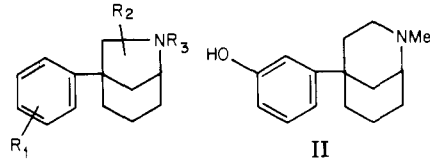
Azabicycloalkanes as Analgetics. 3.[1] Structure–Activity Relationships of 1-Phenyl-6-azabicyclo[3.2.1]octanes and Absolute Stereochemistry of (+)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo[3.2.1]octane and Its 7-*endo*-Methyl Derivative

Mikio Takeda,* Hirozumi Inoue, Katsuyuki Noguchi, Yasushi Honma, Masatoshi Kawamori, Goro Tsukamoto, Yasuhiko Yamawaki, Seiichi Saito, Keiichi Aoe, Tadamasa Date, Seiichi Nurimoto, and Goro Hayashi

Research Laboratories, Tanabe Seiyaku Co. Ltd., Toda, Saitama, Japan. *Received April 26, 1976*

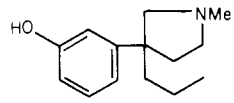
A series of 53 1-phenyl-6-azabicyclo[3.2.1]octanes (I) has been tested for their analgetic and narcotic antagonist activities. Structure–activity relationships were investigated by varying the structural parameters. The most interesting compound in this series, the 1-(3-hydroxyphenyl)-6,7-dimethyl derivative 8, shows the profile of a well-balanced antagonist–analgetic agent with a very mild physical dependence capacity. The absolute stereochemistry of its active enantiomer [(+)-8] was established by the x-ray study and the chemical transformation to the phenylmorphan [(+)-II]. (+)-8 was stereochemically correlated also with the active enantiomer of the 7-demethyl derivative [(+)-7] by chemical transformation and CD measurement. Certain structural and stereochemical correlations between these compounds (7 and 8) and other known antagonist–analgetics are discussed.

As part of our study[2] on the steric aspects of the mixed antagonist–agonist properties of phenylazabicycloalkane analgetics, the synthesis of 1-phenyl-6-azabicyclo[3.2.1]-octanes (I) has been reported previously.[1,2] Structure I can be regarded not only as a five-membered analogue of 5-(3-hydroxyphenyl)-2-methylmorphan (II)[3,4] but also as a "bridged" version of profadol (III)[5] and the hexamethylenimine (IV).[6] These *N*-methyl compounds have been reported to display mixed antagonist–analgetic properties with a low grade of physical dependence capacity in monkey.[7,8]

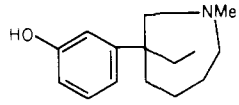


I

II

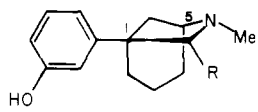


III

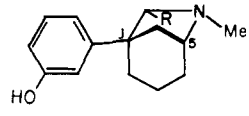


IV

The present paper concerns the structure–activity relationships of a number of the derivatives (I) and the absolute stereochemistry of (+)-1-(3-hydroxyphenyl)-6,-7-dimethyl-6-azabicyclo[3.2.1]octane [(+)-8], the active enantiomer of the most interesting compound of this series, and its 7-demethyl relative (+)-7.



(+)-**8** (1*R*), R = Me
(+)-**7** (1*R*), R = H



(−)-**8** (1*S*), R = Me
(−)-**7** (1*S*), R = H

Structure–Activity Relationships. Analgetic activities were determined in mice by measuring the inhibition of the AcOH-induced writhing response[9] and by the hot-plate method.[10] These results and acute (24 h) toxicities of I are listed in Table I. Some selected compounds were tested for their narcotic antagonist activities by measuring the inhibition of morphine-induced respiratory depression in rabbits[9] (Table II). Also included in Table II are physical dependence capacities and antagonist potencies of I obtained from the Rhesus monkey.[11]

With regard to the analgetic activity, the following structure–activity relationships can be deduced from Table I.

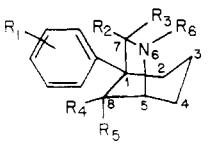
(1) Introduction of OH function into the meta position to the quaternary carbon attachment enhances the activity. The substitution at no other position does this (**17** and **18**) and further substitution of OH function in the para or meta position eliminates the activity (**19**, **20**, and **21**). Methyl etherification of *m*-phenols results in a marked increase in toxicity though activities comparable to the original phenols are retained (**10** and **11**). The various esters of *m*-phenols (**22–27**) also exhibit a considerable degree of the activity.

(2) Changes in the alkyl substituent on the nitrogen (**8** and **44–48**) give an effect analogous to that reported in other classes of analgetics.[12-14] Thus, a change from methyl to ethyl, propyl, and butyl (**44–46**) nearly abolishes the analgetic activity seen in **8**. The activity is restored in the *N*-amyl (**47**) and hexyl (**48**) homologues which are nearly three and 17 times stronger than **8**, respectively, but are more toxic. Contrary to results usually obtained with strong analgetics, *N*-phenethyl substitution (**38**) diminishes the activity. Similar observation has been reported in the phenylmorphan derivatives II.[15,16] Surprisingly, when a methyl group is located on C_7, N-phenethylation causes a marked increase in the activity (**8** vs. **53**). The rather uniform activities seen in the butyrophenone derivatives (**32** and **41–43**) may be associated with their haloperidol-like CNS depressant activities.[17] With one exception (**50**), the substitution of an allyl and related groups on the nitrogen generally results in a marked fall in the agonist activity. The secondary amines **3–6** were found to be inactive.

(3) Introduction of a methyl substituent at C_7 confers an increased activity on the original compound. This tendency is apparent not only in the *N*-methyl derivatives (**7** vs. **8**) but also in the compounds with the larger substituent on the nitrogen (**33** vs. **48**, **34** vs. **50**, and **38** vs. **53**). In one example (**8** and **9**), both the 7-*endo*- and -*exo*-methyl substitutions are equally effective in the enhancement. The 7-*endo*-ethyl substitution (**12**) gives somewhat lower activity and greater toxicity than the 7-methyl derivative **8**. On the other hand, methyl substitution in neither the 8-endo nor 8-exo position (**13** and **15**) gives activity. Further substitution of methyl on C_8 of the 7-methyl derivatives also leads to a disappearance of the activity (**14** and **16**).

(4) It can be seen from the three examples of resolution of optical isomers (**7**, **8**, and **22**) that the dextro isomers

Table I. Analgetic Activity of 1-Phenyl-6-azabicyclo[3.2.1]octanes



Compd[a]	R_1	R_2	R_3	R_4	R_5	R_6	Analgetic act.,[b] ED_{50}, mg/kg		Acute toxicity,[b] LD_{50}, mg/kg
							Writhing[c]	Hot-plate[f]	
1[d,e]	H	H	H	H	H	Me	22.8 (18.4-28.4)[r]		>30
2[d,e]	H	H	Me	H	H	Me	20.0 (16.7-24.0)	~20[o]	>30
3[e,g]	3-OMe	H	H	H	H	H	*h*		>100
4[i,j]	3-OMe	H	Me	H	H	H	*h*		>100
5[e,i]	3-OH	H	H	H	H	H	*h*		>100
6[i,j]	3-OH	H	Me	H	H	H	*h*		>100
7[e,k]	3-OH	H	H	H	H	Me	12.3 (8.2-18.6)	14.3 (11.3-18.2)[t]	132.7 (112.8-156.1)
(+)-7[e,k]	3-OH	H	H	H	H	Me	3.7 (1.6-8.3)	3.6 (2.9-4.6)[u]	90.7 (72.3-114.4)
(−)-7[e,k]	3-OH	H	H	H	H	Me	*h*	~20[p]	155.6 (92.4-262.2)
8[e,i]	3-OH	H	Me	H	H	Me	4.5 (3.4-6.0)	8.0 (6.2-10.2)[v]	112.9 (87.3-145.8)
(+)-8[e,i]	3-OH	H	Me	H	H	Me	1.2 (0.8-1.2)	2.9 (2.2-3.6)[w]	123.1 (97.8-154.8)
(−)-8[e,i]	3-OH	H	Me	H	H	Me	*h*	*q*	82.7 (—)
9[i,j]	3-OH	Me	H	H	H	Me	4.9 (3.6-6.5)		113.5 (96.5-133.5)
10[e,i]	3-OMe	H	H	H	H	Me	8.6 (6.2-11.9)		31.2 (24.2-40.3)
11[e,i]	3-OMe	H	Me	H	H	Me	6.1 (4.1-9.2)		25.9 (22.0-30.5)
12[e,i]	3-OH	H	Et	H	H	Me	8.8 (5.1-15.2)		59.8 (46.2-77.2)
13[j,k]	3-OH	H	H	Me	H	Me	*l*		>30
14[i,j]	3-OH	(H, Me)[s]		Me	H	Me	*l*		>30
15[j,k]	3-OH	H	H	H	Me	Me	*l*		>30
16[i,j]	3-OH	H	Me	H	Me	Me	*l*		>30
17[i,j]	2-OH	H	Me	H	H	Me	*h*		>100
18[i,j]	4-OH	H	Me	H	H	Me	*h*		>100
19[i,j]	3,4-$(OH)_2$	H	Me	H	H	Me	*l*		>10
20[j,k]	3,5-$(OH)_2$	H	H	H	H	Me	*h*		>225
21[i,j]	3,5-$(OH)_2$	H	Me	H	H	Me	*h*		>100
22[d,e]	3-OAc	H	Me	H	H	Me	2.9 (2.0-4.3)	3.5 (2.8-4.5)	123.1 (97.9-154.8)
(+)-22[d,e]	3-OAc	H	Me	H	H	Me	2.4 (1.6-3.5)	3.6 (2.8-4.6)	129.5 (114.1-147.0)
(−)-22[d,e]	3-OAc	H	Me	H	H	Me	*h*	*q*	113.5 (96.5-133.5)
23[e,i]	3-OAc	H	Et	H	H	Me	10.1 (7.1-14.4)	9.9 (6.6-14.9)	55.1 (—)
24[e,i]	3-OCOEt	H	Me	H	H	Me	2.3 (1.8-3.0)	9.9 (6.8-14.5)	113.5 (96.5-133.5)
25[e,i]	3-OCOAm	H	Me	H	H	Me	12.3 (5.5-27.7)		156.2 (128.1-190.5)
26[d,e]	3-OCOPh	H	Me	H	H	Me	5.7 (4.2-7.9)		156.2 (128.1-190.5)
27[d,e]	3-Nicotinoyloxy	H	Me	H	H	Me	5.5 (4.3-7.1)		183.7 (—)
28[e,g]	H	H	H	H	H	CH_2-c-C_3H_5	*h*		>30
29[e,g]	H	H	H	H	H	$CH_2CH{=}CH_2$	*h*		>100
30[e,g]	H	H	H	H	H	$(CH_2)_2Ph$	*h*		>100
31[d,e]	H	H	H	H	H	$(CH_2)_2COPh$	*h*		>100
32[e,i]	H	H	H	H	H	$(CH_2)_3COPh$-*p*-F	4.1 (3.5-4.9)[m]		>200
33[d,e]	3-OH	H	H	H	H	$(CH_2)_5CH_3$	17.5 (10.9-27.0)		>100
34[d,e]	3-OH	H	H	H	H	CH_2-c-C_3H_5	~30		>100
35[d,e]	3-OH	H	H	H	H	CH_2-c-C_4H_7	*l*		>30
36[d,e]	3-OH	H	H	H	H	$CH_2CH{=}CH_2$	*h*		>100
37[e,g]	3-OH	H	H	H	H	$CH_2C{\equiv}CH$	*h*		>100
38[e,g]	3-OH	H	H	H	H	$(CH_2)_2Ph$	*h*		>100
39[d,e]	3-OH	H	H	H	H	$CH_2CH{=}CHPh$	*h*		>100
40[d,e]	3-OH	H	H	H	H	$(CH_2)_2COPh$	10.1 (7.1-14.4)		183.7 (148.3-227.6)
41[d,e]	3-OH	H	H	H	H	$(CH_2)_3COPh$	5.2 (3.1-8.5)[m]		>100
42[d,e]	3-OH	H	H	H	H	$(CH_2)_3COPh$-*p*-F	2.0 (1.4-2.6)[m]		>100
43[d,e]	3-OMe	H	H	H	H	$(CH_2)_3COPh$-*p*-F	3.0 (2.4-3.7)[m]	4.2 (3.4-5.2)	>225
44[d,j]	3-OH	H	Me	H	H	C_2H_5	*h*		>30
45[d,j]	3-OH	H	Me	H	H	C_3H_7	*h*		>30
46[d,j]	3-OH	H	Me	H	H	C_4H_9	*l*		>30
47[d,j]	3-OH	H	Me	H	H	C_5H_{11}	1.5 (1.1-1.9)		36.7 (—)
48[d,j]	3-OH	H	Me	H	H	C_6H_{13}	0.27 (0.22-0.34)		25.4 (21.6-29.9)
49[d,j]	3-OH	H	Me	H	H	$CH_2CH{=}CH_2$	~22.5		>30
50[d,j]	3-OH	H	Me	H	H	CH_2-c-C_3H_5	2.2 (1.8-2.8)	5.8 (3.4-9.6)	59.8 (46.2-77.2)
51[i,j]	3-OH	H	Me	H	H	$CH_2CH{=}CMe_2$	~15		>30
52[d,j]	3-OH	H	Me	H	H	$CH_2C{\equiv}CH$	~22.5		>100
53[d,j]	3-OH	H	Me	H	H	$(CH_2)_2Ph$	0.61 (0.41-0.90)	0.3 (0.2-0.4)	27.6 (—)
Morphine[d]							0.8 (0.6-1.1)	1.2 (0.9-1.3)	407.0 (351.2-461.5)
Codeine[n]							9.5 (7.4-12.1)	7.5 (6.8-8.3)	231.2 (203.5-279.2)
Meperidine[d]							4.5 (2.6-7.8)	4.7 (4.2-5.4)	273.0 (221.0-331.0)
Pentazocine[d]							4.5 (3.2-6.4)	12.3 (9.3-16.3)	190.1 (148.1-244.0)

Footnotes to Table I

[a] Although the stereoformula given in the above column represents one of the two enantiomers for convenience, the compounds were tested as the racemates unless otherwise specified. [b] Tested sc in mice. [c] Determined by the AcOH-induced writhing method. For methodology, see ref 9. [d] Hydrochloride. [e] See ref 2. [f] See ref 10. [g] Oxalate. [h] No effect with doses up to 22.5 mg/kg. [i] Hydrobromide. [j] See ref 1. [k] Administered as free base in dilute HCl. [l] No effect with doses up to 10 mg/kg. [m] With marked CNS depression. [n] Phosphate. [o] 7/10 at 20 mg/kg, a toxic dose. [p] Poor dose-response effect. [q] Inactive up to 100 mg/kg. [r] Confidence interval (95%). [s] The stereochemistry at C_7 was not ascertained. [t] With the onset (4.1), peak (42.3), and duration (137 min) of the action. [u] With the onset (3.8), peak (33.6), and duration (140 min). [v] With the onset (3.6), peak (32.2), and duration (127 min). [w] With the onset (3.8), peak (26.8), and duration (148.6 min).

Table II. Narcotic Antagonist Activity and Physical Dependence Capacity of 1-Phenyl-6-azabicyclo[3.2.1]octanes

Compd	Antagonist activity: Rabbit, AD_{50}, mg/kg[a]	Antagonist activity: Monkey[b]	P.D.C.[c]
2		NT[n]	No (to 10 mg/kg)
7	3.1	No (to 8 mg/kg)[d]	No (to 8 mg/kg)
(+)-**7**	4.1	Yes (3-12 mg/kg)[e]	No (to 6 mg/kg)
(−)-**7**	41% at 5 mg/kg	Yes (5-20 mg/kg)[e]	No (to 10 mg/kg)
8	2.6	Yes (2-8 mg/kg)[g]	No (at 1 mg/kg)
(+)-**8**	42% at 5 mg/kg	Yes (1.5-12 mg/kg)[h]	No (at 1.5 mg/kg)
(−)-**8**	48% at 5 mg/kg	Yes (2.5-20 mg/kg)[g]	No (at 5 mg/kg)
13	1.1		
15	0.18		
22		NT[n]	No (to 8 mg/kg)
(+)-**22**		Yes (1-8 mg/kg)[f,g]	No (at 1 mg/kg)
(−)-**22**		Yes (5-20 mg/kg)[g,m]	No (at 5 mg/kg)
28	41% at 5 mg/kg		
29	2.2		
34	1.8		
35	3.5		
36	1.7		
37	1.6		
39	0.96		
43		No (at 2 mg/kg)[i]	No (up to 16 mg/kg)[i]
45	0.03		
47	*j*		
48	*k*		
49	0.17		
50	0.10	NT[n]	No (up to 8 mg/kg)
51	0.086		
52	0.19		
53	*k*	NT[n]	No (up to 6 mg/kg)
Naloxone[l]	0.0044	Yes	
Levallorphan[l]	0.014	Yes	
Nalorphine[l]	0.16	Yes	
Pentazocine[l]	1.5	Yes	

[a] Antagonism of morphine-induced respiratory depression. Tested iv in rabbits. For methodology, see ref 9. [b] Precipitation of abstinence syndrome in nonwithdrawn morphine-dependent monkeys. See ref 11. [c] Suppression of abstinence syndrome in morphine-dependent monkeys. See ref 11. [d] Slight inconclusive increase in severity of abstinence signs at 4 mg/kg was observed in the withdrawn monkey. [e] Causes mild to moderate abstinence. [f] Approximately $^1/_{40}$th as potent as nalorphine. [g] Of mild to severe abstinence. [h] Of moderate to severe abstinence. [i] Causes marked CNS depression. [j] No effect with doses up to 5 mg/kg. [k] No effect with doses up to 1 mg/kg. [l] Hydrochloride. [m] Approximately $^1/_{100}$th as potent as nalorphine. [n] Not tested.

contain all of the analgetic activities of these racemates.

Thus, as a consequence of variations in factors 1–4, good analgetic activities ranging from the codeine level to the morphine level can be obtained in these compounds.

Although there is a slight quantitative discrepancy between the antagonist activities obtained from rabbit and monkey (Table II), the *N*-methyl derivatives **7** and **8** exhibit nalorphine-like (although much less potent) properties of narcotic antagonism. Accordingly, they possess mixed properties of agonist and antagonist (partial agonist), possibly related to their structural similarity to II, III, and IV. The 6,7-dimethyl derivative **8** is more potent than **7** and about half as strong as pentazocine in the both tests. Contrary to the previous finding that the introduction of a methyl group on C_8 destroys the agonist activity, both of the 6,8-dimethyl compounds **13** and **15** are found to be potent antagonists; in fact, the 8-*endo*-methyl compound **15** and its exo isomer **13** are nearly 17 and three times more potent than **7**, respectively. Thus, **15** exhibits unusually strong (for its *N*-methyl structure) activity comparable to nalorphine in the rabbit. Of significant interest are the antagonist potencies seen in the pairs of optical isomers (**7**, **8**, and **22**). In rabbits, the racemates **7** and **8** showed more potent activities than their enantiomers. On the other hand, in monkeys, the dextro isomers (+)-**7** and (+)-**8** appear to be more potent antagonists than their levo isomers or racemates. The reason for this discrepancy is not clear. Nevertheless, it is apparent that the antagonist activity resides in both of the racemates **7** and **8** and their optical isomers. This constitutes a major deviation from the reported observation in the phenylmorphan (II)[3] (see below).

Replacement of the *N*-methyl group of **7** by an allyl and related groups (**34–37** and **39**) results in little increase in antagonist activity. May and co-workers also failed to produce strong antagonist activity by similar changes in the N-substituent in the phenylmorphan[18] and ketobemidone.[19] Interestingly, however, the effect of N-

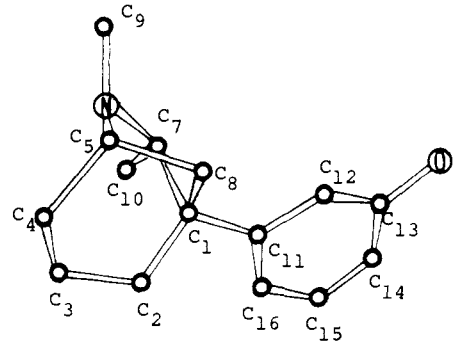


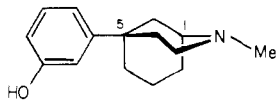
Figure 1. Perspective drawing of (+)-8-HBr from the x-ray data.

substitution on the antagonist activity becomes evident when a methyl group is present on C_7, leading to an appearance of activity comparable to nalorphine (**45** and **49–52**). The order of the activity, *N*-propyl > dimethylallyl > cyclopropylmethyl > allyl and propargyl, appears to be somewhat atypical with respect to the high activity of the dimethylallyl group.[20] The higher *N*-alkyl homologues (**47** and **48**) and the phenethyl compound **53** are devoid of antagonist activity.

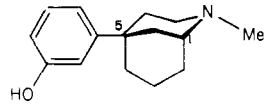
As seen in Table II, none of the compounds tested will sustain morphine dependence in monkeys, indicating a generally low capacity to produce physical dependence of this series.

Stereochemical Studies. As described above, the two *N*-methyl racemates **7** and **8** act as antagonist–analgetics. Upon optical resolution, the analgetic activity of these racemates is found only in the dextro isomers (+)-**7** and (+)-**8**, while the antagonist activity resides in both of their enantiomers. In contrast, May and Takeda[3] reported that the racemic phenylmorphan (II) possesses an analgetic potency nearly equivalent to that of morphine with no antagonist property. Its enantiomers, however, have only a fourfold difference in analgetic activity, with the dextro isomer being the more active. Moreover, it was found that (−)-II is a weak narcotic antagonist, while (+)-II does not possess this property. Because of these differences observed for the enantiomers of the two series, it is of particular interest to establish the absolute stereochemistry of (+)-**7** and (+)-**8**. The absolute configuration of (+)-**8**·HBr, as determined from the anomalous dispersion effect of the bromine atom, is 1*R*,5*S*,7*R* and is shown in Figure 1. The figure indicates that the cyclohexane ring of the 6-azabicyclo[3.2.1]octane system is in a chair conformation with the phenyl substituent equatorial. The *N*-methyl group is oriented away from the plane of the cyclohexane ring, while the C_7-methyl group locates on that plane and is related to the former in a trans manner, providing an unequivocal proof for its endo configuration.[2]

Recently, Cochran[21] established that the absolute configuration of (−)-5-(3-hydroxyphenyl)-2-methylmorphan [(−)-II] is 1*R*,5*S*. Therefore, it is apparent that the chirality at the quaternary carbon of (+)-**8** (1*R*) is related to that of the more potent phenylmorphan enantiomer (+)-II (5*R*).



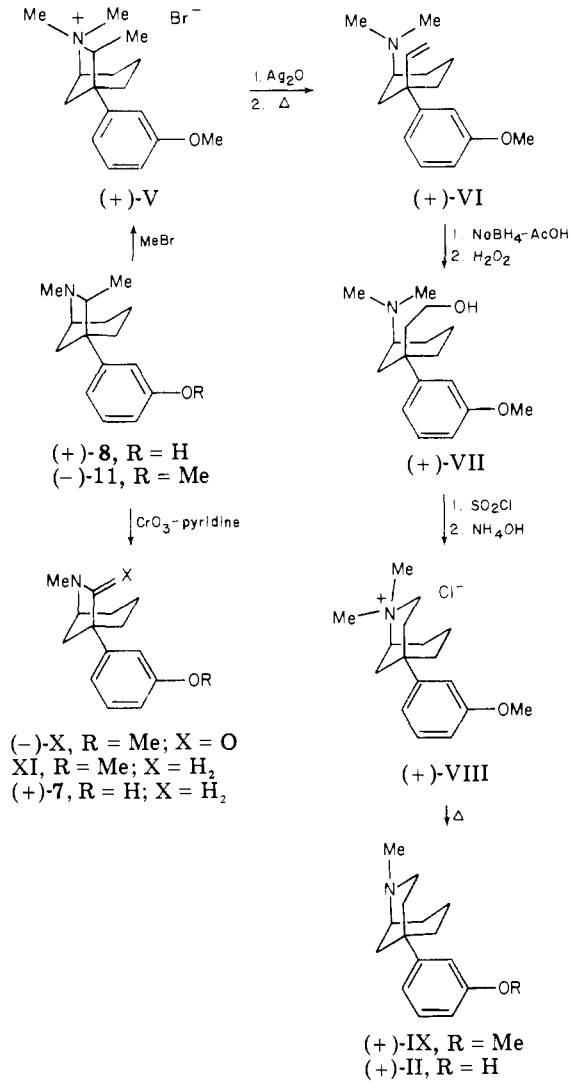
(+)-II (5*R*)



(−)-II (5*S*)

This stereochemical correlation was further proved by the transformation of (+)-**8** to (+)-II outlined in Scheme I. The methoxy derivative (−)-**11**, a precursor[2] of (+)-**8**, gave the olefin (+)-VI as the sole product on Hofmann degradation. The structure of (+)-VI was confirmed by

Scheme I



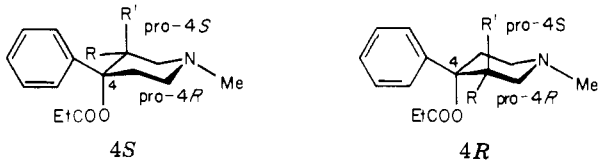
the NMR spectrum which showed a typical terminal vinyl resonance. Hydroboration and subsequent oxidation of (+)-VI afforded the carbinol (+)-VII. Through the chloride, (+)-VII was converted to the phenylmorphan methochloride (+)-VIII which, on dry distillation, yielded the tertiary base (+)-IX. O-Demethylation of (+)-IX gave (+)-II identical in all respects with an authentic sample.[3] This sequence of reactions without affecting the stereochemical integrity of C_1 provides an additional proof of the stereochemistry of (+)-**8**.

The absolute stereochemistry of the 7-demethyl compound (+)- and (−)-**7** was examined by the comparison of their CD curves with those of (+)- and (−)-**8**. The analgetically active enantiomers of both series [(+)-**7** and (+)-**8**] exhibit almost identical curves. Apparently, the sign of Cotton effects is governed chiefly by the immediate stereochemical environment of the chromophore[22,23] and will therefore reflect C_1 rather than C_7 geometry in (+)-**8**, since the latter asymmetric feature is further removed from the phenolic function. The identity of Cotton effect sign and the similarity of peak and trough characteristics of the CD curves of (+)-**7** and (+)-**8** suggest but do not prove the configurational identity of their C_1 chiral center.

This identity was unequivocally established by chemically relating (+)-**8** to (+)-**7**. Oxidation of (−)-**11** with CrO_3 and pyridine[24] gave the lactam (−)-X which was reduced with $LiAlH_4$ to the amine XI. The picrate salt of this amine was identical in all respects with an authentic

sample of (+)-XI·picrate, a precursor of (+)-7.[2] Hence, the absolute configuration of the active enantiomer [(+)-7] is 1*R*,5*S*. Thus, the chirality at the quaternary carbon of both the analgetically active enantiomers (+)-7 and (+)-8 is related to that of the more analgetically active phenylmorphan enantiomer (+)-II, although they appear to be more like (−)-II than (+)-II in other pharmacologic actions (narcotic antagonism and a low grade of physical dependence capacity).

Larson and Portoghese[25] have shown that the α- and β-prodines (XIIa,b) with a 4*S* configuration have signif-



XIIa, R = Me; R′ = H
b, R = H; R′ = Me

icantly more analgetic activity than their corresponding 4*R* enantiomers. They attribute this stereoselectivity in part to the ability of the analgetic receptor to discriminate between the pro-4*R* and pro-4*S* enantiotopic edges of the phenylpiperidine structure. On the basis of these findings, Cochran[21] suggested that a similar discrimination of enantiotopic edges exists in the binding of (+)-II and (−)-II by the analgetic receptor, since the more potent enantiomers of both II [(+)-5*R*] and XII [(+)-4*S*] have substitution on the same enantiotopic edge of the piperidine ring. It is apparent that the chiral phenylpropylamine chain in the analgetically active enantiomers (+)-7 (1*R*) and (+)-8 (1*R*) corresponds to the enantiotopic edge of the piperidine ring bearing substitution in (+)-II and XII (4*S*). This appears to be, at least in part, the cause of the enantiomeric stereoselectivity in the analgetic activity of 7 and 8. The enantiomeric stereoselectivity observed for 7 and 8 cannot be attributed simply to a difference in biodistribution since the analgetically inactive levo enantiomers (−)-7 and (−)-8 exhibit considerable narcotic antagonist activity.

Introduction of a methyl substituent at C_7 in this series invariably confers enhanced pharmacological effects both in the analgetic and antagonist activities. Similarities in onset, peak, and duration of analgetic actions observed for compounds 7 and 8 (Table I) suggest that the effect of the 7-methyl group is a reflection of receptor-related events rather than differential access into the CNS. The great variance in the pharmacological effect produced by identical changes in the N-substituent in the 7-demethyl and the 7-methyl compounds (vide supra) suggests that the mode of the interaction of these two series with analgetic receptors is not identical.[16] As previously proposed by Portoghese and Larson in the prodine series,[25] it appears that there are two possible ways in which the 7-methyl group effects the receptor interaction. Its interaction with a possible hydrophobic pocket on the receptor would constitute a direct effect, while a difference in the conformational preference of certain groups (phenyl and/or nitrogen) due to the presence of the 7-methyl group would represent an indirect effect. Figure 2 illustrates the conformation adopted by the phenyl ring of (+)-8 in the crystalline state. This conformation is nearly identical with that of the more potent phenylmorphan enantiomer (+)-II[21] (with exception of the reversed orientation of the phenolic OH group) and that of the less potent prodine isomers.[25,26] However, we feel that it is difficult to draw any definitive conclusions with respect to the role of the 7-methyl substituent on the phenyl conformation of 8 only

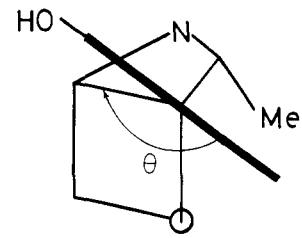


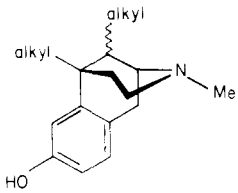
Figure 2. Torsion angle between the phenyl and pyrrolidine rings (C_{16}–C_{11}–C_1–C_8) of (+)-8·HBr. θ = 145.5°.

from the above results obtained in the crystalline state. The conformation of the 7-demethyl compound 7 in the crystalline state would allow a greater insight into this problem. Unfortunately, to date we have been unable to prepare crystalline salts of 7 which are suitable for x-ray analysis.

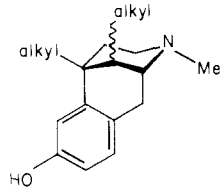
Since the importance of the nitrogen to phenyl distance in structure–analgetic activity relationships has been described recently,[21,27] it is worth noting the result obtained from the x-ray study of (+)-8·HBr. The distance between the cationic nitrogen and the center of the phenyl ring of (+)-8 is 5.1 Å. This value is considerably smaller than those observed for the equatorially oriented 4-phenylpiperidine analgetics (about 5.7 Å).[21] This difference is reasonably expected because of the 3-phenylpyrrolidine structure of 8. Cochran[21] demonstrated that the nitrogen to phenyl distances in the axial and equatorial 4-phenylpiperidines are considerably different (about 4.6 and 5.7 Å, respectively) but the distances between the hydrogen on the cationic nitrogen and the phenyl ring in both series fall in nearly the same range (5.3–5.9 Å). The hydrogen to phenyl distance (5.98 Å)[28] obtained with 8 is nearly identical with the reported values. This may support a possible role of hydrogen bonding in the interaction of analgetics with the receptor as suggested by Cochran.[21]

With respect to the antagonist activity, the striking difference between the enantiomeric potency ratio of the phenylmorphan (II) and that of 7 and 8 suggests that their mode of antagonist action is not identical. Goode and White[6] reported that the hexamethylenimine (IV) and both its enantiomers possess antagonist activity. The antagonist activity of profadol (III) in monkey has been reported to reside mainly in the dextro isomer.[7] However, the results obtained in the guinea-pig ileum[29] and in another experiment in monkey[30] indicate that the activity of profadol resides, qualitatively, in the racemate and both of its optical isomers. Although a direct comparison of the activities between these pairs of enantiomers in a more quantitative manner is not available, it is apparent that 7 and 8 are more like III and IV than II in its very low enantiomeric potency ratio in antagonist activity. This suggests that the mode of the antagonist actions of III, IV, and I (7 and 8) is quite similar. It appears that this similarity arises in part from the *N*-methylphenethylamine fragment commonly incorporated in these compounds. Archer and Harris have already postulated that this fragment is associated with antagonist action.[20,31]

May and co-workers[32,33] reported that optical resolution of the 5,9-dialkyl-6,7-benzomorphans, potent agonist analgetics, leads to an appearance of antagonist activity.[7,29] Since this activity was found only in the levo isomers (−)-XIII and not in the racemates, the enantiomeric stereoselectivity in this case appears to be similar to that of the phenylmorphan (II). 5-Phenylbenzomorphan, a hybrid of phenylmorphan and benzomorphan, synthesized by Yokoyama and co-workers,[34] behaved similarly, the antagonist activity being observed only in the levo isomer

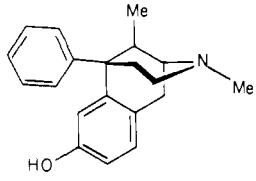


(+)-XIII

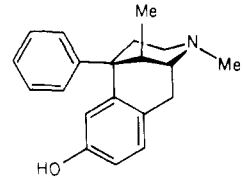


(−)-XIII

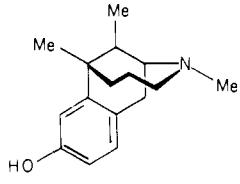
(−)-XIV.[35] Close similarity in the enantiomeric stereoselectivity of II, XIII, and XIV suggests a similar mode in the antagonist actions of these three structures although the orientation of the phenyl substituent in II (equatorial) and XIII (axial) is different. Recently, based on quantum chemical studies, Loew and Jester[45] proposed that the 4-phenylpiperidine analgetics act at the morphine receptor with an identical piperidine rather than phenyl ring site. It seems likely that at least one of the structural requisites for the antagonist action in II, XIII, and XIV is the unsubstituted pro-*S* edge[25] of the piperidine ring commonly involved in these levo isomers. Our previous experience in the homobenzomorphan series appears to provide additional evidence for the above hypothesis. Optical resolution of 2′-hydroxy-2,6,10β-trimethyl-7,8-homobenzomorphan[36] gave the levo isomer (−)-XV,[37] a potent agonist and good suppressor of morphine abstinence phenomena. Neither (−)-XV nor its dextro enantiomer exhibits appreciable antagonist activity in monkey.[38] This could be due to the absence of an unsubstituted pro-*S* edge of the piperidine ring in (−)-XV.



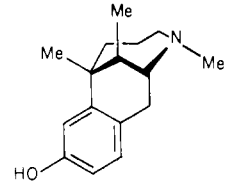
(+)-XIV



(−)-XIV



(+)-XV



(−)-XV

Thus, the information obtained from the structure–activity relationships of I allows certain stereochemical and configurational correlations to be made between I and other known antagonist–analgetics. However, definitive conclusions regarding differences or similarities in receptor binding must await further experimental results, since the exact nature of the receptor binding of antagonist–analgetics has not been ascertained.[39] Further studies in other types of phenylazabicycloalkanes[2] are in progress which, hopefully, will provide a greater insight into the structure–activity relationships.

Finally, (±)-8 was tested for its capacity to produce physical dependence in Rhesus monkey (chronic study for 33 days).[11]

Administration of nalorphine on the 14th and again on the 28th day in a dose of 2 mg/kg caused no precipitation of an abstinence syndrome. Only very mild physical dependence was elicited by naloxone on the 29th day or by abrupt withdrawal of (±)-8 on the 33th day, indicating the very slight abuse potential of (±)-8. In essentially the same test, the dextro isomer (+)-8 produced more appreciable morphine-like dependence in monkey.[11] Thus, (±)-8 shows the profile of a well-balanced analgetic and antagonist agent with a very mild physical dependence capacity.

Experimental Section

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. NMR data (ppm, δ) were obtained with a Model JOEL ME-60 instrument in $CDCl_3$ using Me_4Si as an internal reference. The IR spectra were recorded on a Hitachi IR-215 spectrometer and are consistent with the assigned structures. GC analyses were determined on a Shimadzu 4BPF instrument using a 3% OV-17 column. Optical rotations were obtained with a Jasco DIP-180 polarimeter. CD spectra were measured using 0.1% (w/v) solutions in 2- and 0.5-mm cells with Jasco J-20A and J-40 spectropolarimeters, respectively. Microanalyses were performed by the Analytical Section of this laboratory and are within ±0.4% of the theoretical values. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out in vacuo.

(+)-(1*S*,3*S*)-3-(3-Methoxyphenyl)-*N*,*N*-dimethyl-3-vinylcyclohexylamine Hydrochloride [(+)-VI·HCl]. An aqueous solution (100 ml) of (+)-V[2] (13.4 g, 0.0394 mol) was shaken for 0.5 h with an excess of Ag_2O [freshly prepared from 13.8 g (0.081 mol) of $AgNO_3$]. The aqueous suspension was filtered and the solvent was removed. Distillation of the residue gave 10.2 g of a colorless oil, bp 160–180 °C (bath temperature) (1 mm). This was converted to the HCl salt and recrystallized from Me_2CO giving 11.35 g (97.5%) of (+)-VI·HCl: mp 190–191 °C; NMR (regenerated free base) 2.36 (s, 6 H, NMe_2), 3.84 (s, 3 H, OCH_3), 4.70 (q, J = 17 and 1.5 Hz, 1 H, H_2C=CH–), 4.87 (q, J = 11 and 1.5 Hz, 1 H, H_2C=CH–), 5.93 (q, J = 11 and 17 Hz, 1 H, C*H*=CH_2); $[\alpha]^{25}D$ +14.2° (*c* 1.3, MeOH). Anal. ($C_{17}H_{26}ONCl$) C, H, N.

(+)-(1*S*,3*S*)-1-(3-Methoxyphenyl)-3-dimethylaminocyclohexaneethanol [(+)-VII]. The free base was regenerated from 5.7 g (0.019 mol) of (+)-VI·HCl in the usual manner. To a mixture of this base, $NaBH_4$ (2.57 g, 0.075 mol), and 200 ml of THF (stirring, N_2 atmosphere) was added a solution of AcOH[40] (4.06 g, 0.068 mol) in THF (10 ml) at 20–25 °C and the mixture was refluxed for 42 h. A solution of NaOH (2.88 g, 0.07 mol) in H_2O (20 ml) and 2.9 ml (0.024 mol) of 28% H_2O_2 were added successively to the reaction mixture at 15–20 °C and stirring was continued at 25 °C for 4 h. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic solution was dried and evaporated to give 6 g of an oil. A mixture of this oil, AcOH (60 ml), and dioxane (60 ml) was refluxed for 1 h to decompose an amine–borane complex[41] and evaporated. The residue was dissolved in 5% HCl and washed with Et_2O. The aqueous layer was separated and rendered alkaline with NH_4OH. It then was extracted with Et_2O and dried, and the Et_2O was removed. A mixture of the residue, KOH (5 g), and EtOH (100 ml) was heated at 70 °C for 0.5 h. (Without this treatment, the product was found to contain a considerable amount of the *O*-acetate of VII.) The mixture was evaporated, diluted with H_2O (70 ml), and extracted with Et_2O. Evaporation of the dried Et_2O gave 5.3 g of an oil which was dissolved in $CHCl_3$ and chromatographed over silica gel (200 g). Elution with $CHCl_3$–MeOH (1:1) gave 4.39 g (82%) of crude (+)-VII, contaminated with about 13% of a minor component on GC examination. This minor product appeared to be the tertiary carbinol formed by Markownikoff addition of borane to the double bond, since the NMR spectrum of crude (+)-VII showed a small doublet (J = 6 Hz) at 0.93 assignable to a tertiary CCH_3 group in addition to the signals expected for (+)-VII. A pure sample of (+)-VII was obtained in the following manner. A mixture of crude (+)-VII (0.16 g, 0.58 mmol), pyridine (3 ml), and 3,5-dinitrobenzoyl chloride (0.147 g, 0.64 mmol) was kept at 25 °C overnight. The mixture was evaporated, diluted with H_2O (3 ml), and basified with NH_4OH. Extraction with $CHCl_3$ gave, after drying and evaporation, 0.27 g of the oily benzoate (two spots on TLC) which was purified through preparative TLC [silica gel, developed by $CHCl_3$–MeOH (9:1)]. The benzoate (0.157 g, oil) obtained from the lower fraction was heated with 5% NaOH–EtOH (20 ml) at 80 °C for 2 h. The mixture was evaporated, diluted with H_2O, and extracted with Et_2O. Evaporation of the dried Et_2O gave, after distillation, 0.07 g of pure (+)-VII: bp 180–200 °C (bath temperature) (0.1 mm);

NMR 2.28 (s, 6 H, NMe_2), 3.10 (br s, 1 H, disappeared on addition of D_2O, OH), 3.40 (t, J = 7 Hz, 2 H, CH_2O), 3.81 (s, 3 H, OMe); $[\alpha]^{25}D$ +1.1 (c 0.84, $CHCl_3$). Anal. ($C_{17}H_{27}O_2N$) C, H, N.

(+)-(1S,5R)-5-(3-Methoxyphenyl)-2-methylmorphan Methochloride [(+)-VIII]. A solution of 1.8 g (6.5 mmol) of the crude carbinol (+)-VII described above and $SOCl_2$ (3.65 g, 0.03 mol) in $CHCl_3$ (30 ml) was refluxed for 3 h and evaporated. The residue was dissolved in H_2O and washed with Et_2O. The aqueous layer was basified with NH_4OH and extracted with Et_2O. Evaporation of the dried Et_2O gave an oil (1.75 g) which was refluxed in Me_2CO (50 ml) for 50 h. After cooling, a crystalline precipitate was collected and recrystallized from Me_2CO–i-PrOH–Et_2O to give 1.2 g (62.5%) of (+)-VIII as hygroscopic needles: mp 215–216 °C; $[\alpha]^{25}D$ +15.6° (c 0.51, MeOH). Anal. ($C_{17}H_{26}ONCl$) C, H, N.

(+)-(1S,5R)-5-(3-Methoxyphenyl)-2-methylmorphan Hydrobromide [(+)-IX·HBr]. Dry distillation (0.7 mm) of (+)-VIII (0.83 g, 2.8 mmol) at 240–250 °C (bath temperature) gave 0.6 g of an oil during 0.5 h. Conversion to the HBr salt and recrystallization from Me_2CO gave 0.825 g (90%) of (+)-IX·HBr as needles: mp 194–196 °C; $[\alpha]^{25}D$ +4.9° (c 0.35, MeOH). Anal. ($C_{16}H_{24}ONBr$) C, H, N.

(+)-(1S,5R)-5-(3-Hydroxyphenyl)-2-methylmorphan [(+)-II]. A mixture of 0.6 g (1.84 mmol) of (+)-IX·HBr and 47% HBr (10 ml) was refluxed for 1 h and evaporated. The residue was dissolved in H_2O (5 ml) and basified with NH_4OH. Extraction with $CHCl_3$ gave, after drying and evaporation, 0.4 g (94%) of (+)-II, mp 152–153 °C. Recrystallization from AcOEt gave plates: mp 153–154 °C (lit.[3] mp 153–154 °C); $[\alpha]^{25}D$ +12.8° (c 1.1, 95% EtOH) (lit.[3] $[\alpha]^{20}D$ +12.4°). The HCl salt was crystallized from EtOH in needles and had mp 231–233 °C: $[\alpha]^{25}D$ +4.41° (c 1.36, H_2O) (lit.[3] $[\alpha]^{25}D$ +4.4°). This proved to be identical with an authentic sample[3] in all respects (mixture melting point, IR, NMR, and TLC).

(−)-(1R,5S)-1-(3-Methoxyphenyl)-6-methyl-6-azabicyclo-[3.2.1]octan-7-one [(−)-X]. A mixture of (−)-11[2] (0.74 g, 3.02 mmol), CrO_3 (2 g), and dry pyridine (70 ml) was heated at 60 ± 5 °C for 20 h.[24] The mixture was poured into ice–H_2O (300 ml) and extracted with Et_2O and $CHCl_3$. The combined extracts were washed with 10% HCl and H_2O, dried, and evaporated. Recrystallization of the residue from isopropyl ether gave 0.164 g (22.2%) of (−)-X as prisms: mp 92.5–94 °C; $[\alpha]^{25}D$ −24.2° (c 1.87, EtOH). Anal. ($C_{15}H_{19}O_2N$) C, H, N.

(+)-(1R,5S)-1-(3-Methoxyphenyl)-6-methyl-6-azabicyclo[3.2.1]octane Picrate [(+)-XI·Picrate]. A mixture of (−)-X (0.313 g, 1.28 mmol) and $LiAlH_4$ (0.28 g, 7.35 mmol) in THF–Et_2O (1:1) (55 ml) was refluxed for 7 h. The mixture was decomposed by addition of H_2O under ice cooling and filtered from inorganic material. Evaporation of the dried filtrate left an oil which was found to be a mixture of three components by TLC. This is in accord with our previous experience in the $LiAlH_4$ reduction of racemic X.[2] The mixture was separated by preparative TLC [silica gel, developed by $CHCl_3$–EtOH (9:1)]. The amine XI (0.11 g, 37.3%) obtained from the middle fraction was converted to the picrate and recrystallized from EtOH giving (+)-XI·picrate: mp 138–140 °C; $[\alpha]^{30}D$ +66.3° (c 0.335, $CHCl_3$) (lit.[2] $[\alpha]^{23}D$ +67.5°). This picrate was identical in all respects with an authentic sample[2] (IR, mixture melting point, and NMR).

(+)-(1R,5S,7R)-1-(3-Hydroxyphenyl)-6,7-dimethyl-6-azabicyclo[3.2.1]octane [(+)-8] hydrochloride[2] (Figure 3): CD (c 0.1, MeOH) $[\theta]_{300}$ 0, $[\theta]_{290}$ +40, $[\theta]_{285}$ +190, $[\theta]_{280}$ +310, $[\theta]_{276}$ +360, $[\theta]_{270}$ +310, $[\theta]_{265}$ +225, $[\theta]_{225}$ +75, $[\theta]_{250}$ +40, $[\theta]_{245}$ +25, $[\theta]_{240}$ +40, $[\theta]_{235}$ +250, $[\theta]_{232}$ +700, $[\theta]_{230}$ +875, $[\theta]_{227}$ +1100, $[\theta]_{224}$ +950, $[\theta]_{220}$ +650, $[\theta]_{215}$ +200.

(−)-(1S,5R,7S)-1-(3-Hydroxyphenyl)-6,7-dimethyl-6-azabicyclo[3.2.1]octane [(−)-8] hydrochloride:[2] CD (c 0.1, MeOH) $[\theta]_{300}$ 0, $[\theta]_{290}$ −35, $[\theta]_{285}$ −180, $[\theta]_{280}$ −305, $[\theta]_{276}$ −350, $[\theta]_{270}$ −300, $[\theta]_{265}$ −220, $[\theta]_{255}$ −80, $[\theta]_{250}$ −35, $[\theta]_{245}$ −30, $[\theta]_{240}$ −40, $[\theta]_{235}$ −260, $[\theta]_{232}$ −730, $[\theta]_{230}$ −890, $[\theta]_{227}$ −1080, $[\theta]_{224}$ −960, $[\theta]_{220}$ −680, $[\theta]_{215}$ −220.

(+)-(1R,5S)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo[3.2.1]octane [(+)-7] Hydrochloride (Figure 3). To a solution of the free base[2] in MeOH was added a slight excess of methanolic HCl and the mixture was evaporated. The residue was dissolved in MeOH and the solution was evaporated to dryness. This procedure was repeated four times to remove excess HCl. The residual, amorphous hydrochloride was dried over P_2O_5 at 1 mm overnight and used for CD measurement: CD (c 0.1, MeOH) $[\theta]_{293}$ 0, $[\theta]_{285}$ +120, $[\theta]_{280}$ +210, $[\theta]_{275}$ +320, $[\theta]_{274}$ +330, $[\theta]_{270}$ +310, $[\theta]_{265}$ +220, $[\theta]_{260}$ +170, $[\theta]_{255}$ +90, $[\theta]_{240}$ +35, $[\theta]_{230}$ +675, $[\theta]_{225}$ +1220, $[\theta]_{223}$ +1260, $[\theta]_{220}$ +1170, $[\theta]_{215}$ +720, $[\theta]_{210}$ 0.

(−)-(1S,5R)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo-[3.2.1]octane [(−)-7][2] Hydrochloride. The procedure was made as described above: CD (c 0.1, MeOH) $[\theta]_{293}$ 0, $[\theta]_{285}$ −120, $[\theta]_{280}$ −235, $[\theta]_{275}$ −330, $[\theta]_{274}$ −325, $[\theta]_{270}$ −310, $[\theta]_{265}$ −230, $[\theta]_{260}$ −160, $[\theta]_{255}$ −95, $[\theta]_{240}$ −30, $[\theta]_{230}$ −670, $[\theta]_{225}$ −1210, $[\theta]_{223}$ −1240, $[\theta]_{220}$ −1180, $[\theta]_{215}$ −730, $[\theta]_{210}$ 0.

X-Ray Study. The hydrobromide salt of (+)-8 crystallizes from EtOH: mp 246–248 °C; $[\alpha]^{25}D$ +8.7° (H_2O).[2] The colorless transparent crystals are very thin plates parallel to (010) and elongated in the direction of the crystallographic a axis. The space group and initial unit cell parameters were determined from Weissenberg and precession photographs. Accurate cell parameters were obtained by least-squares treatment of 13 strong 2θ values measured on an automatic four-circle diffractometer (Rigaku) with Cu Kα radiation (λ = 1.5418). Intensity data were also collected on this instrument using graphite-monochromated Cu Kα radiation to $2\theta_{max}$ = 130°. Of the 1525 scanned reflections, 1354 reflections had an intensity exceeding three times the corresponding estimated standard derivation and were corrected for Lorentz and polarization factors but not for absorption and extinction factors. The structure of (+)-8·HBr was solved by the heavy atom method. From a three-dimensional Fourier synthesis using bromine phase angles and a successive Fourier synthesis, all the nonhydrogen atoms were deduced. The structure was then refined by six cycles of block-diagonal least-squares calculations assuming anisotropic thermal factors for all atoms. The weighting scheme was w = 1 and the final reliability index R for the observed reflections was 0.077.

The absolute configuration of (+)-8 was determined by the anomalous dispersion method.[42] The anomalous dispersion corrections used for the scattering factor of the bromine atom were $\Delta f'$ = −0.9 and $\Delta f''$ = 1.5.[43] The structure factors for the Bijvoet's pairs of reflections were calculated and compared with the observed values by assuming a right-handed set of axes. A comparison between the observed and calculated intensities indicated that the assumed configuration was actually the antipode of the true structure. Thus, the absolute configuration of (+)-8 was established as shown in Figure 1, which was drawn by the program ORTEP.[44]

Acknowledgment. We wish to thank Dr. Everette L. May of the NIAMDD for his aid in the determination of analgetic activity (hot-plate) and physical dependence capacity and for a generous supply of an authentic sample of (+)-II. We also extend appreciation to Dr. H. Tomisawa, Professor of the Tohoku College of Pharmacy, Director Michio Yamazaki of this laboratory, Dr. S. Sugasawa, Professor Emeritus of the Tokyo University, Dr. N. Sugimoto, and Dr. H. Kugita for their interest and helpful discussions. Thanks are also due to the staff of the Analytical Section of this laboratory presided over by Dr. K. Kotera for spectral and elemental analyses and to Mr. T. Takakuwa of Japan Spectroscopic Co. Ltd. for the CD measurement.

Supplementary Material Available: a listing of the crystal data (Table III), final atomic parameters (Table IV), comparison of the observed and calculated intensity ratios with the absolute configuration (Table V), CD spectra of (+)-8·HCl and (+)-7·HCl (Figure 3), interatomic bond lengths (Figure 4), and bond angles (Figure 5) (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For paper 2, see M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, and S. Saito, *Chem. Pharm. Bull.*, **24**, 1514 (1976).

(2) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, and S. Saito, *Chem. Pharm. Bull.*, **24**, 1002 (1976).

(3) E. L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970).
(4) M. E. Rogers and E. L. May, *J. Med. Chem.*, **17**, 1328 (1974).
(5) R. E. Bowman, *Chem. Ind. (London)*, 1077 (1969).
(6) P. G. Goode and A. C. White, *Br. J. Pharmacol.*, **43**, 462P (1971).
(7) J. E. Villarreal, "Recent Advances in the Pharmacology of Morphine-Like Drugs, Advances in Mental Science, Vol. II, Drug Dependence", R. T. Harris, W. McIsac, and C. R. Schuster, Ed., University of Texas Press, Houston, Texas, 1970, pp 83–116.
(8) H. H. Swain, J. E. Villarreal, and M. H. Seevers, Addendum, Minutes of the 35th Meeting of the Committee on Problems of Drug Dependence, National Research Council, National Academy of Sciences, 1973.
(9) S. Nurimoto, S. Suzuki, G. Hayashi, and M. Takeda, *Jpn. J. Pharmacol.*, **24**, 461 (1974).
(10) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953). The tests were performed at the NIAMDD, National Institutes of Health. See, also, A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965), footnote 9.
(11) We are indebted to Dr. H. H. Swain, Department of Pharmacology, University of Michigan, and Dr. M. D. Aceto, Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, for these results. See, also, M. D. Aceto, L. S. Harris, W. L. Dewey, and R. L. Balster, Addendum 1, and H. H. Swain and M. H. Seevers, Addendum 2, Minutes of the 37th Meeting of the Committee on Problems of Drug Dependence, National Research Council, National Academy of Sciences, 1975.
(12) B. C. Joshi, C. F. Chignell, and E. L. May, *J. Med. Chem.*, **8**, 694 (1965).
(13) R. S. Wilson, M. E. Rogers, C. B. Pert, and S. H. Snyder, *J. Med. Chem.*, **18**, 240 (1975).
(14) D. L. Larson and P. S. Portoghese, *J. Med. Chem.*, **19**, 16 (1976).
(15) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).
(16) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).
(17) (a) P. A. J. Janssen, C. van de Westeringh, A. H. M. Jageneau, P. J. A. Demoen, B. K. F. Hermans, G. H. P. van Daele, K. H. L. Schellekens, C. A. M. van der Eycken, and C. J. E. Niemegeers, *J. Med. Pharm. Chem.*, **1**, 281 (1959); (b) J. A. Christensen, S. Hernestam, J. B. Lassen, and N. Sterner, *Acta Pharmacol. Toxicol.*, **23**, 109 (1965).
(18) H. H. Ong, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, **17**, 133 (1974).
(19) T. Oh-ishi and E. L. May, *J. Med. Chem.*, **16**, 1376 (1973).
(20) S. Archer and L. S. Harris, *Fortschr. Arzneimittelforsch.*, **8**, 261–320 (1965).
(21) T. G. Cochran, *J. Med. Chem.*, **17**, 987 (1974).
(22) A. F. Casy and A. P. Parulkar, *J. Med. Chem.*, **12**, 178 (1969), and references cited therein.
(23) H. Inoue, M. Takeda, and H. Kugita, *Chem. Pharm. Bull.*, **21**, 2004 (1973).
(24) A. Cavé, C. Kan-Fan, P. Potier, J. Le Men, and M. M. Janot, *Tetrahedron*, **23**, 4691 (1967).
(25) D. L. Larson and P. S. Portoghese, *J. Med. Chem.*, **16**, 195 (1973).
(26) P. S. Portoghese, Z. S. D. Gomaa, D. L. Larson, and E. Shefter, *J. Med. Chem.*, **16**, 199 (1973).
(27) B. Belleau, T. Conway, F. R. Ahmed, and A. D. Hardy, *J. Med. Chem.*, **17**, 907 (1974).
(28) Calculated value, assuming tetrahedral geometry for the nitrogen atom and an N–H distance of 1.0 Å. The position of the hydrogen was not refined.
(29) H. W. Kosterlitz, J. A. H. Lord, and A. J. Watt, "Morphine Receptor in the Guinea-pig Ileum, Agonist and Antagonist Actions of Narcotic Analgesic Drugs", H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, Ed., Macmillan, London and Basingstoke, 1972, pp 45–61.
(30) D. A. McCarthy, *Adv. Biochem. Psychopharmacol.*, **8**, 145 (1974).
(31) L. S. Harris, *Adv. Biochem. Psychopharmacol.*, **8**, 13 (1974).
(32) E. L. May and N. B. Eddy, *J. Med. Chem.*, **9**, 851 (1966).
(33) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969).
(34) N. Yokoyama, F. B. Block, and F. H. Clarke, *J. Med. Chem.*, **13**, 488 (1970).
(35) F. H. Clarke, R. T. Hill, J. K. Saelens, and N. Yokoyama, *Adv. Biochem. Psychopharmacol.*, **8**, 81 (1974).
(36) (a) M. Takeda and H. Kugita, *J. Med. Chem.*, **13**, 630 (1970); (b) M. Takeda, M. Konda, H. Inoue, S, Saito, H. Kugita, and S. Nurimoto, *Adv. Biochem. Psychopharmacol.*, **8**, 113 (1974).
(37) This absolute stereochemistry was established by the ORD measurement: M. Takeda, unpublished results.
(38) We are indebted to Dr. J. E. Villarreal for this results. See, also, J. E. Villarreal and M. H. Seevers, Addendum 6, Minutes of the 33th Meeting of the Committee on Problems of Drug Dependence, National Research Council, National Academy of Sciences, 1971.
(39) W. A. Klee, S. K. Sharma, and M. Nirenberg, *Life Sci.*, **16**, 1869 (1975).
(40) V. Hach, *Synthesis*, 340 (1974).
(41) H. Kugita and M. Takeda, *Chem. Pharm. Bull.*, **12**, 1166 (1964).
(42) J. M. Bijvoet, A. F. Peerdman, and A. J. Bommel, *Nature (London)*, **168**, 271 (1951).
(43) C. H. Dauben and D. H. Templeton, *Acta Crystallogr.*, **8**, 841 (1955).
(44) C. K. Johnson, ORTEP, Oak Ridge National Laboratory Report ORNL-3794, 1965.
(45) G. H. Loew and J. R. Jester, *J. Med. Chem.*, **18**, 1051 (1975).