SYNTHESIS OF TRICYCLIC BENZAZEPINES AND THEIR DOPAMINE D_1- AND D_2-AFFINITY

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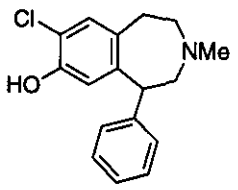
Abstract - A new group of angular 8,9-annelated 3-benzazepines has been found to be potent and selective dopamine D_1-receptor antagonists of interest as possible pharmaceuticals in the treatment of schizophrenia. The synthesis of three new conformationally constrained representatives of this group of benzazepines is described and their affinity to the D_1-receptor evaluated. Although none of these proved superior to the previously examined compounds, useful information on the receptor binding site was obtained.

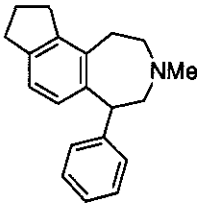
The neurotransmitter dopamine (DA) and its role in the central nervous system (CNS) have been widely investigated for more than 25 years.[1] DA is involved in several diseases in the CNS, e.g. Parkinson´s disease, Huntington´s chorea and schizophrenia. A substantial amount of evidence points to overactivity of the dopaminergic pathways as a reason for schizophrenia.[2] DA antagonists alleviate the symptoms in schizophrenia, but the antipsychotic effect is often accompanied by severe side effects in long-term usage.[3] The discovery of the existence of several types of DA-receptors[4] therefore led to a massive research effort to design and synthesize selective ligands. In 1983, the appearance of the first D_1-selective antagonist of the 3-benzazepine type, SCH 23390 (**1**), was reported.[5]

3-Benzazepines have been extensively reviewed[6] and numerous papers and patents claiming different aspects of binding to the dopamine receptors have appeared. The investigation of the D_1-

pharmacophore by molecular modeling techniques led to the synthesis and evaluation of conformationally constrained benzazepine derivatives.[7,8] In continuation of work on dopamine D_1-ligands, we became interested in conformationally constrained benzazepines with an additional ring attached to the 8,9-position of the 3-benzazepine moiety. This paper describes the synthesis and evaluation of 3-methyl-5-phenyl-1,2,3,4,5,8,9,10-octahydroindeno[5,4-*d*]azepine (**2**), 3-methyl-5-phenyl-2,3,4,5,8,9,10,11-octahydro-1*H*-naphth[2,1-*d*]azepine (**3**) and 3-methyl-5-(benzofuran-7-yl)-1,2,3,4,5,12-hexahydrofluoreno[2,1-*d*]azepine (**4**).



1 SCH 23390



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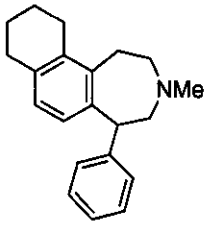

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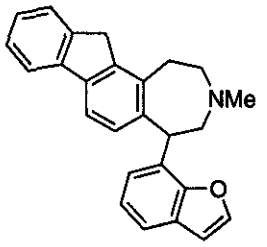

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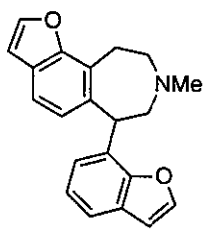
This study is an extension of our recent work on the angularly annelated 3-benzazepines (**5-7**).[9] These compounds surprisingly acted as potent and selective D_1 antagonists despite their lack of the phenolic 7-OH group, which hitherto was thought to be essential for binding at this receptor.[8] Therefore our initial hypothesis was that the oxygen in the furan moiety of compounds (**5-7**) contributes to binding by acting as a hydrogen bond acceptor.



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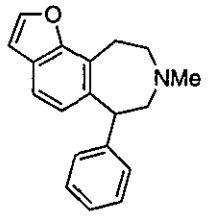

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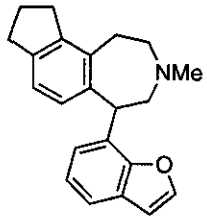

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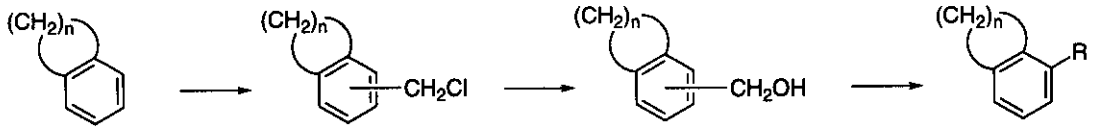
The benzazepines (**5**) and (**7**) are also substituted in the 5-position with benzofuranyl groups. Moreover, the two oxygens of compound (**5**) are in approximately the same distance from nitrogen, compatible with two orientations of the ligand in the receptor binding site. The oxygen in the 5-

substituent could render oxygen in the annelated ring unnecessary and *vice versa*. To examine the role of oxygen, benzazepines (**2-4**) were synthesized and their affinity for the D_1 and D_2 receptors determined.

3-Benzazepines are often synthesized *via* the phenethylamine derivative,[10,11] however, in the case of indane and 1,2,3,4-tetrahydronaphthalene, synthesis of an ethylamine side chain in α-position represents a challenge. The α-cyanomethyl derivatives have been prepared regiospecifically *via* the tricarbonylchromium complexes [12,13] but this is not a feasible method in multigram-scale synthesis. Chloromethylation in most cases [14,15] only leads to small amounts of the α-substituted product due to steric hindrance by the methylene groups.[16] However, under certain reaction conditions an α/β-ratio of 30:70 can be obtained,[17-19] and this method was chosen using the procedure of Wightman *et al.*[19]

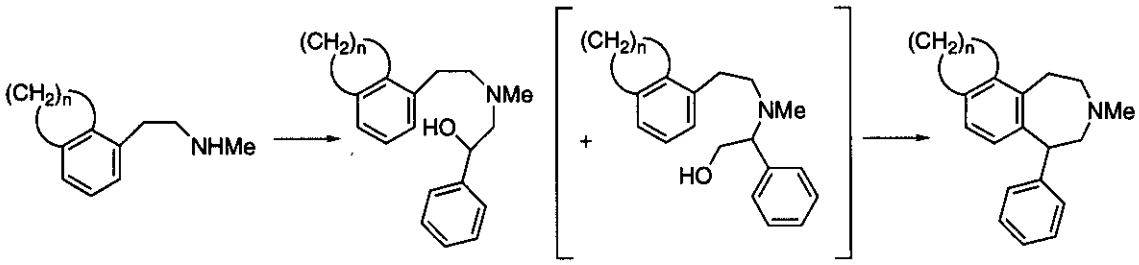


a: n=3
b: n=4

8 R = CHO; **9** R = CH_2OH; **10** R = CH_2Cl; **11** R = CH_2CN; **12** R = CH_2COOH;
13 R = $CH_2CONHMe$; **14** R = CH_2CH_2NHMe

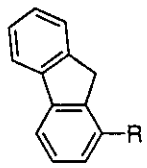
Mixtures of α- and β-chloromethyl derivatives were formed by heating indane (**a**: n=3) and tetralin (**b**: n = 4), respectively, with formaldehyde, HCl and H_2SO_4. In order to purify the chloromethyl derivatives [17] they were transformed into the hydroxymethyl analogues by heating with AcOH and NaOAc followed by NaOH and MeOH. Oxidation to the aldehydes was performed with pyridinium dichromate (PDC).[20] The mixtures of α- and β-carbaldehydes were subsequently separated by column chromatography with toluene on silica gel. The pure α-carbaldehyde (**8**) obtained in 30% yield was reduced to the hydroxymethyl derivative (**9**) with $NaBH_4$ in ethanol. The hydroxy group was easily exchanged to give the chloromethyl derivative (**10**) with thionyl chloride in toluene.[21] Nucleophilic substitution with NaCN in DMSO[22,23] provided the nitrile (**11**), which was hydrolysed in refluxing NaOH to the carboxylic acid (**12**).[24] **12** was converted to the *N*-methylamide (**13**) *via* the acid chloride.[25,26] This is a common path to 3-benzazepines,[27] and it offers some obvious

advantages. Both the carboxylic acid and the amide syntheses are good steps for purification, as the intermediates are often solid substances. As expected, **12** and **13** were easily recrystallized. The following reduction of the amide to the phenethylamine (**14**) with sodium acyloxyborohydride[28] leaves the *N*-methyl group in the correct position. *N*-methylation would otherwise, in the case of a primary amine, demand a protection-deprotection step.



15 **2** and **3**

The amine (**14**) was coupled to styrene oxide by prolonged heating in an inert solvent furnishing the benzylic amino alcohol (**15**) and a primary amino alcohol. The crude mixture of these was cyclized directly. Cyclization to the benzazepines (**2**) and (**3**) occurs smoothly under strongly acidic conditions through a cationic species. The reagents most often applied are conc. sulfuric acid in trifluoroacetic acid, 48% hydrobromic acid or polyphosphoric acid.[6] From the benzylic amino alcohol (**15**) a stable benzylic cation is generated forming the azepine, while the primary amino alcohol can only produce a primary cation and does not undergo cyclization. This difference in polarity of the products meant that **2** and **3** could be purified by precipitation as the hydrochloride, and optionally by recrystallization of the salt.

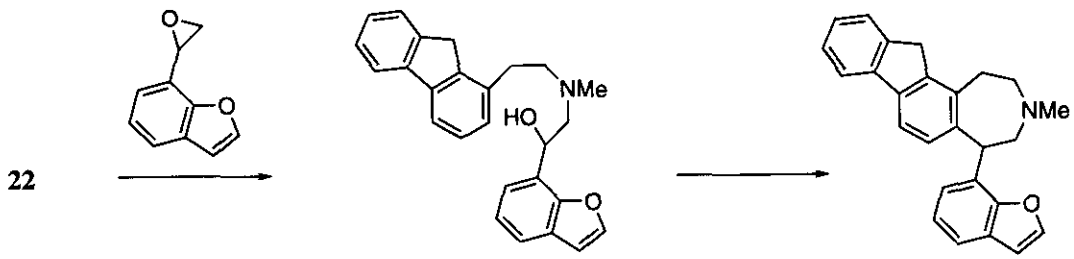


16 R=COOH

17 R = CH_2OH
18 R = CHO
19 R = $CH{=}CH\text{-}NO_2$
20 R = $CH_2CH_2NH_2$
21 R = $CH_2CH_2NHCOCF_3$
22 R = CH_2CH_2NHMe

In the case of the fluorenebenzazepine, commercially available 4-fluorenecarboxylic acid (**16**) was used as starting material. Synthesis of the ethylamine *via* the nitroethenyl derivative had previously proven valuable.[29] Thus, reduction of **16** with $LiAlH_4$ produced 4-hydroxymethylfluorene (**17**). This

was subsequently oxidized with pyridinium dichromate[20] in CH_2Cl_2 at room temperature to give the aldehyde (**18**). 4-(2-Nitroethenyl)fluorene (**19**) was synthesized by way of condensation of **18** with nitromethane in the presence of AcOH and NH_4OAc.[30-32] Reduction of the nitrostyrene derivative with $NaBH_4$ and BF_3[33] was successful, and 2-(fluoren-4-yl)ethylamine (**20**) was isolated in satisfactory yield. The amine function was protected against uncontrolled methylation by trifluoroacetic anhydride in CH_2Cl_2 in the presence of TEA to give (**21**). *N*-Methylation was carried out with MeI and dried KOH powder by refluxing in dry acetone. Removal of the protecting group to give *N*-methyl-2-(fluoren-4-yl)ethylamine (**22**) was easily done by refluxing in water in a one-pot cycle as reported by Johnstone *et al.*[34] Coupling of **22** with benzofuran epoxide in refluxing acetonitrile took place within 96 h. The coupling product (**23**) was cyclized without further purification to the benzazepine (**4**) using 0.5 % conc. H_2SO_4 in TFA.



23 **4**

RECEPTOR AFFINITY

Table 1. K_i binding values (ligand concentration in nM needed to replace 50% of radioligand at the receptors) for compounds (**2** - **7**) (**5** - **7** taken from ref. 9).

K_i/Compound	2	3	4	5	6	7
D_1-receptor	92	128	140	25	14	97
D_2-receptor	342	303	>300	377	413	313

The D_1-receptor binding values (Table I) of **2** and **7** indicate that the presence of a furan ring in the 5-substituent does not change the affinity of the molecule to the D_1-receptor. The D_2-receptor binding

values are both high, and selectivity is thus maintained. An identical conclusion can be drawn from comparing the binding values of **5** and **6**. These results establish that the ligands do not bind to the receptor with the oxygen of the 5-benzofuran substituent. On the other hand, the results of **2** vs **6** and **7** vs **5** show that a furan oxygen in the annelated ring greatly improves affinity for the D_1-receptor and probably fulfills a similar role in the binding as the 7-OH group in e.g. **1**, but presumably at a distinct receptor binding site. The annelated rings are increasingly bulky from **2** through **3** to **4**. Comparison of the D_1 binding values shows that the D_1-affinity is reduced in this sequence indicating a steric requirement of the receptor. Finally, the D_1- and D_2-receptor binding values of **2-4** are remarkable since a significant selectivity for the D_1-receptor is maintained despite the simple structure of the molecules.

EXPERIMENTAL

Receptor binding values The assay for the D_1-receptor was performed on membranes from cells of the clonal cell line D_{1A}-BHK. The membranes were incubated with ^{3}H-SCH 23390 and test substance for 45 min. before scintillation counting.[35] The assay for the D_2-receptor was performed in the same way using membranes from the clonal cell line D_{2S}-Ltk$^-$ and incubation with ^{3}H-spiperone.

Materials

Melting points are uncorrected. ^{1}H and ^{13}C nmr spectra were obtained with a 200 MHz AC spectrometer. ^{13}C Nmr spectra are proton decoupled. The ^{1}H nmr spectra are run in $CDCl_3$ unless otherwise noted and reported as follows: δ (multiplicity, numbers of hydrogen, J in Hz, assignment). TMS was used as internal reference. Mass spectra were run on a Finnigan MAT TSQ 70B with SP-MS EI 70 eV conditions.

Syntheses

4- and 5-Chloromethylindanes With stirring, a mixture of indane (99.94 g, 0.846 mol), formaldehyde (112 ml, 35 %) and conc. HCl (191 ml) was heated at 60°C for 5 h and concentrated sulfuric acid (125 ml) added dropwise. The brown suspension was cooled and toluene (200 ml) added. The dark brown organic phase was separated and washed with water followed by saturated aqueous $NaHCO_3$. Drying and evaporation of the solvent yielded the crude product as a brown oil. Distillation gave 70 g (45%) of a mixture of 4- and 5-isomers, bp 81-91°C/1 mmHg, as a clear, colorless oil. ^{1}H Nmr: 1.95-2.13 (quintet, 2H, J=7.4, H2), 2.88 (t, 4H, J=7.5, H1 and H3), 4.54 (s, 2H, CH_2Cl), 7.10-7.23 (3H, m, H5-H7).

4- and 5-Hydroxymethylindanes A mixture of 4- and 5-chloromethylindanes (68 g, 0.408 mol), sodium acetate trihydrate (68 g) and glacial acetic acid (136 ml) was refluxed for 5 h. The remaining

acetic acid was removed by evaporation, water (150 ml) added to the residue, and the mixture extracted with toluene (100 ml). The organic phase was washed with cold water (2 x 50 ml) followed by cold, saturated aqueous sodium bicarbonate (2 x 50 ml). Evaporation gave the crude mixture of acetates which were hydrolysed directly by reflux with MeOH (150 ml) and 4 M NaOH (100 ml) for 1 h. After cooling, the mixture was acidified with conc. HCl, and CH_2Cl_2 (100 ml) was added. The organic phase was washed with water (2 x 100 ml) and dried (Na_2SO_4). Evaporation yielded the product as a pale, yellow oil from which the 5-isomer separated as white needles on cooling and could be removed. Recrystallisation of the residue from n-hexane gave 20.4 g (33%) of a mixture of 4- and 5-hydroxymethylindanes as a clear, pale yellow oil enriched with respect to the 4-isomer. ^{1}H Nmr: 2.05 (quintet, 2H, J=7.2, H2), 2.82-2.91 (m, 4H, H1 and H3), 4.50 and 4.52 (s, 2H, CH_2OH of 5- and 4-isomer, respectively), 7.10-7.19 (m, 3H, H5-H7).

4-Indanecarbaldehyde [8a] A solution of the mixture of 4- and 5-hydroxymethylindanes (29.3 g, 0.2 mol) in CH_2Cl_2 (100 ml) was slowly added to a stirred suspension of pyridinium dichromate (74.4 g, 0.2 mol) and silica gel (22 g) in CH_2Cl_2 (150 ml) in an exothermic reaction. After stirring for 2.5 h, the dark brown mixture was filtered and the filtrate taken to dryness. Column chromatography (toluene) afforded 8.94 g (30%) of **8a** as a colourless oil with a sweet odour. ^{1}H Nmr: 2.08-2.21 (m, 2H, H2), 2.93 (t, 2H, J=7.3, H1), 3.26 (t, 2H, J=7.5, H3), 7.26-7.35 (m, 1H, H6), 7.47 (d, 1H, J=6.9, H7), 7.62 (d, 1H, J=6.9, H5), 10.12 (s, 1H, CHO). The singlet at 9.93 ppm (CHO of 5-isomer) disappears after column chromatography.

4-Hydroxymethylindane [9a] Sodium borohydride (1.79 g, 47 mmol) was added to a stirred solution of **8a** (4.60 g, 31 mmol) in EtOH (70 ml). After 2 h, tlc (toluene) indicated that all starting material had disappeared. The reaction mixture was taken to dryness and the residue extracted with CH_2Cl_2 (75 ml). The organic phase was washed with ice-cold water (3 x 100 ml), dried over sodium sulfate, and evaporated to give 4.14 g (88 %) of colourless oil shown by ^{1}H nmr to be pure **9a**: 2.05 (quintet, 2H, J=7.2, H2), 2.80-2.87 (m, 4H, H1, H3), 4.52 (s, 2H, CH_2OH), 7.10-7.19 (m, 3H, H5-H7).

4-Chloromethylindane [10a] **9a** (3.96 g, 27 mmol) was dissolved in toluene (100 ml) and thionyl chloride (6.36 g, 54 mmol) added dropwise with cooling to the stirred solution. The mixture was further stirred at room temperature for 1 h, the solvent evaporated, and the residue stripped twice with toluene to give 4.40 g (97 %) of yellowish oil. This was shown by ^{1}H nmr to be pure **10a**: 1.95-2.13 (m, 2H, H2), 2.88 (t, 4H, J=7.5, H1, H3), 4.54 (s, 2H, CH_2Cl), 7.10-7.23 (m, 3H, H5-H7).

(4-Indanyl)acetonitrile [11a] Sodium cyanide (1.94 g, 40 mmol) was added to a stirred solution of **10a** (4.40 g, 26 mmol) in dry DMSO (30 ml). After standing for 3 h the mixture was heated under

reflux for 30 min. The apricot-coloured solution was poured into ice-cold water (100 ml) and extracted with toluene (3 x 50 ml). The combined organic phases were washed with water (2 x 75 ml) followed by saturated aqueous NaCl (75 ml). Drying (Na_2SO_4) and evaporation of the solvent gave 3.72 g (89 %) of **11a** as a pale yellow oil (lit.,[13] mp 38-39°C).

(4-Indanyl)acetic acid [12a] **11a** (3.72 g, 23 mmol) and excess 4 M NaOH (30 ml) were heated under reflux for 6 h until tlc (toluene) indicated complete reaction. The solution was cooled and washed with CH_2Cl_2 (2 x 25 ml). The aqueous phase was acidified with conc. HCl and extracted with CH_2Cl_2 (2 x 50 ml). The extract was washed with water (75 ml), saturated aqueous NaCl (75 ml), dried (Na_2SO_4), and taken to dryness. The crude brown solid was recrystallised from n-hexane to give 2.09 g (51 %) of **12a** as an off-white powder, mp 97-99°C. (Lit.,[36] 101-101.5°C). ^{1}H Nmr: 2.00-2.15 (2H, m, H2), 2.91 (4H, q, J=7.6 , H1 and H3), 3.63 (2H, s, CH_2CO), 7.02-7.19 (3H, m, H5-H7), 10.7 (1H, br s, COOH). Anal. Calcd for $C_{11}H_{12}O_2$: C 74.98, H 6.86. Found C 75.08, H 7.02.

N-Methyl-2-(4-indanyl)acetamide [13a] Thionyl chloride (2.39 g, 20 mmol) was added to a solution of **12a** (1.77 g, 10 mmol) in toluene (35 ml). The mixture was refluxed for 30 min, the solvent evaporated and the remanence stripped once with toluene. The crude acid chloride was dissolved in dry acetone and slowly added to a stirred solution of excess 40 % aqueous methylamine (15 ml), causing a vigorous reaction. The reaction mixture was allowed to cool and the volume reduced to 15 ml *in vacuo*. Ice-cold water (50 ml) was added to the remainder and the separated product filtered off. Washing with ice-cold water yielded 0.86 g (45%) of **13a** as an off-white powder, mp 98-99°C. ^{1}H Nmr: 2.04-2.15 (m, 2H, H2), 2.75 (d, 3H, J=4.9, CH_3), 2.84 (t, 2H, J=7.4, H1), 2.95 (t, 2H, J=7.5, H3), 3.56 (s, 2H, CH_2CO), 5.38 (br s, 1H, NH), 6.95-7.18 (m, 3H, H5-H7). Anal. Calcd for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40. Found C 76.28, H 8.19, N 7.02.

N-Methyl-2-(4-indanyl)ethylamine [14a] In a nitrogen atmosphere, $NaBH_4$ (1.06 g, 28 mmol) was added to **13a** (0.88 g, 4.7 mmol) dissolved in dry dioxane (30 ml). After cooling to room temperature, glacial acetic acid (1.6 ml, 28 mmol) was carefully added through a septum. Vigorous foaming was observed. After the addition was completed the reaction mixture was heated to 70°C inducing a brisk reaction. Reflux was maintained for 30 min after which the milky mixture was allowed to cool. After acidification with conc. HCl the solution was refluxed for 30 min. After cooling, water (50 ml) was added and the mixture washed with CH_2Cl_2 (2 x 20 ml). The aqueous phase was basified with 4 M NaOH and extracted with CH_2Cl_2 (3 x 20 ml). The combined CH_2Cl_2 phases were washed with water (20 ml) followed by saturated NaCl solution (20 ml). Drying (Na_2SO_4) and evaporation gave 621 mg (76 %) of **14a** as a brown oil. ^{1}H Nmr: 1.11 (t, 2H, J=6.7,

CH_2N), 1.98-2.16 (m, 2H, H2), 2.19 (s, 1H, NH), 2.32 (s, 3H, NMe), 2.42-2.53 (m, 2H, benzylic side chain-CH_2), 2.87-2.99 (m, 4H, H1 and H3), 6.94-7.02 (m, 1H, H6), 7.05-7.11 (m, 2H, H5 and H7).

2-[[2-(4-Indanyl)ethyl]methylamino]-1-phenylethanol [15a] **14a** (621 mg, 3.5 mmol) was dissolved in MeCN (25 ml). Styrene oxide (1,7 g, 14 mmol) was added and the mixture heated to near reflux under N_2 for 23 h after which tlc (CH_2Cl_2/MeOH/AcOH 16:3:1) showed that no starting material was left. The bourgogne-coloured mixture was cooled and CH_2Cl_2 (25 ml) added. The amines were isolated as tartrates by thorough extraction with 10 % aqueous tartaric acid (4 x 20 ml). The combined aqueous phases were basified with 4 M NaOH and extracted with CH_2Cl_2 (5 x 20 ml). The CH_2Cl_2 extract was successively washed with 1 N HCl (8 x 20 ml) to remove the more polar amine by-products, with water (50 ml), and with saturated aqueous NaCl (40 ml). After drying (Na_2SO_4), the solvent was evaporated. The coupling product **15a** was isolated as 344 mg light brown, amorphous solid with a sweet odour (33 %). ^{1}H Nmr: Methin proton is seen at 5.37 ppm (br d, J=9.7).

3-Methyl-5-phenyl-1,2,3,4,5,8,9,10-octahydroindeno[5,4-*d*]azepine [2] Following several trials, 5 % H_2SO_4 in TFA was chosen as the appropriate reagent for cyclisation. **15a** (320 mg, 1 mmol) was dissolved in 5 % H_2SO_4 in TFA (68 ml). After stirring for 45 min at room temperature, tlc (CH_2Cl_2/MeOH/AcOH 16:3:1) showed that no starting material was left. The mixture was cooled with ice, basified with 4 M NaOH and extracted with CH_2Cl_2 (3 x 40 ml). The combined organic phases were washed with water (100 ml), brine (50 ml), dried over Na_2SO_4, and the solvent evaporated to give 220 mg (73%) of brown solid **2**. This was dissolved in THF (20 ml) and precipitated with ether saturated with HCl. The hydrochloride was filtered off and washed with dry ether. Yield 245 mg (78 %) of beige powder, mp 238-240°C (decomp.). ^{1}H Nmr: 2.02-2.16 (m, 2H, H9), 5.08 (d, 1H, J=9.9, H5), 6.35 (d, 1H, J=7.8, H7), 6.92 (d, 1H, J=7.8, H6), 7.19-7.45 (m, 5H, phenyl), 13.25 (1H, br s, NH^+). ^{13}C Nmr ($CDCl_3$): δ = 24.8, 27.6, 31.6, 32.8, 44.4, 45.5, 55.7, 61.6, 122.8, 126.2, 127.4, 128.4, 129.0, 133.4, 139.9, 140.3, 142.9, 143.5. Mass spectrum: m/z (% of base peak): 277 (M^+, 31), 262 (16), 233 (15), 220 (71), 186 (75), 173 (base peak), 145 (15), 129 (28), 91 (20), 69 (10), 58 (11). Anal. Calcd for $C_{20}H_{24}NCl$: C 76.54, H 7.71, N 4.46. Found C 76.27, H 7.89, N 4.38.

5- and 6-Chloromethyl-1,2,3,4-tetrahydronaphthalenes 1,2,3,4-Tetrahydronaphthalene (50 g, 0.38 mol), formaldehyde (100 ml, 40 % aq.) and conc. HCl (150 ml) were heated at 65 °C for 30 h. Conc. sulfuric acid (100 ml) was carefully added to the mixture during the first 2 h of heating. The reaction mixture was cooled, extracted with toluene (100 ml), and the extract washed with ice-cold water (3

x 150 ml) and ice-cold, saturated, aqueous $NaHCO_3$ (100 ml). Drying (Na_2SO_4), evaporation of the solvent, and vacuum distillation yielded 41.50 g (60 %) of colourless oil at 112-130°C/2 mmHg. The mixture contains 35 % of the 5-isomer by ^1H nmr. ^1H Nmr: 1.74-1.85 (m, 4H, H2 and H3), 2.71-2.87 (m, 4H, H1 and H4), 4.51 and 5.56 (s, 2H, CH_2Cl, 5- and 6-isomer, respectively), 7.01-7.19 (m, 3H, H6-H8).

5- and 6-(Hydroxymethyl)-1,2,3,4-tetrahydronaphthalenes The mixture of 5- and 6-(chloromethyl)-1,2,3,4-tetrahydronaphthalenes (64.82 g, 0.36 mol) was heated at reflux temperature with glacial acetic acid (200 ml) and sodium acetate (63 g) for 8 h. The reaction mixture was allowed to cool and the remaining acetic acid removed by evaporation. Water (200 ml) and toluene (200 ml) was added to the residue. The organic phase was separated and washed with water (2 x 150 ml) followed by saturated aqueous $NaHCO_3$ (2 x 75 ml). Evaporation of the solvent gave the crude acetate, which was heated at reflux temperature with MeOH (140 ml) and 4 M NaOH (100 ml) for 1 h. The resulting yellow suspension was neutralized with conc. HCl, extracted with CH_2Cl_2 (2 x 75 ml) and the combined organic phases washed with water (100 ml). Drying (Na_2SO_4) and evaporation of the solvent furnished 57.05 g (98 %) of a yellow oil. ^1H Nmr: 1.75-1.88 (br m, 5H, H2, H3 and OH), 2.70-2.81 (m, 4H, H1 and H4), 4.62 (s, 2H, CH_2OH), 7.00-7.22 (m, 3H, H6-H8).

1,2,3,4-Tetrahydronaphthalene-5-carbaldehyde [**8b**] The mixture of 5- and 6-hydroxymethyl-1,2,3,4-tetrahydronaphthalenes (10 g, 61 mmol) was dissolved in CH_2Cl_2 (50 ml) and added to a suspension of pyridinium dichromate (23.18 g, 61 mmol) and silica gel (20 g) in CH_2Cl_2 (70 ml). The dark brown suspension was stirred for 2.5 h and kept at r. t. by cooling. Filtration and evaporation of the solvent yielded 9.20 g of a brown oil. Column chromatography (silica gel, toluene) gave 2.18 g (22%) of pure **8b** as a colourless oil. ^1H Nmr: 2.07-2.18 (m, 4H, H2 and H3), 2.87-2.98 (m, 2H and H4), 3.26 (t, 2H, J=7.1, H1), 7.13-7.70 (m, 3H, H6-H8), 10.17 (s, 1H, CHO).

5-Hydroxymethyl-1,2,3,4-tetrahydronaphthalene [**9b**] To a stirred solution of **8b** (6.73 g, 42 mmol) in EtOH (75 ml) was added sodium borohydride (2.35 g, 63 mmol). The solution was stirred at room temperature for 1.5 h until tlc (toluene) showed full conversion. The solvent was evaporated, the residue extracted with CH_2Cl_2 (100 ml), and the organic phase separated and washed with ice-cold water (3 x 100 ml). Drying (Na_2SO_4) and evaporation of the solvent yielded 5.39 g (79 %) of **9b** as a colourless oil (as in that previously reported[37]). ^1H Nmr: 1.75-1.88 (br m, 5H, H2, H3 and OH), 2.70-2.81 (m, 4H, H1 and H4), 4.62 (s, 2H, CH_2OH), 7.00-7.22 (m, 3H, H6-H8).

5-Chloromethyl-1,2,3,4-tetrahydronaphthalene [**10b**] Thionyl chloride (7.88 g, 66 mmol) was slowly added to a stirred solution of **9b** (5.38 g, 33 mmol) in toluene (50 ml). The reaction was slightly exothermic and the colourless solution turned pale yellow. Stirring was continued for 2 h. The solvent

was evaporated and the residue stripped once with toluene to give 6.2 g (almost quantitative yield) crude **10b** as a brown oil. ^{1}H Nmr indicated this to be pure: 1.74-1.85 (m, 4H, H2 and H3), 2.71-2.87 (m, 4H, H1 and H4), 4.51 (s, 2H, CH_2Cl), 7.01-7.19 (m, 3H, H6-H8).

(1,2,3,4-Tetrahydro-5-naphthyl)acetonitrile [**11b**] Sodium cyanide (2.44 g, 50 mmol) was added to a stirred solution of **10b** (6.00 g, 33 mmol) in dry DMSO (50 ml). The pale yellow solution turned orange during an exothermic reaction. The reaction mixture was stirred for 3 h, poured into ice-cold water (200 ml), and extracted with toluene (3 x 100 ml). The organic phase was separated, washed with ice-cold water (2 x 100 ml), and finally with saturated NaCl solution (150 ml). Drying (Na_2SO_4) and evaporation of the solvent gave 6.57 g (116 %) of crude **11b** as a yellow oil, which crystallized on cooling. A sample was recrystallized from petrol ether, yielding the product as a fluffy white powder, mp 63-65°C. (Lit.,[12] 65-68°C). Anal. Calcd for $C_{12}H_{13}N$: C 84.17, H 7.65, N 8.18. Found C 84.65, H 7.82, N 8.09.

(1,2,3,4-Tetrahydro-5-naphthyl)acetic acid [**12b**] **11b** (6 g, 0.035 mol) was dissolved in 4 M NaOH (100 ml) and heated to reflux temperature. The reaction was followed on tlc (toluene) and found to be complete after 8 h. The mixture was cooled, acidified with conc. HCl, and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phases were washed with water (2 x 50 ml), saturated aqueous NaCl, dried (Na_2SO_4), and the solvent evaporated to yield 5.44g (82%) **12b** as a light brown solid. Recrystallisation of a sample from petrol ether/EtOH 5:1 gave light brown crystals, mp 120-122°C (lit.,[38] mp 161°C).

N-Methyl-(1,2,3,4-tetrahydro-5-naphthyl)acetamide [**13b**] **12b** (2.00 g, 10 mmol) was dissolved in toluene (50 ml). Thionyl chloride (2.29 ml, 32 mmol) was added and the mixture refluxed for 30 min. The solvent was evaporated and the remanence stripped once with toluene. The acid chloride was left as a brown oil, which was dissolved in dry acetone (25 ml) and carefully added to 40 % aqueous methylamine (15 ml) with stirring. Stirring was continued until the exothermic reaction had subsided. The volume of the reaction mixture was reduced *in vacuo* and addition of ice-cold water (75 ml) afforded precipitation of the crude **13b**. Filtration, washing with ice-cold water and drying in vacuum at 50°C gave 1.78 g (83%) pure **13b** as a fine off-white powder, mp 77-78°C. ^{1}H Nmr: 1.77-1.83 (m, 4H, H2 and H3), 2.58-2.82 (m, 7H, H1, H4 and CH_3), 3.54 (s, 2H, CH_2CO), 5.36 (br s, 1H, NH), 6.93-7.15 (m, 3H, H6-H8). Anal. Calcd for $C_{13}H_{17}NO$: C 76.81, H 8.43, N 6.89. Found C 76.32, H 8.07, N 6.63.

N-Methyl-(1,2,3,4-tetrahydro-5-naphthyl)ethylamine [**14b**] **13b** (1.78 g, 9 mmol) was dissolved in dry dioxane (35 ml). $NaBH_4$ (0.99 g, 26 mmol) was added to the reddish solution in an exothermic reaction and the mixture allowed to cool with stirring in a N_2 atmosphere. Glacial acetic acid (1.50

ml, 26 mmol) was slowly added through a septum causing violent foaming and the reaction mixture heated to reflux for 30 min. Tlc (CH_2Cl_2/MeOH/AcOH 95:5:3) of a hydrolysed sample showed that no starting material was present. The mixture was acidified with conc. HCl, refluxed for another 30 min, and extracted with CH_2Cl_2 (2 x 25 ml) to remove traces of amide. The combined CH_2Cl_2 phases were now extracted back with water (2 x 50 ml). The aqueous phases were combined, basified with 4 M NaOH, and extracted with CH_2Cl_2 (6 x 25 ml). The combined CH_2Cl_2 phases were washed with water (2 x 50 ml), dried (Na_2SO_4), and the solvent evaporated. This gave 1.13 g (68%) of crude **14b** as a brown oil. The amine was dissolved in dry ether (50 ml) and impurities were filtered off. The clear yellow solution was made acidic with HCl in ether resulting in a white precipitate. Filtration, washing with dry ether, and drying in vacuum gave 850 mg (51%) of the pure hydrochloride of **14b** as a coarse white powder, mp 130°C (decomp.). ^{1}H Nmr (d-DMSO): 1.65-1.75 (m, 4H, H2 and H3), 2.48-2.78 (m, 7H, NCH_3, side chain-CH_2), 2.86-3.05 (m, 4H, H1 and H4), 6.93-7.09 (m, 3H, H6-H8), 9.19 (2H, br s, NH^+). Anal. Calcd for $C_{13}H_{20}NCl$: C 70.10, H 7.69, N 6.29. Found C 67.86, H 8.91, N 6.14.

2-[[2-(1,2,3,4-Tetrahydro-5-naphthyl)ethyl]methylamino]-1-phenylethanol [15b] **14b** (850 mg, 3.8 mmol) was dissolved in MeCN (20 ml). Styrene oxide (0.65 ml, 5.7 mmol) was added and the mixture heated to near reflux temperature in a N_2 atmosphere for 67 h until tlc (CH_2Cl_2/MeOH/AcOH 16:3:1) showed no further reaction despite addition of fresh styrene oxide. The mixture was cooled, toluene (30 ml) added, and the product worked up using tartaric acid as described for **15a**. This left 752 mg (65 %) crude **15b** as a yellow-brownish syrup. ^{1}H Nmr: Methin proton is seen at 4.68 ppm (br t, J=6.9).

3-Methyl-5-phenyl-2,3,4,5,8,9,10,11-octahydro-1*H*-naphth[2,1-*d*]azepine [3] 5 % H_2SO_4 in TFA was chosen as appropriate for cyclisation as for **15a**. **15b** (657 mg, 2.3 mmol) was dissolved in TFA (32 ml) and 10 % H_2SO_4 in TFA (16.4 ml) added. The mixture was stirred for 60 min at room temperature and then cooled with an ice bath. Tlc (CH_2Cl_2/MeOH/AcOH 95:5:3) showed only one spot and contained no starting material. The reaction mixture was made basic with conc. NaOH and subsequently extracted with CH_2Cl_2 (6 x 100 ml). The combined organic phases were washed with water (100 ml) and with saturated aqueous NaCl (60 ml). Drying (Na_2SO_4) and evaporation of the solvent gave 625 mg (100%) crude **3** as a clear, brown oil. This was dissolved in dry THF and HCl in ether was added until acidic. The solvent was evaporated, the remanence redissolved in the minimum amount of THF, dry ether added, the precipitate filtered off and dried in vacuum to furnish 570 mg (76 %) of light brown crystalline hydrochloride of **3**. Recrystallisation from isopropanol followed by MeCN gave 52 mg of pure product as a fine, white powder with mp 247-250°C. ^{1}H

Nmr: 1.67-1.76 (m, 4H, H2 and H3), 2.50-2.78 (m, 6H, H1, H4 and benzylic CH_2), 3.29-3.70 (m, 7H, NMe and CH_2N), 4.87 (d, 1H, J=9.4, methin), 6.13 (d, 1H, J=7.7, H8), 6.78 (d, 1H, J=7.7, H7), 7.18-7.48 (m, 5H, phenyl), 11.63 (br s, 1H, NH^+). ^{13}C Nmr ($CDCl_3$): δ = 22.0, 23.2, 24.3, 26.5, 29.6, 43.8, 43.9, 53.8, 59.3, 124.0, 127.0, 127.2, 128.5, 128.8, 134.1, 135.6, 136.7, 140.4, 141.2. Mass spectrum m/z (% of base peak): 291 (M^+, 11), 246 (7), 234 (28), 205 (13), 200 (36), 187 (base peak), 141 (9), 129 (16), 91 (12), 57 (9). Anal. Calcd for $C_{21}H_{26}NCl$: C 76.92, H 7.99, N 4.27. Found C 74.65, H 8.50, N 3.60. Correlated for content of 2-propanol (0.85 mol): C 74.64, H 8.72, N 3.70.

4-Hydroxymethylfluorene [17] $LiAlH_4$ (4.06 g, 0.107 mol) was suspended in dry THF (100 ml) under N_2. The slurry was cooled to 5°C and a solution of 4-fluorenecarboxylic acid (15 g, 0.071 mol) in dry THF (80 ml) was slowly added maintaining the temperature at 10°C. After addition was complete the ice bath was removed and the reaction allowed to warm to room temperature. Stirring was continued for 60 min, after which tlc (toluene) showed that no starting material was left. The reddish mixture was carefully hydrolyzed with ice cold water, the solvent evaporated, and water (50 ml) again added to the remanence. The aqueous mixture was extracted with ether (4 x 50 ml), the combined organic phases shaken with dilute NaOH, washed with water (50 ml), and finally with saturated NaCl solution (40 ml). Drying (Na_2SO_4) and evaporation of the solvent gave a yellow crystalline product. Drying in vacuum at 40°C for 5 h afforded 8.18 g (59 %) of **17** as pale yellow crystals, mp 119-123°C. ^1H Nmr: 3.93 (s, 2H, H5), 5.13 (s, 2H, CH_2OH), 7.36 (m, 4H, H6-H9), 7.55 (m, 3H, H1 and H3), 7.98 (d, 1H, J=7.4, OH). Anal. Calcd for $C_{14}H_{12}O$: C 85.68, H 6.16. Found C 85.70, H 6.33.

4-Fluorenecarbaldehyde [18] Pyridinium dichromate (15.36 g, 0.041 mol) and silica gel (*ca.* 10 g) were suspended with stirring in CH_2Cl_2 (100 ml) and a solution of **17** in CH_2Cl_2 (100 ml) added. The colour changed from orange to black during the exothermic reaction. Stirring was continued for 7 h, until tlc (toluene) showed that no starting material was left. The suspension was filtered through kiselgel and evaporation of the solvent left 5.07 g (64 %) of **18** as a pale yellow solid, mp 76-80°C. ^1H Nmr: 3.97 (s, 2H, H5), 7.47 (m, 4H, H6-H9), 7.77 (d, 1H, J=7.3, H1), 7.90 (d, 1H, J=7.6, H3), 8.56-8.60 (m, 1H, H2), 10.66 (s, 1H, CHO). Anal. Calcd for $C_{14}H_{10}O$: C 86.57, H 5.19. Found C 86.60, H 5.30.

4-(2-Nitroethenyl)fluorene [19] To a solution of **18** (4.88 g, 25 mmol) in glacial acetic acid (40 ml) was added nitromethane (1.9 ml, 0.035 mol) and an excess of ammonium acetate (2 g). The reaction mixture was refluxed under N_2 in the dark until tlc (toluene) indicated no further reaction (*ca.* 10 h). The precipitate formed on addition of 96% EtOH to the cooled solution was filtered off and dried

in vacuum at 60°C to give 3.98 g (67 %) of **19** as a bright yellow powder, mp 103-106°C. ^{1}H Nmr: 3.96 (s, 2H, H5), 7.41 (m, 4H, H1 and H3), 7.62 (m, 3H, H6-H9), 7.92 (d, 1H, J=7.2, ethenyl-H), 8.95 (d, 1H, J=13.4, ethenyl-H). Anal. Calcd for $C_{15}H_{11}NO_2$: C 75.94, H 4.67, N 5.90. Found C 75.89, H 4.83, N 5.14.

2-(Fluoren-4-yl)ethylamine [20] $NaBH_4$ (3.19 g, 0.084 mol) was dissolved in dry THF (25 ml) under N_2 in a thoroughly dried vessel. With cooling in an ice bath, BF_3-Et_2O (25.4 ml, 0.101 mol) was carefully added and the mixture was stirred until the exothermic reaction had subsided and the temperature had dropped to room temperature. **19** (4.00 g, 0.017 mol) was dissolved in dry THF (75 ml) and added to the mixture through a septum. The temperature rose to 50°C and the reaction mixture turned yellow. The mixture was refluxed for 3.5 h until tlc (toluene) showed that no starting material was left. The reaction mixture was quenched with water (20 ml), made acidic with aqueous 4 M HCl, refluxed for 30 min and cooled. The separated product was filtered off, washed with H_2O followed by ether, and dissolved in 4 M NaOH. The basic solution was extracted with ether (4 x 20 ml) and the combined ether phases washed with water (50 ml) followed by saturated aqueous NaCl (50 ml). Drying (Na_2SO_4) and evaporation of the solvent afforded 3.43 g (98 %) of **20** as a brownish oil. ^{1}H Nmr: 1.85 (br s, 2H, NH_2), 3.86 (s, 2H, H5), 7.11-7.37 (m, 5H, H2 and H6-H9), 7.53 (d, 1H, J=7.2, H3), 7.85 (d, 1H, J=7.5, H1).

N-Trifluoroacetyl-2-(fluoren-4-yl)ethylamine [21] **20** (0.50 g, 2 mmol) was dissolved in CH_2Cl_2 (35 ml), TEA (0.40 ml, 3 mmol) added, the solution cooled to 0°C, and trifluoroacetic anhydride (0.40 ml, 3 mmol) added in two portions. The turbid honey-coloured reaction mixture was stirred at 0°C for 35 min. The solution turned clear and yellow and tlc (CH_2Cl_2/MeOH/AcOH 20:2:1) indicated complete conversion. The reaction mixture was successively washed with water (10 ml), saturated aqueous $NaHCO_3$, and brine (40 ml). Drying (Na_2SO_4) and evaporation of the solvent left 0.72 g (99 %) of **21** as brittle beige fibers. ^{1}H Nmr: 3.39 (t, 2H, J=7.0, benzylic side chain-CH_2), 3.78 (t, 2H, J=6.7, CH_2NH), 3.93 (s, 2H, H5), 7.12 (d, 1H, J=7.4, H3), 7.23-7.51 (m, 5H, H2 and H6-H9), 7.59 (d, 1H, J=7.1, H1), 7.91 (1H, d, J=7.8, NH). Anal. Calcd for $C_{17}H_{14}NOF_3$: C 66.88, H 4.62, N 4.59. Found C 67.61, H 7.73, N 4.51.

N-Methyl-2-(fluoren-4-yl)ethylamine [22] **21** (0.72 g, 2.4 mmol) was dissolved in dry acetone (35 ml), and MeI (0.44 ml, 7.1 mmol) added. The yellow solution was heated to near reflux temperature, finely ground dry KOH (0.40 g, 7.1 mmol) added in one portion, and the reaction mixture turned greenish. It was refluxed for 10 min, cooled, the solvent evaporated, and the remanence stripped twice with dry acetone. The solid green residue was taken up in water (30 ml), refluxed for 15 min, cooled, and extracted with ether (3 x 45 ml). The combined green ether solutions were washed with

water (100 ml) followed by saturated aqueous NaCl (50 ml). Drying (Na_2SO_4) and evaporation of the solvent yielded 0.33 g (62 %) of **22** as a brown oil. ^{1}H Nmr: 2.46 (s, 3H, NMe), 2.95 (t, 2H, J=7.2, benzylic side chain-CH_2), 3.26 (t, 2H, J=7.2, CH_2NH), 3.88 (s, 2H, H5), 7.13-7.42 (m, 5H, H2 and H6-H9), 7.55 (d, 1H, J=7.0, H3), 7.89 (d, 1H, J=7.5, H1).

2-[[2-(Fluoren-4-yl)ethyl]methylamino]-1-(benzofuran-7-yl)ethanol [23] **22** (0.20 g, 0.9 mmol, free base) was dissolved in dry MeCN (25 ml) and (benzofuran-7-yl)epoxide (0.22 g, 1.34 mmol) added. The mixture was heated to near reflux temperature under N_2 for 7 days until tlc (CH_2Cl_2/MeOH/AcOH 16:3:1) showed full conversion. Toluene (20 ml) was added and the solution extracted with 10 % aqueous tartaric acid (4 x 20 ml). The combined aqueous phases were made basic with NaOH and extracted with CH_2Cl_2 (4 x 20 ml). The combined organic phases were extracted with 1 N HCl (9 x 10 ml) to remove the more polar amines. The CH_2Cl_2 solution was finally washed with water (40 ml) and with saturated aqueous NaCl (50 ml). Drying (Na_2SO_4) and evaporation of the solvent afforded 296 mg (87 %) of **23** as a brown oil. ^{1}H Nmr: Methin proton is seen at 5.30-5.33 ppm (m).

3-Methyl-5-(benzofuran-7-yl)-1,2,3,4,5,12-hexahydrofluoreno[2,1-*d*]azepine [**4**] 0.5 % H_2SO_4 in TFA was chosen as appropriate conditions for cyclisation. Crude **23** (0.40 g) was dissolved in TFA (20 ml). A 10 % solution of conc. H_2SO_4 in TFA (0.64 ml) was added, and the mixture was stirred at room teperature for 45 min after which the reaction mixture had turned dark brown and tlc (CH_2Cl_2/MeOH/AcOH 20:2:1) showed full cyclisation. The reaction mixture was cooled, quenched with 4 M NaOH, and extracted with CH_2Cl_2 (5 x 25 ml). The combined organic phases were washed with water (2 x 100 ml) followed by saturated aqueous NaCl (60 ml). The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated to give 310 mg of **4** as a light brown foam. This was dissolved in dry THF, precipitated once with HCl in ether, the precipitate separated by centrifugation, and finally washed several times with dry ether. The combined supernatants were evaporated, redissolved in dry THF and precipitated with dry ether to give 40 mg of **4** as hydrochloride, a fine off-white powder with mp 170°C (decomp.). The results below refer to the hydrochloride. ^{1}H Nmr: 2.77 (d, 3H, J=4.3, NMe), 3.84 (s, 2H, flu H5), 3.74-4.24 (m, 6H, CH_2 in azepine), 5.57 (d, 1H, J=9.4, methin), 6.42 (d, 1H, J=7.8, flu H2), 6.84 (d, 1H, J=2.1, fur H3), 7.19 (d, 1H, J=7.8, flu H1), 7.21-7.41 (m, 4H, flu H6-H8), 7.58 (d, 1H, J=2.0, fur H2), 7.56-7.93 (m, 3H, flu H4-H6), 13.24 (bs, 1H, NH^+). ^{13}C Nmr ($CDCl_3$): δ = 25.6, 26.4, 37.0, 42.4, 45.2, 107.2, 121.2, 123.4, 124.0, 125.2, 125.3, 125.5, 126.2, 126.8, 127.0, 132.9, 139.7, 140.0, 141.4, 143.4, 144.4, 145.0, 152.9. Mass spectrum m/z (% of base peak): 365 (M^+, 5), 308 (31), 279 (6), 250 (5), 234 (22), 221 (62), 205 (22), 131 (19), 91 (8), 58 (45), 36 (base peak).

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Received, 13th April, 1995