3-Hydroxy-17-aralkylmorphinans as Potential Opiate Receptor-Site-Directed Alkylating Agents

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In an effort to develop opiate receptor-site-directed alkylating agents, a series of 3-hydroxy-17-aralkylmorphinans containing reactive groups was synthesized and tested for analgesic and opiate antagonist activity. Many of the target compounds exhibited the characteristics of agonists and, among this group, some were found to be active blockers of morphine analgesia. One of the more potent antagonists (**41**) was investigated further and it was found that while its action is specifically associated with opiate receptors, **41** could not be classified either as a competitive or noncompetitive antagonist in the classical sense. The duration of antagonist action in vivo of **41** and its in vitro receptor binding characteristics suggest that covalent association with opiate receptors is not an important factor.

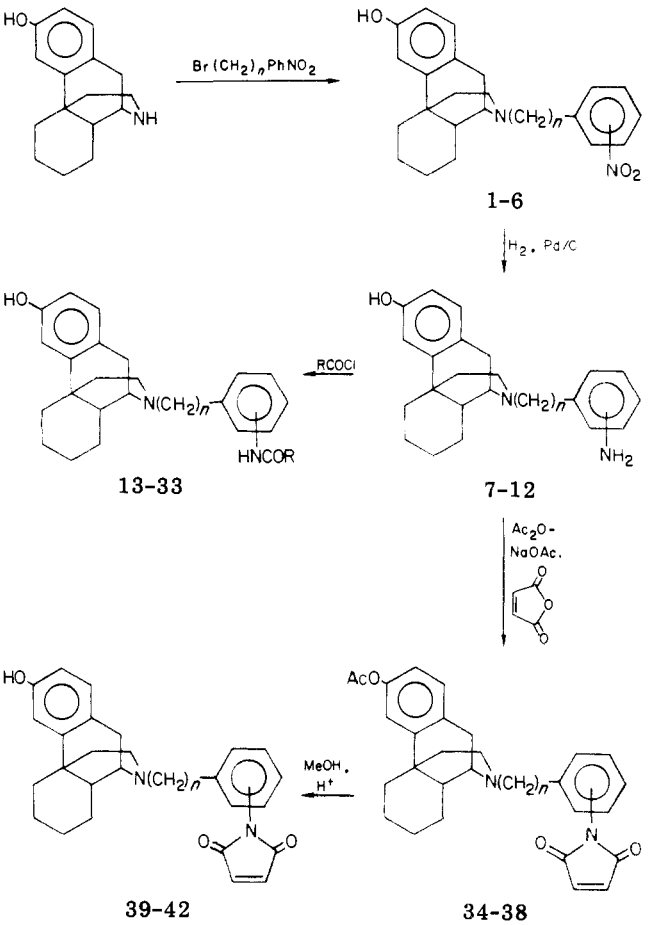
Previous reports[1,2] from these laboratories described the synthesis and biological activity of a series of anileridine derivatives possessing reactive groups. One of the members in this series, *p*-(4-ethoxycarbonyl-4-phenyl-1-piperidinoethyl)fumaranilate, exhibited significant in vivo receptor blocking properties in mice, but a relatively high dose (40 mg/kg) was required. In addition, other members of the series displayed substantial toxicity which was interpreted as arising from nonspecific alkylation.

Since the object of these studies was the development of selective narcotic antagonists capable of forming covalent bonds[3] with analgetic receptor sites, we have investigated derivatives of 3-hydroxymorphinan[4] as receptor-site-directed alkylating agents on the basis that the meta phenolic OH confers greater receptor affinity due to an additional point of attachment.[5] The fact that introduction of the *N*-aralkyl group into the molecule does not have an adverse affect on activity[4] also made this approach attractive. Moreover, as the number of CH_2 groups and the position of an alkylating function on the phenyl group of the aralkyl substituent can be varied, this could provide considerable latitude for reaction with a nucleophilic component which might be in the vicinity of the anionic site. The present report describes the results of this investigation.

Chemistry. The general synthetic route for the target compounds is illustrated in Scheme I. The nitrophenethyl and nitrophenylpropyl bromides employed in the synthesis of intermediates **1–6** were prepared from the corresponding nitrophenylacetic and nitrocinnamic acids, respectively, as described in the Experimental Section. The conversion of 3-hydroxymorphinan[6] to nitrophenalkyl intermediates **1–6** was carried out in DMF in the presence of K_2CO_3 (method A). Catalytic reduction of the nitro group in HCl–EtOH (method B) gave the desired *N*-(aminophenalkyl)-3-hydroxymorphinans **7–12**. The formation of amide derivatives **13–33** was achieved by treatment of the corresponding amines (**7–12**) with the requisite acyl halide (method C). The maleimido compounds were obtained in three steps, the first being the reaction of amines **7–12** with maleic anhydride to form the corresponding maleamic acids. Treatment with acetic anhydride–sodium acetate afforded the 3-acetoxymaleimides[7] **34–38** (method D) which then were transesterified to compounds **39–42** (method E). (See Table I.)

Pharmacological Results. The analgesic ED_{50} values of the compounds are listed in Table II. Morphine and phenazocine were included for purposes of comparison. Most compounds in the phenethyl series caused mild CNS stimulation within 5–10 min, followed by slight sedation

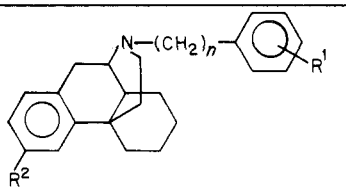
Scheme I



in 30–60 min. All the analgesically active compounds of this series produced various degrees of Straub tail phenomenon. The maximum analgesic activity of these compounds was observed between 30 and 60 min and the duration of action usually varied between 2 and 4 h except with compound **13** which had an unusually long duration of about 6.5 h.

The analgesically active compounds in the phenylpropyl series caused just a very mild sedative effect in that the animals appeared to be easier to handle for testing. No excitation or Straub tail was apparent. With compounds which exhibited no analgesic effect, the behavior of the animals appeared normal even at relatively large doses of 50–100 mg/kg. All compounds of this series were very much less potent than morphine.

Table I. *N*-Aralkylnormorphans



Compd	*n*	R^1	R^2	Mp, °C	Method	Yield,[a] %	Crystn solvent[b]	Formula[c]
1	2	*o*-NO_2	OH	177-178	A	73	Ac	$C_{24}H_{28}N_2O_3$
2	2	*m*-NO_2	OH	159-163	A	41	Ac	$C_{24}H_{28}N_2O_3$
3	2	*p*-NO_2[d]	OH	119-126	A	93	Ac	$C_{24}H_{28}N_2O_3$
4	3	*o*-NO_2	OH	201-203	A	79	Ac	$C_{25}H_{30}N_2O_3$[e]
5	3	*m*-NO_2	OH	175-177	A	64	Ac	$C_{25}H_{30}N_2O_3$
6	3	*p*-NO_2	OH	201-204	A	56	Ac	$C_{25}H_{30}N_2O_3$
7	2	*o*-NH_2	OH	196-198[f]	B	81	IE	$C_{24}H_{30}N_2O$
8	2	*m*-NH_2	OH	252-254[g]	B	87	IE	$C_{24}H_{30}N_2O$
9	2	*p*-NH_2	OH	195-196[h]	B	72	IE	$C_{24}H_{30}N_2O$
10	3	*o*-NH_2	OH	191-193	B	94	IE	$C_{25}H_{32}N_2O$
11	3	*m*-NH_2	OH	167-168	B	96	IE	$C_{25}H_{32}N_2O$
12	3	*p*-NH_2	OH	127-130	B	98	IE	$C_{25}H_{32}N_2O$
13	2	*o*-$NHCOCH_2Br$	OH	214-216	C	64	IE	$C_{26}H_{31}N_2O_2Br \cdot HBr$[i]
14	2	*m*-$NHCOCH_2Br$	OH	247-250	C	53	HTE	$C_{26}H_{31}N_2O_2Br \cdot HCl$
15	2	*p*-$NHCOCH_2Br$	OH	280-282	C	88	IE	$C_{26}H_{31}N_2O_2Br \cdot HBr$
16	3	*o*-$NHCOCH_2Br$	OH	168-172	C	56	HTE	$C_{27}H_{33}N_2O_2Br \cdot HCl$
17	3	*m*-$NHCOCH_2Br$	OH	201-204	C	53	HTE	$C_{27}H_{33}N_2O_2Br \cdot HCl$
18	3	*p*-$NHCOCH_2Br$	OH	205-208	C	85	HTE	$C_{27}H_{33}NOBr \cdot HCl$
19	2	*o*-$NHCOCH_2CH_2CO_2C_2H_5$	OH	160-162	C	67	TE	$C_{30}H_{38}N_2O_4 \cdot HCl$
20	2	*m*-$NHCOCH_2CH_2CO_2C_2H_5$	OH	133-137	C	50	HTE	$C_{30}H_{38}N_2O_4 \cdot HCl$
21	2	*p*-$NHCOCH_2CH_2CO_2C_2H_5$	OH	160-162	C	50	HTE	$C_{30}H_{38}N_2O_4 \cdot HCl$
22	3	*o*-$NHCOCH_2CH_2CO_2C_2H_5$	OH	131-135	C	87	HTE	$C_{31}H_{40}N_2O_4 \cdot HCl$
23	3	*m*-$NHCOCH_2CH_2CO_2C_2H_5$	OH	149-151	C	91	HTE	$C_{31}H_{40}N_2O_4 \cdot HCl$
24	3	*p*-$NHCOCH_2CH_2CO_2C_2H_5$	OH	141-144	C	80	HTE	$C_{31}H_{40}N_2O_4 \cdot HCl$
25	2	*o*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	175-177	C	60	HTE	$C_{30}H_{36}N_2O_4 \cdot HCl$
26	2	*m*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	176-180	C	45	HTE	$C_{30}H_{36}N_2O_4 \cdot HCl$
27	2	*p*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	260-262	C	73	HTE	$C_{30}H_{36}N_2O_4 \cdot HCl$
28	3	*o*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	154-157	C	83	HTE	$C_{31}H_{38}N_2O_4 \cdot HCl$
29	3	*m*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	162-165	C	53	HTE	$C_{31}H_{38}N_2O_4 \cdot HCl$
30	3	*p*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	178-181	C	66	HTE	$C_{31}H_{38}N_2O_4 \cdot HCl$
31	2	*m*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	181-185	C	31	HTE	$C_{30}H_{36}N_2O_4 \cdot HCl$
32	3	*o*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	190-194	C	29	HTE	$C_{31}H_{38}N_2O_4 \cdot HCl$
33	3	*m*-$NHCOC(H)=C(H)CO_2C_2H_5$	OH	179-184	C	72	HTE	$C_{31}H_{38}N_2O_4 \cdot HCl$[j]
34	2	*o*-Maleimido	$OCOCH_3$	175-180	D	75	TE	$C_{30}H_{32}N_2O_4 \cdot HCl$
35	2	*p*-Maleimido	$OCOCH_3$	*k*	D	57	TE	$C_{30}H_{32}N_2O_4 \cdot HCl$
36	3	*o*-Maleimido	$OCOCH_3$	143-147	D	86	HTE	$C_{31}H_{34}N_2O_4 \cdot HCl$
37	3	*m*-Maleimido	$OCOCH_3$	137-140	D	36	HTE	$C_{31}H_{34}N_2O_4 \cdot HCl \cdot 2H_2O$
38	3	*p*-Maleimido	$OCOCH_3$	149-152	D	87	HTE	$C_{31}H_{34}N_2O_4 \cdot HCl \cdot 2H_2O$[l]
39	2	*o*-Maleimido	OH	174-177	E	83	HTE	$C_{28}H_{30}N_2O_3 \cdot HCl$
40	2	*m*-Maleimido	OH	*m*	E	63	HTE	$C_{28}H_{30}N_2O_3 \cdot HCl \cdot H_2O$
41	2	*p*-Maleimido	OH	*n*	E	26	HTE	$C_{28}H_{30}N_2O_3 \cdot HCl \cdot H_2O$[o]
42	3	*m*-Maleimido	OH	156-160	E	27	HTE	$C_{29}H_{32}N_2O_3 \cdot HCl \cdot H_2O$

[a] Yields of 1-6 are based on method A; 7-12 on method B; 13-33 on method C; 34-38 on method D; and 39-42 on method E. [b] Ac = acetone; IE = 2-propanol-EtOH; HTE = HCl-THF-Et_2O; TE = THF-Et_2O. [c] All analyses are within ±0.4% for C, H, and N unless specified. [d] Reported[6] previously as the HCl salt. [e] Calcd: C, 73.86; H, 7.43. Found: C, 74.36; H, 6.81. [f] Lit.[6] 194 °C. [g] Lit.[6] 248-250 °C. [h] Lit.[6] 197-199 °C. [i] Calcd: C, 55.32. Found: C, 54.72. [j] Calcd: C, 69.06. Found: C, 68.58. [k] Mp (with foaming) 170-185 °C. [l] Calcd: C, 65.15. Found: C, 65.87. [m] Foams with decomposition, 220-230 °C. [n] Foams with decomposition, 230-250 °C. [o] Calcd: C, 67.65. Found: C, 68.25.

In order to determine whether the alkylating agents were capable of blocking analgesic activity, mice were treated with these agents at either approximately ED_{99} doses of the analgesically active compounds or relatively high doses (50–100 mg/kg) of the inactive compounds. After the analgesic activity of the compounds had disappeared, the mice were challenged with 10 mg/kg of morphine sulfate. If significant block of morphine analgesia was observed, i.e., >50% of the animals did not exhibit significantly increased reaction times, the ED_{50} of morphine was de-

Table II. Analgesic Activity of *N*-Aralkylmorphinans

Compd	ED_{50} (95% confidence limits),[a] mg/kg	Approx peak effects, min
13	16.0 (11.9-20.8)	30
14	0.58 (0.35-0.93)	30
15	0.13 (0.07-0.18)	30
16	>100	
17	>100	
18	>100	
19	>100	
20	6.0 (4.0-8.9)	60
21	0.71 (0.33-1.39)	60
22	>100	
23	77.9 (49.3-123.1)	30
24	78.2 (49.5-123.6)	30
25	>150	
26	5.6 (3.7-8.6)	60
27	1.2 (0.9-1.6)	60
28	84[b]	15
29	76.5 (46.1-127.0)	30
30	28.4 (20.3-39.8)	30
31	2.3 (1.6-3.4)	60
32	>100	
33	>100	
34	11.7 (7.8-17.7)	30
35	0.59 (0.38-0.90)	30
36	48.4 (30.6-76.5)	30
37	>100	
38	>50	
39	>100	
40	11.4 (7.5-17.3)	30
41	1.1 (0.7-1.8)	30
42	>50	
Morphine sulfate	4.9 (3.8-7.2)	30
Phenazocine hydrobromide	0.53 (0.39-0.72)	30

[a] None of the slopes of the dose-response curves differed significantly from each other. [b] Due to limited supply of the compound, the ED_{50} is an approximation from an incomplete dose-response curve.

termined in similarly pretreated animals. The results are recorded in Table III.

There were seven compounds of the phenethyl series that significantly increased the ED_{50} of morphine. The increases for seven compounds were of the same magnitude of about twofold. None of the slopes of the shifted dose–response curves differed significantly from that of the control dose–response curve of morphine. The dose of the blockers ranged from 2 to 70 mg/kg and the most active blocker at 2 mg/kg was the *p*-maleimide derivative 41 (Table IV). None of the compounds in the phenylpropyl series significantly blocked morphine analgesia.

To further ensure that the site of action of the analgesic blockers of the phenethyl series was at the morphine receptors, a receptor protection study with naloxone was performed with the most potent blocker (41) as follows. Mice were pretreated with the specific narcotic antagonist, naloxone, before the administration of 41. After 2 h, when the effect of naloxone was no longer evident, the analgesic activity of morphine was assessed in the same animals. The results in Table V reveal that naloxone blocked the analgesic effect of 41 and protected the analgesic receptor from interaction with 41. The protection is evident from the fact that the full analgesic effect of morphine was elicited after the effect of naloxone had disappeared.

Those compounds in Table III which appeared to antagonize morphine analgesia (21, 26, 31, 35, 40, and 41) were also tested for their capacity to suppress abstinence in morphine-dependent mice. All the test compounds suppressed abstinence in withdrawn animals and appeared to act like narcotic agonists.

Table III. Antagonism of Morphine Analgesia by *N*-Aralkylmorphinans

Compd	Pretreatment dose, mg/kg[a]	Duration of pretreatment, h[b]	ED_{50} (95% confidence limits) of morphine sulfate, mg/kg[c]
None			4.9 (3.8-6.2)
13	70	6.5	10.9 (7.3-16.6)
14	5.3	3	*d*
15	0.81	2.5	*d*
16	100	1	*d*
17	100	1	*d*
18	100	1	*d*
19	100	1	*d*
20	40	3	*d*
21	2.7	4	9.4 (6.0-14.5)
22	100	2	*d*
23	100	1	*d*
24	100	2	*d*
25	*e*		
26	20	3	9.0 (5.6-14.3)
27	2.6	2.5	*d*
28	350	2	*d*
29	380	5.5	*d*
30	100	2	*d*
31	15	3	14.0 (8.9-22.1)
32	100	2	*d*
33	50	2	*d*
34	20	2	6.7 (4.9-9.1)
35	5	4	8.4 (4.9-14.3)
36	100	3	*d*
37	100	2	*d*
38	50	2	*d*
39	80	1	*d*
40	20	2	12.7 (7.7-20.8)
41	2	2	9.6 (6.4-14.2)
42	50	2	*d*

[a] These are approximately ED_{99} doses that were estimated from the dose-response curves. In cases where the dose-response curve was not determined, the highest dose used for testing was employed. [b] These values also represent the duration of analgesic activity of the pretreatment drugs. [c] None of the slopes of the dose-response curves differed from that of the control dose-response curve of morphine sulfate. [d] After pretreatment with these drugs, eight to ten animals were challenged with 10 mg/kg of morphine sulfate and the animals did not exhibit analgesia that was different from control animals. ED_{50} of morphine sulfate was determined only when the pretreatment drug showed significant antagonism in animals after the 10 mg/kg challenge of morphine sulfate. [e] There was an insufficient amount of this drug to perform the pretreatment studies.

Table IV. Effect of the Dose of 41 on ED_{50} of Morphine

Dose of 41, mg/kg	Pretreatment time, h[a]	Morphine sulfate ED_{50}, mg/kg
2	2	9.6 (6.4-14.2)
8	3	15.2 (10.7-21.7)
32	4	15.9 (10.7-23.5)

[a] Time required for the return of the reaction time to control value after administration of 41.

Compound 41 inhibited the stereospecific binding of [^{3}H]naloxone to putative opiate receptors with an IC_{50} (concentration needed to inhibit the stereospecific naloxone binding by 50%) of 5.3×10^{-9} M. This value was similar to the IC_{50} of naloxone of 5.5×10^{-9} M. Incubation of 41 with the homogenate preparation for 2 h instead of the usual 10 min did not alter the IC_{50} of 41. When the binding assay was performed in the presence of 100 mM NaCl, there was no change in the IC_{50} of naloxone but the IC_{50} of 41 increased by over tenfold to 5.7×10^{-8} M.

Table V. Analgesic Receptor Protection Study with Naloxone

Treatment of animals	No. of mice exhibiting analgesia: no. of mice used
2 mg/kg of 41 sc	9/10
Pretreated with 1 mg/kg of naloxone sc 10 min before injection of 2 mg/kg of 41	0/10
10 mg/kg of morphine sulfate sc to the above mice 2 h after treatment with naloxone and 41	8/10
10 mg/kg of morphine sulfate sc	9/10

Discussion

Many of the target compounds exhibited the characteristics of analgesic agonism. It has been shown previously that the analgesic potencies of the parent phenethyl compounds are ranked 9 > 8 >7.[3] The potency ranking (para > meta > ortho) among the phenethyl compounds appears generally true regardless of the type of substituent; i.e., 15 > 14 > 13, 21 > 20 > 19, 27 > 26 > 25, 41 > 40 > 39. All the para derivatives were much more potent than morphine and their ED_{50}'s ranged approximately 4–40 times less than that of morphine. The meta derivatives had a wide spectrum of potencies with some compounds being more potent than morphine (14, 31), others being comparable to morphine (20, 26) and still others being less potent than morphine (40). The ortho derivatives were all less potent than morphine.

The phenethyl compounds were significantly more potent than the phenylpropyl homologues by a factor of 10–100. Although an identical potency ranking (para > meta > ortho) among the phenylpropyl compounds appears to hold with the fumaramido esters (30 > 29 >28), most of the other derivatives displayed insufficient activity to generalize this ranking.

While analgesic potency was a function of the positional attachment of the substituent, the capacity to antagonize morphine did not show the same type of relationship (Table III). The fact that the ortho (13), meta (26, 31, 40), and para (21, 35, 41) derivatives were all active blockers of morphine analgesia indicates that this effect is not critically dependent on the positional isomerism of the acyl group or on the particular class of reactive function.

In an effort to acquire additional information on the nature of the antagonism, one of the more potent compounds, 41, was investigated further. It was found that pretreatment with 41 produced a parallel shift of the dose–response curve to higher concentration for morphine and that a further shift did not occur beyond 8 mg/kg of 41 (Table IV). The reason for this behavior is not clear and a similar behavior has been observed for a compound in the anileridine series.[2] These data are not consistent either with a competitive or noncompetitive antagonism in the classical sense. This also is suggested by the fact that 41 suppresses the abstinence syndrome in morphine-dependent mice.

That the antagonist action of 41 is specifically associated with opiate receptors was suggested by the ability of naloxone to protect against this action (Table V). On the other hand, in the in vitro binding assay, the ratio of IC_{50} with NaCl/IC_{50} without NaCl for 41 was over 10, which would be classified as a relatively pure opiate agonist.[8] Apparently this in vitro assay was unable to predict the antagonist activity of this compound in vivo. Perhaps the assay is complicated by the unusual type of antagonism observed with 41 as described above. The fact that prolonging the incubation time with 41 did not significantly change its IC_{50} value in the binding assay suggests that the specific antagonism may involve noncovalent binding with the receptor sites in the preparation.

Although many of the compounds which contain alkylating moieties exhibit antagonism, it remains to be clarified whether or not the in vivo blockage of opiate receptors involves covalent association. In view of the above results, the duration of the antagonism, and the fact that 21 (a presumably unreactive member of the series) also exhibits a similar type of activity, it presently seems more likely that alkylation is not involved.

Experimental Section

Levorphanol and levallorphan tartrates were generously supplied by Hoffmann-La Roche Inc., Nutley, N.J. The nitrophenylacetic acids and nitrocinnamic acids were obtained from Aldrich Chemical Co., Milwaukee, Wis. Melting points were determined in open capillaries on a Thomas-Hoover apparatus and are uncorrected. NMR and IR spectra of all compounds are consistent with the assigned structures. C, H, and N analyses were performed by M-H-W, Garden City, Mich., and are within ±0.4% unless otherwise noted. Column chromatography was performed with EM reagent silica gel (70–230 mesh). [15-^{3}H]-Naloxone, 5.3 Ci/mmol, was kindly supplied by Dr. Robert E. Willette of NIDA.

2-(Nitrophenyl)ethyl Bromide. To 10 mmol of *o*-, *m*-, or *p*-nitrophenylacetic acid dissolved in THF (10 mL) was added 20 mL of B_2H_6–THF (20 mL) and the solution was stirred at 20 °C for 2 h. After decomposing the excess B_2H_6 with MeOH, the solvent was removed to afford an oil which was purified on an alumina–$CHCl_3$ (neutral activity III) column. The nitrophenethanols[9-11] which were produced in yields of 90–96% were converted to the corresponding bromides[9,12,13] by heating (110 °C) with PBr_3 for 6 h. The mixture was poured into ice–water, extracted with ether, washed with 10% Na_2CO_3, and dried (Na_2SO_4). After removal of solvent, the chromatographically pure product was obtained in yields of 60–95%.

3-(Nitrophenyl)propyl Bromide. To a stirred mixture of $LiBH_4$ (2.5 mmol) in THF (5 mL) there was added the methyl ester of *o*-, *m*-, or *p*-nitrocinnamate. After heating the reaction mixture to 45 °C for 3 h, it was cooled to 20 °C and the excess $LiBH_4$ was decomposed with HOAc. Removal of solvent afforded an oil which was partitioned between $CHCl_3$ and water. The separated $CHCl_3$ phase was washed with 10% Na_2CO_3 and dried (Na_2SO_4), the solvent was removed, and the residue was chromatographed (neutral alumina, activity III, 1:99 MeOH–$CHCl_3$) to afford the 3-(nitrophenyl)propyl alcohols[14] as oils in yields of 27–69%. Anal. (for ortho, meta, and para isomers) ($C_9H_{11}NO_3$) C, H, N. The nitrocinnamyl alcohols also were obtained as minor components (para, 6%; meta, 22%; ortho, 40%) of the reduction. The *o*-, *m*-, and *p*-3-(nitrophenyl)propyl bromides[15] were obtained in yields of 60–95% by treatment of the corresponding alcohols with PBr_3 as described previously. Anal. (for ortho, meta, and para isomers) ($C_9H_{10}BrNO_2$) C, H, N.

Method A. 3-Hydroxy-17-nitrophenalkylmorphinan (1–6). A mixture of 1.0 mmol of 3-hydroxymorphinan[6] prepared from levorphanol according to the procedure of Abdel-Monem and Portoghese,[16] 1.5 mmol of nitrophenalkyl bromide, and anhydrous K_2CO_3 (3 mmol) was heated in freshly distilled DMF (2 mL) under N_2 at 105 °C for 24 h. The reaction mixture was cooled and filtered, and the solvent was removed from the filtrate in vacuo. The residue was chromatographed on silica gel (3% MeOH–$CHCl_3$) to afford a product which was recrystallized from acetone.

Method B. 3-Hydroxy-17-aminophenalkylmorphinan (7–12). The product (1.0 mmol) obtained from method A was dissolved in 1 N HCl–EtOH (10 mL) and shaken with 5% Pd/C (0.2 g) on a Parr hydrogenator at 45 psi of H_2 for 3 h. The catalyst was separated by filtration and the solvent was removed in vacuo to give the crude HCl salt. The product was dissolved in H_2O, basified with NH_3, and extracted with $CHCl_3$. Evaporation of the solvent afforded material which was recrystallized from *i*-PrOH–Et_2O.

Method C. 3-Hydroxy-17-acylaminophenalkylmorphinan (13–33). The product (1.0 mmol) obtained from the above procedure was dissolved in freshly distilled THF (20 mL) and

mixed with 1.1 mmol of the acyl halide. The mixture was stirred at 25 °C for 2–4 h, after which time the crude product was precipitated by addition of Et_2O (50 mL) and collected. The crude salt either was purified directly by crystallization (*i*-PrOH–Et_2O or THF–Et_2O) or it was converted to the base for chromatographic purification (silica gel, 3% MeOH–$CHCl_3$). The product obtained from chromatographic purification was dissolved in dry THF and converted to the salt with HCl–Et_2O or HBr–Et_2O.

Method D. 3-Acetoxy-17-(pyrrole-2,5-dion-1-ylphenalkyl)morphinan (34–38). A mixture of the product obtained from method B (1.0 mmol) and maleic anhydride (1.2 mmol) was refluxed in THF (5 mL) for 2 h, cooled to 25 °C, and diluted with Et_2O. The crude maleamic acid which precipitated was collected by filtration, suspended in 2% NaOAc–Ac_2O (10 mL), and refluxed for 2 h. The solvent was removed in vacuo and the residue was partitioned between $CHCl_3$ and 10% $NaHCO_3$. After separation of the organic layer and removal of the $CHCl_3$ in vacuo, the residue was chromatographed on silica gel (3% MeOH–$CHCl_3$). The product was dissolved in dry THF and converted to the HCl salt with HCl–Et_2O.

Method E. 3-Hydroxy-17-(pyrrole-2,5-dion-1-ylphenalkyl)morphinan (39–42). A methanolic solution (25 mL) containing 1.0 mmol of the acetoxymaleimide hydrochloride and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 0.5–4 h with monitoring by TLC. When the starting material had been consumed, the mixture was treated with $NaHCO_3$ (1.5 mmol) and the solvent was removed in vacuo. After the residue was partitioned between $CHCl_3$ and water, the organic phase was separated and dried (anhydrous Na_2SO_4), and the solvent was removed. The crude product then was chromatographed (silica gel, 5% MeOH–$CHCl_3$) and converted to the HCl salt by addition of HCl–Et_2O to a THF solution of the product.

Pharmacology. Male Swiss–Webster mice (Sasco or Biolab) weighing 20–25 g were used in all experiments. The test compounds were dissolved in 40% propylene glycol and the final concentration was made so that 10 mL/kg was injected sc at each dose level. Analgesic activity was determined by the method of D'Amour and Smith[17] which was modified for the mouse.[18] The ED_{50} values and the 95% confidence limits were estimated by the method of Litchfield and Wilcoxon.[19]

Inhibition of the binding of [^{3}H]naloxone to putative opiate receptors was determined by the method of Pert and Snyder[21] as modified by Pasternak et al.[20] The procedure included the preincubation step prior to the binding assay. Stereospecificity of the binding was determined by incubation with and without 1×10^{-6} M levallorphan. The concentration of [^{3}H]naloxone used was 1.5×10^{-9} M. The binding was also performed in the absence and presence of 100 mM NaCl in an attempt to discriminate the degree of agonistic and antagonistic properties contained in the drug.[8] The single-dose suppression test in morphine-dependent mice was carried out by the method of Takemori et al.[22]

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References and Notes

(1) P. S. Portoghese, V. G. Telang, A. E. Takemori, and G. Hayashi, *J. Med. Chem.*, 14, 144 (1971).
(2) A. E. Takemori, A. Ward, P. S. Portoghese, and V. G. Telang, *J. Med. Chem.*, 17, 1051 (1974).
(3) A somewhat similar approach for selectively forming covalent bonds between photochemically activated ligands and opiate receptors in vitro also has been employed by others [B. A. Winter and A. Goldstein, *Mol. Pharmacol.*, 8, 601 (1972); R. Schulz and A. Goldstein, *Life Sci.*, 16, 1843 (1975)].
(4) J. Hellerbach, O. Schnider, H. Besendorf, B. Pellmont, N. B. Eddy, and E. May, "Synthetic Analgesics, Part II", Pergamon Press, Oxford, 1966.
(5) P. S. Portoghese, *J. Med. Chem.*, 8, 609 (1965).
(6) A. Grüssner, J. Hellerbach, and O. Schnider, *Helv. Chim. Acta*, 40, 1232 (1957).
(7) M. P. Cava, A. A. Deana, K. Muth, and J. Mitchell, *Org. Synth.*, 41, 93 (1961).
(8) C. B. Pert, G. Pasternak, and S. H. Snyder, *Science*, 182, 1359 (1973).
(9) L. F. Blackwell, P. D. Buckley, K. W. Jolley, and A. K. H. MacGibbon, *J. Chem. Soc., Perkin Trans. 2*, 169 (1973).
(10) S. Sabetay, J. Blêger, and Y. de Lestrange, *Bull. Soc. Chim. Fr.*, 49, 3 (1931).
(11) F. Ehrlich and P. Pistschimuka, *Ber. Dtsch. Chem. Ges.*, 45, 2428 (1912).
(12) E. L. Foreman and S. M. McElvain, *J. Am. Chem. Soc.*, 62, 1435 (1940).
(13) H. Sobotka, *Ber. Dtsch. Chem. Ges.*, 45, 2191 (1929).
(14) L. L. Sergeeva, N. N. Shorygina, and B. V. Lopatin, *Izv. Akad. Nauk SSSR*, 2114 (1967).
(15) W. Davis, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 890 (1955).
(16) M. M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, 15, 208 (1972).
(17) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exp. Ther.*, 72, 74 (1941).
(18) F. C. Tulunay and A. E. Takemori, *J. Pharmacol. Exp. Ther.*, 190, 395 (1974).
(19) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, 96, 99 (1949).
(20) C. B. Pert and S. H. Snyder, *Science*, 179, 1011 (1973).
(21) G. W. Pasternak, H. A. Wilson, and S. H. Snyder, *Mol. Pharmacol.*, 11, 340 (1975).
(22) A. E. Takemori, A. J. Stesin, and F. C. Tulunay, *Proc. Soc. Exp. Biol. Med.*, 145, 1232 (1974).

An Approach to Peripheral Vasodilator–β-Adrenergic Blocking Agents

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The syntheses of 2-phenyl- and 2-pyridyl-4-trifluoromethylimidazoles having a 3-*tert*-butylamino-2-hydroxypropoxy moiety attached to the aryl or heteroaryl substituent are described. Structure–activity relationships based on results from an evaluation of these compounds for antihypertensive, vasodilating, and β-adrenergic blocking activities are discussed.

Peripheral vasodilator drugs are of growing interest as agents for the treatment of moderate to severe hypertension.[1,2] Members of this class include sodium nitroprusside,[3,4] hydralazine,[5] diazoxide,[6] and minoxidil;[7] such agents lower blood pressure by decreasing peripheral resistance through direct action on the vascular smooth