Benzo[*g*]quinolines. I. Synthesis and Pharmacological Evaluation of *cis*- and *trans*-1-Alkyl-5,5-dimethyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-7-ol. A New Class of Narcotic Antagonists[1]

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The stereoselective synthesis of *cis*- and *trans*-1-alkyl-5,5-dimethyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]-quinolin-7-ol is described. These compounds have been assayed for narcotic antagonist activity. The *trans* isomers show little activity, whereas the *cis* isomers possess approximately one-twentieth the activity of the corresponding *trans*-benzomorphans.

In the course of our continuing search for more effective analgetic and narcotic antagonist agents, our interest in the 1-alkyl-5,5-dimethyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-7-ol ring system was stimulated by the observation of Cope and Burrows[2] that 1,5-dimethyl-4-hexenylamine, readily obtained from citral, would react with formaldehyde–formic acid to give α,α,1,6-tetramethyl-3-piperidinemethanol. A similar reaction with *p*-methoxyphenylacetaldehyde might be expected to give the corresponding 2-(*p*-methoxybenzyl) derivative which, after cyclization and ether cleavage, would give 1,2,3,4,4a,5,10,10a-octahydro-1,2,5,5-tetramethylbenzo[*g*]quinolin-7-ol (**8a**). In addition to possessing a phenylethylamine group and a properly situated "central carbon"[3a] the *cis*-fused isomer can assume a conformation (as shown by Dreiding models) in which much of the molecule is superimposable on the *trans*-5,9-dimethyl-6,7-benzomorphan system. Therefore, in compounds of this type, the *cis*-fused isomers were anticipated to possess a higher order of analgetic and narcotic antagonist activity then the corresponding *trans*-fused isomers which are approximately planar and are conformationally rigid. However, our original synthetic approach proved unsuccessful.[4]

Shortly afterward, a group of workers[5] reported the isolation of 1,5-dimethyl-4-ethyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-7-ol (**8b**) as a by-product of a benzomorphan synthesis. This compound was proposed to have a *trans* B/C ring fusion, with the CH_3 group equatorial and the C_2H_5 group axial. Interestingly, **8b** possessed analgetic potency between that of morphine and that of codeine, in seeming defiance of well-established structure–activity relationships among compounds of this type.[3] We were thus encouraged to seek an alternative synthetic approach to compounds of general structure **6**. This paper describes the stereoselective synthesis of *cis*- and *trans*-7-methoxy-5,5-dimethyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]-quinoline (**5a** and **b**) and the narcotic antagonist activity of some selected derivatives.

Chemistry.—Acylation (Scheme I) of diethyl 2-cyanoethylmalonate with *p*-methoxyphenylacetyl chloride using NaH afforded **1**. Catalytic reduction of this crude ketonitrile over Pt gave **2**. Preparation of the carbobenzoxy derivative of **2** followed by treatment with 1 molar equiv of KOH in EtOH–H_2O afforded a crystalline half-acid ester which was decarboxylated at 200° to give **3** as a mixture of stereoisomers. The *cis* isomer[6] **3a** readily crystallized from an ethanol solution. Treatment of **3a** with MeMgI followed by hydrogenolysis of the carbobenzoxy group (Pd–C) afforded **4a**. When **4a** was treated with hot 1:5 H_2SO_4–AcOH, cyclization occurred readily giving **5a**. Only a small amount of **5b** could be detected by tlc.

Hydrogenolysis of the mother liquors from the crystallization of **3a** afforded a mixture of amino esters from which the *trans* isomer could be isolated. Reconversion to **3b** and subsequent treatment as described above for **3a** led to **5b**. Only a small amount of **5a** could be detected by tlc of this cyclization product. Treatment of either **5a** or **5b** with HBr followed by NH_4OH gave the corresponding phenolic norbases (**6**, $R_1 = R_2 = H$). The N-methyl, -allyl, -propyl, and -cyclopropylmethyl derivatives were prepared by the usual procedures.

In order to establish the gross structure of **5**, Hofmann degradation of the methiodides of **5a** and **5b** was performed. When 10% NaOH was used, no reaction occurred and the starting methiodide was recovered. When the TlOH method[7] was used, both methiodides gave **7**, the structure of which was established spectroscopically. When 35% NaOH was used, both methiodides again gave **7**. This is in contrast to the methiodide of the methyl ether of **8b** which, under these conditions, was reported[5] to give quantitative elimination of MeI.

The assignment of the stereochemistry of the B/C ring fusion in **5a** and **5b** was based on four bodies of evidence. First, **3a** and **3b** lead stereoselectively to **5a** and **5b**, respectively. Second, Hofmann degradation of the methiodides of **5a** and **5b** was observed to proceed more rapidly on the **5a** methiodide, in which the leaving groups can assume the favorable anticoplanar orientation.[8] Third, Bohlmann[9] has found that absorptions

(1) Taken in part from the Ph.D. thesis of W. F. Michne, Rensselaer Polytechnic Institute, Troy, N. Y., June 1968.

(2) A. C. Cope and W. D. Burrows, *J. Org. Chem.*, **30**, 2163 (1965).

(3) (a) E. L. May in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 335; (b) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).

(4) *Cf.* R. Grewe, R. Hansen, G. Jacobsen, E. Nalte, and K. Riecke, *Ann.*, **581**, 85 (1953), for a similar cyclization in the morphinan series. Formaldehyde gave 91% ring closure, whereas phenylacetaldehyde gave 95% polymerization.

(5) B. Josh, E. L. May, H. Fabs, J. Daly, and A. E. Jacobson, *J. Med. Chem.*, **8**, 559 (1965).

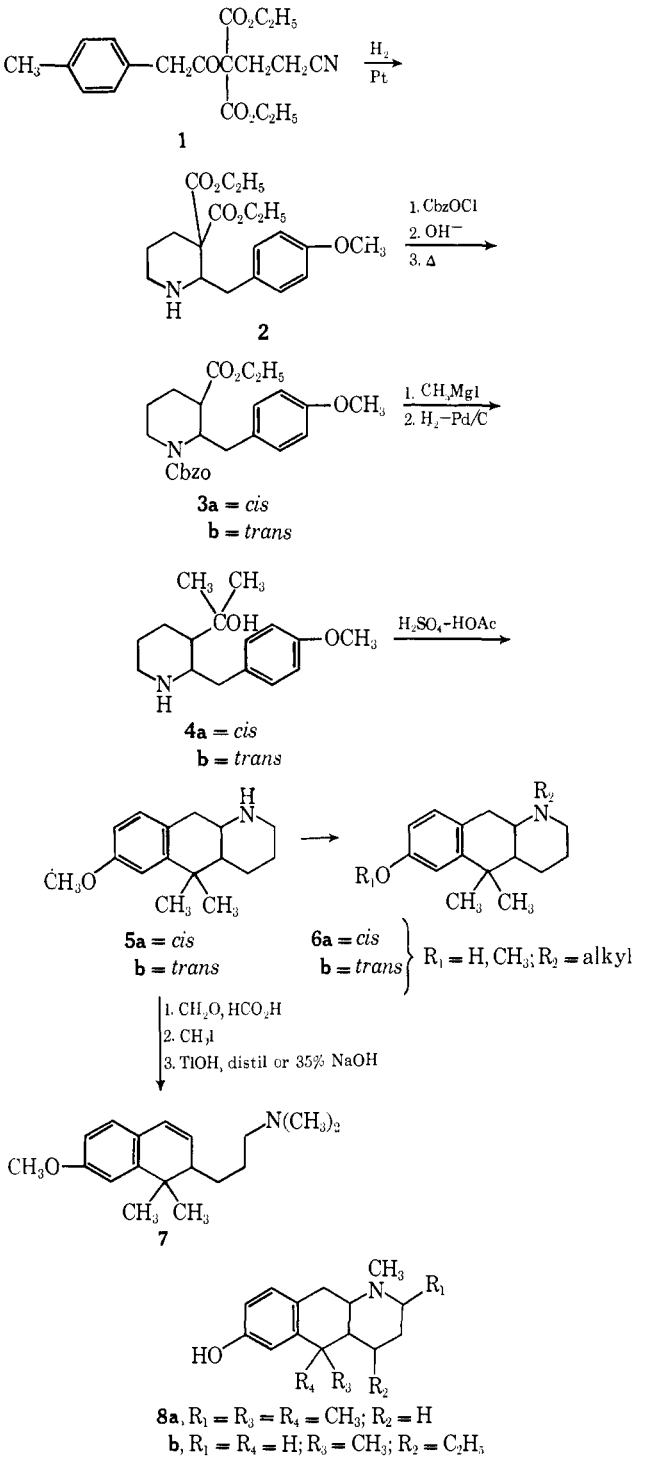
(6) The stereochemistry of this compound was established by NaOEt equilibration.[7]

(7) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961).

(8) (a) K. Jewers and J. M. McKenna, *J. Chem. Soc.*, 1575 (1960); (b) J. McKenna and A. Tolley, *ibid.*, 945 (1960).

(9) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

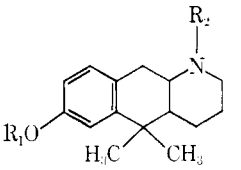
SCHEME I



in the ir at 2800–2700 cm^{-1} occur in tertiary amines which have two hydrogens adjacent to the nitrogen and *trans* to the lone pair. A comparison of Dreiding models of the N-Me derivatives of **5a** and **b** showed that the *trans* isomer always fulfills these conditions due to its conformational rigidity, and the *cis* isomer fulfills them only part of the time owing to conformational interconversions. The ir spectra of the N-methyl derivatives of **5a** and **5b** each showed a band at 2780 cm^{-1}; however, this band was very much more intense for the **5b** (*trans*) derivative. Fourth, the geminal CH_3 groups in each isomer assume different positions relative to the aromatic ring. To the extent that the aromatic ring affects the chemical shifts of these CH_3 groups,[10] the difference will be greater in the *trans* isomers whose CH_3 groups are less symmetrically oriented to the aromatic ring. The average difference of chemical shifts of these CH_3 groups (Table I) in derivatives of **6a** was 5 Hz; of those in derivatives of **6b** it was 13 Hz.

TABLE I

gem-DIMETHYL CHEMICAL SHIFTS[a] AND THEIR DIFFERENCES IN THE STEREOISOMERIC BENZO[g]QUINOLINES



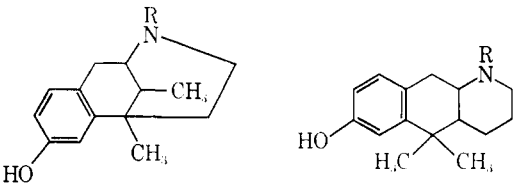
R_1	R_2	δ_{cis}, Hz	δ_{trans}, Hz	Δ_{cis}	Δ_{trans}
CH_3	H	78, 73	78, 67	5	11
CH_3	CH_3	80, 75	78, 65	5	12
H	H[b]	72, 68	72, 60	4	12
H	CH_3[c]	86, 78	86, 72	8	14
H	$CH_2CH_2CH_3$[b]	74, 70	76, 63	4	13
H	CH_2-*c*-C_3H_5[c]	87, 80	87, 73	7	14
H	$CH_2CH{=}CH_2$	77, 72[b]	87, 72[c]	5	15

[a] Internal TMS standard, $CDCl_3$ unless otherwise specified. [b] DMSO-d_6. [c] CF_3CO_2H.

Pharmacology.—The N-methyl, -allyl, -propyl, and -cyclopropylmethyl derivatives of the *cis* and *trans* isomers **6a** and **6b** (R_1 = H) were assayed for analgetic antagonist activity by the rat tail flick method[11] *vs.* meperidine and the results are summarized in Table II.

TABLE II

ANALGETIC ANTAGONIST ACTIVITIES OF SOME DERIVATIVES OF 5,5-DIMETHYL-1,2,3,4,4a,5,10,10a-OCTAHYDROBENZO[g]-QUINOLIN-7-OL[a]



	AD_{50}, mg/kg sc		
	trans-	Benzo[*g*]quinoline	
R	Benzomorphan	*cis*	*trans*
CH_2-*c*-C_3H_5	0.014	0.27	Inactive
$CH_2CH{=}CH_2$	0.019	0.46	11
$CH_3CH_3CH_3$	0.056	1.05	14
CH_3		7.9	Inactive

[a] The dose of compound which will reduce the effect of a standard dose of meperidine by 50%.

The data for the corresponding *trans*-5,9-dimethyl-6,7-benzomorphans are included for comparison. It is seen that the benzo[*g*]quinolines are approximately 5% as active as the corresponding benzomorphans. Investigation of the structure–activity relationships in this new class of compounds is continuing.

Experimental Section

All melting points are uncorrected. Nmr spectra were obtained on a Varian Associates A-60 spectrometer; ir spectra were ob-

(10) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(11) L. S. Harris and A. K. Pierson, *J. Pharmacol., Exp. Ther.*, **143**, 141 (19641.

tained on a Perkin-Elmer Model 257 spectrometer, with the exception of the Bohlmann bands which were observed using a Beckman IR-7 spectrometer. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions are within ±0.4% of the theoretical values.

Diethyl 2-Cyanoethyl-*p*-methoxyphenylacetylmalonate (1).—NaH (46.1 g, 1.1 moles, 57.3% dispersion) was washed twice with 400-ml portions of PhMe, the washes being removed by suction through a sintered-glass plug. PhMe (2 l.) and 213 g (1.0 mole) of diethyl 2-cyanoethylmalonate were then introduced, and the mixture was stirred and refluxed for 8 hr. It was then cooled in an ice bath while a solution of 185 g (1.0 mole) *p*-methoxyphenylacetyl chloride in 600 ml of PhMe was added in a fine stream. After the addition was complete, the mixture was stirred for 3 hr while being allowed to come to room temperature. The mixture was filtered through Filter-cel, and the filtrate was evaporated to dryness *in vacuo* to give 296 g of crude 1. Attempts to purify this material by distillation were unsuccessful due to extensive decomposition. However, the crude material [ir (film) 2250 (C≡N), 1750 and 1725 cm^{-1} (ester and ketone). *Anal.* ($C_{19}H_{23}NO_6$) C, 63.1; H, 6.4; N, 3.9. Found: C, 62.6; H, 6.3; N, 3.4] was found to be satisfactory for the continuation of the synthesis.

Diethyl 2-(*p*-Methoxybenzyl)-3,3-piperidinedicarboxylate Hydrochloride (2).—A solution of 296 g (0.82 mole) of crude 1 in AcOH, 3600-ml total volume, was hydrogenated at 24° (30 atm) using 10 g of PtO_2. After consumption of the theoretical quantity of H_2, the catalyst was filtered, and the filtrate was evaporated to dryness. To the residue was added 600 ml of H_2O and 80 ml of HCl. After washing (Et_2O), the aqueous solution was made basic with NH_4OH and extracted with Et_2O. The combined extracts were washed (H_2O), dried, and filtered. To the filtrate was added 195 ml (0.82 mole) of 4.2 *N* EtOH–HCl, and the solution was cooled at 0° for several hours. The product was filtered, washed with several portions of Et_2O, and dried *in vacuo* at 50° to give 216 g of crude product, mp 160–161°. Two recrystallizations (EtOH–Et_2O) afforded **2**, mp 163–165°. *Anal.* ($C_{19}H_{27}NO_5$) C, H, N.

Ethyl 1-Benzyloxycarbonyl-2-(*p*-methoxybenzyl)-3-piperidinecarboxylate (3).—A mixture of 295 g (0.76 mole) of **2**, 144 g (0.84 mole) of benzyl chloroformate, and 1.5 l. of $CHCl_3$ was stirred with ice cooling while 171 g (1.7 moles) of Et_3N was added dropwise. After the addition, the reaction mixture was stirred at room temperature for 3 hr, then washed successively (H_2O, dilute 1 *N* HCl, saturated $NaHCO_3$). The organic layer was dried, filtered, and evaporated to dryness to give 372 g of syrup. This material, 50 g of KOH pellets, 765 ml of H_2O, and 765 ml of EtOH was stirred and refluxed for 6 hr, then concentrated until only H_2O distilled. More H_2O was added, and the mixture was extracted twice with Et_2O. The combined ether extracts were washed (H_2O), dried, filtered, and evaporated to dryness *in vacuo* to give 169 g of recovered starting material. The H_2O layer was acidified with HCl; addition of a few milliliters of Et_2O and shaking caused crystallization. The product was filtered, washed (H_2O), and dried to give 177 g of product, mp 186° dec. Recrystallization (EtOH) afforded material, mp 186–188° dec. *Anal.* ($C_{24}H_{29}NO_7$) C, H, N.

Heating 120 g (0.26 mole) of this material at 200° caused a smooth evolution of CO_2. The residue (105 g) was dissolved in 260 ml of EtOH and cooled in ice to produce crystalline *cis* isomer **3a**, 59 g, mp 69–71°. *Anal.* ($C_{24}H_{25}NO_5$) C, H, N.

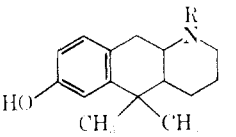
The mother liquor from the crystallization of **3a** was evaporated to dryness to give a syrupy residue (43 g). Hydrogenolysis in EtOH over Pd–C and isolation of the basic components gave 21 g of a syrup. Treatment of this syrup in EtOAc solution with 10.8 g (0.75 equiv) of *p*-toluenesulfonic acid monohydrate gave a crystalline salt. Recrystallization (EtOH–Et_2O) gave material, mp 140–142°. *Anal.* ($C_{16}N_{23}NO_3 \cdot C_7H_8O_3S$) C, H, N.

Treatment of this salt with benzyl chloroformate as described above for **2** gave the *cis*-free (glpc) *trans* isomer **3b**. All efforts to crystallize this material from a variety of solvents failed.

***cis*-2-(*p*-Methoxybenzyl)-α,α-dimethyl-3-piperidinemethanol (4).**—A solution of 121 g (0.29 mole) of **3a** in 1800 ml of Et_2O was added to an excess of ethereal MeMgI. After quenching with dilute HCl, washing the Et_2O layer with $NaHCO_3$, and evaporation of the solvent, there was obtained 105 g of crude carbinol. This material in EtOH (1 l. total volume) was hydrogenated using 20 g of Pd–C. The basic fraction (**4a**, 63.9 g) was converted to its *p*-toluenesulfonate salt, mp 204–206° after recrystallization from EtOH. *Anal.* ($C_{16}H_{25}NO_2 \cdot C_7H_8O_3S$) C, H, N.

TABLE III

PROPERTIES OF BENZO[*g*]QUINOLIN-7-OLS EVALUATED PHARMACOLOGICALLY



R	Config	Formula	Mp, °C	Analyses
CH_3	*cis*	$C_{16}H_{23}NO$	204–207	C, H, N
	trans	$C_{16}H_{23}NO$	270–272	C, H, N
CH_2-*c*-C_3H_5	*cis*	$C_{19}H_{27}NO \cdot HCl$	267–269	C, H, N
	trans	$C_{19}H_{27}NO \cdot HCl$	266 dec	C, H, N
$CH_2CH{=}CH_2$	*cis*	$C_{18}H_{25}NO \cdot HCl$	271–273	C, H, N
	trans	$C_{18}H_{25}NO$	215–218	C, H, N
$(CH_2)_2CH_3$	*cis*	$C_{18}H_{27}NO \cdot HCl$	264–266	C, H, N
	trans	$C_{18}H_{27}NO \cdot HCl$	>300	C, H, N

Similar treatment of **3b** gave **4b** as the hydrochloride, mp 159–160° after recrystallization from EtOH–Et_2O. *Anal.* ($C_{16}H_{25}NO_2 \cdot HCl$) C, H, N.

1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-5,5-dimethylbenzo[*g*]quinoline (5).—A mixture of 8.0 g (0.018 mole) of **4a** *p*-toluenesulfonate, 65 ml of AcOH, and 13 ml of H_2SO_4 was heated on a steam bath for 10 min, poured into H_2O, made basic with NH_4OH, and extracted with Et_2O. The extract was washed (H_2O), dried, filtered, and evaporated to dryness to give 3.6 g (80%) of crude **5a**. This was purified as the hydrochloride, mp 225° after recrystallization from EtOH. *Anal.* ($C_{16}H_{23}NO \cdot HCl$) C, H, N.

Similar treatment of **4b** hydrochloride gave **5b**·HCl, mp 295–298° after recrystallization from EtOH. *Anal.* ($C_{16}H_{23}NO \cdot HCl$) C, H, N.

1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-1,5,5-trimethylbenzo[*g*]quinoline.—A 1.0-g sample of **5a**·HCl was converted to the base with NH_4OH and dried in Et_2O. After filtration and evaporation of the solvent, the residue (0.7 g), 2 ml of HCO_2H, and 2 ml of 35% CH_2O were heated on a steam bath for 1.5 hr, diluted (H_2O), made basic with NH_4OH, and extracted with Et_2O. The extract was washed (H_2O), dried, filtered, and evaporated to dryness. The residue (0.7 g) was distilled, bp 105–110° (0.03 mm). *Anal.* ($C_{17}H_{25}NO$) H, N; C: calcd, 78.71; found, 78.23.

Similar treatment of **5b**·HCl afforded the *trans* isomer, bp 120° (0.02 mm). *Anal.* ($C_{17}H_{25}NO$) C, H, N.

The corresponding methiodides were prepared by treating these bases with 1 equiv of MeI in MeCN. The *cis* methiodide, after recrystallization (H_2O), had mp 288–293°. *Anal.* ($C_{18}H_{28}INO$) C, H, N.

The *trans* methiodide, after recrystallization (MeOH), had mp 301–305°. *Anal.* ($C_{18}H_{28}INO$) C, H, N.

Hofmann Degradations.—The *cis* and *trans* methiodides were subjected to the TlOH degradation procedure.[5] The distillates (**7**) from each methiodide were shown to be identical by tlc and ir, uv, and nmr spectrometry. *Anal.* ($C_{15}H_{25}NO$) C, H, N.

When a mixture of 0.5 g of either methiodide and 12.5 ml of 35% NaOH was stirred and refluxed for 3.5 hr, cooled, and extracted with Et_2O, the *cis* methiodide was found to give **7** in 46% yield, whereas the *trans* methiodide gave **7** in only 23% yield.

Demethylation of 5.—A mixture of either **5a**· or **5b**·HCl and 10 times its volume of 48% HBr was stirred and refluxed for 10 min, then cooled. The product phenolic norbase hydrobromides were filtered, washed (H_2O), and dried. The *cis* hydrobromide had mp 333–336°. *Anal.* ($C_{15}H_{21}NO \cdot HBr$) C, H; N: calcd, 4.49; found, 5.09. The *trans* hydrobromide had mp 294–298°. *Anal.* ($C_{15}H_{21}NO \cdot NBr$) C, H, N.

The bases were obtained by treating warm aqueous solutions of the hydrobromides with NH_4OH. After recrystallization from EtOH, the *cis* norbase had mp 214–216°. *Anal.* ($C_{15}H_{21}NO$) C, H, N. The *trans* norbase, after recrystallization (Me_2CO), had mp 191–193°. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

Derivatives for Pharmacological Evaluation.—The derivatives of the stereoisomeric norbases prepared for pharmacological evaluation were as follows: NCH_3, prepared by reductive alkylation of the norbases with formaldehyde; N-cyclopropylmethyl, prepared by the procedure of Gates and Montzka;[12] and the

(12) M. D. Gates and T. Montzka, *J. Med. Chem.*, 7, 127 (1964).

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).