Improved Synthesis and Additional Pharmacology of the Potent Analgetic (−)-5-*m*-Hydroxyphenyl-2-methylmorphan

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In the dimethylaminoethylation of 2-*m*-methoxyphenylcyclohexanone (2) an improved C:O alkyl ratio (3:4) has been obtained. This combined with a better resolution procedure affords a practicable synthesis of the strong analgetic (−)-5-*m*-hydroxyphenyl-2-methylmorphan (1). An alternative synthesis and additional pharmacology for 1 are also described.

(−)-5-*m*-Hydroxyphenyl-2-methylmorphan (1),[1] an analgetic with morphine-like potency, has no physical dependence capacity in monkeys (single-dose experiments)[1] but will precipitate (like nalorphine) abstinence symptoms in monkeys stabilized and dependent on morphine.[1] The (+) isomer, on the other hand, a very powerful analgetic, is an equally strong suppressor of abstinence.[1] We report herein some additional pharmacology and an improved (as well as an alternative) synthesis for (−)-1, an agent of clinical potential.

Chemistry. The principal drawbacks in the previously reported synthesis of 1[2] were (1) the low yield (*ca.* 20%) of 2-dimethylaminoethyl-2-*m*-methoxyphenylcyclohexanone (3), because of the formation of 75% of O-alkyl product 4, and (2) the tedium of converting $ClCH_2CH_2NMe_2$·HCl to free base. The predominance of O-alkylation is probably due to steric hindrance to C-alkylation and to stabilization of the enolate of 2 by the aromatic nucleus.

Factors listed by House[3] as favoring C-alkylation are (1) an H-bonding solvent, (2) a small, tightly bound cation ($Li^+ > Na^+ > K^+$), (3) an insoluble enolate, and (4) a heavy-atom, leaving group (I > Br > Cl). In addition, O-alkylation is favored by polar, aprotic solvents.[3] With this as background, alkylations of 2 were conducted, varying solvent, base, alkylating agent, and temperature as shown in Table I. Data in the percentage columns are based on glpc analysis; work-up of selected experiments verified the glpc findings which are at some variance with expectations.

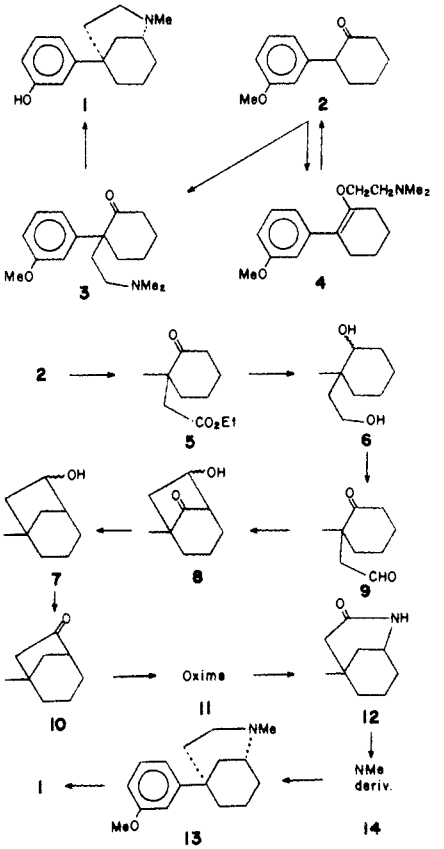
Polar, aprotic solvents, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) gave higher C:O alkyl ratios than the much less polar benzene or benzene–ether or the strongly H-bonding *tert*-butyl alcohol. Reaction was markedly faster in DMF and DMSO than with any other solvents tried. When DMF was the solvent, the commercially available HCl or HBr salts of $ClCH_2CH_2NMe_2$ and $BrCH_2CH_2NMe_2$ could be used directly by use of an appropriate increase in alkylation base. This stratagem saved time and starting halide.

Sodium hydride proved to be the base of choice and reaction was appreciably faster (although yields of 3 did not differ) when $BrCH_2CH_2NMe_2$·HBr rather than chloride·HCl was used. An attempt to generate the iodine *in situ* by NaI addition showed no effect. If the reactive species is the aziridinium ion of $XCH_2CH_2NMe_2$, one would indeed expect little difference in yield with the various halides. Reaction did not go to completion when lithio bases were used; cation effects were, in general, mixed. Surprisingly, lithium diethylamide in benzene gave only 15% of C-alkylation; sodium amide in benzene–ether afforded 27% of C-alkyl. In DMF, Li^+, Na^+, and K^+ gave C-alkylation to the extent of 37, 41, and 33%, respectively, indicating that the nature of the cation is much less influential in polar than in nonpolar solvents. In *tert*-butyl alcohol the yield of C-alkyl was 26% with lithium amide and 22% with potassium *tert*-butoxide.

Finally, per cent C-alkylation varied inversely with temperature while O-alkylation and rate of reaction were favored by higher temperatures. For example, yields of C-alkyl were respectively 30, 41, and 45% at 85°, room temperature (22–25°), and 0–5°. However, at 0–5° reaction proceeded impracticably slowly and at −30°, not at all.

In summary, optimal conditions for the formation of 3 appear to be utilization of DMF, sodium hydride, and $ClCH_2CH_2NMe_2$·HCl at room temperature, conditions which gave a 40% yield. Compound 3 is easily isolated and 2 (mainly regenerated from enol ether 4) is readily recovered. This improvement combined with a better resolution procedure (use of both *l*- and *d*-mandelic acids in that order) makes the synthesis of (−)-1[1] much more attractive.

In the alternative synthesis, alkylation of 2 with $BrCH_2CO_2Et$ (sodium amide–ether) gave C-alkyl product 5 in a surprising 80% yield compared with 20% of 3 under these conditions using $ClCH_2CH_2NMe_2$. Reduction of 5 with lithium aluminum hydride ($LiAlH_4$) gave diol 6 (98%), Sarett oxidation of which afforded keto aldehyde 9



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in 77% yield. Intramolecular aldol condensation of **9** provided a mixture of epimeric alcohols **8** (45% yield), Wolff–Kishner reduction of which gave **7** (epimeric mixture, 93% yield). Sarett oxidation of **7** gave **10** (93%). The noncrystalline oxime **11** (64%) underwent Beckmann rearrangement to give **12** (8%). Direct conversion of **10** to **12** (Schmidt reaction) failed. Reduction of **12** to the corresponding secondary amine by Vitride, $LiAlH_4$, or BH_3 proceeded in very low yield but methylation of **12** followed by reduction (BH_3) gave **13** (~100%) whose hydrobromide salt was identical with authentic material.[2] Principally because of the very-low-yield, Beckmann-rearrangement step, the overall yield of **13** from **2** was only 1%.

Pharmacology. Levo isomer **1**, whose absolute stereochemistry has been determined by Cochran[4] and was found to exhibit mild nalorphine-like properties,[1] was tested for its capacity to produce physical dependence in three Rhesus monkeys.[5] A starting subcutaneous dose of 8 mg/kg was raised to 16 mg/kg during the first 8 days of administration and continued (every 6 hr) for 21 days. An attempt to raise the dose to 32 mg/kg at the end of the eighth day caused convulsions in two of three monkeys. At the end of the 14th day neither nalorphine nor naloxone precipitated appreciable withdrawal symptoms. On abrupt withdrawal of *l*-**1** after 21 days, abstinence symptoms were maximal but mild (grade one as compared with grade eight for morphine)[5] during the first 8–9 hr and barely perceptible after 24 hr. After this, these animals were indistinguishable from normals. Thus the physical dependence liability of this drug would appear to be very slight.[6]

The (24-hr) LD_{50} of *l*-**1** (male white mice, subcutaneous administration) is 137 mg/kg (124–154). This relatively low toxicity combined with an ED_{50} of 1.5 mg/kg;[1] the above-described low physical dependence capacity and antagonist properties[1] render this compound attractive for further study.

Experimental Section

Melting points (Thomas-Hoover apparatus) are corrected. Ir, nmr, and mass spectra were determined on a Perkin-Elmer 257, a Varian Model A-60A (unless otherwise noted), and a Hitachi RMU-6E (70 eV), respectively. Glpc data were obtained on a Beckmann GC-55 (flame-ionization detectors, 6 ft × 1/8 in. column packed with 3% OV-17/GC Chrom Q, 60–80 mesh). Spectral data were consistent with the assigned structures. Tlc analyses were with Analtech uniplates (silica gel GF, 250 μ, prescored). Rotations were made with a Perkin-Elmer Model 141 polarimeter (95% EtOH, Cl).

2-Dimethylaminoethyl-2-*m*-methoxyphenylcyclohexanone (3).[2] To a 50-ml, three-neck flask (N_2 atmosphere, magnetic stirrer, condenser) was added 0.19 g (8.0 mmol) of NaH (57% dispersion in mineral oil, washed with three 10-ml portions of pentane) and 5 ml of dry DMF. Added quickly was 0.5 g (2.5 mmol) of **2** (from Aldrich Chemical Co.) in 5 ml of dry DMF (stirring). After anion formation was complete (clear green solution) 0.7 g (5 mmol) of $ClCH_2CH_2NMe_2 \cdot HCl$ in 5 ml of dry DMF was added. During this addition, ice cooling was necessary when the reaction was "scaled up."

The mixture was stirred overnight and 30 ml of cold H_2O was cautiously added. The mixture was extracted thrice with Et_2O (A). These extracts were shaken with two 5-ml portions of 3 *N* HCl. The acid extracts were warmed to 90° for 30 min, cooled, and extracted with two 30-ml portions of Et_2O (B) and then made alkaline with 20% NaOH. The liberated **3** was extracted with three 30-ml portions of Et_2O from which was obtained in the usual way 0.27 g (40%) of **3**: ir (film) 1710 cm^{-1}; M^+ 275. It was identical with authentic material.[2]

Combined Et_2O extracts A and B above gave 0.25 g (50%) of starting ketone **2** of 90% purity as revealed by glpc. The impurity could be removed by distillation.

When $ClCH_2CH_2NMe_2$ (free base) was used only 3 mmol of the NaH was necessary. When the alkylation reaction was "scaled up" to 20.4 g (100 mmol), the yield of **3** was 36%.

2-Carbethoxymethyl-2-*m*-methoxyphenylcyclohexanone (5). The method of Ong and May‡ was used. To 4.0 g (103 mmol) of $NaNH_2$ and 40 ml of Et_2O (N_2 atmosphere, magnetic stirring) was added dropwise during 15 min 19.4 g (95 mmol) of **2** in 25 ml of Et_2O and 15 ml of C_6H_6. The mixture was refluxed for 4 hr and cooled in ice while adding dropwise 16.8 g (100 mmol) of $BrCH_2CO_2Et$ during 1 hr. After stirring overnight at room temperature, the mixture was cooled in ice and treated with 50 ml of H_2O. The aqueous phase was separated and extracted twice with Et_2O. The extracts were combined with the organic layer above and dried§ to give 22.0 g (80%) of **5**: bp 163–167° (0.17 mm); ir (film) 1735 (ester) and 1710 cm^{-1} (ketone). The semicarbazone (from MeOH) had mp 182–183.5°. *Anal.* Calcd for $C_{18}H_{25}N_3O_4$: C, 62.2; H, 7.3; N, 12.1. Found: C, 62.4; H, 7.5; N, 12.3.

3-Oxo-5-*m*-methoxyphenyl-2-azabicyclo[3.3.1]nonane (12). To 35 ml (52.5 mmol) of 1.5 *M* ethereal $LiAlH_4$ was added dropwise 10.0 g (35 mmol) of **5** in 100 ml of dry Et_2O (stirring). After stirring for 24 hr (tlc showed some **5** after 16 hr), 20 ml of 10% NaOH was added cautiously. The organic layer and two Et_2O extracts of the H_2O layer were combined, washed with 50 ml of saturated NaCl, dried§ and evaporated to give 8.5 g (98%) of oily **6**: ir (film) 3340 cm^{-1}; nmr ($CDCl_3$) δ 2.5 (s, 2, OH).

Using the method of Ratcliffe and Rodehorst,[7] 23.3 g (93 mmol) of **6** was oxidized to 20.5 g of oil which was chromatographed & to give 17.6 g (77%) of **9**: ir (film) 1710 cm^{-1} (br, >C=O, -CHO).

A mixture of 16.2 g (65.8 mmol) of **9**, 1.3 g of NaOH, 40 ml of H_2O, and 160 ml of THF was refluxed for 18 hr and saturated with NaCl. The organic layer, combined with two 50-ml Et_2O extracts of the H_2O layer, was dried§ and evaporated to give 16.0 g of oil which, after chromatography & gave 7.3 g (45%) of **8**: ir (film) 3440 (OH), 1740 cm^{-1} (>C=O); mass spectrum 246 (M^+), 125 (base).

By the procedure of Sarel and Yanuka,[8] 9.1 g (28.8 mmol) of **8** was reduced to give 6.2 g (93%) of oily **7**: ir (film) 3350 cm^{-1}; M^+ (base) 232.

Using the method cited before,[7] 6.0 g (24.0 mmol) of **7** was oxidized to 5 g of **10** (4.3 g, 73% after chromatography): & mass spectrum 230 (M^+), 200 (base).

By the method of Shriner, *et al.*,[9] 1.0 g (4.3 mmol) of **10** gave 0.8 g of oxime, a viscous oil which was chromatographed & to give 0.7 g (64%) of **11**: ir (film) 3250 cm^{-1} (br, OH); mass spectrum 245 (M^+), 228 (base).

The method of Sasaki, *et al.*,[10] was used to prepare **12** from **11**. Tosyl chloride (4.2 g, 21.3 mmol), 5.1 g (21 mmol) of **11**, and 60 ml of DMF were stirred at room temperature for 22 hr and treated with 60 ml of 10% NaOH. Stirring was continued for another hour. The mixture was extracted with two 100-ml portions of

Table I. Variables in the Alkylation of 1

Alkylating agent ($NMe_2CH_2CH_2X$), X =	Base	Solvent	Temp, °C	% C-alkylation[a]	% completion[b]
Cl	$LiNH_2$	$C_6H_6-Et_2O$	37	0	0
Cl	$LiNH_2$	*t*-BuOH	*c*	26	29
Cl	$NaNH_2$	$C_6H_6-Et_2O$	37	27	75
Cl	NaH	DMF	85	30	95
Cl	NaH	$C_6H_6-Et_2O$	37	33	21
Cl–NaI	NaH	DMF	*c*	36	96
Cl	NaH	$C_6H_6-Et_2O$	*c*	38	96
Cl (HCl)	NaH	DMF	*c*	40	99
Cl	NaH	DMSO	*c*	41	92
Br (HBr)	NaH	DMF	*c*	42	69
Cl	NaH	DMF	0–5	45	58
Br (HBr)	NaH	DMF	0–5	45	92
Cl (HCl)	LiH	DMF	*c*	0	0
Cl	$LiNH_2$	DMF	*c*	37	70
Cl	*t*-BuOK	*t*-BuOH	70	22	93
Cl	$LiNH_2$	C_6H_6	*c*	15	30
Cl	*t*-BuOK	DMF	*c*	33	34

[a] Per cent of total alkylation product. [b] Sum of C- and O-alkylation products. [c] Room temperature (22–25°).

‡ H. Ong and E. L. May, personal communication.
§ Over $MgSO_4$.
& Silica gel 60, 30–70 mesh.

$CHCl_3$, which were washed with saturated NaCl and dried.§ Evaporation of the $CHCl_3$ left 5.5 g of oil which was chromatographed & to give 1.4 g of colored powder. This was recrystallized twice from EtOH–H_2O (Norit) to give 0.4 g (8%) of **12**: mp 141.5–143.5°; ir (CCl_4) 3190 (NH), 1665 cm^{-1} [C(=O)N]; nmr ($CDCl_3$) δ 2.63, 2.65 (overlapping s, 2, 4-CH_2), 3.79 (s, 3, OCH_3 over a broad 1-H multiplet); mass spectrum 245 (M^+), 202 (base). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.7; H, 7.9; N, 5.6.

5-*m*-Methoxyphenyl-2-methyl-2-azabicyclo[3.3.1]nonane (5-*m*-Methoxyphenyl-2-methylmorphan) (13) Hydrobromide. Methylation of **12** according to Gassman and Fox[11] gave a 100% yield of oily **14**: ir (film) 1635 cm^{-1} [C(=O)N]; nmr ($CDCl_3$, HA-100) δ 2.62, 2.66 (overlapping s, 2 H, 4-CH_2), (s, 3, NCH_3), 3.66 (m, 1, 1-CH), 3.70 (s, 3, OCH_3); mass spectrum 259 (M^+), 216 (base).

Reduction of **14** according to Brown and Heim[12] gave 100% of oily **13**: mass spectrum 245 (M^+), 202 (base). The HBr salt (from Me_2CO–Et_2O) had mp 163–165° and was identical (melting point, mixture melting point, and mass spectrum) with authentic material.[2]

Optical Resolution of 1. *l*-Mandelic acid (8 g), 10 g of (±)-**1**, and 50 ml of Me_2CO, heated and stirred together briefly, gave 15.7 g of mandelate salts which were dissolved in 500–600 ml of boiling MeOH. Concentration of the solution to 100–150 ml gave 7.5 g of the *l*-mandelate salt of (−)-**1**, mp 220–221°,** which in boiling dilute NH_4OH gave 4.4 g (88%) of (−)-**1**: mp 153–154°; $[\alpha]^{20}D$ −12.3°.[1]

The combined Me_2CO and MeOH filtrates above were concentrated to 50–75 ml and treated with H_2O and NH_4OH, giving 5.5 g of a mixture of (+) and (±) bases. This in 150 ml of hot MeOH was treated with 4.4 g of *d*-mandelic acid giving (after cooling) 7.0 g of the *d*-mandelate salt of (+)-**1**, mp 218–220°, and, as above, 3.5 g (70%) of (+)-**1**, mp 152.5–154°, $[\alpha]^{20}D$ +11.8°.[1]

** A second recrystallization (with minor loss of material) is sometimes necessary.

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Deuterium Isotope Effects in the *in Vivo* Metabolism of Cotinine[1]

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In an attempt to further our understanding of the molecular mechanisms associated with the mammalian oxidative metabolism of foreign substances, we have investigated the deuterium isotope effect involved in the *in vivo* metabolism of the tobacco alkaloid cotinine. Mixtures of cotinine-d_0 and cotinine-3,3-d_2 in varying ratios were administered to Rhesus monkeys. Unchanged drug and several of its oxidized metabolites including *trans*-3-hydroxycotinine were isolated from the 24-hr urine collection. The deuterium contents of these isolated compounds were found to be greater than that present in the administered cotinine except for *trans*-3-hydroxycotinine which showed a substantial decrease in the deuterium to proton ratio. On the basis of these determinations the deuterium isotope effect for the 3-hydroxylation of cotinine was calculated to be between 6 and 7, indicating that carbon–hydrogen bond cleavage is likely to be involved in the rate-determining step in this metabolic conversion.

Current concepts concerning the chemical nature of the active oxygen species responsible for mammalian C-hydroxylations[2] of foreign substances remain vague although many of the biochemical and model chemical studies[3] point to an electron-deficient oxygen functionality. These oxidation reactions involve cleavage of a carbon–hydrogen bond, and therefore it can be anticipated that replacement of hydrogen with deuterium at the center undergoing hydroxylation will lead to a significant deuterium isotope effect ($k_H/k_D > 1$) in the event that rupture of the carbon–hydrogen bond is involved in the rate-determining step in the overall conversion. Deuterium isotope effects ($k_H/k_D < 2$) have been reported in a number of metabolic conversions of foreign substances.[4]

In the present communication we record the results of our deuterium isotope effect studies on the *in vivo* metabolism of cotinine [(*S*)-1-methyl-5-(3-pyridyl)-2-pyrrolidinone, **1a**], the principal mammalian metabolite of the tobacco alkaloid nicotine (**2**). Our studies[5] as well as those of others[6] have led to the structural elucidation of several urinary metabolites of cotinine including desmethylcotinine (**3a**), cotinine *N*-oxide (**4a**), *trans*-3-hydroxycotinine (**5a**), and 5-hydroxycotinine (**6a**). The stability, mass spectral characteristics, and ease of isolation of **5a** together with the stereospecificity of the conversion and the ready availability of cotinine-3,3-d_2 (**1b**)[7] provided an excellent opportunity to investigate the influence on C(3)-hydroxylation by replacing with deuterium the two protons α to the carbonyl group.

Cotinine-3,3-d_2 (**1b**) was easily obtained by deuterium exchange of cotinine† in D_2O in the presence of K_2CO_3. An nmr spectrum of **1b** shows three clean quartets for H_A (δ 6.62 ppm), H_B (δ 2.58 ppm), and H_C (δ 1.90 ppm), whereas the signal for H_A in the proton compound **1a** appears as a multiplet, presumably due to long-range coupling with protons H_D and H_E which together with H_B and H_C provide a complex series of lines between δ 2.8 and 1.7 ppm.

†The cotinine used in these studies was prepared by oxidation of (*S*)-nicotine[7,8] and has been shown to be enantiomerically pure (*S*)-cotinine.[9]