Synthesis of 4-Methoxy-*N*-{2-[3-(Methylamino)heptyl]phenyl}benzamide, an Antiarrhythmic Compound Related to Encainide

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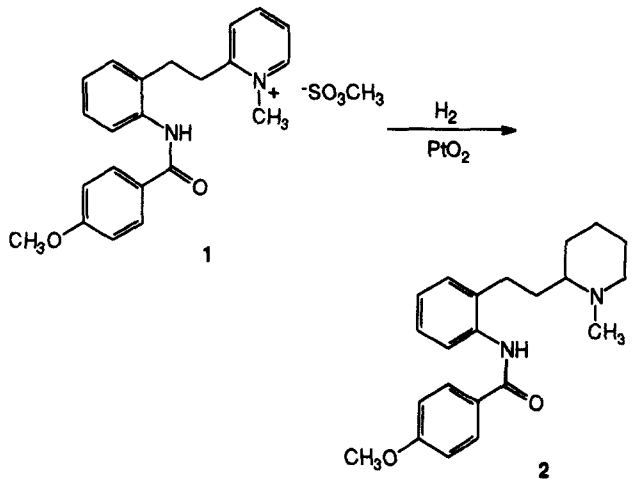
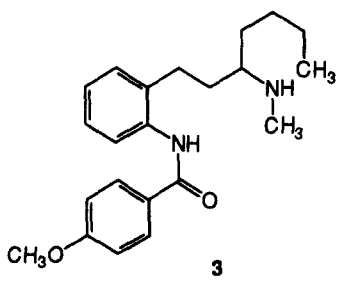
A ring-opened side product **3**, formed during the reduction of a pyridinium precursor to the antiarrhythmic drug, encainide **(2)**, was isolated. The structure of **3** was confirmed by an independent synthesis from *o*-iodonitrobenzene and 1-hepten-3-ol. The key step was a palladium(II) catalyzed coupling to introduce the 3-oxoheptyl side chain onto the aromatic ring. Synthetic **3** exhibited significant antiarrhythmic activity.

Several years ago, a series of piperidines related to lysergic acid was prepared by Dykstra and co-workers.[2] Many of these analogues were noted to possess antiarrhythmic activity. One of these analogues, encainide **(2)**, was further tested in humans and more recently has been marketed as an antiarrhythmic drug. A procedure for the preparation of encainide involved reduction of the quaternized pyridine **1**.[3] The pyridinium ring was reduced to **2** with hydrogen using platinum oxide as the catalyst in approximately 75% yield.

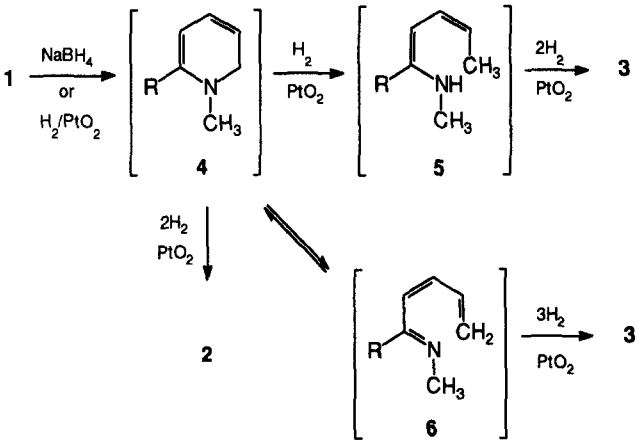


A side product was observed and isolated in trace quantities (< 1%) from a sample of **2**. Spectral studies (^{13}C and ^{1}H NMR, and MS) indicated that side product **3** contained two hydrogens more than **2**. The mass spectrum also indicated the presence of a butyl group. The NMR revealed that the NCH_2 triplet was absent, and an aliphatic methyl was now present at $\delta = 0.82$. These results indicated that the structure of **3** is as shown.[4]



The formation of **3** was unusual and warranted further attention. In exploring the reduction in some detail, variations of the original hydrogenation were performed. Dykstra noted that pretreatment of the pyridinium moiety with sodium borohydride prior to catalytic hydrogenation facilitated the desired reduction.[2] However, when this reaction was repeated using **1**, product **2** was contaminated with 8% (by HPLC) of **3**.[5] Attempts to optimize this reaction for the preparation of **3** were unsuccessful owing to the complex nature of the reaction mixture. Therefore, it was desirable to prepare **3** by synthesis to confirm its structure and to provide an opportunity to evaluate its biological activity.

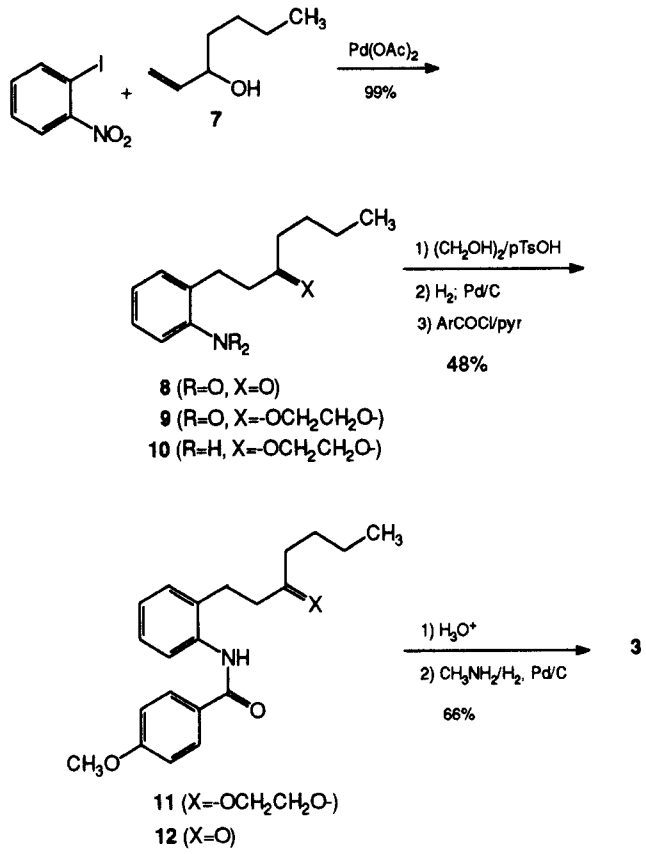
One can rationalize the formation of compound **3** by assuming that initially the carbon–nitrogen double bond of **1** could be reduced with hydrogen or sodium borohydride to give 1,6-dihydropyridine **4** (Scheme 1).[6-9] Diene **4** could either be reduced directly to **2** or undergo hydrogenolysis of the allylic carbon–nitrogen single bond to give **5**. Further reduction of **5** would give **3**. Alternatively, an electrophilic ring opening of **4** could occur giving **6**.[10] Further reduction of **6** would also give **3**.



Scheme 1

The structure of **3** was confirmed by synthesis as outlined in Scheme 2. The key step in this approach was to couple allylic alcohol **7** to an aromatic halide, similar to the chemistry described by Jeffery.[11] The initial allylic alcohol **7** was prepared from valeraldehyde using a Grignard reaction.[12] Alcohol **7** was coupled with *o*-iodonitrobenzene in the presence of palladium(II) acetate to give **8** as an oil.[11] Ketone **8** was protected as the ketal to prevent formation of the tetrahydroquinoline derivative during the reduction step. Resulting ketal **9** was obtained from valeraldehyde in 44% yield. Next, the nitro group was reduced to the amine **10**, which was acylated with *p*-

anisoyl chloride giving solid amide product **11** in 80% yield from **9**. The ketone was deprotected with acid to give **12** in 89% yield. Reductive amination proved to be the most difficult step of the synthesis. Most reactions were incomplete, and a recycling of the reaction mixture was necessary in order to obtain high yields of **3**. Final reductive amination of **12** was accomplished with methylamine, hydrogen, and 10% palladium-on-carbon in 74% yield (includes recycling). Attempts to form the imine from **12** and methylamine, followed by reduction with sodium cyanoborohydride met with only limited success.[13-14]



Scheme 2

The combined overall yield of **3** from 1-hepten-3-ol (**7**) was 31%. Although the melting point of the synthesized hydrochloride salt was slightly higher than isolated **3**, all the spectral properties of the synthetic product matched those of material isolated by chromatography. The difference in melting point behavior may be due to minor impurities present in the isolated **3**. A mixed melting point showed isolated and synthetic **3** to be identical. Initial studies show that **3** is effective against reperfusion arrhythmia ($ED_{50} < 10$ mg/Kg, oral-rat),[15] comparable to encainide.[2] This is the first reported evidence that the piperidine ring does not need to be intact in order to retain antiarrhythmic activity for this class of compound.

Melting points were obtained on a Buchi 510 melting point apparatus utilizing open capillary tubes and are uncorrected. Infrared spectra were obtained on a Nicolet MX-1 infrared spectrophotometer, and all absorptions were reported in wave numbers (cm^{-1}). The NMR spectra were obtained on a Bruker AM-300 spectrometer. Both proton (300 MHz) and carbon spectra (60 MHz) are reported in parts per million (ppm) downfield from internal tetramethylsilane. Chemical ionization (CI) and electron impact (EI) mass spectra (MS) were obtained using a Finnigan series 4000 mass spectrometer. Compounds **3**, **3** · HCl, and **8–12** gave C, H, N analysis ± 0.37%.

Isolation of 4-Methoxy-*N*-{2-[3-(methylamino)heptyl]phenyl}benzamide Hydrochloride (3):

A 190 g sample of encainide hydrochloride which contained **3** as an impurity was recrystallized twice from *i*-PrOH/EtOAc. The two filtrates were combined and solvent was removed. The 12.5 g residue was recrystallized from *i*-PrOH, and the filtrate was concentrated to obtain a 7.4 g residue enriched in **3**, which was converted into free base using dil. NH_4OH, and chromatographed twice [4:1:0.25, CH_2Cl_2/MeOH/NH_4OH (conc); silica gel] to give 380 mg of solid. HPLC was used to examine individual chromatography fractions (Waters 10 SCX ion exchange column; 7:3, MeOH/0.1 M aq ammonium dihydrogen phosphate; UV detection at 254 nm; flow, 1.0 mL/min). The solid was again chromatographed with a center cut giving 55 mg of almost pure **3** as an oily residue. This was converted to the HCl salt using 5 M ethanolic HCl, and was recrystallized from *i*-PrOH/EtOAc. Crystalline solid **3** (15 mg, 0.008% recovery) was obtained; mp 162–167°C.

^{1}H NMR (DMSO-d_6): δ = 0.68 (3 H, t, J = 7 Hz, CH_3), 1.1 (4 H, m, $CH_2CH_2CH_3$), 1.6 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.9 (2 H, m, $ArCH_2CH_2$), 2.44 (3 H, s, NCH_3), 2.7 (2 H, m, $ArCH_2$), 2.9 (1 H, m, NCH), 3.82 (3 H, s, OCH_3), 7.04 (2 H, d, J = 9 Hz, H_{arom}), 7.23 (3 H, m, H_{arom}), 7.36 (1 H, m, H_{arom}), 8.08 (2 H, d, J = 9 Hz, H_{arom}), 9.1 (2 H, s, NH_2^+), 10.1 (1 H, s, NHCO).

^{13}C NMR (DMSO-d_6): δ = 13.4, 21.9, 26.2, 26.6, 28.7, 29.6, 29.7, 55.4, 57.9, 113.4 (2C), 126.3 (2C), 128.0, 129.4, 129.5 (3C), 136.1, 137.6, 161.8, 165.1.

Base Prepared from the Salt:

MS (EI): m/z (%) = 354 (10, M^+), 339 (10, $M-CH_3$), 323 (15, $M-OCH_3$), 297 (14, $M-C_4H_9$), 266 (21), 135 (100, $H_3COC_6H_4CO^{\bullet+}$), 100 (93, $CH_3NHCHC_4H_9^{\bullet+}$).

1-Hepten-3-ol (7):

The described preparation is a modification of the procedure reported by Kenyon and Snellgrove.[12] To a solution of 15.9 mL (0.140 mol) of valeraldehyde in 750 mL of anhydr. Et_2O at 0°C under N_2, a solution of 155 mL (0.155 mol) of 1.0 M vinylmagnesium bromide in THF was added slowly. After the addition was complete (ca. 1 h), the mixture was warmed to r.t. and sat. aq NH_4Cl was added. After 1 h of additional stirring, the organic layer was separated and dried (Na_2SO_4). Solvent was removed under reduced pressure giving an oil. Bulb-to-bulb distillation (50–100°C at 10 mmHg) gave 12.5 g (74% yield) of clear colorless liquid containing ca. 10% pentanol.

IR (film): ν = 3360 (br), 2970, 2940, 2900, 1640, 1440, 1375, 1050, 1030, 990, 920 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.90 (3 H, t, J = 7 Hz, CH_3), 1.3 (4 H, m, CH_2,CH_2,CH_3), 1.5 (2 H, m, $OCHCH_2$), 2.47 (1 H, brs, OH), 4.06 (1 H, q, J = 7 Hz, OCH), 5.07 (1 H, d, J = 10 Hz, vinyl CH_2), 5.19 (1 H, d, J = 17 Hz, vinyl CH_2), 5.85 (1 H, ddd, J = 6, 10, 17 Hz, vinyl CH).

^{13}C NMR ($CDCl_3$): δ = 14.0, 22.7, 27.6, 36.8, 73.2, 114.4, 141.5.

MS (CI): m/z (%) = 97 (100, MH^+-18).

1-(2-Nitrophenyl)-3-heptanone (8):

According to the procedure of Jeffery,[11] a mixture of 21.1 g (0.0848 mol) of *o*-iodonitrobenzene, 12.0 g (0.106 mol) of **7**, 23.8 g (0.0856 mmol) of tetrabutylammonium chloride, 18.1 g (0.215 mmol) of $NaHCO_3$ and 0.35 g (0.0016 mol) of palladium(II) acetate in 100 mL of DMF was warmed at 50°C for 7 h. The mixture was cooled to r.t. and stirred for 40 h. The resulting mixture was poured into water and extracted with CH_2Cl_2. The combined organic phase was washed with water and dried ($MgSO_4$). Solvent was removed under reduced pressure. The resulting residue was diluted with toluene and filtered. The volatiles were removed from the filtrate, and the residue was distilled bulb-to-bulb (125–150°C at 0.20 mmHg) giving 19.6 g (99% yield) of an amber oil. An ana-

lytical sample of **8** was prepared by stirring the ketal **9** (5.50 g) in a mixture of 10 mL of THF, 40 mL of methanol and 10 mL of 5% aqueous HCl at r.t. for 24 h. The mixture was extracted with CH_2Cl_2. The organic phase was washed with water, sat. aq $NaHCO_3$, and dried ($MgSO_4$). Solvent was removed and the residue was distilled bulb-to-bulb (130–145 °C at 0.20 mmHg) giving 4.26 g of a pale yellow oil.

IR (film): ν = 2960, 2940, 2875, 1715, 1525, 1460, 1350, 790, 745 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.89 (3 H, t, J = 7 Hz, CH_3), 1.29 (2 H, sext, J = 7 Hz, CH_2CH_3), 1.53 (2 H, quint, $CH_2CH_2CH_3$), 2.40 (2 H, t, J = 7 Hz, $CH_2CH_2CH_3$), 2.81 (2 H, t, J = 7 Hz, $ArCH_2CH_2$), 3.15 (2 H, t, J = 7 Hz, $ArCH_2$), 7.38 (2 H, m, H_{arom}), 7.51 (1 H, t, J = 8 Hz, H_{arom}), 7.92 (1 H, d, J = 8 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 13.8, 22.3, 25.9, 27.3, 40.1, 42.5, 124.8, 127.3, 132.4, 133.1, 136.4, 149.3, 209.3.

MS (CI): m/z (%) = 236 (100 MH^+).

2-Butyl-2-[2-(2-nitrophenyl)ethyl]-1,3-dioxolane (9):
A mixture of 77.4 g (0.329 mol) of **8**, 200 mL of ethylene glycol and 1 g of *p*-toluenesulfonic acid monohydrate in 350 mL of toluene was heated at reflux for 18 h to expel water. After cooling, two layers were observed. The mixture was separated, and the upper toluene layer was washed with 5% aq $NaHCO_3$ then dried (Na_2CO_3). Solvent was removed under reduced pressure, and the residue was distilled bulb-to-bulb giving 55.1 g (60% yield) of pale-amber liquid; bp 170–210 °C at 0.40 mmHg.

IR (film): ν = 2980, 2880, 1615, 1530, 1460, 1350, 1210, 1150, 1135, 1080, 1040, 950, 860, 790, 745 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.91 (3 H, t, J = 7 Hz, CH_3), 1.4 (4 H, brm, $CH_2CH_2CH_3$), 1.7 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.0 (2 H, m, $ArCH_2CH_2$), 2.9 (2 H, m, $ArCH_2$), 3.97 (4 H, s, OCH_2), 7.35 (2 H, m, H_{arom}), 7.51 (1 H, t, J = 8 Hz, H_{arom}), 7.86 (1 H, d, J = 8 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 14.1, 23.0, 25.9, 27.6, 36.8, 37.8, 65.0 (3C), 111.0, 124.5, 126.9, 131.9, 132.8, 137.3, 149.4.

MS (CI): m/z (%) = 280 (100, MH^+).

2-[2-(Butyl-1,-3-dioxolan-2-yl)ethyl]benzenamine (10):
A mixture of 54.1 g (0.194 mol) of **9** and 5.4 g of 10% palladium-on-carbon in 500 mL of abs. EtOH was stirred under hydrogen gas (ca. 1.1 atm). After uptake of hydrogen was complete, the catalyst was filtered off and solvent was removed under reduced pressure, giving 47.3 g (98% yield) of an amber oil which was used in the next step without further purification. An analytical sample was prepared by two consecutive bulb-to-bulb distillations (130–145 °C at 0.20 mmHg) giving a pale yellow oil.

IR (film): ν = 3460, 3375, 2980, 2940, 1625, 1500, 1455, 1275, 1130, 1080, 1035, 945, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.90 (3 H, t, J = 7 Hz, CH_3), 1.9 (2 H, m, $ArCH_2CH_2$), 2.5 (2 H, m, $ArCH_2$), 3.7 (2 H, brs, NH_2), 3.98 (4 H, s, OCH_2), 6.7 (2 H, m, H_{arom}), 7.01 (2 H, m, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 14.0, 23.0, 25.5, 26.2, 27.0, 36.2, 65.1 (2C), 111.7, 115.4, 118.5, 126.4, 127.0, 129.3, 144.2.

MS (CI): m/z (%) = 250 (91, MH^+), 188 (100).

***N*-{2-[2-(2-Butyl-1,3-dioxolan-2-yl)ethyl]phenyl}-4-methoxybenzamide (11):**
To a mixture of 47.3 g (0.190 mol) of **10** in 200 mL of pyridine at 0 °C under N_2, 30 mL (ca. 0.22 mol) of *p*-anisoyl chloride was added dropwise. The resulting mixture was stirred at r.t.. After 18 h, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was taken up in CH_2Cl_2, washed with water then with 5% aq NaOH. The organic layer was dried ($MgSO_4$), and volatiles were removed under reduced pressure. The residue was crystallized from $(i\text{-Pr})_2O$ giving 59.9 g (82% yield) of white solid; mp 84–87 °C.

IR (0.5% KBr): ν = 3400 (br), 3290, 2950, 2935, 1640, 1605, 1525, 1500, 1480, 1455, 1285, 1260, 1190, 1030, 840, 760 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (3 H, t, J = 7 Hz, CH_2CH_3), 1.94 (2 H, dd, J = 7, 10 Hz, $ArCH_2CH_2CH_3$), 2.71 (2 H, dd, J = 7, 10 Hz, $ArCH_2$), 3.88 (3 H, s, OCH_3), 3.9 (4 H, m, OCH_2), 6.97 (2 H, dd, J = 2, 7 Hz, H_{arom}), 7.08 (1 H, t, J = 8 Hz, H_{arom}), 7.19 (1 H, d, J = 8 Hz, H_{arom}), 7.26 (1 H, t, J = 8 Hz, H_{arom}), 7.95 (2 H, dd, J = 2, 7 Hz, H_{arom}), 8.12 (1 H, d, J = 8 Hz, H_{arom}), 8.27 (1 H, s, NH).

^{13}C NMR ($CDCl_3$): δ = 14.0, 22.9, 25.9, 26.1, 36.8, 37.5, 55.4, 64.9 (2C), 111.4, 113.7 (2C), 123.4, 124.8, 126.9, 127.3, 129.2, 129.6 (2C), 133.0, 135.7, 162.3, 165.4.

MS (CI): m/z (%) = 384 (14, MH^+), 322 (14), 328 (15), 190 (53), 189 (26), 188 (100).

4-Methoxy-*N*-[2-(3-oxoheptyl)phenyl]benzamide (12):
A mixture of 59.5 g (0.155 mol) of **11**, 100 mL of 5% aq HCl, 100 mL of THF and 400 mL of MeOH was stirred at r.t. for 20 h. Sat. aq $NaHCO_3$ was added until neutral pH. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and solvent was removed under reduced pressure. The resulting residue was crystallized from boiling $(i\text{-Pr})_2O$. Drying (40 °C at 15 mmHg) gave 46.7 g (89% yield) of white solid; mp 72–74 °C.

IR (0.5% KBr): ν = 3400 (br), 3300, 2980, 2965, 1710,1640, 1610, 1530, 1510, 1450, 1300, 1250, 1175, 1025, 840, 775, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (3 H, t, J = 7 Hz, CH_2CH_3), 1.23 (2 H, sext, J = 7 Hz, CH_2CH_3), 1.50 (2 H, quint, J = 7 Hz, $CH_2CH_2CH_3$), 2.38 (2 H, t, J = 7 Hz, $CH_2CH_2CH_2CH_3$), 2.9 (4 H, m, $ArCH_2CH_2$), 3.88 (3 H, s, OCH_3), 7.01 (2 H, dd, J = 2, 7 Hz, H_{arom}), 7.11 (2 H, m, H_{arom}), 7.24 (1 H, m, H_{arom}), 7.84 (1 H, d, J = 8 Hz, H_{arom}), 8.16 (2 H, dd, J = 2, 7 Hz, H_{arom}), 9.76 (1 H, s, NH).

^{13}C NMR ($CDCl_3$): δ = 13.7, 22.2, 23.9, 25.9, 42.6, 44.4, 55.3, 113.8 (2C), 125.2, 125.4 (2C), 126.7, 127.3, 129.3, 129.7, 133.6, 136.0, 162.3, 165.4, 212.9.

MS (CI): m/z (%) = 340 (38, MH^+), 190 (62), 188 (100).

Synthesis of 3 from 12:
A mixture of 41.4 g (0.121 mol) of **12** and 8.25 g (0.122 mol) of methylamine hydrochloride in 500 mL of toluene was stirred and heated to reflux as gaseous methylamine was bubbled in slowly. Water (1 mL) was removed by a water trap. This mixture was cooled as gaseous methylamine was continuously added. Once at r.t., the mixture was diluted with 500 mL of abs. EtOH and 2.0 g of 10% palladium-on-carbon was added. The resulting mixture was stirred under a hydrogen atmosphere (approx. 1.1 atm). After 20 h, the catalyst was removed, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOAc giving 29.4 g of a white solid product. The mother liquor contained mostly starting ketone. From the mother liquor, solvent was removed. The residue was taken up in toluene and treated as before with 2.78 g of methylamine hydrochloride, gaseous methylamine, 10% palladium-on-carbon, and hydrogen. The resulting hydrogenated mixture was filtered and solvent was again removed. The residue was treated with EtOAc/$(i\text{-Pr})_2O$ giving 14.0 g of white solid. The combined solid was recrystallized twice from $(i\text{-Pr})_2O$ to give 34.9 g (74% yield) of white solid; mp 173–174 °C.

IR (0.5% KBr): ν = 3450 (br), 3275, 2985, 2970, 2875, 1650, 1610, 1505, 1470, 1305, 1250, 1180, 1030, 770, 750 cm^{-1}.

Other spectral results were identical to those reported for **3** isolated from "impure" encainide.

A sample of **3** free base was made from the HCl salt (4.2 g) by dissolving in a 1 : 1 mixture of 2% NaOH and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and the volatiles were removed. The remaining oil was crystallized from $(i\text{-Pr})_2O$ giving a white solid which was dried in a vacuum oven at 40 °C and 15 mmHg for 4 h. The yield was 3.4 g (89%); mp 80–82 °C.

IR (0.5% KBr): ν = 3425 (br), 3260, 2970, 2960, 2930, 2890, (br), 1645, 1605, 1590, 1540, 1505, 1480, 1450, 1330, 1300, 1250, 1170, 1030, 840, 760, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.82 (3 H, t, J = 7 Hz, CH_2CH_3), 1.0–1.5 (4 H, m, $CH_2CH_2CH_3$), 1.7 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.12 (3 H,

s, NCH_3), 2.2 (1 H, m, $ArCH_2$), 2.7 (1 H, m, $ArCH_2$), 2.9 (1 H, m, NCH), 3.82 (3 H, s, OCH_3), 6.92 (2 H, d, $J = 9$ Hz, H_{arom}), 7.1 (3 H, m, H_{arom}), 7.92 (2 H, d, $J = 9$ Hz, H_{arom}), 8.06 (1 H, d, $J = 8$ Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): $\delta = 14.0, 22.8, 26.7, 27.7, 30.2, 32.2, 34.5, 54.9, 55.3, 113.4$ (2C), 123.9 (2C), 124.6, 126.2, 128.5, 129.4, 129.6, 133.4, 137.2, 162.0, 166.2.

MS (CI): m/z (%) = 335 (100, MH^+).

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