensation of **1** with aromatic aldehydes, we searched for alternate methods. The method of Birkofer [24] held a certain appeal since it was carried out in non-hydroxylic solvents, but in two steps. These researchers reacted ketones with piperidine to form enamines initially, which were subsequently reacted with aromatic aldehydes to form arylidene products [24]. Attempts to apply this method to our system met with limited success, in the sense that a lot of by-products were still formed and the yield of the target compounds was relatively low. However, it was discovered that **1** condenses directly with aromatic aldehydes in the presence of piperidine in hot benzene with azeotropic removal of water to form the α,β-unsaturated ketones without the necessity of isolating any intermediate enamines. The ease by which these one-pot reactions took place was surprising and facilitated the production of the target compounds. Under these mild conditions, **1** condensed with benzaldehyde, 4-chloro- and 4-fluorobenzaldehyde, 3- and 4-pyridinecarboxaldehyde and 1-methyl-2-imidazolecarboxaldehyde to yield (*E*)-**3**-**8**. In addition, 7-benzylidenenaloxone was prepared from **2** and excess benzaldehyde by the previously published method using sodium hydroxide in methanol [21].

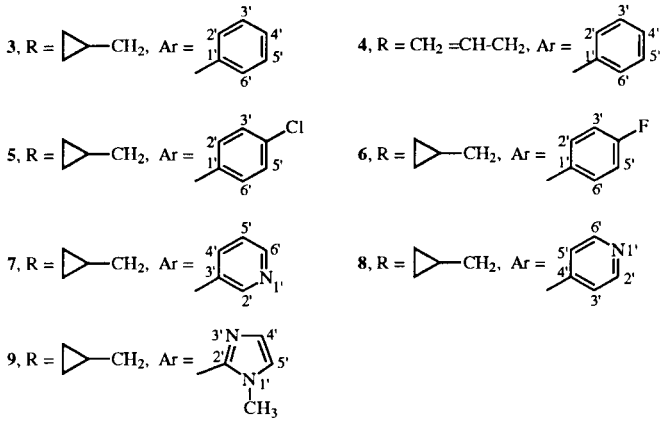
The progress of these one-pot reactions was followed by thin layer chromatography (tlc) and nmr spectra (mostly ^{1}H, some ^{13}C spectra). Examination of these nmr spectra indicated that the product was formed in relatively



1, R =  (naltrexone)

2, R = CH_2 =CH-CH_2 (naloxone)

where in



good yields. In a few instances, the products could be purified by simple crystallization, but for the majority of the reactions, column chromatography was resorted to for pure materials. Each condensation yielded only the (*E*)-stereoisomer, although attempts were made to detect (and isolate) the other stereoisomer. In a series of related Claisen-Schmidt reactions, Hartmann and coworkers [25-27] successfully condensed a series of 1-indanones and 1-tetralones with 4-pyridinecarboxaldehyde in acetic acid, in the presence of piperidine, at 130° (1.5 hours) to obtain only (*E*)-isomers of 2-(4-pyridylmethylene)-1-indanones and 1-tetralones in excellent yield.

Structure Determinations.

In a more recent paper, Portoghese *et al.*, [23] reported that the condensation of **1** with benzaldehyde in methanol containing sodium hydroxide at lower temperature (-5°, 12 hours) provided **3** in 70% yield [23]. It was also claimed that the product consisted of a mixture of (*E*)- and (*Z*)-**3** in the ratio of 98:2. The minor (*Z*) isomer of **3** was separated from (*E*)-**3** using hplc, but apparently was obtained in insufficient amounts for an elemental analysis. The authors based their structure proof on differences of retention times [hplc, 10.98 for (*E*), 9.54 minutes for (*Z*)-**3**], thin layer chromatography (tlc) and ^{1}H chemical shift differences of the vinyl (C*H*=) protons of these isomers [23]. They report vinyl ^{1}H chemical shifts (C*H*=) of their (*E*)-**3** *hydrochloride* at δ 7.59, and that of the (*Z*)-**3**

free base at δ 7.50 (deuteriodimethyl sulfoxide, Table 1) [23]. Such a small chemical shift difference (0.09 ppm), particularly when comparing the shift of a *hydrochloride* with that of a *free base*, is insufficient to distinguish between such stereoisomers. The vinyl ^{1}H chemical shift of our (*E*)-**3** *hydrochloride* is at δ 7.59, our (*E*)-**3** *free base* at δ 7.50 (deuteriodimethyl sulfoxide, Table 1). When both (*E*) and (*Z*) isomers are available, ^{1}H chemical shifts for such vinyl protons fall into two sets of relatively narrow ranges, which on the whole show chemical shift differences that are considerably larger. For example, Hartmann *et al.*, [25,26] reported chemical shift ranges in several series of related stereoisomers: for (*E*), δ 7.55-7.89 and for (*Z*)-isomers, δ 6.92-7.42. These authors surmise that the anisotropic effect of the neighboring carbonyl group deshields the (*E*)-vinyl proton and shields that of the (*Z*)-isomers, causing the chemical shifts of the vinyl proton of the (*Z*) isomers to be upfield from those of the (*E*)-isomers [25].

The challenge in establishing the stereochemistry of trisubstituted alkenes becomes more demanding when only one isomer is isolated [25-28]. Proof of structure is best obtained from extensive correlation and nuclear Overhauser enhancement (nOe) experiments. Every ^{1}H and ^{13}C chemical shift of the products of **1** with benzaldehyde, 3-pyridinecarboxaldehyde and 1-methyl-2-imidazolecarboxaldehyde was assigned. Through a series of ^{1}H and ^{13}C correlation experiments of the HMQC (*H*eteronuclear *M*ultiple *Q*uantum *C*oherence) type, followed by nOe experiments using 2D ROSEY (*R*otating frame *O*verhauser *SpE*ctroscop*Y*), it was possible to establish *rigorously* the (*E*)-stereochemistry of three, **3**, **7** and **9**, of the seven arylidene derivatives. The closeness of the chemical shifts of the other analogs suggests similar stereochemistry.

Since only sketchy ^{1}H chemical shifts were provided by Portoghese *et al.* [21,23] for (*E*)- and (*Z*)-**3**, and the corresponding hydrochlorides (Table 1), the ^{1}H chemical shift

Table 1

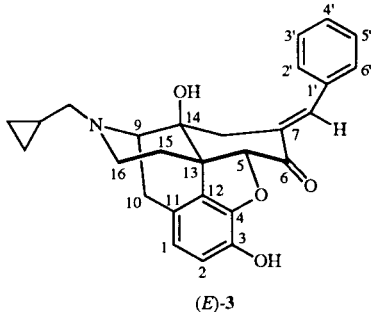
^{1}H Chemical Shifts of (*E*)- and (*Z*)-**3**, and Certain Salts of (*E*)-**3**, **7**, **9** [a]

Compound	*E*-3 [b,c]	*E*-3 [c]	*E*-3 [d]	*Z*-3 [d,e]	*E*-3•HCl [d,e]	*E*-3•HCl [d]	*E*-3 [d & TFA]	*E*-7 [d & TFA]	*E*-9 [d & TFA]
Position									
1	6.61	6.63	6.61	6.68	6.70	6.67	6.67	6.69	6.72
2	6.75	6.74	6.63	6.68	6.70	6.76	6.72	6.77	6.75
5	4.72	4.71	4.63	5.11	4.78	4.83	4.76	4.86	4.97
$8a_{(eq)}$	[f]	[h]	[I]	[k]	[l]	[n]	3.12	3.13	3.01
$8b_{(ax)}$	[f]	[h]	[I]	[k]	[l]	[n]	2.48	2.52	2.60
9	[f]	[h]	[I]	[k]	[l]	[n]	4.00	4.08	3.97
10a	[f]	[h]	[I]	[k]	[l]	[n]	3.38	3.44	3.49
10b	[f]	[h]	[I]	[k]	[l]	[n]	3.21	3.20	3.04
15a	[f]	[h]	[I]	[k]	[l]	[n]	2.55	2.60	2.56
15b	[f]	[h]	[I]	[k]	[l]	[n]	1.65	1.66	1.71
16a	[f]	[h]	[I]	[k]	[l]	[n]	3.05	3.10	3.11
16b	[f]	[h]	[I]	[k]	[l]	[j]	2.71	2.71	2.73
N-CH_{2a}	[f]	[h]	[I]	[k]	[l]	[n]	3.29	3.35	3.42
N-CH_{2b}	[f]	[h]	[I]	[k]	[l]	[n]	2.87	2.93	2.88
CH (cp)	0.79-0.90	0.83	0.85	0.85	0.85	1.05	1.00	1.04	1.03
CH_{2a} (cp)	0.52-0.58	0.53	0.47	0.49	0.49	0.68	0.64	0.67	0.67
$CH_{2a'}$ (cp)	0.52-0.58	0.53	0.47	0.49	0.49	0.41	0.35	0.39	0.40
CH_{2b} (cp)	0.12-0.15	0.12	0.12	0.14	0.14	0.60	0.54	0.56	0.56
$CH_{2b'}$ (cp)	0.12-0.15	0.12	0.12	0.14	0.14	0.46	0.42	0.47	0.47
CH=	[g]	7.66	7.50	7.50	7.59	7.64	7.61	7.61	7.38
2'	[f]	7.33	[j]	[k]	[m]	[o]	7.40	8.82	-
3'	[f]	7.33	[j]	[k]	[m]	[o]	7.35	-	-
4'	[f]	7.33	[j]	[k]	[m]	[o]	7.35	8.19	7.74
5'	[f]	7.33	[j]	[k]	[m]	[o]	7.35	7.68	7.83
6'	[f]	7.33	[j]	[k]	[m]	[o]	7.40	8.69	-
N-CH_3	-	-	-	-	-	-	-		3.81

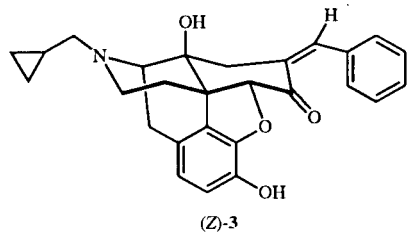
[a] Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane; also, the following abbreviations are used: TFA for trifluoroacetic acid-d; cp for cyclopropyl. [b] Reported by Portoghese *et al.*, Ref 21. [c] Recorded in deuteriochloroform. [d] Recorded in DMSO-d_6. [e] Reported by Portoghese *et al.*, Ref 23. [f] Other reported, but unassigned chemical shifts are δ 1.64 (d), 2.22-2.50 (m), 2.63-2.77 (m), 3.01 (d), 3.13 (d), 3.21(d) and 9.85 (m). [g] No resonance for vinyl proton (C*H*=) was reported in the expected area, between δ 6.75 and 9.85. [h] The complex sets of multiplets between δ 1.62-3.22 were not analyzed. [I] Chemical shifts were not extracted from a series of complex multiplets between δ 1.42-3.18. [j] Aromatic proton resonances are between δ 7.39-7.43.The aromatic resonances are at δ 7.39-7.43. [k] No other aliphatic resonances are reported (others than shown above) and the aromatic ones are stated to be between δ 7.26-7.50. [l] No further aliphatic proton shifts are listed. [m] Aromatic proton resonances are reported between δ 7.38-7.46. [n] The complex multiplets between δ 1.66 and 3.22 were not analyzed. [o] Aromatic proton resonances are between δ 7.42-7.49.

of each proton in the major isomer of **3** was established. To sharpen ^1H nmr signals, particularly in deuteriodimethyl sulfoxide, it is common to "spike" the test solution with small amounts of deuterated trifluoroacetic acid (TFA). While sharper signals are obtained, one is now recording the spectrum of the *trifluoroacetate*. It was found that ^1H and ^{13}C chemical shifts of the free base in deuteriodimethyl sulfoxide solution containing some TFA matched those of the preformed *hydrochloride* (Table 4). Due to virtual insolubility of these *hydrochlorides* in deuteriochloroform, deuteriodimethyl sulfoxide became the solvent of choice. In order to compare appropriate chemical shifts of free bases and corresponding salts, we obtained spectra of some of the free bases in deuteriodimethyl sulfoxide (Tables 3,4). Some of the more significant ^1H or ^{13}C chemical shift differences of free bases and salts of **3-9** are discussed.

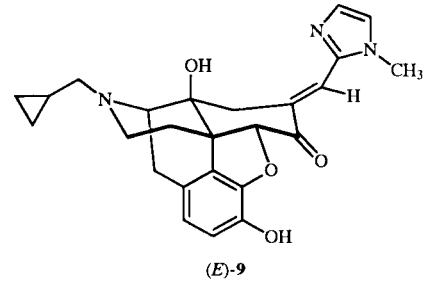
the *(E)* configuration for **3**. This assignment is reinforced by the complete absence of an nOe between the vinyl methine (C*H*=) and H-8 protons. Had the arrangement around the double bond been *(Z)*, one would have expected a considerable nOe between the vinyl C*H*= and either H-8_{ax} and/or H-8_{eq}. For the 3-pyridyl analog **7**, the (*E*)-structure is based on nOe's between H-2' and H-4' of pyridine and H-8 protons. Strong nOe effects between the C*H*= and H-8 protons would have been observed had the configuration been *(Z)*. Substantiating the structure of (*E*)-7-[(1-methyl-2-imidazolyl)methylene]naltrexone (**9**) are strong nOe's between the *N*-methyl and vinyl proton with no nOe observed between the *N*-methyl and H-8 protons, or between the vinyl proton and H-8. From these nOe data, we conclude that the stereochemistry of the major isomer of 7-arylidenenaltrexones we have isolated is *(E)*.



(*E*)-**3**



(*Z*)-**3**



(*E*)-**9**

Crucial data from 2D ROSEY nmr experiments indicate strong nOe's between the *o*-phenyl protons (H-2', H-6') and *both* protons attached to C-8, strongly supporting

The ^{13}C chemical shifts of the alkene carbons of **3**, **7** and **9** were assigned by 2D ^1H-^{13}C correlation nmr (HMQC and HMBC) experiments. It was also hoped that ^{13}C nmr

Table 2

Selected ^1H Chemical Shifts of Allyl, Aromatic, Cyclopropyl and Vinyl Protons of (*E*)-**3-9** and Some Hydrochlorides [a, b]

Compound	**3**	**3**	**3•HCl**	**4**	**5**	**5•HCl**	**6**	**6•HCl**	**7**	**7**	**7•2HCl**	**8**	**8•2HCl**	**9**	**9**	**9•2HCl**
Position	[c]	[d]	[d]	[c]	[c]	[d]	[c]	[d]	[c]	[d]	[d]	[c]	[d]	[c]	[d]	[d]
1	6.63	6.61	6.70	6.65	6.63	6.69	6.63	6.71	6.63	6.60	6.70	6.64	6.70	6.51	6.56	6.70
2	6.75	6.63	6.76	6.75	6.74	6.78	6.74	6.79	6.75	6.64	6.78	6.76	6.82	6.66	6.59	6.77
5	4.71	4.63	4.83	4.69	4.70	4.83	4.70	4.83	4.70	4.66	4.91	4.70	4.98	4.60	4.60	4.98
CH=	7.66	7.50	7.64	7.62	7.56	7.57	7.60	7.59	7.57	7.48	7.63	7.47	7.62	7.44	7.30	7.38
2'	7.33	7.41	7.45	7.32	7.25	7.48	7.05	7.26	8.63	8.66	8.94	8.66	8.91	-	-	-
3'	7.33	7.41	7.45	7.32	7.32	7.53	7.33	7.59	-	-	-	7.47	8.07	-	-	-
4'	7.33	7.41	7.45	7.32	-	-	-	-	7.68	7.89	8.39	-	-	7.00	7.15	7.66
5'	7.33	7.41	7.45	7.32	7.32	7.53	7.33	7.59	7.32	7.44	7.86	7.47	8.07	7.21	7.36	7.79
6'	7.33	7.41	7.45	7.32	7.25	7.48	7.05	7.26	8.59	8.54	8.77	8.66	8.91	-	-	-
CH (cp)	0.82	0.85	1.05	-	0.83	1.07	0.85	1.10	0.85	0.86	1.05	0.85	1.09	0.85	0.90	1.07
(CH_2)a (cp)	0.53	0.47	0.68	-	0.54	0.70	0.54	0.69	0.55	0.47	0.67	0.56	0.69	0.51	0.50	0.71
(CH_2)a' (cp)	0.53	0.47	0.41	-	0.54	0.40	0.54	0.41	0.55	0.47	0.40	0.56	0.40	0.51	0.50	0.42
(CH_2)b (cp)	0.12	0.12	0.60	-	0.12	0.60	0.13	0.58	0.13	0.11	0.59	0.13	0.60	0.13	0.14	0.60
(CH_2)b' (cp)	0.12	0.12	0.46	-	0.12	0.50	0.13	0.51	0.13	0.11	0.51	0.13	0.51	0.13	0.14	0.50
CH_2= (all)	-	-	-	5.18	-	-	-	-	-	-	-	-	-	-	-	-
CH= (all)	-	-	-	5.78	-	-	-	-	-	-	-	-	-	-	-	-
N-CH_3	-	-		-	-	-	-	-	-	-	-	-	-	3.80	3.74	3.82

[a] Chemical shifts (d) are recorded in ppm, downfield from internal tetramethylsilane; abbreviation "cp" is for cyclopropyl, "all" is for allyl. [b] Some exchangeable signals for OH and/or NH^+ were noted, specifically, at d 9.56, 8.96 and 6.56 for **3•HCl**, 6.58 for **4•HCl**, 9.05 and 9.60 for **5•HCl**, 6.49 for **6•HCl**, 9.30 for **7•2HCl**, 9.19 for **8•2HCl**, and 9.15 for **9•2HCl**. [c] Recorded in $CDCl_3$. [d] Recorded in DMSO-d_6.

data might be useful in determining the stereo-assignments of members of this series of arylidene ketones. An analysis of ^{13}C chemical shifts of the free bases and hydrochlorides (Tables 3,4) did not help in this goal, particularly since only one isomer was available. There were relatively little vinyl ^{1}H or ^{13}C chemical shift differences of **3-9**, either as free bases or hydrochlorides. The range of ^{1}H chemical shifts of the vinyl (CH=) resonances of **3-9** was δ 7.65-7.80 (in deuteriochloroform) and that for **3**, **7** and **9** was δ 7.30-7.50 (in deuteriodimethyl sulfoxide, Table 3). For the hydrochlorides of **3-9**, that range was δ 7.35-7.65 (deuteriodimethyl sulfoxide, Table 4). There were relatively few chemical shift differences (less than 5 ppm) of the vinylidene carbon carrying the aryl group (Ar*C*H=) among free bases or salts of **3-8**. However, there was one set of outstanding ^{13}C chemical shift differences in the alkylidene carbon of the free base and hydrochloride of **9**, (about δ 120) compared to those in the phenyl and pyridyl counterparts in **3-8** (around δ 140). The vinyl carbon in **9** is experiencing the effect of the attached electron-rich 1-methyl-2-imidazolyl moiety whose proximal δ-electrons impart a shielding effect. The corresponding vinyl ^{1}H chemical shifts are not that discerning. Apparently, the attached imidazole ring does not influence the ^{1}H chemical shift as much, in the sense, that the magnetic anisotropic effect exerted by π-electrons of the aromatic groups (imidazolyl, phenyl or pyridyl) are similar.

A brief comment is warranted regarding ^{1}H and ^{13}C chemical shift differences of the cyclopropyl ring atoms of free bases and hydrochlorides **3**, **5-9** (Tables 2-4). These shifts are almost diagnostic in distinguishing between free bases and salts. The ^{1}H nmr spectra of the free bases usually showed three sets of ^{1}H signals, around δ 0.12, 0.50 and 0.85 (deuteriochloroform or deuteriodimethyl sulfoxide) while the salts had up to five signals, between δ 0.46 and 1.10 (deuteriodimethyl sulfoxide). Similarly, ^{13}C chemical shifts of the cyclopropyl carbons of the free bases were around δ 3.5, 4.1 and 9.2 and those of the salts, around δ 2.6, 5.2 and 5.7. These chemical shift values compare well with those of naltrexone and salts [29-31].

Conclusion.

The Claisen-Schmidt condensation of naltrexone and naloxone with aromatic aldehydes provided primarily the

Table 3

^{13}C Chemical Shifts of *E*-**3-9** in Deuteriochloroform [a,b]

Compound Position	**3**	**3** [c]	**4**	**5**	**6**	**7**	**7** [c]	**8**	**9**	**9** [c]
1	120.0	119.5	118.2	120.1	120.1	120.2	119.6	120.2	120.2	119.5
2	117.7	117.4	117.9	117.7	117.8	117.8	117.4	117.9	117.4	117.3
3	138.4	138.6	138.6	138.4	138.5	137.4	137.1	143.2	137.9	138.8
4	143.9	143.7	143.8	143.8	143.8	143.9	143.7	143.9	143.6	143.8
5	90.0	88.6	89.9	90.0	89.9	89.9	88.5	89.9	89.7	88.5
6	198.6	196.9	199.2	198.5	198.7	198.0	197.0	198.6	196.6	195.6
7	130.3	130.3	130.2	131.4	131.3	134.6	134.5	136.3	130.4	131.8
8	33.7	34.1	33.6	33.7	33.7	33.8	34.1	33.6	33.8	32.7
9	61.6	60.8	61.8	61.6	61.7	61.6	60.7	61.7	61.3	60.5
10	22.9	22.5	23.0	22.9	22.9	22.8	22.5	22.9	22.9	22.6
11	124.5	124.1	124.3	124.5	124.4	123.4	123.4	124.2	123.3	124.1
12	128.4	128.2	129.0	128.7	129.8	129.7	130.0	129.6	125.0	130.6
13	47.8	46.9	47.8	47.9	47.8	48.0	47.0	48.1	47.7	47.0
14	70.3	69.5	70.4	70.3	70.3	70.3	69.6	70.4	69.9	68.9
15	31.7	31.6	31.5	31.7	31.7	31.8	31.4	31.7	32.3	31.8
16	43.4	42.9	43.1	43.4	43.4	43.4	43.0	43.3	43.3	42.9
N-CH_2	59.4	58.6	57.8	59.4	59.4	59.4	58.5	59.4	59.4	58.6
CH (cp)	9.3	9.0	-	9.3	9.4	9.3	9.0	9.3	9.4	9.1
(CH_2) (cp)	4.2	3.8	-	4.2	4.2	4.2	3.9	4.1	4.3	4.0
(CH_2) cp)	3.8	3.4	-	3.7	3.7	3.6	3.3	3.8	3.7	3.3
CH_2= (all)	-	-	127.8	-	-	-	-	-	-	-
CH= (all)	-	-	128.4	-	-	-	-	-	-	-
CH=	140.6	138.9	135.1	139.0	139.3	136.0	135.1	136.3	120.3	121.6
1'	135.2	134.7	140.5	133.6	131.1	-	-	-	-	-
2'	132.4	132.5	132.5	129.8	132.2 [d]	150.5	150.8	149.7	132.7	142.8
3'	128.9	128.5	130.2	133.0	115.6 [e]	131.2	130.6	124.0	-	-
4'	129.9	129.0	128.5	134.9	163.0 [f]	138.6	138.9	128.3	122.5	124.4
5'	128.9	128.5	130.2	133.0	115.6 [e]	124.4	124.0	124.0	120.4	130.0
6'	132.4	132.5	132.5	129.8	132.2 [d]	149.3	149.4	149.7	-	-
N-CH_3	-	-	-	-	-	-	-	-	33.4	31.9

[a] Chemical shifts (δ) are in ppm, downfield from tetramethylsilane. [b] Abbreviation "all" is for allyl; "cp" for cyclopropyl. [c] Recorded in DMSO-d_6. [d] Doublet, J_{C-F} = 8.3 Hz. [e] Doublet, J_{C-F} = 23.3 Hz. [f] Doublet, J_{C-F} = 243.5 Hz.

Table 4

^{13}C Chemical Shifts of *E*-3-9 Hydrochlorides in DMSO-d_6 [a]

Compound Position	3•HCl	3 [b]	4•HCl	5•HCl	6•HCl	7•2H Cl	7 [b]	8•2HCl	9•2HCl	9 [b]
1	120.3	121.1	120.3	120.2	120.2	120.5	120.5	120.3	120.4	120.5
2	118.2	119.1	118.2	118.2	118.2	118.4	118.4	118.2	118.4	118.3
3	139.6	140.4	139.6	139.2	139.4	139.8	139.7	139.7	139.7	139.6
4	143.8	144.6	143.8	143.8	143.8	143.9	143.9	143.7	143.8	143.8
5	87.3	88.3	87.3	87.3	87.3	87.4	87.3	87.1	87.2	87.0
6	195.6	196.5	195.6	195.7	195.5	196.2	196.0	196.5	195.3	195.2
7	130.2	130.9	129.5	132.4	133.0	134.6	133.7	135.0	139.5	139.4
8	33.8	34.5	33.8	33.7	33.7	33.5	33.5	33.5	34.5	34.3
9	60.1	61.1	60.4	60.0	60.0	60.1	60.1	59.8	60.2	60.2
10	23.3	24.0	22.8	23.3	23.3	23.4	23.4	23.3	23.5	23.3
11	121.3	122.0	121.3	121.3	121.3	121.4	121.4	121.1	120.4	120.9
12	128.3	129.0	128.2	128.5	128.3	128.3	128.3	128	128.1	128.0
13	45.4	46.3	45.3	45.4	45.4	45.7	45.7	45.7	45.8	45.8
14	69.3	70.2	69.3	69.3	69.3	69.6	69.6	69.4	69.2	69.2
15	28.4	29.2	28.4	28.3	28.3	28.3	28.3	28.0	28.2	28.1
16	45.4	46.3	45.4	45.4	45.4	45.6	45.6	45.4	45.4	45.3
N-CH_2	56.9	57.9	55.1	56.8	56.8	57.0	56.9	56.8	56.9	56.9
CH(cp)	5.6	6.2	-	5.6	5.6	5.7	5.7	5.8	5.6	5.5
(CH_2)(cp)	5.2	5.8	-	5.2	5.2	5.4	5.3	5.2	5.2	5.0
(CH_2)(cp)	2.6	3.1	-	2.6	2.6	2.7	2.6	2.5	2.6	2.5
CH_2=(all)	-	-	124.9	-	-	-	-	-	-	-
CH=(all)	-	-	127.7	-	-	-	-	-	-	-
CH=	140.7	141.8	140.6	139.6	139.6	134.9	135.9	135.0	120.2	120.0
1'	134.4	135.2	134.3	134.0	130.1	-	-	-	-	-
2'	130.7	131.3	130.7	133.2	133.2 [c]	144.7	147.8	142.0	139.7	139.5
3'	128.6	129.2	128.6	131.0	115.6 [d]	133.2	131.9	127.2	-	-
4'	129.4	130.1	130.1	128.5	163.0 [e]	143.3	140.9	150.5	121.1	121.1
5'	128.6	129.2	128.6	131.0	115.6 [d]	126.2	124.9	127.2	125.1	125.1
6'	130.7	131.3	130.7	133.2	133.2 [c]	144.1	146.4	142.0	-	-
N-CH_3	-	-	-	-	-	-	-	-	34.5	34.5

[a] Chemical shifts (δ) in ppm, downfield from internal tetramethylsilane; abbreviation "all" is for allyl, "cp" is for cyclopropyl. [b] Free base was dissolved in DMSO-d_6 and one drop TFA-d was added. [c] Doublet, J_{C-F} = 8.3 Hz. [d] Doublet, J_{C-F} = 21.5 Hz. [e] Doublet, J_{C-F} = 248.8 Hz.

(E)-isomers. Steric assignments were made on the basis of extensive analyses of their ^1H and ^{13}C chemical shifts, ^1H-^{13}C correlation, as well as nOe experiments of the free bases and salts.

EXPERIMENTAL

All chemicals were purchased from either Aldrich Chemical Co. or Fisher Scientific and were used without further purification. Naloxone hydrochloride was obtained as a gift from GenDerm, Inc., 600 Knights Bridge Parkway, Lincolnshire, IL. Naltrexone hydrochloride was obtained through the kindness of Dr. P. Hillary, National Institute of Drug Abuse, NIH. Piperidine was distilled, bp 106-109° and was stored over 4 Å molecular sieves which had been dried at 120° before use. Aldehydes were either distilled just prior to use or dried azeotropically with benzene immediately before use. Distillation of solvents, *in vacuo,* implies flash evaporation at about 20-50° by means of a rotary evaporator at about 20-30 torr. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Thin layer chromatography (tlc) was performed on aluminum backed silica gel plates (Aldrich 60 F254) and compounds were detected either by uv light (254 nm) and/or iodine vapor. Flash chromatography was carried out on silica gel (Merck Kieselgel 60, 230 mesh).

The ^1H and ^{13}C nmr spectra were recorded on either a Varian XL-300 spectrometer (at 300 MHz and 75.4 MHz, respectively) or a Varian Unity 500 spectrometer (at 500 and 125 MHz, respectively). Attached proton tests (APT) were utilized when necessary. Regular or high resolution (hr) electron impact (ei) or chemical ionization (ci, methane) mass spectra were obtained at 70 eV on a Finnigan Mat 90 mass spectrometer. Ions with relative intensities less than 10% of the base peak are usually not reported. Infrared spectra (ir) spectra were obtained from a MIDAC FT-IR spectrophotometer. Ultraviolet (uv) spectra were recorded on a Beckman DU-7 spectrophotometer. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

Naltrexone from Its Hydrochloride.

A solution of naltrexone hydrochloride (1.0 g, mp 265°, lit [32] mp 274-276°) in water (20 ml) was neutralized with concentrated ammonium hydroxide to *p*H 8. The product was extracted with dichloromethane (3 x 10 ml). The extract was washed once with brine (10 ml) and dried (sodium sulfate). This solution was passed through a short silica gel column (160 mg silica gel, 60-270 mesh) and eluted with dichloromethane and ether (3:1, 12 ml). Evaporation of the solvent, *in vacuo*, yielded naltrexone

(834 mg, 98%), mp 169-170°, lit [32] mp 168-170°; tlc, R_f = 0.4 (ethyl acetate). For reactions conducted in benzene, it is best to pre-dry the base by azeotropic distillation with benzene.

(*E*)-7-Benzylidenenaltrexone (**3**).

A mixture of **1** (512 mg, 1.5 mmoles), piperidine (70 mg, 0.80 mmole) and benzaldehyde (260 mg, 2.45 mmoles) in benzene (21 ml) was refluxed using a Dean Stark trap and a condenser. The benzene layer in the Dean Stark trap was removed after 2 hours and was replaced with an equal volume of fresh benzene. After 4 hours, solvents were removed, *in vacuo*, to provide a yellow solid (0.9 g). The ^{13}C nmr spectrum of this product indicated that it consisted mainly of (*E*)-**3**, admixed with benzaldehyde, piperidine, a small amount of starting ketone (~5%), and an array of other impurities in minute amounts. All attempts to crystallize (*E*)-**3**, without chromatography failed. The impure product was dissolved in dichloromethane and the solution washed with saturated aqueous sodium bicarbonate solution, the organic layer dried (sodium sulfate), filtered and evaporated, *in vacuo*.

Chromatography on silica gel followed the solvent pattern applicable to related experiments. The first eluates with dichloromethane contained benzaldehyde [tlc, R_f = 0.85 (dichloromethane-ether, 3:1)]. The *arylidene ketone* was eluted either with dichloromethane and dichloromethane-methanol (99:1). Once relatively pure, the product (56%, overall yield) was recrystallized from either benzene-hexane, or ethyl acetate-hexane, mp, softening with partial decomposition 155° and complete meniscus about 172°, lit [21] mp 230° dec; tlc, R_f = 0.41 (chloroform-methanol, 47:3); R_f = 0.28 (dichloromethane-ether, 3:1); lit [21] R_f = 0.60 (chloroform-methanol-acetone, 19:0.5:0.1); ir (potassium bromide): ν 1682 (C=O), 1587 (C=C) cm^{-1}; lit [21] ir (liquid film): 1685, 1611 cm^{-1}; ms: (ei) m/z 429 (M^+, 100), 428 (6), 388 (13), 256 (31), 243 (10), 139 (35), 115 (13); hrms: (ei) Calcd. for $C_{27}H_{27}NO_4$: 429.1940; Found: 429.1936.

Anal. Calcd. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34, N, 3.26. Found: C, 75.60; H, 6.29; N, 3.23.

When attempts were made to form the enamine of **1** with piperidine, independently, by the method of Birkofer [24], followed by a reaction with benzaldehyde [24], the yield of (*E*)-**3** was much poorer. A solution of **1** (200 mg, 0.58 mmole) and piperidine (0.3 ml, 3.0 mmoles) in dry benzene (30 ml) was refluxed 12 hours using a Dean-Stark trap filled with 4 Å molecular sieves to trap water. Solvents were evaporated to dryness, *in vacuo*. To the residue was added an azeotropically dried solution of benzaldehyde (0.3 ml, 4.0 mmoles) in benzene (30 ml) and the resulting mixture was refluxed again (12 hours) using a Dean-Stark trap. Solvents were removed, *in vacuo*, and the gummy residue was purified by column chromatography on silica gel (10 g). After elution of benzaldehyde (dichloromethane), a mixture of three by-products (34 mg), using dichloromethane-ether (6:1), tlc, R_f = 0.40, 0.54, 0.70 (dichloromethane-ether, 3:1). Further elution with dichloromethane-ether (5:1, then 3:1) gave crude (*E*)-**3** (230 mg) which was rechromatographed on a new silica gel column (10 g) to obtain pure (*E*)-**3**. Repetition of the Claisen-Schmidt reaction of **1** with benzaldehyde according to the literature methods [21,23] using sodium hydroxide in methanol, provided (*E*)-**3** after several chromatographic separations.

(*E*)-7-Benzylidenenaltrexone (**3**) Hydrochloride.

Anhydrous hydrogen chloride was introduced into a solution of (*E*)-**3** (70 mg, 0.15 mmole) in ethyl acetate (1 ml) to furnish a yellow precipitate 70 mg (92%). The *salt* was recrystallized from concentrated hydrochloric acid, or ethanol, mp 225°, dec, lit [21] mp 210° dec, lit [23] mp 225° dec; tlc, lit [21] R_f = 0.72 (butanol-acetone-water, 2:1:1); lit [23] R_f = 0.72 (chloroform-methanol-ammonium hydroxide, 9.8:0.2:3 drops); tlc, (alleged) (*Z*)-**3** had lit [23] R_f = 0.74 (chloroform-methanol-ammonium hydroxide, 98:2:1); lit [23] ir (potassium bromide): 1680 (C=O), 1614 (C=C) cm^{-1}, while alleged (*Z*)-**3** hydrochloride, lit [23] ir was 1690 (C=O), 1620 (C=C) cm^{-1}; uv (methanol): λ_{max} 225 nm (ε 12000).

(*E*)-7-Benzylidenenaloxone (**4**) Hydrochloride.

The condensation of **2** with benzaldehyde was carried out according to the general literature procedure [21], using a large excess of benzaldehyde. To a stirred solution of naloxone hydrochloride (150 mg, 0.41 mmole) in methanol (7 ml) at 4° was added dropwise 1 *N* sodium hydroxide (3 ml) and then, benzaldehyde (0.40 ml, 3.9 mmoles). The mixture was kept in a refrigerator at 4° for 14 hrs. The stirred mixture was neutralized by dropwise addition of 1 *N* hydrochloric acid until the *p*H was 8. Solvents were evaporated at 0°, *in vacuo*, to about half the initial volume and the residue was extracted with dichloromethane (3 x 7 ml). The combined dichloromethane extracts were washed with brine (5 ml) and dried (sodium sulfate). After evaporation of solvent, *in vacuo*, the brown residue was purified by flash column chromatography on a silica gel column. Elution with dichloromethane-ether (7:1) afforded a mixture of by-products, one of which was subsequently identified as (*E*)-**4**. Continued elution with the same solvent gave crude **4** as a yellow gum, followed by starting **2**. Rechromatography of impure fractions containing **4** provided pure **4** (20-40%, taking into account recovered naloxone), mp 188°; tlc, R_f = 0.40 (dichloromethane-ether, 3:1); ir (potassium bromide): ν 1695 (C=O), 1591 cm^{-1} (conjugate C=C); ms: (ei) m/z 415 (M^+, 100), 242 (31), 121 (18); hrms: (ei) Calcd. for $C_{26}H_{25}NO_4$: 415.1783; Found: 415.1782.

The hydrochloride was prepared, as usual, mp 230°, dec, uv (methanol): λ_{max} 224 nm (ε 13200). The salt tended to retain water of crystallization, even after extensive drying.

Anal. Calcd. for $C_{26}H_{25}NO_4 \cdot HCl \cdot 1.2H_2O$: C, 65.94; H, 6.04; N, 2.96. Found: C, 65.92; H, 5.77; N, 3.07. Calcd. for $C_{26}H_{25}NO_4 \cdot HCl \cdot 1.6H_2O$: C, 64.95; H, 6.12. Found: C, 65.04; H, 5.76.

(*E*)-7-(4-Chlorobenzylidene)naltrexone (**5**).

Starting from **1** (200 mg, 0.58 mmole), (*E*)-**5** was prepared in 45% yield, after extensive flash column chromatography on silica gel. Elution by hexane-ether (3:1 to 1:1), followed by recrystallization from benzene-hexane provided yellow prisms, mp 126-128°; tlc, R_f = 0.48, (dichloromethane-ether: 3:1); ms: (ci) m/z 464 (M^+); ms: (ei) m/z 463 (M^+, 100), 422 (21), 302 (11), 274 (11), 257 (12), 256 (56), 243 (18), 202 (10), 115 (13); ms: (ci) m/z 464 (M^+).

Anal. Calcd. for $C_{27}H_{26}ClNO_4$: C, 69.90 H, 5.65 N, 3.02. Found C, 69.80; H, 5.48; N, 3.03.

The *hydrochloride* was made in 70% yield after crystallization from concentrated hydrochloric acid, yellow needles, mp 237-240° dec, uv (methanol): λ_{max} 226 nm (ε 13300).

(*E*)-7-(4-Fluorobenzylidene)naltrexone (**6**) Hydrochloride.

The piperidine-catalyzed condensation of **1** (200 mg, 0.58 mmole) with 4-fluorobenzaldehyde in benzene under azeotropic conditions yielded, after extensive chromatography on silica gel (*E*)-**6** in 42% as a gum, which solidified mp 109-110°; tlc, R_f = 0.43 (dichloromethane-ether, 3:1); ms: (ei) m/z 447 (M^+, 100), 406 (13),

258 (12), 257 (11), 256 (50), 243 (15), 171 (11), 167 (20), 149 (53), 133 (35).

The *hydrochloride* was obtained as usual and was recrystallized from concentrated hydrochloric acid, pale yellow needles, mp 227-230° dec, uv (methanol): λ_{max} 226.5 nm (ε 13600).

Anal. Calcd. for $C_{27}H_{26}FNO_4 \cdot HCl \cdot 1.8H_2O$: C, 62.80; H, 5.97; N, 2.71. Found: C, 62.80; H, 5.31; N, 2.66.

(*E*)-7-[(3-Pyridyl)methylene]naltrexone (**7**).

A mixture of **1** (512 mg, 1.5 mmoles), piperidine (60 mg, 0.71 mmole) and 3-pyridinecarboxaldehyde (245 mg, 2.25 mmoles) in benzene (21 ml) was refluxed in a 50 ml round bottom flask equipped with a Dean Stark trap and a condenser in an oil bath maintained between 110-120°. The first ~4 ml benzene distilled into the separator trap and were discarded. The trap was allowed to fill up with benzene (~11 ml) leaving only about 6 ml benzene in the flask. The reaction mixture was refluxed further for 1.5 hours and allowed to cool to room temperature. Tlc indicated the presence of **7**, [tlc, R_f = 0.32, compared to 0.45 for **1** (dichloromethane-methanol, 47:3)]. After 2 hours, yellow needles crystallized. These were filtered, washed with benzene (~5 ml), dried in air to provide **7** (630 mg, 94%), mp 191-192°, recrystallized from benzene and ethyl acetate (5:1), mp 202-206°; ms: (ei) m/z 430 (M^+, 100), 389 (12), 341 (18), 256 (39), 243 (12), 118 (10); hrms: (ei) Calcd. for $C_{26}H_{26}N_2O_4$: 430.1893; Found: 430.1886. For elemental analysis, a sample was dried at 110° *in vacuo*, for 20 minutes.

Anal. Calcd. for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.62; H, 6.04; N, 6.38.

(*E*)-7-[(3-Pyridyl)methylene]naltrexone (**7**) Dihydrochloride.

This yellow *salt* was formed as usual, mp 230° dec, uv (methanol): λ_{max} 286.5 nm (ε 13400).

Anal. Calcd. for $C_{26}H_{26}N_2O_4 \cdot 2HCl$: $0.8H_2O$: C, 60.31; H, 5.76; N, 5.41. Found: C, 60.29; H, 5.75; N, 5.16.

(*E*)-7-[(4-Pyridyl)methylene]naltrexone (**8**).

In a cognate experiment, **1** (467 mg, 1.37 mmoles) and piperidine (43 mg, 0.50 mmole) and 4-pyridinecarboxaldehyde (245 mg, 2.35 mmoles) were condensed in benzene (21 ml) for 6 hours, as described for the synthesis of **7**. After 6 hours it was deemed to be complete (tlc). Upon cooling at room temperature for 18 hours, yellow crystals (260 mg of **8**) were filtered mp 129-130° (pure by ^{1}H-nmr). The solid which separated was filtered, washed with benzene (~5 ml) and dried in to give yellow crystals, The mother liquor was concentrated and diluted with hexanes (10 ml). Solvents were decanted and the residue was triturated with benzene (5 ml) when another crop of **8** (100 mg) precipitated, mp 128-129°, (total 360 mg, 60%). Slow crystallization from benzene raised the mp to 133° dec; tlc, R_f = 0.28 (dichloromethane-ether, 3:1); R_f = 0.28 (dichloromethane-methanol, 47:3); ms: (ei) m/z 430 (M^+, 100), 389 (22), 375 (13), 256 (40), 243 (10), 118 (14), 117 (11); ms: (ci) m/z 431 $(M+1)^+$.

Anal. Calcd. for $C_{26}H_{26}N_2O_4 \cdot C_6H_6$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.61; H, 6.19; N, 5.59.

(*E*)-7-[(4-Pyridyl)methylene]naltrexone (**8**) Dihydrochloride.

This *salt* was formed as usual, mp 232° dec.

Anal. Calcd. for $C_{26}H_{26}N_2O_4 \cdot 2HCl \cdot H_2O$: C, 59.89; H, 5.80; N, 5.37. Found: C, 59.50; H, 5.48; N, 5.18.

(*E*)-7-[(1-Methyl-2-imidazolyl)methylene]naltrexone (**9**).

Condensation of **1** (200 mg, 0.58 mmole) with 1-methyl-2-imidazolecarboxyaldehyde [33] (363 mg, 3.3 mmoles) in benzene and piperidine as the catalyst, the product was worked up as usual and chromatographed on silica gel. There was obtained **9** (57%), mp 248° dec; ms: (ei) m/z 433 (M^+, 100), 338 (14), 336 (21), 335 (55), 321 (10), 320 (12), 319 (23), 318 (10), 263 (35), 256 (13), 243 (13), 191 (12), 150 (10), 149 (92), 133 (18), 122 (12), 121 (37), 120 (15), 119 (13), 107 (11), 105 (11); ms: (ci) m/z 434 $(M+1)^+$.

Anal. Calcd. for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.18; H, 6.27; N, 9.74.

(*E*)-7-[(1-Methyl-2-imidazolyl)methylene]naltrexone (**9**) Dihydrochloride.

This dihydrochloride was formed in the usual manner, mp 230°, (charring indicated); uv (methanol): λ_{max} 208.5 nm (ε 29500).

Anal. Calcd. for $C_{25}H_{27}N_3O_4 \cdot 2HCl \cdot 0.6H_2O$: C, 58.05; H, 5.89; N, 8.12. Found: C, 57.94; H, 5.96; N, 7.89.

Acknowledgments.

Funding of this workby the National Institue of Drug Abuse, NIH through Research Grant 5 RO1-DA108867 is gratefully acknowledged.

REFERENCES AND NOTES

[1] D. M. Zimmerman and J. D. Leander, *J. Med. Chem.*, **33**, 895 (1990).

[2] P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).

[3] C. M. Bertha, J. L. Flippen-Anderson, R. B. Rothman, F. Porreca, P. Davis, H. Xu, K. Becketts, X.-Y Cha and K. C. Rice, *J. Med. Chem.*, **38**, 1523 (1995).

[4] T. D. Nelson, R. D. Davis and W. L. Nelson, *J. Med. Chem.*, **37**, 4270 (1994).

[5] P. S. Portoghese, *J. Med. Chem.*, **34**, 1757 (1991).

[6] P. S. Portoghese, *J. Med. Chem.*, **35**, 1927 (1992).

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

[8] G. A. Koolpe, W. L. Nelson, T. L. Gioannini, L. Angel, N. Appelmans, and E. J. Simon, *J. Med Chem.*, **28**, 949 (1985).

[9] H. Nagase, A. Abe and P. S. Portoghese, *J. Org. Chem.*, **54**, 4120 (1989).

[10] P. S. Portoghese, H. Nagase, K. E. Maloney-Huss, C.-E. Lin and A. E. Takemori, *J. Med. Chem.*, **34**, 1715 (1991).

[11] P. Klein and W. L. Nelson, *J. Med. Chem.*, **35**, 4589 (1992).

[12] P. S. Portoghese, S. T. Moe and A. E. Takemori, *J. Med. Chem.*, **36**, 2572 (1993).

[13] R. D. Davis , T. D. Nelson and W. L. Nelson, *J. Heterocyclic Chem.*, **31**, 1509 (1994).

[14] P. S. Portoghese, A. Garzon-Aburbeh and D. L. Larson, *J. Med. Chem.*, **34**, 1966, (1991).

[15] P. S. Portoghese, F. Farouz-Grant, M. Sultana, and A. E. Takemori, *J. Med. Chem.*, **38**, 402 (1995).

[16] V. L. Korlipara, A. E. Takemori and P. S. Portoghese, *J. Med. Chem.*, **38**, 1337 (1995).

[17] P. Gao and P. S. Portoghese, *J. Org. Chem.*, **60**, 2276 (1995).

[18] J. O. Polazzi, *J. Org. Chem.*, **46**, 4262 (1981).

[19] K. Görlitzer, and E. Meyer, *Arch. Pharm.*, **326**, 181 (1993).

[20] K. Görlitzer and M. Noack, *Arch. Pharm.*, **319**, 406 (1986).

[21] P. S. Portoghese, A. Garzon-Aburbeh, H. Nagase, C.-E. Lin and A. E.Takemori, *J. Med. Chem.*, **34**, 1292 (1991).

[22] P. S. Portoghese, M. Sultana, H. Nagase and A. E. Takemori, *Eur. J. Pharmacol.*, **218,** 195 (1992).

[23] P. S. Portoghese, M. Sultana, S. T. Moe and A. E. Takemori, *J. Med. Chem.*, **37**, 579 (1994).

[24] L. Birkofer, S. M. Kim and H. D. Engels, *Chem. Ber.*, **95**, 1495 (1962).

[25] H. Bayer, C. Batzl, R. W. Hartmann and A. Mannschreck, *J. Med. Chem.*, **34**, 2685 (1991).

[26] R. W. Hartmann, H. Bayer and G. Grün, *J. Med. Chem.*, **37**, 1275 (1994).

[27] R. W. Hartmann, H. Bayer, G. Grün, T. Sergejew, U. Bartz and M. Mitrenga, *J. Med. Chem.*, **38**, 2103 (1995).

[28] L. Kozerski, R. Kawecki, P. Krajewski, P. Gluzinski, K. Pupek, P. E. Hansen, M. P. Williamson, *J. Org. Chem.*, **60**, 3533 (1995).

[29] F. I. Carroll, C. G. Moreland, G. A. Brine and J. A. Kepler, *J. Org. Chem.* **41**, 996 (1976).

[30] G. A. Brine, D. Prakash, C. K. Hart, D. J. Kotchmar, C. G. Moreland and F. I. Carroll, *J. Org. Chem.* **41**, 3445 (1976).

[31] G. W. Caldwell, A. D. Gauthier, J. E. Mills and M. N. Greco, *Magn. Reson. Chem.*, **31**, 309 (1993).

[32] H. Blumberg, I. J. Pachter, and Z. Matossian, U.S. Patent 3,332,950, July 25, 1967; *Chem. Abstr.*, **67**, 100301a (1967).

[33] We thank Dr. J.-W. Kim for this aldehyde; it was made by the method of D. A. Goff, G. A. Koolpe, A. B. Kelson, H. M. Vu, D. L. Taylor, C. D. Bedford, H. A. Musallam, I. Koplovitz and R. N. Harris III, *J. Med. Chem.*, **34**, 1363 (1991).