N-allyl and N-propyl derivatives, prepared by the procedure of Archer and co-workers.[13] The requisite physical date are shown in Table III.

(13) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, 7, 123 (1964).

Acknowledgments.—The authors wish to thank Mr. K. D. Fleischer for elemental analyses, Dr. R. K. Kullnig for spectral data, and Mrs. A. K. Pierson for pharmacological results.

Synthesis of 6,7-Benzomorphan and Related Nonquaternary Carbon Structures with Marked Analgetic Activity

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6,7-Benzomorphan (**9**) has been synthesized from pyridine or 4-phenylpyridine. This compound (**9**), without a quaternary carbon or tertiary nitrogen, is codeine-like in analgetic activity as determined in the mouse hot-plate method. 2-Methyl-6,7-benzomorphan (**8**) and its 2′-hydroxy analog (**15**) are as active as their 5-methyl (quaternary carbon containing) relatives.

Recently,[2] we presented a brief account of the synthesis of 2-methyl-6,7-benzomorphan (**8**) and 6,7-benzomorphan (**9**),[3] the simplest members of a family of strong analgetics[4] of which two (phenazocine[5] and pentazocine[6]) are in medical use. In the present report, details of this synthesis (from 4-phenylpyridine) and a more practicable one (from pyridine) are given. In addition, we have prepared 2′-hydroxy-2-methyl-6,7-benzomorphan (**15**) from either **8** or pyridine and have found that **8**, **9**, and **15** have surprisingly good analgetic activity.

Several methods[7] including the conventional 6,7-benzomorphan and morphinan syntheses[4] proved refractory for **8** before 4-phenylpyridine (**1**) was selected as the starting compound. Through the N-oxide,[8] **1** was converted to **8** by reaction Scheme I, compound **3**[9,10] serving as a key intermediate. Demethylation of **8** with either BrCN[11] or diethyl azodicarboxylate[12] gave **9**.

Yields in this series of reactions were 80–95% except in the cyclization (35%) and N-demethylation (20% with BrCN, 40% with diethyl azodicarboxylate) reactions. Methyl ester **5** could not be converted to **7** with PPA probably because the geometry of the (expected) most stable (2,4-diequatorial) conformation would be such as to defy cyclization.[13] The fact that the corresponding acid **6** gave **5** when treated with methanolic HCl indicates that the stereochemistry of **5** and **6** is identical.[14] Presumably, inversion of **6** (**10**) to the 2,4-diaxial compound (**11**), a favorable conformer for cyclization, takes place to some extent in the presence of hot PPA. At temperatures higher than the optimal 150°, the formation of decomposition products is evidently in competition with the inversion–cyclization process (**10** → **11** → **7**).

Following this success, the Grewe synthesis for 6,7-benzomorphans,[3] which had failed at the cyclization (of 2-benzyl-1-methyl-1,2,5,6-tetrahydropyridine, **12**) stage, was reinvestigated. Treatment of **12** (prepared from 1-methylpyridinium iodide *via* $NaBH_4$ reduction and Stevens rearrangement[4,5] of the benzyl chloride quaternary of the product) with PPA at 155° gave **8** (Scheme II).

Similarly, 2′-hydroxy-2-methyl-6,7-benzomorphan (**15**) was prepared using *p*-methoxybenzyl chloride in the quaternization reaction. Cyclization of **14** was effected with PPA at 205–210°. Compound **15** also resulted in small yield from **8** by the nitration, hydrogenation, and diazotization sequence and was converted to the methyl ether (**16a**) and to the O-acetyl compound (**16b**).

Pharmacology.—In Table I are given analgetic activities (mouse hot plate method)[15] and acute (24 hr) toxicities of **8**, **9**, **15**, **16a**, and **16b**. Comparative data for the 5-methyl homologs of **8**, **15**, and **16a** and for morphine and codeine are also presented. All compounds were administered subcutaneously in water as hydrochloride salts except morphine (sulfate).

It is evident that **8**, **15**, and **16b** are of the same order of potency as their 5-methyl (quaternary carbon)

(1) (a) Former Visiting Associate, now at the University of Nagoya, Japan. (b) Visiting Fellow from Tokyo, Japan.

(2) K. Kanematsu, R. T. Parfitt, A. E. Jacobson, J. H. Ager, and E. L. May, *J. Am. Chem. Soc.*, **90**, 1064 (1968).

(3) *Chemical Abstracts* name: 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine.

(4) E. L. May and L. J. Sargent in "Analgetics," G. deStevens, Ed., Academic Press, Inc., New York, N. Y., 1965; N. B. Eddy and E. L. May, "Synthetic Analgetics," Part IIB, Pergamon Press, Ltd., Oxford, 1966, p 115 ff.

(5) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294, 1435 (1959); J. G. Murphy, J. H. Ager, and E. L. May, *ibid.*, **25**, 1386 (1960); Prinadol®, Narphen®.

(6) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964); Talwin®.

(7) These included a sequence modeled after the isomorphinan synthesis of M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958); one from 2-chloroacetylamino-1,2,3,4-tetrahydronaphthalene (irradiation–cyclization method); and a method in which ethyl 3-nitro-1-naphthylacetate [D. C. Morrison, U. S. Patent 3,177,241 (1965); *Chem. Abstr.*, **62**, 16164 (1965)], prepared from 2,3-dinitronaphthalene, or the corresponding 3-acetamino compound served as intermediates. All attempts to hydrogenate these two compounds to the 1,2,3,4-tetrahydronaphthalene derivatives resulted in saturation of the unsubstituted ring. We are indebted to Dr. Julius Hyman of the Fundamental Research Co., Berkeley, Calif., for a generous supply of 2,3-dinitronaphthalene.

(8) E. Ochiai, *J. Org. Chem.*, **18**, 549 (1953).

(9) W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).

(10) F. H. Case and T. J. Kasper, *ibid.*, **78**, 5842 (1956).

(11) In the von Braun method, the intermediate N-cyano compound could be hydrolyzed only with difficulty. After prolonged treatment with boiling 6% HCl, a mixture of the N-cyano and N-carbamido compounds and desired **9** resulted.

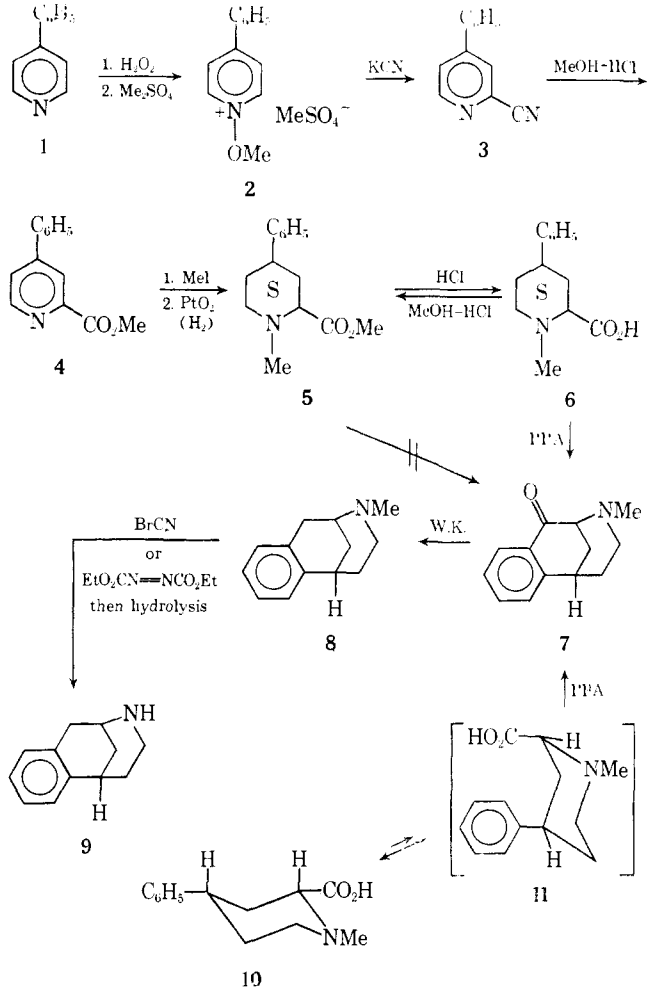
(12) A. Pohland and H. R. Sullivan, U. S. Patent 3,342,824 (Sept 19, 1967).

(13) See N. Sugimoto and S. Ohshiro, *Tetrahedron*, **8**, 296 (1960).

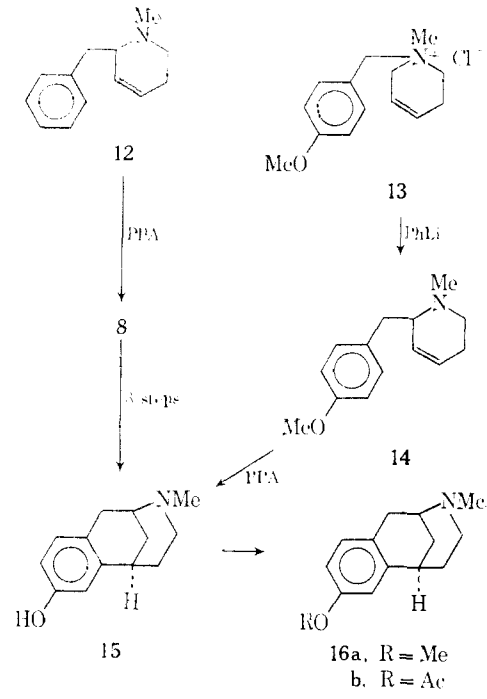
(14) It is possible that the chair form of the 2,4-diequatorial isomer is in equilibrium with the boat form at high temperatures. Molecular models indicate, however, that only the chair-diaxial form is favorable for cyclization. Evidently, there is not sufficient energy available to overcome the steric interaction of the bulky phenyl and ester groups in the chair 2,4-diaxial form of **5**.

(15) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

SCHEME I



SCHEME II



counterparts; it can be predicted with reasonable certainty[16] that the levo isomer of **15** will be half as potent as morphine. Particularly surprising is that the parent compound **9**, without a quaternary carbon or tertiary nitrogen, although rather toxic (some deaths and convulsions at 50 mg/kg), is as active as N-methyl compound **8** and of the order of codeine. The methyl ether of **15** (**16a**) appears to be less effective than 2′-methoxy-2,5-dimethyl-6,7-benzomorphan; because of its high toxicity an analgetic assay for **16a** was not feasible. Otherwise, the acute (24 hr) toxicities of the nor-5-methyl compounds did not differ appreciably from those of the 5-methyl homologs. Preliminary data indicate that 2′-hydroxy-2-methyl-6,7-benzomorphan (**15**) will not support morphine dependence in rhesus monkeys (personal communication from J. Villarreal, University of Michigan).

TABLE I

ANALGETIC ACTIVITY AND ACUTE TOXICITY OF 6,7-BENZOMORPHAN CONGENERS

Compd	ED_{50}, mg/kg	LD_{50}, mg/kg
6,7-Benzomorphan (**9**)	10.2	110
2-Methyl- (**8**)	11.2	150
2,5-Dimethyl-[a]	11.0	148
2′-Hydroxy-2-methyl- (**15**)	4.5	190
2′-Hydroxy-2,5-dimethyl-[a]	3.3	175
2′-Methoxy-2-methyl- (**16a**)[b]		
2′-Methoxy-2,5-dimethyl-[c]	7.2	
2′-Acetoxy-2-methyl- (**16b**)	7.5	140
2′-Acetoxy-2,5-dimethyl-[c]	3.1	
Morphine	1.2	575
Codeine	7.5	270

[a] See N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957). The figures actually given here were obtained as described in A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965). [b] Not effective at subtoxic dose (below 20 mg/kg). [c] J. H. Ager, unpublished results.

Experimental Section

Melting points were determined by capillary (Hershberg apparatus, total-immersion thermometers). Elemental analyses, performed by the Section on Instrumentation of this laboratory, W. C. Alford, Chief, were within ±0.4% of the theoretical values. Ir (Perkin-Elmer) and nmr (Varian Associates A-60) spectra substantiated all structures.

4-Phenylpyridine N-Oxide.—4-Phenylpyridine (7.8 g, Aldrich Chemical Co.), 30 ml of glacial AcOH, and 5 ml of 35% H_2O_2 were heated together (70–80°) for 3.5 hr. An additional 3.5 ml of H_2O_2 was added, and the heating was continued for another 10 hr. Evaporation of the AcOH *in vacuo*, dilution with 100 ml of H_2O, strong basification (10% NaOH), extraction with $CHCl_3$, and drying and evaporation of the $CHCl_3$ gave 8.2 g of the N-oxide of **1**: prisms, mp 148–149° (from Me_2CO). *Anal.* ($C_{11}H_9NO$) C, H.

2-Cyano-4-phenylpyridine (3).[16]—To 6.8 g of 4-phenylpyridine N-oxide was added 5.0 g of Me_2SO_4 so that the temperature was maintained at 80°. The mixture was heated on a steam bath for 2 hr and cooled to give 11.8 g of hygroscopic **2** which in 20 ml of 70% dioxane (or 90% MeOH) was added slowly (stirring) to 5.8 g of NaCN in 50 ml of H_2O cooled to 15–20°. The mixture was stirred for 3 hr at 25° and extracted with two 25-ml portions of $CHCl_3$. The dried extracts (after evaporation of solvent) gave 6.3 g of **3**, mp 99°, after recrystallization from EtOH; λ_{max}^{KBr} 4.48 μ. *Anal.* ($C_{12}H_8N_2$) C, H, N.

2-Carbomethoxy-4-phenylpyridine (4).—Compound **3** (12 g) and 200 ml of MeOH–HCl (saturated) were refluxed for 10 hr and filtered. The filtrate was concentrated *in vacuo*, poured into H_2O made basic with NH_4OH, and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ *in vacuo* and "evaporative distillation" of the residue at 170–175° (3 mm) gave 12.8 g of **4**, $\delta_{TMS}^{CDCl_3}$ 4.01 ppm (3 H, singlet, CO_2Me). *Anal.* ($C_{13}H_{11}NO_2$) C, H, N.

(16) E. L. May and N. B. Eddy, *J. Med. Chem.*, **9**, 851, (1966).

1-Methyl-2-carbomethoxy-4-phenylpiperidine (5).—MeI (8.5 g), 11.7 g of **4**, and 200 ml of Me_2CO were kept at room temperature for 5 hr, diluted with 20 ml of EtOAc, and cooled to −15° to give, quantitatively, the methiodide of **4**, mp 141–142°. *Anal.* ($C_{14}H_{14}INO_2$) C, H, N. This methiodide (21 g), 0.8 g of PtO_2, and 200 ml of MeOH absorbed 3 mole equiv of H_2 (normal temperature and pressure) during 15–20 hr. After removal of catalyst (filtration) and solvent (*in vacuo*), the residue (in H_2O) was made alkaline with $NaHCO_3$. The resultant oil was dried (Na_2SO_4) in $CHCl_3$ to give, on evaporative distillation of the residue at 145–150° (2.5 mm), 12.5 g of oily **5**: $\delta_{TMS}^{CDCl_3}$ (all singlets) 2.33 (3 H, NCH_3), 3.78 (3 H, CO_2CH_3), 7.30 (5 H, C_6H_5) ppm. *Anal.* ($C_{14}H_{19}NO_2$) C, H, N.

1-Methyl-2-carboxy-4-phenylpiperidine (6) Hydrochloride.—Ester **5** (17.8 g) and 200 ml of 12 *M* HCl, refluxed for 10 hr and evaporated to dryness *in vacuo*, gave 17.9 g of **6**·HCl, mp 237–238° dec (from Me_2CO), λ_{max}^{Nujol} 5.8 μ. *Anal.* ($C_{13}H_{18}ClNO_2$) C, H.

Treatment of **6** with refluxing MeOH–HCl gave **5** in 90% yield indicating that inversion did not take place during the hydrolysis of **5**.

2-Methyl-8-oxo-6,7-benzomorphan (7) Picrate and Hydrochloride.—The hydrochloride of **6** (7 g) and 100 g of PPA were heated slowly to 130°, then kept at 145–155° (bath temperature) for 15 hr. The cooled solution was made alkaline with 20% KOH and extracted with $CHCl_3$, and the extracts were dried (Na_2SO_4). Short-path distillation (150–155°, 3 mm) of the residue from evaporation of the $CHCl_3$ gave 2.2 g (36%) of pale yellow oil, *m/e* 201, λ_{max}^{neat} 5.95 μ, nmr consistent with the structure **7**. The **picrate** (from Me_2CO) melted at 194°. *Anal.* ($C_{19}H_{18}N_4O_8$) C, H. The **hydrochloride** (from Me_2CO–HCl, then MeOH), mp 175–178° dec, had *m/e* 201. *Anal.* ($C_{13}H_{15}NO \cdot HCl \cdot 0.5\ H_2O$) C, H.

If cyclization temperature was 100–120°, 3–5% yields of **7** and much starting material were obtained. Temperatures of 150–180° gave *ca.* 25% yields of **7** along with tarry products from which was obtained, in 1–2% yield, **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine**, isolated as the **HCl salt**, mp 251–254.5°, *m/e* 173, δ^{D_2O} [17] 6.10 (broad singlet, 1 H, −HC=C<), identical with an authentic specimen prepared from 4-phenylpyridine methiodide ($NaBH_4$–1 *N* NaOH). *Anal.* ($C_{12}H_{16}ClN$) C, H. Hydrogenation of this by-product (PtO_2) gave **1-methyl-4-phenylpiperidine hydrochloride**, mp 215–218°, *m/e* 175.[18]

2-Methyl-6,7-benzomorphan (8) Hydrochloride. A. From 7.—Triethylene glycol (20 ml), 1.2 g of **7**, 1.2 g of KOH, and 5 ml of 95% $(NH_2)_2$ were kept at 170–180° for 12 hr and at 200° for 10 min. The cooled solution was treated with H_2O and Et_2O. The dried Et_2O layer was evaporated. The residue, after short-path distillation (160–180°, 0.3 mm), gave an oil which was converted to 1.1 g of hydrochloride (Et_2O–HCl gas), mp 225–225.5° (prisms from Me_2CO), *m/e* 187, δ^{D_2O} [17] 2.95 (3 H, singlet, NCH_3) and 7.30 (4 H, singlet, C_6H_4) ppm. *Anal.* ($C_{13}H_{18}ClN$) C, H.

B. From 1-Methylpyridinium Iodide.—$NaBH_4$ (11 g) was added slowly to 58 g of 1-methylpyridinium iodide (prepared from pyridine, MeI, and Me_2CO) in 300 ml of 1 *N* NaOH. An additional 200 ml of 1 *N* NaOH was added, and the mixture was stirred for 2 hr at 60–80°. The solution was cooled in ice and saturated with NaCl. Extraction with Et_2O, drying ($MgSO_4$) of the extracts, and careful removal of solvent (steam bath) gave 23 g (92%) of an oil whose nmr and ir spectra were consistent with the structure of **1-methyl-1,2,3,6-tetrahydropyridine.** This oil (73.6 g) in Me_2CO was treated with 88 ml (1 equiv) of $PhCH_2Cl$ to give (after filtration and drying *in vacuo* at room temperature) 118 g (74%) of hygroscopic 1-benzyl-1-methyl-1,2,3,6-tetrahydropyridinium chloride which was treated (as a powder) with 350 ml (1.4 equiv) of 2.1 *M* PhLi[19] (in C_6H_6–Et_2O) while stirring. After 3 hr, the mixture was poured into ice–H_2O. The organic layer was extracted with excess dilute HCl. The acid extracts were washed (CH_2Cl_2) and made basic (NH_4OH), and the precipitated oil was dried in ether to give 56 g of a reddish oily mixture (glpc and tlc indicated at least five components, two in minor amount). Distillation of the oil[20] gave a fraction of bp 70–84° (0.4–0.5 mm) which on refractionation gave 17 g of principally **12** (two minor components by glpc and tlc), bp 71–72° (0.2–0.3 mm), δ^{CDCl_3} 2.45 (singlet, 3 H, NCH_3), 5.25–5.70 (multiplet, 2 H, CH=CH), 7.20 (singlet, 5 H, C_6H_5), and whose ir data were satisfactory and indicative of *cis* C=C.

Polyphosphoric acid (400 g) and 11 g of **12** were heated and stirred at 150° for 44 hr. Cooling and ice–H_2O addition gave a brown solution which was made basic with 12 *M* NH_4OH and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 12 g of brown oil. This, combined with 3 g from another run, was fractionally distilled[20] to give 9.3 g, bp 80–90° (0.5 mm). It was converted to the hydrochloride (Et_2O–HCl). Two recrystallizations from MeOH–Me_2CO–Et_2O gave 5 g of **8**·HCl, mp 224–225°, identical (mp, ir, nmr, glpc, tlc) with that prepared above from 4-phenylpyridine. An additional 1 g of HCl salt (total over-all yield from pyridine 5%) was obtained from other fractions of the distillate.

2′-Hydroxy-2-methyl-6,7-benzomorphan (15).—To 47 g of crude 1-methyl-1,2,3,6-tetrahydropyridine (see above) in 200 ml of Me_2CO was added 65 g of *p*-methoxybenzyl chloride. After 24 hr at room temperature and 3 hr at −5°, the hygroscopic **1-*p*-methoxybenzyl-1-methyl-1,2,3,6-tetrahydropyridinium chloride (13)** was filtered, washed with Me_2CO, and dried for 2 days over P_2O_5; yield 67 g, mp 144–147°. *Anal.* ($C_{14}H_{20}ClNO$) Cl, N.

To a stirred mixture of 92.6 g of this solid and 200 ml of Et_2O was added 300 ml of 2.1 *M* PhLi[19] in C_6H_6–Et_2O. After 3.5 hr, 28.9 g (48.7%) of **2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (14)**, bp 118–124° (0.5 mm),[20] was obtained as described in the isolation of **12** above. The **picrate** crystallized from MeOH in yellow needles, mp 123–124°. *Anal.* ($C_{20}H_{22}N_4O_8$) C, H, N.

The **14** base (6.5 g) and 60 g of PPA were stirred at 205–210° (bath temperature) for 9 hr and poured into 260 ml of ice–H_2O and 156 ml of 12 *M* HCl, and the mixture was refluxed for 12 hr[21] and filtered (Norit). Addition of excess NH_4OH and extraction with four portions of $CHCl_3$ containing a little EtOH gave, after drying (Na_2SO_4) and *in vacuo* evaporation of the extracts, a residue which crystallized from 5 ml of warm Me_2CO; yield of **15** (after overnight cooling at −5°) 2.4 g (40%), mp 220–224°. It crystallized from MeOH in plates, mp 228–230° dec. *Anal.* ($C_{13}H_{17}NO$) C, H, N. The **hydrochloride** (plates from MeOH) melted at 226–228° dec. *Anal.* ($C_{13}H_{18}ClNO$) C, H.

When cyclization was carried out at 140–150°, the yield of **15** was 8% and the phenolic tetrahydropyridine corresponding to **14** was obtained also.

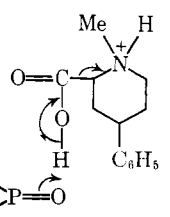
The **O-acetyl** derivative **16b** was obtained as the **hydrochloride** in 78% yield by refluxing 0.4 g of **15**, 10 ml of Ac_2O, and 1 ml of pyridine together for 1 hr, diluting with 30 ml of Et_2O, acidifying with EtOH–HCl, filtering, and washing the precipitate with Me_2CO; needles from MeOH–Et_2O, mp 267–269° dec, λ_{max}^{Nujol} 5.74 μ. *Anal.* ($C_{15}H_{20}ClNO_2$) C, H, N.

2′-Methoxy-2-methyl-6,7-benzomorphan (16a) Hydrochloride.—To 1.6 g of **15** and 5 ml of MeOH was added 75 ml of 3% CH_2N_2 in Et_2O (stirring). The mixture was stirred at 25–27° for 4 days and evaporated to dryness *in vacuo*. The residue was dissolved in Et_2O, and the solution was washed twice with 1 *N* NaOH. The residue from drying and evaporation of the Et_2O was evaporatively distilled at 120–140° (0.02 mm) to give 1.2 g of oil which was converted to 1.25 g (63%) of hydrochloride with EtOH–Et_2O–HCl. It crystallized from MeOH–Me_2CO–Et_2O in needles, mp 271–273° dec. *Anal.* ($C_{14}H_{20}ClNO$) C, H, N.

From the NaOH washings above 0.48 g (30%) of **15**, mp 217–221°, was recovered.

6,7-Benzomorphan (9) Hydrochloride.—The base **8** from 0.2 g of HCl salt, 0.2 g of diethyl azodicarboxylate (Aldrich Chemical

(17) 3-Trimethylsilyl-1-propanesulfonic acid sodium salt as reference standard. The acidic decarboxylation reaction leading to this by-product may be considered analogous to that (carbonium ion mechanism) described in J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 309. The postulated imine intermediate formed as shown could then



rearrange to the more stable Δ^3 isomer with the double bond in conjugation with the aromatic ring during its isolation from a basic medium.

(18) See A. Ziering, L. Berger, S. D. Heineman, and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(19) From Lithium Corp. of America, Inc.

(20) Nester-Faust spinning-band column.

(21) Without the HCl treatment, no **15** could be isolated. Apparently the phosphate ester of **15** is quite stable.

Co.), and 10 ml of $CHCl_3$ were refluxed for 3 hr. Solvent was removed *in vacuo*. The residue, 0.15 g of pyridine hydrochloride, 5 ml of H_2O, and 10 ml of EtOH were kept overnight at 25–27°, made alkaline with 10% NaOH, and extracted with $CHCl_3$. The residue left from drying and evaporation of the $CHCl_3$ was acidified (in Et_2O) with dry HCl giving 85 mg of **9**·HCl, mp 261–262° (needles from MeOH–Me_2CO). *Anal.* ($C_{12}H_{16}ClN$) C, H. The **picrate** (yellow prisms from MeOH) melted at 171–173°. *Anal.* ($C_{18}H_{18}N_4O_7$) C, H.

N-Demethylation of **8** with BrCN[22] gave, after prolonged hydrolysis of the N-cyano intermediate with 6% HCl, 2-cyano-6,7-benzomorphan (λ_{max}^{Nujol} 4.5 μ), 2-carbamido-6,7-benzomorphan (λ_{max}^{Nujol} 5.9 μ), and a 22% yield of **9**. The hydrochloride of **9** and 2-carbamido-6,7-benzomorphan formed a well-characterized "double" compound, mp 165–166°, which was separated into its components by converting to the picrate.

(22) J. von Braun, *Ber.*, **47**, 2312 (1914).

Acknowledgment.—We are indebted to Mr. J. Harrison Ager of the permanent NIH staff and Dr. Robert T. Parfitt, formerly Visiting Associate, now at Glasgow, Scotland, for attempts to synthesize **8**, by some of the synthetic routes mentioned in footnote 7.

Irreversible Enzyme Inhibitors. CLII.[1,2] Proteolytic Enzymes. X.[3] Inhibition of Guinea Pig Complement by Substituted Benzamidines

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The inhibition of guinea pig complement was investigated with 54 amidines, alkylamines, aralkylamines, and guanidines previously synthesized for inhibition of trypsin; based on these results, 15 new candidate inhibitors were synthesized. The best inhibitors were derived from benzanidine, the latter being a fair inhibitor. Inhibition by benzamidine was considerably enhanced by *meta* substituents such as isoamyloxy (**18**), phenoxypropyloxy (**22**), and *p*-acetamidophenylbutyl (**27**). Of 28 *para*-substituted benzamidines, only the benzamidine with an $O(CH_2)_4OC_6H_4$-*p*-$NHCONHC_6H_3$-2-OMe-5-SO_2F substituent (**37**) showed good inhibition. The most potent inhibitor in the literature, maleopimaric acid (**2**), showed about 50% inhibition at 0.5 m*M*; the same concentration of **18**, **22**, and **27** showed 50% inhibition, whereas only 0.062 m*M* of **37** was required. However, maleopimaric acid showed better total inhibition than the three benzamidines when the concentrations of the four compounds were increased.

Among the myriad of serum proteases involved in a number of disease states[4] is the complement system utilized for lysis of bacterial, protozoan, or foreign mammalian cells.[5–7] Complement consists of nine components which arise from eleven distinct proteins, all of which are required for cell lysis.[6] Since cell lysis begins with the combining of an antibody with a foreign cell which then triggers the complement system, two avenues for inhibition of rejection of organ or tissue transplants are available. Either antibody formation[8] or the function of the complement system could be inhibited. Inhibition of antibody formation has the disadvantage that the complement system for control of bacterial infection also cannot operate and infection becomes a serious problem with organ transplantation. Inhibition of the complement system could have two disadvantages: (a) there are a variety of other serum proteases that might be inhibited giving serious side reactions,[4] and (b) the function of the complement system for controlling bacterial infection may also be inhibited. There is little doubt that suppression of antibodies will not be selective with respect to bacterial infection; there is reasonable doubt that the complement systems for lysis of mammalian cells and bacterial cells are identical, since the cell wall composition of bacteria and mammalian cells are so different.

The selective inhibition of the complement system with minimal inhibition of other serum proteases may be possible with active-site-directed irreversible inhibitors that operate by the exo mechanism.[9] These exo-type irreversible inhibitors have an extra dimension of specificity not present with reversible inhibitors, particularly if an area on the enzyme adjacent to the active site[10] is employed for covalent bond formation;[11] thus enzymes closely related mechanistically[12] or even isozymes can be selectively inhibited.[13] At the time we embarked on our studies on proteolytic enzymes, no exo-type irreversible inhibitors of this type were known, although several endo-type irreversible inhibitors had been investigated.[4] Therefore we started studies on two different types of proteolytic enzymes that were readily available, namely trypsin[4] and chymotrypsin,[14] to determine if exo-type irreversible inhibitors could be designed; a variety of irreversible inhibitors of the exo-

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(2) For the previous paper of this series see B. R. Baker and R. B. Meyer, Jr., *J. Med. Chem.*, **12**, 224 (1969).

(3) For the previous paper on proteolytic enzymes see B. R. Baker and J. A. Hurlbut, *ibid.*, **12**, 221 (1969).

(4) For key references see B. R. Baker and E. H. Erickson, *ibid.*, **10**, 1123 (1967).

(5) Ciba Foundation Symposium, Complement, G. E. W. Wolstenholme and J. Knight, Ed., Little, Brown and Co., Boston, Mass., 1965.

(6) For a review see H. J. Müller-Eberhard, *Advan. Immunol.*, **8**, 1 (1968).

(7) P. H. Schur and K. F. Austen, *Ann. Rev. Med.*, **19**, 1 (1968).

(8) G. H. Hitchings and G. B. Elion, *Ann. N. Y. Acad. Sci.*, **129**, 709 (1966).

(9) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors. The Organic Chemistry of the Enzymic Active-Site," John Wiley and Sons, Inc., New York, N. Y., 1967.

(10) The active site is defined as those regions of an enzyme necessary for complexing the substrate(s) and catalyzing the reaction; see ref 9, p 188.

(11) See the bridge principle of specificity in ref 9, pp 172–184.

(12) See ref 9, Chapter IX.

(13) (a) B. R. Baker and R. B. Meyer, Jr., *J. Med. Chem.*, **11**, 489 (1968), paper CXIX of this series; (b) B. R. Baker, G. J. Lourens, R. B. Meyer, Jr., and N. M. J. Vermeeden, *ibid.*, **12**, 67 (1969), paper CXXXIII of this series.

(14) B. R. Baker and J. A. Hurlbut, *ibid.*, **10**, 1120 (1967), paper CVII of this series.