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Synthesis and Pharmacological Activity of Some *N*-Alkyl-Substituted 9α-Ethyl-2′-hydroxy-5-methyl-6,7-benzomorphans[1,2]

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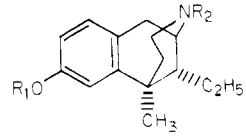
A series of N-substituted 9α-ethyl-2′-hydroxy-5-methyl-6,7-benzomorphans was synthesized and evaluated for their narcotic analgesic and antagonistic activities. Compounds **2a** and **22** were as potent as morphine in the writhing (PPQ) and hot-plate tests, while a number of compounds demonstrated antagonistic activities greater than nalorphine. Generally, the compounds in this series show activities somewhat greater than the comparable compounds in the 5,9α-dimethyl-6,7-benzomorphan series for analgesic effect and similar or slightly less antagonistic potency.

Due to the interesting analgesic and antagonistic activities of benzomorphans[3-6] and continuing the search for better, longer acting, orally active medicinal agents in the series, the title compounds were synthesized. The synthesis, the narcotic analgesic and the antagonistic activity in rodents, and single dose suppression (SDS) and precipitated withdrawal test (PPT) in monkeys are herein described.

Chemistry. Norbenzomorphan (1) was chosen as the key intermediate for the synthesis of various N analogues. This intermediate was obtained in 94% yield by N-demethylation of the 6,7-benzomorphan compound **2a** via a modification of the procedure of Rice.[8] It was unnecessary, for example, to hydrolyze the *N*,*O*-dicarbonyl compound **2b** to the carbamate **2c** or to eliminate the phenol formed in both steps of the process until the final crystallization of **1**. The fragmentation pattern of **1** (M^+ 231) was that expected for a 9α-6,7-benzomorphan.

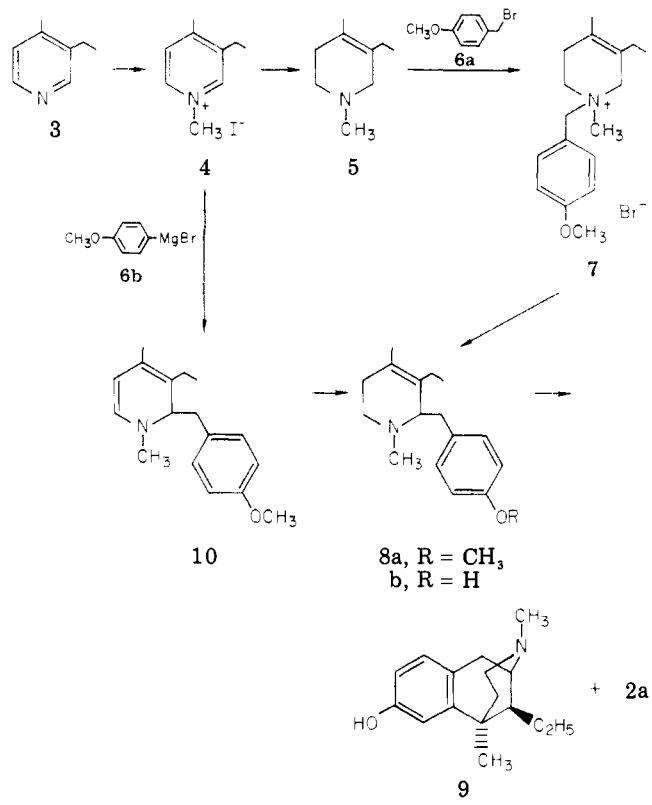


1, $R_1 = R_2 = H$
2a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = R_2 =$ OCOPh
c, $R_1 = H$; $R_2 =$ OCOPh

The synthetic routes to **2a** are those of May et al.[7] (Scheme I) except that anisyl bromide[9] and anisylmagnesium bromide[10] were used rather than the corresponding chlorides.

Quaternization of **3** with methyl iodide, followed by $NaBH_4$ reduction, gave the tetrahydropyridine **5**. Reaction of **5** with anisyl bromide (**6a**)[11] gave the quaternary bromide **7** in 50% yield (based on **4**). Stevens rearrangement of **7** (PhLi) gave **8a** (51% yield) and other undesirable side products.[12] Pure **8a** could be obtained readily through the HBr or picrate salt. Cyclization of **8a** with refluxing 48% HBr gave a 10:1 mixture of the 9α- and 9β-benzomorphans **2a** and **9**.[7] The two isomers were separated by fractional crystallization (Me_2CO) and their stereochemistry was established by mass spectroscopy (M^+ 245). The fragmentation pattern of each isomer, upon electron impact (70 eV), is characteristic. The relative intensity of the (M^+) and ($M^+ - C_5$) ions varies for each isomer (70 and 50% for the 9α isomer and 50 and 100% for the 9β isomer, respectively).[13]

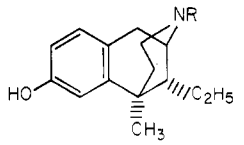
Scheme I



Compound **8a** was also synthesized by treating **4** with anisylmagnesium bromide (**6b**) to give the dihydropyridine **10** which is then reduced by $NaBH_4$.[14] Further, when **8b** was cyclized with 85% phosphoric acid at 185 °C,[15] a 5:1 mixture of **2a** and **9** was obtained.

To get the various analogues (Table I), two procedures were used. (a) The Archer and Harris procedure[4b] was followed for the synthesis of compounds **11–20**. In this procedure, the norbenzomorphan **1** was refluxed with the desired alkyl halide in dimethylformamide (DMF) and $NaHCO_3$ for 4–5 h. The products were crystallized from $CHCl_3$–Et_2O, Me_2CO, or MeOH. (b) Compounds **21** and **22** were synthesized following established literature procedures for the acylation of secondary amines and the subsequent reduction of the resulting amides or *N*,*O*-dicarbonyl compounds.[16,17] Thus, compound **1** was refluxed with the appropriate cycloalkylcarbonyl halide in triethylamine and methylene chloride. The resulting adduct

Table I. Physical Properties of N-Substituted 9α-Ethyl-2'-hydroxy-5-methyl-6,7-benzomorphans



Compd	R	Mp, °C	Formula	% yield	Analyses
1	H	281-284	$C_{15}H_{21}NO$	95.5	C, H, N
2a[a]	CH_3	217-219	$C_{16}H_{23}NO$	69	C, H, N
11[b]	C_2H_5	197-200	$C_{17}H_{25}NO$	71	C, H, N
12[a]	n-C_3H_7	167-170	$C_{18}H_{27}NO$	84	C, H, N
13[c]	n-C_4H_9	146-147.5	$C_{19}H_{29}NO$	77	C, H, N
14[a]	n-C_5H_{11}	145-147	$C_{20}H_{31}NO$	72	C, H, N
15[a,c]	n-C_6H_{13}	127-129	$C_{21}H_{33}NO$	73	C, H, N
16[c]	n-C_7H_{15}	123-124.5	$C_{22}H_{35}NO$	69	C, H, N
17[c]	n-C_8H_{17}	92-95	$C_{23}H_{37}NO$	45	C, H, N
18[c]	$CH_2CH=CH_2$	92.5-95.5	$C_{18}H_{25}NO$	82	C, H, N
19[c]	$(CH_2)_3CH=CH_2$	134.5-136	$C_{20}H_{29}NO$	68	C, H, N
20[b]	$CH_2CH=C(CH_3)_2$	139-141.5	$C_{20}H_{29}NO$	61	C, H, N
21[b]	CH_2-c-C_3H_5	183-185	$C_{19}H_{27}NO$	66	C, H, N
22[b]	CH_2-c-C_4H_7	135-137.5	$C_{20}H_{29}NO$	84	C, H, N

[a] Crystallized from Me_2CO. [b] Crystallized from MeOH. [c] Crystallized from $CHCl_3$-Et_2O (the compound was dissolved in a little $CHCl_3$; then Et_2O was added followed by chilling).

Table II. Analgesic and Antagonistic Data[a]

Compd	Analgesic act. (ED_{50}, mg/kg sc)			Antagonistic AD_{50}[18] act., mg/kg sc
	Tail-flick	PPQ	Hot-plate	
1[b]	NA	NA	NA	NA
2a[c]	6.4 (3.1-12.8)	0.2 (0.008-0.7)	1.3 (0.9-2.0)	NA
11[d]	NA	NA	21.3 (13.4-33.9)	5.5 (1.8-16.9)
12[e]	NA	NA	NA	0.7 (0.36-1.36)
13[f]	NA	13.0 (4.7-35.6)	NA	2.38 (0.81-7.02)
14[g]	28.1 (14.1-56.3)	1.8 (0.9-3.5)	4.2 (3.2-5.5)	NA
15[h]	18.7 (9.5-37.0)	5.7 (3.1-10.4)	6.2 (4.5-8.5)	NA
16	14.0 (5.5-35.6)	7.3 (3.0-18.0)	9.9 (6.8-14.4)	NA
17[i]	NA	15.13 (2.97-77.0)	NA	NA
18[j]	NA	15.7 (5.0-49.4)	NA	0.6 (0.23-1.56)
19[k]	NA	2.56 (0.78-8.4)	NA	1.18 (0.44-3.13)
20[l]	NA	NA	8.9 (4.9-16.3)	3.1 (1.148-8.37)
21[m]	NA	2.1 (1.1-4)	NA	0.19 (0.075-0.48)
22[n]	NA	0.31 (0.1-0.94)	1.8 (1.2-2.8)	0.477 (0.154-1.48)
Morphine[o]	5.34 (4.77-5.98)	0.23 (0.2-0.26)	1.2 (0.9-1.3)	NA
Nalorphine[p]	NA	0.60 (0.25-1.44)	36.3 (27.1-48.7)	2.6 (0.69-9.75)

[a] Tail-flick, PPQ-writhing, and antagonistic activities tests were performed at the MCV Department of Pharmacology Laboratories. Compounds tested were free bases to which either dilute HCl (compounds 11, 12, and 19-22) or lactic acid (compounds 1, 2a, 13-16, and 18) was added for solution. Hot-plate and Nilsen tests were performed at NIH. NA means not active. 95% confidence limits are shown in parentheses. [b] 37% activity at 30.0 mg/kg (TF), 45% activity at 30.0 mg/kg (PPQ), and NA at 30.0 mg/kg (TF antagonism). [c] NA at 1.0 and 10.0 mg/kg (TF antagonism). [d] 27% activity at 30.0 mg/kg (PPQ). [e] 55% activity at 10.0 mg/kg (PPQ); animals become hyperactive and ataxic at 3.0 and 10.0 mg/kg doses. The compound is inactive at 10.0, 20.0, and 40.0 mg/kg (Nilsen). [f] NA at 30.0 mg/kg (TF), toxic at 50.0 mg/kg (HP), NA at 20.0 mg/kg (Nilsen). [g] 39% activity at 30 mg/kg (TF antagonism). [h] NA at 30.0 mg/kg (TF antagonism). [i] Compound 17 was given in agar suspension. [j] NA at 30.0 mg/kg (TF) and NA at 20.0 and 50.0 mg/kg (HP). [k] NA at 30.0 mg/kg (TF); NA at 100.0 mg/kg (HP); NA at 50.0 mg/kg (Nilsen). [l] 36% activity at 10.0 mg/kg (PPQ). Nilsen ED_{50}, 26.8 mg/kg (12.2-58.8). [m] 12% activity at 10.0 mg/kg (TF). NA and toxic at 5.0 and 10.0 mg/kg (Nilsen). [n] NA at 10.0 mg/kg (TF); Nilsen ED_{50}, 2.9 mg/kg (1.9-4.1). [o] Nilsen ED_{50}, 0.8 mg/kg (0.6-1.2) as sulfate. [p] NA at 1 or 10 mg/kg (TF); Nilsen ED_{50}, 4.8 mg/kg (2.7-8.5) (ref 21).

was reduced with $LiAlH_4$; the products were crystallized from methyl alcohol. Table I lists the compounds synthesized and their physical data.

Pharmacological Studies and a Brief Discussion. The analgesic activities of the compounds (racemates) were determined by the tail-flick,[18] writhing-PPQ (2-phenyl-*p*-quinone),[19] hot-plate,[20] and Nilsen tests.[21] The narcotic antagonistic activities were determined by the tail-flick procedure in rodents[18] and by single dose suppression (SDS) and precipitated withdrawal (PPT) tests in morphine-dependent monkeys.[22]

Based on the data shown in Table II, compound **2a** is the most active agonist and is equipotent to morphine.[7] This is followed by **22**, **14**, and **15**. Compounds **11**–**13** are essentially inactive as agonists as is norbenzomorphan (**1**). The 9β isomer **9** is more active than **2a**.[7,23]

In the tests for antagonism, compounds **12**, **13**, **18**, **19**, and **21** show activity greater than that of nalorphine (compound **20** shows similar antagonistic activity to that of nalorphine). Compound **22** shows mixed agonist–antagonist activity. When compared with the corresponding compounds in the 5,9α-dimethyl-6,7-benzomorphan series,[24] the present compounds generally show slightly greater analgesic activity but similar or less antagonistic potency.[3] Further, the effects of alkyl substitution on the nitrogen are similar to those seen in other benzomorphans[24] and in N-substituted normorphines where comparative data are available.[25]

In the SDS and PPT test in monkeys,[26-29] compound **2a** alone substituted for morphine completely. Compounds

18 and 21 are antagonists: 18 appears to be one-tenth as active as naloxone and has a similar onset and longer duration of action, while 21 is more potent and longer lasting than nalorphine. Compound 19 produces CNS depression with marked motor incoordination, convulsions, and precipitation of abstinence signs in morphine-dependent animals. Compound 22 caused marked CNS depression which was partially reversed by naloxone but not by nalorphine. It did not suppress the signs of morphine abstinence. Compound 15 was an analgesic that did not substitute for morphine in the dose range tested (2.5–20.0 mg/kg). It was of sufficient interest to warrant chronic administration tests. The results of this and further studies on the other compounds will be reported later.

Experimental Section

Melting points were determined (capillary tubes) using a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra and elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of the Laboratory of Chemistry, NIAMDD, NIH. All compounds gave mass spectra consistent with the proposed formulas. Elemental analyses, indicated by the symbols of the elements, were within ±0.4% of the calculated values.

***p*-Methoxybenzyl Bromide (6a).** This was prepared via a modification of the procedure of Kornblum.[9a] Thus, anisyl alcohol (48.0 g, 0.35 mol) in 75 mL of Et_2O was added slowly to 48% HBr (80 g) in 75 mL of Et_2O and stirred for 0.5 h. The reaction mixture was then quenched with $NaHCO_3$. The organic layer was combined with the ethereal extracts of the aqueous layer, washed with H_2O, and dried (Na_2SO_4). The Et_2O was evaporated in vacuo and the crude anisyl bromide distilled [bp 92–95 °C (0.02 mm); lit.[9b] 105–110 °C (8 mm)] to give 62.4 g (89%) of a colorless liquid. However, the crude anisyl bromide could be used directly since it was essentially pure.

***p*-Methoxybenzylmagnesium Bromide (6b).** This was prepared using the literature procedure for the preparation of *p*-alkoxy Grignard reagents.[10a] *p,p'*-Dimethoxybibenzyl was isolated as a side product in this reaction: mp 123-127 °C (lit.[10b] 128 °C).

1,4-Dimethyl-3-ethyl-2-(*p*-methoxybenzyl)-1,2,5,6-tetrahydropyridine (8a). (a) **From 7.** To 4 (116.1 g, 0.44 mol)[7] was added (stirring) NaOH (28.5 g, 0.71 mol) in H_2O (480 mL), MeOH (225 mL), and $NaBH_4$ (17.1 g, 0.45 mol). The temperature rose to ca. 60 °C during the first 0.5 h and was maintained at 55–65 °C for an additional 1.5 h. The mixture was diluted with cold H_2O (100 mL) and extracted with 3 × 200 mL of Et_2O. The combined extracts were washed once with H_2O (100 mL), dried (Na_2SO_4), and evaporated to give 60.3 g (98%) of crude 5. This material was treated (stirring) with 97.7 g (0.49 mol) of 6a in 175 mL of Me_2CO. After 2 h at room temperature and 12 h at −15 °C the hygroscopic material was washed with Et_2O (2 × 200 mL) to give 75.21 g (0.22 mol, 50%) of 7.

To a slurry of 7 (170 g, 0.53 mol) in dry Et_2O (300 mL) was added 1.86 M PhLi (1045 mL, 1.94 mol) in C_6H_6–Et_2O (70:30) as rapidly as possible with efficient stirring. The brisk refluxing subsided after a few minutes and stirring was continued for 2 h. After refluxing for 0.5 h, the mixture was poured onto ice–H_2O. The ethereal layer was shaken with 1 N HCl (5 × 100 mL), and the combined extracts were made alkaline with NH_4OH. The liberated, oily base was shaken into Et_2O, dried (Na_2SO_4), and evaporated to give 96.5 g of crude 8a. This base, in 200 mL of EtOH, was added to 60 g of picric acid in 600 mL of EtOH. Left at room temperature for 2 h and at 0 °C for 3 h, the solution deposited 137.0 g of 8a picrate, mp 134–136 °C (lit.[7] 139–140 °C). The hydrobromide salt of 8a was made by passing HBr gas into the oily base in Et_2O: mp 149–153 °C.

The 8a picrate was hydrolyzed with an excess of 3% LiOH solution and the mixture was extracted with ligroine, washed (H_2O), and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave 70 g (0.27 mol, 51%) of 8a as a brown oil.

(b) From 4 and 6b. To a vigorously stirred mixture of 4 (13.2 g, 0.05 mol) in Et_2O (200 mL) was added slowly an ethereal solution of **6b** prepared from 13 g (0.065 mol) of anisyl bromide and Mg (8.0 g, 0.33 g-atom) turnings/powder (1:1 ratio). The reaction mixture separated into two layers during a 5-h stirring period, after which it was poured into ice–H_2O. The Et_2O layer was acidified with dilute HCl (200 ml), alkalinized with concentrated NH_4OH, and extracted with Et_2O. Evaporation of the Et_2O gave crude **10** (8.3 g, 63%) as a dark oil. This was treated, as described for 4 above, with $NaBH_4$ (1.3 g, 35 mmol), NaOH (2.4 g, 60 mmol), H_2O (30 mL), and MeOH (15 mL). After the usual work-up, a brown oily base (6.1 g, 73%) was obtained. This base was identical with 8a prepared previously.

1,4-Dimethyl-3-ethyl-2-(*p*-hydroxybenzyl)-1,2,5,6-tetrahydropyridine (8b). To 5.52 g (21.3 mmol) of 8a was added (stirring) 48% HBr (50 mL) and the mixture vigorously refluxed for 20 min. The reaction mixture was cooled and make alkaline with NH_4OH, extracted with $CHCl_3$, and dried ($MgSO_4$). Evaporation of the $CHCl_3$ left a residue which crystallized from acetone to yield 4.96 g (95%) of **8b**: mp 108.5–112 °C; M^+ 245. Anal. ($C_{16}H_{23}NO$) C, H, N.

(±)-2,5-Dimethyl-9α-ethyl-2'-hydroxy-6,7-benzomorphan (2a).[7] (a) **From 8a.** Compound 8a, 35 g (0.135 mol), and 48% HBr (320 mL) were kept at 140–150 °C (bath temperature) for 24 h. The mixture was cooled, poured onto crushed ice, and made alkaline with NH_4OH. The resultant semisolid was dissolved in $CHCl_3$ (900 mL), washed with H_2O, and dried ($MgSO_4$). Evaporation of the solvent in vacuo left 32.0 g of tan crystalline material. Fractional crystallization (Me_2CO) gave 22.8 g of **2a** (69%) and 2.3 g of **9** (7%) based on 8a.

(b) From 8b. Compound **8b**, 26.5 g (0.11 mol), and 120 mL of 85% H_3PO_4 were kept at 185–190 °C (bath temperature) for 36 h. The cooled mixture was made alkaline with NH_4OH and extracted with $CHCl_3$ (4 × 125 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give a semisolid which was digested with Me_2CO (400 mL) and treated as above to give 10.25 g (41.8%) of **2a** and 2.1 g (8.4%) of **9**.

(±)-9α-Ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan (1).[8] Phenyl chloroformate (26.0 g, 166 mmol) was added to a slurry of **2a** (4.19 g, 17.1 mmol) in $CHCl_3$ (500 mL). After stirring for several minutes, the reaction mixture became homogeneous and $KHCO_3$ (34.0 g, 340 mmol) was added. The mixture was refluxed 48 h and cooled and H_2O (100 mL) added (stirring). When the inorganic material had dissolved, the $CHCl_3$ layer was separated and washed with 1 N HCl (50 mL) and H_2O (200 mL). The $CHCl_3$ was evaporated and to the residual, crude **2b** was added 64% hydrazine (50 mL) and 95% hydrazine (50 mL). The mixture was stirred (under N_2), refluxed (behind a safety shield) for 20 h, and cooled. The white solid was filtered and washed well with H_2O and then Et_2O (20 mL). The resulting white solid was dried in vacuo at 65 °C to yield 3.7 g (93.7%) of pure 1, mp 281–284 °C.

General Procedure for Compounds 11–20.[4b] In a typical experiment, a stirred mixture of 1 (2.0 g, 8.6 mmol), 8.6 mmol of the appropriate alkyl halide, 12.3 mmol of $NaHCO_3$, and 25 mL of DMF was refluxed for 4–5 h. The reaction mixture was filtered and the filter cake washed with EtOH. The solvent was removed in vacuo to leave a crude product which could be crystallized from $CHCl_3$–Et_2O, Me_2CO, or MeOH (Table I).

(±)-2-Cyclobutylmethyl-9α-ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan (22). To a stirred suspension of 1 (1.0 g, 4.33 mmol), 12 mL of Et_3N, and 40 mL of CH_2Cl_2 was added (cooling) 1.7 g (14.3 mmol) of cyclobutylcarbonyl chloride in 2.0 mL of CH_2Cl_2. The resulting clear solution was refluxed overnight, washed with 10% HCl and then H_2O, dried (Na_2SO_4), and evaporated to dryness. The viscous, semisolid residue (1.6 g of *N,O*-dicarbonyl compound) was reduced with 0.7 g of $LiAlH_4$ in refluxing THF for 20 h to give an oily base (after the usual work-up). Crystallization from MeOH gave 1.0 g (84%) of **22**.

(±)-2-Cyclopropylmethyl-9α-ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan (21). This was prepared as described above for **22**.

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