Synthesis and Analgetic Activity of 3- and 4-Methyl-6,7-benzomorphans

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2,5-Dimethyl-6,7-benzomorphans bearing piperidine bridge 3- and 4-Me substituents (**4** and **8**) have been synthesized *via* the 2-benzyltetrahydropyridines **3a**, **3b**, and **7**. *N*-Phenethyl (**13a** and **13b**), dimethylallyl (**10a** and **10b**), and cyclopropylmethyl (**14a** and **14b**) derivatives were also prepared, and the methiodides **17a** and **17b** were degraded to the corresponding dihydronaphthalenes (**18a** and **18b**). Compound **14a** exhibits analgetic activity equiv to about half that of morphine.

Synthetic studies in the 6,7-benzomorphans have resulted in potent analgetic agents in which analgesia and physical dependence have, to a large extent, been separated.[1-3] This has been particularly true in the case of analgetics of the antagonist type which are not capable of supporting morphine-like dependence.[4,5] Furthermore, recent investigations have uncovered a surprising level of analgetic potency in 6,7-benzomorphans lacking a quaternary C at C-5 and bearing only a secondary N,[6,7] and in a series of B-norbenzomorphans.[8]

In order to extend the present knowledge of structure–activity relationships in the 6,7-benzomorphans, particularly the effect of steric crowding of N, we have synthesized novel pairs of isomeric compounds possessing either a 3- or 4-Me substituent. These compounds correspond to amidone and isoamidone analogs.

Alkylation of 1-methyl-2-tetralone by 2-chloro-*N*,*N*-dimethylpropylamine following the standard procedure[9] gave the expected mixture of 1-methyl-1-(2-dimethylaminopropyl)- and 1-methyl-1-(2-dimethylaminoisopropyl)-2-tetralones, which could be separated only with difficulty and in low yields. The Grewe route therefore appeared to be a more attractive possibility.

Treatment of $C_6H_5CH_2MgCl$ with 1,2,4-trimethylpyridinium iodide (**1**) gave 75% of the desired 2-benzyl-1,4,6-trimethyl-1,2-dihydropyridine (**2**) as its crystalline perchlorate. Pmr examination of **2**·base in $CDCl_3$ confirmed the assigned structure. The principle features were a finely split doublet at δ 1.70 (J = 1.2 Hz) for 4-C**H**$_3$, and a broad singlet at δ 1.87 for 6-C**H**$_3$. Conversion of **2**·base to the perchlorate resulted in spectral shifts similar to those reported previously.[10] BH_4^- reduction of **2** gave an approximately equimolar mixture of the tetrahydropyridines **3a** and **3b** as indicated by pmr examination. The doublets (J = 7 Hz) corresponding to 6-C**H**$_3$ in **3a** and **3b** occurred at δ 1.10 and 1.00, respectively. Similar isomeric mixtures of 4-alkyl-2-*p*-methoxybenzyl-1-methyltetrahydropyridines formed from $NaBH_4$ reduction of a single dihydropyridine precursor have been reported recently.[11] Cyclization of the isomeric mixture to a single product (±)-2,3,5-trimethyl-6,7-benzomorphan (**4**) in refluxing HBr in aq HOAc occurred smoothly and in high yield.

(±)-2,4,5-Trimethyl-6,7-benzomorphan (**8**), our second objective, was synthesized *via* a modified Grewe route. $NaBH_4$ reduction of 3,4-lutidine methiodide (**5**) in the presence of KCN gave the nitrile **6** together with 1,3,4-trimethyl-1,2,5,6-tetrahydropyridine, the expected by-product.[12] Treatment of **6** with $C_6H_5CH_2MgCl$ afforded the required benzyltetrahydropyridine **7**, which cyclized readily in boiling 48% aq HBr to **8** in high yield.

It is now well established that variation of the benzomorphan N-substituent is able to afford both agonist- and antagonist-type analgetics.[4,5] In our series 2 compounds in each category were investigated; *N*-Me and *N*-phenethyl as agonist and *N*-cyclopropylmethyl and *N*-dimethylallyl as antagonist agents.

Following the standard procedure N-demethylation of **4** and **8** was accomplished by the von Braun CNBr method to yield 3,5-dimethyl- and 4,5-dimethyl-6,7-benzomorphan (**9a** and **9b**, respectively) *via* their isolated *N*-nitriles.

Both **9a** and **9b** were converted to the corresponding 2-dimethylallyl derivatives (**10a** and **10b**) by direct alkylation with 1-bromo-3-methylbut-2-ene in DMF.

Preparation of the 2-phenethyl (**13a** and **13b**) and 2-cyclopropylmethyl (**14a** and **14b**) derivatives was achieved through the corresponding 2-phenacetyl- (**11a** and **11b**) and 2-cyclopropylcarbonyl- (**12a** and **12b**) 6,7-benzomorphans, by direct acylation followed by LAH reduction of the amide intermediates.

On examination of the pmr spectra (Table I) of both series of benzomorphans it was apparent that the 4-C**H**$_3$ absorption always occurred in a strongly shielded position at approximately δ 0.6. In the 3-methyl-6,7-benzomorphans, where the 3-C**H**$_3$ group is analogous to that found in amidone, the 3-C**H**$_3$ resonance signal was seen in an unexceptional position. The 5-C**H**$_3$ shift remains constant in both series. During synthetic studies it was anticipated that pairs of compounds isosteric about positions 3 and 4 would be generated in the final cyclization steps (*i.e.*, **3** → **4** and **7** → **8**). In each instance only a single isomer was isolated, although traces of the second isomer were apparent in pmr spectra of the crude reaction product. The deshielding which occurs in the case of the 4-C**H**$_3$ signal may be

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(1) N. B. Eddy and E. L. May "Synthetic Analgesics, Part IIB, 6,7-Benzomorphans," Pergamon Press, London, 1966, pp 138 ff.
(2) E. L. May and N. B. Eddy, *J. Med. Chem.*, **9**, 851 (1966).
(3) J. H. Ager, A. E. Jacobson, and E. L. May, *ibid.*, **12**, 288 (1969).
(4) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *ibid.*, **7**, 123 (1964).
(5) M. Gates and T. A. Montzka, *ibid.*, **7**, 127 (1964).
(6) K. Kanematsu, R. T. Parfitt, A. E. Jacobson, J. H. Ager, and E. L. May, *J. Amer. Chem. Soc.*, **90**, 1064 (1968).
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(9) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).
(10) A. E. Jacobson and R. T. Parfitt, *ibid.*, **32**, 1894 (1967).
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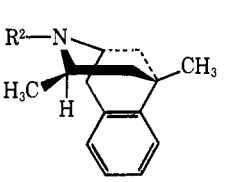
TABLE I

CHEMICAL SHIFTS (δ) OF THE 3-, 4- AND 5-CH_3 PROTONS (10% SOLUTIONS IN $CDCl_3$)

Compd	3-CH_3, d, J = 6.5 Hz	4-CH_3, d, J = 6.5 Hz	5-CH_3, s
4	0.92		1.37
8		0.60	1.36
9a	0.92		1.38
9b		0.61	1.35
10a	0.96		1.36
10b		0.60	1.35
13a	0.98		1.38
13b		0.62	1.36
14a	0.92		1.37
14b		0.60	1.35

explained by reference to Dreiding stereomodels and the Johnson–Bovey shielding map.[13] When the benzomorphan piperidine ring is in the favorable chair conformation and the 4-Me is equatorial, the latter group resides in the positive shielding cone above the plane of the aromatic ring. The 3-C**H**$_3$, on the other hand, has a normal proton resonance signal at about δ 1. This also indicates an equatorial conformation (piperidine chair), since had the group been in an axial position then it too would have overhung the aromatic ring and would have been subjected to a considerable shielding influence. In both series of congeners, therefore, the epimers isolated bear their 3- or 4-Me groups in an equatorial conformation on the piperidine chair (**15** and **16**, respectively).



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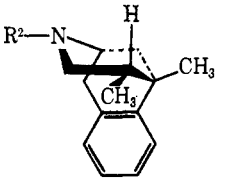

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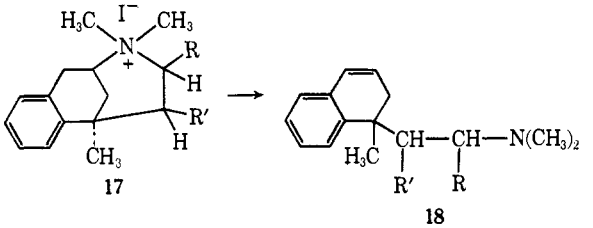
The methiodides (**17a** and **17b**) of the 6,7-benzomorphans **4** and **8** on treatment with thallous hydroxide gave Hofmann elimination products **18a** and **18b**, respectively. In its pmr spectrum the dihydronaph-



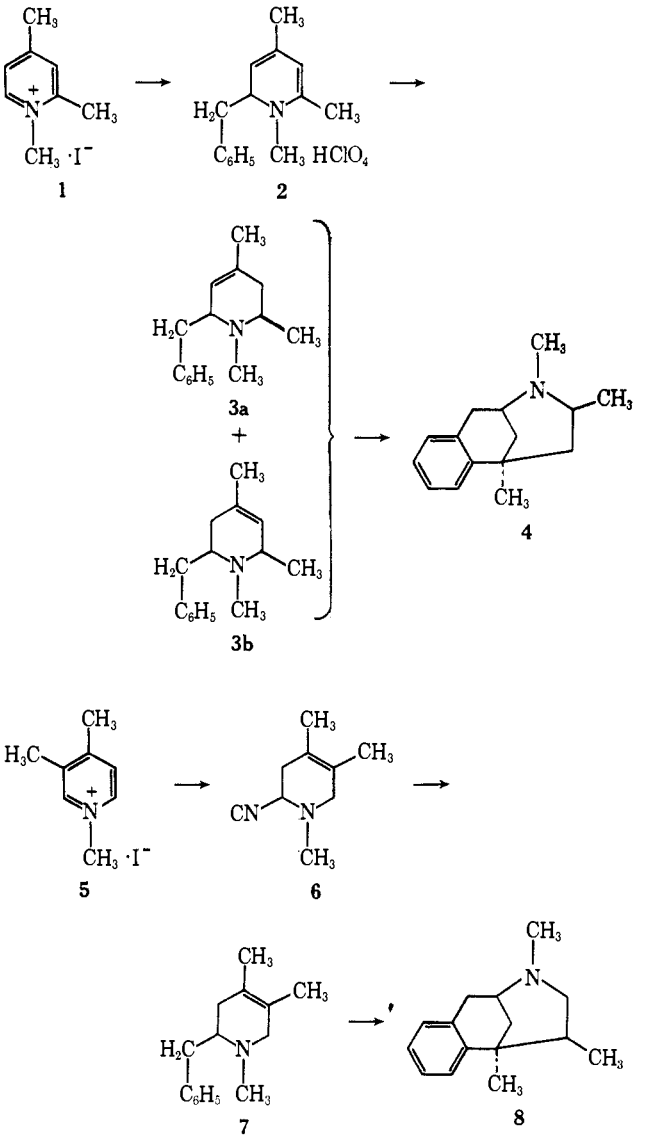
17 **18**

a, R = CH_3; R′ = H
b, R′ = CH_3; R = H

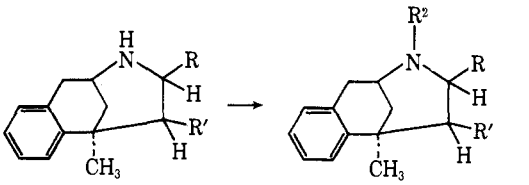
thalene **18a** shows little change in the chemical shifts of the Me groups corresponding to the benzomorphan 3-C**H**$_3$ (δ 0.95) and 5-C**H**$_3$ (δ 1.42) from those of the parent compound **4** (δ 0.92 and δ 1.37). The isomeric tetrahydronaphthalene **18b**, on the other hand, exhibits a shift of the 4-C**H**$_3$ signal from the aromatic ring-shielded position (δ 0.60) in **8** to δ 0.92 in the nonconstrained state. In both Hofmann elimination

(13) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

SCHEME I



SCHEME II



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10, $R^2 = CH_2CH{=}C(CH_3)_2$
11, $R^2 = COCH_2C_6H_5$
12, $R^2 = CO$–cyclopropyl
13, $R^2 = CH_2CH_2C_6H_5$
14, $R^2 = CH_2$–cyclopropyl

a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

products the olefinic proton shifts and coupling patterns are consistent with the structures **18a** and **18b**.

Biological Results.—2,4,5-Trimethyl-6,7-benzomorphan (**8**) hydrochloride exhibits an analgetic potency almost 3 times greater than that of the isomer **4**, in which hindrance of the tertiary N is apparent, and approximately twice that of codeine·HCl. Surpris-

ingly the phenethyl derivatives in both series (**13a** and **13b**) are without activity at subtoxic doses. Although these analogs lack a phenolic OH, significant activity was expected.

The most significant result was the high level of agonist potency, approximately 0.5 that of morphine, shown by 2-cyclopropylmethyl-3,5-dimethyl-6,7-benzomorphan (**14a**) hydrobromide. In contrast, the isomeric **14b** was inactive at subtoxic doses. No suppression of abstinence syndrome was observed when **14a** was substituted in monkeys physically dependent on morphine. It would be reasonable to expect analgesic potency to be enhanced in this series by the inclusion of a 2-phenolic hydroxyl group.

Hindrance of the tertiary N in morphine-like analgetics may have some bearing on both the level and type of analgetic activity exhibited. Further investigations of this parameter, therefore, are in progress.

TABLE II

ANALGETIC ACTIVITY OF SOME 3- AND 4-METHYL-6,7-BENZOMORPHANS

Compd	ED_{50},[a] mg/kg, sc
4·HBr	11.9
8·HCl	4.2
10a·HCl	*b*
10b·HCl	19.2
13a·HBr	*c*
13b·HCl	*c*
14a·HBr	2.2
14b·HCl	*b*
Morphine·HCl	1.2
Codeine·HCl	7.5

[a] The compds were tested for analgetic activity by the Eddy–Leimbach (C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958)) mouse hot-plate procedure employing Caesarian Derived General Purpose (CDCP) mice (N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953)). The hot-plate test is a nonspecific screen for analgesia and it is possible that antagonist agents may exhibit activity by virtue of muscle relaxant properties. Further testing is planned by a modified Nilsen procedure (P. Nilsen, *Acta Pharmacol. Toxicol.*, **18**, 10 (1961); G. C. Holsky, J. A. Richman, C. D. Lunsford, H. Jenkins, R. P. Mays, W. H. Funderburk, and D. N. Johnson, *J. Med. Chem.*, **71**, 472 (1968); E. L. May, personal communication). [b] Inactive at subtoxic dose <50 mg/kg. [c] Inactive at subtoxic dose <100 mg/kg.

Experimental Section

Melting points were obtained on a Reichert apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer 157 spectrophotometer (s = strong, m = medium, w = weak). Uv spectra were recorded on a Unicam SP800 spectrophotometer and pmr spectra on a Perkin-Elmer Model R-12 (60 MHz, TMS at δ 0.0 ppm as internal standard) with $CDCl_3$ as solvent unless otherwise indicated (s = singlet, d = doublet, m = multiplet). Mass spectra data were obtained on an AEI MS902 double-focussing spectrometer at 80 eV. Spectral data were consistent with the structures assigned.

2-Benzyl-1,4,6-trimethyl-1,2-dihydropyridine Perchlorate (2).—To a stirred ice-cooled suspension of 1,2,4-trimethylpyridinium iodide (54.4 g) in anhyd Et_2O (200 ml) was added $C_6H_5CH_2MgCl$ (from 55.2 g of $C_6H_5CH_2Cl$) in Et_2O (200 ml) during 20 min. The mixt was stirred at 0° for 2 hr and then added to a mixt of 72% $HClO_4$ (88 ml) and crushed ice (400 g) to give a 3-phase mixt. The center layer crystd on scratching and the product (37.5 g) was collected after 30 min. The center layer was sepd, washed 3 times with petr ether (bp 40–60°), and left to stand overnight at −15° under fresh petr ether, to give a further 4 g of **2**. Repeating this process yielded a further 9.4 g of product. The aq layer gave 0.4 g of product on standing making the total yield of **2**, 51.4 g (75%). It was recrystd from MeOH as colorless plates, mp 165–168°. *Anal.* ($C_{15}H_{20}ClNO_4$) C, H, N.

2-Benzyl-1,4,6-trimethyl-1,2,3,6-tetrahydropyridine (3b) and -1,2,5,6-tetrahydropyridine (3a).—To a stirred suspension of **2** (30.7 g) in a mixt of MeOH (92 ml) and aq 1 *N* NaOH (272 ml) was added $NaBH_4$ (5 g) during 20 min. The stirred mixt was maintained at 55–60° for 30 min, dild with H_2O (200 ml), and extd with Et_2O (4 × 200 ml). The exts were dried (Na_2SO_4), and the solvent was removed to give 17.9 g of product.† The mixed isomers were cyclized without sepn.

2,3,5-Trimethyl-6,7-benzomorphan·HBr (4·HBr).—A mixt of **3a** and **3b** (17.9 g), 48% aq HBr (50 ml), and 45% HBr in AcOH (30 ml) was heated under reflux for 48 hr. The cooled soln was basified with NH_4OH and extd with Et_2O (3 × 100 ml). The Et_2O soln was extd with 2 *N* HCl (3 × 100 ml), and the combined acid soln was basified with NH_4OH. Extn with Et_2O (3 × 100 ml) followed by evapn of the dried (Na_2SO_4) exts afforded crude **4** (16.8 g, 94%). Distn over a short path [88° (1.2 mm)] gave pure **4** base (12.3 g, 73%). The hydrobromide sepd as colorless plates from EtOH–Et_2O and had mp 180–182°. *Anal.* ($C_{15}H_{22}BrN$) C, H, N. The methiodide was prepd in dry Me_2CO and pptd by the addn of anhyd Et_2O. Recrystn from EtOH gave **17a** (56%) as colorless plates, mp 264–265.5. *Anal.* ($C_{16}H_{24}IN$) C, H, N.

1-Methyl-1-(2-dimethylaminopropyl)-1,2-dihydronaphthalene·HBr (18a·HBr).—To a soln of the methiodide **17a** (0.11 g) in H_2O (5 ml) was added 0.1 *M* thallous hydroxide soln until pptn ceased. The suspension was refluxed for 30 min and filtered, and the filtrate was evapd to dryness *in vacuo*. Distn of the residue at 105° (0.25 mm) gave 25 mg (36%) of **18a**. The **hydrobromide** crystd as colorless needles from EtOH–Et_2O, mp 172–173°. *Anal.* ($C_{16}H_{24}BrN$) C, H, N.

2-Benzyl-1,4,5-trimethyl-1,2,3,6-tetrahydropyridine·HBr (7·HBr).‡—To a stirred dry soln of 2-cyano-1,4,5-trimethyl-1,2,3,6-tetrahydropyridine[12] (3.9 g) in Et_2O (40 ml) was added $PhCH_2MgCl$ (from 10.0 g of $PhCH_2Cl$) in Et_2O (60 ml). After 2 hr the mixt was quenched with ice (50 g), the Et_2O layer was sepd, and the aq phase was washed with Et_2O (3 × 20 ml). The combined Et_2O soln was extd with aq 2 *N* HCl (3 × 100 ml), and the acid exts were basified (NH_4OH) and extd into Et_2O (3 × 100 ml). Evapn of the dried (Na_2SO_4) ethereal soln gave **7** (2.96 g, 66%) which was purified by short-path distn [90° (0.2 mm)]. The hydrobromide crystd as plates from EtOH–Et_2O, mp 151–154°. *Anal.* ($C_{15}H_{22}BrN$) C, H, N.

2,4,5-Trimethyl-6,7-benzomorphan·HCl (8·HCl).§—The base **7** (17.1 g) was heated in boiling aq 48% HBr (200 ml) for 30 hr. The cooled mixt, basified with NH_4OH, was extd with Et_2O (3 × 150 ml), the Et_2O soln was extd with 2 *N* HCl (3 × 100 ml), and the combined acid exts were basified (NH_4OH). Ether extn (3 × 100 ml) followed by evapn of the dried (Na_2SO_4) exts gave crude product (15.4 g, 90%). Distn over a short path gave the pure 6,7-benzomorphan base (14.0 g).# The hydrochloride crystd as colorless plates from EtOH–Et_2O and had mp 188°. *Anal.* ($C_{15}H_{22}ClN$) C, H, N. The methiodide (**17b**) was prepd in dry Me_2CO and pptd by the addn of anhyd Et_2O. It was recrystd as colorless prisms from EtOH–Et_2O and had mp 172–173°. *Anal.* ($C_{16}H_{24}IN$) C, H, N.

1-Methyl-1-(1-methyl-2-dimethylamino)ethyl-1,2-dihydronaphthalene·HCl (18b·HCl).—Hofmann elimination was performed by the method described for **17a**. The methiodide **17b** (0.3 g) gave 0.122 g (63%) of the dihydronaphthalene **18b**. The **hydrochloride** crystd as colorless needles from EtOH–Et_2O, mp 189–192°. *Anal.* ($C_{16}H_{24}ClN$) C, H, N.

3,5-Dimethyl-6,7-benzomorphan·HBr (9a·HBr).—To a stirred, ice-cooled soln of CNBr (0.5 g) in dry $CHCl_3$ was added 2,3,5-trimethyl-6,7-benzomorphan (0.74 g) in $CHCl_3$ (20 ml) during 5 min. The mixt was stirred for 1 hr and then heated under reflux for 2 hr. The solvent was evapd, and the residue was treated with a mixt of H_2O (10 ml) and Et_2O (10 ml). The combined Et_2O layer and Et_2O washings (2 × 10 ml) of the aq

† See the discussion section. The isomers proved very difficult to isolate in a pure state, but it was clear that they would both cyclize to an identical product.

‡ Although referred to previously[11] the preparation of this compound has not been described.

§ Although referred to previously,[11] this 6,7-benzomorphan has neither been isolated in a pure state nor characterized.

See discussion.

layer were washed successively with H_2O (2 × 20 ml), 2 *N* HCl (2 × 20 ml), and 10% aq Na_2CO_3 (2 × 20 ml) and dried (Na_2SO_4).

Removal of solvent gave the oily 2-nitrile (0.67 g, 87%), which recrystd as colorless needles, mp 104–108°, from Me_2CO–Et_2O: ν_{max}^{Nujol} 2200 cm^{-1} (s) CN; P^+, *m/e* 226.146668 ($C_{15}H_{18}N_2$).

A soln of the nitrile (0.205 g) in 6% HCl (20 ml) was heated under reflux for 18 hr. The cooled soln was basified (NH_4OH) and extd with Et_2O (3 × 20 ml), and the Et_2O soln in turn was extd wih 2 *N* HCl (3 × 20 ml).

Basification (NH_4OH) of the acid soln followed by Et_2O (3 × 20 ml) extn, gave on evapn of the dried (Na_2SO_4) soln **9a**·base (0.14 g, 78%).** **3,5-Dimethyl-6,7-benzomorphan·HBr** crystd as prisms from EtOH–Et_2O and had mp 228–230°. *Anal.* ($C_{14}H_{20}BrN$) C, H, N.

4,5-Dimethyl-6,7-benzomorphan·HCl (9b·HCl).—By the method described above the base **8** (13.1 g) and CNBr (16.8 g) gave a cryst (plates) *N*-nitrile (8.3 g, 60%): ν_{max}^{film} 2200 cm^{-1} (s) CN; P^+, *m/e* 226,146887 ($C_{15}H_{18}N_2$). Hydrolysis of the nitrile (8.3 g) by aq 6% HCl (500 ml) gave 4,5-dimethyl-6,7-benzomorphan (4.36 g, 59%). The hydrochloride was recrystd from EtOH–Et_2O as colorless prisms, mp 215–219°. *Anal.* ($C_{14}H_{20}ClN$) C, H, N.

2-Cyclopropylmethyl-3,5-dimethyl-6,7-benzomorphan·HBr (14a·HBr).—To a soln of 3,5-dimethyl-6,7-benzomorphan (0.64 g) in a mixt of CH_2Cl_2 (35 ml) and Et_3N (6.0 ml) was added cyclopropanecarbonyl chloride (2.0 g). The mixt was refluxed for 12 hr, cooled, and washed successively with 2 *N* HCl (3 × 20 ml) and H_2O (3 × 20 ml). The CH_2Cl_2 soln was dried (K_2CO_3) and evapd to yield the cryst amide **12a** (0.336 g, 42%).

A dry Et_2O soln of **12a** (0.336 g, 20 ml) was added dropwise to a stirred suspension of LAH (1.0 g) in Et_2O. The mixt was refluxed for 6 hr, cooled, and quenched with H_2O. The Et_2O phase was decanted and the inorg gel washed with Et_2O (3 × 20 ml). The dried (Na_2SO_4) Et_2O solns gave, on evapn, the base **14a** (3.4 g, 79%) which solidified. The hydrobromide recrystd on colorless plates, mp 187–188°, from EtOH–Et_2O. *Anal.* ($C_{18}H_{26}BrN$) C, H, N.

2-Cyclopropylmethyl-4,5-dimethyl-6,7-benzomorphan·HCl (14b·HCl).—By the method described for **14a**, 4,5-dimethyl-6,7-benzomorphan (0.316 g) afforded **14b**·base (0.208 g, 52%). The HCl salt was recrystd from EtOH–Et_2O as colorless plates, mp 202–204°. *Anal.* ($C_{18}H_{26}ClN$) C, H, N.

2-Phenethyl-3,5-dimethyl-6,7-benzomorphan·HBr (13a·HBr).—Phenylacetyl chloride (0.5 ml) in MeOH (2 ml) was added, during 5 min, to a stirred suspension of **9a** (0.51 g) in a mixt of K_2CO_3 (0.5 g), MeOH (8 ml), and H_2O (3 ml). The mixt was stirred for 4 hr and was then extd with Et_2O (4 × 20 ml). The exts were washed successively with 2 *N* HCl (2 × 20 ml) and 10% aq $NaHCO_3$ (2 × 20 ml) and dried (Na_2SO_4), and the solvent was evapd to give the intermediate amide.

The crude amide in dry Et_2O (45 ml) was added dropwise to a stirred suspension of LAH (1.0 g) in Et_2O (20 ml), and the mixt was refluxed for 6 hr. Excess LAH was destroyed by the addn of H_2O, and the ethereal supernatant was decanted. The Et_2O soln together with Et_2O washings (3 × 20 ml) of the inorganic residue was extd with 2 *N* HCl (3 × 50 ml), the exts were basified (0.88 ammonia) and extd with Et_2O (3 × 50 ml). Evapn of the dried (Na_2SO_4) ethereal soln afforded the *N*-phenethylbenzomorphan (0.52 g, 68%). The **hydrobromide hemihydrate** recrystd as colorless plates, mp 134–137°, from EtOH–Et_2O. *Anal.* ($C_{22}H_{28}BrN \cdot 0.5H_2O$) C, H, N.

2-Phenethyl-4,5-dimethyl-6,7-benzomorphan·HCl (13b·HCl).—Prepd by the method described for **13a**, **9b** (0.25 g) gave 2-phenethyl-4,5-dimethyl-6,7-benzomorphan (0.295 g, 79%). The **hydrochloride** recrystd as colorless plates, mp 229–231°. *Anal.* ($C_{22}H_{28}ClN$) C, H, N.

2-(2-Methyl-3-butenyl)-3,5-dimethyl-6,7-benzomorphan·HCl (10a·HCl).—To a stirred suspension of **9a** (0.324 g) and NaHCO (0.5 g) in DMF (15 ml) was added 1-bromo-3-methylbut-2-ene (0.24 g) and the mixt was heated under reflux for 8 hr, cooled, and filtered. The filtrate, plus EtOH washings, was evapd to dryness, and the residue was dissolved in Et_2O, filtered, and extd with 2 *N* HCl (3 × 20 ml). Basification (NH_4OH) of the exts followed by Et_2O extn (3 × 20 ml), gave on evapn of dried (Na_2SO_4) soln, 0.294 g (68%) of the benzomorphan base **10a**. The hydrochloride was recrystd from EtOAc–petr ether (bp 40–60°) as prisms, mp 183–185°. *Anal.* ($C_{19}H_{25}ClN$) C, H, N.

2-(2-Methyl-3-butenyl)-4,5-dimethyl-6,7-benzomorphan·HCl (10b·HCl).—By the method described for **10a**, **9b** (0.415 g) and 1-bromo-3-methylbut-2-ene (0.30 g) yielded 0.407 g (73%) of **10b**·base. The **hydrochloride** was recrystd from EtOH–Et_2O–petr ether (bp 40–60°) as colorless plates, mp 178–179°. *Anal.* ($C_{19}H_{25}ClN$) C, H, N.

** It was sometimes necessary to distil the base over a short path [70° (0.7 mm)] before converting it to the HBr salt.

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Vitamin B_6 Analogs. 4. 4-Desoxyisopyridoxal and the Phosphonic Acid Analog of 4-Desoxypyridoxine Phosphate[1,2]

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The phosphonic acid analogs II and III of 4-desoxypyridoxine phosphate and pyridoxine phosphate were synthesized from 4-desoxyisopyridoxal (IV) and pyridoxal, respectively, by means of the modified Wittig reaction. 4-Desoxyisopyridoxal (IV) and its 3-acetyl derivative XVI exhibited antivitamin B_6 activity against *Saccharomyces carlsbergensis* and cytotoxicity against human epidermoid cells in culture. No antileukemic activity was observed for the phosphonic acid analogs II and III or 4-desoxyisopyridoxal (IV) against mouse leukemia L1210.

4-Desoxypyridoxine (I) has been shown to be an inhibitor of several types of tumors in animals maintained on a vitamin B_6 deficient diet. After phosphorylation the vitamin analog I can serve as a substrate for enzymes that use pyridoxal phosphate as a cofactor.[3] Because I shows only weak competitive inhibition, as shown by the fact that a deficient diet is necessary for *in vivo* activity, we are engaged in a program of synthesis of analogs of I that might be effective antineoplastic agents on a complete diet.

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