Azabicyclo Chemistry. I. Synthesis of 1,5-Methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepines. B-Norbenzomorphans

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1,5-Methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (**10**) and its N-methyl derivative (**11**) (B-norbenzomorphans) have been synthesized from 5-methoxyindan-1-one-3-acetic acid (**4**) *via* the oxime **6**, which was converted to the amino acid **8**. Cyclization was effected by carbodiimides to the lactam **9**, which was reduced to **10**, N-methylation of which gave **11**. Both **10** and **11** have analgetic activity, the former, half that of codeine, and **11** was found to be comparable to codeine.

The marked analgetic activity of a 6,7-benzomorphan without a quaternary carbon[1] prompted the synthesis of the homologous B-norbenzomorphans, a new heterocyclic ring system. The B-norbenzomorphans superficially resemble 6,7-benzomorphans. However, superimposition of their aromatic rings (Dreiding molecular models) indicates a major spatial foreshortening of the distance between the nitrogen and oxygen atoms. The B-norbenzomorphans are considerably less bulky, although the configurations of the two types of molecules are somewhat similar.[2] Assuming equivalent transport of both (by *a priori* assumption of similar electronic and lipophilic character) to a receptor site, we were interested in seeing whether binding to this site could be effected by the sterically dissimilar B-norbenzomorphans, ascertainable through determination of of analgetic activity.[3]

Chemistry.—A route to the 1,5-methanotetrahydro-2-benzazepines was chosen which would provide the lactam **9** as an intermediate (desired for other purposes), the reduction of which would give a secondary amine base which could presumably be substituted *ad libitum*.

The starting material, 5-methoxyindan-1-one-3-acetic acid (**4**), was prepared by known procedures.[4] The keto acid **4** was esterified and converted to its oxime **6** (Scheme I). Although an isomeric mixture of oximes would be anticipated, no attempt was made to separate them, the entire product being hydrogenated (1 g of 10% Pd–C in MeOH acidified with HCl gas/1.5 g of oxime) to methyl 1-amino-5-methoxyindan-3-acetate hydrochloride (**7**). Lesser amounts of catalyst or different solvent systems (or different catalysts) gave incomplete reduction of the oxime. Simply heating the amino ester **7** to solution in dilute HCl hydrolyzed the ester to give 1-amino-5-methoxyindan-3-acetic acid hydrochloride (**8**), fortuitously insoluble in the cold acidic solution.

Cyclization of the amino acid **8**[5] to the desired lactam **9** was achieved, finally, by use of carbodiimides.[7] 1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluene sulfonate[6] was found to be the reagent of choice for the condensation; the urea coproduct was water soluble and could easily be removed. Yields of about 50% of recrystallized 1,5-methano-3-oxo-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (**9**) were consistently obtained. The lactam **9** was easily reduced with diborane to 1,5-methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (**10**); LAH gave inferior yields. The over-all yield of amine **10** from **4** was about 20%.

Methylation of **10** in CH_2O–formic acid gave 1,5-methano-7-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine, from which the hydrochloride salt **11** was prepared.

Biological Results.—Compounds **10** and **11**[8] are more active than 2′-methoxy-2-methyl-6,7-benzomorphan (Table I) and, more noteworthy, **11** is as active as α-2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan or its levo isomer.

Conclusion.—The 1,5-methanotetrahydro-2-benzazepines are analgetically active compounds, more so than the comparable 6,7-benzomorphans. Thus, the considerable steric change from the 6,7-benzomorphans to the B-norbenzomorphan molecule may enhance analgetic activity and by inference, drug–receptor interaction, even though the B-norbenzomorphans lack both a "central" carbon atom and a free benzylic group, the former occurring in almost all of the known analgetics which have morphine-like activity.

The determination of the dependence liability of **11** and the synthesis of 7-hydroxy analogs of various N-

(1) K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 405 (1969).

(2) It should be noted that the N atom is directly attached to the benzylic carbon in the B-norbenzomorphans; the 6,7-benzomorphans have a free benzylic group. Also, there is no "central" carbon atom. (E. L. May in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 335).

(3) L. Grumbach and H. I. Chernov, *J. Pharmacol. Exp. Ther.*, **149**, 385 (1965).

(4) D. H. Hey and D. H. Kohn, *J. Chem. Soc.*, 3177 (1949). The Friedel–Craft procedure was modified, as noted in the Experimental Section. An alternative procedure (PCl_5 to form the acid chloride and anhydrous $SnCl_4$ for ring closure) gave a mixture from which **4** and the isomeric 7-methoxyindan-1-one-3-acetic acid [mp 192.5–195°; *m/e* 220 (M^+), 175 (base); λ_{max}^{Nujol} 1724, 1678 cm^{-1}; λ_{max}^{EtOH} 219, 256, 312 mμ (ε 17,200, 10,200, 4300)] was obtained.

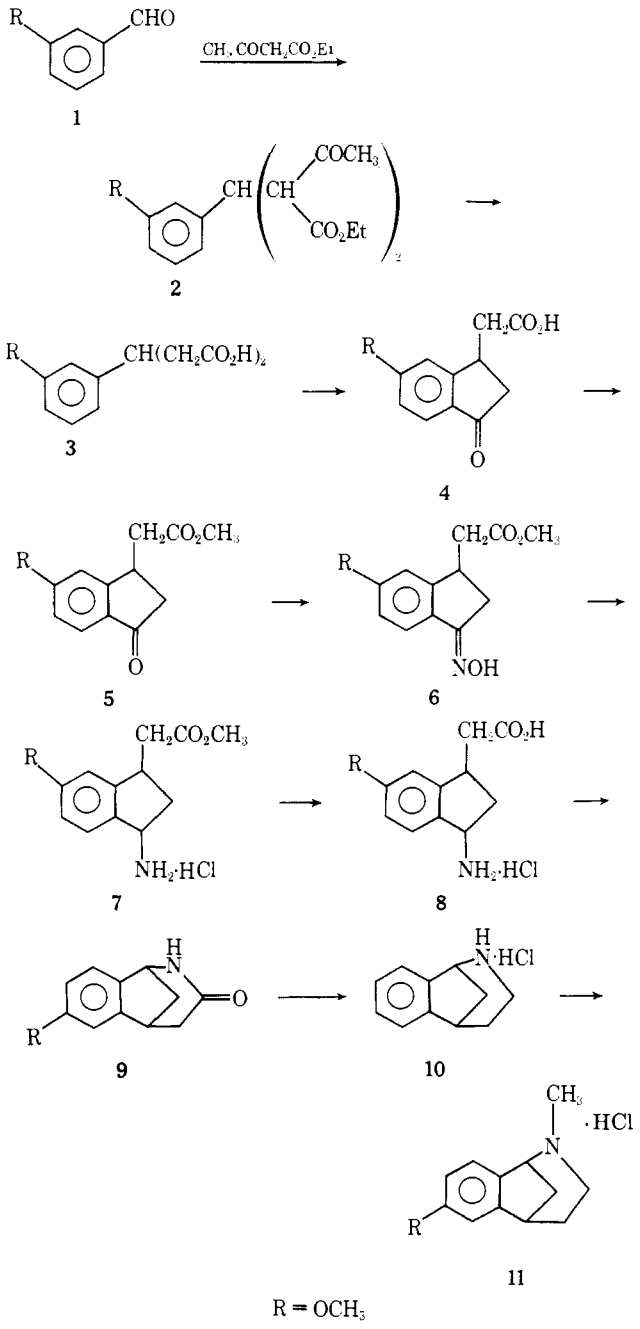
(5) Attempted condensation of **8** in polyphosphoric acid, trifluoroacetic anhydride, or with N-ethyl-5-phenylisoxazolium 3′-sulfonate[6] (see R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron, Suppl.*, **8**, 321 (1966)) gave little or no lactam. Heating of **7** or **8** (as the base) in a sealed tube at various temperatures gave poor yields of lactam.

(6) Aldrich Chemical Co., Milwaukee, Wis.

(7) Dicyclohexylcarbodiimide in various solvents (CH_2Cl_2, THF, $CHCl_3$, etc.) was also satisfactory for the condensation of **8**. Pyridine proved to be the best medium, obviating the addition of a tertiary base, Et_3N. Unfortunately, dicyclohexylurea, the coproduct in the reaction, was extremely difficult to separate from **9**.

(8) The 2′-hydroxy analogs of the 6,7-benzomorphans invariably display increased analgetic activity when compared with their 2′-methoxy counterparts. Thus, the meperidine-like **11**, a methoxy analog, shows considerable promise.

SCHEME I



alkylated B-norbenzomorphans is in progress and will be the subject of a future report.

Experimental Section[9]

5-Methoxyindan-1-one-3-acetic Acid (4).—Ethyl *m*-methoxybenzylidenebisacetoacetate (**2**) was prepared from **1** and hydrolyzed to *β-m*-methoxyphenylglutaric acid[4] (**3**, 60% from **1**): mp 129–129.5° (lit.[4] 126–126.5°, 58%); nmr ir spectra as expected,[9] *m/e* 238 (M^+), 91 (base).

The diacid **3** was converted to its acid chloride in oxalyl chloride and cyclized with $AlCl_3$ in CH_2Cl_2 solution ($AlCl_3$ addition at 0°, followed by stirring 2 hr at 25°) to the keto acid **4** (56%): mp 148.5–150 (lit.[4] 151); λ_{max}^{Nujol} 1725 (CO_2H) and 1675 (Ar C=O) cm^{-1}; λ_{max}^{EtOH} 224, 268, 287 and 294 mμ (ε 13,260, 14,660, 10,430, and 10,150); *m/e* 220 (M^+), 175 (base).

Methyl 5-Methoxy-1-oximinoindan-3-acetate (6).—Keto acid **4** (22.7 g) was esterified in MeOH (120 ml) containing H_2SO_4 (4 ml) to give an oil, methyl 5-methoxyindan-1-one-3-acetate (**5**, 24.5 g); for spectra, see ref 9. *Anal.* ($C_{13}H_{14}O_4$) C, H.

The keto ester (**5**, 69.4 g) was dissolved in EtOH (225 ml), and H_2O (300 ml), $HONH_2 \cdot HCl$ (26.3 g), and $NaOAc \cdot 3H_2O$ (51 g) were added. The mixture was refluxed (3 hr) to give, after cooling, the oxime **6** (66.5 g, 90%), mp 120–121.5° (recrystallized in EtOH). For spectra, see ref 9. *Anal.* ($C_{13}H_{15}NO_4$) C, H, N.

Methyl 1-Amino-5-methoxyindan-3-acetate Hydrochloride (7).—Oximinoester **6** (25 g) was dissolved in MeOH (250 ml), acidified with HCl gas, and hydrogenated over Pd–C (10%, 17 g). Removal of solvent *in vacuo* left a yellow solid which was washed with acetone[10] until the color was removed to give the amino ester hydrochloride (**7**, 23.1 g), mp 204.5–206° (sublim) (recrystallized from a MeOH–Me_2CO mixture). Glpc of **7** indicated a single compound (1.36 min, 177°; 6.54 min, 177°[11]). *Anal.* ($C_{13}H_{18}ClNO_3$) C, H.

1-Amino-5-methoxyindan-3-acetic Acid Hydrochloride (8).—The amino ester hydrochloride (**7**, 23.1 g) was stirred and heated (90°, 3 hr) in 12% HCl (600 ml). The amino acid hydrochloride **8** crystallized in the cooled solution. The solid was filtered, washed with H_2O, and dried *in vacuo* to give **8** (20.0 g, 81%[10] from **6**), mp 208–209°. *Anal.* ($C_{12}H_{16}ClNO_3$) C, H.

1,5-Methano-7-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine (9).—Compound **8** (6.87 g) was dissolved in pyridine (1 l.) and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[8] (12 g) was added. The yellow, cloudy mixture was stirred for 5.5 days (25°).[12] The solvent was removed *in vacuo* and a mixture of CH_2Cl_2 (100 ml) and H_2O (50 ml) were added. The aqueous solution was extracted with CH_2Cl_2. AcOH (4 ml) was added to the combined organic extracts and the mixture was stirred (0.5 hr, 25°) and washed successively with H_2O, 12% HCl, H_2O, 5% NaOH (which removed the bright yellow color), and H_2O. The aqueous solutions were reextracted with CH_2Cl_2 and the combined, pale yellow, organic solution (~300 ml) was dried ($MgSO_4$). Filtration and removal of solvent *in vacuo* gave an off-white solid (2.85 g). The solid was dissolved in Me_2CO (~150 ml) and filtered to remove some insoluble material, and the solution was concentrated (to ~40 ml) to give, after cooling, white crystals of lactam **9** (2.5 g, 47%): mp 187.5–188°; $\lambda_{max}^{CHCl_3}$ 3410 (s), 1658 (s) (1675 sh m) cm^{-1}; λ_{max}^{Nujol} 3285 (m), 1659 (m), 1620 (s), 1588 (m) cm^{-1}; δ 2.2 (2 H, m, C-10), 2.63 (2 H, m, C-4), 3.4 (1 H, m, C-5), 3.80 (3 H, s, OCH_3), 4.4 (1 H, m, C-1), 6.57–7.32 (3 H, m, aromatic), 7.68 (1 H, m, N–H); *m/e* 203 (M^+ and base); glpc 2.96 min (180°). *Anal.* ($C_{12}H_{13}NO_2$) C, H, N.

TABLE I

ANALGETIC ACTIVITY OF B-NORBENZOMORPHANS

Compd	ED_{50}, mg/kg
7-Methoxy-B-norbenzomorphan (**10**)	14.7
7-Methoxy-2-methyl-B-norbenzomorphan (**11**)	8.1
2′-Methoxy-2-methyl-6,7-benzomorphan[a]	*b*
α-2′-Methoxy-2,5,9-trimethyl-6,7-benzomorphan[c]	9.8
α-(−)-2′-Methoxy-2,5,9-trimethyl-6,7-benzomorphan[c]	8.7
Codeine	7.5

[a] See ref 1. The figures 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 (<20 mg/kg). [c] E. L. May and L. J. Sargent in "Analgetics," G. deStevens, Ed., Academic Press, New York–London, 1965, Chapter IV.

(9) Elemental analyses, performed by the Section on Instrumentation, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, W. C. Alford, Chief, were within ±0.4% of the theoretical values. Melting points were obtained on a Fisher-Johns apparatus. Ir were determined on a Perkin-Elmer 237 or 257 grating spectrophotometer (±6 cm^{-1}) (s = strong, m = medium, w = weak, sh = shoulder), mass spectral data on an Hitachi RMU-6E double-focusing spectrometer at 80 eV, and nmr on a Varian A-60 (60 MHz, TMS at δ 0.0 ppm as internal standard, $CDCl_3$ as solvent unless otherwise specified (s = singlet, m = multiplet)). Ir and nmr spectra are reported only if they were not as expected. Glpc were obtained isothermally at a flow rate of 50 ml/min on an SE 30 (Chromosorb WAW) (unless otherwise specified) glass column (0.915 m, 6.3-mm diameter) with detection by flame ionization.

(10) A yellow solid was obtained from the acetone washings and found to be mostly amino acid hydrochloride **8**, presumably formed by hydrolysis in the acidic medium during reduction. The solid was completely converted to **8** (0.8 g) by warming (steam bath) in 12% HCl.

(11) Glass column (1.83 m, 6.3-mm diameter) containing 3% QF-1 on Chromosorb P.

(12) The cloudy yellow mixture became a clear yellow solution after stirring for 1–2 days and, soon after, quite cloudy again.

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).