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A Study and Identification of Potential By-Products of Sibutramine†

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Abstract:

In the synthesis and process development of sibutramine (9), the isolation and characterization of two potential by-products namely heptane dinitriles (4a−b) and bis-cyclobutyl alkylamine (10) have been studied. The key steps in the synthesis of sibutramine which have contributed to the formation of above by-products are cycloalkylation of 4-chlorophenyl acetonitrile (1) and tandem Grignard reduction on 1-(4-chlorophenyl)-cyclobutyl carbonitrile (3).

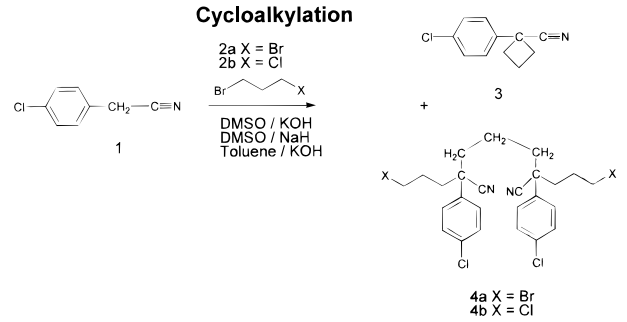
Introduction

Obesity is a serious health risk associated with increased mortality due to a range of conditions including hypertension, hypercholesterolaemia, and diabetes.[1,2] It is clear that weight loss can significantly lower these risks; in practice, maintenance of the required energy balance over long periods of time is very difficult and often unsuccessful due to the many psychological and physiologic pressures to eat normally. In view of this there is considerable interest in the development of drugs which control the obesity.

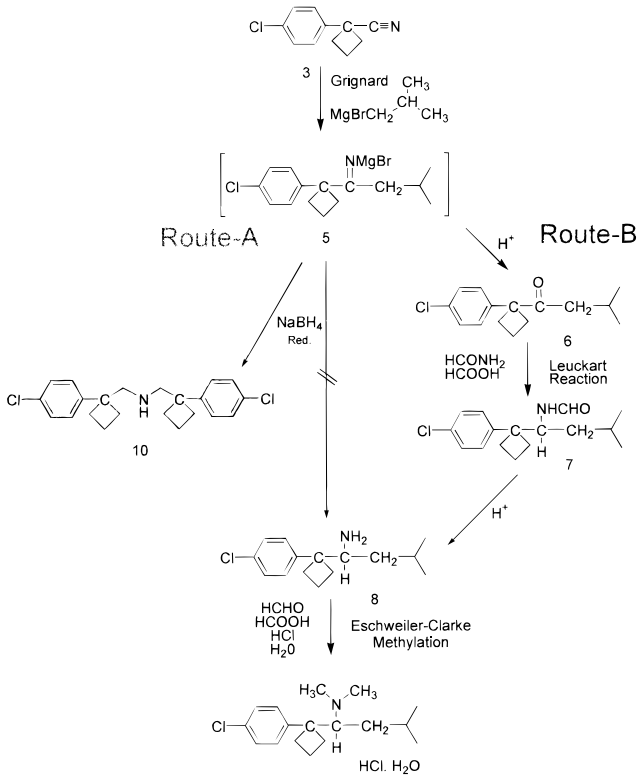
Sibutramine hydrochloride monohydrate *N*-{1-(4-chlorophenyl)cyclobutyl]-3-methyl butyl}-*N*,*N*-dimethylamine (**9**) is the first of a new class of compounds for the treatment of obesity. In clinical trials sibutramine hydrochloride monohydrate has been shown to cause marked weight reduction, and unlike other currently available drugs it remains effective in the longer term (>12 months).[3−8]

During our attempts to improve the yields of sibutramine from the reported[9−12] procedures, we have isolated three by-products, namely, heptane dinitriles (**4a** and **4b**) and bis-cyclobutyl alkylamine (**10**). The isolation, characterization, and formation of these by-products are presented.

Scheme 1



Scheme 2



Results and Discussion

The synthesis of sibutramine (Schemes 1 and 2) involves cycloalkylation and tandem Grignard reduction[13,14] in route A or cycloalkylation and Grignard reaction followed by Leuckart reaction[15] in route B, to yield penultimate primary amine (**8**) from 4-chloro-phenyl acetonitrile (**1**). Sibutramine

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Table 1. **Reported cycloalkylation**

methodology	reagents	% yields of (**3**)
Butler and Pollatz[9]	DMSO/NaH	78
Jeffrey and Kerrig[11]	DMSO/KOH	~78
Barker and Clark[12]	toluene/KOH	53

(**9**) was prepared from the primary amine (**8**), in good yield by Eschweiler−Clarke methylation.[16]

During the reinvestigation of the cycloalkylation and tandem Grignard reduction of sibutramine $HCl \cdot H_2O$ synthesis, three by-products were isolated. These major by-products, **4a** and **4b,** were isolated by recrystallization of the reaction mass in the cycloalkylation step, whereas **10** was the only product formed in the tandem Grignard reduction step of route A. On the basis of NMR and mass spectroscopic studies, the by-products were characterized as 2,6-di(4-chlorophenyl)2,6-di(3-chloropropyl)heptane-dinitrile (**4a**), 2,6-di(4-chlorophenyl)2,6-di(3-bromopropyl) heptane dinitrile (**4b**), and bis[4-(chlorophenyl) cyclobutane methyl]-amine (**10**), respectively.

1. Cycloalkylation Step. In the synthesis of sibutramine the cycloalkylation of aryl acetonitrile is an important step in terms of improving the overall yield of sibutramine. This step (Scheme 1) involves the condensation of 1,3-dibromopropane (**2a**) or 3-bromo-1-chloropropane (**2b**), on the active methylene of 4-chlorophenyl acetonitrile (**1**) by the elimination of NaX/KX, resulting in 1-(4-chlorophenyl)-cyclobutane carbonitrile (**3**).

The cycloalkylation step was reinvestigated, following the reported methods (shown in Table 1). The major by-products **4a** and **4b** were formed in about 20−25% yields when **2a** and **2b** were used in the cycloalkylation, respectively. These products were consistently formed in each of the reported methods in about 20-25% yields.

2. Tandem Grignard Reduction Step in Route A. The conversion of cyclobutane carbonitrile (**3**) to the primary amine (**8**) (Scheme 2), which is the penultimate intermediate in the synthesis of sibutramine, involves tandem Grignard reduction step in route A. The imine salt (**5**) is expected to yield **8** when treated with sodium borohydride. To our surprise, the intermediate **3** upon treatment with the tandem Grignard reduction process using reported conditions ($NaBH_4$/IPA) gave bis[4-(chlorophenyl)cyclobutane methyl]amine (**10**) only, instead of the anticipated 1-[1-(4-chlorophenyl)-cyclobutyl]-3-methyl butylamine (**8**).

3. Grignard Reduction and Leuckart Reaction in Route B. As the reported tandem Grignard reduction step in route A did not result in the expected **8**, route B was followed.

In route B, the compound **3** on Grignard reaction with isobutylmagnesium bromide, followed by hydrolysis of the intermediate imine salt (**5**) gave a ketone (**6**) in 81% yield. Leuckart reaction of the ketone (**6**) gave the formamide (**7**) in 39% yield, which was hydrolyzed to give the primary amine (**8**) in about 96% yield.

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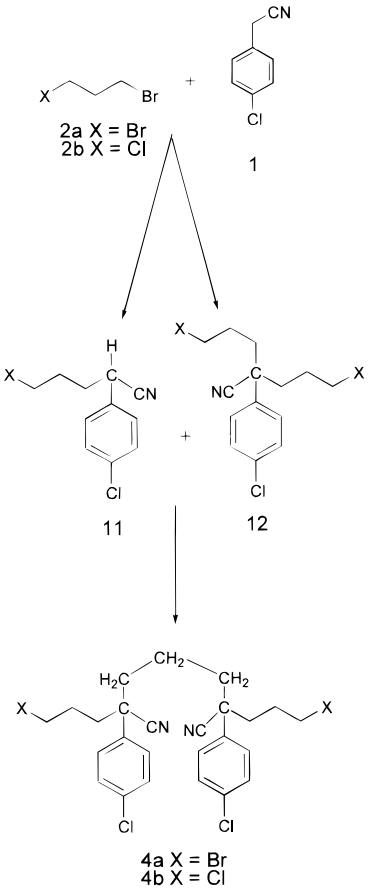
Scheme 3. **Proposed mechanism for the formation of 4a and 4b**



Conclusions

The formation of **4a** and **4b** can be explained in terms of excess reaction of **2a** and **2b**, respectively, with **1** to yield intermediates **11** and **12** which further react to give the heptane dinitriles (Scheme **3**).

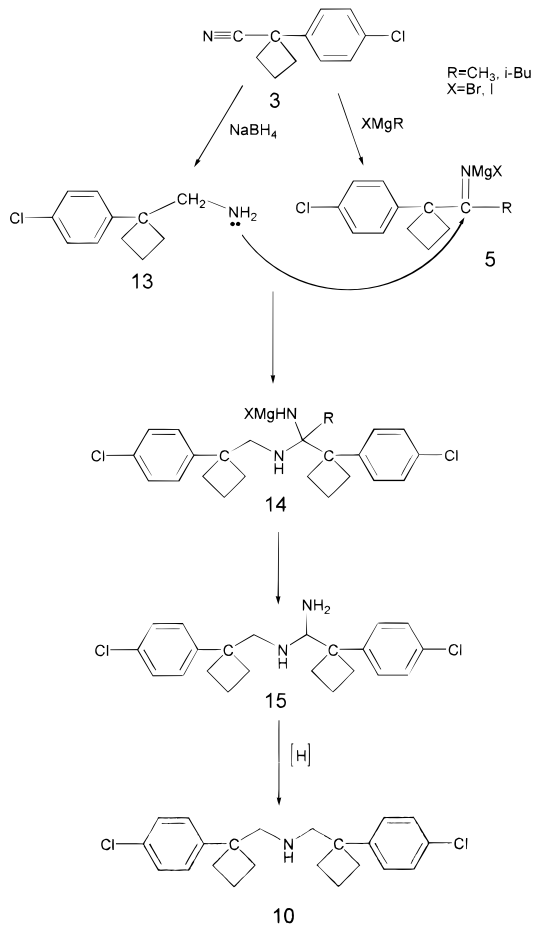
In the tandem Grignard reduction step apart from the formation of imine salt (**5**), the nitrile (**3**) reduces to give an amine (**13**), which on further condensation with **5** yields **10** possibly via transient intermediates **14** and **15** (Scheme 4). The borohydride reduction of **3** does not form **10,** but it gave simple primary amine (**13)**.

Experimental Section

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1650 FT5R spectrometer. NMR spectra were determined using a Varian 200 MHz, FT NMR spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained on HP model 5989A mass spectrometer. Elemental analyses were performed on Perkin-Elmer Series II CHN analyser 2400. Evaporation of extracts refers to the removal of volatile materials under reduced pressure on a Buchi Rotavapor. Reaction solvents were dried over $LiAlH_4$ or molecular sieves as appropriate.

1-(4-Chlorophenyl)cyclobutane Carbonitrile (3) and Heptane Dinitrile (4a).[11]A solution of 4-chlorophenyl acetonitrile (**1**) (119 g, 0.78 mol) and 1,3-dibromopropane

Scheme 4. **Proposed mechanism for the formation of 10**



(**2a**) (82 mL, 163.1 g, 0. 81 mol) in ether (220 mL) was added dropwise at 20−25° over 30 min to a vigorously stirred suspension of finely powdered potassium hydroxide (188.5 g) in dimethyl sulfoxide (600 mL). After the addition was complete, the mixture was stirred for 1 h and cooled to 15° and quenched at <20° by dropwise addition of ice-cold water (400 mL). Ether (500 mL) was added, and the mixture was filtered which resulted in the ethereal layer with enriched **3** and solid material (**4a**).

The combined ethereal solutions were washed with water (3 × 50 mL), dried over ($MgSO_4$), and evaporated to leave an orange oil which was distilled to give **3** (reported data[9]) 52 g, 35% yield as a pale yellow oil: bp 118−120 °/1.5 mmHg (lit.[11]168−169°/20 mm Hg).

The filter cake was washed well with ether and recrystallized in chloroform (600 mL). The recrystallised solid is identified as heptane dinitrile (**4a**) 56 g (25%) as cream colour solid: mp 148−150°. IR (KBr) 2956 (C−H str), 2236 (C≡N str), 1493, 1098. ^{1}H NMR ($CDCl_3$) δ 1.8−2.1 (m, 14H), 3.4−3.5 (m, 4H), 7.0−7.4 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 20.70, 27.98, 37.59, 40.37, 43.93, 46.85, 121.08, 126.97, 129.11, 133.93, 135.55. (Found: C, 58.8; H, 5.0; N, 5.7%. Calcd for $C_{25}H_{26}N_2Cl_2Br_2$, C, 60.5; H, 5.3; N, 5.6%.) Mass (*m*/*z*) = 494, 470, 418, 392, 356, 342, 320, 268, 227, and 162.

2,6-Di(4-chlorophenyl)-2,6-di(3-chloropropyl)heptane Dinitrile (4b). A solution of 4-chlorophenyl acetonitrile (**1**) (119 g, 0.78 mol) and 1-bromo-3-chloropropane (**2b**) (77 mL, 122 g, 0. 81 mol) in ether (220 mL) was added dropwise at 20−25° over 30 min to a vigorously stirred suspension of finely powdered potassium hydroxide (188.5 g) in dimethyl sulfoxide (600 mL). After the addition was complete, the mixture was stirred for 1 h, cooled to 15°, and quenched at <20° by dropwise addition of ice-cold water (400 mL). Ether (500 mL) was added, the mixture was filtered, and the filter cake was washed well with ether and recrystallized in chloroform (600 mL). The recrystallised solid is identified as heptane dinitrile (**4b**) 56 g (25%) as a cream-colored solid: mp 178−183 °C. IR (KBr) 2950 (C−H str), 2236 (C≡N str), 1494, 1096. ^{1}H NMR ($CDCl_3$) δ 1.8−2.1 (m, 14H), 3.2−3.4 (m, 4H), 7.0−7.4 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 20.73, 28.08, 32.44, 39.6, 40.8, 46.97, 121.16, 126.97, 129.26, 129.11, 134.01, 135.56. (Found: C, 63.4; H, 5.1; N, 6.2%. Calcd for $C_{25}H_{26}N_2Cl_4$, C, 60.7; H, 5.26; N, 5.66%.) Mass (*m*/*z*) = 505, 356, 343, 272, 231, 190, 176, 150, and 125.

Bis-[4-(chlorophenyl) Cyclobutane Methyl]amine (10). A solution of 1-(4-chlorophenyl) cyclobutane carbonitrile (**3**) (50 g, 0.26 mol) in dry toluene (180 mL) was added dropwise under nitrogen to a stirred solution of isobutylmagnesium bromide [from isobutylbromide (54.2 g, ∼43 mL, 0.395 mol) and magnesium turnings (9.6 g, 0.395 mol)] in dry ether (180 mL). During the addition the ether was removed by distillation at a rate approximately equal to the addition of nitrile solution. When the addition was complete and sufficient ether was removed for the internal temperature to reach 90 °C, distillation was stopped, and the mixture was stirred for 18 h, at 90 °C. The mixture was then allowed to cool to 75 °C and was added to a slurry of sodium borohydride (30 g, 0.79 mol) in propan-2-ol (1000 mL). The resulting slurry was heated under reflux for 6 h, allowed to stand at ambient temperature for 18 h, and evaporated. The residue was diluted with water (1000 mL) and allowed to stand at room temperature for 30 min, and the product was extracted with ethyl acetate (3 × 300 mL). The extracts were washed with water (2 × 200 mL), dried over (Na_2SO_4), and evaporated to leave an oil which was distilled to give the title compound (**10**) (25 g, 52%) as light brown oil: bp 150−158 °C/0.11 mmHg, which solidifies slowly (mp 40−42 °C). IR (KBr) 3362 (broad, −N−H str), 2933 (C−H str), 1491, 1459 (CH_3 bend and CH_2 scissor), 1089 (p-substituted, aromatic), 1014 (aromatic C−H in plane bend). ^{1}H NMR ($CDCl_3$) δ 1.75−2.30 (12H, m, CBCHs), 2.75 (4H, S, $-CH_2-$N-), 6.84 (4H, m, ArH), 7.32 (4H, m, ArH). ^{13}C NMR ($CDCl_3$) δ 16.0, 31.1, 46.6, 60.2, 127.0, 127.8, 131.0, 147.3. (Found: C, 70.5; H, 6.8; N, 3.7%. Calcd for $C_{22}H_{25}NCl_2$, C, 70.6; H, 6.7; N, 3.7%.) Mass *m*/*z* = 373 (M^+), 208, 179 and 125.

A solution of oily free base (**10**) (25 g. 0.067 mol) in ether (500 mL) was saturated with hydrogen chloride, and the precipitated solid was filtered, ground to a powder, and dried in a vacuum to give the hydrochloride salt of (**10**) (21 g, 80%) as white crystalline solid: (mp 240−242 °C). IR (KBr) 3439 (broad, −N−H str), 3189, 3033 (aromatic C−H str), 2966, 2944 (C−H str), 1491, 1440, 1420 (CH_3 bend and CH_2 scissor), 1091 (p-substituted, aromatic), 1012 (aromatic C−H in plane bend). ^{1}H NMR ($CDCl_3$) δ 1.75−

2.30 (12H, m, CBCHs), 2.75 (4H, S, $-CH_2-N-$), 6.84 (4H, m, ArH), 7.32 (4H, m, ArH). ^{13}C NMR ($CDCl_3$) δ 16.0, 31.1, 46.6, 60.2, 127.0, 127.8, 131.0, 147.3. (Found: C, 64.0; H, 6.3; N, 3.4%. Calcd for $C_{22}H_{26}NCl_3$, C, 64.3; H, 6.4; N, 3.4%.) Mass *m*/*z* = 373, 208, 179, and 125.

1-[1-(4-Chlorphenyl)cyclobutyl]-3-methyl butan-1-one (6). A solution of 1-(4-chlorophenyl)cyclobutane carbonitrile (**3**) (50 g, 0.26 mole) in dry toluene (180 mL) was added dropwise under nitrogen to a stirred solution of isobutylmagnesium bromide [from isobutyl bromide (54.2 g, ~43 mL, 0.395 mol) and magnesium turnings (9.6 g, 0.395 mol)] in dry ether (180 mL). During the addition the ether was removed by distillation at a rate approximately equal to the addition of nitrile solution. When the addition was complete and sufficient ether was removed for the internal temperature to reach 90 °C, distillation was stopped, and the mixture was stirred for 18 h at 90 °C. It was cooled to ambient temperature, water (1 L) was added to the reaction mixture, and the mixture was acidified by addition of 5 M hydrochloric acid. The reaction mixture was heated at 90−95 °C for 2 h with stirring and allowed to cool. The product was extracted into ether (3 × 200 mL). The extracts were washed with water (2 × 100 mL), dried over (Na_2SO_4), and evaporated. The residue was distilled to give title compound (**6**), (52.9 g, 81%) as colorless oil, bp 100−120 °C/0.2 mm/Hg: IR (neat) 2957 (C−H str), 1707 (C═O str), 1491, 1417 (CH_3 bend and CH_2 scissor), 1084 (p-substituted, aromatic), 1013 (aromatic C−H in plane bend). ^1H NMR ($CDCl_3$) 0.70 (6H, d, *J* = 7.0 Hz $-CHMe_2$), 1.85 (2H, m, −CBCHs), 1.90 (1H, m,$-CH_2CHMe_2$), 2.05 (2H, m, $-CH_2CHMe_2$), 2.35 (2H, m, −CBCHs), 2.75 (2H, m, −CBCHs), 7.15 (2H, d, *J* = 7.0 Hz −ArH), 7.30 (2H, d, *J* = 7.0 Hz −ArH). ^{13}C NMR ($CDCl_3$) δ 15.69, 22.06, 23.87, 30.25, 45.24, 58.48, 127.57, 129.49, 128.73, 141.41. Mass (*m*/*z*), 250, 165, 137.

***N*-{1-[1-(4-Chlorophenyl/cyclobutyl]-3-methyl Buty} Formamide (7).** A mixture of ketone (**6**) (35.15 g, 0.14 mol) and formic acid (9.5 mL) was added dropwise at 160 °C to formamide (25 mL) in about 30 min. The reaction mixture was heated at 180 °C for 24 h (the water formed in the reaction was removed by distillation). The reaction mixture was cooled to ambient temperature and diluted with water (500 mL). The product was extracted with dichloromethane (3 × 50 mL), and extracts were washed with water (2 × 50 mL), dried over (Na_2SO_4), and evaporated. The oily residue was triturated with petroleum ether (60−80 °C), and the resulting solid was filtered and dried in a vacuum to give formamide (**7**), (11.9 g, 39%) as a colorless solid: mp 110−112 °C. IR (KBr) 3340 (broad, −N−H str), 2955 (C−H str), 1650 (−C═O str), 1492, 1470 (CH_3 bend and CH_2 scissor), 1091 (p-substituted, aromatic), 1012 (aromatic C−H in plane bend). ^1H NMR ($CDCl_3$) 0.60−0.77 (1H, m, $-CH_2CHMe_2$), 0.81−0.97 (6H, m, $-CHMe_2$ [includes 0.82, d, (*J* = 6.8 Hz) and 0.95, d, (*J* = 6.4 Hz)], 1.22 (1H, br, t, $-CH_2CHMe_2$), 1.49 (1H, m, $-CHMe_2$), 1.86 (1H, m, −CBCH), 2.0−3.5 (5H, m, −CBCHs), 3.61 (0.28H, m, $CHBu^iNH$), 4.62 (0.72H, m, $CHBu^iNH$), 7.15 (2H, d, *J* = 7.0 Hz −ArH), 7.37 (2H, d, *J* = 7.0 Hz −ArH) 8.11 (0.28H, d, *J* = 11.4 Hz, NH*CH*O), 8.29 (0.72H, d, *J* = 11.4 Hz, NH*CH*O). ^{13}C NMR ($CDCl_3$) δ 14.9, 20.9 23.6, 31.1, 38.8, 39.2, 49.7, 51.4, 57.1, 127.7, 128.0, 131.8, 143.7, 161.2, 163.5. Mass (*m*/*z*) 279, 235, 224, 179.

1-[1-(4-Chlorphenyl)cyclobutyl)]-3-methyl Butylamine (8). A mixture of formamide (**7**) (8.7 g, 0.03 mole), bis(2-methoxy ethyl) ether (65 mL), concentrated hydrochloric acid (22 mL), and water (22 mL) was stirred and heated under reflux for 18 h. The reaction mixture was cooled and diluted with water (80 mL). The resulting solution was washed with ether (2 × 50 mL) andthen basified by addition of 5 M aqueous sodium hydroxide (35 mL). The product was extracted into ether (3 × 50 mL), and the extracts were washed with brine (50 mL) and water (50 mL), dried over Na_2SO_4, and evaporated. The residue was the crude title compound (**8**), (7.5 g, 96%) as a brown oil: bp 120−128 °C /0.25−0.8 mmHg. IR (neat) 2970−2950, (br) (−NH, CH_3, CH_2, and CH str), 1492, 1466 (CH_3 bend and CH scissor), 1367 (C−H bend), 1094 (p-substituted aromatic), 1013, 824 (aromatic C−H). ^1H NMR ($CDCl_3$) 0.85 (3H, d, *J* = 6.6 Hz $-CHMe$), 0.90 (3H, d, *J* = 6.6 Hz $-CHMe$), 0.50−1.00 (1H, m, $-CH_2CHMe_2$), 1.20 (1H, t, $-CH_2CHMe_2$), 1.66−1.75 (2H, m, −CBCHs), 1.90−1.98 (1H, m, $-CHMe_2$), 2.25−2.36 (2H, m, −CBCHs),), 2.45−2.55 (2H, m, −CBCHs), 3.05 (1H, d, *J* = 8.8 Hz, $CHBu^iNH_2$), 7.10 (2H, d, *J* = 7.0 Hz −ArH), 7.25 (2H, d, *J* = 7.0 Hz −ArH). ^{13}C NMR ($CDCl_3$) δ 15.1, 21.1, 23.9, 31.2, 41.0, 50.5, 56.0, 127.3, 128.6, 131.3, 144.1. Mass (*m*/*z*) 251, 235, 179, 153.

A solution of the oily free base (**8**) (3.3 g, 0.013 mol) in ether (20 mL) was saturated with hydrogen chloride. The precipitated solid was filtered, ground to a powder, and dried in a vacuum to give the hydrochloride salt of (**8**), (1.73 g, 46%), as a white crystalline solid (mp 163−165 °C). IR (KBr) 3000−2870 (br) (NH, CH_3, CH_2, CH, str), 1586 (NH bend), 1484, 1467 (CH_3, CH_2, str), 1369 (CH_3 bend), 1096 (p-substituted aromatic), 1010 (aromatic), 829 (aromatic). ^1H NMR (CDCl3) 0.85 (3H, d, *J* = 6.6 Hz $-CHMe$), 0.90 (3H, d, *J* = 6.6 Hz $-CHMe$), 1.20 (1H, t, $-CH_2CHMe_2$), 1.90−1.98 (1H, m, $-CHMe_2$), 1.8−2.2 (2H, m, −CBCHs), 2.3−2.7 (4H, m, −CBCHs), 3.55 (1H, br, $CHBu^iNH_2$), 7.25 (2H, d, *J* = 7.0 Hz −ArH), 7.35 (2H, d, *J* = 7.0 Hz −ArH). ^{13}C NMR ($CDCl_3$) δ 15.1, 21.1, 23.9, 31.2, 41.0, 50.5, 56.0, 127.3, 128.6, 131.3, 144.1. Mass (*m*/*z*) 251, 235, 179, 153.

1-(4-Chlorophenyl)cyclobutyl Methylamine (13). A mixture of carbonitrile (**3**), (90 g, 0.47 mol), 2-propanol (540 mL), and sodium borohydride (69 g, 1.88 mol) was stirred and heated to reflux for 30 min. Methanol (125 mL) was added to reflux temperature dropwise in about 3 h and refluxed further for 18 h. The reaction mixture was brought to ambient temperature, and the solvent was distilled off under vacuum and diluted with water (500 mL). The product was extracted with ethyl acetate (3 × 500 mL), and the extracts were washed with water (2 × 250 mL), dried over (Na_2SO_4), and evaporated. The residue was the crude title compound (**13**), (64 g, 70%) as a brown oil, bp 200/0.1 mmHg. A solution of the oily free base (**13**) (50 g, 0.256 mole) in ether (500 mL) was saturated with hydrogen chloride. The precipitated solid was filtered, ground to a

powder, and dried in a vacuum to give the hydrochloride salt of (**13**), (32 g, 54%) as a white crystalline solid (mp 170−172 °C). IR (KBr) 3500−2560 (br) (NH, CH-str), 1598 (−NH bend), 1492, 1460 (CH_2, str), 1092 (p-substituted aromatic), 1014 (aromatic), 825 (aromatic). ^{1}H NMR (CD_3-OD), 1.92−2.60 (6H, m, −CBCHs), 3.35 (2H, s, $-CH_2NH_2$), 7.25 (2H, d, J = 7.0 Hz −ArH), 7.45 (2H, d, J = 7.0 Hz −ArH). ^{13}C NMR (CD_3OD), 16.21, 31.85, 49.75, 128.93, 129.94, 133.66, 144.78. Mass (m/z): 195, 165, 149, 137.

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