SYNTHESIS OF SOME BIS(*N*-1,2,3,4-TETRAHYDROISOQUINOLINYL)METHANES IN CONC. H_2SO_4 USING BENZOTRIAZOLE AS AUXILIARY

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Abstract
The preparation of some bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes 4a-g from their corresponding *N,N*-bis(benzotriazol-1-ylmethyl)phenylethylamines 3a-h in conc. H_2SO_4 is described. It is proposed that with the involvement of the acid, the removal of the two benzotriazolyl moieties leads to an intra- and also intermolecular reaction *via* the corresponding iminium ions. The reaction conditions have to be adjusted according to the nature of the aromatic substituent(s), the obtained yields for the final product are generally good to excellent.

Introduction

1,2,3,4-Tetrahydroisoquinolines have attracted considerable interest as possible inhibitors of phenylethanolamine *N*-methyltransferase (PNMT), an enzyme, which is mainly found in the adrenal medulla and catalyses the final step in the epinephrine biosynthesis. A selective interference with PNMT is therefore likely to be of medicinal value, particularly in the treatment of anxiety or ischemic heart diseases (1). Deactivated α-methylphenylethylamines (2) and benzylamines (3) as well as 1,2,3,4-tetrahydroisoquinolines with deactivating chloro-substituents on the aromatic moiety (4-6) have been found to be effective PNMT inhibitors, their potential, however, decreases proportionately to the size of any *N*-alkyl substituent (1). In comparison, 1,2,3,4-tetrahydroisoquinolines linked *via* a *N,N*-unsubstituted alkylene chain of varying length exhibit a substantially increased activity, which is likely to be associated with a second interaction at a further enzyme site. It also appears that in these bis-compounds the length of the *N,N*-alkylene bridge has a significant influence on their activity, with shorter linkages displaying an increased potential (1).

Bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)alkanes with more than one methylene group in the bridge can be obtained from the reaction between 1,2,3,4-tetrahydroisoquinolines and the respective ω-

haloacyl halides followed by reduction. Alternatively, the corresponding dihalides can also be employed (1). Bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes, which can be expected to be potent PNMT-inhibitors due to the minimal bridge length between the two tetrahydroisoquinolinyl moieties, are, however, not accessible by these routes. The only reported preparation (7) of a *N,N*-methylene bridged bis-tetrahydroisoquinoline is the reaction of the bis(aminol ether) *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine with trichloromethylsilane (TCMS) and subsequent alkaline hydrolysis.

Following a similar tandem principle, the preparation of some bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes 4a-h from the corresponding *N,N*-bis(benzotriazol-1-ylmethyl)phenylethylamines 3a-h is described in this paper[1]. This Friedel-Crafts reaction with conc. H_2SO_4 employs benzotriazole as auxiliary and yields good to excellent quantities of the final product. Although no pharmacological studies have been undertaken, it can be assumed that these *N,N*-methylene bridged bis-tetrahydroisoquinolines also display a significant PNMT inhibitory potential.

Results and Discussion

Starting material for the reaction are the respective *N,N*-bis(benzotriazol-1-ylmethyl)-phenylethylamines 3a-h, which are obtained from the reaction between the corresponding 2-phenylethylamines 1a-h and 1-hydroxymethylbenzotriazole 2 (Scheme 1, Table 1) (8, 9). The latter is a popular auxiliary in benzotriazole chemistry and is easily prepared from benzotriazole and formalin (10). The reaction between 2 and primary aliphatic amines is well established in the literature and usually proceeds in a 2:1 ratio to give high yields of the corresponding bis(benzotriazolyl) adducts (11).

The benzotriazolyl moiety can be removed from a molecule under strongly acidic conditions; Katritzky and co-workers (12), for instance, reported the intramolecular cyclisation of *N*-(α-benzotriazolylalkyl)arylamides to 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones in conc. H_2SO_4. Compounds 3a-h are in this work reacted in a similar fashion (Scheme 2). After alkaline work-up, the corresponding bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes 4a-h are obtained as crystalline

[1] Parts of this work were already presented at the 17th International Congress of Heterocyclic Chemistry in Vienna, Austria (1. - 6. August 1999)

products from an oily solution and are in most cases recrystallised from EtOH. Compound 4c is, however, a liquid and therefore also characterised as its corresponding picrate.

Scheme 1

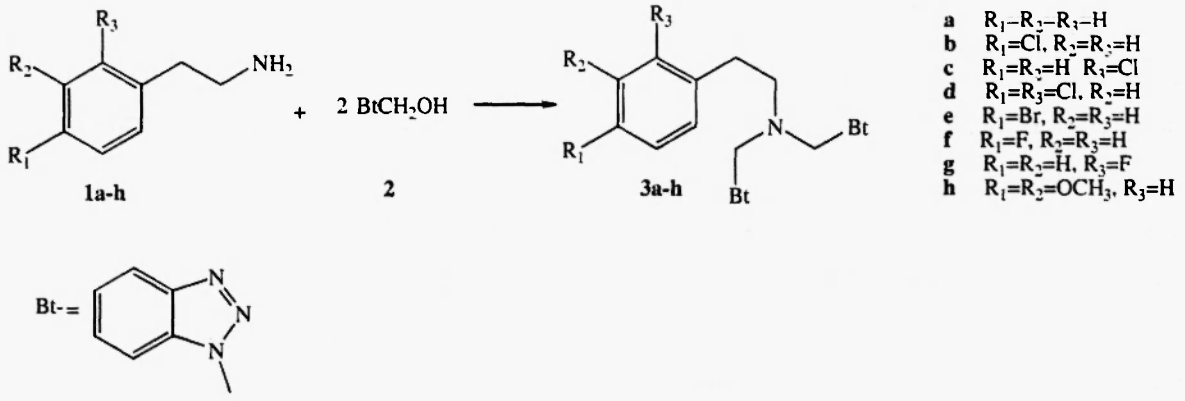
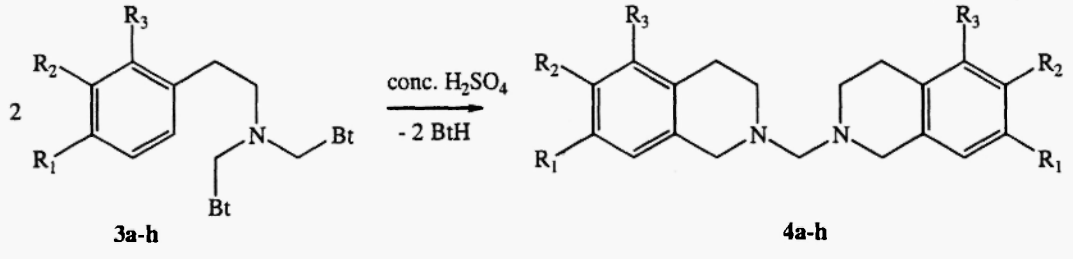


Table 1 *N,N*-Bis(benzotriazol-1-ylmethyl)phenylethylamines 3 (8, 9)

Compound	R_1	R_2	R_3	Yield (%)	Mp/°C (EtOH)	δ [Bt-CH_2-N] (ppm)
3a	H	H	H	92	123-124	5.62 (s, 4H)
3b	Cl	H	H	92	149-150	5.62 (s, 4H)
3c	H	H	Cl	80	116-118	5.68 (s, 4H)
3d	Cl	H	Cl	88	125-126	5.68 (s, 4H)
3e	Br	H	H	92	143-145	5.63 (s, 4H)
3f	F	H	H	89	117-118	5.64 (s, 4H)
3g	H	H	F	98	116-117	5.66 (s, 4H)
3h	OCH_3	OCH_3	H	76	91-93	5.64 (s, 4H)

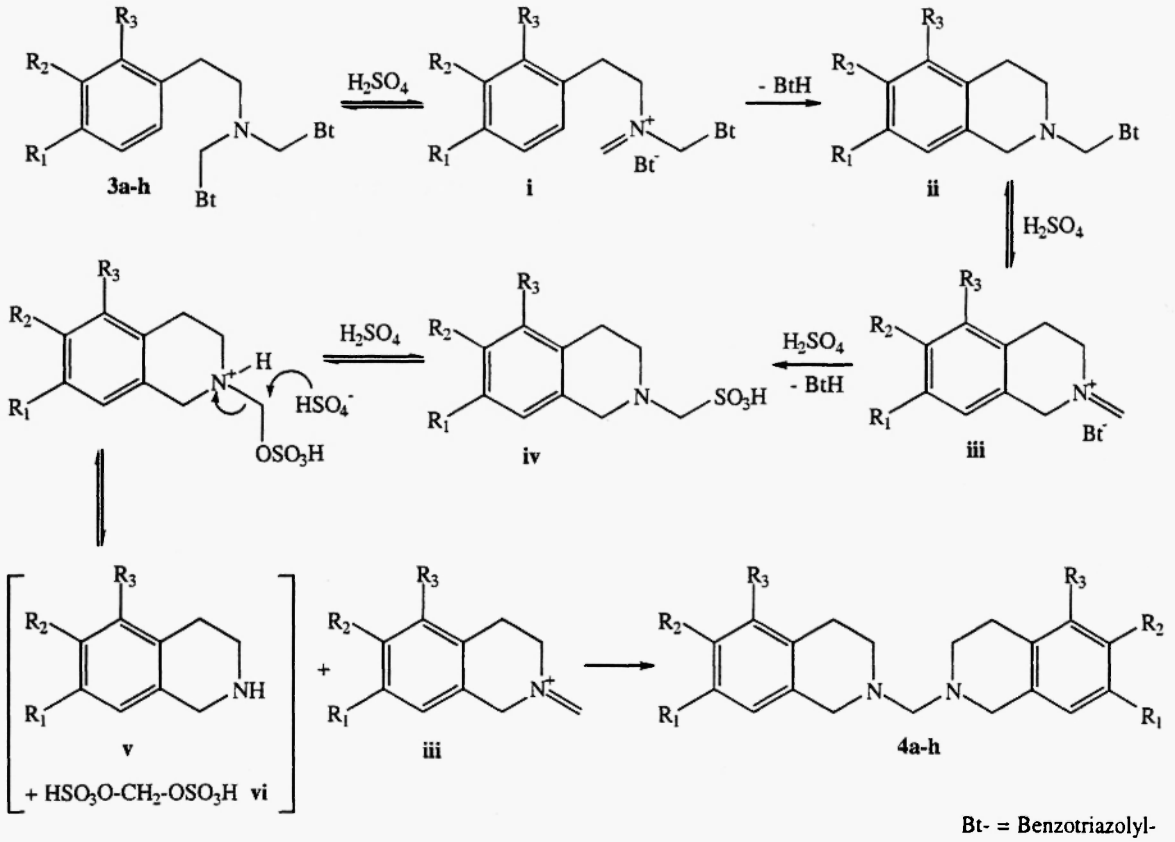
Scheme 2



Bt- = Benzotriazolyl-

The following reaction mechanism is assumed to underlie the formation of the bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes 4a-h (Scheme 3): The loss of the first benzotriazolyl moiety from the *N,N*-bis(benzotriazol-1-ylmethyl)phenylethylamine 3a-h leads to the formation of an iminium ion (i) which cyclises intramolecularly (ii). The removal of the second benzotriazolyl initiates the formation of a *N*-1,2,3,4-tetrahydroisoquinolinylmethylhydrogensulfate (iv) *via* a second iminium ion (iii), which can react to the corresponding 1,2,3,4-tetrahydroisoquinoline (v) with the involvement of a further acid molecule. The free secondary amine (v) formed during this phase of the reaction is then available for a nucleophilic reaction with the iminium ion (iii) to form the final product 4a-h; as an acetal, the methylenebis(bisulfate) (vi) can be expected to undergo rapid hydrolysis during work-up procedure. Thus, it is proposed that the reaction proceeds *via* an intra- and intermolecular tandem-reaction.

Scheme 3



Bt- = Benzotriazolyl-

The obtained bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes 4a-h all show a characteristic resonance of approx. δ_H 3.3 and δ_C 80 for the methylene group in the bridge [NCH_2N] (Table 2). As

expected, the reaction conditions have to be adjusted according to the nature of the aromatic substituent. The activated *N,N*-bis(benzotriazol-1-ylmethyl)-3,4-dimethoxyphenylethylamine 3h as well as the unsubstituted compound 3a undergo the intramolecular cyclisation more readily and therefore require a considerably shorter reaction time and decreased temperature compared to the deactivated derivatives.

By-products of the reaction are the corresponding 1,2,3,4-tetrahydroisoquinolines, evident in a small peak at approx. δ_H 4.0 [$ArCH_2N$]. In the absence of characteristic benzotriazole resonances they are likely to be a sign of the beginning decomposition of the products.

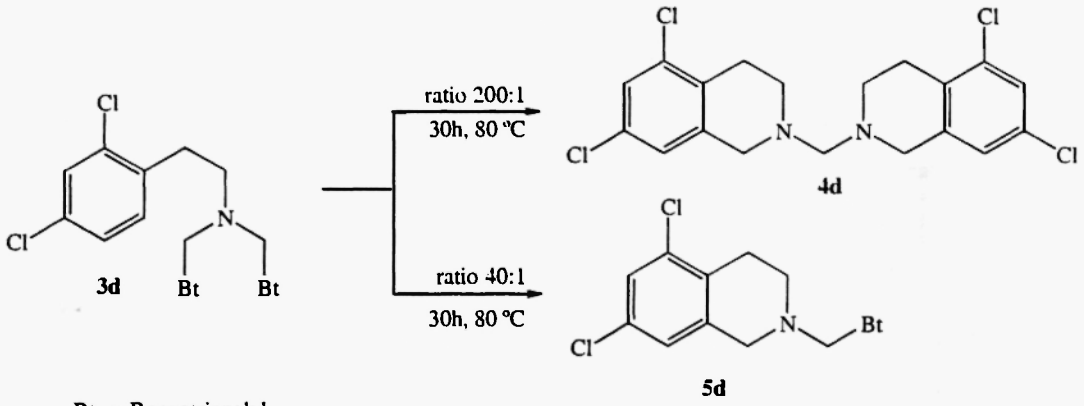
Table 2 Bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)methanes 4

Compound	R_1	R_2	R_3	Yield (%)	Mp/°C (EtOH)	δ_H [NCH_2N] (ppm)	δ_C [NCH_2N] (ppm)
4a	H	H	H	96	84-85	3.28 (s, 2H)	80.7
4b	Cl	H	H	96	118-119	3.26 (s, 2H)	80.1
4c	H	H	Cl	99	192-195[a]	3.26 (s, 2H)	80.1
4d	Cl	H	Cl	93	99-102	3.26 (s, 2H)	79.5
4e	Br	H	H	87	137-139	3.26 (s, 2H)	80.0
4f	F	H	H	85	103-104	3.27 (s, 2H)	80.2
4g	H	H	F	90	81-82	3.28 (s, 2H)	80.3
4h	OCH_3	OCH_3	H	73	122-123	3.27 (s, 2H)	80.5

[a] as picrate

An impact of reaction time and temperature is anticipated, but interestingly, it appears that the ratio of starting material to H_2SO_4 also has an influence on the success of the reaction, as is demonstrated by the different products obtained from *N,N*-bis(benzotriazol-1-ylmethyl)-2,4-dichlorophenylethylamine 3d (Scheme 4). A ratio of 1:200 yields the corresponding bis-product 4d after stirring for 30h at approx. 80 °C; under the same conditions, but in a ratio of 1:40, the corresponding *N*-benzotriazol-1-ylmethyl-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline 5d is obtained (9). This compound is characterised by a resonance at δ_H 5.6 for the benzotriazolyl-methylene group [$BtCH_2N$] as well as at δ_H 3.8 [$ArCH_2N$], indicating a successful intramolecular ring closure. Compound 5d has previously not been accessible by cyclisation of 3d with $AlCl_3$, a milder Friedel-Crafts catalyst (8). A similar reaction pattern is also observed for the other deactivated compounds (3b,c as well as 3e-g), which all yield the corresponding *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines when reacted for 2h at 4 °C, followed by 2h stirring at room temperature in a ratio starting material to H_2SO_4 of 1:45 (9).

Scheme 4



Bt- = Benzotriazolyl-

Conclusion

The intra- and intermolecular tandem-reaction of the *N,N*-bis(benzotriazol-1-ylmethyl)phenylethylamines 3a-h in conc. H_2SO_4 leads to the corresponding bis(*N*-1,2,3,4-tetrahydroisoquinolinyl)-methanes 4a-h and is a further example for the versatility of benzotriazole as auxiliary in heterocyclic chemistry. The nature of any aromatic substituent dictates the reaction conditions, but it appears that the ratio of conc. H_2SO_4 to starting material also has an influence on the final product of the reaction. The obtained crystalline bis-products 4a-h are likely to be potent inhibitors of the enzyme phenylethanolamine *N*-methyltransferase with possible therapeutic applications.

Experimental

All reagents used were AR grade. Melting points were determined on a Gallenkamp Melting Point Apparatus and are uncorrected. FTIR spectra were taken on a Mattson Polaris FTIR-Spectrophotometer in Nujol and UV/Vis data on a Varian CARY 1 UV-Visible Spectrophotometer, using ethanol as solvent. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (200 / 50 MHz) in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal reference. ^1H NMR chemical shifts (δ) are reported in parts per million (ppm, δ_{TMS}= 0.00) and ^{13}C NMR results (in ppm) are referenced to $CDCl_3$ (δ 77.0 for centre line). Coupling patters are indicated as s (singlet), d (doublet) and m (multiplet). Elemental analyses were performed in the Research School of Chemistry, Australian National University, Canberra, Australia.

General procedure for compounds 3a-h: The respective 2-phenylethylamines 1a-h (1 equiv.) are added to 1-hydroxymethylbenzotriazole 2 (2 equiv.). The mixture is heated in EtOH (20 ml) with stirring for 1 hour. The corresponding *N,N*-bis(benzotriazol-1-ylmethyl)phenylethylamines 3a-h are obtained as crystalline products and recrystallised from EtOH. Mp and spectral data for compounds 3a-h were already reported elsewhere (8, 9).

General procedure for compounds 4a-h: Bis(N-1,2,3,4-tetrahydroisoquinolinyl)methane 4a

N,N-Bis(benzotriazol-1-ylmethyl)phenylethylamine 3a (3.00 g, 7.8 mmol) was slowly added to 43.6 ml H_2SO_4 (784.8mmol) at 4 °C with stirring. The mixture was stirred for a further 30 min at this temperature, then poured onto ice (approx. 50 g) and brought to pH 12 with NaOH 10 M (185 ml). The layers were separated and the aqueous solution extracted with CH_2Cl_2 (4 x 150 ml). The combined organic extracts were rewashed with NaOH 2M (150 ml), dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Compound 4a crystallised from an oily solution as white, glittery flakes (1.04 g, 96%), which were recrystallised from EtOH. Mp 84-85 °C; δ_H 7.13-7.05 (m, 8H), 3.75 (s, 4H, $ArCH_2N$), 3.28 (s, 2H, NCH_2N), 2.88 (s, 8H, CH_2CH_2); δ_C 135.2, 135.0, 128.9, 126.8, 126.1, 125.7, 80.7 (NCH_2N), 54.3 ($ArCH_2N$), 49.0 (NCH_2CH_2), 28.9 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 273 (611), 266 (667), 216 (6611); ν_{max} (cm^{-1}) 1305, 1280, 1150, 1100, 930, 745; Anal. calc. for $C_{19}H_{22}N_2$: C 82.0; H 8.0; N 10.1; Found: C 81.8; H 7.9; N 10.0 %.

Bis(N-7-chloro-1,2,3,4-tetrahydroisoquiolinyl)methane 4b

Compound 4b (2.00 g, 96%) was obtained from the reaction of *N,N*-bis(benzotriazol-1-ylmethyl)-4-chlorophenylethylamine 3b (5.00g, 12.0 mmol) and conc. H_2SO_4 (66.6 ml, 1198.8 mmol) for 4 hours at RT. The white, glittery flakes were recrystallised from EtOH. Mp 118-119 °C; δ_H 7.09-7.01 (m, 6H), 3.70 (s, 4H, $ArCH_2N$), 3.26 (s, 2H, NCH_2N), 2.85 (s, 8H, CH_2CH_2); δ_C 136.9, 133.4, 131.2, 130.2, 126.7, 126.3, 80.1 (NCH_2N), 53.9 ($ArCH_2N$), 48.7 (NCH_2CH_2), 28.3 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 280 (554), 272 (554), 210 (6851); ν_{max} (cm^{-1}) 1325, 1270, 1250, 1150, 1080, 895, 555; Anal. calc. for $C_{19}H_{20}N_2Cl_2$: C 65.7; H 5.8; N 8.1; Found: C 65.4; H 5.9; N 8.0 %.

Bis(N-5-chloro-1,2,3,4-tetrahydroisoquinolinyl)methane 4c

The reaction between *N,N*-bis(benzotriazol-1-ylmethyl)-2-chlorophenylethylamine 3c (2.00 g, 4.8 mmol) and 26.6 ml conc. H_2SO_4 (478.8 mmol) for 4 hours at ambient temperature yielded compound 4c (0.82 g, 99%) as a yellow oil. Mp (picrate) 192-195 °C; δ_H 7.20 (d, 2H, 8 Hz), 7.06 (t,

2H, 6 Hz), 6.94 (d, 2H, 8 Hz), 3.72 (s, 4H, $ArCH_2N$), 3.26 (s, 2H, NCH_2N), 2.88 (s, 8H, CH_2CH_2); δ_C 137.4, 134.4, 133.1, 126.9, 126.6, 125.2, 80.1 (NCH_2N), 54.2 ($ArCH_2N$), 48.7 (NCH_2CH_2), 27.1 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 256 (2215), 219 (9862); ν_{max} (cm^{-1}) 1475, 1150, 1125, 775, 750, 700; Anal. calc. for $C_{31}H_{26}N_8O_{14}Cl_2$: C 46.2; H 3.3; N 13.9; Found: C 45.8; H 3.5; N 13.8 %.

Bis(N-5,7-dichloro-1,2,3,4-tetrahydroisoquinolinyl)methane 4d

N,N-Bis(benzotriazol-1-ylmethyl)-2,4-dichlorophenylethylamine 3d (4.00 g, 8.9 mmol) was added to 99.0 ml (1782.0 mmol) conc. H_2SO_4 at RT and the mixture heated for 30 hours at approx. 80 °C. Compound 4d (1.72 g, 93%) was obtained as a pink oil, which was triturated with EtOAc. Recrystallisation from EtOH yielded a very fine white powder. Mp 99-102 °C; δ_H 7.22 (d, 2H, 2 Hz), 6.96 (d, 2H, 2 Hz), 3.68 (s, 4H, $ArCH_2N$), 3.26 (s, 2H, NCH_2N), 2.87-2.82 (m, 8H, CH_2CH_2); δ_C 138.6, 135.0, 131.7, 126.8, 125.3, 79.5 (NCH_2N), 53.9 ($ArCH_2N$), 48.4 (NCH_2CH_2), 26.6 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 283 (539), 274 (654), 218 (10871); ν_{max} (cm^{-1}) 1575, 1170, 1130, 950, 850, 840, 725; Anal. calc. for $C_{19}H_{18}N_2Cl_4$: C 54.8; H 4.4; N 6.7; Found: C 54.7; H 4.5; N 6.7 %.

Bis(N-7-bromo-1,2,3,4-tetrahydrisoquinolinyl)methane 4e

The reaction between *N,N*-bis(benzotriazol-1-ylmethyl)-4-bromophenylethylamine 3e (1.30 g, 2.8 mmol) and conc. H_2SO_4 (15.6 ml, 280.8 mmol) for 4 hours at RT yielded compound 4e as white crystals (0.53g, 87%), which were recrystallised from EtOH. Mp 137-139 °C; δ_H 7.26-7.18 (m, 4H), 6.98 (d, 2H, 8 Hz), 3.69 (s, 4H, $ArCH_2N$), 3.26 (s, 2H, NCH_2N), 2.83 (s, 8H, CH_2CH_2); δ_C 137.4, 134.0, 130.5, 129.6, 129.2, 119.2, 80.0 (NCH_2N), 53.7 ($ArCH_2N$), 48.6 (NCH_2CH_2), 28.3 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 281 (306), 273 (349), 206 (6201); ν_{max} (cm^{-1}) 1340, 1265, 1250, 1145, 1100, 940, 875, 800, 550; Anal. calc. for $C_{19}H_{18}N_2Cl_4$: C 54.8; H 4.4; N 6.7; Found: C 54.7; H 4.5; N 6.7 %.

Bis(N-7-fluoro-1,2,3,4-tetrahydroisoquinolinyl)methane 4f

The white crystals 4f (0.33 g, 85%) were obtained from the reaction of *N,N*-bis(benzotriazol-1-ylmethyl)-4-fluorophenylethylamine 3f (1.00 g, 2.5 mmol) in 13.9 ml conc. H_2SO_4 (250 mmol) after 4 hours stirring at ambient temperature. The product was recrystallised from EtOH. Mp 103-104 °C; δ_H 7.09-7.02 (m, 2H), 6.83-6.71 (m, 4H), 3.71 (s, 4H, $ArCH_2N$), 3.27 (s, 2H, NCH_2N), 2.85 (s, 8H, CH_2CH_2); δ_C 161.2 (245 Hz), 137.0 (7 Hz), 130.4, 130.2 (9 Hz), 113.2 (9 Hz / 21 Hz), 80.2

(NCH_2N), 54.1 ($ArCH_2N$), 48.9 (NCH_2CH_2), 28.2 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 276 (1352), 270 (1321), 211 (6352); ν_{max} (cm^{-1}) 1500, 1330, 1260, 1240, 1140, 1100, 1030, 760, 740, 580; Anal. calc. for $C_{19}H_{20}N_2F_2$: C 72.6; H 6.4; N 8.9; Found: C 72.1; H 6.1; N 8.8 %.

Bis(N-5-fluoro-1,2,3,4-tetrahydroisoquinolinyl)methane 4g

N,N-Bis(benzotriazol-1-ylmethyl)-2-fluorophenylethylamine 3g (1.00 g, 2.5 mmol) was slowly added to 14.0 ml conc. H_2SO_4 (252.0 mmol). After stirring for 4 hours at RT, product 4g (0.35 g, 90%) crystallised slowly from an oily residue. Mp 81-82 °C; δ_H 7.10-7.04 (m, 2H), 6.89-6.81 (m, 4H), 3.74 (s, 4H, $ArCH_2N$), 3.28 (s, 2H, NCH_2N), 2.86 (s, 8H, CH_2CH_2); δ_C 161.1 (245 Hz), 137.8 (9 Hz), 126.7 (13 Hz), 122.2, 112.4 (21 Hz), 80.3 (NCH_2N), 53.8 ($ArCH_2N$), 48.2 (NCH_2CH_2), 22.3 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 255 (3868), 215 (9277); ν_{max} (cm^{-1}) 1350, 1250, 1230, 1015, 920, 725; Anal. calc. for $C_{19}H_{20}N_2F_2$: C 72.6; H 6.4; N 8.9; Found: C 72.3; H 6.2; N 8.7 %.

Bis(N-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)methane 4h

The reaction of *N,N*-bis(benzotriazol-1-ylmethyl)-3,4-dimethoxy-phenylethylamine 3h (2.27 g, 5.1 mmol) in 28.4 ml conc. H_2SO_4 (511.2 mmol) for 7 min at 4 °C yielded compound 4h as white crystals (0.74 g, 73%), which were recrystallised from EtOH. Mp 122-123 °C; δ_H 6.62 (s, 2H), 6.55 (s, 2H), 3.84 (d, 12H, 6 Hz, OCH_3), 3.68 (s, 4H, $ArCH_2N$), 3.27 (s, 2H, NCH_2N), 2.84 (s, 8H, CH_2CH_2); δ_C 147.6, 147.4, 127.0, 126.7, 111.5, 109.7, 80.5 (NCH_2N), 55.8 (OCH_3), 53.9 ($ArCH_2N$), 49.1 (NCH_2CH_2), 28.4 ($ArCH_2CH_2$); λ_{max} (nm / $dm^3mol^{-1}cm^{-1}$) 283 (7012), 225 (11076); ν_{max} (cm^{-1}) 1525, 1230, 1150, 1020, 850, 800, 725; Anal. calc. for $C_{23}H_{30}N_2O_4$: C 69.3; H 7.6; N 7.0; Found: C 69.0; H 7.8; N 7.0 %.

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