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A NEW SYNTHESIS OF 5-PHENYLMORPHANS[1,2]

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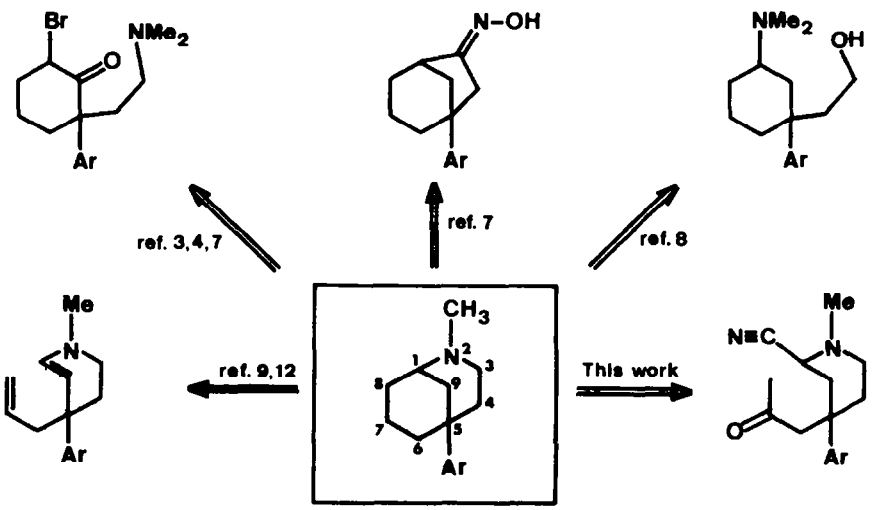
Abstract - A new procedure for the synthesis of 2-azabicyclo-[3.3.1]nonanes by intramolecular cyclization of 4-acetonyl-2-piperidinecarbonitriles under acidic conditions is described. The procedure allows the preparation of the pharmacologically interesting 5-phenylmorphans and involves the initial formation of 4-acetonylidenepiperidine **4**, conjugate addition of a diaryl-cuprate, and cyclization of the resulting 4-acetonylpiperidine by way of the corresponding 2-cyano derivative.

INTRODUCTION

5-Phenylmorphans are simplified morphine analogues that have received considerable attention both from a synthetic and a pharmacological standpoint.[3-13] The synthesis of these compounds has been accomplished through several routes, as outlined in the following scheme.[14] Most of them imply the construction of the piperidine ring from appropriately functionalized cyclohexane derivatives. Only one of these syntheses utilizes piperidine precursors;[9,12] it involves the closure of the carbocyclic ring in a late step by formation of C_1-C_8 bond from a 4-allyl-4-aryl-1,2,3,4-tetrahydropyridine.



1. Ar = m-HOC_6H_4
2. Ar = m-$MeOC_6H_4$
3. Ar = C_6H_5

We present here a new and efficient synthetic route to 5-phenylmorphans by cyclization of 2-cyano-4-acetonyl-4-arylpiperidines, in which the bond formed in the key step is also C_1-C_8. The procedure has been successfully applied to the synthesis of 5-(*m*-hydroxyphenyl)-2-methylmorphan (**1**),[4,7] a compound having strong antinociceptive properties.[5]

RESULTS AND DISCUSSION

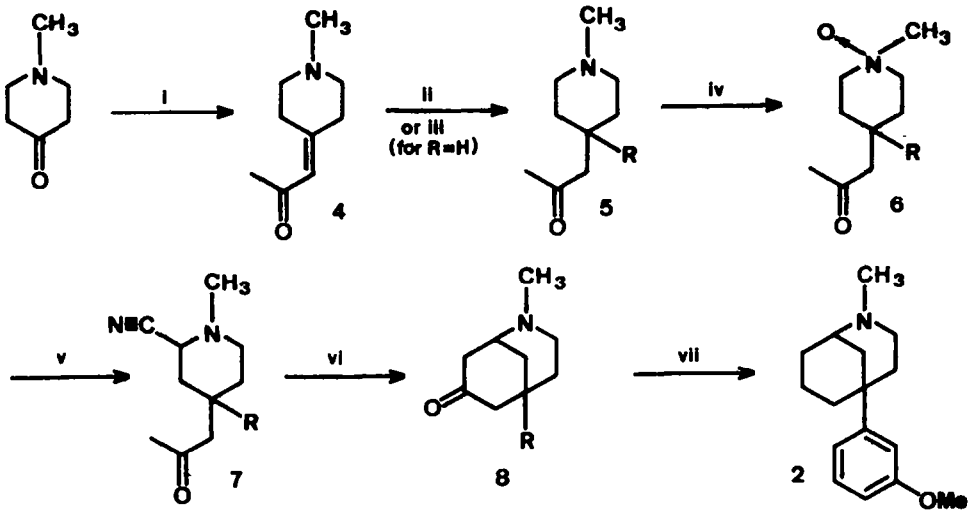
Some years ago, we reported the synthesis of 2-azabicyclo[3.3.1]nonan-7-ones by oxidative cyclization of 4-acetonylpiperidines using mercuric acetate. The required piperidine derivatives were obtained by hydrogenation of the mixture of α,β- and β,γ-unsaturated ketones resulting from condensation between a 4-piperidone and diethyl 2-oxopropylphosphonate.[15] The isomerization of the initially formed conjugated double bond to a β,γ position has been frequently observed in the Wadsworth-Emmons reaction from 4-piperidones.[16] To achieve the synthesis of 5-phenylmorphans we decided to take advantage of the 4-acetonylidenepiperidine isomer formed in the above reaction and to incorporate the required aryl substituent by means of a conjugate addition. In order to obtain the desired exocyclic double bond isomer **4** as the sole product, avoiding the isomerization to an endocyclic position, the reaction conditions[15] of the Wadsworth-Emmons condensation were modified. The complete regiocontrol of the process was attained by using an excess (1.3 eq) of the condensating agent with respect to the base (1.1 eq) and the substrate (1 eq).

With pure α,β-unsaturated ketone **4** in hand, piperidine **5a** was obtained by reaction of **4** with diphenylcuprate, which was generated from phenylmagnesium bromide and cuprous iodide.[17] The overall yield of the process from 1-methyl-4-piperidone was 63%. In an identical manner, piperidine **5b** was obtained in 58% overall yield.

Some NMR spectral features of piperidines **5a** and **5b** are worthy of comment since they are indicative of their conformational behavior. Thus, as a consequence of the equilibrium between two chair conformations, the chemical shift of the piperidine protons in the ^{1}H-NMR spectra is partially averaged, although both the low β effect (+3 ppm) exerted by the aryl substituent upon C-3 and the chemical shift (δ 143-144) of C(aryl)-1 in the ^{13}C-NMR spectra[18] suggest that the preferred conformation is that in which the larger phenyl group is axial, as occurs in 1-methyl-1-phenylcyclohexane and related systems.[19]

Attempts to obtain azabicyclo **8a** by oxidative cyclization with mercuric acetate, either from acetonylpiperidine **5a** or from the corresponding piperidineacetoacetate **9**, according to the methods previously used for the synthesis of **8c**,[15,20] were unsuccessful. For this reason, we decided to examine an alternative procedure to generate the iminium salt required for the cyclization step. Taking into account that 2-cyanopiperidines constitute synthetic equivalents of 2,3,4,5-tetrahydropyridinium salts,[21] we turned our attention to the preparation of 4-acetonyl-2-cyanopiperidines **7**.

The more readily available acetonylpiperidine **5c**,[15] lacking the aryl substituent at C-4, was selected as a model starting material to explore the efficiency of the method for the obtention of the 2-azabicyclo[3.3.1]nonane skeleton.[22] This piperidine was converted to the corresponding *N*-oxide **6c**, which was then subjected to the modified Polonovski reaction conditions[23] followed by cyanide trapping[24] to give the required 2-cyanopiperidine **7c**. Alternatively, the above two-step sequence was carried out in a one-pot reaction.[25] As expected, when **7c** was treated with methanol-hydrochloric acid (9:1) for long reaction times,[26] the cyclized product **8c** was obtained (52% overall yield from **5c**). This yield clearly improves the one reported by the mercuric acetate procedure.[15]



a. R = C_6H_5; b. R = m-MeOC_6H_4; c. R = H

Reagents: (i) $(EtO)_2POCH_2COCH_3$, KOH, EtOH; (ii) ArMgBr, CuI, THF; (iii) H_2, Pd-C; (iv) *m*-CPBA; (v) TFAA; then aq. KCN,pH 4; (vi) 12 N HCl-MeOH (1:9); (vii) Zn, HCl-Et_2O.

In order to apply the same methodology to the synthesis of phenylmorphans **8a,b**, 2-cyanopiperidines **7a,b** were prepared by way of the corresponding *N*-oxides **6a,b**. Whereas in the ^{1}H-NMR spectrum of 2-cyanopiperidine **7c** the narrow absorption ($W_{\frac{1}{2}}$=8 Hz) observed for 2-H indicated that the cyano group was in the expected axial position,[21,27] the NMR data of **7a** and **7b** revealed that in these compounds the cyano group is located equatorially in the preferred conformation. Such a situation would explain the doublet of doublets (J=8 and 3.5 Hz) at δ3.34 attributable to the C-2 methine proton and the resonance at δ118.6 for the nitrile carbon.[28] On the other hand, the axial disposition of the aryl substituent was inferred from the ^{13}C-NMR data,[18,19] which correlate with those observed for piperidines **5a** and **5b**.

Cyclization of 2-cyanopiperidines **7a** and **7b** took place by heating in methanol containing 10% of concentrated hydrochloric acid. The corresponding 5-phenylmorphans, **8a** and **8b**, were obtained in excellent yields. The most significant ^{1}H-NMR signals of both phenylmorphans were a multiplet at δ3.47 due to the C-1 methine proton and a doublet of quartets at δ2.94 due to the equatorial proton at C-8.

Finally, reduction of the ketone carbonyl group of **8b** by a modified Clemmensen reaction[29,30] afforded phenylmorphan **2**,[31] which had previously been converted into the target compound **1**.[4]

In conclusion, by the above short reaction sequence 5-(3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (**2**) was readily prepared.[32] Formation of the morphan nucleus by acidic treatment of 4-acetonyl-2-piperidinecarbonitriles constitutes a new entry to this framework, which is present in many natural (morphine and *Strychnos* indole alkaloids) and synthetic products (morphine related analgesics).

EXPERIMENTAL

General. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer using TMS as internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. TLC was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm), and the spots were located with UV light or iodoplatinate reagent. Flash column chromatography was carried out on SiO_2 (silica gel 60, 0.040-0.063 mm, Macherey Nagel) or Al_2O_3 (aluminium oxide 90, neutral

activity I, 0.063-0.200 mm, Merck). Drying of organic extracts during the workup of reactions was performed over anhydrous sodium sulfate. Microanalyses were performed on a Carlo Erba analyzer by Instituto de Química Bio-Orgánica, Barcelona.

4-Acetonylidene-1-methylpiperidine (**4**). 1-Methyl-4-piperidone (2.6 ml, 22.9 mmol) was added to a stirred solution of diethyl 2-oxopropylphosphonate (5.77 g, 29.7 mmol) and potassium hydroxide (1.34 g, 24.0 mmol) in ethanol (20 ml) cooled at 5°C. The resulting mixture was stirred at room temperature for 3 h, the ethanol was evaporated, and the residue was digested several times with ether at room temperature. The ethereal solution was dried and evaporated to afford crude α,β-unsaturated ketone **4**[15] in quantitative yield.

4-Acetonyl-1-methyl-4-phenylpiperidine (**5a**). A solution of phenylmagnesium bromide[33] was prepared under argon atmosphere from magnesium (2.15 g, 88.6 mmol) and bromobenzene (10.2 ml, 96.8 mmol) in tetrahydrofuran (130 ml) and cooled to -5°C. Cuprous iodide (7.45 g, 39.1 mmol) was added and the resulting mixture was stirred at -5°C for 3 min, and then rapidly cooled to -70°C. A solution of crude enone **4** (3.5 g) in dry tetrahydrofuran (30 ml) was added dropwise to the mixture, which was then stirred for 1 h at -70°C and allowed to warm to room temperature. The reaction mixture was poured into a saturated aqueous ammonium chloride solution (80 ml) and tetrahydrofuran was evaporated *in vacuo*. The resulting residue was extracted with methylene chloride and the organic layer was acidified with 1.2 N hydrochloric acid. The methylene chloride solution was discarded and the aqueous layer was basified with solid sodium carbonate and extracted with methylene chloride. The organic extracts were washed twice with brine and once with saturated aqueous ammonium chloride solution, dried, and evaporated to afford 4-acetonylpiperidine **5a** (3.33 g, 63% overall yield from 1-methyl-4-piperidone) of sufficient purity to be used in the next step; IR (NaCl): 1700 (C=O); ^{1}H-NMR: 1.54 (s, 3H, $COCH_3$), 2.04 (ddd, J= 13, 9 and 3 Hz, 2H, 3- and 5-Hax), 2.20 (s, 3H, NCH_3), 2.2-2.4 (m, 4H, 2- and 6-Hax, 3- and 5-Heq), 2.5-2.6 (m, 2H, 2- and 6-Heq), 2.65 (s, 2H, $COCH_2$), 7.2-7.3 (m, 5H, ArH); ^{13}C-NMR: 32.2 ($COCH_3$), 35.5 (3- and 5-C), 38.8 (4-C), 46.1 (NCH_3), 51.8 (2- and 6-C), 53.4 ($COCH_2$), 126.3 (*p*-C), 126.7 (*o*-C), 128.5 (*m*-C), 143.1 (*ipso*-C), 208.2 (C=O). The picrate melted at 126-127°C (ethanol). (Found: C, 54.69; H, 5.34; N, 12.11. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.21; N, 12.17).

4-Acetonyl-4-(3-methoxyphenyl)-1-methylpiperidine (**5b**). Operating as above, a tetrahydrofuran (60 ml) solution of enone **2**, obtained from 1-methyl-4-piperidone (5.3 ml, 45.8 mmol), diethyl 2-oxopropylphosphonate (11.54 g, 59.5 mmol), and potassium hydroxide (2.68 g, 48.0 mmol) in ethanol (40 ml), was added dropwise to a solution of bis(3-methoxyphenyl)magnesium cuprate prepared from magnesium (4.3 g, 177.2 mmol), 3-bromoanisole (24.4 ml, 193.6 mmol) and cuprous iodide (14.9 g, 78.3 mmol) in tetrahydrofuran (200 ml). After the usual work-up, pure piperidine **5b** (6.96 g, 58%) was obtained; IR (NaCl): 1700 (C=O); ^{1}H-NMR: 1.61 (s, 3H, $COCH_3$), 2.04 (ddd, J= 15, 9 and 4 Hz, 2H, 3- and 5-Hax), 2.27 (s, 3H, NCH_3), 2.2-2.4 (m, 4H, 2- and 6-Hax, 3- and 5-Heq), 2.5-2.7 (m, 2H, 2- and 6-Heq), 2.66 (s, 2H, $COCH_2$), 3.81 (s, 3H, OCH_3), 6.80-6.95 (m, 3H, ArH), 7.28 (apparent t, J= 8 Hz, 1H, 5-ArH); ^{13}C-NMR: 32.3 ($COCH_3$), 35.5 (3- and 5-C), 38.9 (4-C), 46.0 (NCH_3), 51.8 (2- and 6-C), 54.6 ($COCH_2$), 55.2 (OCH_3), 113.5 (2-C), 119.1 (4-C), 124.5 (6-C), 129.0 (5-C), 144.2 (1-C), 159.8 (3-C), 208.1 (C=O). The picrate melted at 150-152°C (ethanol). (Found: C, 53.93; H, 5.19; N, 11.54. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.30; N, 11.42).

4-Acetonyl-1-methylpiperidine (**5c**). Piperidine **5c** was obtained by catalytic hydrogenation of enone **4** as previously described[15]; ^{1}H-NMR: 1.26 (qd, J= 12, 12, 12 and 3.6 Hz, 2H, 3- and 5-Hax), 1.68 (dm, J= 12 Hz, 2H, 3- and 5-Heq), 1.7-1.8 (m, 1H, 4-Hax), 1.96 (td, J= 12, 12 and 2.4 Hz, 2H, 2- and 6-Hax), 2.14 (s, 3H, $COCH_3$), 2.26 (s, 3H, NCH_3), 2.36 (d, J= 6 Hz, 2H, $COCH_2$), 2.82 (dm, J= 12 Hz, 2H, 2- and 6-Heq); ^{13}C-NMR: 30.6 ($COCH_3$), 31.2 (4-C), 32.2 (3- and 5-C), 46.4 (NCH_3), 50.3 ($COCH_2$), 55.7 (2- and 6-C), 208.1 (C=O).

Methyl 1-Methyl-4-phenyl-4-piperidineacetoacetate (**9**). Dimethyl carbonate (4.3 ml, 50.8 mmol) was added under nitrogen to a suspension of sodium hydride (2.21 g, 50.8 mmol) in dry tetrahydrofuran (30 ml). The resulting mixture was heated at reflux, and then some drops of absolute methanol and a solution of piperidine **5c** (3.9 g, 16.9 mmol) in dry tetrahydrofuran (50 ml) were added dropwise. The mixture was refluxed for 8 h, cooled, and brought to pH 6-7 by careful addition (0°C) of concentrated acetic acid. Cold water was added and the mixture was extracted with ether. The ethereal extract was discarded, the aqueous layer was basified at 0°C with concentrated ammonium hydroxide, and the product was isolated by ether extraction. Flash chromatography (silica gel, 98:2 ether-diethylamine) gave pure β-keto ester **9** (3.4 g, 74%) as an oil; IR (NaCl): 1740 (C=O ester), 1710 (C=O ketone); ^{1}H-NMR: 2.0 (br t, J=12 and 12 Hz, 2H, 3- and 5-Hax), 2.23 (s, 3H, NCH_3), 2.2-2.4 (m, 4H, 2- and 6-Hax, 3- and 5-Heq), 2.54 (m, 2H, 2- and 6-Heq), 2.75 and 2.79 (2s, 4H, $COCH_2$), 3.61 (s, 3H, OCH_3), 7.2-7.4 (m, 5H, ArH); ^{13}C-NMR: 35.7 (3- and 5-C), 39.3 (4-C), 46.4 (NCH_3), 51.0 and 51.9 ($COCH_2$), 52.2 (2- and 6-C), 52.5 (OCH_3), 126.7 (*p*-C), 127.0 (*o*-C), 129.1 (*m*-C), 144.4 (*ipso*-C), 167.7 (C=O ester), 202.1 (C=O ketone). The picrate melted at 109-111°C (ethanol). (Found: C, 53.68; H, 4.88; N, 10.82. Calcd. for $C_{23}H_{26}N_4O_{10}$: C, 53.28; H, 5.01; N, 10.81).

4-Acetonyl-1-methylpiperidine N-oxide (**6c**) A solution of *m*-chloroperbenzoic acid (Carlo Erba 70%, 5.4 g, 22 mmol) in dry methylene chloride (25 ml) was added dropwise to a solution of piperidine **5c** (3.1 g, 20 mmol) in dry methylene chloride (25 ml). After stirring at -10°C for 1 h 30 min and at room temperature for 15 min, an excess of solid potassium carbonate was added to the reaction mixture, which was stirred at room temperature for an additional 15 min period. The mixture was then filtered through celite and the solid material was washed copiously with methylene chloride. The combined organic solutions were concentrated and the residue was chromatographed on alumina through a flash column utilizing a gradual increase in concentration of eluant from 1% to 2% methanol-methylene chloride. Pure *N*-oxide **6c** (2.32 g, 68%) was obtained as a solid, mp 72-73°C (chloroform-ether); IR ($CHCl_3$): 1705 (C=O); ^{1}H-NMR: 1.62 (dm, J= 13.5 Hz, 2H, 3- and 5-Heq), 1.8-2.3 (m, 3H, 2- and 6-Hax, 4-H), 2.16 (s, 3H, $COCH_3$), 2.50 (d, J= 6 Hz, 2H, $COCH_2$), 3.1-3.3 (m, 4H,

2- and 6-Heq, 3- and 5-Hax), 3.23 (s, 3H, NCH_3); ^{13}C-NMR: 26.8 (3- and 5-C), 29.6 (4-C), 31.1 ($COCH_3$), 49.4 ($COCH_2$), 61.7 (NCH_3), 66.8 (2- and 6-C), 207.7 (C=O).

4-Acetonyl-1-methyl-4-phenylpiperidine N-*oxide* (**6a**). The reaction of piperidine **5a** (2.89 g, 12.5 mmol) and *m*-chloroperbenzoic acid (70%, 3.39 g, 13.7 mmol) in dry methylene chloride (50 ml) was carried out and worked up according to the above procedure. The *N*-oxide **6a** (1.95 g, 63%) was obtained as an oil after flash chromatography on alumina (increase from 1% to 2% methanol-methylene chloride); IR (NaCl): 1700 (C=O); ^{1}H-NMR[34]: 1.66 (s, 3H, $COCH_3$), 2.49 (br d, J= 12 Hz, 2H, 3- and 5-Heq), 2.67 (td, J= 12, 12 and 4 Hz, 2H, 2- and 6-Hax), 2.72 (s, 2H, $COCH_2$), 3.05 (br t, J= 12 and 12 Hz, 2H, 3- and 5-Hax), 3.19 (s, 3H, NCH_3), 3.21 (br d, J= 12 Hz, 2H, 2- and 6-Heq), 7.2-7.4 (m, 5H, ArH); ^{13}C-NMR: 30.0 (3- and 5-C), 32.0 ($COCH_3$), 38.3 (4-C), 56.7 ($COCH_2$), 60.3 (NCH_3), 63.2 (2- and 6-C), 125.6 (*p*-C), 126.8 (*o*-C), 129.1 (*m*-C), 140.3 (*ipso*-C), 206.6 (C=O). The picrate melted at 155-157°C (chloroform-ether). (Found: C, 52.68; H, 5.35; N, 12.10. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.04; N, 11.76).

4-Acetonyl-4-(3-methoxyphenyl)-1-methylpiperidine N-*oxide* (**6b**). Operating as above, from *m*-chloroperbenzoic acid (70%, 5.2 g, 21 mmol) and piperidine **5b** (5 g, 19.1 mmol) in dry methylene chloride (100 ml), the *N*-oxide **6b** (3.68 g, 69%) was obtained as an oil after purification by flash chromatography on alumina (increase from 1% to 2% methanol-methylene chloride); IR (NaCl): 1700 (C=O); ^{1}H-NMR[34]: 1.69 (s, 3H, $COCH_3$), 2.45 (br d, J= 12 Hz, 2H, 3- and 5-Heq), 2.66 (td, J= 12, 12 and 4 Hz, 2H, 2- and 6-Hax), 2.70 (s, 2H, $COCH_2$), 2.9-3.4 (m, 4H, 2- and 6-Heq, 3- and 5-Hax), 3.10 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 6.8-7.0 (m, 3H, ArH), 7.25-7.40 (m, 1H, 5-ArH); ^{13}C-NMR: 30.2 (3- and 5-C), 32.1 ($COCH_3$), 38.4 (4-C), 55.3 (OCH_3), 56.7 ($COCH_2$), 60.6 (NCH_3), 63.4 (2- and 6-C), 111.3 (2-C), 113.9 (4-C), 119.2 (6-C), 130.0 (5-C), 142.2 (1-C), 160.2 (3-C), 206.6 (C=O). The picrate melted at 143-145°C (chloroform-ether). (Found: C, 52.19; H, 4.87; N, 11.04. Calcd. for $C_{22}H_{26}N_4O_{10}$: C, 52.17; H, 5.17; N, 11.06).

4-Acetonyl-1-methyl-2-piperidinecarbonitrile (**7c**).

Method A. Trifluoroacetic anhydride (2.6 ml, 18.7 mmol) was slowly added under argon atmosphere to a solution of *N*-oxide **6c** (1.6 g, 9.3 mmol) in dry methylene chloride (30 ml) cooled to 0°C. The resulting mixture was stirred at 0°C for 1 h and at room temperature for 15 min. A solution of potassium cyanide (0.9 g, 13.9 mmol) in water (5 ml), adjusted to pH 4 by addition of citric acid, was then carefully added while the pH of the reaction mixture was also adjusted to 4 by addition of sodium acetate. Vigorous stirring was continued at room temperature for an additional 15 min period. The two-phase mixture was basified with 10% aqueous sodium carbonate and extracted with methylene chloride. The organic extracts were dried and evaporated to afford 2-cyanopiperidine **7c** (nearly quantitative yield), which was used without further purification in the next step.

Method B. *m*-Chloroperbenzoic acid (70%, 0.73 g, 2.9 mmol) in dry methylene chloride (10 ml) was added under argon atmosphere to a stirred solution of piperidine **5c** (0.42 g, 2.7 mmol) in dry methylene chloride maintained at 0°C. The mixture was stirred at 0°C for 1 h and then cooled to -15°C. Trifluoroacetic anhydride (0.91 ml, 6.4 mmol) was added dropwise to the resulting solution and stirring was continued at -15°C for 1 h and at room temperature for 15 min. A solution of potassium cyanide (0.35 g, 5.4 mmol) in water (2.8 ml) was then added and the pH adjusted to 5 by the addition of solid sodium acetate. The two-phase mixture was vigorously stirred for 30 min at room temperature, basified with 10% aqueous sodium carbonate, and extracted with methylene chloride. The organic extracts were washed twice with water, dried, and evaporated to give an oil which was purified by flash chromatography on silica gel. On elution with 98:2 ether-diethylamine, 0.36 g (74%) of **7c** were obtained; IR (NaCl): 2230 (CN), 1710 (CO); ^{1}H-NMR: 1.27 (td, J= 13, 13 and 4.5 Hz, 1H, 5-Hax), 1.54 (ddd, J= 13, 12 and 4.5 Hz, 1H, 3-Hax), 1.75 (dm, J= 13 Hz, 1H, 5-Heq), 1.96 (ddd, J= 13, 6.5 and 2.5 Hz, 1H, 3-Heq), 2.0-2.2 (m, 1H, 4-Hax), 2.15 (s, 3H, $COCH_3$), 2.3-2.5 (m, 1H, 6-Hax), 2.38 (d, J= 7 Hz, 2H, $COCH_2$), 2.38 (s, 3H, NCH_3), 2.72 (dm, J= 12 Hz, 1H, 6-Heq), 3.83 (deformed t, J= 4.5 Hz, 1H, 2-Heq); ^{13}C-NMR: 27.6 (4-C), 30.3 ($COCH_3$), 31.3 (5-C), 34.4 (3-C), 43.9 (NCH_3), 49.5 (6-C), 50.4 ($COCH_2$), 54.5 (2-C), 116.0 (CN), 206.8 (C=O). (Found: C, 66.37; H, 9.23; N, 15.50. Calcd. for $C_{10}H_{16}N_2O$: C, 66.66; H, 8.88; N, 15.55).

4-Acetonyl-1-methyl-4-phenyl-2-piperidinecarbonitrile (**7a**). Operating as above, from trifluoroacetic anhydride (2.12 ml, 15.0 mmol) and *N*-oxide **6a** (1.86 g, 7.5 mmol) in dry methylene chloride (35 ml) and a solution of potassium cyanide (0.73 g, 11.3 mmol) in water (4 ml), 2-cyanopiperidine **7a** (1.68 g, 87%) was obtained as an oil of sufficient purity to be used in the next step; IR (NaCl): 2250 (CN), 1700 (C=O); ^{1}H-NMR: 1.66 (s, 3H, $COCH_3$), 2.06 (ddd, J= 13, 8.5 and 4 Hz, 1H, 5-Hax), 2.28 (m, 1H, 5-Heq), 2.37 (s, 3H, NCH_3), 2.3-2.5 (m, 2H, 3-H), 2.58 (ddd, J= 13, 4 and 1.5 Hz, 1H, 6-Heq), 2.70 (m, 1H, 6-Hax), 2.74 and 2.88 (2d, J_{AB}= 15 Hz, 1H each, $COCH_2$), 3.34 (dd, J= 8 and 3.5 Hz, 1H, 2-H), 7.2-7.4 (m, 5H, ArH); ^{13}C-NMR: 32.1 ($COCH_3$), 34.6 (5-C), 38.1 (3-C) 38.4 (4-C), 44.1 (NCH_3), 49.5 (6-C), 51.8 (2-C), 54.0 ($COCH_2$), 118.6 (CN), 126.2 (*o*-C), 126.8 (*p*-C), 128.8 (*m*-C), 143.2 (*ipso*-C), 206.9 (C=O).

4-Acetonyl-4-(3-methoxyphenyl)-1-methyl-2-piperidinecarbonitrile (**7b**).

Method A. Operating as above, from trifluoroacetic anhydride (4.3 ml, 30.7 mmol) and *N*-oxide **6b** (4.26 g, 15.4 mmol) in dry methylene chloride (80 ml) and a solution of potassium cyanide (1.49 g, 23.1 mmol) in water (10 ml), 2-cyanopiperidine **7b** (2.47 g, 56%) was obtained as an oil after purification by flash chromatography (silica gel, 98:2 ether-diethylamine); IR (NaCl): 2240 (CN), 1700 (C=O); ^{1}H-NMR: 1.70 (s, 3H, $COCH_3$), 2.04 (ddd, J= 13, 8.5 and 4 Hz, 1H, 5-Hax), 2.1-2.5 (m, 3H, 3-H and 5-Heq), 2.38 (s, 3H, NCH_3), 2.56 (ddd, J= 14, 4 and 1.5 Hz, 1H, 6-Heq), 2.65 (m, 1H, 6-Hax), 2.74 and 2.87 (2d, J_{AB}=15 Hz, 1H each, $COCH_2$), 3.34 (dd, J= 8 and 3.8 Hz, 1H, 2-H), 3.81 (s, 3H, OCH_3), 6.75-6.92 (m, 3H, ArH), 7.29 (apparent t, J= 7.5 Hz, 1H, 5-ArH); ^{13}C-NMR: 32.1 ($COCH_3$), 35.1 (5-C), 38.1 (3-C), 38.5 (4-C), 44.0 (NCH_3), 49.6 (6-C), 51.8 (2-C), 54.0 ($COCH_2$), 55.3 (OCH_3) 111.1 and 113.2 (2- and 4-C), 118.6 (6-C), 118.8 (CN), 129.8 (5-C), 144.9 (1-C), 159.9 (3-C), 206.9 (C=O).

Method B. By use of a procedure identical to that described for the preparation of **7c**, piperidine **5b** (8.5 g, 32.5 mmol) was treated sequentially with *m*-chloroperbenzoic acid (70%, 8.83 g, 35.8 mmol), trifluoroacetic anhydride (11.0 ml, 78.2 mmol) in dry methylene chloride (200 ml), and a solution of potassium cyanide (4.23 g, 65.1 mmol) in water (34 ml). Workup followed by flash chromatography (silica gel, 98:2 ether-diethylamine) of the crude reaction product gave pure 2-cyanopiperidine **7b** (3.72 g, 40%).

2-Methyl-2-azabicyclo[3.3.1]nonan-7-one (**8c**). A solution of 2-cyanopiperidine **7c** (0.9 g, 4.8 mmol) in methanol (20 ml) containing 12 N hydrochloric acid (2 ml) was refluxed for 24 h under nitrogen atmosphere. Methanol was evaporated *in vacuo* and the residue was basified with 10% aqueous sodium carbonate and extracted with methylene chloride. The evaporation of the extracts left an oil which was purified by flash cromatography (silica gel, 97:3 ether-diethylamine) to yield pure ketone **8c**[15] (0.51 g, 70%).

2-Methyl-5-phenyl-2-azabicyclo[3.3.1]nonan-7-one (**8a**). Operating as above, from 2-cyanopiperidine **7a** (0.60 g, 2.3 mmol) and 12 N hydrochloric acid (2 ml) in methanol (20 ml) for 40 h, ketone **8a** (0.45 g, 84%) was obtained as a pale yellow solid after recrystalization from ether, mp 126-127°C; IR ($CHCl_3$): 1700 (C=O); ^{1}H-NMR: 1.96 (ddd, J= 13, 4.5 and 1.5 Hz, 1H, 4-Heq), 2.18 (dd, J= 16 and 4.5 Hz, 1H, 8-Hax), 2.20 (dt, J= 12, 2.2 and 2.2 Hz, 1H, 9-H *syn*), 2.36 (dd, J= 12 and 3 Hz, 1H, 9-H *anti*), 2.3-2.4 (m, 1H, 6-Hax), 2.42 (s, 3H, NCH_3), 2.43 (td, J= 13, 13 and 5.3 Hz, 1H, 4-Hax), 2.45 (apparent t, J= 16 Hz, 1H, 3-Hax), 2.72 (ddd, J= 13, 5 and 2.2 Hz, 1H, 6-Heq), 2.82 (dt, J= 16, 2.2 and 2.2 Hz, 1H, 3-Heq), 2.94 (dq, J= 16, 4.5 and 1.5 Hz, 1H, 8-Heq), 3.47 (m, $W_{\frac{1}{2}}$= 11 Hz, 1H, 1-Heq), 7.2-7.4 (m, 5H, ArH); ^{13}C-NMR: 37.8 (4-C), 38.1 and 38.3 (8- and 9-C), 38.6 (5-C), 42.7 (NCH_3), 47.4 (3-C), 53.3 (6-C), 55.9 (1-C), 124.5 (*o*-C), 126.5 (*p*-C), 128.6 (*m*-C), 148.2 (*ipso*-C), 210.2 (7-C). (Found: C, 78.89; H, 8.61; N, 6.05. Calcd. for $C_{15}H_{19}NO$: C, 78.60; H, 8.29; N, 6.11).

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-one (**8b**). By use of a procedure identical to the one described for the preparation of **8a**, 2-cyanopiperidine **7b** (2.35 g, 8.2 mmol) was treated with 12 N hydrochloric acid (7 ml) in methanol (70 ml) to give **8b** (1.74 g, 82%) after flash chromatography (silica gel, 97:3 ether-diethylamine); IR (NaCl): 1700 (C=O); ^{1}H-NMR: 1.96 (ddd, J= 13, 5 and 1.7 Hz, 1H, 4-Heq), 2.17 (dd, J= 17 and 5 Hz, 1H, 8-Hax), 2.19 (dt, J= 12, 3.5 and 3.5 Hz, 1H, 9-H *syn*), 2.3-2.5 (m, 2H, 6-Hax and 9-H *anti*), 2.40 (s, 3H, NCH_3), 2.42 (apparent t, J= 17 Hz, 1H, 3-Hax), 2.42 (td, J= 13, 13 and 5 Hz, 1H, 4-Hax), 2.72 (ddd, J= 17, 3 and 3 Hz, 1H, 3-Heq), 2.94 (dq, J= 17, 5 and 2 Hz, 1H, 8-Heq), 3.47 (m, $W_{\frac{1}{2}}$= 10 Hz, 1H, 1-Heq), 6.7-7.0 (m, 3H, ArH), 7.29 (apparent t, J= 8 Hz, 5'-ArH); ^{13}C-NMR: 37.8 (4-C), 38.1 and 38.3 (8- and 9-C), 38.6 (5-C), 42.7 (NCH_3), 47.4 (3-C), 53.2 (6-C), 55.2 (OCH_3), 55.9 (1-C), 111.2 and 111.3 (2'- and 4'-C), 116.9 (6'-C), 129.6 (5'-C), 150.0 (1'-C), 159.8 (3'-C), 210.2 (7-C). The picrate melted at 118-119°C (ethanol). (Found: C, 53.89; H, 5.19; N, 11.55. Calcd. for $C_{22}H_{24}N_4O_9$: C, 54.09; H, 4.91; N, 11.47).

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane (**2**). Ketone **8b** (0.2 g, 0.77 mmol) was dissolved in ether saturated with hydrogen chloride (30 ml) at 0°C. Active zinc powder (2 g) was slowly added to the resulting solution. After being stirred at 0°C for 1 h, the reaction mixture was poured into a large amount of ice-water. The aqueous solution was basified with solid sodium carbonate and extracted thoroughly with ether. The organic extract was dried and evaporated to give pure phenylmorphan (0.19 g, nearly quantitative yield) as a pale yellow oil; ^{1}H-NMR: 1.6-2.5 (m, 10H), 2.47 (s, 3H, NCH_3), 2.84 (qd, J= 12, 7 and 2 Hz, 1H, 3-Heq), 3.0-3.1 (m, 2H, 1-Heq and 3-Hax), 3.81 (s, 3H, OCH_3), 6.7-7.0 (m, 3H, ArH), 7.25 (apparent t, J= 8 Hz, 5'-ArH); ^{13}C-NMR: 22.7 and 23.9 (7- and 8-C), 34.5 (5-C), 37.0, 38.1, and 38.6 (4-, 6- and 9-C), 42.8 (NCH_3), 51.1 (3-C), 54.5 (1-C), 55.2 (OCH_3), 110.5 and 111.4 (2'- and 4'-C), 117.2 (6'-C), 129.2 (5'-C), 153.0 (1'-C), 159.6 (3'-C); MS, *m/e* (relative intensity): 245 (M^+, 9.5), 203 (13), 202 (100), 115 (13), 96 (11.5) 91 (10), 77 (12), 70 (49), 44 (13), 43 (12), 42 (52), 41 (10). The hydrobromide melted at 156-157°C (acetone-ether). [Lit[7] 163-165°C].

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