Experimental Section

Melting points were determined on a Fisher-Johns apparatus; uv spectra were recorded on a Cary Model 14 spectrophotometer. Optical rotations are equilibrium values and were determined on a Perkin-Elmer Model 141 polarimeter at 0.5 *M* concentration in methanol. Solvent concentration was conducted under reduced pressure in a rotary evaporator. Satisfactory analytical results (C, H, N, and S within 0.4% of the theoretical values) were obtained from Robertson Laboratory, Florham Park, N.J.

Preparation of the Protected Anomeric Nucleosides IIa–e. Pyrimidine bases were converted to their trimethylsilyl derivatives by treatment with boiling hexamethyldisilazane[5] in the presence of a catalytic amount of trimethylchlorosilane. The excess of hexamethyldisilazane was removed by repeated coevaporation with dry toluene (three times), and the remaining crude trimethylsilyl ethers were used immediately in the next step. A mixture of 0.01 mol of 2,3,5-tri-*O*-acetyl-4-thio-D-ribofuranosyl chloride,[15] 0.011 mol of the 2,4-bis(*O*-trimethylsilyl) derivative of uracil[16] (Ia) or of Ib–e,[17] and 0.01 mol of mercuric acetate in 100 ml of dry toluene was stirred at 95–100° for 2 days. The mixture was cooled to 22° and was concentrated to a syrup, which was dissolved in EtOAc (150 ml). The solution was washed successively with a 20% KI solution (2 × 80 ml) and with H_2O (100 ml), dried (Na_2SO_4), and evaporated to a syrup. The syrupy residue was purified by column chromatography on silica gel in a C_6H_6–Me_2CO (8:1, v/v) mixture. The anomeric mixtures of the nucleosides IIa–e were obtained after evaporation of the solvent as glassy residues. The yields were as follows: IIa = 42%, IIb = 48%, IIc = 35%, IId = 60%, and IIe = 27%.

Preparation of the Nucleosides IIIa–e and IVa–e. The syrupy mixtures of the α and β anomers of the acetylated nucleosides IIa–e (0.005 mol) were dissolved in 50-ml portions of dry MeOH. NaOMe (100 mg) was added, and the solutions were kept at 22° for 15 hr. Dowex-50 (H^+) ion exchange resin (3 ml) was added, the mixtures were filtered, and the resin was washed with MeOH (40 ml). Each combined filtrate was concentrated to a syrup, which was dissolved in 95% EtOH (50 ml), and the resulting solution was evaporated to a syrup. The syrupy residue was dissolved in 95% EtOH (5 ml), and the solution kept at 22° for 15 hr. The crystalline compounds IVa–e were collected by filtration, washed with cold EtOH (2 ml), and recrystallized. The mother liquors were combined with the respective washings and concentrated to approximately 2 ml. The solutions were applied to 2 × 60 cm columns of dry silica gel, and these compounds were eluted with $CHCl_3$–MeOH (6:1, v/v). The α anomers eluted from the columns first and they, as well as the β anomers, crystallized after evaporation of the solvent and were recrystallized. The ratio of α:β anomers obtained by this procedure was approximately 1:6. Some of the pertinent physical–chemical characteristics of the newly synthesized compounds are shown in Table I.

Biological and Biochemical Assay Procedures. The techniques used for assaying the growth inhibitory activity of the analogs in the bacterial[18] and tumor cell systems,[19] and the procedures employed for isolating the fluoropyrimidine resistant strains,[20] have been published previously. The effect of the agents on RNA, DNA, and protein synthesis in *S. faecium* was determined by procedures also described previously.[18]

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Synthesis and Pharmacology of 5-Noralkyl-9β-methyl-6,7-benzomorphans and Stereochemistry of Some Intermediates

Hirozumi Inoue,† Tokuro Oh-ishi,‡ and Everette L. May*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014. *Received March 19, 1975*

2,9β-Dimethyl-2′-hydroxy-6,7-benzomorphan (**18**) has been synthesized from *m*-methoxyphenylacetone (**6a**) or *m*-methoxyphenylacetonitrile (**1**) via bromo-α-tetralone (**10**). Isomeric bromo-α-tetralone **9**, instead of undergoing cyclization to a 6,7-benzomorphan, gave aromatization product **12**. The structures and stereochemical assignments of **9**, **10** (and thus **7** and **8**), and **18** follow from analogy and from NMR data of **9**, **10**, **17**, and **18**. Compound **18** and the deoxy analog **16** are as potent as morphine and codeine, respectively, as analgetics (mice) and are without physical dependence capacity (monkeys).

Recently,[1] we reported that 2,9-dimethyl-6,7-benzomorphan (**16**), not obtainable in the usual way[2] from 3-methylpyridine, could be synthesized in 12 steps from phenylacetonitrile, only the β isomer being formed. By some modifications of this sequence we have now prepared the 2′-hydroxy relative **18**. Described below are the synthesis of **18** and the analgetic and other pharmacologic properties of **16** and **18** and two analogs, **15** and **17**.

† Visiting Associate from Tanabe Laboratories, Tokyo.
‡ Visiting Associate (1971–1973) from Tanabe Laboratories, Tokyo.

Table I. NMR Data for **9** and **10**

In C_5D_5N (220 MHz)		In D_2O (100 MHz)[a]	
C-2 H	C-3 CH_3	C-3 H[b]	C-3 CH_3
10·HBr δ 5.03 (d, $J_{2,3}$ = 7 Hz)	δ 1.17 (d, 7 Hz)	δ 2.79 (q, $J_{2,3}$ = 8 Hz, $J_{3,4}$ = 4 Hz)	δ 1.33 (d, 7 Hz)
9·HBr δ 5.40 (d, $J_{2,3}$ = 3.3 Hz)	δ 1.28 (d, 6.5 Hz)	δ 2.67 (d, $J_{3,4}$ = 6.2 Hz)	δ 1.30 (d, 6.5 Hz)

[a] Measured as quickly as possible after solution. [b] C-3 CH_3 was irradiated.

Chemistry. Alkylation of *m*-methoxyphenylacetonitrile (**1**) with $ClCH_2CH_2NMe_2$ [KOH, dimethyl sulfoxide (Me_2SO)] gave butyronitrile (**2**) in 82% yield. Methyl ketonization of **2**, via acid **3** with MeMgI or MeLi, gave the 2-pentanone **6** in low yield contrary to experience with analogs.[3] However, **6** was obtained in 64% yield by dimethylaminoethylation (Me_2SO, KOH) of *m*-methoxyphenylacetone (**6a**) similar to the results of Wilson[4] with $PhCH_2COMe$.

Reaction of **6** (which gave erratic results in the Reformatski reaction) with lithioethyl acetate, after the method of Rathke,[5] gave a quantitative yield of hydroxy ester **5**. Dehydration of **5** and catalytic reduction of the product gave a 1:1 mixture of diastereoisomers (**4**) which was hydrolyzed to the acids. These were cyclized (polyphosphoric acid, PPA) to α-tetralones **7** and **8**, which were separated by recrystallization of the HBr salts (24 and 22% yields, respectively).

Bromination of **7**, then cyclization (by internal quaternization of the resultant **10**), gave benzomorphan methobromide (**11**). Similar treatment of the bromination product (**9**) of **8** gave no benzomorphan but a 71% yield of the naphthol **12**. Expulsion of MeBr from **11** to give **14** was effected thermally (triethylene glycol, bp 180–195°).

Wolff–Kishner reduction of **14** gave (in low yield) **15** which was better prepared by catalytic hydrogenation of **14** (10% Pd/C, $HClO_4$, HOAc, 40°, 50 psi) or of the 8-hydroxy derivative **17**. Compound **17**, designated as the 8β-OH epimer ($J_{8,9}$ = 6 Hz), resulted from catalytic (Pd/C, $HClO_4$, EtOH) or $LiAlH_4$ reduction of **14**. The final product, 2,9β-dimethyl-2′-hydroxy-6,7-benzomorphan (**18**),[§] whose structure and stereochemistry have been assigned from NMR data of **18**·HBr and **17**·HCl (in D_2O) at 100 MHz (δ 1.45, 1.33, respectively, d, J = 7 Hz, C-9 Me)[6] and by analogy with **16**,[1,7] was prepared in good yield from **15** (refluxing 48% HBr) or **17** (refluxing HI-red P).

Structural and configurational designations for **7–10** are based on NMR data and cyclization behavior analogous to results obtained in the demethoxy series.[1]

The C-3 methyl of **7**·HBr showed a doublet (D_2O) at δ 1.07 (J = 7 Hz) which was shifted to 0.92 (J = 7 Hz) in **8**·HBr due to anisotropy. Irradiation of the methyl in **7** and **8** gave a doublet for the C-3 H centered at δ 2.38 and 2.40 ($J_{3,4}$ = 3.7 and 3.0 Hz), respectively; the C-2 proton was not observable in **7** or **8** because of rapid exchange with deuterium.[1] Furthermore, the cis relationship of the C-3 and C-4 protons in **7** could not be distinguished from their trans relationship in **8** because of a rapid equilibrium of each (e.g., the diaxial 3,4-protons in **8** are in equilibrium with their diequatorial counterparts).[&] However, assignments for **7** and **8** could be made retrospectively from NMR data of bromotetralones, **10** and **9**.

Evidence for a (predominantly) trans, diequatorial arrangement of the C-2 Br and C-3 Me and a cis orientation of the C-3 Me and C-4 $CH_2CH_2NMe_2$ in **10** was obtained from coupling constants ($J_{2,3}$ = 7–8 Hz, $J_{3,4}$ = 4.0 Hz). In contrast, for **9**, $J_{2,3}$ = 3.3 Hz and $J_{3,4}$ = 6.2 Hz (see Table I). Thus, **9** and **10** (and **7** and **8**) must be mostly in the conformations shown in Scheme I. Assignment of the Br in **10** as equatorial and in **9** as axial was substantiated by ir carbonyl frequencies (1682 and 1670 cm^{-1}, respectively).

As in the demethoxy series,[1] cyclization of **10** to **11** occurred readily, but **9** underwent only aromatization to **12**. Apparently **9**, with its 3(a)-H trans to the 2(a)-Br, loses HBr before it can change to a conformer amenable to cyclization.

Pharmacology. Compound **16** and the 2′-hydroxy relative **18** are comparable in analgetic activity to codeine and morphine, respectively, in both the hot-plate and Nilsen tests (subcutaneous administration of the HCl and HBr salts, respectively).[8] The ED_{50}'s of **16** were 6.5 (5.2–8.9, hot-plate) and 7.7 (4.0–14.7, Nilsen) mg/kg and those of **18** were 1.1 (0.8–1.4) mg/kg in both tests. Neither **16** nor **18** would support to any degree (at 1–8 mg/kg) morphine dependence in Rhesus monkeys. In fact **18** precipitated (at 1 mg/kg) withdrawal symptoms when substituted for morphine in dependent monkeys.[9] This is similar to behavior shown by 2′-hydroxy-2-methyl-6,7-benzomorphan, the second instance of high analgetic activity and no physical dependence capacity for rigid (morphine-like) structures not containing a quaternary carbon.[10] Methoxy compound **15** showed codeine-like activity; the 8β-hydroxy analog **17** was marginally active in mice.

Experimental Section

Melting points (Hershberg) are corrected. Ir, NMR, and mass spectra were obtained on a Perkin-Elmer 257, a Varian Model A-60A (unless otherwise noted), and a Hitachi RMU-6E (70 eV), respectively. GLC analyses were made on a Beckman GC-55 instrument (flame-ionization detectors). Analytical results are indicated only by symbols of the elements when within ±0.4% of theory.

4-Dimethylamino-2-*m*-methoxyphenylbutyronitrile (2). To 10 g (0.05 mol) of **1** in 30 ml of dry DMSO was added 3.3 g (0.05 mol) of powdered KOH (87% purity) at 10–15° (stirring, N_2 atmosphere). After 30 min, the $ClCH_2CH_2NMe_2$ generated from 10 g (0.07 mol) of HCl salt (Aldrich) in Me_2SO was added to the stirred mixture at 10°. The mixture was stirred at room temperature for 30 min and at 50–60° for 3 hr, cooled, poured into ice–H_2O, and extracted with Et_2O. The Et_2O was shaken with dilute HCl. The HCl extracts were made basic with NH_4OH and extracted with Et_2O. Drying ($MgSO_4$) and distillation of the Et_2O gave 8.5 g (82%) of **2**: bp 135–145° (0.3 mm) of 93% purity (GLC). The picrate, yellow needles from EtOH, had mp 115–118°. Anal. ($C_{19}H_{21}N_5O_8$) C, H, N.

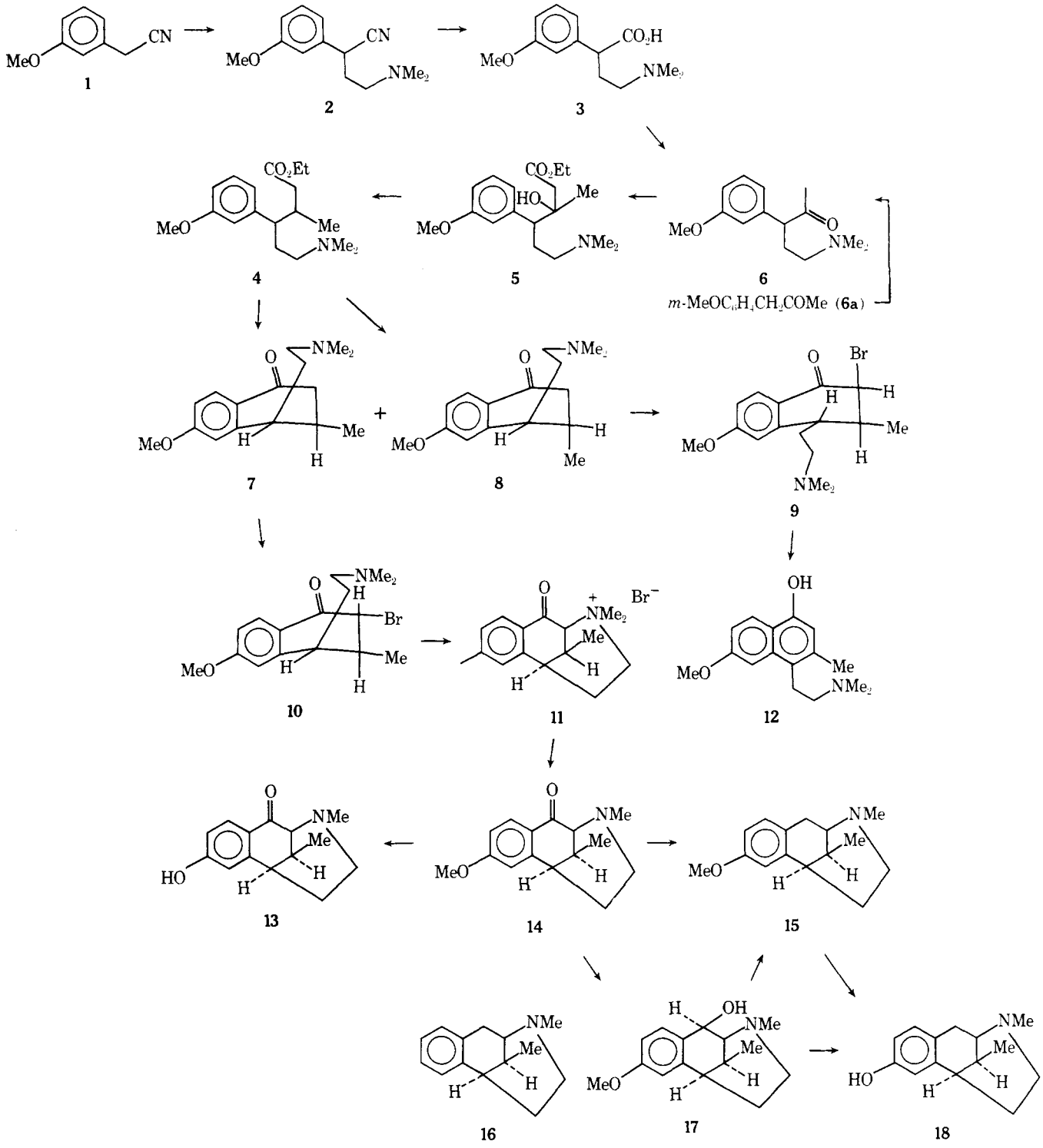
When NaH was used in place of KOH, the yield of **2** was 84%; $NaNH_2$ in C_6H_6[11] gave 29.3% of **2**.

5-Dimethylamino-3-*m*-methoxyphenyl-2-pentanone (6). (a) From 6a. Powdered KOH (0.8 g, 0.01 mol) was added to 2 g (0.01 mol) of **6a** in 7 ml of DMSO at 10–15° (stirring, N_2 atmosphere). The mixture was stirred at room temperature for 30 min and treated (at 5–15°) with $ClCH_2CH_2NMe_2$ [from 2.6 g (0.02 mol) of HCl

[§] See ref 1 for the Chemical Abstracts name. The β designation is with reference to the hydroaromatic ring.

[&] Cyclohex*enones* **7**, **8**, **9**, and **10** have quasi equatorial and axial positions compared with cyclohex*ane*.

Scheme I



salt] in 2 ml of C_6H_6. The mixture was stirred for 30 min at room temperature and for 1.5 hr at 50–60°, poured into ice–H_2O, and extracted with Et_2O. The Et_2O layer was extracted with dilute HCl. From the Et_2O, 0.5 g (28%) of **6a** was recovered. The HCl extrccts were made basic (NH_4OH) and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$), and evaporated to give 1.8 g (64%) of **6**: bp 133–140° (0.6 mm) [lit.[12] bp 110–113° (0.15 mm)].

(b) From 2. Nitrile **2** (3.2 g, 0.014 mol), 1.5 g (0.02 mol) of KOH, 15 ml of EtOH, and 15 ml of H_2O were refluxed for 60 hr. After evaporation of the EtOH in vacuo, the mixture was acidified with HOAc and extracted with 5:1 $CHCl_3$–MeOH. The extract was dried ($MgSO_4$) and evaporated to give a viscous oil which was treated with EtOAc (50 ml)–Et_2O (50 ml) to give 2.4 g (60%) of 4-dimethylamino-2-*m*-methoxyphenylbutyric acid (**3**): mp 116–119° (from EtOH–EtOAc, mp 120–122°); mass spectrum 237 (M^+), 219, 58. Anal. ($C_{13}H_{19}NO_3 \cdot 2H_2O$) C, H, N.

To a suspension of 4.9 g (0.02 mol) of **3** in 20 ml of THF was added (stirring, N_2, −10 to −30°) 150 ml of 1 *M* ethereal MeLi. The mixture was stirred at 0–5° for 2 hr, poured into ice–H_2O, and extracted with C_6H_6. The C_6H_6 was dried and evaporated to give 3.2 g of oil which was chromatographed (Al_2O_3). Elution with C_6H_6 and then C_6H_6–Et_2O (9:1) gave 1.7 g (35% from **3**) of **6** identical with that prepared as described in (a).

MeMgI (4 equiv) in Et_2O–PhMe and **3** gave a 14% yield of **6**; MeLi in Et_2O gave 13%.

Ethyl 6-Dimethylamino-4-*m*-methoxyphenyl-3-methylhexanoate (4). To 54.2 g (0.34 mol) of hexamethyldisilazane (Aldrich) in 100 ml of Et_2O (stirring, N_2 atmosphere) was added slowly 250 ml of 1.7 *M sec*-BuLi in hexane. The mixture was refluxed for 0.5 hr and evaporated to dryness. The resultant hexamethyldisilazyllithium in 315 ml of THF was treated during 10 min (stirring, N_2 atmosphere, −68 to −72°) with 32 ml (0.33 mol) of EtOAc. After

stirring for an additional 15 min, 62.9 g (0.27 mol) of **6** in 45 ml of Et_2O was added at −66 to −72° during 20 min and after 2 hr, 100 ml of H_2O was added at −70 ± 5°. The mixture was allowed to warm to room temperature and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated to give 89 g (100%) of pale-yellow, oily **ethyl 6-dimethylamino-3-hydroxy-4-*m*-methoxyphenyl-3-methylhexanoate (5)**: ir (film) 3500, 1730, 1720 cm^{-1} (sh); mass spectrum 323 (M^+), 315, 236, 58 (base); NMR ($CDCl_3$) δ 1.24 (s, 3, C-3 CH_3), 1.24 (t, J = 7 Hz, 3, CH_2CH_3), 2.20 (s, 6, NCH_3), 3.82 (s, 3, OCH_3), 4.18 (q, J = 7 Hz, OCH_2CH_3).

Carbinol **5** (104 g, 0.32 mol), 123 g (0.65 mol) of $TsOH·H_2O$, 445 ml of C_6H_6, and 955 ml of PhMe were refluxed for 64 hr with collection (Dean-Stark tube) of 19 ml of H_2O. The cooled mixture was treated with H_2O and basified with NH_4OH. The aqueous layer was extracted with C_6H_6. This extract combined with the organic layer gave 85 g of viscous red oil (olefin) which in 700 ml of MeOH was shaken under H_2 with 3.0 g of PtO_2 for 9 hr (room temperature and pressure). Filtration of the catalyst and distillation of the filtrate gave 74 g (75% based on **5**) of **4**: bp 135–150° (0.05 mm); a 1:1 mixture of diastereomers (not separable by GLC using OV-17 or SE-30 columns) as indicated by NMR data ($CDCl_3$) δ 1.21, 1.25 (2 t, J = 7 Hz for both, OCH_2CH_3), 4.07, 4.15 (2 q, J = 7 Hz for both, OCH_2CH_3), 2.13 (s, 6, NCH_3), 3.82 (s, 3, OCH_3) and two broad doublets at 0.81, 1.01 (J = 7 Hz, $>CHCH_3$); mass spectrum 307 (M^+), 262, 220, 58 (base).

***cis*-3,4-Dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone (7) Hydrobromide.** The above **4** mixture (74 g, 0.24 mol) and 760 ml of 20% HCl were refluxed for 4 hr and evaporated to dryness in vacuo. The residual acid (74 g) and 750 g of PPA were kept at 100–110° (bath temperature) for 3 hr (vigorous stirring). The cooled mixture was dissolved in water, made basic with NH_4OH, and extracted with Et_2O. The washed (H_2O) and dried ($MgSO_4$) extract gave 38 g (60%) of a mixture of **7** and **8**: bp 155–165° (0.02 mm). It was converted to the HBr salt (30% HBr–AcOH, Et_2O) which was dissolved in 30–40 ml of absolute EtOH. At room temperature, 20 g of crystals separated. They were recrystallized from EtOH to give 18.0 g of **7**·HBr: mp 204–206°; ir (Nujol) 2750–2450, 1672 cm^{-1}. Anal. $C_{16}H_{24}BrNO_2$) C, H, N.

The combined EtOH filtrates were evaporated to dryness. The residue in about 10 ml of EtOH gave **8**·HBr which when recrystallized from Me_2CO gave 15.6 g of the trans isomer **8**·HBr: mp 165–167°; ir (Nujol) 2700–2300, 1670 cm^{-1}. Anal. ($C_{16}H_{24}BrNO_2$) C, H, N. From the above combined filtrates, an additional 1.6 g of **7**·HBr (total yield 24%) and 2.6 g of **8**·HBr (total yield 22%) were obtained.

2-Bromo-2,3-*trans*-3,4-*cis*-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2*H*)-naphthalenone (10) Hydrobromide. To 19 g (0.06 mol) of **7**·HBr in 95 ml of HOAc was added (stirring, 18–20°) 9.0 g (0.06 mol) of Br_2 in 38 ml of HOAc during 10 min. After stirring for an additional 10 min, the mixture was evaporated to dryness in vacuo below 50°. The residue was treated with Me_2CO to give 20.6 g (88%) of **10**·HBr: mp 153–154°, after recrystallization from EtOH–Me_2CO–Et_2O; ir (Nujol) 2660–2400, 1682 cm^{-1}. Anal. ($C_{16}H_{23}Br_2NO_2$) C, H, N.

Similarly, the **2,3-cis-3,4-trans compound 9** was obtained from **8** in 88% yield as the HBr salt: mp 138–140° (from EtOH–Et_2O); ir (Nujol) 2660–2460, 1670 cm^{-1}. Anal. ($C_{16}H_{23}Br_2NO_2$) C, H, N.

2,9β-Dimethyl-2′-methoxy-8-oxo-6,7-benzomorphan Methobromide (11). The hydrobromide of **10** (21.2 g, 0.05 mol) was dissolved in a little H_2O and made basic with 12 M NH_4OH. The mixture was shaken with 200 ml of Et_2O in three portions. The extract was washed quickly with H_2O and evaporated to dryness in vacuo. The residue and 200 ml of Me_2CO were kept under reflux for 1 hr and at room temperature overnight to give 13.3 g (78%) of **11**, mp 215–216°, after recrystallization from 95% EtOH: NMR (D_2O) δ 1.68 (d, J = 7 Hz, 3 $CHCH_3$), 3.21 (s, 3, NCH_3), 3.56 (s, 3, NCH_3), 4.10 (s, 3, OCH_3); mass spectrum 245 ($M^+ - CH_3Br$), 230, 202, 174, 94 (base), 96 (CH_3Br). Anal. ($C_{16}H_{22}BrNO_2$) C, H, N.

4-(2-Dimethylaminoethyl)-6-methoxy-3-methyl-1-naphthol (12). As described in the preparation of **11**, 1.7 g (4.0 mmol) of **9**·HBr was converted to the free base which was kept in Me_2CO (50 ml) for 2 weeks at room temperature. The Me_2CO was evaporated and the residue partitioned between dilute NH_4OH and Et_2O. The Et_2O was washed with H_2O, dried, and evaporated to give (from 95% EtOH) 0.74 g (71%) of **12**: mp 186–188°; NMR (Me_2SO) δ 2.44 (s, 3, C-3 CH_3), 2.38 (s, 6, NCH_3), 3.97 (s, 3, OCH_3), 6.70 (s, 1, C-2 H), 7.13 (q, J = 9 and 2.5 Hz, 1, C-7 H), 7.36 (d, J = 2.5 Hz, 1, C-5 H), 8.18 (d, J = 9 Hz, 1, C-8 H). Anal. ($C_{16}H_{21}NO_2$) C, H, N.

The HBr salt melted at 216–217°.

In refluxing Me_2CO the results were essentially the same; only the naphthol, **12**, was obtained.

2,9β-Dimethyl-2′-methoxy-8-oxo-6,7-benzomorphan Hydrochloride (14). Triethylene glycol (130 ml) and 12.7 g (0.03 mol) of **11** were kept at 180–195° for 1 hr and at 195–220° for 20 min. The cooled solution was poured into ice–H_2O, made basic with 12 M NH_4OH, and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated to give 10.8 g of oil which was dissolved in Et_2O and acidified MeOH–HCl) giving 7.6 g (72%) of **14**·HCl: mp 227–229°. Recrystallization from 95% EtOH gave ir (Nujol) 1675 cm^{-1}; NMR (D_2O) 1.37 (d, J = 7 Hz, 3, C-9 CH_3), 2.80 (s, 3, NCH_3), 3.91 (s, 3, OCH_3). Anal. ($C_{15}H_{20}ClNO_2$) C, H, N.

The picrate of **14** melted at 212–215° dec.

2,9β-Dimethyl-8β-hydroxy-2′-methoxy-6,7-benzomorphan (17) Hydrochloride. A mixture of **14**·HCl (300 mg, 1.06 mmol), 10 ml of H_2O, 0.3 ml of 36 N H_2SO_4, and 10 mg of PtO_2 was hydrogenated at 40° and 50 psi during 50 hr. After filtration from catalyst, the mixture was basified with 12 M NH_4OH and extracted with $CHCl_3$. The residue from drying and evaporation of the $CHCl_3$ gave 234 mg (78%) of **17**·HCl: mp 234–236° dec; prisms from 95% EtOH; NMR (D_2O) δ 1.33 (d, J = 7 Hz, 3, 9β-CH_3), 5.18 (d, J = 6 Hz, 1, C-8 H). Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

Compound **17** was prepared in 83% yield by similar reduction of **14**·HCl with 10% Pd/C (EtOH–60% $HClO_4$, 80–85°, atmospheric pressure, 24 hr) and in 90% yield with $LiAlH_4$ in refluxing dioxane (2 hr).

2,9β-Dimethyl-2′-methoxy-6,7-benzomorphan (15) Oxalate. (a) From 14. The hydrochloride of **14** (400 mg, 1.42 mmol), 1.2 ml (10.7 mmol) of 60% $HClO_4$, 12 ml of glacial HOAc, and 150 mg of 10% Pd/C were shaken with H_2 (50 psi, 40°) for 2.5 days. Removal of catalyst and solvent (in vacuo) left a gummy residue which was dissolved in H_2O, basified with 12 M NH_4OH, and extracted with Et_2O. Washing (H_2O), drying, and evaporation of the Et_2O gave 380 mg (83%) of oily **15** which was converted to the **oxalate**: mp 204–205°; plates from 95% EtOH; NMR (D_2O) δ 1.42 (d, J = 7 Hz, 3, 9β-CH_3); mass spectrum 231 (M^+, base), 216, 110, 84. Anal. ($C_{17}H_{23}NO_5$) C, H, N.

Wolff–Kishner reduction of **14** according to Nagata and Itazaka[13] gave, after chromatography (SiO_2), a 16% yield of **15** oxalate.

(b) From 17. Essentially as described in the catalytic reduction of **14**·HCl to **15**, a 70% yield of **15** oxalate was obtained from **17**·HCl.

2,9β-Dimethyl-2′-hydroxy-8-oxo-6,7-benzomorphan Hydrobromide (13). Compound **14**·HCl (100 mg, 0.36 mmol) and 1 ml (8.8 mmol) of 48% HBr were refluxed together for 1 hr and evaporated to dryness in vacuo. Trituration in Me_2CO gave 99 mg of **13**·HBr: mp 257–260° dec; prisms from MeOH–Et_2O; ir (Nujol) 1670 cm^{-1}. Anal. ($C_{14}H_{18}BrNO_2$) C, H, N.

2,9β-Dimethyl-2′-hydroxy-6,7-benzomorphan Hydrochloride. (a) From 15. The oxalate of **15** (50 mg, 0.16 mmol) and 1 ml (8.8 mmol) of 48% HBr, refluxed for 1 hr, evaporated to dryness in vacuo, and the residue treated with Me_2CO, gave 43 mg (93%) of **18**·HBr: prisms from 95% EtOH; mp 243–245° dec; mass spectrum 217 (M^+, base), 202, 110, 84. Anal. ($C_{14}H_{20}BrNO$) C, H, N.

(b) From 17. The hydrochloride of **17** (700 mg, 2.5 mmol), 28 ml (0.16 mol) of 50% HI, 56 ml of glacial HOAc, 14 ml of H_2O, and 280 mg (9.0 mmol) of red P were refluxed together for 5 hr and diluted with 10 ml of H_2O. After filtration and evaporation to dryness in vacuo, the residue was dissolved in H_2O, basified with 12 M NH_4OH, and extracted with 3:1 $CHCl_3$–EtOH. Drying ($MgSO_4$) and evaporation of the extract gave 520 mg of white solid which was converted to 680 mg (93%) of **18**·HBr identical with that described under (a).

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Microbial Models of Mammalian Metabolism. O-Dealkylation of 10,11-Dimethoxyaporphine

J. P. Rosazza,* A. W. Stocklinski, M. A. Gustafson, J. Adrian,

Division of Medicinal Chemistry and Natural Products, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242

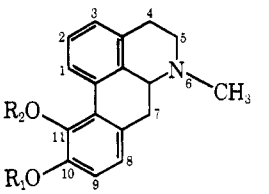
and R. V. Smith

Drug Dynamics Institute, College of Pharmacy, The University of Texas at Austin, Austin, Texas 78712. *Received April 14, 1975*

Microbial transformations of 10,11-dimethoxyaporphine were studied to determine the potential of microorganisms to produce monomethoxyaporphines. Ten microorganisms were identified as being capable of yielding apocodeine and/or isoapocodeine as the major metabolite of this compound. A *Streptomyces* species (SP-WISC 1158) gave a mixture of apocodeine and isoapocodeine in 24 and 20% yield, respectively. *Cunninghamella blakesleeana* (ATCC 9245) converted 10,11-dimethoxyaporphine quantitatively into isoapocodeine. O-Dealkylation of this aporphine system is a facile microbial transformation, and the 10-methoxyl group is more susceptible to metabolic cleavage than the sterically hindered 11-methoxyl group. Selectivity in O-dealkylation may be accomplished with different microorganisms. This is the first report dealing with the microbial transformation of an aporphine system.

Smith and Rosazza have commenced a series of studies designed to develop microbial transformation systems as useful adjuncts in drug metabolism studies.[1-3] Recent developments in comparative biochemistry have made it possible to link diverse metabolic systems through similarities in the pathways by which they alter xenobiotics. It is suggested that microbial metabolic systems consisting of a selected series of microorganisms may be used to produce metabolites normally obtained in very low amounts in mammalian systems.[1] In practice, microbial and mammalian biotransformation studies may be conducted simultaneously. Metabolites produced in common by both metabolic systems could be readily obtained by routine fermentation scale-up procedures. Other advantages of this application of microbial transformation systems center about the mild conditions and the selectivity with which such biotransformations are accomplished, especially with polyfunctional substrates. Initial studies using microbial models of mammalian metabolism have been successfully conducted on aromatic hydroxylation as a reaction type.[1] Microbial patterns of phenolic metabolites from a broad array of aromatic substrates were similar to those obtained with cytochrome P-450 monooxygenases of hepatic microsomes and/or in vivo mammalian systems. This report is the first one dealing with O-dealkylation as a reaction type and is concerned with the metabolism of 10,11-dimethoxyaporphine by microorganisms.

Considerable interest has been demonstrated in apomorphine (1) due to its application in the treatment of Parkinsonism[4] and because of suggested relationships of this compound to dopamine.[5-7] The metabolic fate of apomorphine in mammalian systems has been studied by several groups, and glucuronidation[8-11] and methylation[12,13] appear to be important pathways in the biodisposition of this compound.[14,15] Both metabolic reactions occur predominantly at the 10-phenolic position of apomorphine (1). A COMT preparation from rat liver yielded a mixture of apocodeine (2) and isoapocodeine (3) in a ratio of 81:1.[12] To facilitate studies on the COMT reaction with apomorphine (1), three possible O-methylation products, 10,11-dimethoxyaporphine (4), 10-methoxy-11-hydroxyaporphine (apocodeine, 2), and 10-hydroxy-11-methoxyaporphine (isoapocodeine, 3), were prepared.[12] Isoapocodeine (3) could be prepared in only 5% yield, while 2 and 4 were more readily obtained. Smith and Cook have shown that apocodeine (2) may be O- and N-dealkylated in vivo by rats to 1 and norapomorphine.[16]



1, $R_1 = R_2 = H$ (apomorphine)
2, $R_1 = CH_3$, $R_2 = H$ (apocodeine)
3, $R_1 = H$; $R_2 = CH_3$ (isoapocodeine)
4, $R_1 = R_2 = CH_3$ (10,11-dimethoxyaporphine)

Results and Discussion

Initial screening experiments were conducted to obtain microorganisms which metabolized 10,11-dimethoxyaporphine (4). For this purpose, 65 microorganisms were selected from our culture collection, based on previous work by which O-dealkylation had been observed[1,3] and on literature reports describing cultures capable of accomplishing O-dealkylation.[17-20] Some steroid metabolizing cultures were also chosen for early screening experiments. The ten cultures which actively metabolized 4 included representatives of seven genera (Table I). It is interesting that *Cun-*