1,5-Methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine Hydrochloride (10).—The lactam **9** (0.98 g) was dissolved in warm THF (50 ml), cooled, and added dropwise to a large excess of B_2H_6 (0°, 55 ml of a THF solution, 1 *M* in BH_3).[13] The mixture was stirred (1 hr, 0°) and then refluxed overnight to give a clear, colorless solution. The solution was cooled (0°) and HCl (18%, 25 ml) was added dropwise, slowly, with stirring. This mixture was refluxed (0.5 hr) to cleave amine–borane complexes. Cooling and removal of solvent *in vacuo* gave a white solid to which H_2O (50 ml) and NaOH (pellets, 10 g) were added. The resultant cloudy mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and dried ($MgSO_4$), and solvent was removed *in vacuo* to give an oil (0.89 g) containing a small amount of solid. Distillation (140° bath temperature, 0.1 mm) gave the amine **10** as a colorless oil: λ_{max}^{film} 3310 and 3220 broad (m), 1620 (sh m), 1610 (s), 1590 (s) cm^{-1}; $\lambda_{max}^{CHCl_3}$ 3320 (w) cm^{-1}; δ 1.53–2.83 (6 H, m, C-3, 4, and 10), 2.45 (1 H, s, NH exchangeable with D_2O), 3.15 (1 H, m, C-5), 3.80 (3 H, s, OCH_3), 4.2 (1 H, m, C-1), 6.63–6.89 (2 H, m, aromatic *ortho* to OCH_3), 7.07–7.29 (1 H, m, aromatic *meta* to OCH_3); *m/e* 189 (M^+), 160 (base); glpc 0.92 min (170°), 3.34 min (170°).[11]

Salt **10** was prepared and recrystallized from Me_2CO–MeOH–Et_2O to give white crystals (0.59 g, 54% from **9**), mp 183.5–185° (sublim). *Anal.* ($C_{12}H_{16}ClNO$) C, H, N.

1,5-Methano-7-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine Hydrochloride (11).—The base **10** (0.43 g), formic acid (91%, 0.57 ml), and CH_2O (35–40% solution, 0.47 ml) were stirred (2 hr, 95°). The resultant clear solution was cooled, a 15% NaOH solution (15 ml) was added and the mixture was extracted with CH_2Cl_2. The organic solution was washed with H_2O and dried ($MgSO_4$). Removal of solvent *in vacuo* gave an oil (0.4 g), which was distilled (160° bath temperature, 0.1 mm) to give N-methylamine **11** base (0.39 g, 84%): λ_{max}^{film} 2790 (s), 2770 (m), 2720 (w), 2690 (w) (N-methyl), 1620 (s), 1613 (s), 1590 (s) cm^{-1}; glpc 1.16 min (175°), 3.6 min (172°).[11]

The hydrochloride salt **11** was prepared and recrystallized from Me_2CO–Et_2O (0.26 g, 47%); mp 179.5–181.5; *m/e* 203 (M^+ and base); δ (D_2O) 1.6–2.6 (5 H, m), 2.80 (3 H, s, N^+CH_3), 2.95–3.6 (2 H, m, C-3), 3.95 (3 H, s, OCH_3), 4.5–4.7 (1 H, m, C-1), 6.9–7.2 (2 H, m, aromatic *ortho* to OCH_3), 7.5–7.75 (1 H, m, aromatic *meta* to OCH_3). *Anal.* ($C_{13}H_{18}ClNO$) C, H, N.

(13) Metal Hydrides, Inc., Beverly, Mass.

3′-Methyl, 8-Methyl, and 8-Phenyl Derivatives of 5,9-Dimethyl-6,7-benzomorphans

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Aminoalkylation of the 5,9-dimethyl-6,7-benzomorphans **1a** and **1b** followed by hydrogenolysis yielded the 3′-methyl analogs **3** and **4**. N-demethylation of **3** gave the secondary amine **5**, from which a number of N-substituted derivatives were prepared. Oxidation of 2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan (**11**) gave the 8-keto compound **12** which, on treatment with phenyllithium and methyllithium, gave the corresponding tertiary carbinols **13** and **14**. Hydrogenolysis of **13** afforded the 8-phenyl analog **15** while dehydration of **14** followed by reduction gave the 8-methyl derivative **17**.

Several potent analgetics have evolved from studies of the 6,7-benzomorphan skeleton[1] and among the more interesting substances are the 2′-hydroxy-5,9-dimethyl-6,7-benzomorphans carrying a variety of substituents at the 2 position (N). Compounds substituted either at the 3′ position of the aromatic ring or at the benzylic 8 position have been largely ignored. Consequently, in line with our continuing interest in compounds which affect the central nervous system, we decided to determine what effect substituents at these positions would have on the analgetic activity of 5,9-dimethyl-6,7-benzomorphans.

The synthesis of 3′-methylbenzomorphan derivatives (Chart I) was accomplished by use of a procedure which had previously been applied in the morphinan series.[2] Thus the benzomorphan **1a** whose structure and configuration is well secured[3,4] was aminomethylated and the resulting product **2a** was hydrogenolyzed to the 3′-methylbenzomorphan **3**. The corresponding N-propyl derivative **4** was prepared in identical fashion. Acetylation of **3** followed by von Braun degradation gave the secondary amine **5** which could be alkylated directly, or indirectly *via* reduction of the appropriate amides with LAH, to give the benzomorphans **6**–**10** (see Table I).

The synthesis of 8-phenyl- and 8-methylbenzomorphan derivatives (Chart II) first required functionalization of the 8 position (Table I). This was accomplished by utilizing an oxidation procedure which had previously been employed in the morphinan series[5] for the introduction of a carbonyl function at this site. Thus, treatment of the benzomorphan **11** with CrO_3 gave a 64% yield of the ketone **12**, the structure of which is fully compatible with spectral data. In particular, the uv and ir spectra show the presence of an aromatic ketone.

Subsequent transformations of **12** are also outlined in Chart II. Reaction with PhLi gave the 8-phenyl-8-hydroxy compound **13** which was isolated in 30% yield. Hydrogenolysis of **13** with Raney Ni provided the desired 8-phenyl derivative **15**. By another reaction sequence, **12**, upon treatment with MeLi, afforded the 8-methyl-8-hydroxy **14** which was isolated in 70% yield. Dehydration of **14**, which occurred upon mild acid treatment, gave the olefin **16**. The structure of this compound, in particular the presence of an exocyclic CH_2, is clearly established by uv and nmr data.

(1) N. B. Eddy and E. L. May, "Synthetic Analgesics. Part IIB. 6,7-Benzomorphans," Permagon Press, London, 1966, p 113.

(2) (a) O. Schnider, German Patent 1,188,606 (1965); (b) J. Hellerbach, O. Schnider, H. Besendorf, and B. Pellmont, "Synthetic Analgesics. Part IIA. Morphinans," Permagon Press, London, 1966, p 39.

(3) In this compound and the derivatives described here, the methyl groups at the 5 and 9 positions are *cis* with respect to the tetralin moiety as indicated in Charts I and II. Accordingly, the compounds belong to the so-called α series and are all racemic.

(4) (a) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959); (b) A. F. Casy and A. P. Parulkar, *J. Med. Chem.*, **12**, 178 (1969); (c) J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960); (d) S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(5) O. Häfliger, A. Brossi, L. H. Chopard-dit-Jean, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **39**, 2053 (1956).

Catalytic reduction of **16** in the presence of Pd–C gave the 8-methylbenzomorphan **17**. Demethylation of the ethers **15** and **16** was readily accomplished with HBr to give the corresponding phenols **18** and **19**, respectively. The latter was reduced to the 2'-hydroxy-8-methylbenzomorphan **20** which was also obtained by direct hydrolysis of the methyl ether **17**. The configurational assignments at position 8 indicated on Chart II are based on analyses of the nmr spectra.

Table II summarizes the results of various tests for analgetic, antiinflammatory, and morphine-antagonist activity. While most of the compounds showed a degree of activity in some of the tests none approached the potency of morphine. Antimorphine activity in the order of nalorphine was exerted by five of the compounds. However, since high potency coupled with good antimorphine activity was not observed, none of the substances are of particular interest.

Experimental Section[6]

2'-Hydroxy-3',5,9-trimethyl-6,7-benzomorphan (5). **a. 3'-Diethylaminomethyl-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan Dihydrochloride** (**2a**·2HCl).—A mixture of 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (**1a**)[4b] (23.1 g, 0.10 mol), Et_2NH (10.8 g, 0.15 mol), paraformaldehyde (10 g, 0.33 mol), and PhMe (100 ml) was refluxed for 20 hr, cooled, extracted twice with H_2O (50 ml), dried (K_2CO_3), and evaporated to dryness yielding 30.9 g of residue, which was used directly in the next experiment. A crystalline dihydrochloride of **2a** was characterized.

b. 2'-Hydroxy-2,3',5,9-tetramethyl-6,7-benzomorphan (**3**) **and Hydrochloride** (**3**·HCl).—A solution of the crude base **2a** (30.9 g) in EtOH (200 ml) was hydrogenated for 10 hr with 10% Pd–C catalyst (2 g) at 135° and 31.64 kg/cm². After filtration and evaporation of the solvent *in vacuo*, a residue (21.7 g) was obtained, which was used directly for the preparation of **5**. The crystalline base **3** and its hydrochloride were characterized.

c. 2'-Hydroxy-3',5,9-trimethyl-6,7-benzomorphan (**5**).—A solution of crude **3** (21.3 g) in Ac_2O (50 ml) was heated on a steam bath for 3 hr, the solvent was removed *in vacuo*, and the residue was dissolved in EtOAc (300 ml). After washing with 5% Na_2CO_3 (200 ml), the organic layer was separated, dried (K_2CO_3), and evaporated *in vacuo*. A solution of this O-acetylated material (25 g) in $CHCl_3$ (150 ml) was added dropwise with stirring over 2 hr to a solution of CNBr (10.4 g) in $CHCl_3$ (100 ml) at room temperature. The solution was refluxed for 3 hr, cooled to room temperature, washed with 5% HCl (50 ml), dried (K_2CO_3), and evaporated *in vacuo*. To this residue (25 g) of crude N-cyano compound, 9% HCl (480 ml) was added, and the mixture was refluxed for 8 hr. After cooling and decantation from some tarry substance, the solution was made alkaline with concentrated NH_4OH and extracted three times with BuOH (100 ml). Removal of the BuOH at reduced pressure gave a residue, which gradually hardened on refluxing with cyclohexane (300 ml). The solid was filtered and crystallized from MeOH–*i*-PrOH to yield 12.7 g of **5**.

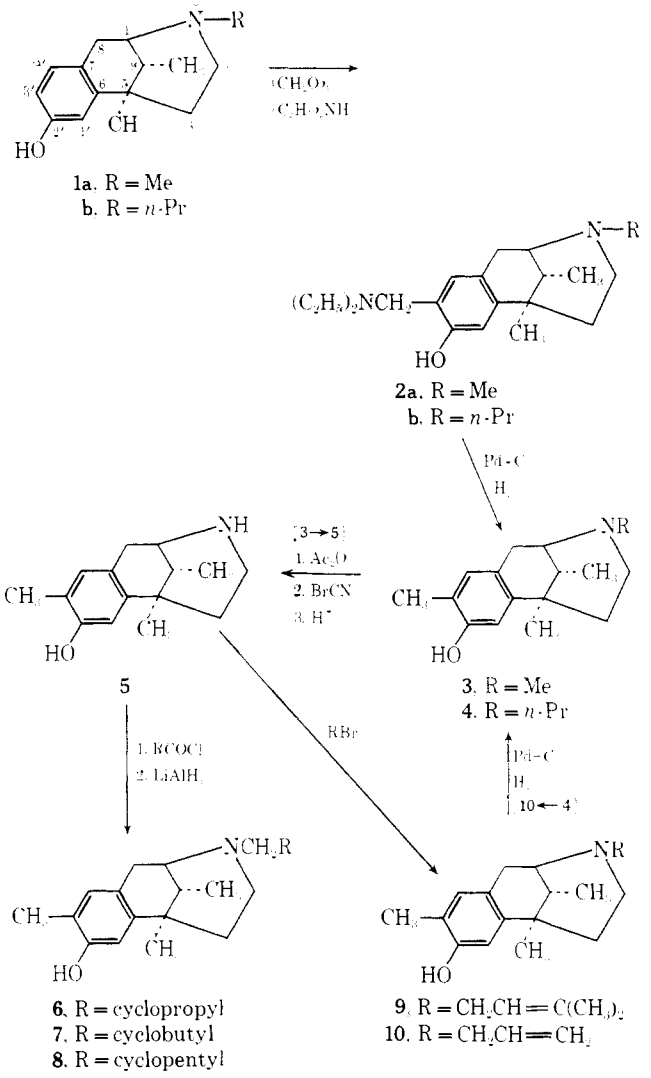
2'-Hydroxy-2-propyl-3',5,9-trimethyl-6,7-benzomorphan Hydrochloride (**4**·HCl). **a. 3'-Diethylaminomethyl-2'-hydroxy-2-propyl-5,9-dimethyl-6,7-benzomorphan** (**2b**).—A mixture of 2'-hydroxy-2-propyl-5,9-dimethyl-6,7-benzomorphan (**1b**)[4c] (1.5 g), Et_2NH (0.65 g), paraformaldehyde (0.6 g), and PhMe (100 ml) was refluxed for 20 hr. The solution was extracted twice with H_2O (50 ml), dried (K_2CO_3), and filtered and the solvent was evaporated *in vacuo* from a steam bath. The viscous crude residue **2b** weighed 1.6 g.

b. 2'-Hydroxy-2-propyl-3',5,9-trimethyl-6,7-benzomorphan Hydrochloride (**4**·HCl).—A mixture of 1.6 g of crude **2b** and 0.5 g of 10% Pd–C in 50 ml of EtOH was hydrogenated at 135° and 31.64 kg/cm² for 10 hr. The catalyst was removed by filtration and the solution was concentrated to a small volume *in vacuo*. The amine was converted to the hydrochloride by the addition of a saturated solution of HCl in EtOAc. The solvents were evaporated *in vacuo* and the residue, crystallized from MeOH–Me_2CO, yielded 0.8 g of **4**·HCl. This salt was also obtained by catalytic reduction of the N-allylbenzomorphan hydrochloride (**10**·HCl).

(6) All melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Ir spectra were measured on a Beckman IR-5 instrument. Uv spectra were recorded on a Cary recording spectrophotometer, Model 14.

CHART I

3',5,9-TRIMETHYL-6,7-BENZOMORPHANS



2-Cycloalkylmethyl-2'-hydroxy-3',5,9-trimethyl-6,7-benzomorphan Hydrochlorides (**6**·HCl, **7**·HCl, **8**·HCl). **a. 2-Cycloalkylcarbonyl-6,7-benzomorphans.**—A solution of the appropriate cycloalkylcarbonyl chloride (0.01 mol) in $CHCl_3$ (20 ml) was added dropwise with stirring at room temperature during 15 min to a mixture of **5** (0.01 mol), Et_3N (0.01 mol), and $CHCl_3$ (75 ml). Stirring was continued for 1 hr after which time a clear solution resulted. After removal of the $CHCl_3$ *in vacuo*, H_2O (50 ml) was added, and the mixture was extracted with *i*-BuOH (100 ml). The *i*-BuOH extract was washed [5% HCl (20 ml), dilute $NaHCO_3$] and dried (K_2CO_3). Removal of the *i*-BuOH *in vacuo* left the crude amide as a viscous residue. Only the 2-cyclopropylcarbonyl compound was characterized, mp 217–219°.[7]

The 2-cyclobutylcarbonyl and the 2-cyclopentylcarbonyl derivatives, prepared in an analogous manner, were used directly in crude form for the next step.

b. Reduction of the Amides with LAH.—A solution of the crude 2-cycloalkylcarbonyl compound, prepared as above from 0.01 *M* quantities of reactants, in THF (50 ml) was added dropwise with stirring during 15 min at room temperature to a solution of LAH (0.03 mol) in THF (75 ml). After the addition the solution was refluxed for 8 hr and cooled in an ice bath, and H_2O

(7) The analytical sample was recrystallized from MeCN. *Anal.* Calcd for $C_{15}H_{25}NO_2$: C, 76.25; H, 8.37. Found: C, 76.14; H, 7.95.

TABLE I

Compound	Mp, °C	Recrystn solvent[b]	Formula[c]	Analyses
		A. 3′-Substituted 6,7-Benzomorphans[a]		
2a·2HCl	258–260	MeOH–EtOAc	$C_{20}H_{32}N_2O\cdot 2HCl$	C, H, N
3	175–176	Heptane	$C_{16}H_{23}NO$	C, H
3·HCl	183–185	MeOH–MeCN	$C_{16}H_{23}NO\cdot HCl$	C, H
4·HCl	260–262	MeOH–Me_2CO	$C_{15}H_{27}NO\cdot HCl$	C, H
5	210–212	MeOH–*i*-PrOH	$C_{15}H_{21}NO$	C, H, N
6·HCl	273–275	MeOH–MeCN	$C_{19}H_{27}NO\cdot HCl$	C, H
7·HCl	300–301	MeOH–MeCN	$C_{20}H_{29}NO\cdot HCl$	C, H
8·HCl	>300	MeOH–EtOAc	$C_{21}H_{31}NO\cdot HCl$	C, H, N
9·HCl	248–250	MeOH–Me_2CO	$C_{20}H_{29}NO\cdot HCl$	C, H, N
10	148–150	C_6H_6–heptane	$C_{18}H_{25}NO$	C, H
10·HCl	235–236	MeOH–Me_2CO	$C_{18}H_{25}NO\cdot HCl$	C, H
		B. 8-Substituted 6,7-Benzomorphans[a]		
12	91–93	Petr ether–heptane	$C_{16}H_{21}NO_2$	C, H, N
12·HCl	203–205	EtOAc	$C_{16}H_{21}NO_2\cdot HCl$	C, H
13	159–160	MeOH	$C_{22}H_{27}NO_2$	
13·HCl	212–214	MeCN	$C_{22}H_{27}NO_2\cdot HCl$	C, H, N
14	60–62	Pentane	$C_{17}H_{25}NO_2$	C, H
15·HCl	284–285	MeCN	$C_{22}H_{27}NO\cdot HCl$	C, H
16·HCl	178–180	EtOAc	$C_{17}H_{23}NO\cdot HCl$	C, H, N
17·HCl	221–223	MeOH–EtOAc	$C_{17}H_{25}NO\cdot HCl$	C, H, N
18·HBr	288–289	MeOH–MeCN	$C_{21}H_{25}NO\cdot HBr$	C, H
19·HBr	239–241	MeOH–EtOAc	$C_{16}H_{21}NO\cdot HBr$	C, H
20	192–195	C_6H_6–cyclohexane	$C_{16}H_{23}NO$	C, H, N
20·HBr·XH_2O	173–175	MeOH–EtOAc	$C_{16}H_{23}NO\cdot HBr\cdot H_2O$	

[a] See ref 3. [b] In cases of solvent mixtures, the substance is much more soluble in the first solvent. [c] The hydrochlorides were generally prepared by adding a solution of HCl in EtOAc to a solution of the base in a suitable solvent.

(2 ml) was added dropwise with caution. After filtration and removal of the solvent *in vacuo*, the residue was dissolved in MeCN or *i*-PrOH and treated with a slight excess of a solution of HCl in EtOAc. The yields of the crystalline hydrochlorides ranged from 15 to 25%.

2′-Hydroxy-2-(3-methyl-2-butenyl)-3′,5,9-trimethyl-6,7-benzomorphan Hydrochloride (9·HCl).—A mixture of **5** (2.31 g), 1-bromo-3-methyl-2-butene (1.49 g), $NaHCO_3$ (1.2 g), and DMF (30 ml) was refluxed for 5 hr and the solvent was removed *in vacuo*. H_2O (35 ml) was added, and the insoluble oil was extracted with $CHCl_3$. After drying (K_2CO_3), the $CHCl_3$ was evaporated and the residue was digested with heptane. The heptane solution was decanted from an oily by-product and treated with HCl–EtOAc to give the crude hydrochloride. Crystallization from MeOH–Me_2CO yielded 2 g (60%) of **9**·HCl.

2-Allyl-2′-hydroxy-3′,5,9-trimethyl-6,7-benzomorphan (10) and Hydrochloride (10·HCl).—A mixture of **5** (2.31 g), allyl bromide (1.21 g), K_2CO_3 (0.7 g), and EtOH (50 ml) was refluxed for 24 hr and the solvent was removed *in vacuo*. Addition of H_2O, extraction with $CHCl_3$, drying (K_2CO_3), and removal of $CHCl_3$ *in vacuo* gave a residue which was digested with C_6H_6 and filtered. Crystals of the 2-allyl base were obtained on concentration of the C_6H_6 filtrate and addition of heptane; yield 1.4 g (52%). Both base and hydrochloride were prepared.

2′-Methoxy-8-oxo-2,5,9-trimethyl-6,7-benzomorphan (12) and Hydrochloride (12·HCl).—CrO_3 (4 g) was added in small portions with stirring at room temperature during 1 hr to a mixture of **11**[4a] (8 g) and dilute H_2SO_4 (40 g of concentrated H_2SO_4 was added to 500 ml of H_2O). An additional amount of concentrated H_2SO_4 (35 g) was added at room temperature during 6 hr, after which the mixture was allowed to stand overnight, made alkaline with concentrated NH_4OH with cooling, and extracted five times with $CHCl_3$ (300 ml). After drying (K_2CO_3), the solvent was removed *in vacuo* and the residue was crystallized first from petroleum ether (bp 30–60°) and then from heptane to yield 5.4 g (64%) of **12**: uv max (*i*-PrOH) 228 mμ (ε 12,100), 286 (16,120), and 367 (375); ir ($CHCl_3$) 1667 (s) and 1595 cm^{-1} (s). The hydrochloride was prepared in the usual manner.

2′-Methoxy-8-phenyl-8-hydroxy-2,5,9-trimethyl-6,7-benzomorphan Hydrochloride (13·HCl).—To a solution of **12** (2.6 g) in dry Et_2O (100 ml), a 2.14 *M* solution of PhLi (7 ml) in C_6H_6–Et_2O[8] was added with stirring at room temperature. The solution was refluxed for 2 hr and then decomposed, with cooling in an ice bath, by the dropwise addition of H_2O (10 ml). After separation of the Et_2O layer, drying (K_2CO_3), and removal of the Et_2O, the residue was crystallized from MeOH to yield 1.0 g (30%) of the base **13** which was characterized as the hydrochloride.

2′-Methoxy-8-phenyl-2,5,9-trimethyl-6,7-benzomorphan Hydrochloride (15·HCl).—A solution of **13** (1.6 g) in EtOH (50 ml) was hydrogenated with Raney Ni at an initial pressure of 14.06 kg/cm^2. The temperature was gradually increased to 119° over 4 hr, heating was discontinued, and the autoclave was allowed to cool overnight with shaking. After filtration of the catalyst and removal of the solvent, the residue was dissolved in EtOAc and treated with a solution of HCl in the same solvent to give **15**·HCl which weighed 0.9 g after purification

2′-Hydroxy-8-phenyl-2,5,9-trimethyl-6,7-benzomorphan Hydrobromide (18·HBr).—The hydrochloride of **15** (1.4 g) was added to 20 ml of 48% HBr and the solution was refluxed for 2 hr. It was then evaporated *in vacuo* from a steam bath and the solid residue was crystallized from MeOH–CH_3CN to yield 1 g of **18**·HBr.

8-Hydroxy-2′-methoxy-2,5,8,9-tetramethyl-6,7-benzomorphan (14).—To a solution of **12** (10.6 g) in dry Et_2O (100 ml), a 2.3 *M* solution of LiMe (40 ml) in Et_2O[8] was added dropwise with stirring at room temperature. The solution was refluxed for 7 hr, allowed to stand overnight at room temperature, and finally treated with H_2O (25 ml). The Et_2O layer was separated, dried (K_2CO_3), and evaporated *in vacuo*. The residue was dissolved in pentane (35 ml) and yielded, after overnight crystallization in the refrigerator, 7.9 g (70%) of **14**, ir ($CHCl_3$) 3600 cm^{-1} (weak, sharp).

2′-Methoxy-8-methylene-2,5,9-trimethyl-6,7-benzomorphan Hydrochloride (16·HCl).—Compound **14** (4 g) was dissolved in 30 ml of EtOAc and a saturated solution of HCl in EtOAc was added to precipitate **16** as the hydrochloride; yield 1.9 g; uv max (*i*-PrOH) 225 mμ (ε 12,960), 276 (16,150), 305 (4000), infl 295 (6700).

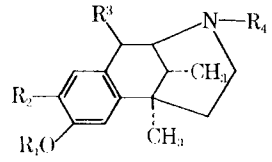
2′-Hydroxy-8-methylene-2,5,9-trimethyl-6,7-benzomorphan Hydrobromide (19·HBr).—To 0.5 g of **16**·HCl was added 10 ml of 48% HBr. The solution was refluxed for 1 hr and evaporated *in vacuo* from a steam bath, and the residue was crystallized from MeOH–EtOAc; yield 0.4 g.

2′-Methoxy-2,5,8,9-tetramethyl-6,7-benzomorphan Hydrochloride (17·HCl).—A mixture of the **16**·HCl (1.8 g), MeOH

(8) Obtaind from Alfa Inorganics, Inc., Beverly, Mass.

TABLE II

ANALGETIC, ANTIINFLAMMATORY, AND MORPHINE ANTAGONIST ACTIVITY OF

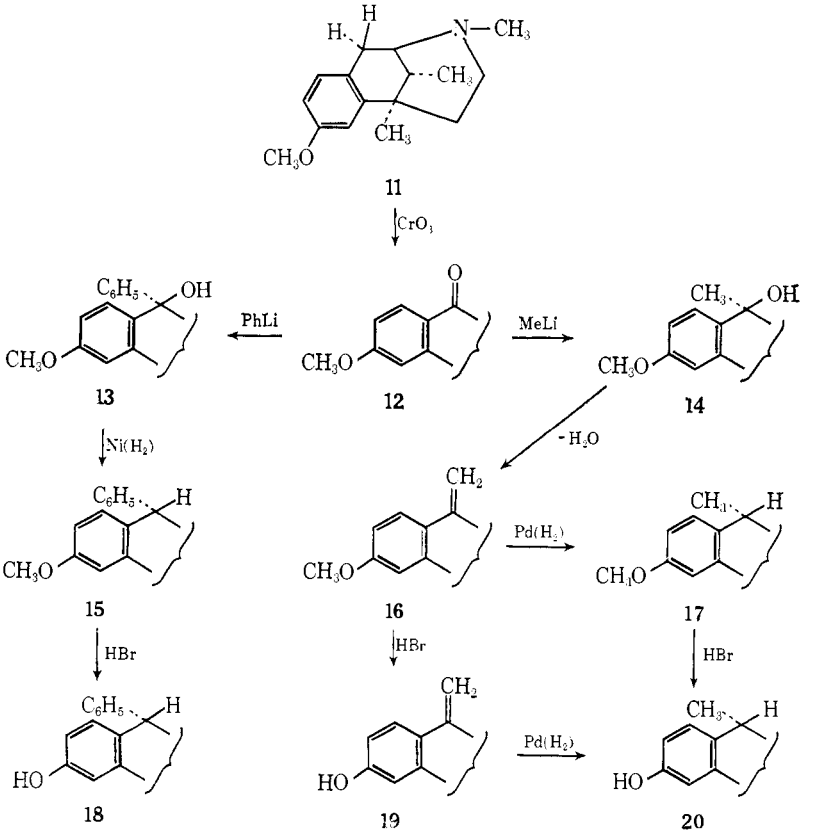


Compd	R_1	R_2	R_3	R_4	Analgetic[a] Hot plate[c]	Analgetic[a] Writhing[c]	Analgetic[a] Tail flick[c]	Analgetic[a] Infl foot[d]	Antiinflam[b] Antiedema[d]	Morphine antag[a] Tail flick[c]
6·HCl	H	Me	H		>50 *po*	17.5 *po*	24 *po*	*Ca.* 100 *po*	40 *po*	0.8 sc
7·HCl	H	Me	H		>200 *po*	>200 *po*	>100 *po*, >100 sc	*Ca.* 100 *po*	51.3 *po*	0.48 sc
8·HCl	H	Me	H		>200 *po*	*Ca.* 200 *po*	>100 sc	>100 *po*	>100 *po*	12.5 sc
3·HCl	H	Me	H	Me	*Ca.* 100 *po*	24.6 *po*	>100 *po*	*Ca.* 100 *po*	<100 *po*	7 sc
4·HCl	H	Me	H	Pr	100 *po*, toxic	78 *po*, 18 sc	37.5 sc	70 *po*	88 *po*	16 sc
10·HCl	H	Me	H	$CH_2CH{=}CH_2$	48 *po*	66.1 *po*	42.5 sc	80 *po*	39 *po*	0.26 sc
9·HCl	H	Me	H	$CH_2CH{=}CMe_2$	*Ca.* 100 *po*	24 *po*	47 sc	>100 *po*	>100 *po*	7.5 sc
12·HCl	Me	H	=O	Me	>100 *po*	>100 *po*		>100 *po*	>100 *po*	4.9 sc
13·HCl	Me	H	Ph, OH	Me	>100 *po*	40 *po*		>100 *po*		
15·HCl	Me	H	Ph, H	Me		49 *po*				1.1 sc
18·HBr	H	H	Ph, H	Me	>200 *po*	70 *po*, 43 sc		<100 *po*	>100 *po*	2.5 sc
16·HCl	Me	H	$=CH_2$	Me	>100 *po*	64 *po*		>50 *po*	>100 *po*	Inact.
19·HBr	H	H	$=CH_2$	Me	>100 *po*	12 *po*		>100 *po*	>100 *po*	Inact.
14	Me	H	Me, OH	Me	>100 *po*	*Ca.* 200 *po*		>100 *po*	>100 *po*	Inact.
20·HBr	H	H	Me, H	Me	>100 *po*	0.7 *po*		>100 *po*	>100 *po*	0.6 sc
17·HCl	Me	H	Me, H	Me		43.5 *po*, 4.3 sc			>100 *po*	6.25 sc
Morphine					3.8 *po*, 1.4 sc	3.7 *po*, 0.98 sc	21.4 *po*, 5 sc	25 *po*, 0.8 sc	100 *po*	
Pentazocine					*Ca.* 200 *po*	50.8 *po*, 1.3 sc	>80 *po*	>100 *po*	>100 *po*	20.4 sc
Nalorphine					>200 *po*	0.54 sc	>200 *po*	>200 *po*		0.52 sc
Codeine					50 *po*, 26 sc	22.8 *po*, 3.9 sc	66 *po*, 41 sc	40 *po*		

[a] ED_{50}, mg/kg. [b] ED_{30}, mg/kg. [c] Mouse. [d] Rat.

CHART II

8-PHENYL- AND 8-METHYL-5,9-DIMETHYL-6,7-BENZOMORPHANS



(150 ml), and 10% Pd-C catalyst (0.5 g) was hydrogenated during 2 hr at room temperature under an initial pressure of 3.5 kg/cm² until the theoretical amount of H_2 was absorbed. Filtration of the catalyst, removal of solvent, and crystallization of the residue from MeOH–EtOAc gave 1.4 g of **17**·HCl.

2'-Hydroxy-2,5,8,9-tetramethyl-6,7-benzomorphan (20) and Hydrobromide Hydrate (20·HBr·xH_2O).—Two grams of **19**·HBr was dissolved in 150 ml of MeOH containing 0.5 g of 10% Pd-C catalyst and the mixture was hydrogenated at room temperature at an initial pressure of 3.5 kg/cm² over a 2-hr period. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was crystallized from MeOH–EtOAc to yield 1.5 g of a hydrobromide, mp 173–175°, containing an indefinite amount of H_2O. The free base, obtained by the addition of 5% Na_2CO_3 solution to a solution of the hydrobromide in H_2O, was extracted with $CHCl_3$. The $CHCl_3$ solution was dried (K_2CO_3), the solvent was evaporated *in vacuo*, and the residue (**20**) was crystallized.

Demethylation of **17**·HCl (20 mg) by refluxing for 1 hr with 3 ml of 48% HBr and conversion to the base in the usual way yielded **20** identical by ir, tlc, and mmp with material prepared by hydrogenation of **19**·HBr.

Biological Procedures.—The substances described in this report were tested for analgetic, antiinflammatory, and morphine-antagonist activity. Analgetic activity was determined by the hot plate,[9] writhing,[10] tail flick,[11] and the yeast-inflamed foot[12] tests. The carrageenin antiedema[13] test was used as a measure of antiinflammatory activity. The tail flick test was used to measure morphine antagonism which was calculated according to the formula of Harris and Pierson.[14]

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