Synthesis of sibutramine, a novel cyclobutylalkylamine useful in the treatment of obesity, and its major human metabolites

James E. Jeffery, Frank Kerrigan,* Thomas K. Miller, Graham J. Smith and Gerald B. Tometzki

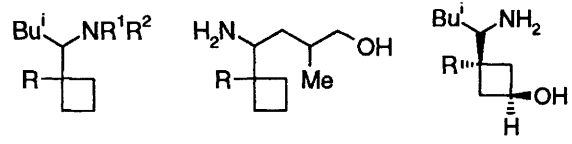
Knoll Pharmaceuticals, Research and Development Department, Pennyfoot St., Nottingham NG1 1GF, UK

Synthetic routes to *N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*,*N*-dimethylamine (sibutramine) 1 and its demethylated and hydroxylated human metabolites *N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*-methylamine 2, 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine 3, 4-amino-4-[1-(4-chlorophenyl)cyclobutyl]-2-methylbutan-1-ol 4 and *c*-3-(1-amino-3-methylbutyl)-3-(4-chlorophenyl)cyclobutan-*r*-1-ol 5a are described. Key steps are tandem Grignard–reduction reactions on 1-(4-chlorophenyl)cyclobutanecarbonitrile 7 and its 3-(tetrahydropyran-2-yloxy)-substituted analogue 14 and a convenient one-pot conversion of 4-chlorophenylacetonitrile 6 into the 3-hydroxycyclobutanecarbonitrile 13.

Obesity has been described as the most important nutritional disorder of the western world,[1] with approximately 8% of the population of developed countries clinically at risk from being obese.[2,3] It is a serious health risk, associated with increased morbidity and mortality due to a range of conditions including hypertension, hypercholesterolaemia and diabetes.[4,5] Although it is clear that weight loss by the obese can significantly lower these risks, in practice maintenance of the required negative energy balance (energy output > energy input due to food intake) over long periods of time is very difficult and often unsuccessful due to the many physiological and psychological pressures to eat normally. Consequently there is considerable interest in the development of drugs which aid the treatment of obesity.

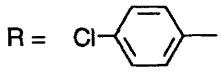
Sibutramine (*N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*,*N*-dimethylamine **1**) is the first of a new class of compounds for the treatment of obesity. It is a serotonin and noradrenaline re-uptake inhibitor (SNRI)[6] which has a dual action, enhancing both satiety and metabolism. In clinical trials sibutramine hydrochloride monohydrate has been shown to cause marked weight reduction and, unlike other currently available drugs, remains effective in the longer term (> 12 months).[7–12]

Sibutramine undergoes rapid and extensive metabolism in humans, initially resulting in the demethylated amines **2** and **3**. *In vivo* the pharmacological activity of sibutramine is mediated predominantly by these two metabolites.[13] Further oxidative metabolism results in the hydroxylated amines **4** and **5a** which are excreted as glucuronide conjugates. The synthesis of sibutramine and its secondary and primary amine metabolites **2** and **3** has been outlined in brief.[14] In this paper we describe in full the synthesis of these three amines and the hydroxylated metabolites **4** and **5a**.



	R^1	R^2
1	Me	Me
2	H	Me
3	H	H

4 **5a**

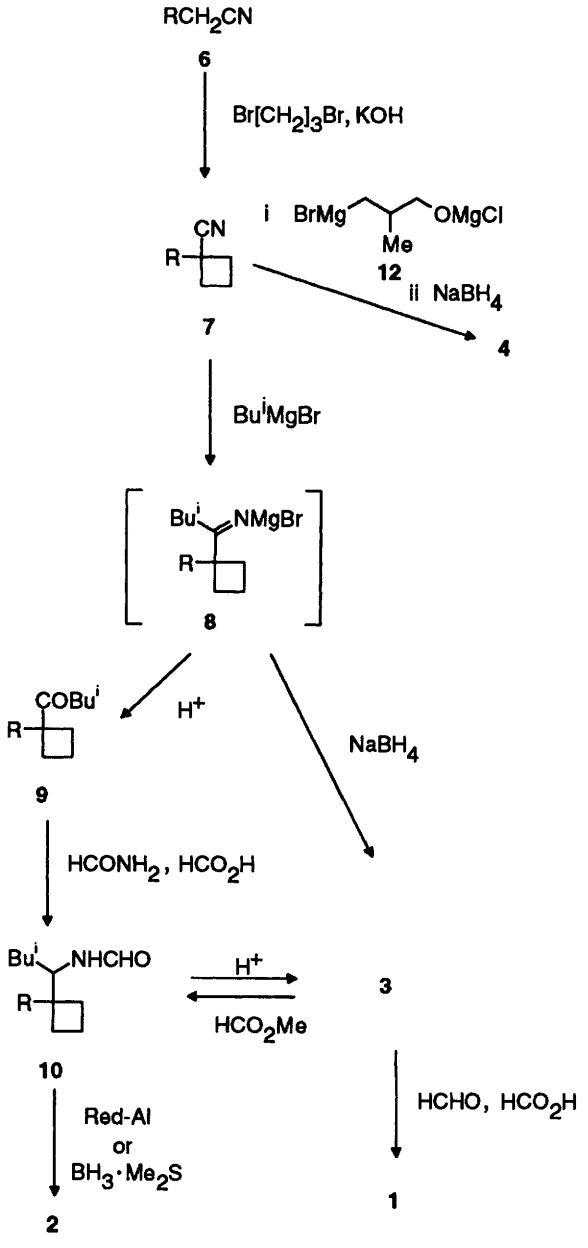


Results and discussion

Sibutramine and its primary amine metabolite **3** have been prepared *via* two routes from 4-chlorophenylacetonitrile **6** (Scheme 1).[14] Both commence with cycloalkylation of **6** with 1,3-dibromopropane to give the cyclobutanecarbonitrile **7**. We found that sodium hydride, used as the base by Butler and Pollatz,[15] could conveniently be replaced with finely powdered potassium hydroxide with no significant reduction in yield. The original synthetic route then involved conversion of **7** into the ketone **9** by a Grignard reaction with isobutylmagnesium bromide, followed by hydrolysis of the intermediate imine salt **8**. The Grignard reaction gave optimum yields (80%) when performed at 95–100 °C; to achieve this, the ethereal solvent used for formation of the Grignard reagent was removed by distillation and replaced by toluene. Leuckart reaction[16] of the ketone **9** gave the formamide **10** which was hydrolysed to give the primary amine **3**. Sibutramine was then prepared in good yield (80%) by Eschweiler–Clarke methylation[17] of the primary amine **3**.

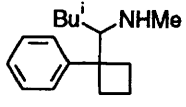
The main problem with this route arose at the Leuckart reaction which gave poor yields even under forcing conditions (180 °C, 18 h), presumably as a result of steric hindrance at the carbonyl group. We found that a more efficient synthesis (> 75% yield *vs.* < 25% yield using the Leuckart route) of the primary amine **3** could be achieved by direct reduction of the imine salt **8** using sodium borohydride. This method proved to be of wide scope and was used in the synthesis of many analogues of sibutramine.[18] Similar tandem Grignard–reduction reactions of nitriles using lithium in ammonia and zinc borohydride as reducing agents have been reported.[19,20]

The secondary amine **2** was accessed *via* formylation of the primary amine **3** by heating with methyl formate, followed by reduction of the formamide **10**. The ^{1}H NMR spectrum of the formamide exhibited two sets of signals arising from the presence, in solution, of two stable conformers. The more stable had the *N*-substituent *cis* relative to the carbonyl oxygen (*cis*-



Scheme 1

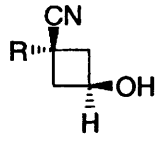
$J_{NH,CH}$ 1.7 Hz; *trans*-$J_{NH,CH}$ 11.4 Hz). The *cis*:*trans* ratio was solvent-dependent [2.6:1 in $CDCl_3$; 7.3:1 in $(CD_3)_2SO$], but was unchanged on heating the $(CD_3)_2SO$ solution to 90 °C. For the reduction, sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®) tended to be non-selective, giving up to 5% of the dechlorinated product **11**, and we found borane–dimethyl sulfide complex to be superior, giving an overall conversion of **3** into **2** of the order of 70%, with no contamination by **11**.



11

The development of the tandem Grignard–reduction process for the conversion of nitriles into α-substituted amines enabled a facile synthesis of the hydroxylated metabolite **4**, simply requiring the use of a Grignard reagent derived from a suitably protected halo alcohol. Cahiez *et al.*[21] reported the synthesis and reactions of Grignard reagents derived from halo alcohols transiently protected as magnesium salts, and Courtois and Miginiac used related reagents for the conversion of iminium salts into tertiary amino alcohols.[22] Reaction of the cyclobutanecarbonitrile **7** with the Grignard reagent **12** derived from 2-(bromomethyl)propan-1-ol,[23] followed by reduction with sodium borohydride gave a moderate yield (45%) of the required primary amino alcohol **4** as a 3.8:1 mixture of pairs of diastereoisomers (Scheme 1).

The hydroxylated metabolite **5a** proved a more difficult target. An obvious route involved a tandem Grignard–reduction reaction of the 3-hydroxycyclobutanecarbonitrile **13a**, or an *O*-protected derivative, with isobutylmagnesium bromide.



13a

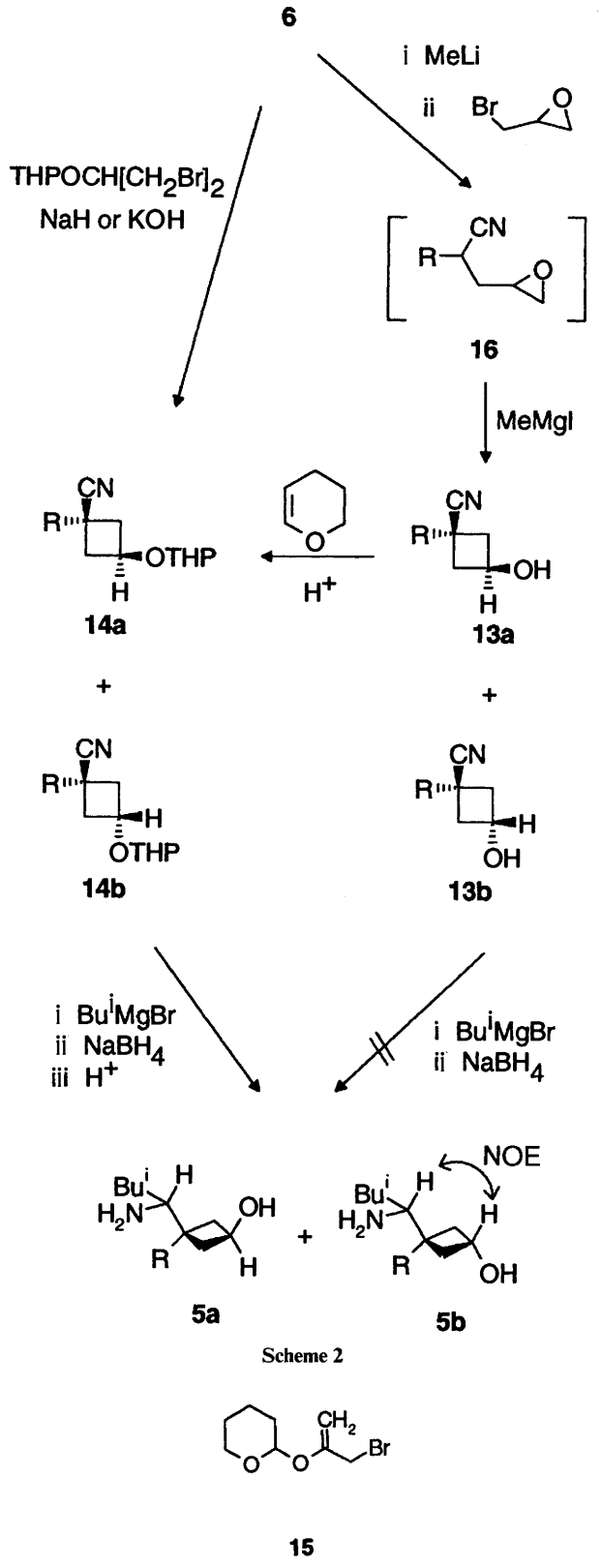
Our first approach involved the use of a protected 1,3-dibromopropan-2-ol for the cycloalkylation step, and was non-stereoselective, ultimately resulting in a 1:1 mixture of the metabolite **5a** and its *trans*-isomer **5b**. We subsequently devised a more selective route commencing with a base-catalysed cyclisation of 3-oxiranyl-2-(4-chlorophenyl)propionitrile (Scheme 2).

The first approach commenced with cycloalkylation of 4-chlorophenylacetonitrile **6** with 2-[2-bromo-1-(bromomethyl)-ethoxy]tetrahydropyran[24] using either sodium hydride or finely powdered potassium hydroxide as the base. This gave a 1:1 mixture of the required *O*-protected *cis*-alcohol **14a** and the corresponding *trans*-isomer **14b** in good yield, but relatively modest purity (~80%). This may be due in part to the reported propensity of this reagent to undergo base-catalysed elimination of hydrogen bromide to produce the enol ether **15**.[24]

Separation of the two isomeric protected alcohols **14a** and **14b** proved impractical. Therefore the mixture was subjected to the tandem Grignard–reduction reaction with isobutylmagnesium bromide followed by sodium borohydride. After acid-catalysed removal of the protecting group, a 1:1 mixture of the amino alcohols **5a** and **5b** was obtained in high yield (>90%). However, poor chromatographic resolution made separation of the two extremely difficult. Eventually **5a** and **5b** were isolated in poor yield (3% and 11% respectively) by preparative scale HPLC.

The *cis*- and *trans*-geometry for the two isomers was assigned on the basis of NOE experiments on the free bases. Irradiation of the C*H*(OH) proton in **5b** showed an NOE to the C*H*Bu^{i}NH$_2$ proton. This indicates that the two protons in **5b** have the *cis*-geometry, and therefore the two principal groups (hydroxy and aminoalkyl) are *trans*. No such NOE was observed in **5a**, indicating this to be the *cis*-isomer.

For the preparation of multigram quantities of **5a** a more convenient process was required. Corbel and Durst[25] reported the synthesis of 3-hydroxy-1-phenylcyclobutane-1-carbonitrile by base-catalysed cyclisation of 3-oxiranyl-2-phenylpropionitrile. These workers also reported that the methyl ketone by-product, arising from the use of methylmagnesium iodide as the base, was a 2.8:1 mixture of geometrical isomers, although no conclusions were drawn as to which was the predominant isomer. In the hope that the reaction would favour the *cis*-isomer and that we would be able to suppress ketone formation, we decided to use this cyclisation in an alternative route to **5a**. The reported methodology was modified to give a convenient one-pot process for both the synthesis and cyclisation of the intermediate oxirane **16** (Scheme 2).



Scheme 2

15

Alkylation of 4-chlorophenylacetonitrile **6** at −70 °C with epibromohydrin using methyllithium as the base, followed by *in situ* cyclisation of **16** with one equivalent of methylmagnesium iodide gave a 2.6 : 1 mixture of the 3-hydroxycyclobutanecarbonitriles **13a,b** in 76% yield. Under our conditions there was no evidence of further reaction to give the methyl ketones. The tandem Grignard–reduction reaction on the unprotected hydroxy nitriles proved unsuccessful, so they were first protected as the tetrahydropyran derivatives **14a,b**. Good conversion into the amino alcohols **5a,b** was then achieved as described above. The crude product was obtained as a 3.3 : 1 mixture of **5a** and **5b**, indicating that the oxirane cyclisation had indeed favoured the *cis*-isomer. With this favourable isomer ratio it was possible to isolate **5a** by simple crystallisation of the fumarate salt from 10% aqueous acetonitrile. Although the yield was still poor (17.5%), this method was considerably more convenient than the previous chromatographic technique.

In summary we have synthesised the primary amine metabolite **3** of sibutramine **1** *via* a high-yielding tandem Grignard–reduction process. Both the secondary amine metabolite **2** and sibutramine itself are readily accessible from **3**. The tandem Grignard–reduction method, using the reagent **12** derived from 2-(bromomethyl)propan-1-ol, also proved applicable to the synthesis of the hydroxylated metabolite **4**. For the preparation of the hydroxycyclobutane metabolite **5a** we developed two approaches, the more selective of which included a convenient one-pot process for the synthesis of the hydroxycyclobutanecarbonitriles **13a,b** based on the method of Corbel and Durst.

Experimental

Mps were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were conducted with a Carlo Erba model CE1106 CHN analyser; halogen was determined by argentometric titration; water was determined by Karl Fischer analysis. IR spectra were recorded using either a Perkin-Elmer 298 or a Unicam 3020 FT-IR spectrometer. NMR spectra were determined using a Bruker AC250 or a Bruker AM360 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. ^{1}H NMR coupling constants (J values) are reported in Hz, spin multiplicities are reported as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), multiplet (m) and broad (br), and CB CH refers to cyclobutane protons. Evaporation of extracts refers to the removal of volatile materials under reduced pressure on a Buchi Rotavapor. HPLC refers to high performance liquid chromatography. Reaction solvents were dried over sodium–lead alloy or molecular sieves as appropriate. Ether refers to diethyl ether.

1-(4-Chlorophenyl)cyclobutanecarbonitrile 7

A solution of 4-chlorophenylacetonitrile (119 g, 0.78 mol) and 1,3-dibromopropane (82 cm^3, 163.1 g, 0.81 mol) in ether (220 cm^3) was added dropwise at 20–25 °C over 30 min to a vigorously stirred suspension of finely powdered potassium hydroxide (188.5 g) in dimethyl sulfoxide (600 cm^3). After the addition was complete the mixture was stirred for 1 h, then it was cooled to 15 °C and quenched at < 20 °C by the dropwise addition of ice-cold water (400 cm^3). Ether (500 cm^3) was added, the mixture was filtered through Celite®, and the filter cake was washed well with ether. The filtrate and washings were combined, and the aqueous layer was separated and washed with ether (2 × 500 cm^3). The combined ethereal solutions were washed with water (3 × 500 cm^3), dried ($MgSO_4$) and evaporated to leave an orange oil which was distilled to give the *title compound* (110.5 g, 74%) as a pale yellow oil, bp 118–120 °C/1.5 mmHg (lit.,[15] 168–169 °C/20 mmHg).

1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutylamine 3 (tandem Grignard–reduction method)

A solution of 1-(4-chlorophenyl)cyclobutanecarbonitrile **7** (50 g, 0.26 mol) in dry toluene (180 cm^3) was added dropwise under nitrogen to a stirred solution of isobutylmagnesium bromide [from isobutyl bromide (43 cm^3, 54.2 g, 0.395 mol) and magnesium turnings (9.6 g, 0.395 mol)] in dry ether (180 cm^3). 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 had been removed for the internal temperature to reach 90 °C, distillation was stopped, and the mixture was stirred at 90 °C for 18 h. The

mixture was then allowed to cool slightly, and was added to a hot slurry of sodium borohydride (30 g, 0.79 mol) in propan-2-ol (1000 cm^3). 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 cm^3), allowed to stand at ambient temperature for 30 min, and the product was extracted into ethyl acetate (3 × 300 cm^3). The extracts were *washed with* water (2 × 200 cm^3), dried ($MgSO_4$) and evaporated to leave an oil which was distilled to give the *title compound* (49.9 g, 76%) as a colourless oil, bp 120–128 °C/0.25–0.8 mmHg.

A solution of the oily free base (22.2 g, 0.088 mol) in ether (500 cm^3) was saturated with hydrogen chloride and then evaporated. The resulting semisolid was triturated with water (50 cm^3) to give an oily suspension, concentrated hydrochloric acid (5 cm^3) was added, and the mixture was allowed to stand at ambient temperature until complete crystallisation of the salt had occurred. The salt was collected by filtration, ground to a powder, and dried *in vacuo* at 75 °C to give the *hydrochloride salt* of the *title compound* (20.0 g, 79%) as a white powder, mp 162–165 °C (Found: C, 62.7; H, 8.1; N, 4.7; Cl, 24.45. Calc. for $C_{15}H_{22}ClN{\cdot}HCl$: C, 62.5; H, 8.0; N, 4.85; Cl, 24.6%); ν_{max}(KCl)/cm^{-1} 2870–3000 (br) (NH, CH_3, CH_2 and CH stretch), 1586 (NH bend), 1513 (NH bend + aromatic C=C stretch), 1484 and 1467 (CH_3 bend and CH_2 scissor), 1369 (CH_3 bend), 1096 (*p*-substituted aromatic), 1010 (aromatic CH in plane bend) and 829 (aromatic CH out of plane bend); δ_H[360 MHz; $(CD_3)_2SO$] 0.81 (3 H, d, *J* 6.6, CH*Me*), 0.87 (3 H, d, *J* 6.4, CH*Me*), 0.9–1.0 (1 H, m, CH_2CHMe_2), 1.20 (1 H, t, CH_2CHMe_2), 1.66–1.75 (2 H, m, CB CHs), 1.92–1.98 (1 H, m, $CHMe_2$), 2.25–2.36 (3 H, m, CB CHs), 2.45–2.55 (1 H, m, CB CH), 3.45 (1 H, d, *J* 8.8, $CHBu^iNH_2$), 7.34 (2 H, m, ArH), 7.42 (2 H, m, ArH) and 7.96 (3 H, br, NH_3^+).

1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutylamine 3 (Leuckart method)

The reaction of 1-(4-chlorophenyl)cyclobutanecarbonitrile **7** with isobutylmagnesium bromide was carried out as described above. After the mixture had been stirred at 90 °C for 18 h, it was cooled to ambient temperature, added to water (1000 cm^3), acidified by the addition of 5 M hydrochloric acid, heated at 90–95 °C for 2 h with occasional stirring, and allowed to cool. The product was extracted into ether (3 × 200 cm^3), and the extracts were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and evaporated. The residue was distilled to give 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutan-1-one **9** (52.9 g, 81%) as a colourless oil, bp 100–120 °C/0.2 mmHg.

A mixture of the ketone **9** (35.15 g, 0.14 mol) and formic acid (9.4 cm^3) was added dropwise at 160 °C to formamide (25 cm^3), then the mixture was heated at 180 °C for 17 h (while water formed in the reaction was removed by distillation), cooled to ambient temperature, and diluted with water (500 cm^3). The product was extracted into dichloromethane (3 × 50 cm^3), and the extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated. The oily residue was triturated with light petroleum (bp 40–60 °C) followed by ether, and the resulting solid was collected by filtration and dried *in vacuo* to give *N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}formamide **10** (11.9 g, 30%) as a colourless solid, mp 110–112 °C.

A mixture of the formamide **10** (8.7 g, 0.03 mol), bis(2-methoxyethyl) ether (65 cm^3), concentrated hydrochloric acid (22 cm^3) and water (22 cm^3) was stirred and heated under reflux for 18 h, then cooled and diluted with water (80 cm^3). The resulting solution was washed with ether (2 × 50 cm^3) then basified by the addition of 5 M aqueous sodium hydroxide. The product was extracted into ether (3 × 50 cm^3) and the extracts were washed with brine (50 cm^3) and water (50 cm^3), dried ($MgSO_4$) and evaporated to leave the crude *title compound* (7.5 g, 96%) as a brown oil.

A sample (3.3 g) of the free base was converted into the hydrochloride salt by dissolution in a mixture of propan-2-ol (4 cm^3) and ether (20 cm^3), and addition of concentrated hydrochloric acid (1.5 cm^3). The solvents were evaporated, and the residue was dried by repeated dissolution in ethanol (50 cm^3) and evaporation of the solvent. The dried residue was then triturated with light petroleum (bp 60–80 °C) and the resulting solid was collected by filtration and dried *in vacuo* to give the *hydrochloride salt* of the *title compound* (1.73 g, 46%) as a white solid, mp 163–165 °C (Found: C, 62.8; H, 8.0; N, 4.65; Cl, 24.3. Calc. for $C_{15}H_{22}ClN{\cdot}HCl$: C, 62.5; H, 8.0; N, 4.85; Cl, 24.6%).

N-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}formamide 10

A mixture of 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine **3** (16.6 g, 0.066 mol) and methyl formate (100 cm^3) was stirred and heated under reflux for 16 h, then the excess of methyl formate was evaporated. The residue was crystallised twice from light petroleum (bp 60–80 °C), and the resulting solid was collected by filtration and dried *in vacuo* at 50 °C to give the *title compound* (13.6 g, 74%) as a white solid, mp 110–111 °C (Found: C, 68.2; H, 7.9; N, 4.9; Cl, 12.7. Calc. for $C_{16}H_{22}ClNO$: C, 68.7; H, 7.9; N, 5.0; Cl, 12.7%); ν_{max}(KBr)/cm^{-1} 3341 (NH stretch), 2955 (br) and 2872 (CH_3, CH_2 and CH stretch), 1650 (C=O stretch—amide I band), 1511 (NH bend—amide II band), 1493 (aromatic C=C stretch), 1471 (CH_3 bend and CH_2 scissor), 1396 and 1382 (CH_3 bend), 1092 (*p*-substituted aromatic), 1013 (aromatic CH in plane bend), 835 and 825 (aromatic CH out of plane bend); δ_H(250 MHz; $CDCl_3$) 0.62–0.77 (1 H, m, CH_2CHMe_2), 0.81–0.97 (6 H, m, $CHMe_2$) [includes 0.82 (d, *J* 6.8) and 0.95 (d, *J* 6.4)], 1.22 (1 H, br t, CH_2CHMe_2), 1.49 (1 H, m, $CHMe_2$), 1.86 (1 H, m, CB CH), 2.0–3.5 (5 H, m, CB CHs), 3.61 (0.28 H, m, $CHBu^iNH$, *trans* conformer), 4.62 (0.72 H, m, $CHBu^iNH$, *cis* conformer), 4.96 (0.72 H, br d, *J* ~ 10.0, NHCHO, *cis* conformer), 5.06 (0.28 H, br d, *J* ~9.0, NHCHO, *trans* conformer), 7.06 (2 H, m, ArH), 7.29 (2 H, m, ArH), 8.11 (0.28 H, d, *J* 11.8, NHCHO, *trans* conformer) and 8.29 (0.72 H, s, NHCHO, *cis* conformer); δ_H[360 MHz; $(CD_3)_2SO$] 0.73–0.84 (7 H, m, $CHMe_2$ + CH_2CHMe_2), 0.96–1.03 (1 H, m, CH_2CHMe_2), 1.41 (1 H, m, $CHMe_2$), 1.72 (1 H, m, CB CH), 1.93 (1 H, m, CB CH), 2.09–2.22 (3 H, m, CB CHs), 2.50 (1 H, m, CB CH), 3.47 (0.12 H, m, $CHBu^iNH$, *trans* conformer), 4.29 (0.88 H, m, $CHBu^iNH$, *cis* conformer), 7.15 (2 H, m, ArH), 7.37 (2 H, m, ArH), 7.46 (0.12 H, br t, NHCHO, *trans* conformer), 7.58 (0.88 H, br d, NHCHO, *cis* conformer), 8.07 (0.12 H, d, *J* 11.4, NHCHO, *trans* conformer) and 8.15 (0.88 H, d, *J* 1.7, NHCHO, *cis* conformer).

N-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*-methylamine 2

A solution of borane–dimethyl sulfide complex (10 M in dimethyl sulfide; 24 cm^3, 0.24 mol) in dry tetrahydrofuran (15 cm^3) was added dropwise at 15–20 °C under nitrogen to a stirred solution of the formamide **10** (13.6 g, 0.05 mol) in dry tetrahydrofuran (50 cm^3), then the mixture was stirred at ambient temperature for 19 h, cooled to 0 °C, quenched during 40 min by the slow, dropwise addition of water (40 cm^3), and basified by the addition of 2.5 M aqueous sodium hydroxide. The product was extracted into ether (3 × 100 cm^3), and the extracts were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and evaporated. Concentrated hydrochloric acid (100 cm^3) was added, then the stirred mixture was heated at 95 °C for 1 h, diluted with water (300 cm^3), cooled to ambient temperature, and basified by the addition of 5 M aqueous sodium hydroxide. The product was extracted into ether (3 × 200 cm^3), and the extracts were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and evaporated to leave the *title compound* as a yellow oil (10.5 g). The oil was dissolved in light petroleum (bp 60–80 °C) (150 cm^3), then the solution was filtered, and saturated with hydrogen chloride. The resulting solid was collected by

filtration, washed with light petroleum (bp 60–80 °C) and dried *in vacuo* to give the *hydrochloride salt* of the *title compound* (10.1 g, 67%) as a white solid, mp 232–236 °C (Found: C, 63.8; H, 8.1; N, 4.8; Cl, 23.1. Calc. for $C_{16}H_{24}ClN{\cdot}HCl$: C, 63.6; H, 8.3; N, 4.6; Cl, 23.45%); ν_{max}(KCl)/cm^{-1} 2958 and 2868 (CH_3, CH_2 and CH stretch), 2703 (NH stretch), 1586 (NH bend), 1494 (aromatic C=C stretch), 1469 (CH_3 bend and CH_2 scissor), 1393 and 1368 (CH_3 bend), 1096 (*p*-substituted aromatic), 1014 (aromatic CH in plane bend) and 822 (aromatic CH out of plane bend); δ_H[360 MHz; $(CD_3)_2SO$] 0.86 (6 H, 2 × overlapping d, CH*Me*$_2$), 1.09–1.14 (1 H, m, C*H*$_2$CHMe$_2$), 1.21–1.28 (1 H, m, C*H*$_2$CHMe$_2$), 1.5–1.65 (1 H, m, CB CH), 1.65–1.75 (1 H, m, CB CH), 1.93–1.96 (1 H, m, C*H*Me$_2$), 2.29–2.37 (2 H, m, CB CHs), 2.34–2.44 (1 H, m, CB CH), 2.55 (3 H, s, NMe), 2.55–2.61 (1 H, m, CB CH), 3.44 (1 H, br, C*H*Bu^{i}NHMe), 7.45 (4 H, m, ArH) and 8.1–8.7 (2 H, br, N*H*$_2$Me$^+$).

N-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*,*N*-dimethylamine 1 (sibutramine)

Formic acid (460 cm^3) was added slowly to stirred, ice-cold 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine **3** (152 g, 0.604 mol), then aqueous formaldehyde (37–40% w/v; 92 cm^3) was added, and the mixture was heated at 90–95 °C for 1 h. Further aqueous formaldehyde (92 cm^3) was added, and heating at 90–95 °C was continued for 19 h, then the mixture was cooled to ambient temperature and added to a stirred mixture of ice (1000 g) and 16 M aqueous sodium hydroxide (650 cm^3). The product was extracted into ether (4 × 500 cm^3), and the extracts were washed with saturated brine (2 × 200 cm^3) and water (2 × 200 cm^3), dried ($MgSO_4$) and evaporated. The residue was distilled to give the *title compound* (141.5 g, 84%) as a pale yellow oil, bp 130–155 °C/1.0–1.3 mmHg, which solidified slowly at ambient temperature to give a pale yellow solid, mp 51–55 °C.

A mixture of the free base (1 g, 3.6 mmol) and 5 M hydrochloric acid (1 cm^3) was heated with the minimum amount of 1,2-dimethoxyethane required to give a clear solution, then allowed to cool to ambient temperature and stored at 4 °C for 3 h. The resulting solid was collected by filtration and dried *in vacuo* at ambient temperature for 18 h to give the *hydrochloride salt monohydrate* of the *title compound* (1.0 g, 83%) as colourless plates, mp 191–192 °C (shrinks, 145 °C) (Found: C, 61.0; H, 8.7; N, 3.9; Cl, 20.9; H_2O, 5.6. Calc. for $C_{17}H_{26}ClN{\cdot}HCl{\cdot}H_2O$: C, 61.1; H, 8.7; N, 4.2; Cl, 21.2; H_2O, 5.4%); ν_{max}(KBr)/cm^{-1} 2963 and 2866 (CH_3, CH_2 and CH stretch), 2700 (NH stretch), 1492 (aromatic C=C stretch), 1483 and 1474 (isobutyl CH_3 bend and CH_2 scissor), 1428 and 1407 (NCH_3 bend), 1395 and 1370 (isobutyl CH_3 bend), 1092 (*p*-substituted aromatic), 1011 (aromatic CH in plane bend) 834 and 823 (aromatic CH out of plane bend); δ_H[360 MHz; $(CD_3)_2SO$] 0.99 (6 H, overlapping dd, CH*Me*$_2$), 1.36 (2 H, overlapping dd, C*H*$_2$CHMe$_2$), 1.65 (1 H, m, CB CH), 1.80 (1 H, m, CB CH), 1.90 (1 H, m, C*H*Me$_2$), 2.07 (3 H, d, *J* 4.9, NMe), 2.25–2.35 (2 H, m, CB CHs), 2.6–2.75 (2 H, m, CB CHs), 2.79 (3 H, d, *J* 5.0, NMe), 3.79 (1 H, t, C*H*Bu^{i}NMe$_2$), 7.46 (2 H, m, ArH), 7.69 (2 H, m, ArH) and 9.8–9.95 (1 H, br, N*H*Me$_2^+$).

4-Amino-4-[1-(4-chlorophenyl)cyclobutyl]-2-methylbutan-1-ol 4

A solution of 2-(bromomethyl)propan-1-ol[22] (303 g, 1.98 mol) in dry ether (1500 cm^3) was added under nitrogen at −25 to −20 °C over 45 min to a stirred solution of isopropylmagnesium chloride [from isopropyl chloride (270 cm^3, 231 g, 2.85 mol) and magnesium turnings (55.8 g, 2.28 mol)] in dry ether (1500 cm^3), then the stirred mixture was allowed to warm to ambient temperature over 1 h. Magnesium turnings (81 g, 3.375 mol) were added in one portion, and the mixture was stirred without heating for 1 h. During this time an exothermic reaction set in, and the mixture came to reflux temperature. When the exotherm ceased, and the internal temperature had fallen to 24 °C, a solution of 1-(4-chlorophenyl)cyclobutanecarbonitrile **7** (180 g, 0.94 mol) in dry ether (200 cm^3) was added dropwise over 20 min. The mixture was then stirred at ambient temperature for 1.5 h, and added in portions to a hot slurry of sodium borohydride (150 g, 3.97 mol) in propan-2-ol (6000 cm^3). The ether was removed by distillation, then the mixture was heated under reflux for 3 h, allowed to stand at ambient temperature for 14 h, and quenched by the slow addition of ice–water (2000 cm^3) followed by concentrated hydrochloric acid (100 cm^3). The mixture was basified by the addition of 5 M aqueous sodium hydroxide, and concentrated under reduced pressure to remove propan-2-ol, then the product was extracted into ether (6 × 1000 cm^3). The extracts were washed with water (3 × 500 cm^3), dried ($MgSO_4$) and evaporated to leave the crude amino alcohol **4** (182.7 g) as an oil. The oil was dissolved in dry ether (1600 cm^3), the solution was saturated with hydrogen chloride, and the resulting solid was collected by filtration, washed with ether, and dried *in vacuo* to give a white solid (133.5 g). A second crop of white solid (10.75 g) was obtained by resaturation with hydrogen chloride of the ethereal liquors. The combined solids were triturated with dry acetone (600 cm^3), collected by filtration, washed with dry acetone (100 cm^3) and dry ether (250 cm^3), and dried *in vacuo* at ambient temperature to give the *hydrochloride salt* of the *title compound* (131.8 g, 46%) (in the form of a 3.8:1 mixture of pairs of diastereoisomers) as a white solid, mp 191–195 °C (Found: C, 59.05; H, 7.5; N, 4.4; Cl, 23.5; H_2O, 0.6. Calc. for $C_{15}H_{22}ClNO{\cdot}HCl{\cdot}0.1H_2O$: C, 58.9; H, 7.6; N, 4.6; Cl, 23.2; H_2O, 0.6%); ν_{max}(KBr)/cm^{-1} 3280 (OH stretch), 2800–3100 (br) (NH, CH_3, CH_2 and CH stretch), 1603 and 1510 (NH bend), 1492 (aromatic C=C stretch), 1460 and 1380 (CH_3 bend and CH_2 scissor), 1096 (*p*-substituted aromatic), 1012 (aromatic CH in plane bend) 838 and 825 (aromatic CH out of plane bend); δ_H[360 MHz; $(CD_3)_2SO$] 0.77 (2.37 H, d, *J* 7.4, CH*Me*, diastereoisomer 1), 0.82 (0.79 H, obscured by 2 × dd, C*H*$_2$CHMe, diastereoisomer 1), 0.84 (0.63 H, d, *J* 6.6, CH*Me*, diastereoisomer 2), 1.09 (0.21 H, m, C*H*$_2$CHMe, diastereoisomer 2), 1.20 (0.21 H, m, C*H*$_2$CHMe, diastereoisomer 2), 1.55 (0.79 H, m, C*H*$_2$CHMe, diastereoisomer 1), 1.73 (2 H, m, CB CH and C*H*Me), 1.95 (1 H, m, CB CH), 2.30 (3 H, m, CB CHs), 2.50 (1 H, m, CB CH), 3.12 (0.21 H, dd, *J* 10.0, 6.4, C*H*$_2$OH, diastereoisomer 2), 3.21 (0.21 H, dd, *J* 10.00, 5.7, C*H*$_2$OH, diastereoisomer 2), 3.28 (0.79 H, dd, *J* 10.6, 5.1, C*H*$_2$OH, diastereoisomer 1), 3.40 (0.79 H, dd, *J* 10.7, 4.8, C*H*$_2$OH, diastereoisomer 1), 3.46 (0.21 H, br d, *J* 9.0, C*H*Bu^{i}NH$_2$, diastereoisomer 2), 3.64 (0.79 H, dd, *J* 10.2, 2.2, C*H*Bu^{i}NH$_2$, diastereoisomer 1), 6.5–7.6 (4 H, br, NH_3^+ + OH), 7.33 (2 H, m, ArH) and 7.42 (2 H, m, ArH).

t-3-(1-Amino-3-methylbutyl)-3-(4-chlorophenyl)cyclobutan-*r*-1-ol 5b

A solution of 2-[2-bromo-1-(bromomethyl)ethoxy]tetrahydropyran[24] (78.1 g, 0.259 mol) and 4-chlorophenylacetonitrile (39.2 g, 0.259 mol) in ether (to total 150 cm^3) was added dropwise over 2.5 h at 15–20 °C to a vigorously stirred suspension of finely powdered potassium hydroxide (65 g) and 18-crown-6 (1 g) in dimethyl sulfoxide (350 cm^3), then the mixture was stirred at ambient temperature for 2 h, cooled to 15 °C, quenched by the dropwise addition of water (250 cm^3), diluted with ether (250 cm^3) and filtered through Celite®. The filter pad was washed well with ether, then the aqueous phase of the filtrate was separated and washed well with ether. The combined ethereal solutions were washed with water, dried ($MgSO_4$) and evaporated to leave an orange oil which was partially purified by flash chromatography over silica using a 7:3 mixture of light petroleum (bp 40–60 °C) and acetone as eluent. A 1:1 mixture of 1-(4-chlorophenyl)-*c*-3-tetrahydropyran-2-yloxycyclobutane-*r*-1-carbonitrile **14a** and 1-(4-chlorophenyl)-*t*-3-tetrahydropyran-2-yloxycyclobutane-*r*-1-carbonitrile **14b** (54.2 g, 71.7%) was thus obtained ~90% pure as a pale orange oil.

A solution of the above 1:1 mixture of nitriles **14a,b** (41.7 g, ~0.143 mol) in dry toluene (200 cm^3) was added slowly at ambient temperature under nitrogen to a stirred solution of isobutylmagnesium bromide [from isobutyl bromide (31 cm^3, 39.1 g, 0.285 mol) and magnesium turnings (7.3 g, 0.3 mol)] in dry ether (200 cm^3), then ether was removed by distillation until the internal temperature of the mixture had risen to 70 °C. The mixture was heated at 70 °C for 18 h, then added to a hot slurry of sodium borohydride (40 g, 1.06 mol) in propan-2-ol (3000 cm^3), heated under reflux for 7 h, allowed to stand at ambient temperature for 18 h, and evaporated. The residue was diluted with water (1000 cm^3), the product was extracted into ether (4 × 300 cm^3), and the combined extracts were washed with water (3 × 200 cm^3), dried ($MgSO_4$) and evaporated. The residual oil was dissolved in industrial methylated spirit (500 cm^3), concentrated hydrochloric acid (20 cm^3) was added, then the mixture was heated under reflux for 0.5 h and evaporated. The residue was diluted with water (500 cm^3), basified by the addition of 5 M aqueous sodium hydroxide, and the product was extracted into ether (3 × 300 cm^3). The extracts were washed with water (2 × 200 cm^3), dried ($MgSO_4$) and evaporated to leave a 1:1 mixture of the crude *title compound* **5b** and the *corresponding* c-*isomer* **5a** as a viscous brown oil (36.1 g).

The two components were separated *via* preparative scale HPLC on a 2″ diameter Dynamax C_{18} column using a 70:30 mixture of methanol and water as eluent. The faster-running component was the *title compound* **5b** (2.05 g, 10.8%), obtained as a pale yellow syrup. This was converted into its fumarate salt by dissolution in dry ether (30 cm^3) and addition of a saturated ethereal solution of fumaric acid (0.9 g, 7.76 mmol). Concentration of the mixture to ~50 cm^3, and filtration gave the *fumarate salt* 0.45 *hydrate* of the *title compound* (1.95 g, 64.9%) as an amorphous white powder (containing 3.4% of the corresponding *c*-isomer), mp (decomp.) > 110 °C (Found: C, 58.4; H, 6.9; N, 3.3; Cl, 8.9; H_2O, 2.05. Calc. for $C_{15}H_{22}ClNO{\cdot}C_4H_4O_4{\cdot}0.45H_2O$: C, 58.2; H, 6.9; N, 3.6; Cl, 9.0; H_2O, 2.1%); ν_{max}(KBr)/cm^{-1} 3430 (br) (OH stretch), 2600–3200 (NH, CH_3, CH_2 and CH stretch), 1630–1710 (br) (C=O stretch), 1550 (br) (asymmetric carboxylate stretch), 1495 (aromatic C=C stretch), 1370 (br) (symmetric carboxylate stretch and CH_3 bend), 1095 (*p*-substituted aromatic), 1015 (aromatic CH in plane bend) and 830 (aromatic CH out of plane bend); δ_H[360 MHz; $(CD_3)_2SO$] 0.81 (3 H, d, *J* 6.5, CH*Me*$_2$), 0.85 (3 H, d, *J* 6.4, CH*Me*$_2$), 0.92 (1 H, m, C*H*$_2$CHMe$_2$), 1.28 (1 H, br t, C*H*$_2$CHMe$_2$), 1.61 (1 H, m, C*H*Me$_2$), 2.01 (1 H, dd, *J* 12.0, 7.2, CB CH), 2.10 (1 H, dd, *J* 11.9, 7.5, CB CH), 2.66 (1 H, m, CB CH), 2.94 (1 H, m, CB CH), 3.24 (1 H, d, *J* 10.1, C*H*Bu^{i}NH$_2$), 4.24 (1 H, m, C*H*OH), 4.5–6.0 (~5 H, br, NH_2·fumarate and OH), 6.46 (2 H, s, fumaric acid C*H*=C*H*), 7.19 (2 H, m, ArH) and 7.40 (2 H, m, ArH).

The slower-running component was c-3-(1-*amino*-3-*methylbutyl*)-3-(4-*chlorophenyl*)*cyclobutan*-r-1-*ol* **5a** (0.6 g, 3.2%), obtained as a pale yellow syrup. This was converted into its fumarate salt in a manner similar to that described above, giving c-3-(1-*amino*-3-*methylbutyl*)-3-(4-*chlorophenyl*)-*cyclobutan*-r-1-*ol fumarate* 0.35 *hydrate* (0.45 g, 51.5%) as an amorphous white powder (containing 1% of the corresponding *t*-isomer), mp (decomp.) > 110 °C.

c-3-(1-Amino-3-methylbutyl)-3-(4-chlorophenyl)-*r*-1-cyclobutanol 5a

Methyllithium (complex with lithium bromide; 1.5 M solution in ether; 132 cm^3, 0.2 mol) was added dropwise at −70 °C under nitrogen to a stirred solution of 4-chlorophenylacetonitrile **6** (30 g, 0.2 mol) in dry tetrahydrofuran (600 cm^3), then the mixture was stirred at −70 °C for 1 h. A solution of 1-bromo-2,3-epoxypropane (epibromohydrin) (27.6 g, 0.2 mol) in dry tetrahydrofuran (120 cm^3) was added dropwise at −70 °C, stirring was continued at the same temperature for 1 h, then a solution of methylmagnesium iodide [from iodomethane (28.8 g, 0.2 mol) and magnesium turnings (4.9 g, 0.2 mol)] in dry ether (120 cm^3) was added dropwise at −70 to −60 °C. The stirred mixture was allowed to warm to ambient temperature over 18 h, then it was cooled to 0 °C, quenched by the addition of water (150 cm^3), acidified by the addition of 5 M hydrochloric acid, and sodium chloride was added until the layers fully separated. The aqueous layer was washed with ether (2 × 100 cm^3), then the combined organic solutions were washed with saturated aqueous sodium thiosulfate (100 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$) and evaporated to leave a 2.7:1 mixture of 1-(4-*chlorophenyl*)-c-3-*hydroxycyclobutane*-r-1-*carbonitrile* **13a** and 1-(4-*chlorophenyl*)-t-3-*hydroxycyclobutane*-r-1-*carbonitrile* **13b** (32 g, 78%) as a viscous orange oil. A sample (5 g) was purified by flash chromatography over silica using ether as eluent to give a 2.5:1 mixture of **13a** and **13b** (2.2 g) as a pale yellow viscous oil (Found: C, 63.2; H, 4.85; N, 6.8; Cl, 17.3. Calc. for $C_{11}H_{10}ClNO$: C, 63.6; H, 4.85; N, 6.7; Cl, 17.1%); δ_H(360 MHz; $CDCl_3$) 2.49 (0.57 H, m, 2 × CB CH, *t*-isomer), 2.60 (1 H, br, OH), 2.75–3.0 (2.86 H, m, 4 × CB CH, *c*-isomer), 3.18 (0.57 H, m, 2 × CB CH, *t*-isomer), 4.45 (0.71 H, m, C*H*OH, *c*-isomer), 4.74 (0.29 H, m, C*H*OH, *t*-isomer) and 7.37 (4 H, m, ArH). For subsequent reactions the crude mixture was used without chromatographic purification.

A solution of the crude mixture of **13a** and **13b** (135 g, 0.65 mol), 3,4-dihydro-2*H*-pyran (200 cm^3) and toluene-4-sulfonic acid (1 g) in dry ether (1500 cm^3) was stirred at ambient temperature for 18 h, neutralised by the addition of a saturated solution of ammonia in tetrahydrofuran, and filtered through a short column of silica. The column was washed with ether (2000 cm^3), then the combined solutions were evaporated to leave a mixture of 1-(4-*chlorophenyl*)-c-3-*tetrahydropyran*-2-*yloxycyclobutane*-r-1-*carbonitrile* **14a** and 1-(4-*chlorophenyl*)-t-3-*tetrahydropyran*-2-*yloxycyclobutane*-r-1-*carbonitrile* **14b** as a dark orange oil which was used without purification.

Half of the oil was dissolved in dry toluene (500 cm^3) and added under nitrogen to a stirred solution of isobutylmagnesium bromide [from isobutyl bromide (92 cm^3, 115.9 g, 0.85 mol) and magnesium turnings (21 g, 0.85 mol)] in dry ether (300 cm^3). Ether was removed by distillation until the internal temperature rose to 70 °C, then the mixture was maintained at this temperature without stirring for 18 h. This resulted in the deposition of a solid black mass. The supernatant solution was removed by decantation, the black solid was ground to a coarse powder, and both were added to a hot slurry of sodium borohydride (75 g) in propan-2-ol (3000 cm^3). The mixture was heated under reflux for 6 h, allowed to stand at ambient temperature for 18 h, and evaporated. The residue was diluted with water (2000 cm^3), the product was extracted into ether (5 × 300 cm^3), and the extracts were washed with water (3 × 200 cm^3) and evaporated. The residual viscous red oil was dissolved in methanol (1000 cm^3), acidified by the addition of concentrated hydrochloric acid, stirred at ambient temperature for 1 h, basified by the addition of 5 M aqueous sodium hydroxide, concentrated *in vacuo* to remove the methanol, and diluted with water (1000 cm^3). The product was extracted into ether (5 × 300 cm^3), and the extracts were washed with water (3 × 200 cm^3), dried ($MgSO_4$) and evaporated to leave a crude 3.3:1 mixture of the *title compound* **5a** and its corresponding t-*isomer* **5b** as a red oil. The remainder of the **14a,b** mixture was treated similarly, and the two batches of crude product were combined and converted into the fumarate salt as follows.

The mixture of **5a** and **5b** was dissolved in dry ether (2000 cm^3) and the solution was heated to reflux temperature. A suspension of fumaric acid (94 g) in dry ether (2000 cm^3) was heated under reflux for 20 min, then the solid was allowed to settle, the hot supernatant solution was added to the **5a,b** mixture, and the resulting suspension was concentrated by distillation to ~2000 cm^3. This process was repeated until all of the fumaric acid had been dissolved and added to the mixture of amines, then the suspension was concentrated to ~500 cm^3 and

allowed to cool. The supernatant solution was removed by decantation, and the residual solid was crystallised from 10% aqueous acetonitrile to give a 28:1 mixture of *c*-3-(1-amino-3-methylbutyl)-3-(4-chlorophenyl)cyclobutan-*r*-1-ol fumarate and *t*-3-(1-amino-3-methylbutyl)-3-(4-chlorophenyl)cyclobutan-*r*-1-ol fumarate (47.8 g) as colourless prisms. To remove entrapped acetonitrile, the salt was rebasified by dissolution in water, addition of 5 M aqueous sodium hydroxide, and extraction with ether, then the extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was treated with fumaric acid (14.25 g) by the method described above. This resulted in the 0.9 *fumarate salt* 0.2 *hydrate* of the *title compound* (42.5 g, 17.4%) as an amorphous white powder (containing 3.7% of the corresponding *t*-isomer), mp 175–180 °C (decomp.) (Found: C, 59.4; H, 6.9; N, 3.5; Cl, 9.5; H_2O, 1.1. Calc. for $C_{15}H_{22}ClNO{\cdot}0.9C_4H_4O_4{\cdot}0.2H_2O$: C, 59.4; H, 7.0; N, 3.7; Cl, 9.4; H_2O, 0.95%); ν_{max}(KCl)/cm^{-1} 3400 (br) (OH stretch), 2600–3200 (NH, CH_3, CH_2 and CH stretch), 1630–1700 (br) (C=O stretch), 1550 (br) (asymmetric carboxylate stretch), 1495 (aromatic C=C stretch), 1370 (shoulder) (CH_3 bend), 1350 (symmetric carboxylate stretch), 1145 (cyclobutanol CO stretch), 1096 (*p*-substituted aromatic), 1015 (aromatic CH in plane bend) 840 and 820 (aromatic CH out of plane bend); δ_H[360 MHz; $(CD_3)_2SO$] 0.78 (3 H, d, *J* 3.2, $CHMe_2$), 0.80 (3 H, d, *J* 3.0, $CHMe_2$), 0.86 (1 H, m, CH_2CHMe_2), 1.05 (1 H, m, CH_2CHMe_2), 1.63 (1 H, m, $CHMe_2$), 2.06 (1 H, dd, *J* 11.3, 7.6, CB CH), 2.22 (1 H, dd, *J* 11.6, 7.7, CB CH), 2.66 (1 H, m, CB CH), 2.74 (1 H, m, CB CH), 3.28 (1 H, d, *J* 8.2, $CHBu^iNH_2$), 3.72 (1 H, m, CHOH), 5.5–6.8 (~5 H, br, NH_2·fumarate and OH), 6.47 (1.8 H, s, fumaric acid CH=CH) and 7.41 (4 H, m, ArH).

Acknowledgements

We thank Dr G. Haran and Mrs H. J. Barnes for spectroscopic discussions and Dr B. J. Sargent for help in the preparation of this manuscript.

References

1 T. Silverstone, *Drugs*, 1992, **43**, 820.
2 P. Kopelman, *Br. J. Clin. Pract.*, 1991, **45**, 234.
3 G. A. Bray, in *Progress in Obesity Research*, ed. Y. Oomura, John Libbey, 1990, 639.
4 National Institutes of Health Consensus Development Panel, *Ann. Intern. Med.*, 1985, **103**, 1073.
5 Royal College of Physicians, *J. R. Coll. Physicians*, London, 1983, **17**, 3.
6 W. R. Buckett, P. C. Thomas and G. P. Luscombe, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 1988, **12**, 575.
7 M. Weintraub, A. Rubio, A. Golik, L. Byrne and M. L. Scheinbaum, *Clin. Pharmacol. Ther.*, 1991, **50**, 330.
8 G. A. Bray, G. L. Blackburn, J. M. Ferguson, F. L. Greenway, A. Jain, P. E. Kaiser, J. Mendels, D. Ryan and S. L. Schwarz, *Int. J. Obes.*, 1994, **18**(Suppl. 2), 60.
9 P. Drouin, C. Hanotin, S. Courcier and E. Leutenegger, *Int. J. Obes.*, 1994, **18**(Suppl. 2), 60.
10 S. P. Jones, B. M. Newman and F. M. Romanec, *Int. J. Obes.*, 1994, **18**(Suppl. 2), 61.
11 F. Kelly, A. G. Wade, S. P. Jones and S. G. Johnson, *Int. J. Obes.*, 1994, **18**(Suppl. 2), 61.
12 J. Mendels, G. L. Blackburn, G. A. Bray, J. M. Ferguson, F. L. Greenway, A. Jain, P. E. Kaiser, D. Ryan and S. L. Schwarz, *Int. J. Obes.*, 1994, **18**(Suppl. 2), 61.
13 G. P. Luscombe, R. H. Hopcroft, P. C. Thomas and W. R. Buckett, *Neuropharmacology*, 1989, **28**, 129.
14 P. J. Harris and W. R. Buckett, *Drugs of the Future*, 1988, **13**, 736.
15 D. E. Butler and J. C. Pollatz, *J. Org. Chem.*, 1971, **36**, 1308.
16 M. L. Moore, *Org. React.*, (*N. Y.*), 1941, **5**, 301.
17 H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 1933, **55**, 4571.
18 A. Kozlik, E. C. Wilmshurst and J. E. Jeffery, BP 2 098 602/1982; A. Kozlik and W. H. Wells, BP 2 127 819/1984; B. J. Armitage, J. R. Housley, J. E. Jeffery and D. N. Johnston, BP 2 128 991/1984; J. R. Housley, J. E. Jeffery, D. N. Johnston and B. J. Sargent, USP 5 047 432/1991.
19 F. J. Weiberth and S. S. Hall, *J. Org. Chem.*, 1986, **51**, 5338.
20 H. Kotsuki, N. Yoshimura, I. Kadota, Y. Ushio and M. Ochi, *Synthesis*, 1990, 401.
21 G. Cahiez, A. Alexakis and J. F. Normant, *Tetrahedron Lett.*, 1978, 3013.
22 G. Courtois and P. Miginiac, *Bull. Soc. Chim. Fr.*, 1983, 21.
23 A. V. Bogatskii, A. M. Turyanskaya, A. I. Gren, E. Bal'trusch and A. Voigt, *Vopr. Stereokhim.*, 1974, **4**, 49 (*Chem. Abstr.*, 1975, **83**, 57924x).
24 D. E. Horning, G. Kavadias and J. M. Muchouski, *Can. J. Chem.*, 1970, **48**, 975.
25 B. Corbel and T. Durst, *J. Org. Chem.*, 1976, **41**, 3648.

Paper 6/03968E
Received 6th *June* 1996
Accepted 15th *July* 1996