5-Allyl-9-oxobenzomorphans. 3. Potent Narcotic Antagonists and Analgesics–Antagonists in the Series of Substituted 2′,9β-Dihydroxy-6,7-benzomorphans

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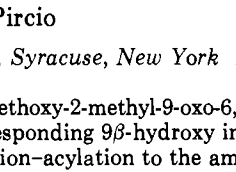
5-Allyl-2′-methoxy-2-methyl-9-oxo-6,7-benzomorphan methiodide (**1**) has been converted in a selective two-step process to the corresponding 9β-hydroxy intermediates **4** and **6**, which in turn were transformed via modified von Braun demethylation–acylation to the amides **11** and **21**, respectively. These were reduced and demethylated to give a series of 5-allyl-2′,9β-dihydroxy-2-substituted 6,7-benzomorphans **13** and **23**, some of which have been found to be highly potent narcotic antagonists and/or analgesics. The resolution of the most interesting compounds (**23a** and **23b**) and pharmacological properties of the optical isomers are also described. Reduction of the double bond in **13** and **23** to give **14** and **24**, with one exception, did not appreciably alter pharmacological profiles, while cyclization to the tetrahydrofuranobenzomorphans **25** substantially reduced the level of activities.

In paper 2 of this series[1] we have reported the synthesis of 5-allyl-2′-methoxy-2-methyl-9-oxo-6,7-benzomorphan methiodide (**1**) (Scheme I) and the corresponding dequaternized base **2** as versatile intermediates for studying structure–activity relationships in the 2′,9-dihydroxy-6,7-benzomorphan series.

In this paper we wish to report on the chemical transformations of **1** and **2** to substituted 5-allyl- (propyl-) 2′,9β-dihydroxy-6,7-benzomorphans **13**, **14**, **23**, and **24** (Schemes I and II), which are structurally related to 3,14-dihydroxymorphinans, butorphanol and oxilorphan.[2] Some of these compounds have been found to possess a high level of narcotic antagonist and/or analgesic activity, comparable in laboratory animal tests to butorphanol and oxilorphan.



butorphanol, R = CH$_2$-c-C$_4$H$_7$

oxilorphan, R = CH$_2$-c-C$_3$H$_5$

The level of activity was drastically reduced by cyclization of these compounds to the corresponding tetrahydrofuranobenzomorphans **25** (Scheme III).

Chemistry. Two selective transformations of **1** or **2** were necessary in order to carry out our synthetic designs. First was a selective reduction of the carbonyl function to give exclusively the 9β-hydroxy intermediate **4**, in which the double bond is preserved. This was accomplished directly by reduction of **2** with NaBH$_4$ or by reduction of **1** using the same reagent to give **3** followed by thermal dequaternization to give **4** in a comparable overall yield from **1** (~44%). Second was a selective addition of a suitable organometallic reagent to give the 9β-hydroxy intermediate as a major product. This was accomplished as anticipated by addition of CH$_3$MgI to give **5** and subsequent thermal dequaternization of **5** to give **6** in overall yield of 59%. The same product (**6**) was obtained exclusively upon treatment of **2** with CH$_3$Li, which is surprising in view of the previous results in this field.[3,4]

The stereochemical assignments of the products were made by analogy to earlier work[3-5] and by oxygen to nitrogen acyl migrations as will be shown later.

Attempted von Braun cyanogen bromide demethylation of **4** and **6** was unsuccessful, giving as major products water-soluble materials, presumably of the cyclic isourea structure similar to those recently reported in the literature.[6] This was simply circumvented by esterification of the hydroxyl function prior to demethylation. In addition, since most of our target compounds involve an amide intermediate such as **11** and **21** and since analogous amide compounds in the 14-hydroxycodeine series[7] have been successfully synthesized from the corresponding cyano esters by simultaneous hydrolysis of the cyano function and migration of the acyl group from oxygen to nitrogen atom, we decided to explore this one-step approach in our synthesis. The amino alcohols **4** and **6** were first esterified by treatment with appropriate acid chlorides or acetic anhydride and then demethylated with BrCN. Treatment of cyano esters **18d** and **18e** with boiling aqueous acetic acid yielded in one step corresponding amides **21a** and **21b** in good yields. Under similar reaction conditions, acyl groups failed to migrate in the case of **9a** and **9b**, the intermediate amino esters **10a** and **10b** being isolated as the sole reaction products. However, the migration was effected cleanly by heating of a xylene solution of the amino esters at reflux temperature to give **11a** and **11b**, respectively.

These transformations are not only useful as a method for conversion of an *N*-alkyl to an *N*-acyl substituent but also serve as an unambiguous method for determination of relative stereochemistry of oxygen and nitrogen atoms when both are part of a rigid system such as 9-hydroxylbenzomorphan.

For obvious reasons esters of 9α-hydroxybenzomorphans could not give similar intramolecular acyl migrations.

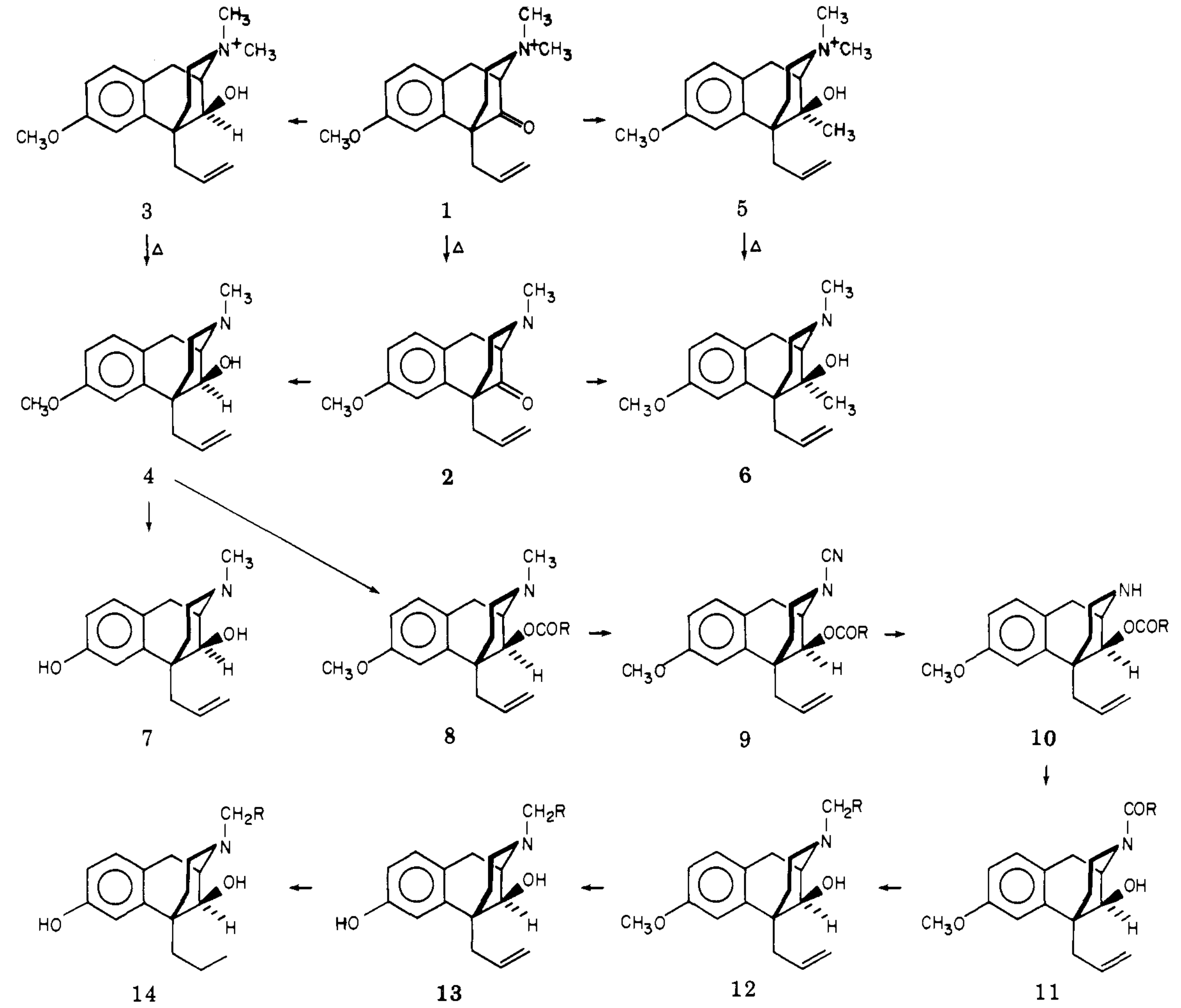
Reduction (LiAlH$_4$) of **11** and **21** followed by demethylation (BBr$_3$ or thioethoxide ion in boiling DMF)[8,9] yielded dihydroxybenzomorphans **13** and **23**, respectively. Alternatively, the nor base **20** obtained by LiAlH$_4$ reduction of cyano ester **19** was utilized to prepare *N*-furfuroyl and *N*-propargyl derivatives **21c** and **22d**, respectively, which were similarly converted to **23**.

Hydrogenation of **13** and **23** gave **14** and **25**, respectively, while treatment of the same with concentrated hydrochloric acid gave tetrahydrofuranobenzomorphans **25c–e**.[5] Treatment of **4** and **6** with boiling 48% hydrobromic acid effected both cyclization and demethylation in one step to give respectively **25a** and **25b**.

The dihydroxybenzomorphans **23a** and **23b** were resolved by treatment with *d*- and *l*-tartaric acids and fractional crystallization of the tartarate salts from methanol.

Pharmacological Results and Discussion. The final

Scheme I



a, R = -c-C_3H_5 ; b, R = -c-C_4H_7

products (Table I) were assayed for analgesic and narcotic antagonist activities according to the methods given in the Experimental Section. Preliminary screening indicated that the most active compounds in the series of 2′,9β-dihydroxybenzomorphans are those bearing a cyclopropylmethyl or cyclobutylmethyl substituent on the nitrogen atom (**13**, **14**, **23**, **24**). In addition, tests with optical isomers of **23a** and **23b** revealed that all the activity resided with (−) isomers, while (+) isomers were inactive. It is interesting to note that the level of activities and distribution of agonist vs. antagonist activity in all compounds going from the 5-allyl to 5-propyl substituent did not change appreciably, except in the case of (−)-**23b** and (−)-**24b**. Here, with the saturation of the double bond, both agonist and antagonist activities appear to be decreased up to three times, although in another test the antagonist activity was found to be the same in both compounds. (See Table II.)

Substitution of 9α-H with 9α-methyl decreases appreciably (up to 500 times) the analgesic activity as exemplified by the difference in activities of **13a** and **23a**. Similarly, in both series (**13** and **23**) formation of the methyltetrahydrofurano ring drastically decreases the analgesic activity (up to 400 times) and to a lesser extent antagonist activities (up to 80 times). The earlier reported[5] compounds **26** also exhibited a low level of analgesic activity in the mouse hot-plate test.

The most interesting compounds in the series, **23a,b** and **24a,b** were further investigated and the comparative data with butorphanol, oxilorphan, and naloxone are given in Table II. The results indicate that (−)-**23b** is comparable as an analgesic agent to butorphanol and in all three tests, it appears to be more potent as an antagonist than butorphanol. Similarly, (−)-**24a** appears to be more potent than oxilorphan in every test as an antagonist and less potent as an analgesic. In fact, its marginal analgesic activity and high antagonist activity render a pharmacological profile approaching that of naloxone, the only pure narcotic antagonist.

Experimental Section

Melting points are uncorrected; microanalyses were provided by micro-Tech Laboratories, Skokie, Ill.; results are indicated by symbols of the element and are within 0.4% of theory. The NMR and IR spectra are consistent with assigned structures.

Methods of Biological Evaluation. The method used for evaluation of analgesic activity was essentially that described by Siegmund et al.[10] Compounds were administered subcutaneously (15 min) before the intraperitoneal injection of phenylquinone (2 mg/kg). Beginning 5 min after the phenylquinone injection, the animals were observed for writhing and the number of writhes was counted over a period of 10 min. The dose which produced a 50% reduction in the number of writhes, as compared to the control group, was called the ED_{50}.

The antagonist assays were as follows. Mice were injected with oxymorphone (2 mg/kg sc), and the potential antagonist was administered subcutaneously 10 min after oxymorphone. The antagonist ED_{50} was defined as the dose which antagonized the Straub tail response (elevation greater than 45 °C) in 50% of the mice.

The ability to reverse oxymorphone narcosis in the rat was used as a measure of narcotic antagonist activity.[11]

Table I. Pharmacological Data of the 5-Allyl- (propyl-) 2′,9β-dihydroxy-(9α-methyl)-6,7-benzomorphans (7, 3, 14, 16, 17, 23, 24) and Corresponding Tetrahydrofurano Analogues 25 and 26

	ED$_{50}$, mg/kg (95% confidence limits unless specified otherwise)	
Compd[a]	Analgesic act. (mouse writhing)	Antagonist act. (oxymorphone-induced Straub tail)
7[b]	~1.9[c] (2.5/78, 1.25/14)[d]	>40
13a[b]	0.08	0.50
13b[b]	0.3	1.80
14a[c]	0.07	0.62
14b[b]	0.24	2.5
16[b]	2.1	>40
17[f]	2.0	>40
23a[b]	45	0.12
(−)-23a[g]	44	0.08
(+)-23a[h]	>40	>40
23b[e]	0.23	0.72
(−)-23b[h]	0.06	0.43
(+)-23b[g]	>40	>40
23c[f]	~36[c] (40/66, 20/0)[d]	1.3
23d[b]	>40	1.41
(−)-24a[b]	44	0.074
(−)-24b[e]	0.18	1.17
25a[b]	~19[c] (20/63, 10/0)[d]	>40
25b[b]	~18[c] (20/65, 10/5)[d]	>40
25c[b]	~30[c] (40/67, 20/23)[d]	8.0
25d[b]	>40	0.63
25e[b]	~40[c] (40/50, 20/33)[d]	~3.0[c] (5/100, 2.5/33)[d]
26a[b,j]	~30[c] (32/56, 16/44)[k]	>40
26b[e,j]	~16[c] (32/113, 16/50)[k]	>40
26c[i,j]	~64[c] (64/67, 32/46)[k]	>40
26d[e,j]	>40	>40
Butorphanol	0.05	0.98
Oxilorphan	13	0.19

[a] Tested subcutaneously as 0.4% solutions in saline starting with 40 mg/kg; free bases were dissolved in 0.1 N HCl and the concentration was adjusted to 0.4% with saline. [b] Free base. [c] Approximate value obtained graphically from the dose-response determinations given in parentheses. [d] Dose/percent response. [e] HCl salt. [f] Oxalate salt. [g] (+)-Tartarate. [h] (−)-Tartarate. [i] HBr salt. [j] Oral administration; mouse hot-plate test. [k] Maximal percent increase in response time over predose-response time.

Table II. Analgesic and Narcotic Antagonist Activities of Dihydroxybenzomorphans 23 and 24 Compared with Butorphanol, Oxilorphan, and Naloxone

	ED$_{50}$, mg/kg[a] (95% confidence limits)				
	Analgesic act.		Antagonist act.		
Test compd	Phenylquinone writhing in mice	Phenylquinone writhing in rats	Oxymorphone induced Straub tail	Oxymorphone induced narcosis	Antagonism of morphine analgesia (rat tail flick)
23a	45	ND	0.12 (0.09-0.16)	0.02	0.018 (0.009-0.035)
(−)-23a	44	8 (5.2-10.9)	0.08	0.005	0.006 (0.002-0.023)
23b	0.23 (0.16-0.35)	ND[b]	0.72 (0.52-1.0)	ND[b]	0.42 (0.23-0.75)
(−)-23b	0.06 (0.030-0.091)	0.01 (0.004-0.0151)	0.43 (0.28-0.62)	0.05 (0.02-0.09)	0.08 (0.04-0.11)
(−)-24a	44 (23-120)	30 (21-145)	0.074 (0.061-0.088)	0.013 (0.008-0.020)	0.008 (0.006-0.012)
(−)-24b	0.18 (0.14-0.23)	ND[b]	1.17 (0.08-1.71)	ND[b]	0.084 (0.04-0.131)
Butorphanol	0.051 (0.039-0.066)	0.04 (0.023-0.070)	0.98 (0.73-1.30)	0.27 (0.19-0.39)	0.43 (0.27-0.68)
Oxilorphan	12.8 (5.1-32.5)	8.0 (5.1-12.7)	0.19 (0.13-0.27)	0.03 (0.02-0.04)	0.012 (0.007-0.020)
Naloxone hydrochloride	>80	>80	0.09 (0.02-0.17)	0.02 (0.01-0.03)	0.01 (0.006-0.16)

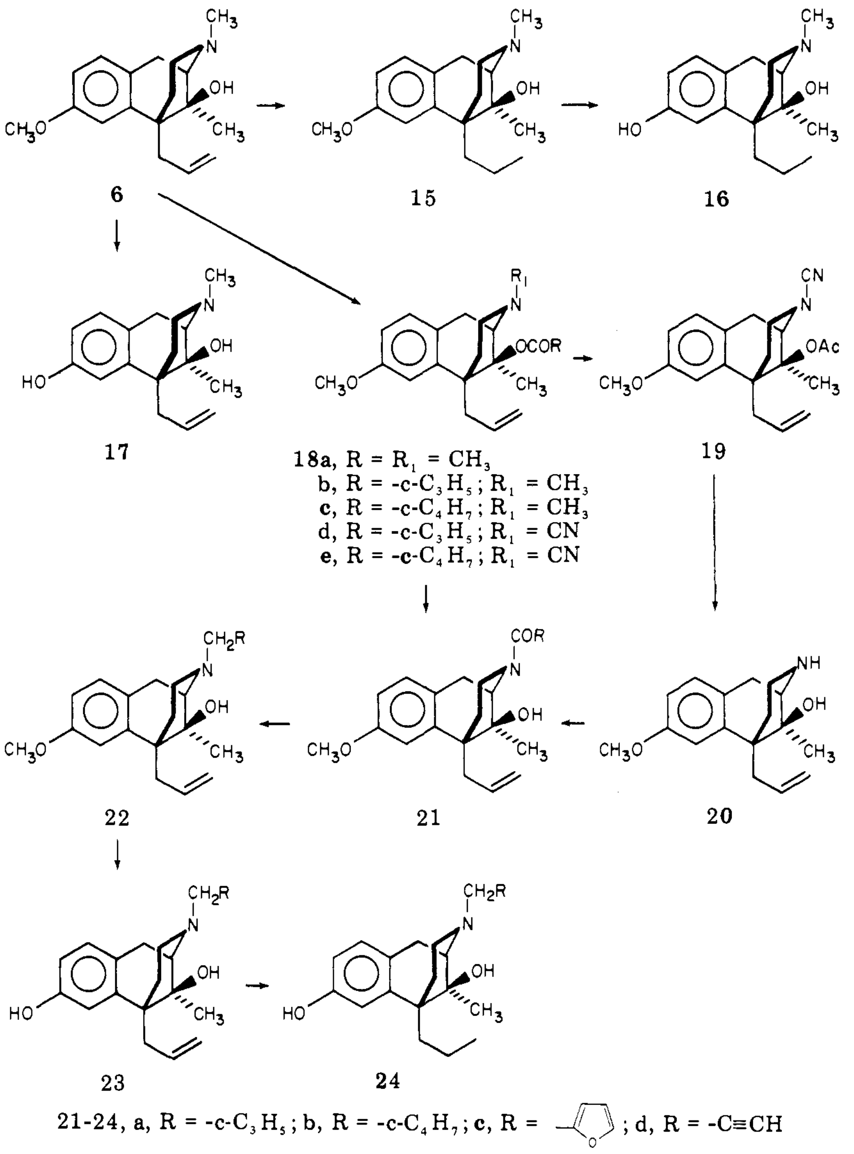
[a] Subcutaneous administration. [b] Not determined.

The antagonist ED$_{50}$ was defined as the dose which reversed the loss of righting reflex in 50% of the rats.

The percent antagonism and the ED$_{50}$ of morphine-induced analgesia were calculated as described by Harris and Pierson.[12] The compounds 26 were tested according to the Eddy's hot-plate technique in mice.[13]

5-Allyl-9β-hydroxy-2′-methoxy-2-methyl-6,7-benzomorphan Methobromide (3). To a stirred suspension of 1[1] (5.9 g, 16.1 mmol) in absolute EtOH (50 mL) was added $NaBH_4$ (0.35 g, 9.0 mmol) and stirring continued for 1 h. The mixture was carefully treated with dilute HBr (0.80 g of 48% in 10 mL of H_2O) followed by concentration in vacuo. The residual oil was extracted with CH_2Cl_2. The extract was filtered, dried, and evaporated to dryness. The residue was crystallized from *i*-PrOH–H_2O to give 4.2 g (72.3%) of 3: mp 193 °C. Anal. ($C_{17}H_{23}NO_2 \cdot CH_3Br$) C, H, N.

Scheme II



5-Allyl-9β-hydroxy-2′-methoxy-2-methyl-6,7-benzomorphan (4). To boiling 1-octanol (50 mL) was added methiodide 3 (4.87 g, 13.7 mmol) and the mixture heated at reflux for 15 min. After cooling, it was partitioned between Et_2O and diluted HCl. The organic phase was washed several times with H_2O and the washings were combined with the acidic phase and washed with petroleum ether. The acidic phase was made alkaline with NH_4OH and extracted with Et_2O. The extract was dried and evaporated in vacuo. The residual oil crystallized from cyclohexane to give 2.2 g (61%) of 4: mp 93–94 °C. Anal. ($C_{17}H_{23}NO$) C, H, N.

Alternatively, 4 was prepared in 88% yield by treatment of 2 with $NaBH_4$ in boiling EtOH for 1 h, followed by the usual work-up.[5]

5-Allyl-2,9α-dimethyl-9β-hydroxy-2′-methoxy-6,7-benzomorphan Methiodide (5). A mixture of 7 (5.0 g, 13.6 mmol) and Grignard reagent prepared from MeI (11.38 g, 79 mmol) and Mg (2.07 g) in Et_2O (50 mL) was stirred until all the solid was dissolved (ca. 2 h). The mixture was cooled (ice–H_2O) and treated with H_2O (5 mL), 5 N HCl (15 mL), and KI (5 g in 10 mL of H_2O), followed by stirring for 2 h. The resulting precipitate was collected by filtration to give 4.3 g (78%) of 5: mp 184–185 °C. Anal. ($C_{18}H_{25}NO_2 \cdot 0.5H_2O$) C, H, N.

5-Allyl-2,9α-dimethyl-9β-hydroxy-2′-methoxy-6,7-benzomorphan (6) was prepared in 75.5% yield from 5 by the procedure given for the preparation of 4: free base, mp 57 °C; oxalate, mp 180 °C (MeOH–Et_2O). Anal. ($C_{18}H_{25}NO_2 \cdot C_2H_2O_4 \cdot 0.5MeOH$) C, H, N.

Alternatively, 6 was prepared in 92% yield by treatment of a solution of 2 in Et_2O with 3 equiv of MeLi in Et_2O at −10 °C for 2 h, followed by usual work-up.

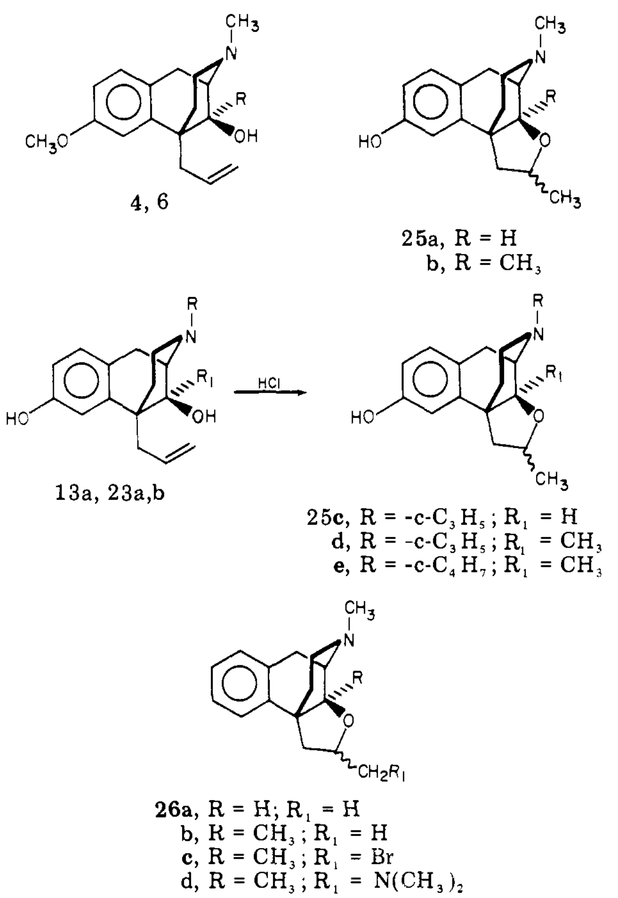
5-Allyl-2′,9β-dihydroxy-2-methyl-6,7-benzomorphan (7) (Method A). To a stirred cooled (ice) solution of BBr_3 (0.93 g, 3.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of 4 (1.0 g, 3.7 mmol) in CH_2Cl_2 (20 mL), and the mixture was allowed to stand at room temperature for 16 h. Then it was partitioned between ice–aqueous NH_4OH and $CHCl_3$. The organic phase was dried and concentrated and the residue crystallized from toluene–petroleum ether to give 0.46 g (48%) of 7: mp 60–64 °C. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

5-Allyl-9β-cyclopropylcarbonyloxy-2′-methoxy-2-methyl-6,7-benzomorphan (8a) (Method B). To a solution of 4 (26.5 g, 97 mmol) and triethylamine (20 mL) in CH_2Cl_2 (200 mL) was added a solution of cyclopropane carboxylic acid chloride (12.5 g, 120 mmol). The mixture was heated at reflux for 16 h, cooled, washed with dilute NH_4OH, dried, and concentrated in vacuo. The residual oil was dissolved in Et_2O, filtered, and concentrated to small volume. Cooling and filtration afforded 24.0 g (72%) of 8a, mp 108–109 °C. Anal. ($C_{21}H_{27}NO_3$) C, H, N.

5-Allyl-9β-cyclobutylcarbonyloxy-2′-methoxy-2-methyl-6,7-benzomorphan (8b) was obtained by method B in 69% yield: mp 114–115 °C (Et_2O). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

5-Allyl-2-cyano-9β-cyclopropylcarbonyloxy-2′-methoxy-6,7-benzomorphan (9a) (Method C). To a solution of amino ester 8a (20.0 g, 58.7 mmol) in C_6H_6 (200 mL) was added BrCN

Scheme III



(9.5 g, 90 mmol). The mixture was heated at reflux for 2.5 h, cooled, washed with water, dried, and concentrated in vacuo. The residual oil crystallized from cyclohexane to give 19.5 g (94%) of **9a**: mp 112–114 °C (toluene–hexane). Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

5-Allyl-2-cyano-9β-cyclobutylcarbonyloxy-2′-methoxy-6,7-benzomorphan (9b) was obtained by method C in 81% yield from **8b**: mp 105–106 °C (*i*-PrOH). Anal. ($C_{22}H_{26}N_2O_3$) C, H, N.

5-Allyl-9β-cyclopropylcarbonyloxy-2′-methoxy-6,7-benzomorphan (10a). A mixture of cyanomide **9a** (18.6 g, 53 mmol), AcOH (225 mL), and H_2O (75 mL) was heated under reflux for 5.5 h, followed by evaporation in vacuo. The residual oil was dissolved in CH_2Cl_2, washed with dilute NH_4OH, dried, and treated with ethereal HCl. Concentration to small volume and addition of Et_2O caused crystallization to give 13.8 g (71.5%) of **10a** hydrochloride: mp 233–234 °C (MeCN). Anal. ($C_{20}H_{25}NO_3$·HCl) C, H, N.

5-Allyl-9β-cyclobutylcarbonyloxy-2′-methoxy-6,7-benzomorphan (10b) was obtained similarly in 75% yield, purified as the oxalate: mp 176–178 °C (MeOH–Et_2O). Anal. ($C_{21}H_{27}NO_3$·$C_2H_2O_4$) C, H, N.

5-Allyl-2-cyclopropylcarbonyl-9β-hydroxy-2′-methoxy-6,7-benzomorphan (11a). A solution of amino ester **10a** (13.0 g) in xylene (350 mL) was heated at reflux for 18 h and then concentrated in vacuo. The residual oil was dissolved in MeOH and treated with dilute aqueous HCl to give crude product. Recrystallization from C_6H_6–Et_2O gave 10.2 g (78%) of **11a**: mp 142–144 °C. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

5-Allyl-2-cyclobutylcarbonyl-9β-hydroxy-2′-methoxy-6,7-benzomorphan (11b) was similarly prepared in 71% yield: mp 166–168 °C (C_6H_6–petroleum ether). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

5-Allyl-2-cyclopropylmethyl-9β-hydroxy-2′-methoxy-6,7-benzomorphan (12a) (Method D). A solution of amide **11a** (3.27 g, 10 mmol) in anhydrous THF (30 mL) was added dropwise to a boiling solution of $LiAlH_4$ (0.80 g) in THF (20 mL) under nitrogen, and the mixture was heated at reflux for 7.5 h. The excess hydride was carefully decomposed with 1 N NaOH (4 mL), the inorganic salts were removed by filtration, and the filtrate was concentrated in vacuo. The residual oil was dissolved in Et_2O and extracted with HCl. The extract was made alkaline and extracted with Et_2O. This was dried and filtered over Al_2O_3 (40 g) to give 2.2 g (70%) of pure **12a**: mp 60–61 °C. Anal. ($C_{20}H_{29}NO_2$) C, H, N.

5-Allyl-2-cyclobutylmethyl-9β-hydroxy-2′-methoxy-6,7-benzomorphan (12b) was prepared by method D in 88% yield from **11b** oil: bp (pot temperature) 125–130 °C (0.2 Torr). Anal. ($C_{21}H_{29}NO_2$) C, H, N.

5-Allyl-2-cyclopropylmethyl-2′,9β-dihydroxy-6,7-benzomorphan (13a) (Method E). A solution of EtSNa was prepared by addition of EtSH (2 mL, 26 mmol) to a suspension of NaH (1.14 g, 26 mmol of a 55% dispersion in mineral oil washed with C_6H_6) in anhydrous DMF (20 mL). To this was added a solution of **12a** (1.49 g, 4.8 mmol) in DMF (10 mL) and the mixture heated under reflux for 4 h. After cooling, it was poured onto a mixture of ice–H_2O and NH_4Cl, and a solid precipitate recrystallized from MeOH to give 1.16 g (81.3%) of **13a**: mp 155–157 °C. Anal. ($C_{19}H_{25}NO_2$) C, H, N. The hydrochloride crystallized from EtOH–Et_2O: mp 242–244 °C.

5-Allyl-2-cyclobutylmethyl-2′,9β-dihydroxy-6,7-benzomorphan (13b) was prepared by method E in theoretical yield from **12b** as an oil: bp 165–170 °C (0.02 Torr). Anal. ($C_{20}H_{27}NO_2$) C, H, N. The hydrochloride crystallized from Et_2O: mp 145–150 °C.

2-Cyclopropylmethyl-2′,9β-dihydroxy-5-propyl-6,7-benzomorphan (14a) (Method F). To a solution of **13a** (660 mg, 2.2 mmol) in absolute EtOH (50 mL) was added 10% Pd/C (250 mg) and the mixture was hydrogenated at 60 psi for 1 h to give 590 mg (89%) of **14a**: mp 152–154 °C (EtOH–Et_2O). Anal. ($C_{19}H_{27}NO_2$) C, H, N. The hydrochloride crystallized from MeOH–Et_2O: mp 247–249 °C.

2-Cyclobutylmethyl-2′,9β-dihydroxy-5-propyl-6,7-benzomorphan (14b) was prepared by method F in 88.8% yield from **13b**: mp 160–162 °C (Et_2O). Anal. ($C_{20}H_{20}NO_2$) C, H, N.

2,9α-Dimethyl-9β-hydroxy-2′-methoxy-5-propyl-6,7-benzomorphan (15) was prepared by method F in theoretical yield: mp 101–102 °C (petroleum ether) (lit.[14] mp 101–102 °C).

2′,9β-Dihydroxy-2,9α-dimethyl-5-propyl-6,7-benzomorphan (16). To a stirred, cooled (ice) solution of BBr_3 (1.30 g, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of **15** (0.50 g, 1.9 mmol) in CH_2Cl_2 (2 mL) and the mixture was allowed to stand at room temperature for 2 h. Then it was poured onto ice–NH_4OH and extracted with $CHCl_3$. Drying and evaporation of solvent followed by recrystallization of the residue from C_6H_6 gave 0.37 g (78%) of **16**: mp 165–166 °C. Anal. ($C_{17}H_{25}NO_2$) C, H, N.

5-Allyl-2′,9β-dihydroxy-2,9-dimethyl-6,7-benzomorphan (17) was prepared in 47.5% yield by method A. The product was purified as its oxalate by recrystallization from Me_2CO: mp 195 °C. Anal. ($C_{17}H_{23}NO_2$·$C_2H_2O_4$) C, H, N.

9β-Acetoxy-5-allyl-2,9α-dimethyl-2′-methoxy-6,7-benzomorphan (18a). A mixture of **6** (2.87 g, 10 mmol), acetic anhydride (10 mL, 0.1 mol), and pyridine (0.8 g, 10.2 mmol) was heated at reflux for 1 h and then concentrated in vacuo. The residue was partitioned between Et_2O and H_2O–NH_4OH, and organic layer was dried and evaporated to give theoretical amount of **18** as an oil. The oxalate was crystallized from MeOH–Me_2CO: mp 181–182 °C. Anal. ($C_{20}H_{27}NO_3$·$C_2H_2O_4$) C, H, N.

5-Allyl-9β-cyclopropylcarbonyloxy-2,9α-dimethyl-2′-methoxy-6,7-benzomorphan (18b) was prepared in 85% yield by method B: mp 93–94 °C (petroleum ether). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

5-Allyl-9β-cyclobutylcarbonyloxy-2,9α-dimethyl-2′-methoxy-6,7-benzomorphan (18c) was prepared by method B in 81.5% yield: mp 64–65 °C (MeOH–H_2O). Anal. ($C_{22}H_{31}NO_3$) C, H, N.

5-Allyl-2-cyano-9β-cyclopropylcarbonyloxy-2,9α-dimethyl-2′-methoxy-6,7-benzomorphan (18d) was prepared by method C in 77.5% yield: mp 89–90 °C (C_6H_6–petroleum ether). Anal. ($C_{22}H_{26}N_2O_3$) C, H, N.

5-Allyl-2-cyano-9β-cyclobutylcarbonyloxy-2,9α-dimethyl-2′-methoxy-6,7-benzomorphan (18e) was prepared by method C in 77% yield: mp 75–76 °C (Et_2O–petroleum ether). Anal. ($C_{23}H_{28}N_2O_3$) C, H, N.

5-Allyl-9β-acetoxy-2-cyano-2′-methoxy-9α-methyl-6,7-benzomorphan (19) was prepared by method C in 85% yield from 18: mp 124–125 °C (EtOH). Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

5-Allyl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (20) was prepared in 75% yield by method D: mp 80–82 °C (cyclohexane). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

5-Allyl-2-cyclopropylcarbonyl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (21a). To a solution of **20** (3.0 g, 11 mmol) and triethylamine (0.50 g) in CH_2Cl_2 (50 mL) was added slowly with cooling and stirring cyclopropanecarboxylic acid chloride (1.10 g, 10.7 mmol). The reaction mixture was washed with water, dried, and concentrated in vacuo. The residual oil crystallized from Et_2O to give 3.3 g (97%) of **21a**: mp 121–122 °C. Anal. ($C_{21}H_{27}NO_3$) C, H, N.

Alternatively **21a** was obtained from **18d** by the following procedure. A solution of **18d** (1.2 g, 3.3 mmol) in AcOH (6 mL) and H_2O (3 mL) was heated under reflux for 5 h. The mixture was cooled and partitioned between CH_2Cl_2–aqueous NH_4OH. The organic phase was dried and concentrated in vacuo. The residual oil crystallized from ether to give 0.85 g (71%) of **21a**.

5-Allyl-2-cyclobutylcarbonyl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (21b) was similarly prepared in 82% yield from **20** and in 74.5% from **18e**, respectively: mp 131–132 °C (Et_2O). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

5-Allyl-2-furfuroyl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (21c) was prepared similarly from **20** in 92% yield: mp 137–138 °C (Et_2O). Anal. ($C_{22}H_{25}NO_4$) C, H, N.

5-Allyl-2-cyclopropylmethyl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (22a) was prepared as an oil by method D from **21a** and purified as the hydrochloride by crystallization from Me_2CO–Et_2O (77% yield): mp 192–194 °C. Anal. ($C_{21}H_{29}NO_2{\cdot}HCl$) C, H, N.

5-Allyl-2-cyclobutylmethyl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (22b) was prepared by method D from **21b** in 82% yield: hydrochloride; mp 211–212 °C (MeOH–Et_2O). Anal. ($C_{22}H_{31}NO_2{\cdot}HCl{\cdot}0.5H_2O$) C, H, N.

5-Allyl-2-furfuryl-9β-hydroxy-2′-methoxy-9α-methyl-6,7-benzomorphan (22c) was prepared by method D in 80% yield: hydrochloride; mp 208–209 °C (MeOH–Et_2O). Anal. ($C_{22}H_{27}NO_3{\cdot}HCl$) C, H, N.

5-Allyl-9β-hydroxy-2′-methoxy-9α-methyl-2-propargyl-6,7-benzomorphan (22d). A mixture of **20** (0.50 g, 1.8 mmol), $NaHCO_3$ (0.30 g, 3.6 mmol), and propargyl bromide (0.225 g, 1.8 mmol) in anhydrous DMF (5 mL) was stirred for 18 h at room temperature, diluted with Et_2O, and filtered. The filtrate was extracted with diluted HCl; the extract was made basic with aqueous NH_4OH and extracted with Et_2O. Drying and evaporation of the solvent afforded 0.51 g (91%) of **22d**: mp 95–96 °C. The hydrochloride was recrystallized from MeOH–Et_2O: mp 210–212 °C. Anal. ($C_{20}H_{25}NO{\cdot}HCl$) C, H, N.

5-Allyl-2-cyclopropylmethyl-2′,9β-dihydroxy-9α-methyl-6,7-benzomorphan (23a) was obtained in 70.5% yield from **22a** by method E. The product was recrystallized from MeOH: mp 163–164 °C. Anal. ($C_{20}H_{27}NO_2$) C, H, N.

5-Allyl-2-cyclobutylmethyl-2′,9β-dihydroxy-9α-methyl-6,7-benzomorphan (23b) was prepared by method A in 49.5% yield from **22b**: mp 132–134 °C. The hydrochloride was recrystallized from MeOH–Me_2CO: mp 243–244 °C. Anal. ($C_{21}H_{29}NO_2{\cdot}HCl$) C, H, N.

5-Allyl-2′,9β-dihydroxy-2-furfuryl-9α-methyl-6,7-benzomorphan (23c) was prepared in 35% yield from **22c** by method E: an oil; oxalate; mp 96–100 °C (Me_2CO_2). Anal. ($C_{21}H_{25}NO_2{\cdot}C_2H_2O_4$) C, H, N.

5-Allyl-2′,9β-dihydroxy-9α-methyl-2-propargyl-6,7-benzomorphan (23d) was prepared by method A in 53% yield from **22d**: mp 159–161 °C (MeOH–H_2O). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

Resolution of 23a. To a hot solution of **23a** (80.8 g, 0.258 mol) in MeOH (700 mL) was added (+)-tartaric acid (37.5 g, 0.25 mol) and the mixture was swirled until a clear solution was obtained. This was seeded with (−)-**23a** (+)-tartarate and allowed to crystallize at room temperature for 10 days to give 59.6 g (68.5%) of (−)-**23a** (+)-acid tartarate: mp 213–214 °C; $[-\alpha]^{23}_{D}$ −59.6° (*c* 0.57, MeOH). An analytical sample was recrystallized from MeOH: mp 217–218 °C; $[\alpha]_D$ −63.9° (*c* 0.2, MeOH). Anal. ($C_{20}H_{27}NO_2{\cdot}C_4H_6O_4$) C, H, N.

The free base was obtained by treatment of a hot H_2O solution of (−)-**23a** (+)-acid tartarate with NH_4OH: mp 156–157 °C (MeOH); $[\alpha]_D$ −103.6° (*c* 0.42, MeOH). Anal. ($C_{21}H_{25}NO_2$) C, H, N.

From the combined filtrate and washings was isolated free base which was treated similarly with (−)-tartaric acid to give (+)-**23a** (−)-acid tartarate: mp 217–218 °C; $[\alpha]_D$ +63.5° (*c* 0.2, MeOH).

Resolution of 23b. A solution of (±)-**23b** (26.0 g, 80 mmol) and (−)-tartaric acid (12 g, 80 mmol) in MeOH (100 mL) was allowed to crystallize at room temperature for 5 days to give 6.7 g of (−)-**23b** (−)-acid tartarate: mp 191–193 °C; $[\alpha]^{23}_{D}$ −67.5° (*c* 0.25, MeOH). An analytical sample was obtained by recrystallization from MeOH: mp 195–196 °C; $[\alpha]_D$ −71.0° (*c* 0.65, MeOH). Anal. ($C_{21}H_{29}NO_2{\cdot}C_4H_6O_6$) C, H, N.

The free base obtained in the same manner as (−)-**23a** had mp 130–132 °C (MeOH) and $[\alpha]_D$ −84.8° (*c* 0.21, MeOH).

From the combined filtrate and washings was isolated free base which was treated similarly with (+)-tartaric acid to give (+)-**23b** (+)-acid tartarate: mp 193–195 °C; $[\alpha]^{23}_{D}$ +70.0° (*c* 0.40, MeOH).

L-2-Cyclopropylmethyl-2′,9β-dihydroxy-9α-methyl-5-propyl-6,7-benzomorphan [(−)-24a] was prepared by method F in 58% yield from (−)-**23a**. The reaction time was 4 h: mp 189–190 °C (MeOH–H_2O).

L-2-Cyclobutylmethyl-2′,9β-dihydroxy-9α-methyl-5-propyl-6,7-benzomorphan [(−)-24b] was prepared similarly in 85% yield by hydrogenation of (−)-**23b**. The product was purified as the hydrochloride by recrystallization from MeOH–Et_2O: mp 216–218 °C; $[\alpha]_D$ −91.4° (*c* 0.39, MeOH). Anal. ($C_{21}H_{31}NO_2{\cdot}HCl$) C, H, N.

Tetrahydrofuranobenzomorphan (25a). A solution of **4** (0.7 g, 2.5 mmol) in 48% HBr (10 mL) was heated under reflux under N_2 for 5 min, cooled, made alkaline with ice–NH_4OH, and filtered to give 430 mg (67%) of crude **25a**. This was recrystallized from toluene to give a sample: mp 120 °C dec. Anal. ($C_{16}H_{21}NO$) C, H, N.

Tetrahydrofuranobenzomorphan (25b) was prepared in 75% yield by treatment of **6** with HBr for 10 min, followed by work-up as above. The product was recrystallized from MeOH: mp 265 °C. Anal. ($C_{17}H_{23}NO_2$) C, H, N.

Tetrahydrofuranobenzomorphan (25c) (Method G). A solution of **13a** (500 mg, 1.6 mmol) in concentrated HCl (8 mL) was briefly heated at reflux, cooled, made alkaline with ice–NH_4OH, and filtered to give crude **25c**. This was chromatographed (silica, $CHCl_3$–15% MeOH) to give 220 mg (44%) of the product as an amorphous solid. This was distilled at 160–170 °C (0.02 Torr) to give an analytical sample: mp 90–95 °C. Anal. ($C_{19}H_{25}NO_2{\cdot}0.5H_2O$) C, H, N.

Tetrahydrofuranobenzomorphan (25d) was prepared by method G in 56% yield from **23b**. It was purified by recrystallization from Me_2CO–H_2O: mp 95–100 °C. Anal. ($C_{20}H_{27}NO_2$).

Tetrahydrofuranobenzomorphan (25e) was obtained by method G in 89% yield: mp 112–113 °C (Me_2CO). Anal. ($C_{21}H_{29}NO_2{\cdot}2H_2O$) C, H, N.

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Synthesis and Narcotic Agonist–Antagonist Evaluation of Some 2,6-Methano-3-benzazocine-11-propanols. Analogues of the Ring C Bridged Oripavine-7-methanols[1]

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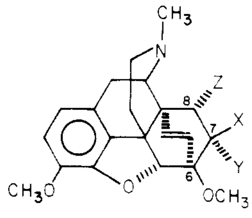
A general synthesis of variously substituted 2,6-methano-3-benzazocine-11-propanols is described. Nine *N*-CH_3 derivatives and their corresponding *N*-cyclopropylmethyl counterparts were prepared and studied in the mouse acetylcholine induced writhing and rat phenazocine antagonism tests. The results are compared with literature information on the bridged oripavine methanols. It is concluded that the synthetic analogues have a different structure–activity profile, in general being weak agonists but potent antagonists.

In 1967, Bentley and his colleagues postulated that a separation of some of morphine's pharmacological effects might be achieved by making molecules more rigid and complex than the morphine molecule, thereby rendering the new derivatives less acceptable at some receptor surfaces. To this end, thebaine was condensed with a variety of dienophiles[2-5] to produce ring C bridged adducts of general structure 1. These rigid molecules possessed functionalities at positions 7 and 8 which were manipulated to produce compounds of still further complexity. In addition, variations at other positions of 1 were made and their effects on biological activity studied. While the hoped for separation of effects may not have been fully realized, compounds of extremely high potency were found. Of particular interest has been the series of ring C bridged oripavines 2 bearing an asymmetric methanol functionality at position 7. The high potency of some of these derivatives, which could not be explained by differences in brain concentrations alone, led to the postulation of a specific receptor interaction. In addition to the anionic, planar, and cavity sites on the analgesic receptor model as proposed by Beckett and Casy,[6] a lipophilic fourth site was proposed to accommodate the group attached to position 7.[7] This proposal was strengthened by the fact that destruction of the aromatic ring of 1 [Z = X = H; Y = $C(CH_3)(C_3H_7)OH$] by ozonolysis did not result in complete loss of analgesic activity.[8] The extensive chemistry[9] and pharmacology[7,10] of the 1 series have been reviewed.

While a few synthetic analogues of the series 2 have been reported,[8,11,12] none are capable of interacting simultaneously with all four of the proposed sites on the analgesic receptor. Synthetic compounds which can so interact might be of value in more precisely defining the structural requirements for narcotic agonist and antagonist activities and may give rise to even better analgesic agents than are currently available. The 2,6-methano-3-benzazocine ring system, a part structure of morphine, can interact with the three original sites proposed by Beckett and Casy. Substitution of this ring system for the morphine skeleton of 2 and attachment of the methanol functionality of 2 to position 11 by a two-carbon chain gives 2,6-methano-3-benzazocine-11-propanols such as 3 which should be capable of a four-point receptor interaction. One of us recently reported[13] the stereospecific synthesis of 3 which was about 40% as potent as morphine in a conventional rodent test. We have now extended this synthesis to the preparation of a series of compounds 4 which possess a number of structural features found in 2 but not in 3, namely, (a) a phenolic hydroxyl group; (b) quaternary substitution of position 11 which corresponds to position 14 in 2; (c) an asymmetrically substituted alcohol bearing carbon atom; and (d) nitrogen substituent R^2 = cyclopropylmethyl (CPM) as well as methyl. All of the compounds prepared have been tested for narcotic agonist and antagonist properties.



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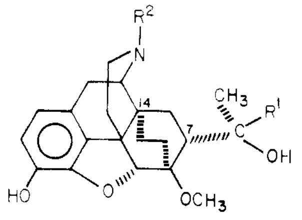

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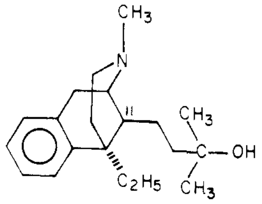

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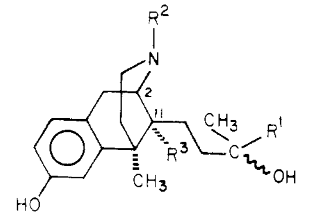

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Chemistry. 3,4-Dimethyl-1-(phenylmethyl)pyridinium chloride (**5a**, Scheme I) was allowed to react[14] with the Grignard reagent from 4-methoxyphenylmethyl chloride to produce an unstable mixture of dihydropyridines. This crude product was immediately treated with excess ethyl acrylate in refluxing benzene and the adduct **6a** was isolated. The stereochemistry of position 6 is of no consequence since it will be destroyed later in the synthesis.[15] The relative stereochemistry of positions 3 and 4 is exactly that of positions 2 and 11, respectively, in 4 which they are destined to become. The stereochemistry of position 3 follows from the fact that treatment of **6a** with anhydrous hydrogen fluoride results in cyclization to **7a** which, of course, cannot occur with the opposite stereo-