Condensation Reactions of Activated Picolines with Anthranilate Esters and *o*-Nitrobenzaldehyde: Improved Syntheses of the Antiarrhythmic Drug Encainide

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Two new and improved syntheses of the antiarrhythmic drug Encainide, **1**, are presented. The first approach is based on the condensation of 2-picolyllithium with the *p*-anisoyl amide of methyl anthranilate, **3**, followed by a series of catalytic hydrogenations and methylation. The second route relies on a particularly facile condensation reaction between *N*-methylpicolinium methyl sulfate and *o*-nitrobenzaldehyde to produce the alcohol **17c** in high yield which is converted to the olefin **18c** by a novel dehydration procedure and then to the final molecule, by catalytic hydrogenation over platinum followed by acylation.

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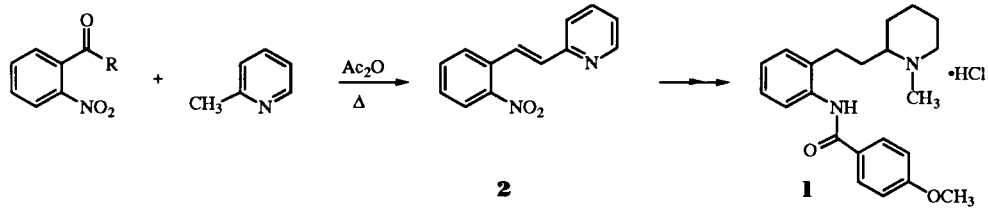
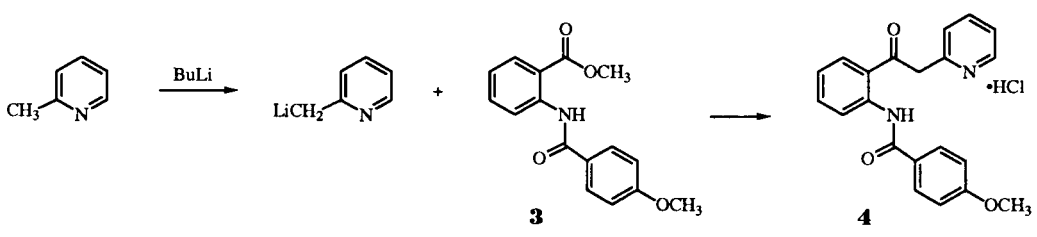
Enhancement of acidity of the α-methyl hydrogens in picolines through resonance stabilization of the resulting anion by the ring nitrogen has been utilized to effect condensation reactions with aromatic electrophiles such as esters and aldehydes (Scheme I) [1,2]. Such an approach was exploited in a key step during an early synthesis of the novel antiarrhythmic drug Encainide (Enkade®) [3,4], **1**, by reaction of *o*-nitrobenzaldehyde with 2-picoline in refluxing acetic anhydride to produce **2**. However, this reaction was limited since it required three days to reach completion. This prompted us to examine alternate methods of condensation and two efficient protocols were developed leading to the large-scale synthesis of **1**.

Treatment of **3**, the product of acylation of methyl anthranilate with *p*-anisoyl chloride, with 2-picolyllithium [5] produced **4** which was isolated as the hydrochloride salt in 88% yield (Scheme II). We envisioned that reduction of **4** would proceed readily either before or after methylation. Catalytic hydrogenation over a metal catalyst would then provide **1** directly. However, this vision was not borne out

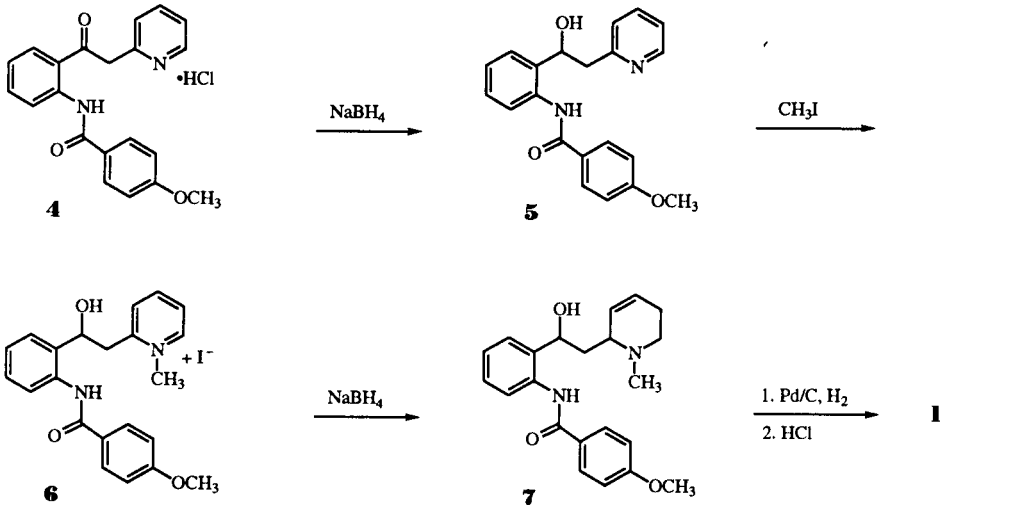
Scheme I



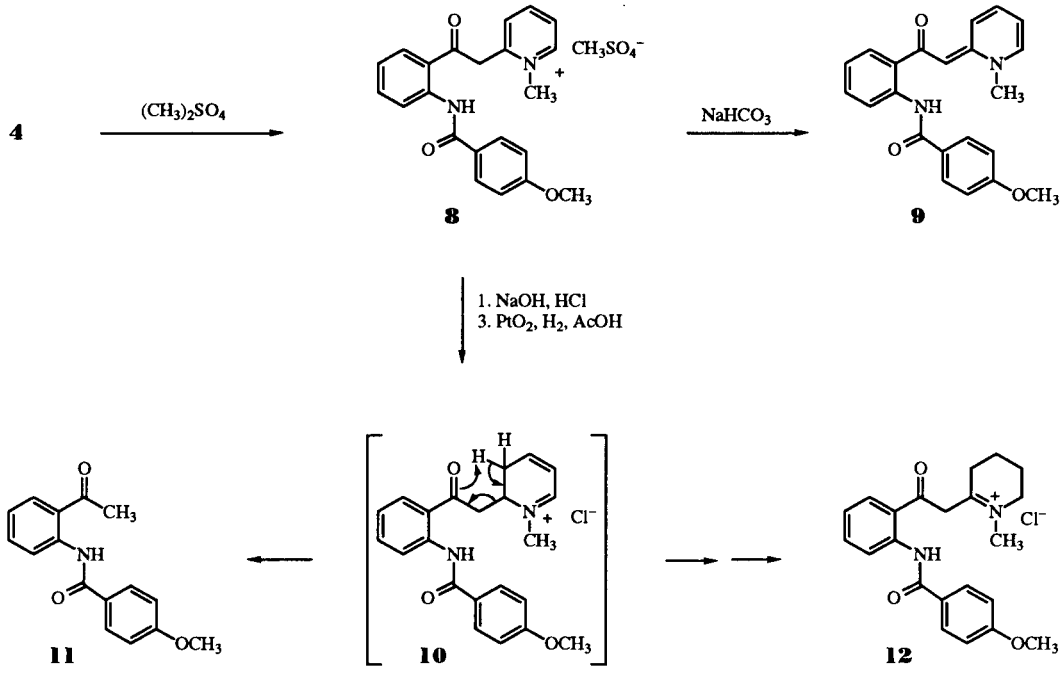
Scheme II



Scheme III



Scheme IV



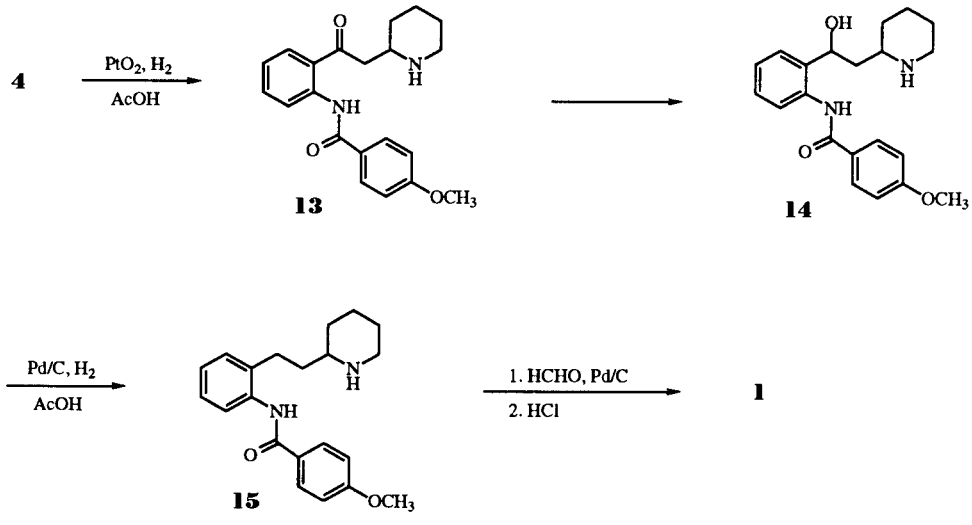
in practice. Hydrogenation of **4** in the presence of Raney nickel gave a complex mixture of products and no reaction occurred when palladium-on-carbon was used as catalyst in THF, ethanol or acetic acid at 25°.

Reduction of **4** with sodium borohydride [6] provided alcohol, **5**, which was quaternized with methyl iodide giving the pyridinium salt, **6**. This further reduced with sodium borohydride to the olefin, **7**, which was converted to Encainide, **1**, by catalytic hydrogenolysis over palladium-on-carbon (Scheme III). This was a tedious series of reductions requiring a large excess of sodium borohydride, so attention was turned to reduction of the quaternized form of **4**.

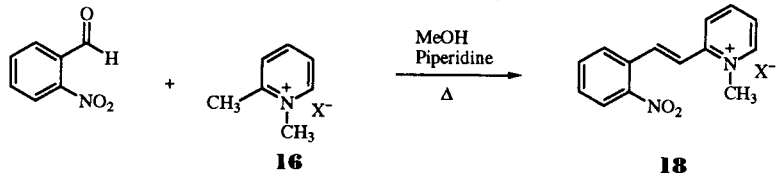
Quaternization of **4** with dimethyl sulfate afforded the white, water soluble pyridinium salt **8** which could be deprotonated with sodium bicarbonate to yield the brilliant yellow, water insoluble compound **9** (Scheme IV).

Neither **8** nor **9** could be successfully reduced to **1**. Attempted hydrogenation of **8** (after conversion to the chloride salt) with platinum metal catalyst produced a mixture of compounds **11** and **12**. Ketone **11** was presumably formed by fragmentation of an initially formed dihydropy-

Scheme V



Scheme VI



a. X = I⁻, **b**. X = Br⁻, **c**. X = $CH_3SO_4^-$

ridine, **10** [7]. Alternatively, isomerization and reduction gave **12** which was inert to further reduction. Reaction of **8** with sodium borohydride also yielded the vinylogous amide **9**, through deprotonation and was inert to further reduction.

A successful approach involved catalytic hydrogenation of **4** with platinum metal catalyst in acetic acid which produced the piperidyl alcohol **14**, initially by rapid absorption of three moles of hydrogen to form the piperidyl ketone **13**, and then by slow absorption of an additional mole of hydrogen (Scheme V).

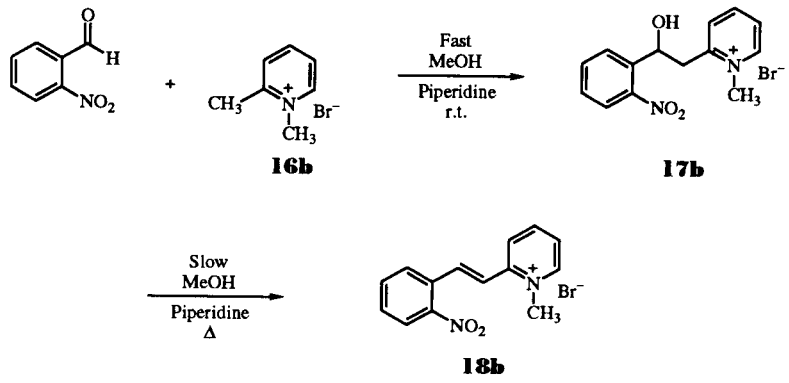
Hydrogenolysis of **14** in acetic acid with palladium on carbon catalyst, produced **15** which was converted to encainide, **1**, by reductive methylation with formaldehyde over palladium-on-carbon.

The series of reductions of **4** to **1** were then assembled in a one pot process. A solution of the hydrochloride of **4** with platinic oxide was stirred at 25° in acetic acid until three moles of hydrogen were absorbed, then the platinum was replaced with palladium on carbon. Reduction was continued until two additional moles of hydrogen were absorbed. Formalin was then added to the mixture and stirring was continued until hydrogen uptake was complete. In this manner **1** was prepared in 76% overall yield from **4**.

The involved nature of the various reductions by this methyl anthranilate based route prompted us to reexamine the earlier condensation of 2-picoline with *o*-nitrobenzaldehyde [3]. Quaternization of the ring nitrogen leads to enhanced acidity of the α-methyl hydrogens and it was shown by Horwitz [8] and Phillips [9] that styryl pyridinium salts could be prepared by condensation of picolinium methiodide, **16a**, with aromatic aldehydes, using piperidine as catalyst in refluxing methanol (Scheme VI). As the final target molecule, **1**, contains an *N*-methylpiperidyl function, this would effect two conversions in one step. However, the yield in the condensation of **16a** with *o*-nitrobenzaldehyde was disappointingly low [8].

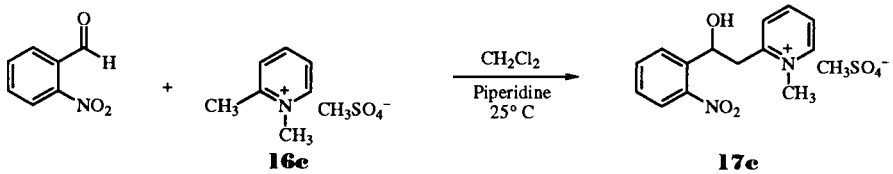
For cost factors, we reexamined the reaction with bromide salt, **16b** to determine the reasons behind this low yield. Alkylation of 2-picoline with methyl bromide proceeded readily in methanol at room temperature, to produce **16b** as a hygroscopic salt, which was not isolated, but reacted directly with *o*-nitrobenzaldehyde using a catalytic quantity of piperidine at room temperature, to afford not the expected olefin but rather the alcohol **17b** in 70% yield after concentration and crystallization from 2-propanol. Even under reflux, the production of olefin was slow (Scheme VII).

Scheme VII



16b 17b 18b

Scheme VIII

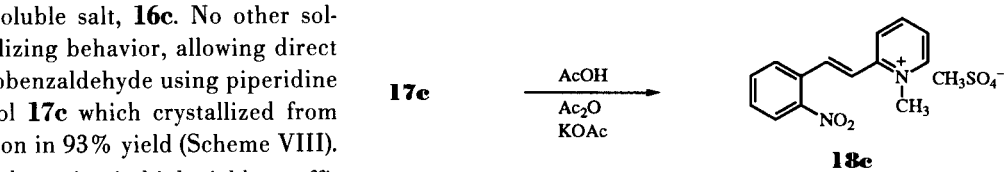


16c 17c

The mild conditions for production of alcohol **17b** were encouraging and we examined the use of other methylating agents and less polar solvents with hopes of effecting quaternization, condensation and subsequent direct crystallization of the alcohol in a one pot process. It was found that the reaction of 2-picoline with dimethyl sulfate proceeded at room temperature in 8-10 hours in dichloromethane to produce the soluble salt, **16c**. No other solvents exhibited this solubilizing behavior, allowing direct reaction of **16c** with *o*-nitrobenzaldehyde using piperidine catalysis to provide alcohol **17c** which crystallized from the dichloromethane solution in 93% yield (Scheme VIII).

Having achieved the condensation in high yield, an efficient dehydration procedure was required. However, this proved to be a non-trivial process. Hydrogenolysis of the alcohol in the presence of palladium-on-carbon did not work, unlike the case with **14**. Several acid catalyzed approaches including hydrogen chloride/heat, methanesulfonic acid *etc.* were unsuccessful. Mesylation followed by treatment with triethylamine did not give the required olefin. Refluxing **17c** in acetic anhydride led to decomposition while refluxing in a mixture of acetic acid and acetic anhydride gave a mixture of the highly insoluble sulfate salts of **17** and **18**. However, when a catalytic amount of potassium acetate was added to the mixture of acetic acid/acetic anhydride the dehydration was quite facile leading to a 96% yield of olefin **18c** after concentration and crystallization from 2-propanol Scheme IX). The ^{1}H nmr revealed **18c** to be the expected *trans* olefin.

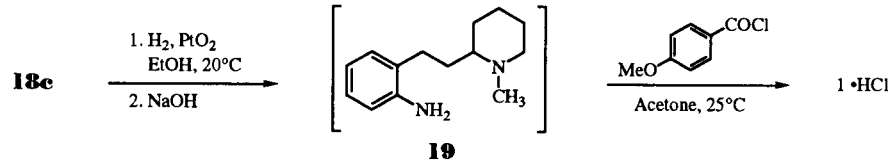
Scheme IX



18c

All three functional moieties in the olefin **18c** could be reduced by hydrogenation over platinum metal in ethanol to provide, after neutralization, the diamine precursor **19** to encainide, **1** [10] (Scheme X). This sequence required only one catalytic hydrogenation with one noble metal catalyst as opposed to two for the previous route. The diamine was not isolated but used directly in the next step. In this case, the unique structural features of **19** were exploited by using the *N*-methylpiperidyl moiety as an internal hydrogen chloride acceptor, and upon acylation of **19** with *p*-anisoyl chloride in acetone, the hydrochloride salt

Scheme X



19

of **1** crystallized directly from solution. Recrystallization of **1** from 2-propanol-methanol gave encainide in 56% overall yield from **18c**. This obviated the need to convert the free base form of **1** to the hydrochloride salt in a separate reaction.

In conclusion, two new methods for the preparation of Encainide were developed. Both have been successfully employed to prepare multikilogram quantities in an efficient manner.

EXPERIMENTAL

General.

All solvents were reagent grade and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless otherwise specified. Melting points were determined on a Mel-Temp capillary apparatus and were uncorrected. The ^{1}H nmr spectra were recorded on a Bruker AM 360 FT Spectrometer. The ir were taken on a Bio-Rad Digilab FTS-45 spectrometer. Elemental analyses were performed by the Pharmaceutical Research Institute, Analytical Research and Development Department of Bristol-Myers Squibb Company.

4-Methoxy-*N*-[2-(2-pyridinylacetyl)phenyl]benzamide (**4**).

n-Butyllithium (1.6*M*/hexane, 713 ml, 1.14 moles) was added to 530 ml of THF, and then 115.0 g (1.14 moles) of diisopropylamine was added, followed by 108.0 g (1.16 moles) of 2-picoline, all under nitrogen at $\leq 15°$. A solution of 100.0 g (3.51 mole) of **3** [11] in 675 ml of THF was added with stirring to the solution above at $\leq 15°$. The solution was warmed to 20° and stirred for 15 minutes and then it was added slowly with stirring to 2 ℓ of 10% acetic acid. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 300 ml). The combined organic layers were concentrated *in vacuo*. The residue was dissolved in 2.38 ℓ of hot 2-propanol. The solution was concentrated by distillation to 1.2 ℓ and then chilled to 0°. The resulting brilliant yellow solid was collected on a filter, rinsed with 2-propanol (100 ml) and air dried to give 108.2 g of **4** (89% of theory), mp 148.5-150.5°; ^{1}H nmr (DMSO-d_6): (approximately 50:50 keto-enol tautomers) δ 3.78 (1.5H, s, OCH_3), 3.80 (1.5H, s, OCH_3), 4.60 (1H, s, CH_2), 6.05 (0.5H, s, vinyl), 10.65-11.40 (12H, m, ArH), 10.65 (0.5H, s, NHCO), 11.40 (0.5H, s, NHCO).

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.48; H, 5.23; N, 7.89.

The hydrochloride of **4** was prepared by dissolving 25.0 g (72 mmoles) of the base in 500 ml of warm THF to give a bright yellow solution. The solution was stirred in an ice-bath as 6.5 ml (78 mmoles) of 12*N* hydrochloric acid was added. The white solid was collected on a filter, rinsed with 50 ml of THF and air-dried to give 24.7 g (99% of theory) of **4**·HCl, mp 190.5-191.5° dec.

4-Methoxy-*N*-[2-[1-hydroxy-2-(2-pyridinyl)ethyl]phenyl]benzamide (**5**).

A solution of 5.0 g (14 mmoles) of **4** in 100 ml of THF was stirred at 20° as a solution of 0.54 g (14 mmoles) of sodium borohydride in 10 ml of water was slowly added. The solution was stirred 2 hours at 20°, and then 3.5 g (58 mmoles) of acetic acid and 150 ml of water were added. The THF was distilled *in vacuo*, and the residue was extracted with dichloromethane (2 x 50 ml). The combined extracts were dried (potassium carbonate) and concentrated *in vacuo* to give 5.0 g of yellow oil.

An ethanol/propyl ether solution of the base was treated with hydrogen chloride. The resulting solid was collected on a filter and air-dried. It was recrystallized from absolute ethanol to give a slightly yellow solid, **5**·HCl·H_2O, mp 175-178° dec; ^{1}H nmr (Me_2SO-d_6): δ 3.58 (2H, d, CH_2), 3.78 (3H, s, OCH_3), 5.33 (1H, t, OCH), 6.98-8.83 (12H, m, ArH), 10.43 (1H, s, NHCO).

Anal. Calcd. for $C_{21}H_{20}N_2O_3$·HCl·H_2O: C, 62.60; H, 5.75; N, 6.96. Found: C, 62.69; H, 5.66; N, 6.91.

2-[2-Hydroxy-2-[2-(4-methoxybenzoyl)amino]phenyl]ethyl-1-methylpyridinium Iodide (**6**).

A solution of 25.1 g of **5** in 100 ml of acetonitrile was treated with 11.4 g (80 mmoles) of methyl iodide; the solution was heated under reflux for 3 hours. The solvent was distilled *in vacuo*, and the residue was triturated with ether (2 x 30 ml) and then acetone (1 x 30 ml). The solid was collected on a filter and air-dried to give 35.3 g (100% of theory) of **6** as a pale yellow solid; ^{1}H nmr (DMSO-d_6): δ 3.33 (2H, d, CH_2), 3.70 (3H, s, OCH_3), 4.13 (3H, s, $-NCH_3)^+$, 5.15 (1H, bt, OCH), 6.88-8.97 (12H, m, ArH), 10.25 (1H, s, NHCO). The material was used without purification.

Reduction of **6**.

A solution of 6.0 g (12 mmole) of **6** in 300 ml of methanol was stirred in an ice-bath as a solution of 23.4 g (618 mmoles) of sodium borohydride in 450 ml methanol was added over 20 minutes; the solution was stirred an additional hour at 25°. Then 850 ml of water was added, and the methanol was distilled *in vacuo*. The mixture was first acidified with hydrochloric acid and then adjusted to *p*H 11 with sodium hydroxide. The resultant oil was extracted with dichloromethane (3 x 200 ml); the extracts were washed with water (1 x 300 ml). The solvent was distilled *in vacuo* to give 6.0 g of yellow oil **7** which was used directly in the next step.

Reduction of **7**.

The yellow oil **7** was dissolved in 100 ml of 95% ethanol and 2.5 ml of 37% hydrochloric acid. The solution was stirred with 1.0 g of 50% water-wet 5% Pd/C under hydrogen at 65° for 16 hours. The mixture was cooled and filtered. The filtrate was distilled *in vacuo*, and the residue was dissolved in 250 ml of water. The solution was made basic (*p*H 12) with sodium hydroxide. The resulting gum was extracted with dichloromethane (3 x 50 ml). The combined extracts were washed with water (1 x 100 ml), dried (magnesium sulfate) and distilled to dryness *in vacuo* to 3.2 g (69% based on **6**) of **1** as a white solid, mp 130.5-132.0°, mixed mp 130.5-132.5° with **1** prepared according to Scheme I.

2-[2-[2-(4-Methoxybenzoyl)amino]phenyl]-2-oxoethyl-1-methylpyridinium Methyl Sulfate (**8**).

A solution of 41.0 g (0.118 mole) of **4** and 29.8 g (0.236 mole) of dimethyl sulfate in 225 ml of dichloromethane was stirred at reflux for 24 hours. The mixture was chilled to 5°, and the solid was collected on a filter and air-dried. The slightly yellow solid weighed 51.0 g (91% of theory). A sample was recrystallized from water (1.83 ml/g at 60°) with 65% recovery to give a nearly white solid, mp 209-212° dec.

The elemental and spectral analyses of the recrystallized material were consistent for the assigned structure as an approximately equal mixture of hydrogensulfate and methyl sulfate salts; ^{1}H nmr (Me_2SO-d_6): δ 3.54 (1.5H, s, OSO_3CH_3), 4.00 (3H, s, OCH_3),

4.52 (3H, s, N^+CH_3), 5.62 (2H, s, CH_2), 7.2-9.0 (12H, bm, ArH), 9.50 (1H, bs, OSO_3H), 13.70 (1H, bs, NHCO).

Anal. Calcd. for $C_{22}H_{21}N_2O_3^+ \cdot 0.5CH_3OSO_3^- \cdot 0.5HOSO_3^-$: C, 58.06; H, 4.98; N, 6.02. Found: C, 57.79; H, 4.96; N, 5.89.

Deprotonation of **8**.

A solution of 4.73 g (10 mmoles) of **8** in 130 ml of water was stirred as a solution of 3.36 g (40 mmoles) of sodium bicarbonate in 40 ml of water was added. The intensely yellow solid was collected on a filter, rinsed with several portions of water, and air-dried to give 3.6 g (100% of theory) of **9**, mp (open capillary) 140-190° dec, (sealed capillary under nitrogen) 183-190° dec; ^1H nmr (DMSO-d_6): δ 3.79 (3H, s, NCH_3), 3.92 (3H, s, OCH_3), 5.83 (1H, s, vinyl), 6.67-9.58 (12H, m, ArH and vinyl), 13.70 (1H, s, NHCO).

Anal. Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 72.78; H, 5.57; N, 7.68.

Reduction of **8**.

A solution of 12.0 g (0.025 mole) of **8** in 400 ml of water was stirred as 4.0 g of 50 wt% sodium hydroxide (0.05 mole) was added. The bright yellow solid was collected on a filter, rinsed with water and air-dried. A solution of the material in 300 ml of THF was filtered, and then it was chilled as 2.6 ml of 12*N* hydrochloric acid (0.031 mole) was slowly added. The resulting solid was collected on a filter, rinsed with THF and air-dried to give 9.9 g of light-yellow solid (100% of theory).

A solution of 4.9 g (0.0123 mole) of this pyridinium chloride in 50 ml of acetic acid containing 250 mg of platinic oxide was stirred under hydrogen for 4 hours by which time 3.93 equivalents of hydrogen had been absorbed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting oil was dissolved in 50 ml of water. The solution was made basic with sodium hydroxide until no more material separated from solution. The supernatant was decanted and the semi-solid was rinsed with water. It was recrystallized from 20 ml of hot 95% ethanol to give 3.0 g of solid. This material was recrystallized from 20 ml of 50 vol% of 2-propanol to give 1.4 g of white solid. A portion of the solid, 1.1 g, was stirred with 20 ml of 10% hydrochloric acid. The insoluble material was collected on a filter, rinsed with water and air-dried to give 0.25 g of white solid, identified as **11**; MW Calcd. for $C_{16}H_{15}NO_3$: 269. Found ms: M^+ 269, MH^+ 270; ^1H nmr (deuteriochloroform): δ 12.63 (1H, bs, NH), 8.90 (1H, d, J = 8 Hz), 7.48 (4H, AB, J_{AB} = 9 Hz, $\Delta\nu_{AB}$ = 31 Hz), 7.2-7.9 (3H, m), 3.75 (3H, s, OCH_3), 2.53 (3H, s, $COCH_3$).

The acidic filtrate was adjusted to *p*H 12, and the resulting solid was collected on a filter, rinsed with water and air-dried to give 0.75 g of **12**; MW Calcd. for $(C_{22}H_{25}N_2O_3)^+$: 366. Found ms: M^+ 366, MH^+ 367; ^1H nmr (deuteriochloroform): δ 12.63 (1H, bs, NH), 8.90 (1H, d, J = 8 Hz), 7.48 (4H, AB, J_{AB} = 9 Hz, $\Delta\nu_{AB}$ = 31 Hz), 7.2-7.9 (3H, m), 3.80 (3H, s), 2.5-3.7 (4H, m), 2.30 (3H, s), 1.55 (6H, bs).

4-Methoxy-*N*-[2-(2-piperidinylacetyl)phenyl]benzamide Hydrochloride (**13**).

A solution of 50.0 g (144 mmoles) of **4** in 1.0 ℓ of acetic acid and 30 ml of 12*M* methanolic hydrogen chloride containing 1.0 g of platinic oxide was stirred under hydrogen (1 atm) at 23° until 3 equivalents of hydrogen had been absorbed (approximately 18 hours). The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue solidified after standing two weeks. The solid was recrystallized from a boiling mixture of 500 ml of absolute ethanol and 900 ml of methanol to give 39.5 g (71% of theory) of **13** as a pale yellow compound, mp 230-231.5°. A second crop, 6.0 g, brought the yield to 81% of theory; ^1H nmr (DMSO-d_6): δ 1.83 (6H, bs, $-(CH_2)_3-$), 2.9-4.0 (5H, bm, -CH-N-CH_2- and $-COCH_2$), 4.08 (3H, s, OCH_3), 7.5-9.3 (8H, m, ArH), 9.4-10.5 (2H, bs, $NH_3)^+$, 11.1 (1H, bs, NHCO); uv (10/ml of ethanol): λ max (nm) 340 (ϵ 8700), 270 (ϵ 19,600), 251 (ϵ 29,100), 216 (ϵ 20,500).

Anal. Calcd. for $C_{21}H_{24}N_2O_3 \cdot HCl$: C, 64.86; H, 6.48; Cl, 9.12; N, 7.20. Found: C, 65.02; H, 6.43; Cl, 9.06; N, 7.09.

Catalytic Reduction of **4** to **14**.

A solution of 5.36 g (14 mmoles) of **4**·HCl in 50 ml of acetic acid, 1.0 g of 10 wt% Pd/C and 0.1 g of platinic oxide were stirred together under hydrogen at 23° for 48 hours. The mixture was warmed and 95% ethanol was added just to dissolved a solid in the mixture. The mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was recrystallized from 2-propanol/methanol to give 5.0 g of **14**·HCl. The nmr spectrum was identical to authentic **14**·HCl.

4-Methoxy-*N*-[2-[2-(2-piperidinyl)ethyl]phenyl]benzamide (**15**).

A mixture of 12.7 g (33.2 mmoles) of **4**·HCl, 250 mg of platinic oxide and 250 ml of acetic acid was stirred under hydrogen (1 atm) at 23° for 24 hours. The mixture was warmed gently, and then it was filtered. The filtrate was stirred with 2.5 g of 10 wt% Pd/C at 75° under hydrogen (1 atm) for 6 hours. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The oil was dissolved in 300 ml of water, and 0.27 g of 4-methoxybenzoic acid (mp 179-182°) was removed by filtration. The filtrate was adjusted to *p*H 13 with sodium hydroxide, and the solid was collected on a filter, rinsed with water and air-dried. The solid was recrystallized from 25 ml of acetonitrile to give 6.9 g (62% of theory) of white crystalline **15**, mp 123-125°. A second recrystallization from acetonitrile (2 ml/g) and once from methanol (1 ml/g) gave material mp 125-126°; ^1H nmr (deuteriochloroform): δ 0.2-3.2 (14H, bm, CH, $(CH_2)_6$, NH), 3.75 (3H, s, OCH_3), 6.8-8.3 (8H, m, ArH), 11.3 (1H, s, NHCO).

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.55; H, 7.67; N, 8.11.

Reductive Methylation of **15**.

A solution of 0.5 g (1.47 mmoles) **15** in 10 ml of acetic acid containing 100 mg of 10 wt% Pd/C and 0.5 ml of 37% formalin was stirred under hydrogen (1 atm) at 23° for 16 hours. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from 1 ml of acetonitrile to give **1** (free base), mp 128-131°. The nmr spectrum was identical to that reported for **1** below.

4-Methoxy-*N*-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]benzamide (**1**). One-Pot Process.

A mixture of 53.5 g (140 mmoles) of **4**·HCl, 1.0 g of platinic oxide and 1.0 ℓ of acetic acid was stirred under hydrogen (1 atm) at 23° for 20 hours, by which time 3.08 equivalents of hydrogen had been absorbed. The mixture was filtered, and the filtrate was stirred with 10.0 g 10 wt% Pd/C under hydrogen (1 atm) at 60±3° for 6.5 hours, whereby an additional 2.0 equivalents of hydrogen were absorbed. The mixture was cooled to 25°, and 22.7 g of formalin (37 wt% formaldehyde, 8.4 g, 280 mmoles) was injected into the flask. The mixture was stirred under hydrogen

(1 atm) at 23° for 20 hours, during which time 1.04 equivalents of hydrogen were absorbed. The mixture was filtered and the filtrate was concentrated *in vacuo* to a thick oil. Twice the oil was mixed with 200 ml of 2-propanol and concentrated *in vacuo*. Then the material was recrystallized from 200 ml of boiling 2-propanol. The product was collected on a filter, rinsed with cold 2-propanol and dried *in vacuo* at 70° for 4 hours to give 36.6 g (67% of thory) of fine white crystalline **1**·HCl mp 181.5-184.5°. A second crop of 4.7 g of **1**·HCl was isolated from the filtrate bringing the total yield to 76% of theory; ^{1}H nmr (DMSO-d_6): δ 1.70 (8H, m, -$(CH_2)_4$-), 2.65 (3H, bs, N-CH_3), 3.10 (5H, m, CH, $(CH_2)_2$), 3.92 (3H, s, OCH_3), 7.30 (6H, m, ArH), 8.21 (2H, bd, ArH), 10.24 (1H, bs, NHCO).

Anal. Calcd. for $C_{22}H_{28}N_2O_2$·HCl: C, 67.94; H, 7.52; Cl, 9.12; N, 7.20. Found: C, 67.61; H, 7.57; Cl, 9.02; N, 7.03.

2-(1-Methylpyridinium-2-yl)-1-(2-nitrophenyl)ethanol Methyl Sulfate (**17c**).

To a solution containing 61.6 g (0.66 mole) of 2-picoline in 650 ml of dichloromethane was added 78.5 g (0.63 mole) dimethyl sulfate. A gentle reflux resulted and the solution was cooled to 25° and held for 8-10 hours. *o*-Nitrobenzaldehyde, 95 g (0.63 mole) was added and, after a solution was obtained, piperidine (3.9 ml) was added. The mixture was held for 2 hours and the resulting slurry cooled to 5° and filtered, washing with 250 ml of dichloromethane. The solid was dried *in vacuo* to give **17c** as an off-white solid. Analytically pure material was obtained by recrystallization from methanol/2-propanol, mp 157.5-159.5°, ^{1}H nmr (DMSO-d_6): δ 9.01 (d, J = 6.1 Hz, 1H), 8.54 (t, J = 7.8 Hz, 1H), 8.00 (M, 3H), 7.93 (d, J = 7.8 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H) 7.61 (m, 1H), 6.11 (d, J = 4.3 Hz, 1H), 5.49 (m, 1H), 4.41 (S, 3H), 3.55 (m, 2H), 3.35 (S, 3H).

Anal. Calcd. for $C_{15}H_{18}N_2O_7S$: C, 48.60; H, 4.91; N, 7.56. Found: C, 48.71; H, 4.91; N, 7.38.

2-(2-Nitrostyryl)-1-methylpyridinium Methyl Sulfate (**18c**).

To a mixture containing 400 ml of glacial acetic acid and 50 ml of acetic anhydride was added 100 g (0.27 mole) of **17c** and 2 g of potassium acetate. The mixture was refluxed for 2 hours and cooled to 40°. The solvents were removed by concentration *in vacuo*. 2-Propanol (600 ml) was added to crystallize **18c**. The slurry was cooled to 5°, filtered and washed with 2-propanol (250 ml). The solid was dried *in vacuo* at 25° to give 91.3 g (96%) of **18c** as a yellow crystalline solid. Analytically pure material was obtained by recrystallization from methanol-2-propanol, mp 145-146°; ^{1}H nmr (DMSO-d_6): δ 9.00 (d, J = 6.1 Hz, 1H), 8.57 (t, J = 7.8 Hz, 1H), 8.44 (d, J = 7.4 Hz, 1H), 8.14 (m, 2H), 8.08 (d, J = 16 Hz, 1H), 8.01 (m, 1H), 7.88 (t, J = 7.3 Hz), 7.73 (m, 1H), 7.63 (d, J = 16 Hz, 1H), 4.42 (S, 3H), 3.36 (S, 3H).

Anal. Calcd. for $C_{15}H_{16}N_2O_6S$: C, 51.12; H, 4.59; N, 7.95. Found: C, 50.82; H, 4.60; N, 7.90.

2-(2-Aminophenethyl)-1-methylpiperidine (**19**).

Olefin **18c** (25 g, 0.07 mole) and 10 g of 5% platinum on carbon (50% water wet) were stirred in 300 ml of 95% ethanol in a 2 ℓ Parr hydrogenation flask. Hydrogen was admitted at 2 psi and the mixture reacted for 16 hours. The hydrogenation mixture rapidly turned orange and slowly became colorless as the solid dissolved. The catalyst was removed by filtration and the solvent removed by concentration *in vacuo*. The resulting oil was dissolved in 50 ml of water and the *p*H raised to 11 with 50% w/w sodium hydroxide solution. The aqueous phase was extracted sequentially with 50 ml and 25 ml portions of dichloromethane, the extracts were combined and dried (anhydrous potassium carbonate), and after filtration the solvent was removed by concentration *in vacuo* to yield 14.3 g of a crude oil which was used directly in the next step. In a separate experiment, the diamine was isolated as a monohydrochloride salt by dissolving the crude oil in 2-propanol and adding gaseous hydrogen chloride, mp 138-139°; ^{1}H nmr (DMSO-d_6): δ 6.90 (M, 2H), 6.61 (d, J = 7.9 Hz, 1H), 6.49 (t, J = 6.9 Hz, 1H), 3.4-1.3 (m, 16H).

Anal. Calcd. for $C_{14}H_{23}N_2Cl$: C, 65.99; H, 9.12; N, 10.99. Found: C, 66.22; H, 9.34; N, 10.67.

4-Methoxy-2′-[2-(1-methyl-2-piperidyl)ethyl]benzamide Hydrochloride (**1**·HCl).

Unpurified **19** (14.3 g) from the prior step was dissolved in 100 ml of acetone and *p*-anisoyl chloride (12.1 g, 0.071 mole) was added. The reaction mixture was stirred 16 hours, cooled to 5° and filtered, washing with 25 ml of cold acetone. The solid was dried *in vacuo* at 25° for 6 hours. The dried solid was recrystallized from methanol-2-propanol to give 15.5 g (56% from **18c**) of **1**·HCl, mp 183-185°, ^{1}H nmr (DMSO-d_6): δ 10.21 (S, 1H), 9.92 (S, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.34 (m, 7.24) (m, 3H), 7.05 (d, J = 8.8 Hz, 2H), 3.83 (S, 3H), 3.4-2.5 (m, 8H), 2.2-1.2 (M, 8H).

Anal. Calcd. for $C_{22}H_{29}ClN_2O_2$: C, 67.93; H, 7.53; N, 7.20. Found: C, 68.06; H, 7.60; N, 7.12.

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