Regioselective Reductive Ring Cleavage of 3-Benzyltetrahydro-1,3-oxazines to 3-Dialkylaminopropanols and of 3-Benzyl-3-methyltetrahydro-1,3-oxazinium Iodides to Alkyl 3-Dialkylaminopropyl Ethers

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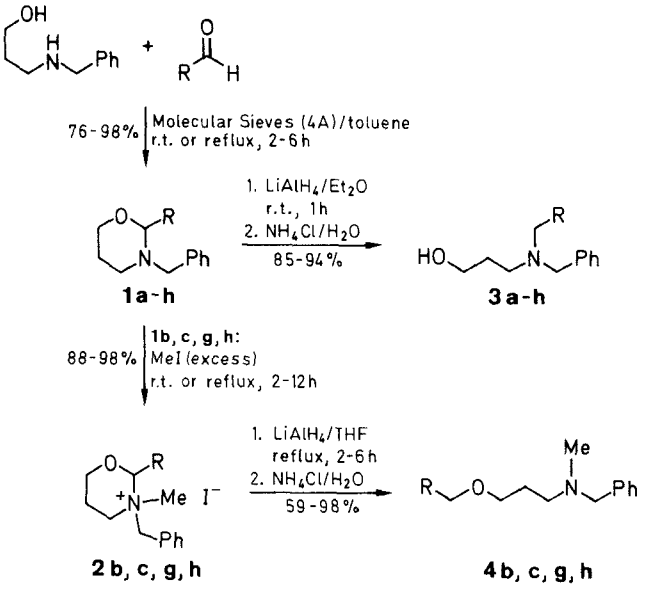
3-Benzyltetrahydro-1,3-oxazines and their methiodides are ring-cleaved upon reduction with lithium aluminum hydride to give 3-dialkylaminopropanols or alkyl 3-dialkylaminopropyl ethers, respectively, in good yields. The reducing agent regioselectively cleaves the C–O bond in tetrahydro-1,3-oxazines and the C–N bond in the tetrahydro-1,3-oxazinium salts.

Although the chemistry of tetrahydrooxazines has been studied and reviewed[1–3] there is only fragmentary information on the opening of tetrahydro-1,3-oxazines by nucleophilic agents. *N*-Disubstituted 3-aminopropanols of analgesic activity have been synthesized by hydrogenolytic cleavage[4,5] of these heterocycles and lithium aluminium hydride (LAH) has been used to reduce such substrates in the synthesis of indolylalkylaminoalcohols,[6] dihydrosolasodenol,[7] and diastereoisomeric aminopropanols.[8,9]

Sodium borohydride does not reduce tetrahydro-1,3-oxazines;[10] it has thus been used for the selective reduction of side chains of tetrahydro-1,3-oxazines in an enantioselective synthesis of α-hydroxyacids.[11] On the other hand, the cleavage of the homologous oxazolidines with LAH,[12,13] sodium borohydride,[14,15] or borane-THF complex[16] has been widely used in the synthesis of 2-aminoethanol derivatives, the reaction of *O,N*-acetals with certain reducing agents to give amino compounds is also a well-documented process,[17–19] and the LAH reduction of quaternary ammonium iodides constitutes an efficient method for the preparation of tertiary amines.[20,21] Furthermore, *N,N*-disubstituted 3-aminopropanol derivatives have been synthesized by condensation of secondary amines with 3-halopropanol derivatives,[22–24] but in some cases the yields are unsatisfactory due to the drastic experimental conditions (high temperatures and long periods of heating).

We describe here the synthesis of *N,N*-dialkyl-3-aminopropanols **3** and alkyl *N,N*-dialkylaminopropyl ethers in two or three steps, respectively: formation of tetrahydro-1,3-oxazines **1** and their methiodides **2** and the reductive ring cleavage of these *O,N*-heterocycles by reaction with lithium aluminum hydride. Compounds **1a–h** are prepared in high yield by condensation of 3-benzylaminopropanol with aldehydes (Table 1), and the tetrahydro-1,3-oxazinium iodides **2-b,c,g,h** are obtained from **1-b,c,g,h** by reaction with excess of methyl iodide[25,26] (Table 2).

The reductive cleavage of tetrahydro-1,3-oxazines **1** with lithium aluminum hydride is carried out under mild conditions; it proceeds regioselectively, with cleavage of the C–O bond, to afford the *N,N*-disubstituted 3-aminopropanols **3** in high yields. On the other hand, the reductive cleavage of the 3-benzyl-3-methyltetrahydro-1,3-oxazinium iodides **2** with lithium aluminum hydride under more drastic conditions proceeds regioselectively at



1–4	R	1–4	R
a	Me	**e**	$PhCH_2CH_2$
b	Et	**f**	PhCH=CH
c	*i*-Bu	**g**	Ph
d	n-C_8H_{17}	**h**	4-$MeOC_6H_4$

Table 1. 2-Substituted 3-Benzyltetrahydro-1,3-oxazines **1** Prepared

Product	Reaction Conditions: Temperature (°C), Time (h)	Yield[a] (%)	mp (°C)[b] or bp (°C)/Torr	Molecular Formula[c] or Lit. Data
1a	20, 6	76	86–87/1.0	126/37[27]
1b	20, 4	98	80–83/0.8	$C_{13}H_{19}NO$ (205.3)
1c	20, 2	98	114–117/0.5	$C_{15}H_{23}NO$ (233.3)
1d	110, 2	94	150–154/0.6	$C_{19}H_{31}NO$ (289.4)
1e	110, 3	94	47–88[d]	$C_{19}H_{23}NO$ (281.3)
1f	110, 3	91	49–50[d]	$C_{19}H_{21}NO$ (279.3)
1g	110, 3	98	75–76[d]	$C_{17}H_{19}NO$ (253.3)
1h	110, 3	91	51–52[d]	$C_{18}H_{21}NO_2$ (283.3)

[a] Yield of isolated pure product.
[b] Uncorrected; measured in a capillary tube.
[c] Satisfactory microanalyses: C ±0.16, H ±0.14, N ±0.12.
[d] From petroleum ether (bp 40–60 °C).

Table 2. 2-Substituted 3-Benzyl-3-methyltetrahydro-1,3-oxazinium Iodides **2** Prepared

Product	Reaction Conditions		Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]
	Ratio **1** : CH_3I	Temperature (°C), Time (h)			
2b	1:2	20, 4	91	157–158	$C_{14}H_{22}INO$ (347.2)
2c	1:2	reflux, 2	90	158–160	$C_{16}H_{26}INO$ (375.2)
2g	1:3	reflux, 4	98	158–159	$C_{18}H_{22}INO$ (395.2)
2h	1:3	20, 12	88	148–150	$C_{19}H_{24}INO_2$ (425.3)

[a,b] See Table 1.
[c] Satisfactory microanalyses: C ±0.16, H ±0.16, N ±0.17.

Table 3. *N,N*-Disubstituted 3-Aminopropanols **3** and Alkyl 3-Aminopropyl Ethers **4** Prepared

Product	Reaction Conditions	Yield[a] (%)	mp (°C)[b] or bp (°C)/Torr	Molecular Formula[c]
	Temperature (°C), Time (h)			
3a	20, 1	85	oil [66–67][d,e]	$C_{12}H_{19}NO$ (193.2)
3b	20, 1	94	oil [91–92][d,e]	$C_{13}H_{21}NO$ (207.3)
3c	20, 1	92	oil [46–47][d,e]	$C_{15}H_{25}NO$ (235.3)
3d	20, 1	92	oil [49–50][d,e]	$C_{19}H_{33}NO$ (291.4)
3e	20, 1	91	oil [45–46][d,e]	$C_{19}H_{25}NO$ (283.4)
3f	20, 1	87	oil [103–104][d,f]	$C_{19}H_{23}NO$ (281.3)
3g	20, 1	90	oil [120–121][d,f]	$C_{17}H_{21}NO$ (255.3)
3h	20, 1	92	oil [110–111][d,f]	$C_{18}H_{23}NO_2$ (285.3)
4b	67, 2	78	76–80/0.1	$C_{14}H_{23}NO$ (221.3)
4c	67, 5	98	95–97/0.1	$C_{16}H_{27}NO$ (249.3)
4g	67, 6	59	120–123/0.1	$C_{18}H_{23}NO$ (269.3)
4h	67, 3	78	138–140/0.1	$C_{19}H_{25}NO_2$ (299.2)

[a,b] See Table 1.
[c] Satisfactory microanalyses: C ±0.16, H ±0.18, N ±0.17.
[d] Numbers in parenthesis refer to mp of the 3,5-dinitrobenzoate.
[e] From hexane.
[f] From hexane/toluene.

the C–N bond to afford alkyl *N*-benzyl-*N*-methyl-3-aminopropyl ethers **4** in high yields.

The use of aluminum hydride or chloroaluminum hydrides (from $LiAlH_4$ and $AlCl_3$) in place of lithium aluminum hydride in the reduction of compounds **1** and **2** leads to mixtures of products, 3-aminopropanols **3** and 3-aminoalkyl ethers **4** being obtained in only poor yields.

The procedure described here can be regarded as a useful alternative[22–24] method for the preparation of *N,N*-dialkyl-3-aminopropanols and as a new and versatile synthesis of alkyl *N,N*-dialkyl-3-aminopropyl ethers from commercially available starting materials.

Compounds **1** are prepared by a modified literature procedure.[27]

2-Substituted 3-Benzyltetrahydro-1,3-oxazines 1; General Procedures:

Method A, For Compounds **1a–c**: A mixture of 3-benzylaminopropanol (1.65 g, 10 mmol), the appropriate aldehyde (11 mmol), and molecular sieves 4 Å (4 g) in toluene (20 mL) is stirred under N_2 at r.t. until the reaction is complete (TLC). The mixture is filtered through a pad of celite, and the celite washed with toluene (3 × 15 mL). The solvent is evaporated and the oily residue purified by distillation under reduced pressure.

Method B, For Compounds **1d–h**: A solution of 3-benzylaminopropanol (1.65 g, 10 mmol), the appropriate aldehyde (11 mmol), and *p*-toluenesulfonic acid (100 mg) in toluene (50 mL) is refluxed with azeotropic removal of water (Dean-Stark) for 2–3 h. The mixture is then cooled to r.t., washed sequentially with sat. Na_2CO_3 solution (20 mL), H_2O (30 mL), and brine (30 mL), dried (solid KOH), and evaporated (rotavapor) and the residue is distilled **(1d)** or recrystallized from petroleum ether **(1e–h)**.

3-Benzyl-3-methyltetrahydro-1,3-oxazinium Iodides 2; General Procedure:

A mixture of the appropriate 3-benzyltetrahydro-1,3-oxazine **1** (50 mmol) and MeI (100 mmol for **1b,c**; 150 mmol for **1g,h**) is stirred at room temperature **(1b,h)** or reflux **(1c,g)** until a white precipitate is formed. For compounds **2b** and **2c**, the mixture is filtered and the solid washed with hot EtOAc (3 × 25 mL) and dried at 25°C/10 Torr. For compounds **2g** and **2h**, the gelatinous precipitate is taken up in MeOH (10 mL) and stirred at r.t. until a crystalline solid is formed. This solid is separated by suction and dried at 50°C/10 Torr.

***N,N*-Disubstituted 3-Aminopropanols 3; General Procedure:**

To a stirred suspension of $LiAlH_4$ (380 mg, 10 mmol) in anhydrous Et_2O (10 mL) in an ice bath is added dropwise, under N_2, a solution of the tetrahydro-1,3-oxazine **1** (10 mmol) in anhydrous Et_2O (10 mL). After the addition, the mixture is allowed to reach r.t. and stirred for 1 h. The flask is immersed in an ice bath and sat. NH_4Cl solution (5 mL) is added. The mixture is filtered, the solid washed with Et_2O (2 × 15 mL), and the filtrate dried ($MgSO_4$). The solvent is evaporated and the oily residue is purified on a short silica gel column (10 × 2 cm, 230–400 mesh) using EtOAc as eluent.

***N,N*-Disubstituted Alkyl 3-Aminopropyl Ethers 4b,c,g,h; General Procedure:**

To a stirred suspension of $LiAlH_4$ (380 mg, 10 mmol) in anhydrous THF (10 mL) is slowly added, under N_2 at r.t., a solution of the tetrahydro-1,3-oxazinium salt **2** (10 mmol) in the same solvent (150 mL), and the mixture is heated until the reaction is complete (TLC). The mixture is cooled (ice water bath) and quenched with sat. NH_4Cl solution (5 mL). The precipitate is isolated by suction and washed with THF. The solvent is evaporated to a volume of 50 mL. The mixture is partitioned between $CHCl_3$ (100 mL) and a 5 M solution of $Na_2S_2O_3$ (25 mL); the aqueous phase is discarded and the organic layer is again washed with $Na_2S_2O_3$ solution (25 mL) and brine (50 mL), and dried ($MgSO_4$). The solvent is evaporated (rotavapor) and the residue purified by distillation under reduced pressure.

Table 4. Spectral Data of Compounds **1–4**

Compound	MS (70 eV)[a], *m/z* (%)	^{1}H-NMR (solvent/TMS)[b], δ, *J*(Hz)
1a	191 (M^+, 2); 176 (36); 91 (100)	1.27 (d, 3H, J = 7, CH_3), 1.98 (m, 2H, 5-CH_2), 2.80 (m, 2H, 4-CH_2), 3.60 (m, 2H, 6-CH_2), 3.80 (s, 2H, $C\underline{H}_2Ph$), 4.20 (q, 1H, J = 7, 2-CH), 7.25 (m, 5H_{arom})
1b	205 (M^+, 2); 176 (25); 91 (100)	0.95 (t, 3H, J = 7, CH_3), 1.60 (m, 2H, $C\underline{H}_2CH_3$), 2.00 (m, 2H, 5-CH_2), 2.80 (m, 2H, 4-CH_2), 3.60 (m, 2H, 6-CH_2), 3.80 (s, 2H, $C\underline{H}_2Ph$), 4.20 (t, 1H, J = 6, 2-CH), 7.25 (m, 5H_{arom})
1c	233 (M^+, 4); 176 (94); 91 (100)	0.95 [d, 6H, J = 6, $CH(C\underline{H}_3)_2$], 1.50 (dd, 2H, J = 5, 8, $CHC\underline{H}_2$), 1.80 [m, 1H, $C\underline{H}(CH_3)_2$], 2.00 (m, 2H, 5-CH_2), 2.80 (m, 2H, 4-CH_2), 3.60 (m, 2H, 6-CH_2), 3.80 (s, 2H, $C\underline{H}_2Ph$), 4.25 (t, 1H, J = 5, 2-CH), 7.25 (m, 5H_{arom})
1d	289 (M^+, 3); 176 (85); 91 (100)	0.90 (t, 3H, J = 5, CH_3), 1.20–1.60 [m, 14H, $(C\underline{H}_2)_7$], 1.95 (m, 2H, 5-CH_2), 2.75 (m, 2H, 4-CH_2), 3.70 (m, 2H, 6-CH_2), 3.80 (s, 2H, $C\underline{H}_2Ph$), 4.20 (t, 1H, J = 6, 2-CH), 7.25 (m, 5H_{arom})
1e	281 (M^+, 5); 176 (26); 91 (100)	1.80 (m, 4H, 5-CH_2, $CH_2C\underline{H}_2Ph$), 2.70 (m, 4H, 4-CH_2, $CH_2C\underline{H}_2Ph$), 3.70 (m, 2H, 6-CH_2), 3.80 (s, 2H, $NC\underline{H}_2Ph$), 4.15 (t, 1H, J = 6, 2-CH), 7.20 (m, 10H_{arom})
1f	279 (M^+, 6); 176 (14); 91 (100)	2.00 (m, 2H, 5-CH_2), 2.80 (m, 2H, 4-CH_2), 3.70 (m, 2H, 6-CH_2), 3.80 (s, 2H, $NC\underline{H}_2Ph$), 4.80 (d, 1H, J = 4, 2-CH), 6.15 (dd, 1H, J = 4, 16, $C\underline{H}$=CHPh), 6.80 (d, 1H, J = 16, CH=$C\underline{H}$Ph), 7.20 (m, 10H_{arom})
1g	253 (M^+, 7); 176 (28); 91 (100)	2.00 (m, 2H, 5-CH_2), 2.85 (m, 2H, 4-CH_2), 3.35 (d, 1H, J = 15, NCHPh), 3.85 (d, 1H, J = 15, NC$\underline{H}$Ph), 3.90 (m, 2H, 6-CH_2), 5.20 (s, 1H, 2-CH), 7.20–7.60 (m, 10H_{arom})
1h	283 (M^+, 9); 176 (37); 91 (100)	2.00 (m, 2H, 5-CH_2), 2.90 (m, 2H, 4-CH_2), 3.30 (d, 1H, J = 16, NC$\underline{H}$Ph), 3.70 (s, 3H, OCH_3), 3.75 (d, 1H, J = 16, NC$\underline{H}$Ph), 4.10 (m, 2H, 6-CH_2), 5.00 (s, 1H, 2-CH), 6.80 (d, 2H, J = 9, *m*-H_{arom}), 7.20 (m, 5H_{arom}), 7.40 (d, 2H, J = 9, *o*-H_{arom})
2b		1.05 (t, 3H, J = 7, CH_3), 1.90 (m, 2H, $C\underline{H}_2CH_3$), 2.20 (m, 2H, 5-CH_2), 3.00, 3.10 (2s, 3H, diastereoisomeric NCH_3), 3.45 (m, 2H, 6-CH_2), 4.20 (m, 2H, 4-CH_2), 4.50 (m, 2H, $NC\underline{H}_2Ph$), 4.85 (m, 1H, 2-CH), 7.50 (s, 5H_{arom})
2c		1.05 [d, 6H, J = 6, $CH(C\underline{H}_3)_2$], 1.70–1.90 [m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$], 2.15 (m, 2H, 5-$CH_2$), 3.00, 3.10 (2s, 3H, diast. NCH_3), 3.45 (m, 2H, 6-CH_2), 4.15 (m, 2H, 4-CH_2), 4.50 (m, 2H, $NC\underline{H}_2Ph$), 5.00 (m, 1H, 2-CH), 7.60 (s, 5H_{arom})
2g		2.10 (m, 2H, 5-CH_2), 2.90, 3.15 (2s, 3H, diast. NCH_3), 3.50 (m, 2H, 6-CH_2), 4.20 (m, 2H, 4-CH_2), 4.40 (m, 2H, $NC\underline{H}_2Ph$), 6.10 (s, 1H, 2-CH), 7.40–7.90 (m, 10H_{arom})
2h		2.00 (m, 2H, 5-CH_2), 2.90, 3.05 (2s, 3H, diast. NCH_3), 3.55 (m, 2H, 6-CH_2), 3.95 (s, 3H, OCH_3), 4.20 (m, 2H, 4-CH_2), 4.50 (m, 2H, $NC\underline{H}_2Ph$), 6.00 (s, 1H, 2-CH), 7.20 (d, 2H, J = 9, *m*-H_{arom}), 7.50 (m, 5H_{arom}), 7.70 (d, 2H, J = 9, *o*-H_{arom})
3a	193 (M^+, 1); 178 (17); 91 (100)	1.00 (t, 3H, J = 7, CH_3), 1.80 (m, 2H, 2-CH_2), 2.45 (q, 2H, J = 7, $NC\underline{H}_2CH_3$), 2.50 (t, 2H, J = 5, 3-CH_2), 3.50 (s, 2H, $C\underline{H}_2Ph$), 3.55 (t, 2H, J = 5.5, 1-CH_2), 4.55 (s, 1H, OH), 7.20 (m, 5H_{arom})
3b	207 (M^+, 2); 178 (24); 91 (100)	0.90 (t, 3H, J = 7, CH_3), 1.80 (m, 4H, 2-CH_2, $C\underline{H}_2CH_3$), 2.40 (m, 4H, 3-CH_2, $C\underline{H}_2CH_2CH_3$), 3.50 (s, 3H, $C\underline{H}_2Ph$), 3.55 (t, 2H, J = 5.5, 1-CH_2), 4.40 (s, 1H, OH), 7.20 (m, 5H_{arom})
3c	235 (M^+, 1); 178 (38); 91 (100)	0.90 [d, 6H, J = 6, $(CH_3)_2$], 1.25–1.60 (m, 3H, $CH_2C\underline{H}$), 1.70 (m, 2H, 2-CH_2), 2.50 (m, 4H, 3-CH_2, $C\underline{H}_2CH_2CH$), 3.55 (s, 2H, $C\underline{H}_2Ph$), 3.60 (t, 2H, J = 5.5, 1-CH_2), 4.30 (s, 1H, OH), 7.20 (m, 5H_{arom})
3d	291 (M^+, 2); 178 (43); 91 (100)	0.90 (t, 3H, J = 6, CH_3), 1.25 [m, 12H, $(C\underline{H}_2)_6CH_3$], 1.60 (m, 4H, 2-CH_2, NCH_2–$C\underline{H}_2$), 2.50 (m, 4H, 3-CH_2, $NC\underline{H}_2(CH_2)_7$), 3.50 (s, 2H, $C\underline{H}_2Ph$), 3.55 (t, 2H, J = 5.5, 1-CH_2), 4.05 (s, 1H, OH), 7.20 (m, 5H_{arom})
3e	283 (M^+, 1); 178 (20); 91 (100)	1.70 (m, 4H, 2-CH_2, $NCH_2C\underline{H}_2$), 2.45 (m, 6H, 3-CH_2, $NC\underline{H}_2CH_2C\underline{H}_2Ph$), 3.50 (s, 2H, $C\underline{H}_2Ph$), 3.55 (t, 2H, J = 5.5, 1-CH_2), 4.10 (s, 1H, OH), 7.15 (m, 10H_{arom})
3f	281 (M^+, 1); 178 (26); 91 (100)	1.80 (m, 2H, 2-CH_2), 2.55 (t, 2H, J = 6, 3-CH_2), 3.10 (d, 2H, J = 5, $NC\underline{H}_2CH$=), 3.50 (s, 2H, $C\underline{H}_2Ph$), 3.55 (t, 2H, J = 5, 1-CH_2), 4.25 (s, 1H, OH), 5.90 (dt, 1H, J = 16, 5, $CH_2C\underline{H}$=CH), 6.35 (d, 1H, J = 16, CH=$C\underline{H}$Ph), 7.20 (m, 10H_{arom})
3g	255 (M^+, 1); 178 (31); 91 (100)	1.75 (m, 2H, 2-CH_2), 2.60 (t, 2H, J = 6, 3-CH_2), 3.60 [s, 4H, $(C\underline{H}_2Ph)_2$], 3.60 (t, 2H, J = 5.5, 1-CH_2), 3.80 (s, 1H, OH), 7.30 (m, 10H_{arom})
3h	285 (M^+, 1); 178 (22); 91 (100)	1.70 (m, 2H, 2-CH_2), 2.55 (t, 2H, J = 6, 3-CH_2), 3.50 (s, 2H, $C\underline{H}_2Ph$), 3.55 (s, 2H, $C\underline{H}_2Ar$), 3.60 (t, 2H, J = 5, 1-CH_2), 3.70 (s, 3H, OCH_3), 3.95 (s, 1H, OH), 6.80 (d, 2H, J = 8, *m*-H_{arom}), 7.15 (d, 2H, J = 8, *o*-H_{arom}), 7.25 (m, 5H_{arom})
4b	221 (M^+, 2); 134 (52); 91 (100)	0.95 (t, 3H, J = 6, $CH_2C\underline{H}_3$), 1.40–2.00 (m, 4H, 2-CH_2, $C\underline{H}_2CH_3$), 2.20 (s, 3H, NCH_3), 2.50 (t, 2H, J = 7, 3-CH_2), 3.35 (t, 2H, J = 6, OCH_2), 3.45 (t, 2H, J = 6, OCH_2), 3.50 (s, 2H, $C\underline{H}_2Ph$), 7.30 (m, 5H_{arom})
4c	249 (M^+, 1); 134 (48); 91 (100)	0.95 [d, 6H, J = 6, $CH(C\underline{H}_3)_2$], 1.35–2.00 [m, 5H, 2-CH_2, $CH_2C\underline{H}(CH_3)_2$], 2.20 (s, 3H, NCH_3), 2.40 (t, 2H, J = 7.5, 3-CH_2), 3.40 (m, 4H, CH_2OCH_2), 3.50 (s, 2H, $C\underline{H}_2Ph$), 7.25 (m, 5H_{arom})
4g	269 (M^+, 2); 134 (50); 91 (100)	1.90 (m, 2H, 2-CH_2), 2.20 (s, 3H, NCH_3), 2.40 (t, 2H, J = 7, 3-CH_2), 3.35 (s, 2H, $NC\underline{H}_2Ph$), 3.40 (t, 2H, J = 6.5, OCH_2), 4.30 (s, 2H, $OC\underline{H}_2Ph$), 7.25 (m, 10H_{arom})
4h	299 (M^+, 3); 134 (37); 91 (100)	1.85 (m, 2H, 2-CH_2), 2.10 (s, 3H, NCH_3), 2.40 (t, 2H, J = 7, 3-CH_2), 3.40 (t, 2H, J = 6.5, OCH_2), 3.40 (s, 2H, $NC\underline{H}_2Ph$), 3.70 (s, 3H, OCH_3), 4.30 (s, 2H, $OC\underline{H}_2Ar$), 6.85 (d, 2H, J = 8, *m*-H_{arom}), 7.15 (d, 2H, J = 8, *o*-H_{arom}), 7.25 (m, 5H_{arom})

[a] Recorded on a Hewlett-Packard 5988A mass spectrometer.
[b] Recorded on a Bruker AC80 at 80 MHz; $CDCl_3$ for **1a–h**, **3a–h**, and **4b–h**; D_2O for **2b–h**.

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