5.47–5.80 Å; $C_{7(8)}\cdots C_{3\alpha(4')}$, 3.11–3.68 Å; $C_{7\beta(8\beta)}\cdots C_{3\alpha(4')}$, 3.20–4.26 Å; $N_{4(5)}\cdots C_{3\alpha(4')}$, 2.44–2.54 Å. The analogous distances in **6** are near the lower end of the quoted ranges.

(24) Bacterial β-lactamases are thought to undergo conformational changes upon binding to β-lactam antibiotics; see A. Samuni and A. Y. Meyer, *Mol. Pharmacol.*, 14, 704 (1978), and references cited therein.

(25) The conformational freedom of the dipeptide may be one of the factors related to the diminished antibacterial activity of 6(7) α-substituted penicillins (cephalosporins). Even though D-Ala-D-Ala has a methyl group in the *topologically* analogous position, the *topographical* location can be different in the dipeptide compared to the β-lactam compounds. See D. B. Boyd, *J. Chem. Educ.*, **53**, 483 (1976), for references and further comment. Topology considers only the number of bonds and configuration of atoms, whereas topography pertains to the three-dimensional relationship between two molecules.

(26) P. P. K. Ho, R. D. Towner, J. M. Indelicato, W. A. Spitzer, and G. A. Koppel, *J. Antibiot.*, **25**, 627 (1972); P. P. K. Ho, R. D. Towner, J. M. Indelicato, W. J. Wilham, W. A. Spitzer, and G. A. Koppel, *ibid.*, **26**, 313 (1973); J. M. Indelicato, T. T. Norvilas, R. R. Pfeiffer, W. J. Wheeler, and W. L. Wilham, *J. Med. Chem.*, 17, 523 (1974); J. M. Indelicato and W. L. Wilham, *ibid.*, 17, 528 (1974); D. F. Mahoney, G. A. Koppel, and J. R. Turner, *Antimicrob. Agents Chemother.*, **10**, 470 (1976). See also ref 8; R. F. Pratt and M. J. Loosemore, *Proc. Natl. Acad. Sci. U.S.A.*, **75**, 4145 (1978).

Syntheses, Analgetic Activity, and Physical Dependence Capacity of 5-Phenyl-6,7-benzomorphan Derivatives[1,2]

Naokata Yokoyama,* Prabodh I. Almaula, Fred B. Block,[3] Frank R. Granat, Norman Gottfried, Ronald T. Hill,[3] Elihu H. McMahon, Walter F. Munch, Howard Rachlin, Jeffrey K. Saelens, Merrell G. Siegel, Hollis C. Tomaselli, and Frank H. Clarke

Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Ardsley, New York 10502.
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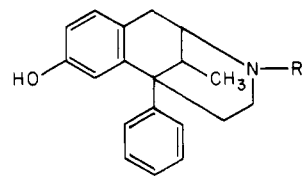
The synthesis, analgetic activity, and physical dependence capacity of a large number of 5-phenyl-6,7-benzomorphan derivatives are described. Observations made during the Stevens' rearrangement of 1-benzyl-1-methyl-Δ^3-piperidinium salt derivatives (V) under various conditions are discussed. The absolute configuration of the 9-demethyl series and the 2'-deoxy series is established by comparison of their ORD and CD spectra with those of **49**, whose absolute configuration was previously established by X-ray crystallography.[2] A convenient synthesis of ^{3}H-labeled phenols using $^3H_3PO_4$ is described, as well as the preparation of ^{14}C-labeled compounds by conventional methods.

l-β-2'-Hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan[2] (**49**; I, R = CH_3; GPA 1657) is a potent, orally effective analgetic.[2,4] **49** provides a structural link from the benzomorphans to the 4-phenylpiperidines[4-6] and the diphenylpropylamine analgetics.[5,7] **49** and its analogues display interesting pharmacological properties. For instance, **49** is an analgetic antagonist not only in reversal of morphine analgesia and precipitation of withdrawal symptoms in monkeys treated chronically with morphine[4] but also in opiate receptor binding studies;[8] **214** (the *N*-propargyl analogue of **49**) is a pure, long-acting antagonist in the guinea pig ileum assay[9] and binds more strongly to the opiate receptor in the presence of sodium ion than in its absence;[8] **207** and **219** [the *N*-(dimethylallyl) and *N*-(cyclobutylmethyl) analogues, respectively, of **49**] are both mixed agonist–antagonists;[4] and both optical isomers of the 9-demethyl and the 2'-deoxy-9-demethyl analogues of **49** are about equally potent as analgetics in the mouse phenylquinone writhing test.[5]

In this paper, we will describe the synthesis and summarize the pharmacology of the extensive series of 5-phenylbenzomorphans from which the above compounds were derived.

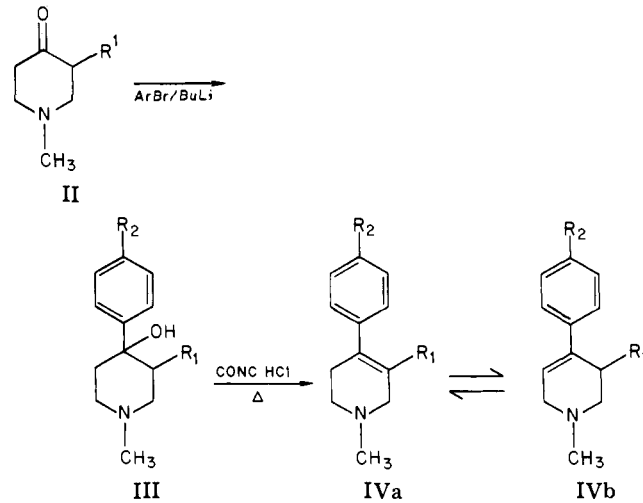
Chemistry. The synthesis of compounds related to **49** (I, R = CH_3) was similar to that described already for **49**[2] and its 9-demethyl analogue.[10] As shown in Scheme I, most of the required Δ^3-piperideine intermediates, IVa (see Table I), were prepared by reacting 4-piperidinones, II, with an aryllithium, generated in situ from the corresponding aryl bromide, followed by acid-catalyzed dehydration of the resulting 4-aryl-4-piperidinols, III. Compound **8** (Table I) was prepared by reacting 1-methyl-4-phenyl-3-piperidone[11] with ethyllithium and dehydrating the resulting 3-ethyl-3-piperidinol derivative. During the dehydration reaction, prolonged refluxing with

Scheme I[a]



I

49, R = CH_3
214 R = $CH_2C{\equiv}CH$
207 R = $CH_2CH{=}C(CH_3)_2$
219 R = CH_2-c-C_4H_7



[a] See Table I.

HCl usually provided a preponderance of the Δ^3-piperideines, IVa, which were separated by recrystalization of

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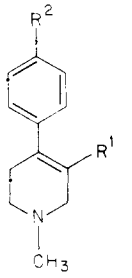
Table I. 4-Aryl-1-methyl-Δ^3-piperidine Derivatives

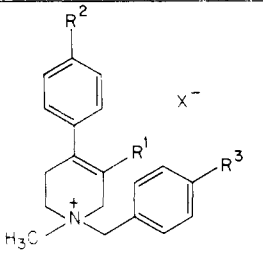


IVa

no.	R^1	R^2	M[a]	solv[a]	mp, °C	emp form.	anal.
1	H	H			40-42[b]	$C_{12}H_{15}N$	
2	H	Cl			90-91[c]	$C_{12}H_{14}ClN$	
3	H	OH			205-208[d]	$C_{12}H_{15}NO$	
4	H_5C_6	H			195-196[e]	$C_{13}H_{17}N\cdot HCl$	
5	CH_3	H			189-190[e]	$C_{13}H_{17}N\cdot HCl$	
6	CH_3	Cl	1a		oil	$C_{13}H_{16}ClN$	
7	CH_3	F	1b		oil	$C_{13}H_{16}FN$	
8	C_2H_5	H	2	M/B	175-176	$C_{14}H_{19}N\cdot HCl$	C, H, N, Cl

[a] See Experimental Section for method of preparation and list of solvents of crystallization. [b] C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, 78, 425 (1956). [c] F. H. Clarke, U.S. Patent 3 320 265 (1967). [d] S. M. McElvain and R. S. Berger, *J. Am. Chem. Soc.*, 77, 2848 (1955). [e] A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef, *Tetrahedron*, 21, 3387 (1965).

Table II. 4-Aryl-1-methyl-1-benzyl-Δ^3-piperidinium Derivatives



V

no.	R^1	R^2	R^3	X^-	M[a]	solv[a]	yield, %	mp, °C	emp form.	anal.
9	H	Cl	OCH_3	Cl	3		96	194-196	$C_{20}H_{23}Cl_2NO\cdot 0.5H_2O$	C, H, Cl
10	H	H	H	Br	3		94	228	$C_{19}H_{22}BrN$	
11	H	H	3,4-$(OCH_3)_2$	Cl	3		98	203-207	$C_{21}H_{26}ClNO_2$	
12	H	H	F	Cl	3		59	243-247	$C_{19}H_{21}ClFN$	
13	H	H	3,4,5-$(OCH_3)_3$	Cl	3		44	225-226	$C_{22}H_{28}ClNO_3$	
14	C_2H_5	H	OCH_3	Cl	3	M	86	218-220	$C_{22}H_{28}ClNO$	C, H, N, Cl
15	CH_3	Cl	OCH_3	Cl	3	M	85	202-204	$C_{21}H_{25}Cl_2NO$	
16	CH_3	F	OCH_3	Cl	3	M	73	195-196	$C_{21}H_{25}ClFNO$	C, H, N, Cl
17	H_5C_6	H	OCH_3	Cl	3		85	216	$C_{21}H_{26}ClNO$	
18	H	OH	OCH_3	Cl	3	C	90	223-224	$C_{20}H_{24}ClNO_2$	
19	H	Cl	H	Br	3		83	235-237	$C_{19}H_{21}ClBrN$	
20	CH_3	H	H	Br	3		75	198-199	$C_{20}H_{24}BrN$	C, H, N, Br

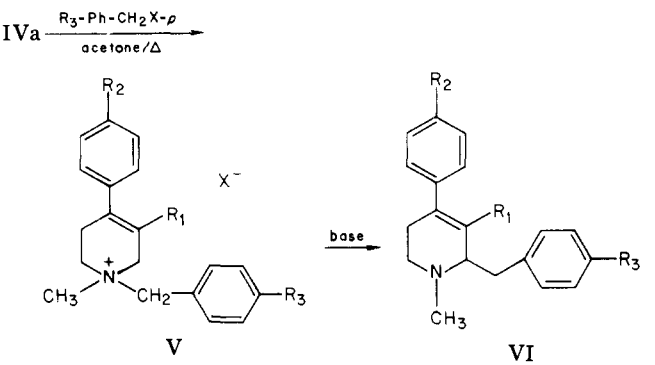
[a] See footnote *a* in Table I.

their hydrochloride salts. When R_2 of III was CF_3 or OCH_3, however, satisfactory products could not be obtained.

The intermediates of structure IVa are listed in Table I. Compounds IVa were quaternized to compound V (Scheme II) with the appropriate benzyl halide in refluxing acetone. Many of the compounds V (Table II) crystallized readily from acetone and were analyzed. Others were hygroscopic, and spectral data (IR, UV, and NMR) were used for their identification.

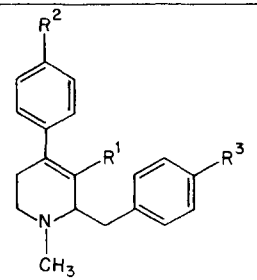
The Stevens' rearrangement of compound V yielded compounds VI (see Scheme II) in yields of 65–75% with a strong base in an inert solvent. The use of powdered KOH in benzene or toluene[2] required heat, while KO-*t*-Bu was effective in benzene or dioxane at room temperature.

Scheme II[a]



[a] See Tables II and III.

Table III. 4-Aryl-2-benzoyl-Δ^3-piperidine Derivatives

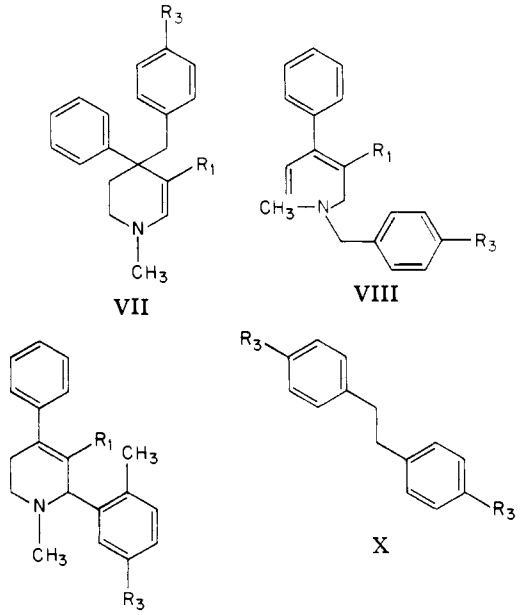


VI

compd	R^1	R^2	R^3	M[a]	solv[a]	mp, °C	yield, %	emp form.	anal.	analgetic act. TF[b]	analgetic act. PQW[c]	mouse jump. test[d] rate	mouse jump. test[d] freq
21	H	Cl	OCH_3	4a	D/M/N	181-182	28	$C_{20}H_{22}ClNO \cdot HBr$	C, H, Br	+/40 po		0	0/10
22	H	H	H	4b	M	162-164	88	$C_{19}H_{21}N \cdot HBr$	C, H, N, Br	2+/40 sc	6.6 sc 37.0 po	0	0/10
23	H	H	3,4-$(OCH_3)_2$	4a	D	189-192	59	$C_{21}H_{25}NO_2 \cdot HBr$	C, H, N, Br	2+/40 sc		1.2	1/5
24	H	H	F	4a		172-175[e]	23	$C_{19}H_{20}FN$	C, H, N	2+/80 sc			
25	H	H	3,4,5-$(OCH_3)_3$	4c	D	235-236	47	$C_{22}H_{27}NO_3 \cdot HCl$	C, H, N, Cl	2+/80 po			
26	C_2H_5	H	OH	4c	J	110-113	46	$C_{21}H_{25}NO$	C, H, N	2+/80 sc		0	0/10
27	CH_3	Cl	OH	4c	E	148-150	23	$C_{20}H_{22}ClNO$	C, H, N, Cl				
28	CH_3	F	OH	4c	E	132-133	27	$C_{20}H_{22}FNO$	C, H, N				
29	H_5-CH_3	H	OCH_3	4c		oil	85	$C_{21}H_{25}NO$					
30	H	OH	OCH_3	4b	B	228-229	54	$C_{20}H_{23}NO_2 \cdot HBr$	C, H, N, Br				
31	H	Cl	H	4d	N	201-203	52	$C_{19}H_{20}ClN \cdot HCl$					
32	CH_3	H	H	4b	M	205-206	35	$C_{20}H_{23}N \cdot HBr$	C, H, N, Br	+/160 sc	45 sc		
33	H	H	OCH_3	*f*		167-169				2+/80 sc		0	0/10
33a	H	H	OH	4c	A/C	212	40	$C_{19}H_{21}NO$	C, H, N	+/20 sc	1.5 sc 27.0 po	0	0/10
34	CH_3	H	OH	*g*		148-150				2+/160 sc	5 sc	0	0/10
morphine										2+/4 sc 2+/16 po	1 sc 8.9 po	55.7	10/10

[a] See footnote *a* in Table I. [b] Mouse tail-flick test (maximum effective dose); see Experimental Section for the method. [c] Mouse phenylquinone writhing test, ED_{50} (mg/kg); see Experimental Section for the method. [d] Mice treated with test compound for 2 days and then challenged with naloxone. J. K. Saelens, F. R. Granat, and W. K. Sawyer, *Arch. Int. Pharmacodyn. Ther.*, 190, 213 (1971). [e] Boiling point, °C (0.01 Torr). [f] See ref 10. [g] See ref 2.

Scheme III



VII VIII

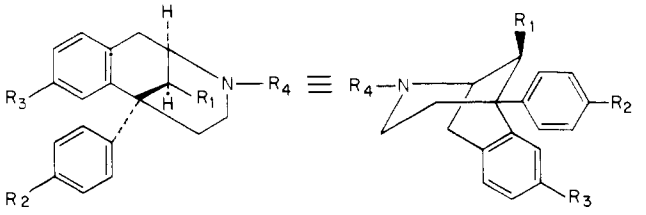
IX X

a, R_1 = H; R_3 = H; b, R_1 = H; R_3 = OCH_3; c, R_1 = CH_3; R_3 = H; d, R_1 = CH_3; R_3 = OCH_3

Table III describes the Stevens' products VI and notes the synthetic methods used. Many of the products were purified and characterized directly as salts. Those with a methoxy substituent were usually cleaved first to the corresponding phenol with brief boiling in 48% HBr. In some cases, KNH_2 in liquid ammonia was used to carry out the Stevens' rearrangement. Under these conditions, 3-unsubstituted compounds V (R_1 = H; Table II) gave pure products VI (Table III). In most cases, however, the Stevens' rearrangement gave mixtures containing side products, especially when there was a methyl substituent at C_3 (see Scheme III). When KOH in toluene or KO-*t*-Bu in benzene was used as the base, the product contained the "escape product" X from the radical pair intermediate.[12,13] When there was a C_3 methyl group, these conditions gave, besides the Stevens' product VI, the product of 1,4 rearrangement, VII (see Experimental Section), and the Hoffmann methine, VIII.[2] With a C_3 methyl group, KNH_2 in liquid ammonia gave the 2,3 Sommelet–Hauser rearrangement product, IXc. Similar side products have been isolated by other workers in analogous reactions.[14,15]

Cyclization of the purified Stevens' rearrangement products, VI, was carried out with refluxing 48% HBr to provide the substituted 5-phenylbenzomorphans, XI (R_4 = CH_3; Scheme IV; Table IV). When R_1 was a methyl or ethyl group, it was necessary to purify compounds VI prior to cyclization because the presence of even a small amount of the 1,4 rearrangement products greatly reduced the yield of benzomorphan. During the cyclization reaction methoxy groups were cleaved to provide phenols. As was the case with **49**,[2] only 9β-methylbenzomorphans, XI, were isolated in the cyclization of the 4-aryl-3-methyl-2-benzyl-Δ^3-piperidines, VI (see Table III, **27**, **28**, and **32**). Cyclization of **26** gave the 9β-ethylbenzomorphan **53** (Table IV), and **29** yielded the 4β-methylbenzomorphan **44**. Intermediates to **29** are **4** (Table I) and **17** (Table II). The β orientation of the alkyl group in the cyclized products was confirmed by the rate of quaternization study.[2] In many cases the phenolic benzomorphans were converted to ethers and esters (Table V). Some of the parent

Scheme IV



XI

benzomorphans were resolved into their optical isomers by fractional crystallization of the mandelate and tartrate salts.

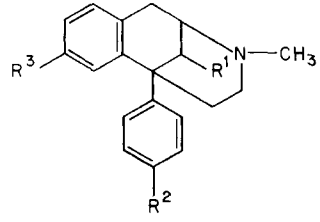
In order to obtain a variety of N-substituted benzomorphans, the *N*-methyl substituent was first removed by von Braun degradation with cyanogen bromide[10] or via the ethylurethane derivative.[16] Phenolic groups were first protected by esterification or ether formation with diazomethane. The *N*-cyano intermediates XIa (Table VI, R^4 = CN) were most conveniently converted to the nor compound XIc (R^4 = H) with $LiAlH_4$ in refluxing THF. Urethanes XIb (R^4 = COOEt) were hydrolyzed with KOH in carbitol at 170 °C, although acid hydrolysis was also used in some cases. Phenolic ester groups were cleaved during these hydrolytic procedures. The properties of compounds XIa, XIb, and XIc are listed in Table VI.

Table VII lists 111 substituted 5-phenylbenzomorphans, XI, in which the *N*-methyl group has been replaced with a different substituent, R^4. Two general methods were used to prepare the *N*-alkyl derivatives from the nor base XIc. In one method, XIc was alkylated directly with an alkyl halide, usually without protection of the phenolic hydroxyl group. Very reactive halides, such as propargyl bromide, produced some of the *O,N*-dipropargyl derivative. Quaternization was minimal when only 1 equiv of the alkyl halide was used. Acylation followed by reduction was a more versatile procedure. One equivalent of acyl halide usually gave the *N*-acyl derivative selectively, but ester amides were obtained with an excess of acyl halide. Phenolic and ester amides were easily reduced with $LiAlH_4$ or B_2H_6 in refluxing THF to provide phenolic tertiary amines in good yield. Table VII includes intermediate amides when these were isolated and characterized.

Table VIII gives the $[\alpha]_D$ values of all optically active compounds listed in Tables IV through VII. With many compounds, the optical rotation was measured not only at 589 nm (sodium D line) but also at 578, 546, 436 and 365 nm. Thus, it was clear that compound **199** belonged to the levorotatory series (in addition to chemical evidence), although it had $[\alpha]_D$ 0°.

Furthermore, ORD and CD curves of two 9-demethyl *d* and *l* pairs, compounds **36** and **37** and **42**[17] and **43**, were determined and compared with ORD and CD curves of compounds **49**[17] and **50** (see Figure 1, A–D). From the curves, the absolute configuration of **42**, the 9-demethyl analogue of **49**, is obviously the same as that of **49**, whose absolute configuration was established by X-ray crystallography of its *O*-*p*-bromobenzoate ester **88**.[2,5] In contrast to very small differences in peak position and amplitudes between **42** and **49**, the ORD and CD curves of **36** are different due to the lack of the 2′-hydroxy group. Thus, the bands ascribed to the long-wavelength $\pi \rightarrow \pi^*$ transitions (above 280 nm) are missing in the curves of **36**. Nevertheless, there are three distinct negative Cotton effects in the 250–270-nm region which are common for **36** and **42**, as well as for **49**, and which establish the equivalence of their absolute configurations. (These are due to the 5-phenyl substituent, $^1A_1g \rightarrow {}^1B_2u$.) In addition,

Table IV. 2-Methyl-5-phenylbenzomorphans



no.	opt isomer	R^1	R^2	R^3	M[a]	solv[a]	mp, °C	yield, %	emp form.	anal.	analgetic act. TF[b]	analgetic act. POW[c]	mouse jump. test[d] rate	mouse jump. test[d] freq
35	*dl*	H	H	H	5	C	267-270	78	$C_{19}H_{21}N\cdot HBr$	C, H, N, Br	2+/20 sc 2+/40 po		14.7	6/8
36	*l*	H	H	H	6a	B/E	195-196	50	$C_{19}H_{21}N\cdot C_4H_6O_6$[e]	C, H, N	2+/20 sc	5.5 sc	0.0	0/10[f]
37	*d*	H	H	H	6a	B/E	195-197	60	$C_{19}H_{21}N\cdot C_4H_6O_6$[g]	C, H, N	0/320 sc	8.0 sc	20.1	4/7
38	*dl*	CH_3	H	H	5	D	261-262	57	$C_{20}H_{23}N\cdot HBr\cdot H_2O$	C, H, N, Br	2+/40 sc 2+/80 po			
39	*dl*	H	Cl	H	5	C	137-138	96	$C_{19}H_{20}ClN$	C, H, Cl	2+/80 sc 2+/160 po			
40	*dl*	H	H	F	5	E	231-234	59	$C_{19}H_{20}FN\cdot HBr$	C, H, N, Br	0/80 sc	33 po		
41	*dl*	H	H	OH	*h*		249-252				+/20 sc			
42	*l*	H	H	OH	6b	F	308-312	61	$C_{19}H_{21}NO\cdot HCl$	C, H, N, Cl	0/80 sc	5.6 sc		
43	*d*	H	H	OH	6b	F	308-313	70	$C_{19}H_{21}NO\cdot HCl$	C, H, N, Cl	0/60 sc	5.5 sc	0.6	1/6
44	*dl*	$H_{4\beta\text{-}CH_3}$	H	OH	5	C	217-218	57	$C_{20}H_{23}NO$	C, H, N	+/160 sc			
45	*dl*	H	H	2′,3′-$(OH)_2$	5		254-258	23	$C_{19}H_{21}NO_2$	C, H, N	0/320 sc			
46	*dl*	H	H	1′,2′,3′-$(OH)_3$	5	C	293-294	23	$C_{19}H_{21}NO_3\cdot HBr$	C, H, N, Br	0/160 po			
47	*dl*	H	Cl	OH	5	B	272-274	57	$C_{19}H_{20}ClNO$	C, H, Cl	2+/40 sc			
48	*dl*	CH_3	H	OH	*i*		226-228				2+/5 sc 2+/10 po		6.4	3/10[j]
49	*l*	CH_3	H	OH	*i*		312-315				2+/2 sc	0.5 sc	41.5	10/10[j]
50	*d*	CH_3	H	OH	*i*		310-312				2+/20 sc 2+/40 po	4.2 sc	12.4	5/10[j]
51	*dl*	CH_3	Cl	OH	5	C	233-234	77	$C_{20}H_{22}ClNO$	C, H, N, Cl	2+/10 sc 2+/20 po			
52	*dl*	CH_3	F	OH	5	B	214-215	84	$C_{20}H_{22}FNO$	C, H, N	2+/2.5 sc 2+10 po		11.2	7/10
53	*dl*	C_2H_5	H	OH	5	E	203-205	92	$C_{21}H_{25}NO$	C, H, N	2+/20 sc		23.0	6/8
54	*dl*	H	OH	OH	5	B	324-325	73	$C_{19}H_{21}NO_2\cdot HBr$	C, H, N, Br	0/320 po			

[a-d] See footnotes *a-d* in Table III. [e] *l*-Tartrate. [f] Mice treated with test compound for 2 days and then challenged with nalorphine (nalorphine dose = 100 mg/kg) (see ref *d*, Table III). [g] *d*-Tartrate. [h] See ref 10. [i] See ref 10. [j] For monkey data, see ref 4.

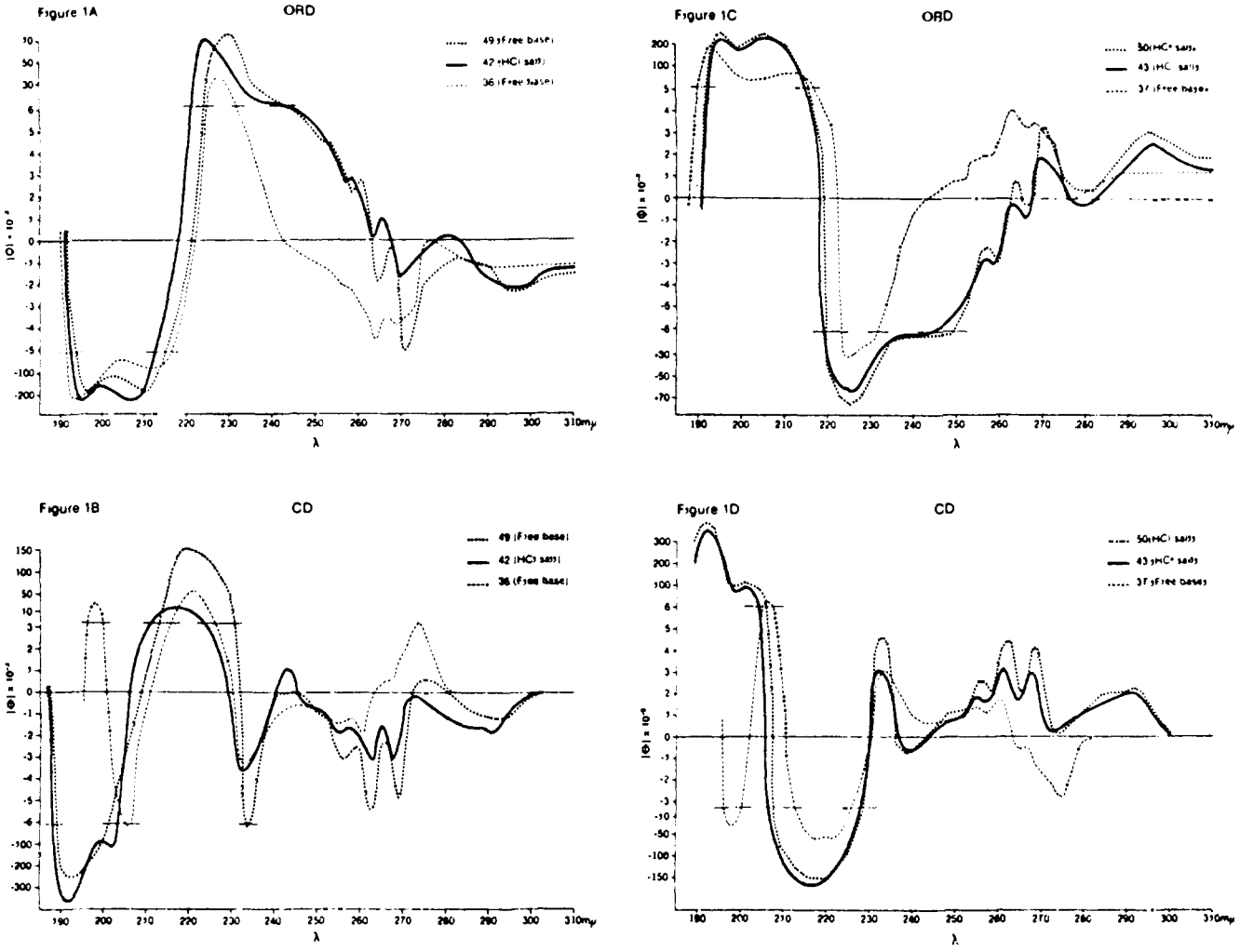
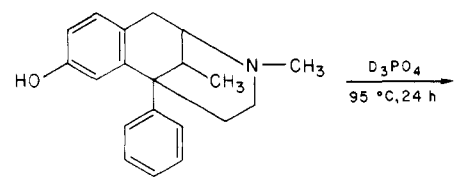


Figure 1. ORD and CD curves of optical isomers. Compounds **49** and **50** are, respectively, the *l* and *d* isomers of 2,9-dimethyl-2′-hydroxy-5-phenyl-6,7-benzomorphan. **42** and **43** are the corresponding 9-demethyl analogues. **36** and **37** are the corresponding 9-demethyl-2′-deoxy analogues.

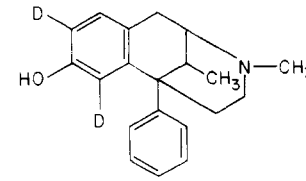
all three compounds have similar negative Cotton effects around 235 nm ($^1A_1g \rightarrow {}^1B_1u$). Differences of the CD curve of **36** from those of **42** and **49** below 210 nm are again due to the absence of a phenolic hydroxy group ($^1A_1g \rightarrow {}^1E_1u$).[18] It should be noted that the comparison among **36**, **42**, and **49** are made with the free base, HCl salt, and the free base, respectively, while the comparison among **37**, **43**, and **50** are made with the free base (**37**) and HCl salts (**43** and **50**). However, as was pointed out previously by Karliner,[17] ORD and CD curves of the free base and HCl salt of **49** and **50** have similar spectral characteristics with only minor differences in peak position and amplitudes. Clearly, the ORD and CD spectroscopic evidence establishes the absolute stereochemistry of the optically active compounds of Figure 1. By inference, the absolute configuration of all the other compounds is also established, since they were prepared from common intermediates, respectively.

In order to facilitate the study of their biological disposition,[19] several ^3H- and ^{14}C-labeled compounds were prepared (see Experimental Section). A very convenient and effective ^3H-labeling technique was developed. In a model experiment, **49** was heated with D_3PO_4 at 95 °C for 24 h[20] (Scheme V). The NMR spectrum of the product showed that the 1′- and 3′-H had been selectively exchanged with D to the extent of 98%. Tritiation of **49** with tritiated H_2O and P_2O_5 readily afforded ^3H-labeled **49** with a specific activity of 17 mCi/mmol. Compounds with a labile substituent were prepared from a ^3H-labeled *N*-nor

Scheme V



49

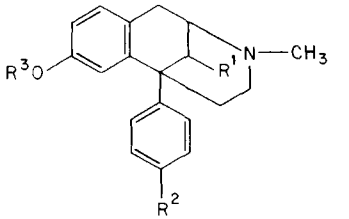


49-*d*

compound **110**. Since ^3H's ortho to a phenolic hydroxy group could be lost under physiological conditions in some circumstances,[19] the *N*-methyl ^{14}C-labeled **49** was prepared from **110** by alkylation of **110** with $^{14}CH_3I$ at low temperature.

Pharmacology. Much of the pharmacology of the most interesting compounds of this series has been published (see references in Table IX). Since many publications have identified these compounds by their GPA numbers, a number of these are tabulated in Table IX together with the corresponding compound numbers of Tables IV to VII.

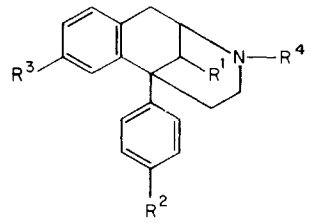
Table V. Derivatives of 2′-Hydroxy-2-methyl-5-phenyl-6,7-benzomorphan



no.	opt isomer	R¹	R²	R³	M[a]	solv[a]	mp, °C	yield, %	emp form.	anal.	analgetic act. TF[b]	analgetic act. PQW[c]	mouse jump. test[d] rate	mouse jump. test[d] freq
55	*dl*	H	H	$COCH_3$	*e*	Q	250-253				0/80 sc	9.4 sc	0.0	0/10
56	*d*	H	H	$COCH_3$	8a		110-111	75	$C_{21}H_{23}NO_2$					
57	*l*	H	H	$COCH_3$	8a	E	110-111	77	$C_{21}H_{23}NO_2$					
58	*d*	H	H	CH_3	7a	A	238-240	89	$C_{20}H_{23}NO\cdot HCl\cdot H_2O$	C, H, N, Cl	0/30 sc	16 sc	0.7	2/10[f]
59	*l*	H	H	CH_3	7a	A	246-248	84	$C_{20}H_{23}NO\cdot HCl\cdot H_2O$	C, H, N, Cl	0/320 po			
60	*dl*	H	H	CH_3	*g*		204-207				0/100 sc	14 sc	3.1	3/10
61	*dl*	H	H	p-$SO_2C_6H_4CH_3$	8g	C/B	232-235	65	$C_{26}H_{27}NO_3S\cdot HBr$	C, H, N, S, Br	0/80 sc			
62	*dl*	H	H	$SCN(CH_3)_2$	8h	B	180-182	95	$C_{22}H_{26}N_2OS$	C, H, N, S	0/40 sc 0/320 po			
63	*dl*	H	Cl	$COCH_3$	8a	Q	115-117	82	$C_{21}H_{22}ClNO_2$	C, H, Cl	+/100 sc	20 sc		
64	*dl*	CH_3	H	$COCH_3$	8a	N	149-150	69	$C_{22}H_{25}NO_2$	C, H, N				
65	*d*	CH_3	H	$COCH_3$	8a	B	172-174	81	$C_{22}H_{25}NO_2$	C, H, N				
66	*l*	CH_3	H	$COCH_3$	8a	E	172-174	79	$C_{22}H_{25}NO_2$	C, H, N	2+/4 sc 2+/10 po		4.8	5/10[f]
67	*dl*	H	$OCOCH_3$	$COCH_3$	8a	N	121-122	71	$C_{23}H_{25}NO_4$	C, H, N				
68	*d*	CH_3	H	CH_3	7b	A	233-235	40	$C_{21}H_{25}NO\cdot HCl\cdot H_2O$	C, H, N, Cl	2+/80 sc			
69	*l*	CH_3	H	CH_3	7b	M	253-255	85	$C_{21}H_{25}NO\cdot HCl$	C, H, N, Cl	2+/40 sc 2+/20 po			
70	*l*	CH_3	H	COC_2H_5	8b	B	141-142	20	$C_{23}H_{27}NO_2$	C, H, N	2+/2.5 sc			
71	*l*	CH_3	H	COC_3H_7	8b	B	99-100	56	$C_{24}H_{29}NO_2$	C, H, N	2+/10 po 2+/20 po		9.6	9/10[f]
72	*l*	CH_3	H	*n*-COC_4H_9	8b	E	94-95	62	$C_{25}H_{31}NO_2$	C, H, N	2+/1.5 sc 2+/10 po		7.7	9/10[f]
73	*l*	CH_3	H	CO-c-C_4H_7	8c	E	111-112	26	$C_{25}H_{29}NO_2$	C, H, N	2+/2.5 sc 2+/20 po			
74	*l*	CH_3	H	$CONHCH_2$-$COOC_2H_5$	8i	B	166-168	40	$C_{25}H_{30}N_2O_4$	C, H, N	2+/40 sc +/80 po			
75	*l*	CH_3	H	CH_2OCH_3	7d	E	78-80	47	$C_{22}H_{27}NO_2$	C, H, N	2+/5 sc 2+/20 po			
76	*l*	CH_3	H	SO_2CH_3	8j	E	107-108	60	$C_{21}H_{25}NO_3S$	C, H, N, S		5.3 sc	10.5	3/7
77	*l*	CH_3	H	$COCH_2Cl$	8c	E	139-140	20	$C_{22}H_{24}ClNO_2$	C, H, N, Cl	2+/2.5 sc			
78	*l*	CH_3	H	*p*-$SO_2C_6H_4CH_3$	8g	M	263-264	75	$C_{27}H_{29}NO_3S\cdot HCl$	C, H, N, Cl, S		>100 sc		
79	*l*	CH_3	H	COC_6H_5	8c	E	115-116	60	$C_{27}H_{27}NO_2$	C, H, N		0.5 sc	3.6	5/8[f]
80	*l*	CH_3	H	*o*-COC_6H_4Cl	8c	E	164-165	65	$C_{27}H_{26}ClNO_2$	C, H, N, Cl		49 po	24.8	10/10[f]
81	*l*	CH_3	H	*m*-COC_6H_4Cl	8c	E	110-111	63	$C_{27}H_{26}ClNO_2$	C, H, N, Cl	2+/1.2 sc		7.6	6/8[f]
82	*l*	CH_3	H	*p*-COC_6H_4Cl	8c	E	168-169	91	$C_{27}H_{26}ClNO_2$	C, H, N, Cl	2+/1.2 sc		18.6	8/10[f]
83	*l*	CH_3	H	2,6-$COC_6H_3Cl_2$	8c	E	152-153	45	$C_{27}H_{25}Cl_2NO_2$	C, H, N, Cl		>100 sc		
84	*l*	CH_3	H	*o*-COC_6H_4F	8c	E	142-143	84	$C_{27}H_{26}FNO_2$	C, H, N, F		0.5 sc	17.4	5/5[f]
85	*l*	CH_3	H	*p*-COC_6H_4F	8c	E	148-149	86	$C_{27}H_{26}FNO_2$	C, H, N, F		0.7 sc	1.9	7/10[f]
86	*l*	CH_3	H	*m*-$COC_6H_4NO_2$	8c	E	150-151	52	$C_{27}H_{26}N_2O_4$	C, H, N	2+/1.2 sc		22.7	10/10[f]
87	*l*	CH_3	H	*p*-$COC_6H_4NO_2$	8c	E	165-166	78	$C_{27}H_{26}N_2O_2$	C, H, N		0.6 sc	12.0	4/7[f]
88	*l*	CH_3	H	*p*-COC_6H_4Br	*g*	E	161-162				2+/5 sc 2+/1.2 po		16.0	8/10[f]

[a-d] See footnotes *a–d* in Table III. [e] See ref 10. [f] Mice treated with test compound for 2 days and then challenged with nalorphine (nalorphine dose = 50 mg/kg sc)(See reference given in footnote *d*, Table III). [g] See ref 2.

Table VI. Intermediates to *N*-Substituted 5-Phenyl-6,7-benzomorphans



XIa, R^4 = CN
b, R^4 = COOEt
c, R^4 = H

no.	type	opt isomer	R^1	R^2	R^3	M[a]	solv[a]	mp, °C	yield, %	emp form.	anal.	analgetic act. TF[b]	analgetic act. PQW[c]	mouse jump. test[d] rate	mouse jump. test[d] freq
89	a	*dl*	H	H	$OCOCH_3$	*e*		206-208							
90	b	*dl*	H	H	$OCOCH_3$	10a	H	105-107	63	$C_{23}H_{25}NO_4$	C, H, N	0/320 po	>100 po		
91	c	*dl*	H	H	OH	*e*		236-237				0/320 sc 0/160 po	>100 sc		
92	a	*l*	H	H	$OCOCH_3$	9a	E	178-180	62	$C_{21}H_{20}N_2O_2$	C, H, N				
93	c	*l*	H	H	OH	9b	E	261-263	63	$C_{18}H_{19}NO \cdot C_3H_8O$[f]	C, H, N	0/320 po	>100 sc		
94	b	*dl*	H	H	OCH_3	7c		120[g]	35	$C_{22}H_{25}NO_3$	C, H, N				
95	c	*dl*	H	H	OCH_3	7a	E	255-256	95	$C_{19}H_{21}NO \cdot HCl$	C, H, N, Cl	0/320 sc	100 sc		
96	a	*dl*	H	Cl	$OCOCH_3$	9a	C	168-170	49	$C_{21}H_{19}ClN_2O_2$	C, H, N, Cl	0/100 po	>100 sc		
97	c	*dl*	H	Cl	OH	9b	E	275-278	47	$C_{18}H_{18}ClNO$	C, H, N	0/320 sc			
98	c	*dl*	H	OH	OH	9c	B	341-343	68	$C_{18}H_{19}NO_2 \cdot HCl$	C, H, N, Cl	0/320 po			
99	a	*dl*	H	H	H	9a	D	153-155	81	$C_{19}H_{18}N_2$	C, H, N				
100	c	*dl*	H	H	H	9b	D	277-278	80	$C_{18}H_{19}N \cdot HCl$	C, H, N, Cl[h]	2+/80 sc		2.7	4/10
101	a	*l*	H	H	H	9a		oil	100						
102	c	*l*	H	H	H	9c	C	295-298	85	$C_{18}H_{19}N \cdot HCl$	C, H, N, Cl	+/160 sc			
103	a	*d*	H	H	H	9a		oil	100						
104	c	*d*	H	H	H	9c	C	297-300	75	$C_{18}H_{19}N \cdot HCl \cdot 0.33H_2O$	C, H, N, Cl				
105	a	*dl*	H	Cl	H	9a	D	153-154	76	$C_{19}H_{17}ClN_2$					
106	c	*dl*	H	Cl	H	9b	D	323-324	63	$C_{18}H_{18}ClN \cdot HCl$					
107	a	*dl*	CH_3	H	$OCOCH_3$	9a	D	188-189	85	$C_{22}H_{22}N_2O_2$	C, H, N				
108	c	*dl*	CH_3	H	OH	9b	F	291-292	65	$C_{19}H_{21}NO \cdot C_3H_8O$[f]	C, H, N				
109	a	*l*	CH_3	H	$OCOCH_3$	9a	D	183-184	74	$C_{22}H_{22}N_2O_2$	C, H, N				
110	c	*l*	CH_3	H	OH	10a, 10b	E	309-311	76	$C_{19}H_{21}NO$	C, H, N	0/320 sc 0/320 po			
111	a	*d*	CH_3	H	$OCOCH_3$	9a	D	185-186	74	$C_{22}H_{22}N_2O_2$	C, H, N				
112	c	*d*	CH_3	H	OH	10a, 10b	E	310-312	78	$C_{19}H_{21}NO$	C,[i] H, N	0/320 po			

[a-d] See footnotes *a-d* in Table III. [e] See ref 10. [f] Isopropanolate. [g] Boiling point, °C(0.1 Torr). [h] Cl; calcd, 12.41; found, 11.16. [i] C; calcd, 81.68; found, 80.34.

Antagonist potency in the guinea pig ileum assay has been correlated recently with opiate receptor binding for a number of these compounds.[21] Tables III to VII inclusively list the analgetic potencies and physical dependence capacities that were measured in mice. Conclusions based on quantitative comparisons are difficult to make, because not all compounds were studied in each test and by the same route of administration. In the tail-flick (TF) test, the activity is listed on a scale of 0 to +2 at the indicated dose in mg/kg and the indicated route of administration. Numbers listed for the phenylquinone writhing test (PQW) are ED_{50} doses for the indicated route of administration (see Experimental Section). In the mouse jumping test (loc. cit.), mice are treated chronically with the test compound for 2 days and then challenged with naloxone. The average number of jumps (rate) and the number of mice affected (frequency) are listed.

Compound **22**, in which $R_1 = R_2 = R_3 = H$, was the most potent of the 4-aryl-2-benzyl-Δ^3-piperideine derivatives of Table III as an analgetic. These compounds are less potent than morphine, but most of them are free of physical dependence capacity in mice.

Of the 5-phenylbenzomorphans, *l* isomers are more potent as analgetics than *d* isomers, but when there is no 9β-methyl substituent the difference in analgetic potency is very much diminished[5] [compare compounds **42** and **43**, **36** and **37**, and **49** and **50** (Table IV) and **154** and **155** (Table VII)]. The *l* isomers with antagonist-like substituents (Table VII, compounds **203** through **219**) are less potent than the corresponding 5,9-dialkyl-6,7-benzomorphans, morphinans, or normorphine derivatives either as analgetics or as antagonists,[22] and most *d* isomers with antagonist-like substituents (Table VII, compounds **146–148**) are inactive or very weak as analgetics. The *N*-phenethyl analogue (**180** of Table VII) of **49** (Table IV) is actually less active than **49**. This is a surprising result in view of the fact that in the 5,9α-dimethylbenzomorphan series the phenethyl substituent enhances the analgetic activity. In these aspects, the 5-phenyl-6,7-benzomorphans are hybrids between 5,9-dialkyl-6,7-benzomorphans and 5-phenylmorphans in their SAR characteristics.[23] It is interesting to note that esters of **49**, particularly chlorobenzoyl esters, are as potent analgetics as the parent compound by subcutaneous administration. However, none of these esters were free of physical dependence capacity in the mouse (Table V). Of the *N*-alkyl analogues of **49**, the *n*-pentyl compound **174** (Table VII) is one of the most potent analgetics of this series, whereas the ethyl and the *n*-propyl compounds **172** and **173** (Table VII) are practically inactive and the β-hydroxyethyl and 2-(furylmethyl) compounds **203** and **195** (Table VII) demonstrated antagonistic characteristics in the guinea pig ileum assay.[24]

Experimental Section

Chemistry. Most of the methods described below are generalized procedures and were used for many of the compounds listed in the tables. Where analyses are indicated by symbols of the elements, the microanalytical results were within ±0.4% of the theoretical values. Melting points and boiling points are uncorrected. Optical rotations are provided in Table VIII.

Values of $[\alpha]_D$ have been determined on a Perkin-Elmer 141 polarimeter. ORD and CD curves were determined with a Durrum-Jasco Model J-20 at a sample cell compartment temperature of 26 °C. Sample cells of 0.1- and 1.0-mm fixed path lengths were employed with a concentration range of 10^{-2} to 10^{-4} M. The NMR spectra were determined on a Varian A/60 spectrometer in deuterated solvents with an internal standard (Me_4Si). Chemical shifts are recorded in δ values (ppm downfield from the reference signal). In NMR descriptions, the following abbreviations were used: s, singlet; d, doublet; q, quartet; m, multiplet. Specific radioactivity of ^{14}C- and ^{3}H-labeled compounds were determined with a Packard Tri-Carb Model 3380 scintillation spectrophotometer.

List of Solvents. A, water; B, methanol; C, 95% ethanol; D, absolute ethanol; E, 2-propanol; F, butanol; G, petroleum ether; H, cyclohexane; I, hexane; J, heptane; K, benzene; L, toluene; M, acetone; N, ether; O, THF; P, chloroform; Q, ethyl acetate; R, pyridine; S, dimethyl sulfoxide; T, sublimation in vacuo; U, precipitated from aqueous base; V, 1 N NaOH; W, methanol–chloroform (1:1); X, methanol–chloroform (3:1).

Preparation of 4-Aryl-Δ^3-piperidine Derivatives (Table I). 4-(*p*-Chlorophenyl)-1,3-dimethyl-Δ^3-piperidine (6; Method 1a). To a solution of 375 mL (0.6 mol) of 1.6 N *n*-butyllithium in hexane at −25 °C was slowly added, with stirring, 105 g (0.55 mol) of *p*-chlorobromobenzene in 200 mL of ether. After storing the solution for 2.5 h at −25 °C, a solution of 63.5 g (0.5 mol) of 1,3-dimethyl-4-piperidone was added slowly, and the mixture was warmed to room temperature and stirred an additional 2 h. Then, 200 mL of water was added, and the organic layer was separated and extracted with 1 N hydrochloric acid. The acidic extract was basified with ammonia and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated to leave 70.4 g (59%) of 4-(*p*-chlorphenyl)-1,3-dimethyl-4-piperidinol as a white solid, mp 107–109 °C. Anal. ($C_{13}H_{18}ClNO$) C, H, N, Cl. A solution of 76.0 g (0.32 mol) of the piperidinol in 400 mL of 12 N hydrochloric acid was refluxed for 48 h, cooled, basified with ammonia, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to provide 66.7 g (95%) of the product as a brown oil. The oil was converted to the quaternary ammonium salt without purification.

4-(*p*-Fluorophenyl)-1,3-dimethyl-Δ^3-piperidine (7; method 1b) was obtained as a brown oil in 77% crude yield from the corresponding 4-(*p*-fluorophenyl)-4-piperidinol. The piperidinol melted at 124–126 °C. Anal. ($C_{13}H_{18}FNO$) C, H, N.

3-Ethyl-1-methyl-4-phenyl-Δ^3-piperidine (8; method 2) was obtained in a similar manner from 3-ethyl-1-methyl-4-phenyl-3-piperidinol. In this case, the product was characterized as its hydrochloride salt, which was recrystallized first from acetone and then from methanol. The intermediate 3-piperidinol was obtained from 1-methyl-4-phenyl-3-piperidone hydrochloride[11] with ethyllithium in benzene. The 3-piperidinol was obtained as an oil, bp 95–99 °C (0.2 mm) (75%). Anal. ($C_{14}H_{21}NO$) C, H, N.

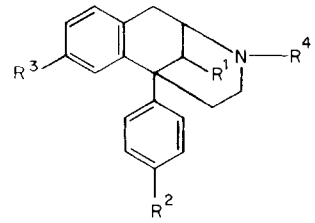
Quarternization of 4-Aryl-1-methyl-Δ^3-piperidines (Table II; Method 3). To a solution of 64.4 g (0.29 mol) of crude **6** in 150 mL of acetone was added slowly a solution of 45.25 g (0.29 mol) of *p*-anisyl chloride in 50 mL of acetone. The solution was then stirred and refluxed for 5 h and cooled, and the solid was collected to give 42.5 g (85%) of **15** as a white crystalline powder, mp 200–203 °C. A sample for analysis was obtained by recrystallization from acetone.

Stevens' Rearrangement of a Quaternary *N*-Benzyl-Δ^3-piperidinium Salt (Table III). With C_6H_5Li (Method 4a). To a slurry of 18.0 g (0.05 mol) of quaternary salt **11** in 100 mL of ether at 5–10 °C was added 26.6 mL (0.06 mol) of phenyllithium solution. After stirring the solution for 0.5 h, 50 mL of 1 N HCl was added. The aqueous layer was separated and basified with NH_3, and the product was extracted with ether to give 9.6 g (59%) of an oil. The oil was first converted to its picrate salt (mp 198–203 °C from acetone) and then to its hydrobromide salt (2.6 g, mp 189–192 °C from ethanol) of **23**. Similarly, **24** was purified via its picrate salt (mp 149–152 °C from acetone–ether). Compound **21** gave a hydrobromide salt from ethanol–acetone–ether.

With KNH_2 (Method 4b). To a solution of 0.84 mol of KNH_2 in 1.2 L of NH_3 (*l*) was added 121 g (0.35 mol) of compound **18** over 0.3 h. The red solution was stirred 0.6 h, then excess KNH_2 was destroyed with 8.4 g of NH_4Cl, and the NH_3 (*l*) was allowed to evaporate. The residue was taken up in aqueous HCl and ether, and the acidic solution was separated, basified with NH_3, and extracted with ethyl acetate. The extract was dried (Na_2SO_4), concentrated to 300 mL in vacuo, and treated with ethanolic HBr to give 97.4 g (71%) of crude **30**, mp 224–226 °C. Recrystallization from 2 L of MeOH gave 74 g (54%) of purified **30**.

When the quaternary salt **20** (163 g, 0.46 mol) was treated in a similar manner, the crude base was chromatographed on neutral

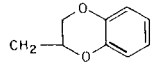
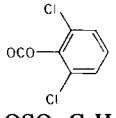
Table VII. N-Substituted 5-Phenyl-6,7-benzomorphans



no.	opt isomer	R^1	R^2	R^3	R^4	M[a]	solv[a]	mp, °C	emp form.	anal.	analgetic act. TF[b]	analgetic act. PQW[c]	mouse jump. test[d] rate	mouse jump. test[d] freq
113	*dl*	H	H	$OCOCH_3$	$COCH_3$	8a	L/H	148-150	$C_{22}H_{23}NO_3$	C, H, N	0/30 po	>100 sc		
114	*dl*	H	H	OH	$COCH_3$	11	C	258-260	$C_{20}H_{21}NO_2$	C, H, N	0/100 po	>100 sc		
115	*dl*	H	H	OH	C_2H_5	12a	B	232-234	$C_{20}H_{23}NO$	C, H, N	0/30 sc	>30 sc		
116	*dl*	H	H	OH	n-C_5H_{11}	13a	C	314-316	$C_{23}H_{29}NO\cdot HCl$	C, H, N, Cl	0/320 po	23 sc		
117	*dl*	H	H	OH	$CH_2CH_2C_6H_5$	13a	A/S	347-349	$C_{26}H_{27}NO\cdot HCl$	C, H, N, Cl	2+/40 sc			
118	*dl*	H	H	OH	$CH_2CH_2C_6H_4NO_2$-p	13a	F	252-255	$C_{26}H_{26}N_2O_3$	C, H, N	0/320 sc			
119	*dl*	H	H	OH	$CH_2CH_2C_6H_4NH_2$·p	15	B	228-232	$C_{26}H_{28}N_2O\cdot 0.25H_2O$	C, H, N				
120	*dl*	H	H	OH	$(CH_2)_3C_6H_5$	13a	C	187-190	$C_{27}H_{29}NO$	C, H, N	2+/160 po	>100 po	7.5	5/10
121	*dl*	H	H	OH	$CH_2CH{=}CHC_6H_5$	13a	B	274-277	$C_{27}H_{27}NO\cdot HCl$	C, H, N, Cl	2+/320 po			
122	*dl*	H	H	OH	$(CH_2)_4C_6H_5$	13a	C	174-176	$C_{28}H_{31}NO$	C, H, N	0/320 po	>100 po		
123	*dl*	H	H	OH	CH_2CH_2-2-c-C_4H_3S	13a	B	317-318	$C_{24}H_{25}NOS\cdot HCl$	C, H, Cl, S	0/320 po			
124	*dl*	H	H	OH	CH_2CH_2-c-$N(CH_2CH_2)_2O$	13a	B	281-282	$C_{24}H_{31}N_2O_2\cdot 2HBr$	C, H, N	0/320 po	>100 sc		
125	*dl*	H	H	OH	$CH_2CH_2CO_2Et$	14	C	162-165	$C_{23}H_{27}NO_3$	C, H, N	0/320 sc	78 sc >100 po		
126	*dl*	H	H	OH	$CH_2CH_2CONMe_2$	14	B	189-192	$C_{23}H_{28}N_2O_2$	C, H, N	0/50 sc			
127	*dl*	H	H	OH	$(CH_2)_3NMe_2$	12a	M	165-168	$C_{23}H_{30}N_2O$	C, H, N	0/320 sc			
128	*dl*	H	H	OH	CH_2CH_2OH	13a	N	178-181	$C_{20}H_{23}NO_2$	C, H, N	0/320 sc	>100 sc		
129	*dl*	H	H	OH	$CH_2CH{=}CH_2$	13a	D	238-240	$C_{21}H_{23}NO$	C, H, N	A/200 po[e]	>100 sc		
130	*dl*	H	H	OCH_3	$CH_2CH{=}CH_2$	7a	M	202-204	$C_{22}H_{25}NO\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl	A/20 sc			
131	*dl*	H	H	OH	$CH_2C{\equiv}CH$	13a	B	238-239	$C_{21}H_{21}NO$	C, H, N	A/20 sc			
132	*dl*	H	H	OH	$CH_2CH{=}CHCl$	13a	D	195-197	$C_{21}H_{22}ClNO$	C, H, N	A/40 sc	>100 sc	0.0	0/10
133	*dl*	H	H	OH	$CH_2CH{=}CMe_2$	13a	D	174-176	$C_{23}H_{27}NO$	C, H, N	P/40 sc[e]	15 sc	0.3	1/6
134	*dl*	H	H	$OCOC_6H_5$	$CH_2C{\equiv}CH$	8c	E	147-148	$C_{28}H_{25}NO_2$	C, H, N		>100 sc		
135	*dl*	H	H	OH	$CH_2CH{=}C(Cl)CH_3$	13a	E	184-186	$C_{22}H_{24}ClNO$	C, H, N	p/20 sc	>100 sc		
136	*dl*	H	H	OH	$CH_2C(Br){=}CH_2$	13a	N	165-167	$C_{21}H_{22}BrNO$	C, H, N, Br	A/40 sc	>100 sc		
137	*dl*	H	H	OCO-c-C_3H_5	CO-c-C_3H_5	8e	N	135-138	$C_{26}H_{27}NO_3$	C, H, N	0/60 po	>100 sc		
138	*dl*	H	H	OH	CH_2-c-C_3H_5	12a	E	194-196	$C_{22}H_{25}NO\cdot HCl\cdot C_3H_8O$[f]	C, H, N, Cl	A/10 sc	33 sc 107 po	0.0	0/40[g]
139	*dl*	H	H	OH	CH_2-c-C_4H_7	8e, 12a	A/B	310-312	$C_{23}H_{27}NO\cdot HCl$	C, H, N, Cl		6.2 sc 124 po	0.0	0/40[g]
140	*dl*	H	H	n-$OCOC_4H_9$	CH_2-c-C_4H_7	8c	P/N	262-264	$C_{28}H_{35}NO_2\cdot HCl$	C, H, N, Cl		>100 po		
141	*dl*	H	H	OCH_3	CH_2-c-C_4H_7	7b	C	238-240	$C_{24}H_{29}NO\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl		>100 po		
142	*l*	H	H	OH	$CH_2CH_2C_6H_5$	13a	B/N	306-307	$C_{26}H_{27}NO\cdot HCl$	C, H, N, Cl	2+/80 po	7.4 sc	34.2	10/10
143	*l*	H	H	OH	$CH_2CH{=}CH_2$	13a	D	240-242	$C_{21}H_{23}NO$	C, H, N	A/20 sc	>80 sc		
144	*l*	H	H	OH	CH_2-c-C_3H_5	8e, 12a	E	203-205	$C_{22}H_{25}NO\cdot HCl\cdot C_3H_8O$[f]	C, H, N, Cl	A/10 sc	>33 sc		
145	*l*	H	H	OH	CH_2-c-C_4H_7	8e, 12a	B	338-340	$C_{23}H_{27}NO\cdot HCl$	C, H, N, Cl		2.8 sc 34 po	0.0	0/10
146	*d*	H	H	OH	$CH_2CH{=}CH_2$	13a	D	242-244	$C_{21}H_{23}NO$	C, H, N	0/320 po	>30 sc		
147	*d*	H	H	OH	CH_2-c-C_3H_5	8e, 12a	E	252-253	$C_{22}H_{25}NO$	C, H, N		tox/33 sc		
148	*d*	H	H	OH	CH_2-c-C_3H_5	8e, 12a	B/N	335-338	$C_{23}H_{27}NO\cdot HCl$	C, H, N, Cl		15 sc		
149	*dl*	H	Cl	OH	$CH_2CH_2C_6H_5$	13a	S/A	>350	$C_{26}H_{26}ClNO\cdot HCl$	C, H, N, Cl	0/80 po	>100 sc		

150	*dl*	H	Cl	H	$CH_2CH_2C_6H_5$	13a	B	311-312	$C_{26}H_{26}ClN\cdot HBr$	C, H, N	0/320 po	>100 sc		
151	*dl*	H	H	H	$CH_2CH_2C_6H_5$	13a	E	314-315	$C_{26}H_{27}N\cdot HCl$	C, H, N, Cl	2+/160 po			
152	*dl*	H	H	H	C_2H_5	13b	E	234-235	$C_{20}H_{23}N\cdot HBr$	C, H, N, Br	0/320 sc	16 sc	1.2	2/6
153	*dl*	H	H	H	$(CH_2)_3COC_6H_4F$-*p*	13b	B	252-254	$C_{28}H_{28}FNO\cdot HCl$	C, H, N, Cl		>150 po		
154	*l*	H	H	H	$CH_2CH_2C_6H_5$	13a	E	258-260	$C_{26}H_{27}N\cdot HCl$	C, H, N, Cl	0/160 sc			
155	*d*	H	H	H	$CH_2CH_2C_6H_5$	13b	Q/B	207-210	$C_{26}H_{27}N\cdot CH_4O_3S$[h]	C, H, N, S		>100 sc		
156	*dl*	CH_3	H	OH	*n*-C_5H_{11}	13a	D	154-155	$C_{24}H_{31}NO$	C, H, N	2+/5 sc			
157	*dl*	CH_3	H	OH	$CH_2CH_2C_6H_5$	13a	E	169-171	$C_{27}H_{29}NO$	C, H, N	2+/20 sc 2+/40 po			
158	*dl*	CH_3	H	OH	CH_2CH_2OH	13a	J/N	183-184	$C_{21}H_{25}NO_2$	C, H, N	0/160 sc 0/320 po	44 sc >100 po	0.4	1/10
159	*dl*	CH_3	H	OH	$CH_2CH{=}CMe_2$	13b	E	264-265	$C_{24}H_{29}NO\cdot CH_4O_3S$[h]	C, H, N, S				
160	*dl*	CH_3	H	OH	$CH_2CH{=}C(Cl)Me$	13a	J	119-121	$C_{23}H_{26}ClNO$	C, H, N, Cl	0/160 sc	>100 sc		
161	*dl*	CH_3	H	OH	CH_2-*c*-C_4H_7	8e, 12b	E	249-250	$C_{24}H_{29}NO\cdot CH_4O_3S$[h]	C, H, N, S		>100 po		
162	*d*	CH_3	H	OH	*n*-C_5H_{11}	13b	J	110-111	$C_{24}H_{31}NO$	C, H, N	+/160 sc	>100 po		
163	*d*	CH_3	H	OH	*n*-C_3H_7	8e, 12a	B/A	315-317	$C_{22}H_{27}NO\cdot HCl$	C, H, N, Cl		14 sc >100 po	21.5	7/9
164	*d*	CH_3	H	OH	CO-*c*-$C_{10}H_{15}$[i]	8e, 11	B	183-184	$C_{30}H_{35}NO_2\cdot H_2O$	C, H, N	+/320 po	>100 po		
165	*d*	CH_3	H	OH	CH_2-*c*-$C_{10}H_{15}$[i]	12a	M	320-322	$C_{30}H_{37}NO\cdot HCl$	C, H, N, Cl	0/320 po	>100 po		
166	*d*	CH_3	H	OH	$CH_2CH_2CH(C_6H_5)_2$	13b	B	263-265	$C_{34}H_{35}NO\cdot HBr\cdot 0.75H_2O$	C, H, N, Br	0/320 po	>100 sc		
167	*d*	CH_3	H	OH	$CH_2CH_2C(CN)(C_6H_5)_2$	13b	B	236-238	$C_{35}H_{34}N_2O$	C, H, N	0/320 po	110 sc >100 po		
168	*d*	CH_3	H	OH	$CH_2CH{=}CH_2$	13a	E	214-219	$C_{22}H_{25}NO\cdot HCl\cdot C_3H_8O$[f]	C, H, N, Cl	p/320 sc			
169	*d*	CH_3	H	OH	$CH_2CH{=}CMe_2$	13a	C	278-280	$C_{24}H_{29}NO\cdot HCl$	C, H, N, Cl	p/160 sc	41 sc		
170	*d*	CH_3	H	OH	CH_2-*c*-C_3H_5	8e, 12a	E	218-220	$C_{23}H_{27}NO\cdot HCl\cdot C_3H_8O$[f]	C, H, N, Cl	p/80 sc	100 sc		
171	*d*	CH_3	H	OH	CH_2-C_4H_7	8e, 12b	B/A	278-280	$C_{24}H_{29}NO\cdot HCl$	C, H, N, Cl		>100 sc		
172	*l*	CH_3	H	OH	C_2H_5	13b	D	189-190	$C_{21}H_{25}NO$	C, H, N	+/140 sc			
173	*l*	CH_3	H	OH	*n*-C_3H_7	8e, 12a	E	311-313	$C_{22}H_{27}NO\cdot HCl$	C, H, N, Cl	0/320 sc	>100 sc		
174	*l*	CH_3	H	OH	*n*-C_5H_{11}	13b	D	112-113	$C_{24}H_{31}NO$	C, H, N	2+/2.5 sc			
175	*l*	CH_3	H	$OCOCH_3$	*n*-C_5H_{11}	8a	E	257-258	$C_{26}H_{33}NO_2\cdot HCl$	C, H, N, Cl	2+/5 sc 2+/40 po			
176	*l*	CH_3	H	OH	*i*-C_5H_{11}	16	M	312-314	$C_{24}H_{31}NO\cdot HCl$	C, H, N, Cl	2+/160 po			
177	*l*	CH_3	H	OH	*n*-$C_{10}H_{21}$	13b	D	130-140	$C_{29}H_{41}NO\cdot HCl$	C, H, N, Cl	0/320 po	70 sc >100 po		
178	*l*	CH_3	H	OH	CO-*c*-$C_{10}H_{15}$[i]	8e, 11	B	277-278	$C_{30}H_{35}NO_2$	C, H, N	0/320 po	>100 sc		
179	*l*	CH_3	H	OH	CH_2-*c*-$C_{10}H_{15}$[i]	12a	M	322-324	$C_{31}H_{37}NO$	C, H, N, Cl	0/320 po	>100		
180	*l*	CH_3	H	OH	$CH_2CH_2C_6H_5$	13b	B	163-164.5	$C_{27}H_{29}NO$	C, H, N	2+/10 sc 2+/80 po			
181	*l*	CH_3	H	OH	$CH_2CH_2C_6H_4NO_2$-*p*	13a	E	280-281	$C_{27}H_{28}N_2O_3\cdot HCl$	C, H, N, Cl	0/320 sc 0/320 po	>100 po		
182	*l*	CH_3	H	OH	$CH_2CH_2C_6H_4NH_2$-*p*	15	B	310	$C_{27}H_{30}N_2O\cdot 2HCl$	C, H, N, Cl	2+/1.2 sc 2+/10 po			
183	*l*	CH_3	H	OH	$CH_2COC_6H_3$	13b	C	264-268(d)	$C_{27}H_{27}NO_2\cdot HBr$	C, H, N, Br		>100 sc		
184	*l*	CH_3	H	OH	$(CH_2)_3COC_6H_4F$-*p*	13b	M	188-190	$C_{29}H_{30}FNO_2\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl, F	0/50 sc	>100 sc	0.0	0/10
185	*l*	CH_3	H	OH	$(CH_2)_4C_6H_5$	13b	C	174-176	$C_{29}H_{33}NO\cdot C_3H_6O_3$[j]	C, H, N	0/100 sc	>100 po		
186	*l*	CH_3	H	$OCOCH(C_6H_5)_2$	$COCH(C_6H_5)_2$	8f	N	115-116	$C_{47}H_{41}NO_3\cdot 0.5H_2O$	C, H, N	0/320 po	>100 sc		
187	*l*	CH_3	H	OH	$CH_2CH(C_6H_5)_2$	12a	M	234-236	$C_{33}H_{33}NO\cdot HCl\cdot H_2O$	C, H, N, Cl	0/160 po			
188	*l*	CH_3	H	OH	$CH_2CH_2CH(C_6H_5)_2$	13b	B	262-264	$C_{34}H_{35}NO\cdot HBr\cdot 0.75H_2O$	C, H, N, Br	0/320 po	>100 sc		
189	*l*	CH_3	H	OH	$CH_2CH_2C(CN)(C_6H_5)_2$	13b	B	238-240	$C_{35}H_{34}N_2O$	C, H, N	0/320 po	>100 po	0.0	0/10[k]
190	*l*	CH_3	H	OH	$CH_2CH_2COC_6H_5$	13b	B/N	186.5-189	$C_{28}H_{29}NO_2\cdot HCl$	C, H, N, Cl	+/160 po		4.8	4/10[k]
191	*l*	CH_3	H	OH	$CH_2CH_2C(OH)(C_6H_5)_2$	17	M	274-275.5	$C_{34}H_{35}NO_2$	C, H, N	0/320 po	>100 sc		
192	*l*	CH_3	H	OH	$CH_2CH_2COCH_3$	18	C	203-204	$C_{23}H_{27}NO_2\cdot CH_4SO_3$	C, H, N, S		>100 po		
193	*l*	CH_3	H	OH	$CH_2CH_2C(OH)(CH_3)_2$	19	C	178-180	$C_{24}H_{31}NO_2$	C, H, N	0/320 sc	78 sc		
194	*l*	CH_3	H	OCO-2-*c*-C_4H_3O	CO-2-*c*-C_4H_3O	8f	N/G	115-116	$C_{29}H_{25}NO_5$	C, H, N	0/60 po			
195	*l*	CH_3	H	OH	CH_2-2-*c*-C_4H_3O	12a	C/G	220-221	$C_{24}H_{25}NO_2\cdot HCl\cdot 1.25H_2O$	C, H, N, Cl	0/320 sc			

Table VII (*Continued*)

no.	opt isomer	R^1	R^2	R^3	R^4	M[a]	solv[a]	mp, °C	emp form.	anal.	analgetic act. TF[b]	analgetic act. PQW[c]	mouse jump. test[d] rate	mouse jump. test[d] freq
196	*l*	CH_3	H	OH	CH_2CH_2-2-c-C_4H_3S	13a	B/N	305	$C_{25}H_{27}NOS\cdot HCl\cdot H_2O$	C, H, N, Cl		>100 sc >100 po		
197	*l*	CH_3	H	OH	$CH_2CH{=}CH$-2-c-C_4H_3S	13b	E	159-161	$C_{26}H_{27}NOS\cdot C_3H_6O_3$[j]	C, H, N, S	0/320 po	>100 po		
198	*l*	CH_3	H	OH		13b	B	240-242.5	$C_{28}H_{29}NO_3\cdot HBr$	C, H, N, Br		84 sc >100 po		
199	*l*	CH_3	H	OH	CH_2CH_2-c-$N(CH_2CH_2)_2O$	13a	C	245.5-247.5	$C_{25}H_{32}N_2O_2$	C, H, N	0/320 po	>100 sc >100 po		
200	*l*	CH_3	H	OH	CH_2COOH	20	U	283-284	$C_{21}H_{23}NO_3$	C, H, N		>100 sc		
201	*l*	CH_3	H	OH	$CH(CH_3)COOC_2H_5$	13b	E	151-154	$C_{24}H_{29}NO_3$	C, H, N	0/320 sc	>100 sc		
202	*l*	CH_3	H	OH	$(CH_2)_3N(CH_3)_2$	14, 12a	C	210-212	$C_{24}H_{32}N_2O$	C, H, N		>120 sc		
203	*l*	CH_3	H	OH	CH_2CH_2OH	13a	J	173-175	$C_{21}H_{25}NO_2$	C, H, N	0/80 sc			
204	*l*	CH_3	H	OH	$CH_2CH{=}CH_2$	13a	E	204-206	$C_{22}H_{25}NO\cdot HCl\cdot C_3H_7OH$	C, H, N, Cl	A/40 sc	>100 sc		
205	*l*	CH_3	H	OH	$CH_2CH{=}CHCl$	13a	N	211-213	$C_{22}H_{24}ClNO$	C, H, N, Cl	A/160 sc 0/320 po	>100 sc		
206	*l*	CH_3	H	OH	$CH_2CH{=}C(Cl)CH_3$	13a	J	134-136	$C_{23}H_{26}ClNO$	C, H, N, Cl	0/80 sc	>100 sc		
207	*l*	CH_3	H	OH	$CH_2CH{=}C(CH_3)_2$	13a	C	272-274	$C_{24}H_{29}NO\cdot HCl$	C, H, N, Cl	A/40 sc	39 sc	0.0	0/10
208	*l*	CH_3	H	$OCOCH_3$	$CH_2CH{=}C(CH_3)_2$	8a	M	252-253	$C_{26}H_{31}NO_2\cdot HCl$	C, H, N, Cl	0/320 sc			
209	*l*	CH_3	H	OCH_3	$CH_2CH{=}C(CH_3)_2$	7b	E	81-82	$C_{25}H_{31}NO$	C, H, N	0/320 sc	>100 sc		
210	*l*	CH_3	H	$OCOC_6H_5$	$CH_2CH{=}C(CH_3)_2$	8c	B	149.5-150	$C_{31}H_{33}NO_2$	C, H, N		>100 sc		
211	*l*	CH_3	H		$CH_2CH{=}C(CH_3)_2$	8c	B	122-123	$C_{31}H_{31}Cl_2NO_2$	C, H, N, Cl		>100 sc		
212	*l*	CH_3	H	$OSO_2\cdot C_6H_4\cdot CH_3$-*p*	$CH_2CH{=}C(CH_3)_2$	8g	B	106-108	$C_{31}H_{35}NO_3S$	C, H, N, S		>100 sc		
213	*l*	CH_3	H	OH	$CH_2C(Br){=}CH_2$	13b	E	216-217	$C_{22}H_{24}BrNO\cdot HCl$	C, H, N	0/40 sc	>100 sc	0.0	0/10
214	*l*	CH_3	H	OH	$CH_2C{\equiv}CH$	13a	J/N	270-271	$C_{22}H_{23}NO\cdot CH_4O_3S$[h]	C, H, N, S			0.0	0/10
215	*l*	CH_3	H	$OCH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	13a	K/I	103-105	$C_{25}H_{25}NO$	C, H, N				
216	*l*	CH_3	H	OCH_3	$CH_2C{\equiv}CH$	7b	E	125-127	$C_{23}H_{25}NO$	C, H, N	A/80 sc	>100 sc		
217	*l*	CH_3	H	OH	CO-c-C_3H_5	8e, 11	E	258-260	$C_{23}H_{25}NO_2$	C, H, N	0/320 po	>100 sc		
218	*l*	CH_3	H	OH	CH_2-c-C_3H_5	8e, 12a	E	261-265	$C_{23}H_{27}NO\cdot HCl\cdot C_3H_8O$[f]	C, H, N, Cl	A/20 sc	>100 sc		
219	*l*	CH_3	H	OH	CH_2-c-C_4H_7	8e, 12b	M	290-292	$C_{24}H_{29}NO\cdot HCl$	C, H, N, Cl	A/25 sc	28 sc 300 po	0.0	0/10
220	*l*	CH_3	H	OH	CH_2-c-C_5H_4	8e, 12a	T	285-286	$C_{25}H_{31}NO\cdot HCl$	C, H, N, Cl				
221	*l*	CH_3	H	OH	c-C_5H_9	13b	T	327-328	$C_{24}H_{29}NO\cdot HCl$	C, H, N, Cl		120 sc		
222	*l*	CH_3	H	OH	$CH_2COOC_2H_5$	13b	E	173-175	$C_{23}H_{27}NO_3$	C, H, N	0/320 sc			

[a-d] See footnotes *a-d* in Table III. [e] Joint effect, the activity (A, antagonist; P, potentiator) in the tail-flick test when administered with morphine. See Experimental Section for the method. [f] Isopropanolate. [g] See ref 4 for monkey data. [h] Methanesulfonate. [i] c-$C_{10}H_{15}$ = 1-adamantyl. [j] Lactate. [k] Mice treated with test compound for 2 days and then challenged with nalorphine (nalorphine dose, 50 mg/kg sc). See reference cited in footnote *d*.

Table VIII. Optical Rotations of D Line of Na

no.	$[\alpha]_D$	temp, °C	concn, g/100 mL	solv[a]	no.	$[\alpha]_D$	temp, °C	concn, g/100 mL	solv[a]
36	−52	20	2.5	B	171	+138	25	1.00	B
37	+54	20	2.5	B	172	−70	25	1.12	B
42	−92	20	0.66	B	173	−96	27	1.00	B
43	+91	20	0.66	B	**174**	−72	25	1.00	B
58	+51	25	1.02	A	**175**	−91	25	1.70	B
59	−52	28	2.86	A	176	−122	25	1.00	B
68	+82	27	1.88	A	177	−144	25	1.00	B
69	−88	25	1.0	B	178	−216	25	1.00	P
70	−80	27	4.27	P	179	−104	25	1.00	B
71	−73	26	1.20	B	180	−141	25	1.10	B
72	−79	26	5.09	B	**181**	−67	28	1.14	B
73	−74	26	5.16	B	**182**	−139	25	0.253	B
74	−75	28	1.78	P	**183**	−154		1.00	R
75	−75	27	2.36	P	**184**	−113	25	0.48	B
76	−87	25	1.00	B	185	−116	25	1.00	B
77	−106	27	4.59	B	186	−107	25	1.00	B
78	−80	26	1.00	B	187	−75	25	1.00	B
79	−92	29	1.00	B	**188**	−89	25	1.00	B
80	−63	25	1.00	W	189	−96	25	1.00	O
81	−82	25	1.00	W	190	−105	25	0.865	B
82	−72	25	0.50	W	191	−46	25	1.00	W
83	−48	25	0.67	W	192	−80	25	1.00	B
84	−77	25	1.00	W	193	−121	25	1.00	B
85	−73	25	1.00	W	194	−240	25	0.50	B
86	−77	25	1.00	W	**195**	−158	25	1.0	B
87	−86	25	1.00	W	**196**	−147	26		B
92	−149	26	1.04	P	197	−93		1.00	B
93	−52	26	1.03	W	198	−133	25	1.00	O
102	−75.5	22	2.6	B	199[b]	0[b]	25	1.00	B
104	−73.2		1.50	B	200	−111	25	1.12	V
109	−166	25	1.00	B	**201**	−143	25	1.00	B
110	−96	25	0.50	B	202	−133	25	1.00	B
111	+164	25	1.15	B	203	−136	27	1.00	B
112	+100	27	0.42	B	**204**	−117	27	1.00	B
142	−85		4.6	B	205	−152	26	1.25	W
143	−115	28	0.82	X	206	−140	27	1.00	B
144	−78	24	1.27	B	207	−165	26	1.11	B
145	−102		1.1	B	208	−106	25	1.07	B
146	+123	27	1.30	X	209	−131	25	0.50	B
147	+86	28	1.42	B	**210**	−125	25	1.00	W
148	+106		1.1	B	211	−89	25	1.00	W
154	−109	20		B	**212**	−118	25	1.00	B
155	+95		2.3	B	213	−97	25	1.00	B
162	+74	25	1.00	B	214	−161	27	1.00	B
163	+128	26.5	1.00	B	215	−128	25	0.63	B
164	+216	25	1.00	P	216	−157	25	1.00	B
165	+105	25	1.00	B	217	−256	25	0.31	B
166	+88	25	1.00	B	**218**	−123	26	1.05	B
167	+95	25	1.00	O	219	−143	25	1.00	B
168	+118	26		B	220	−149	25	1.00	B
169	+166	26	1.01	B	221	−132	25	1.00	B
170	+125	26	1.03	B	222	−117	25	1.00	B

[a] See the list of solvents under Experimental Section. [b] 199: $[\alpha]^{25}_{365}$ −259.3° (MeOH, *c* 1.00, 25 °C).

alumina (1.5 kg). The benzene eluate (89 g of oil) was converted to its hydrobromide salt with ethanolic HBr to give 46 g, mp 218–224 °C. Recrystallization from methanol gave 24 g (13%), mp 239–241 °C, of **1,3-dimethyl-2-(2-methylphenyl)-4-phenyl-1,2,5,6-tetrahydropyridine hydrobromide (IXc)**: NMR ($CDCl_3$, free base) δ 1.25 (br s, 3 H, C_3-Me), 2.23 (s, 3 H, N-Me, shifts to low field upon addition of acid), 2.53 (s, 3 H, aromatic Me), 2.50–3.30 (m, 4 H, ring CH_2), 3.87 (br s, 1 H, C_2-H), 7.08–7.45 (m, 9 H, aromatic H). Anal. ($C_{20}H_{23}N$·HBr) C, H, N, Br.

The mother liquor from crude IXc was concentrated and allowed to stand overnight at room temperature, whereupon 22.5 g of crude **32** was deposited, mp 190–195 °C. Recrystallization from acetone gave 15.0 g (8%), mp 205–206 °C.

The quaternary salt **10** gave crude **22** in 88% yield as a brown oil, which was converted to its hydrobromide salt in ether and recrystallized from acetone.

With KOBu (Method 4c). The quaternary salt **14** (20.8 g, 0.06 mol) and 7.2 g (0.64 mol) of KO-*t*-Bu were stirred in benzene for 2 h at room temperature. The reaction mixture was then filtered and the filtrate concentrated to provide 16.8 g of brown oil. A solution of the oil in 100 mL of 48% HBr was refluxed for 15 min, cooled, poured into cold concentrated aqueous NH_3, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, the residue was taken up in ether, and the solution was filtered and extracted with 1 N HCl. The acidic solution was basified with NH_3, the product was taken up in ether, washed with water, dried (Na_2SO_4), and evaporated, and the residue crystallized from *n*-heptane raised the melting point of **26** to 112–114 °C. Compounds **27** and **28** were recrystallized from 2-propanol, while **25** was recrystallized as its hydrochloride salt from absolute ethanol.

With KOH in DMF (Method 4d). To a solution of 30.0 g (0.08 mol) of compound **19** and 4.8 g (0.086 mol) of KOH in 350 mL of warm distilled DMF was added 350 mL of benzene, and the solution was refluxed overnight. The solvent was then distilled in vacuo and the residue taken up in water and ether. The ether layer was dried (Na_2SO_4) and evaporated, and the residue was

Table IX. Correlation of Compound Numbers (Tables IV-VII) to GPA, NIH[d] and UM[e] Numbers

no.	GPA no.	NIH no.	UM no.	ref
36	2068	8305	673	5, 25
37	2069	8306	674	5, 26
48	1579[a]/1656[b]	8217	605	4, 8a, 28
49	1657	8240	623	4, 6b, 8a, 9a, 27
50	1658	8241	624	4, 6b, 8a
69	2259	8481	798	27
72	1966	8302	670	30
131	1467			4, 9a, 21
132	1364			9a, 19
144	1833			9a, 21
145	4622			4
168	1847			4, 9b,c
203	1866			21
204	1843			4, 9a-c, 28
205	1894			9a, 21
207	1841[a]/2164[b]/2443[c]	8303	671	4, 26
214	1867[a]/2163[c]	8304	672	4, 8b, 9a, 21
219	3154	8576	808	4, 9a, 21

[a] Free base. [b] HCl salt. [c] Methanesulfonate. [d] National Institutes of Health. [e] The University of Michigan, Department of Pharmacology.

converted to the hydrochloride salt of **31** in ethanol, yield 13.6 g (52%).

With KOH in Toluene. Isolation of Byproducts VIId and Xd (Method 4e). Compound V (R_1 = Me, R_2 = H, R_3 = OMe;[2] 200 g; 0.58 mol) in 750 mL of toluene was treated with 39 g (0.7 mol) of powdered KOH according to the procedure of ref 2 to give 170 g of crude **34** *O*-methyl ether as a brown oil. A portion of the oil was redissolved in toluene, and the solution was extracted with 1 N HCl and then with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from ether–pentane to provide white leaflets of Xd: mp 124–125 °C, lit.[13] mp 124–126 °C; NMR ($CDCl_3$) δ 2.80 (s, 4 H, benzylic CH_2), 3.77 (s, 6 H, OMe), 6.79 (d, J = 9 Hz, 4 H, aromatic H ortho to OMe), 7.08 (d, J = 9 Hz, 4 H, aromatic H ortho to CH_2).

The crude free base of VI (R_1 = Me; R_2 = H; R_3 = OMe) generated from the acid extract (160 g) was treated with 80 g of *d,l*-tartaric acid in 1 L of hot acetone. The solution was allowed to stand and cool to give 40 g of a white crystalline solid, which was recrystallized from methanol to give 24 g, mp 186–187 °C. The solid was identified as the *d,l*-tartrate salt of **1,3-dimethyl-4-phenyl-4-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridine (VIId)**: NMR ($CDCl_3$; free base) δ 1.61 (d, $J_{Me\text{-}C_2H}$ = 1.5 Hz, 3 H, 3-Me), 1.75–2.80 (m, 4 H ring CH_2), 2.36 (s, 3 H, N-Me), 3.11 (s, 2 H, benzylic CH_2), 3.70 (s, 3 H, OMe), 5.84 (q, $J_{C_2H\text{-}Me}$ = 1.5 Hz, 1 H, C_2H), 6.69–7.50 (m, 9 H, aromatic H). Anal. ($C_{21}H_{25}NO{\cdot}C_4H_6O_6$) C, H, N.

From the mother liquor remaining from the isolation of VIId, the major product, the OMe derivative of **34**, was obtained.

Cyclization of the Stevens' Base (Table IV; Method 5). The purified Stevens' rearrangement products (Table III) were cyclized by refluxing in 48% HBr,[2] to provide the products described in Table IV. In some cases the products were converted to bases or to hydrochloride salts for purification. Compounds **35, 39, 47, 53,** and **54** were obtained after reflux times of 14–20 h; compounds **40** and **51** required 3 days and compound **44** required 6 days of refluxing with the addition of HBr gas to the refluxing solution. Compounds **45** and **46** were obtained after only 1 h of reflux time. The β configuration of compound **44** was confirmed by the finding that it was only 18% quaternized after 7 h (see ref 2 for method).

Optical Resolution of *N*-Methyl-5-phenylbenzomorphan Derivatives (Table IV). With *d*- and *l*-Tartaric Acids (Method 6a). Compounds **36** and **37** were obtained by resolution of **35** with *d*- and *l*-tartaric acids, respectively. The free base of **35** (10.52 g, 40 mmol) and *d*-tartaric acid (6.0 g, 40 mmol) were dissolved in about 100 mL of a 7:3 mixture of Me_2CO and MeOH with heating. The solution was concentrated and cooled to precipitate crystalline solid: 7.7 g; mp 175–192 °C. One recrystallization of the crude product from an *i*-PrOH–MeOH mixture yielded 4.0 g of the purified product, mp 195–196 °C. Similarly, the treatment of the free base of **35** (3.5 g, 13.3 mM) with *l*-tartaric acid (1.90 g, 12.8 mM) gave 1.80 g of the crude product, mp 190–197 °C. This material was recrystallized from an *i*-PrOH–MeOH mixture to yield 1.60 g of white crystals, mp 195–197 °C.

With *d*- and *l*-Mandelic Acids (Method 6b). Compounds **42** and **43** were obtained by resolution of **41** with *d*- and *l*-mandelic acids, respectively. A solution of the free base of **41** (43.94 g, 158 mmol) and *d*-mandelic acid (24.04 g, 158 mmol) in a mixture of MeOH (1250 mL) and *i*-PrOH (500 mL) was concentrated to a volume of approximately 700 mL and cooled to precipitate a white solid: 27.84 g; mp 233–237 °C. This material was slurried in 325 mL of diluted NH_4OH with heating and filtered. The solid was collected (18.0 g, mp 267–271 °C) and recrystallized from *n*-BuOH to yield 11.8 g of white crystals: mp 267–273 °C; $[\alpha]^{20}_D$ −92.4° (*c* 0.66, *l* 1.0, MeOH). This material was converted to the HCl salt in *n*-BuOH by treatment with enthanolic HCl obtaining 10.8 g of **42** as white crystals, mp 308–312 °C.

The mother liquor remaining from the isolation of the **42** *d*-mandelate salt was taken to dryness, and the residue was treated with diluted NH_4OH and filtered. The collected solid (25.1 g, 90 mM, mainly the free base of **43**) was treated with *l*-mandelic acid (13.7 g, 90 mmol) in a mixture of *i*-PrOH and MeOH obtaining 23.1 g of **43** *l*-mandelate, mp 237–240 °C. The salt was converted to the free base by slurrying in diluted NH_4OH and recrystallized from *n*-BuOH to yield 11.36 g of white crystals: mp 273–275 °C; $[\alpha]^{20}_D$ +91.2° (*c* 0.66, *l* 1.0, MeOH). The free base (5.0 g) was converted to the HCl salt in *n*-BuOH by treatment with ethanolic HCl obtaining 5.0 g of **43** as white crystals, mp 308–313 °C.

Modification of the 2′-Hydroxy Group of 5-Phenylbenzomorphan Derivatives (Table V). Etherification (Method 7). With CH_2N_2 (Method 7a). The phenolic base was treated with diazomethane and the reaction worked up according to the procedure described for **60**.[2]

With Me_2SO_4 (Method 7b). A suspension of 10 g (34 mmol) of the phenolic base of **49**[2] in 90 mL of Me_2SO and 37.5 mL of 1 N NaOH was heated on the steam bath for 0.5 h to obtain a clear solution. A solution of 4.52 g (36 mmol) of Me_2SO_4 in 25 mL of Me_2SO was added, and the solution was heated on the steam bath for 2 h and then cooled to deposit crystals of the base of **69** (9.6 g, 85%, mp 133–138 °C). The base was converted to the hydrochloride salt and crystallized first from water and then from acetone.

With MeI and NaH in DMF (Method 7c). The phenolic compound was converted to the sodium salt with NaH in DMF and heated for 1 h with a large excess of CH_3I. The solvent was removed in vacuo and the residue was taken up in ether and water. The ether solution was dried ($MgSO_4$) and evaporated to leave the product as an oil.

***l*-2′-Methoxymethoxy-2,9β-dimethyl-5-phenyl-6,7-benzomorphan (75; Method 7d).** The sodium salt of the phenolic base of **49**[2] (3.1 g; 10.6 mmol) was prepared with NaOMe and the solvent removed. The anhydrous sodium salt was dissolved in 200 mL of $CHCl_3$ and 0.86 g (10.7 mmol) of chloromethyl methyl ether was added. The mixture was refluxed overnight and evaporated, and the residue was taken up in benzene and 1 N NaOH. The benzene solution was washed with water, dried, and evaporated. The residue, **75**, was recrystallized from 2-propanol.

Esterification (Method 8). With Ac_2O (Method 8a). The phenolic compound in acetic anhydride was heated to 100 °C for 1 h and worked up as described for **55**.[10]

With Other Acid Anhydrides (Method 8b). The phenolic compound in benzene was treated with a solution of the anhydride in benzene and stirred and refluxed for 3 h, evaporated in vacuo, and purified by recrystallization.

With Acid Chloride and Diisopropylethylamine in C_6H_6 (Method 8c). A solution of 11.7 g (46 mmol) of the phenolic base of **49**,[2] 1.1 equiv of the acid chloride, and 1.1 equiv of diisopropylethylamine in 300 mL of benzene was refluxed for 16–20 h and evaporated. A solution of the residue in $CHCl_3$ was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was recrystallized from 2-propanol. For the preparation of **83**, the reflux time was only 2 h.

With Acid Chloride and Diisopropylethylamine in THF (Method 8d). A solution of the phenolic base, 1.05 equiv of acid chloride, and diiospropylethylamine in THF was stirred at room temperature for 1 h, refluxed for 4 h, and then cooled and evaporated in vacuo. The residue was triturated with benzene and dilute ammonia, and the benzene layer was dried ($MgSO_4$) and evaporated to leave the crude product, which was converted to its hydrochloride salt for purification.

With Acid Chloride and Pyridine in Toluene. N,O-Diacylation (Method 8e). A solution of the phenolic secondary base in pyridine was treated with 2.4 equiv of the acid chloride in toluene solution. The mixture was stirred and refluxed for 2.5 h and evaporated in vacuo, and the residue was taken up in $CHCl_3$ and 1 N HCl. The $CHCl_3$ layer was washed with water, dried (Na_2SO_4), treated with charcoal, and evaporated. The residue was triturated with ether and the product crystallized from the ether solution.

With Acid Chloride in Pyridine. N,O-Diacylation (Method 8f). A mixture of the phenolic base and 2.0 equiv of acid chloride in pyridine was stirred overnight and poured into ice and water. The precipitated product was recrystallized.

Tosylation of the 2'-Hydroxy Group in 5-Phenylbenzomorphan Derivatives (Method 8g). A pyridine solution of phenolic base and 1.1 equiv of tosyl chloride was refluxed for 3 h, cooled, and poured into water. After the solution was left standing at room temperature for several hours, the aqueous layer was decanted and the residue was recrystallized from 2-propanol, converted to the base, and finally converted to the hydrobromide salt. The latter salt was recrystallized from ethanol–methanol to give **61**.

***dl*-2-Methyl-2'-[(dimethylthiocarbamyl)oxy]-5-phenyl-6,7-benzomorphan (62; Method 8h).** To a stirred suspension of 2.8 g (10 mM) of the phenolic base **41**[10] in 40 mL of DMF was added 410 mg (1 equiv) of 58% of NaH in mineral oil dispersion. Stirring was continued at room temperature for 0.5 h and cooled to 5 °C, and 1.3 g (10% excess) of dimethylthiocarbamyl chloride was added. The mixture was stirred for 0.5 h at room temperature, then for 1 h at 80 °C, and finally cooled and poured into 200 mL of 1% NaOH. The precipitate was collected, washed with water, and dried to give 3.5 g (95%) of **62**, mp 171–180 °C.

***l*-2'-[[(Carbethoxymethyl)carbamyl]oxy]-2,9β-dimethyl-5-phenyl-6,7-benzomorphan (74; Method 8i).** To a solution of 1.50 g (5.06 mmol) of **49**[2] as the free base in 60 mL of THF was added 0.98 g (7.58 mmol) of carbethoxymethyl isocyanate. The solution was refluxed for 24 h and then taken to dryness in vacuo to quantitatively yield a crystalline solid. Two recrystallizations from methanol yielded 0.78 g (40%) of **74**.

***l*-2'-[(Methanesulfonyl)oxy]-2,9β-dimethyl-5-phenyl-6,7-benzomorphan (76; Method 8j).** To a mixture of **49**[2] (5.87 g as the free base, 20 mmol) and diisopropylethylamine (2.6 g, 20 mmol) in benzene (100 mL) was added methanesulfonyl chloride (2.3 g, 20 mmol). The reaction mixture was refluxed on a steam bath overnight, then cooled, washed (H_2O), and extracted with 1 N HCl. The acid layer was washed (Et_2O), neutralized (NH_4OH), and extracted with $CHCl_3$. Chloroform extract was dried ($MgSO_4$), decolorized, and evaporated to dryness, leaving a foam solid which was crystallized from 2-propanol, yielding white crystals: mp 107–108 °C; 4.48 g (60%).

N-Demethylation of 5-Phenylbenzomorphan Derivatives (Table V). Formation of *N*-Cyano Derivatives (Method 9a). The base was treated with CNBr in $CHCl_3$ according to the procedure described for **89**.[10]

Conversion of *N*-Cyano Derivatives to *N*-Nor Derivatives with $LiAlH_4$ in THF (Method 9b). The *N*-cyano derivative was reduced with LAH in THF according to the procedure described for **91**.[10]

Conversion of *N*-Cyano Derivatives to *N*-Nor Derivatives by HCl Hydrolysis (Method 9c). The *N*-cyano derivative was prepared by method 9a and refluxed overnight in an excess of 6% HCl. The solution was cooled and basified with ammonia, and the product was extracted into $CHCl_3$. After removal of the $CHCl_3$, the base was converted to its hydrochloride salt.

Formation of *N*-Carbethoxy Derivatives[16] (Method 10a). Compound **65** (131 g, 0.39 mol) in benzene (500 mL) was added to a stirred suspension of 84 g (1 mol) of $NaHCO_3$ and 107.4 g (1 mol) of ethyl chloroformate in 300 mL of benzene over a period of 45 min with ice cooling. Additional benzene (150 mL) was added, and the mixture was refluxed for 16 h, cooled, and filtered. The filtrate was washed with 1 N HCl and water, dried (Na_2SO_4), and evaporated to leave 179 g of the *N*-carboethoxy derivative.

Hydrolysis of *N*-Carbethoxy Derivatives to *N*-Nor Derivatives (Method 10b). The crude *N*-carboethoxy derivative derived from **111** by method 10a (166 g) was dissolved in 600 mL of carbitol and added slowly to a stirred suspension of 166 g of powdered KOH in 400 mL of carbitol. The reaction mixture was stirred and refluxed for 18 h, cooled, and stirred with a solution of 160 g of NH_4Cl in 1 L of water. The precipitate was collected and dried. A second crop was obtained by extraction of the carbitol solution with $CHCl_3$, the $CHCl_3$ was removed, water was added, and the solid was collected. The combined product was crystallized from 1-butanol to give 76.8 g (78%) of **112**. The preparation of **110** was carried out in a similar manner.

Modification of the Nitrogen Function of 5-Phenylbenzomorphan Derivatives (Table VII). N-Acylation. Various *N*-acyl derivatives were prepared from the corresponding *N*-nor derivatives utilizing reaction conditions described for the esterification of the 2'-hydroxy group of 5-phenylbenzomorphan derivatives (see method 8).

***dl*-2-Acetyl-2'-hydroxy-5-phenyl-6,7-benzomorphan (114; Method 11).** A solution of the *O,N*-diacetyl compound **113** in ethanol was treated with a 10% excess of 1 N NaOH and refluxed for 3 h. After cooling and adjusting the pH to neutral, the solution was allowed to stand to deposit the crystalline product.

Reduction of *N*-Acyl Derivatives (Method 12). With $LiAlH_4$ in THF (Method 12a). A solution of the amide in THF was added to a stirred suspension of an excess of LAH in THF. The mixture was refluxed for 2–24 h, except for **179** which required a 72-h reflux. The reaction was worked up to obtain the product in the usual manner (see ref 2 for example).

With Red-Al® in C_6H_6 (Method 12b). **161** was prepared by reduction of the amide with sodium (2-methoxyethoxy)aluminum hydride in benzene.

Alkylation of *N*-Nor Derivatives with RX (Method 13). With RX and Inorganic Base in DMF (Method 13a). A mixture of the secondary amine, a slight excess of the alkyl bromide or chloride, and $NaHCO_3$ (or Na_2CO_3 or K_2CO_3) in DMF was heated at 100 °C or at reflux, usually for 4 h but sometimes for as long as 14 h. The solvent was evaporated and the product was purified in the usual manner.

With RX and Diisopropylethylamine in DMF (Method 13b). The procedure was the same as for method 13a, except that diisopropylethylamine (1 equiv) was used as the base. For **166** and **167** refluxing was continued for 72 h, while for **183** only 1.5 h at room temperature was required.

Michael Addition Reaction (Method 14). A slurry of the secondary amine **91** was stirred in ethyl acrylate at room temperature for 15 h, cooled, and filtered to obtain **125**. For **126**, the secondary amine was treated with dimethylacrylamide and Triton B in DMF at reflux temperature for 6 h.

Catalytic Hydrogenation of *N*-*p*-Nitrophenethyl Derivatives (Method 15). The nitro compound was reduced by catalytic hydrogenation using 5% Pd/C in THF or ethanol.

***l*-2'-Hydroxy-2-isopentyl-9β-methyl-5-phenyl-6,7-benzomorphan (176; Method 16).** **176** was prepared from **207** by catalytic hydrogenation using PtO_2 in ethanol.

***l*-2'-Hydroxy-2-(3-hydroxy-3,3-diphenylpropyl)-9β-methyl-5-phenyl-6,7-benzomorphan (191; Method 17).** **191** was prepared from **190** in the following manner. To a solution of PhLi (19.4 mmol) in THF, a solution of 1.75 g of the free base generated from **190** in THF was added at −20 °C over a period of 0.5 h. The mixture was stirred overnight at room temperature and then water was added to the mixture and evaporated to dryness. The residue was treated with H_2O and $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried ($MgSO_4$), decolorized (Darco), and evaporated to dryness, leaving a white solid which was crystallized from acetone, obtaining 1.35 g (65%) of white microcrystals, mp 274–275.5 °C.

***l*-2'-Hydroxy-2,9β-dimethyl-2-(3-oxobutyl)-5-phenyl-6,7-benzomorphan (192; Method 18).** **192** was prepared from **110** in the following manner. A mixture of 100 g (0.27 mol) of **110**, methanesulfonic acid (26 g, 0.27 mol), 80 mL of 13 M aqueous CH_2O in 200 mL of Me_2CO, and 100 mL of EtOH was refluxed

under a nitrogen atmosphere for 20 h. Then the solution was cooled to 0 °C in an ice bath. The precipitated product was collected by filtration, washed with ether, and dried, obtaining 70.5 g of white crystals, which were recrystallized from EtOH, mp 203–204 °C.

l-2′-**Hydroxy-2-(3-hydroxy-3-methylbutyl)-9β-methyl-5-phenyl-6,7-benzomorphan (193; Method 19).** **193** was prepared from the free base of **207** in the same manner as for the deuterium exchange of 1′ and 3′ hydrogens of benzomorphan (see test). Thus, 1.5 g of the free base of **207** was heated at 95–100 °C and stirred overnight in a mixture of 1.65 g of P_2O_5 and 2.94 mL of H_2O. The reaction mixture was then poured onto a mixture of concentrated NH_4OH and ice and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to leave a residue which was crystallized from *i*-PrOH and recrystallized from EtOH, obtaining white crystals: mp 178–180 °C; 0.5 g.

l-2-**(Carboxymethyl)-2′-hydroxy-9β-methyl-5-phenyl-6,7-benzomorphan (200; Method 20).** **200** was prepared from **222** in the following manner. To a solution of 2 g (5.47 mmol) of **222** in 60 mL of EtOH was added 12.0 mL of 1 N NaOH. The resulting solution was refluxed for 2 h and evaporated to dryness in vacuo, and the residue was taken up in H_2O. A clear solution resulted. The basic solution was acidified with 16.5 mL of 1 N HCl. The precipitated solid was collected by filtration and dried, obtaining 1.56 g (84%) of white solid, mp 283–284 °C.

Synthesis of Radioactive Compounds. *l*-2′-**Hydroxy-2-[^{14}C]methyl-9β-methyl-5-phenyl-6,7-benzomorphan Hydrochloride (^{14}C-Labeled 49).** A solution of 340 mg (2.39 mmol, 11 mCi) of ^{14}C-labeled CH_3I in 80 mL of 5% MeOH in DMF was kept in a dry ice–acetone bath. To this was added 1.340 g (4.84 mmol) of *l*-2′-hydroxy-9β-methyl-5-phenyl-6,7-benzomorphan (**110**). The reaction mixture was refrigerated for 4 days at 5 °C with occasional shaking. After the reaction mixture was evaporated to dryness, the recovered solvent showed no radioactivity. The residue was extracted with warm EtO_2 in the presence of 4 g of anhydrous K_2CO_3. Extraction with Et_2O was repeated several times. The combined Et_2O extracts were filtered to remove the starting material. To the ethereal filtrate was added *n*-heptane. After boiling off most of the Et_2O, the solution was filtered, concentrated to a smaller volume, and cooled to deposit white crystals, 0.60 g. This material was converted to the HCl salt in EtOH (5 mL) with ethanolic HCl. After crystallization of the HCl salt was induced, the ethanolic solution was diluted with Et_2O (5 mL) and kept at −5 °C for 1 h. Crystals were collected by decanting, washed with an EtOH–Et_2O mixture and then with Et_2O, and air-dried to obtain 556 mg of the labeled **49** (71%). Anal. C, H, N, Cl.

The ^{14}C-labeled **50** was prepared from 171 mg (1.2 mmol, 6 mCi) of CH_3I and 675 mg (2.4 mmol) of **111** in the same manner, yield 320 mg (80%). Anal. C, H, Cl.

l-2′-**Hydroxy-2,9β-dimethyl-5-phenyl-6,7-[1′,3′-^{2}H]benzomorphan (Dideuterated 49 Free Base).** This experiment was conducted as a model experiment for the preparation of tritiated **49**.

Deuterated phosphoric acid was obtained by adding 1.96 mL of D_2O dropwise to 1.10 g of P_2O_5 at −40 °C. To this was added 1.00 g of the free base generated from **49**, and the mixture was heated at 95–100 °C for 24 h. After quenching with ice-water, the reaction mixture was basified with aqueous NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract yielded crude product (0.9 g), which was recrystallized from MeOH–hexane to obtain 600 mg of the free base of deuterated **49**, mp 196–198 °C. The percent of deuteration was determined by NMR, which showed approximately 98% deuteration at C_1' and C_3' of the benzomorphan molecule.

l-2′-**Hydroxy-2,9β-dimethyl-5-phenyl-6,7-[1′,3′-^{3}H]benzomorphan Hydrochloride (Tritiated 49).** Tritiated phosphoric acid was prepared from 4.8 g of P_2O_5 and 3.0 mL (3 Ci) of tritiated H_2O. To this was added 3.0 g of the free base generated from **49**, and the mixture was heated at 95–100 °C for 4 h. The reaction mixture was neutralized with concentrated NH_4OH while cooling in an ice bath and filtered. The precipitate was dissolved in Et_2O and dried (K_2CO_3), and HCl gas was passed through to precipitate the HCl salt. The HCl salt was collected by filtration and recrystallized from absolute EtOH to obtain 2.85 g of white crystals (84%), mp 309–311 °C; specific activity 17 mCi/mmol. Anal. C, H, N, Cl.

l-2-**(Cyclobutylmethyl)-2′-hydroxy-9β-methyl-5-phenyl-6,7-[1′,3′-^{3}H]benzomorphan Hydrochloride (Tritiated 219).** Tritiated phosphoric acid was prepared from 4.8 g of P_2O_5 and 3.0 mL (3 Ci) of tritiated H_2O. To this was added 3.5 g of **219**, and the mixture was heated at 120 °C for 3 h with stirring. The reaction mixture was cooled, neutralized with 10 g of KOH in 50 mL of H_2O, and extracted with Et_2O (2 × 50 mL). The Et_2O extract was dried (Na_2SO_4), decolorized with charcoal, and acidified with HCl gas to precipitate the HCl salt. The HCl salt was collected by filtration and recrystallized from aqueous MeOH to obtain white needles, 2.45 g (70%), mp 287–288 °C.

l-2′-**Hydroxy-9β-methyl-2-(3-methyl-2-butenyl)-5-phenyl-6,7-[1′,3′-^{3}H]benzomorphan Methanesulfonate (Tritiated 207 Methansulfonate).** Tritiated phosphoric acid was prepared from 5.6 g of P_2O_5 and 2.0 mL (2 Ci) of tritiated H_2O. To this was added 2.97 g of *l*-2′-hydroxy-9β-methyl-5-phenyl-6,7-benzomorphan (**110**), and the reaction mixture was heated at 100 °C for 3 h. The reaction mixture was cooled and diluted with H_2O, and tritiated **110** was precipitated with NH_4OH. The precipitate was collected by filtration, washed several times with H_2O, and finally washed with Me_2CO.

The crude, dry, tritiated **110** was slurried in 30 mL of dry dimethylformamide, and 1.53 mL of diisopropylamine and 1.25 mL of dimethylallyl bromide were added. After 5 min, a near complete solution had resulted which did not clear after 1 h. The mixture was filtered and the clear filtrate concentrated to an oil, which was extracted with ammonium hydroxide and ether–methylene chloride (3:2). The organic layer yielded 4.6 g of solid, which was dissolved in 50 mL of isopropyl alcohol and treated with 1.2 mL of methanesulfonic acid. After cooling the solution at −20 °C for 15 h, 2.09 g of a crystalline material had formed, mp 215–217 °C. The test sample was recrystallized from isopropyl alcohol–heptane: 1.67 g (35%); mp 216–217 °C; specific activity 5.68 mCi/mmol. Anal. C, H, N.

Pharmacology. Mouse Tail-Flick Analgetic Test. Male CF-1 mice, 18–24 g, were used. The animals were allowed food and water up until the time of testing. Soluble compounds were dissolved in distilled water and administered orally, subcutaneously, or intraperitoneally. Insoluble compounds were suspended in 3% colloidal cornstarch containing 5% PEG-400 and 0.5% Tween 80. In all administrations, the dose volume was adjusted to 0.1 mL/10 g of body weight. A constant intensity heat stimulus was used to induce a tail-flick response.[31] The apparatus was modified in that a light source with a built-in parabolic reflector (Sylvania, T-12, 150 W) was focused from a point 5-cm below the tail of the mouse. The control reaction time was measured twice in each of ten animals. To standardize the procedure, the intensity of the stimulus was adjusted so that the control values were between 3.5 and 4.5 s. Thus, in a series of 16 experiments, the mean (±SD) control value was 3.5 ± 0.33 s. A group of five mice was used for each dose level. Reaction time (T_r) was measured prior to and 30, 60, 90, and 120 min after drug administration on a Schaer Algesiometer®. A dose which caused an increase of reaction time by more than 1 s but less than 2 s compared to the average control value was rated as +. If the increase in reaction time was more than 2 s, the dose was rated as ++ (2+).

Mouse Tail-Flick Analgetic Test. Joint Action with Morphine. The method was the same as described in the preceding section. Test compounds were administered to the animals in conjunction with morphine hydrochloride, 10 mg/kg sc, and changes in the reaction time were observed. Typical examples are illustrated in Tables X and XI.

Mouse Phenylquinone Writhing Analgesia Test. Male CF_1S (Carworth Farms) mice, 16–25 g, were used. The animals had free access to food and water up until the time of the experiment, unless the drug was to be administered orally, in which case the animals were fasted for 18 h. A short version of the phenylquinone writhing test was employed (modification of the method of Taber et al.[32]) with the phenylquinone solution prepared as described by Blumberg et al.[33] Administration of test compounds to the animals was done in the same manner as described in the preceding section. An appropriate number of control animals received distilled water or 3% colloidal cornstarch, in the same volume to body weight ratio each time the test was

Table X. Joint Action of 130 with Morphine (Mouse Tail-Flick Method)

130 dose, mg/kg sc	T_r[a] (s)		
	130 alone	morphine alone	130 + morphine
5	−0.6	+4.5	+3.4
10	−0.2		+5.3
20	+0.3		+2.6[b]
40	−0.4		+2.1[b]

[a] T_r = reaction time of treated animal minus reaction time of control animal. [b] Observed values are significantly smaller ($p < 0.05$) than the value for morphine alone. Thus, 130 exhibited morphine analgesia antagonism at 20 and 40 mg/kg sc.

Table XI. Joint Action of 133 with Morphine (Mouse Tail-Flick Method)

133 dose, mg/kg sc	T_r[a] (s)		
	133 alone	morphine alone	133 + morphine
40	−0.2	+3.5	+4.5[b]
80	0.0		+4.4[b]

[a] T_r = reaction time of treated animal minus reaction time of control animal. [b] Observed values are significantly greater ($p < 0.05$) than the value for morphine alone. Thus, 133 enhanced morphine analgesia at 40 and 80 mg/kg sc.

run. At various time intervals after administration of the test compound, the mice received 0.1 mL/10 g of body weight of a 0.25 mg/mL solution of phenyl-*p*-quinone made in 5% aqueous ethanol (2.5 mg/kg) via the intraperitoneal route. Five minutes later, the animals were placed in clear Plexiglas cages containing San-i-cel® bedding, and the number of animals which did not perform a characteristic writhe during the next 10 min were recorded. Under these conditions, this dose of phenylquinone has been demonstrated to induce one or more writhes in 95% of the mice in a large separate control study.

Statistical analysis (optional) on the quantal data (number of mice not writhing/total number of mice tested) was performed by the logit method of Berkson,[34] which generated the ED_{50}, slope, and 95% confidence limits.

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References and Notes

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