NEW BENZOFURAN-TYPE ANTIARRHYTHMIC COMPOUNDS RELATED TO PROPAFENONE

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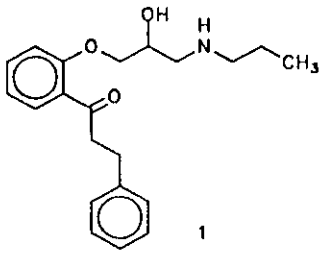
Abstract - Synthesis of two benzofuran compounds (**2a** and **2b**), which are structurally and - by their action as sodium channel blockers - also pharmacologically related to propafenone is described.

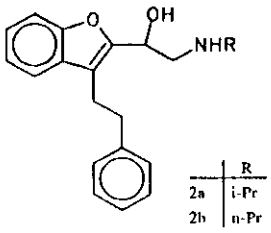
INTRODUCTION

The pharmacological activity of the class Ic antiarrhythmic propafenone (**1**) is mainly due to the block of cardiac sodium channels.[1] As recently shown for flecainide and encainide by the Cardiac Arrhythmia Suppression Trial, the major risk in the use of class Ic antiarrhythmic drugs for treatment of ventricular arrhythmias is their high potential for pro-arrhythmic side effects.[2] One of the electrophysiological characteristics of class Ic agents is their relative long time constant of recovery from channel-blockade (> 10 sec. versus < 0.5 sec. for class Ib agents;[3] propafenone: 8-10 sec.[4]), which may be one of the reasons for the pro-arrhythmic potential of this subgroup.[5] Propafenone is a highly flexible molecule. Rigidization of the molecule by incorporation of the ether-oxygen into a benzofuran-moiety, which at the same time renders the compound an arylethanolamine, should influence the pattern of pharmacological activity. To assess the effect of this structural modification, mainly in view of enhancing sodium channel blocking activity and lowering the pro-arrhythmic side effects, we synthesized the new benzofuran derivatives (**2a** and **2b**).

Dedicated with best wishes to Prof. Bernhard Unterhalt on the occasion of his 60th birthday



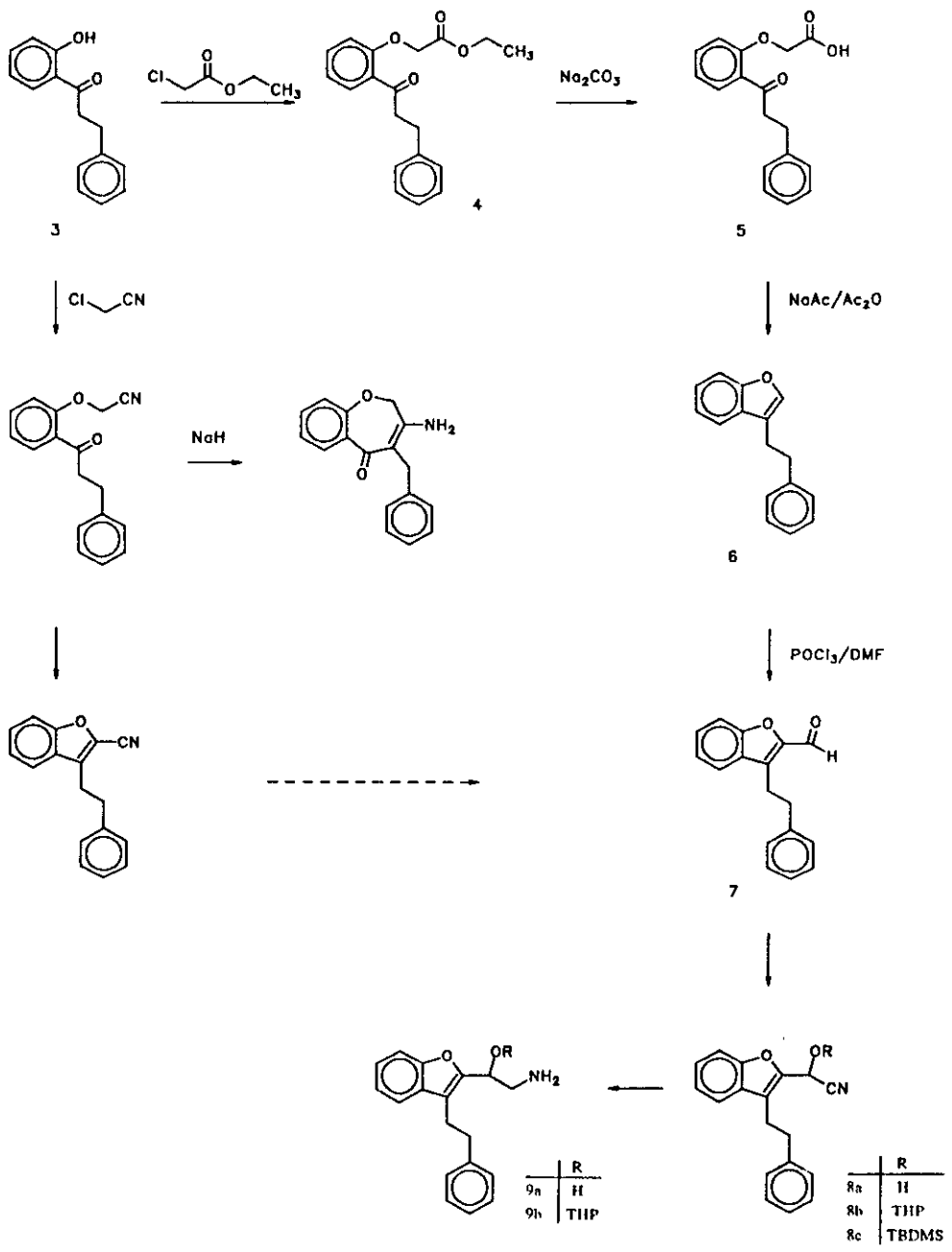
1



	R
2a	i-Pr
2b	n-Pr

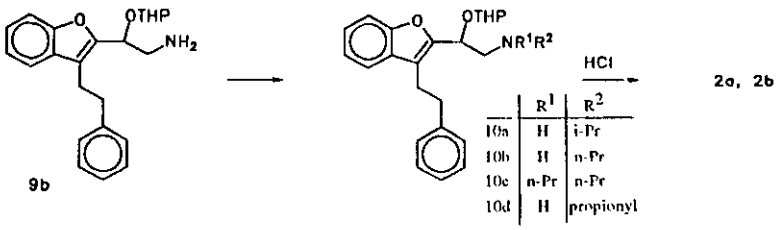
RESULTS AND DISCUSSION

Various attempts failed to synthesize 3-(2-phenylethyl)benzofurans appropriately substituted at position 2 *via* ring closure of 2-acylphenyl ethers in acceptable yield. In most cases the corresponding 1-benzoxepin-5-ones were main products.[6] Therefore the approach described by Nielek *et al.* for 3-methylbenzofuran[7] was chosen to synthesize 3-(2-phenylethyl)benzofuran (**6**) starting from the phenyl ether (**4**), which was obtained by alkylation of 1-(2-hydroxyphenyl)-3-phenyl-1-propanone (**3**) with ethyl chloroacetate. Hydrolysis using aqueous sodium carbonate lead to the acid (**5**), which could be easily cyclized under Perkin conditions.[8] Vilsmeier formylation of **6** followed by addition of HCN gave cyanohydrin (**8a**) which due to its instability was reacted immediately with dihydropyran. Reduction of the corresponding THP ether (**8b**) with $LiAlH_4$ lead to the key intermediate (**9b**). In an alternative approach we used *tert*-butyldimethylsilyl chloride/KCN, which resulted in formation of the *tert*-butyldimethylsilyl-protected cyanohydrin (**8c**), which was sufficiently stable for chromatographic purification using silica gel. After reduction of **8c** with $LiAlH_4$ the aminoethanol (**9a**) was isolated in 35% yield (Scheme 1). Because of the relatively high costs of *tert*-butyldimethylsilyl chloride preference was given to the previously described route over this method for conversion of aldehydes to aminoethanols.


OH
Cl
O
O
CH3
Na2CO3
OH
3
4
5
Cl
CN
NaAc/Ac2O
CN
NaH
NH2
6
POCl3/DMF
CN
H
7
OR
NH2
OR
CN
R
9a H
9b THP
R
8a H
8b THP
8c TBDMS

Scheme 1

The isopropyl substituted compound (**10a**) was obtained easily *via* reductive alkylation of **9b** and converted to the hydrochloride of **2a** with concomitant cleavage of the tetrahydropyranyl protecting group by use of an ethereal solution of hydrogen chloride. With the use of propionaldehyde instead of acetone an increasing amount of the tertiary amine (**10c**) was observed in the reaction mixture, although the primary amine (**9b**) was still present. Therefore an alternative route *via* acylation of **9b** with propionyl chloride followed by reduction of the amide (**10d**) with $LiAlH_4$ was chosen, which proved to be more feasible in the synthesis of **10b**. Cleavage of the THP-group yielded the hydrochloride of **2b** (Scheme 2).



Scheme 2

Preliminary results from the pharmacological tests of compound (**2b**) show, that it is a very selective sodium channel blocker with an offset twice faster than propafenone.[9]

EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (Merck). Infrared spectra were recorded as thin films on salt discs on a Perkin Elmer 298 spectrophotometer. Mass spectra were performed on a Varian MAT 111A spectrometer by A. Nikiforov (Institut für Organische Chemie, Universität Wien). Nmr spectra were recorded on the spectrometers Varian EM 390 and Bruker AC 80, using tetramethylsilane as internal standard. Microanalyses were determined by J. Zak and J. Theiner (Institut für Physikalische Chemie, Universität Wien).

Ethyl 2-(3-phenylpropionyl)phenoxyacetate (4)

7.2g (52 mmol) of K_2CO_3 and 8 ml (75 mmol) of ethyl chloroacetate was added to a solution of 11.7g (51.7 mmol) of 1-(2-hydroxyphenyl)-3-phenyl-1-propanone (**3**) in 40 ml of acetone. The mixture was refluxed for 24 h, filtered and evaporated to dryness. The oily residue was dissolved in CH_2Cl_2 and washed twice with water. After drying over Na_2SO_4 the solvent was removed to give 15.52g (96%) of **4** as colourless oil which crystallized spontaneously. mp 51-52°C (ethanol); ^{1}H-nmr (90 MHz): δ(ppm) 1.2 (3H, t, J = 7.5 Hz, $-CH_3$), 2.9-3.6 (4H, m, $-CH_2-CH_2-$), 4.3 (2H, q, J = 7.5 Hz, $-C\underline{H}_2-CH_3$), 4.7 (2H, *s*, $-O-CH_2-$), 6.8-7.8 (9H, m, aromatic-H); ir: 1730 (CO), 1665 (CO); ms (m/z): 312 (M^+). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.37; H, 6.46.

2-(3-Phenylpropionyl)phenoxyacetic acid (5)

10.7g (34.3 mmol) of **4** was suspended in a solution of 4.5g (42.5 mmol) of Na_2CO_3 in 70 ml of water. The mixture was refluxed for 3 h, cooled, acidified with 6 M HCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness to give 8.14g (84%) of **5** as colourless oil which solidified slowly. mp 121-124°C ($CHCl_3$/petroleum ether); ^{1}H-nmr (90 MHz): δ(ppm) 2.9-3.5 (4H, m, $-CH_2-CH_2-$), 4.8 (2H, s, $-O-CH_2-$), 6.9-7.8 (9H, m, aromatic-H), 9.6 (1H, s, -COOH); ir: 1735 (CO), 1665 (CO); ms (m/z): 284 (M^+). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.82; H, 5.67.

3-(2-Phenylethyl)benzofuran (6)

5.3 g (18.6 mmol) of **5** was dissolved in 33 ml (350 mmol) of acetic anhydride followed by addition of 6.6 g (80.5 mmol) of sodium acetate. The mixture was refluxed for 2 h, cooled, diluted with ether and poured into ice-water. After basification with powdered NaOH the organic layer was separated and the aqueous phase was extracted twice with ether. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated to dryness to give 3.65 g (88%) of **6** as yellow oil, which was put into the next reaction step without further purification. ^{1}H-Nmr (90 MHz, crude product): δ(ppm) 3.0 (4H, s, $-CH_2-CH_2-$), 7.2-7.6 (10H, m, aromatic-H); ms (m/z): 222 (M^+).

3-(2-Phenylethyl)-2-benzofurancarbaldehyde (7)

15.2 g (68.4 mmol) of **6** was dissolved in 60 ml of DMF and added slowly to a mixture of 30 ml (321.9 mmol) of $POCl_3$ and 40 ml of DMF at 5°C under argon atmosphere. The resulting mixture was heated to

100°C and stirred overnight. After cooling and dilution with ether the mixture was poured into ice-water and neutralized cautiously with powdered $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted twice with ether. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated to dryness to give 16.1 g (95.6%) of **7** as yellowish oil. ^{1}H-Nmr (90 MHz; crude product): δ(ppm) 2.9-3.5 (4H, m, $-CH_2-CH_2-$), 7.0-7.7 (9H, m, aromatic-H), 9.7 (1H, s, -CHO); ir: 1680 (CO); ms (m/z): 250 (M^+). Dinitrophenylhydrazone: mp 281°C (dioxane); ms (m/z): 430 (M^+). Anal. Calcd for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.22; H, 4.39; N, 12.88.

α-Hydroxy-3-(2-phenylethyl)-2-benzofuranacetonitrile (8a)

5.4 g (110.2 mmol) of NaCN was dissolved in 50 ml of water and added to a solution of 5.2 g (48.1 mmol) of **7** in 75 ml of ether. After cooling to 5°C a mixture of 20 ml of 6 M HCl and 2 ml of glacial acetic acid was added dropwise under vigorous stirring (caution! HCN), which was continued overnight. The organic layer was separated and the aqueous phase was extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and, after addition of a few drops of glacial acetic acid to avoid retro-cyanohydrin reaction, evaporated to dryness to give 5.58 g (96.8%, crude product) of **8a** as yellow oil, which was immediately put into the next reaction step. ^{1}H-Nmr (90 MHz, crude product): δ(ppm) 3.0-3.2 (4H, m, $-CH_2-CH_2-$), 3.8 (1H, broad s, -OH), 5.2 (1H, s, -CH(OH)), 7.0-7.7 (9H, m, aromatic-H).

3-(2-Phenylethyl)-α-(2-tetrahydropyranyloxy)-2-benzofuranacetonitrile (8b)

4.5 ml (49.6 mmol) of 3,4-dihydro-2*H*-pyran and catalytic amounts of *p*-toluenesulfonic acid were added to a solution of 4.47 g (16.1 mmol) of crude **8a** in 45 ml of CH_2Cl_2. The mixture was stirred for 1 h at room temperature and washed twice with saturated $NaHCO_3$-solution. The combined aqueous phases were re-extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. Purification of the oily residue *via* column chromatography (silica gel, petroleum ether/ether = 20/1) gave 4.02 g (68%) of **8b** (mixture of diastereomers) as colourless oil. ^{1}H-Nmr (90 MHz): δ(ppm) 1.4-1.9 (6H, m, $-C(O)-CH_2-CH_2-CH_2-$), 2.9-3.2 (4H, m, $Ph-CH_2-CH_2-$), 3.5-4.1 (2H, m, $-O-CH_2-$), 4.5, 5.1 (0.7H, 0.3H, each m, -O-CH-O-), 5.4, 5.6 (0.7H, 0.3H, each s, -CH(O)-CN), 7.1-7.7 (9H, m, aromatic-H); ms (m/z): 361 (M^+). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.25; H, 6.23; N, 3.65.

α-(*tert*-Butyldimethylsilyloxy)-3-(2-phenylethyl)-2-benzofuranacetonitrile (8c)

1 g (4 mmol) of **7** was dissolved in 20 ml of dry acetonitrile and 1.3 g (8.6 mmol) of *tert*-butyldimethylsilyl chloride, 1.5 g (23.1 mmol) of KCN and catalytic amounts of $ZnCl_2$ were added. After stirring for 16 h (argon atmosphere) the acetonitrile was removed under reduced pressure and the residue was suspended in ether and filtered. The etheral solution was washed with water, dried over Na_2SO_4 and evaporated to dryness. Purification of the oily residue *via* column chromatography (silica gel, petroleum ether/ether = 15/1) gave 0.92 g (59%) of **8c** as colourless oil. ^{1}H-Nmr (90 MHz): δ(ppm) 0.2 (3H, s, Si-CH_3), 0.3 (3H, s, Si-CH_3), 1.0 (9H, s, Si-$(CH_3)_3$), 2.9-3.3 (4H, m, -CH_2-CH_2-), 5.4 (1H, s, -CH-CN), 7.2-7.6 (9H, m, aromatic-H); ms (m/z): 391 (M^+). Anal. Calcd for $C_{24}H_{29}NO_2Si$: C, 73.61; H, 7.46; N, 3.58. Found: C, 73.81; H, 7.51; N, 3.52.

α-Aminomethyl-3-(2-phenylethyl)-2-benzofuranmethanol (9a)

5.0 g (12.8 mmol) of **8c** was dissolved in 40 ml of dry ether and added dropwise to 25 ml (25 mmol) of a 1 M solution of $LiAlH_4$ in THF at -40°C. After 2 h of stirring 2 ml of water was added and the mixture was allowed to warm up to room temperature. The slurry was filtered and washed carefully with ether. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness to give 2.93 g (81.5%) crude **9a** as a yellowish oil. Purification *via* column chromatography (silica gel, CH_2Cl_2/methanol/conc. NH_4OH = 150/10/1) yielded 1.47 g (40.8%) of **9a** as colourless oil which solidified slowly. mp 92-95°C (ethyl acetate/cyclohexane); ^{1}H-nmr (90 MHz): δ(ppm) 1.7 (3H, broad, -NH_2, -OH), 2.7-3.1 (6H, -CH_2-CH_2-, -CH_2-N), 4.4 (1H, dd, J = 5 Hz, J = 7.5 Hz, -CH(O)-), 7.0-7.6 (9H, m, aromatic-H); ms (m/z): 281 (M^+). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.69; H, 6.79; N, 4.97.

3-(2-Phenylethyl)-β-(2-tetrahydropyranyloxy)-2-benzofuranethanamine (9b)

4.0 g (11.1 mmol) of **8b** was dissolved in 20 ml of dry ether and added dropwise to 11 ml (11 mmol) of a 1 M solution of $LiAlH_4$ in THF at -40°C. The mixture was stirred for 2 h at -40°C and hydrolyzed by addition of water (1 ml). After warm up to room temperature the slurry was filtered off and washed carefully with ether. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. Purification of the oily residue *via* column chromatography (silica gel, CH_2Cl_2/methanol/conc. NH_4OH = 150/10/1) gave 2.6 g (64%) of **9b** (mixture of diastereomers) as colourless oil. ^{1}H-Nmr (90 MHz): δ(ppm) 1.1-1.8 (8H, m, -C(O)-CH_2-CH_2-CH_2-, -NH_2), 2.5-4.1 (8H, m, Ph-CH_2-CH_2-, -O-CH_2-, -CH_2-N), 4.4-4.9 (2H, m,

-CH(O)-, -O-CH-O-), 7.0-7.6 (9H, m, aromatic-H); ms (m/z): 365 (M^+). Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.72; H, 7.77; N, 3.70.

N-Isopropyl-3-(2-phenylethyl)-β-(2-tetrahydropyranyloxy)-2-benzofuranethanamine (10a)

2.0 g (5.5 mmol) of **9b** was dissolved in 20 ml of methanol and 0.7 ml of acetone was added. After stirring for 30 min 0.43 g (6.8 mmol) of $NaCNBH_3$ was added and the stirring was continued for 10 min. Then the procedure was repeated using 0.5 ml of acetone and 0.3 g (4.8 mmol) of $NaCNBH_3$. Ether was added and the mixture was washed twice with water. After re-extraction with ether the combined organic layers were dried over Na_2SO_4 and evaporated to dryness to give 2.02 g of crude product as yellow oil. Purification *via* column chromatography (silica gel, CH_2Cl_2/methanol/conc. NH_4OH = 300/10/1) gave 1.24 g (55.6%) of **10a** (mixture of diastereomers) as colourless oil. ^{1}H-Nmr (90 MHz): δ(ppm) 1.0 (3H, d, J = 6 Hz, $-CH_3$), 1.1 (3H, d, J = 6 Hz, $-CH_3$), 1.3-1.8 (7H, m, $-C(O)-CH_2-CH_2-CH_2-$, -NH), 2.5-3.6 (9H, $-CH_2-N-CH-$, $-O-CH_2-$, $Ph-CH_2-CH_2-$), 4.8-5.0 (2H, m, -CH(O)-, -O-CH-O-), 7.1-7.6 (9H, m, aromatic-H); ms (m/z): 407 (M^+).

3-(2-Phenylethyl)-N-propyl-β-(2-tetrahydropyranyloxy)-2-benzofuranethanamine (10b)

1.9 g (4.7 mmol) of **10d** was dissolved in 40 ml of dry ether and added dropwise to 6 ml (6 mmol) of a 1 M solution of $LiAlH_4$ in THF at room temperature. After stirring overnight the mixture was cooled to -40°C and then hydrolyzed with 0.5 ml of water. The slurry was filtered and washed carefully with ether. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. Purification of the residual yellow oil (1.4 g) *via* column chromatography (silica gel, CH_2Cl_2/methanol/conc. NH_4OH = 200/10/1) gave 0.96 g (52%) of **10b** (mixture of diastereomers) as colourless oil. ^{1}H-Nmr (80 MHz): δ(ppm) 0.9 (3H, t, J = 8 Hz, $-CH_3$), 1.2-2.0 (9H, m, $-C(O)-CH_2-CH_2-CH_2-$, $-C\underline{H}_2-CH_3$, NH), 2.5-2.8 (3H, m, $-CH_a-N-CH_2-$), 2.9-3.6 (7H, m, $Ph-CH_2-CH_2-$, $-CH_b-N-$, $-O-CH_2-$), 4.4 (0.3H, m, -O-CH-O-), 4.7-5.1 (1.7H, m, -CH(O)-, -O-CH-O-), 7.0-7.6 (9H, m, aromatic-H).

N-(2-(3-(2-Phenylethyl)-2-benzofuranyl)-2-(2-tetrahydropyranyloxy)ethyl)propanamide (10d)

3.0 g (8.2 mmol) of crude **9b** was dissolved in 30 ml (371 mmol) of pyridine and after cooling in an ice bath 0.72 ml (8.3 mmol) of propionyl chloride was added. The reaction vessel was closed and cooled in a refrigerator for 20 h. Ether was added and the mixture was washed with 1 M HCl to remove pyridine. After

washing with saturated $NaHCO_3$-solution and then water the organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification of the residual dark oil *via* column chromatography (silica gel, petroleum ether/ether = 1/1) gave 1.58 g (45.7%, two steps) of **10d** (mixture of diastereomers) as colourless oil which solidified slowly. mp 85-93°C; ^{1}H-*nmr* (90 MHz): *δ(ppm)* 1.1, 1.12 (3H, each t, J = 7.5 Hz, $-CH_3$), 1.3-1.8 (6H, m, $-C(O)-CH_2-CH_2-CH_2-$), 2.15, 2.20 (0.6H, 1.4H, each q, J = 7.5 Hz, $CO-CH_2-$), 2.9-3.1 (4H, m, $Ph-CH_2-CH_2-$), 3.3-3.8 (4H, m, $-O-CH_2-$, $-CH_2-N$), 4.4 (0.3H, m, -O-CH-O-), 4.8-5.0 (1.7H, m, -O-CH-O-, -CH(O)-), 5.7, 5.9 (0.7H, 0.3H, each m, NH), 7.1-7.6 (9H, m, aromatic-H); ir: 3300 (NH), 1650 (CO), 1550 (CO); ms (m/z): 421 (M^+). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.87; H, 7.35; N, 3.29.

α-(Isopropylaminomethyl)-3-(2-phenylethyl)-2-benzofuranmethanol, Hydrochloride (2a)

1.1 g (2.7 mmol) of **10a** was dissolved in 20 ml of dry ether and 0.2 ml of methanol and 5 ml of a 1 M solution of HCl in ether were added. Removal of the solvent and crystallization from ethyl acetate (twice) gave 0.49 g (50.4%) of **2a**. mp 160-163°C; ^{1}H-nmr (90 MHz; $CDCl_3/D_2O$): δ(ppm) 1.3 (3H, d, J = 6 Hz, $-CH_3$), 1.4 (3H, d, J = 6 Hz, $-CH_3$), 2.5 (1H, dd, J = 3 Hz, J = 14 Hz, $-CH_a-N$), 2.9-3.4 (6H, m, $Ph-CH_2-CH_2-$, $-CH_b-N-CH-$), 5.4 (1H, dd, J = 3 Hz, J = 10 Hz, -CH(O)), 7.0-7.5 (9H, m, aromatic-H). Anal. Calcd for $C_{21}H_{26}NO_2Cl$: C, 70.08; H, 7.28, N, 3.89; Cl, 9.85. Found: C, 69.79; H, 7.25; N, 3.88; Cl, 9.81.

3-(2-Phenylethyl)-α-(propylaminomethyl)-2-benzofuranmethanol, Hydrochloride (2b)

1.0 g (2.1 mmol) of **10b** was dissolved in 20 ml of dry ether and 0.1 ml of methanol and 4.5 ml of a 1 M solution of HCl in ether were added. Removal of the solvent and crystallization from ethyl acetate (twice) gave 0.42 g (54.8%) of **2b**. mp 150-152°C; ^{1}H-nmr (90 MHz): δ(ppm) 0.9 (3H, t, J = 6 Hz, $-CH_3$), 1.8 (2H, sext., J = 6 Hz, $-CH_2-CH_3$), 2.4 (1H, dd, J = 3 Hz, J = 14 Hz, $-CH_a-N$), 2.7-3.1 (6H, m, $Ph-CH_2-CH_2-$, $N-CH_2$), 3.3 (1H, dd, J = 11 Hz, J = 14 Hz, $-CH_b-N$), 5.4 (1H, dd, J = 3 Hz, J = 11 Hz, -CH(O)), 7.0-7.6 (9H, m, aromatic-H). Anal. Calcd for $C_{21}H_{26}NO_2Cl$: C, 70.08; H, 7.28; N, 3.89; Cl, 9.85. Found: C, 69.85; H, 7.29; N, 3.87; Cl, 9.82.

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