Tetrahedron Vol. 40, No. 1, pp. 215 to 220, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd.

A NOVEL APPROACH TO 4-BENZYLISOQUINOLINES

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(*Received in Germany* 26 *June* 1983)

Abstract - The reaction of quinone methides with 3.4-dihydroisoquinoline or isoquinoline leads to benzylisoquinoline derivatives. NMR and ms investigations as well as chemical degradation prove that benzylation takes place at C-4 of the isoquinoline nucleus. Spectroscopic data are given for all new compounds.

Introduction

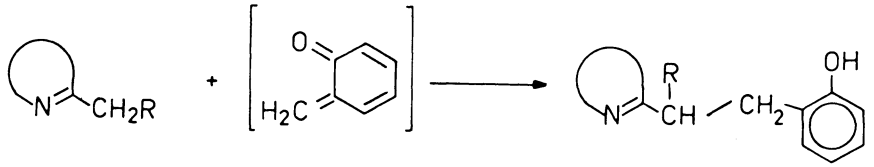
Quaternary isoquinolinium salts can be alkylated in the presence of an aromatic aldehyde under reductive conditions (Grewe-Bobitt-reaction[1)]), 1.2-dihydroisoquinolines react in acidified alcoholic solution with aromatic aldehydes (Dyke-reaction[2)]), to yield 4-benzylisoquinoline derivatives.

Results and discussion

According to v. Standtmann[3)] 6.7-dimethoxy-3.4-dihydroisoquinoline and o-naphthoquinone methide form a 1:1-adduct with 1.3-oxazine structure. Structural assignment was based on elemental analyses and absence of an OH-band in the IR- and of the phenolic proton signal in the NMR-spectrum, respectively. Recently we have shown, that o- and p-benzoquinone methides 1 are alkylated by CH-acidic ketimines 2 of the Δ1-pyrroline, 3H-indole and 3.4-dihydroisoquinoline type to yield hydroxybenzyl derivatives 3[4)] (fig. 1).

When o-hydroxybenzyl alcohol is heated with an excess of 3.4-dihydroisoquinoline in a sealed tube, a benzylated aromatic isoquinoline derivative 4 of the molecular formula $C_{16}H_{13}NO$ is obtained. Mass spectrometric investigations on adducts of type 3 indicate, that the $[M-C_7H_6O]^{+\cdot}$-ion is not the result of a retro-Diels-Alder-reaction (as expected for dihydro-1.3-oxazines[5)]), this fragmentation, however, includes hydrogen transfer from the OH-group to the heterocyclic nitrogen atom[6)]. Therefore, the intensive peak at m/z 129 in the mass spectrum of 4 is not of conclusive evidence for an oxazine structure. The OH-stretching vibration in the IR-spectrum, and the NMR-spectrum displaying two singlets at 9.15 and 8.41 ppm for the C-1 and C-3 isoquinoline protons[7,8)] and a singlet at 4.41 ppm for the benzylic group are incompatible with a dihydrooxazine structure for 4a (table 1). The ^{13}C-NMR data of 4a and 4b (table 2) are in accordance with the proposed 4-benzylisoquinoline structure, too (fig. 2).

π-Electron density calculations[9)] did not succeed in predicting unequivocally the site of benzylation in the isoquinoline system, as the C-4, C-6, and C-8 values are very similar.



2 1 3

Fig.1

Further information on the constitution of 4 is gathered by converting 4 to 5 via quaternization and reduction. Benzylation at the aromatic nucleus can be excluded in as much as the singlet for the benzylic protons in 4 becomes part of a complex ABCDE-system in the NMR-spectrum of 5. The C-1 protons in 5a and 5b are nonequivalent and form AB-patterns with coupling constants of 15.65 and 14.82 Hz (table 1); coupling constants and chemical shifts (table 1) are in close agreement with those of reported compounds[10].

First it seemed difficult to make a structural assignment by means of the ms fragmentation of 4a and 4b as either loses unexpectedly the ortho substituent from the molecular ion with high intensity (43, 100 % rel. intensity, resp.). Corresponding to literature the dominant feature for 1-, 3- or 4-benzyltetrahydroisoquinolines is benzyl fragmentation which usually leads to the base peak[11]. The mass spectra of our tetrahydroisoquinoline derivatives 5a/5b, however, are characterized by an intensive peak for the molecular ion besides signals for a retrograde Diels-Alder reaction, fragments preceded by migration of the hydroxyl proton and loss of the ortho-substituents; benzyl fragmentation occurs with low intensity only. Likewise, loss of ortho substituents takes place with comparable intensity using 1-o-chlorobenzyl- and 1-o-methoxybenzyl-naphthaline (9, 10; experimental section) as model compounds. So we propose an intramolecular radicalic aromatic substitution[12] (in ortho or peri position) for the observed ms elimination of ortho-substituents in the isoquinoline derivatives 4 and 5.‡

Hofmann degradation of 5b to 6b together with the listed NMR (table 1) and ms data (experimental section) are of convincing evidence for the reaction at C-4 of the isoquinoline nucleus. The ^{13}C-NMR data of 6b (two triplets in the sp^3 and one triplet in the sp^2 region) unambigiously rule out benzylation at C-1 or C-3 (table 2).

Consequently the benzylation described proceeds via an electrophilic substitution at the isoquinoline, which is formed by dismutation of the 3.4-dihydroisoquinoline. This well known dismutation[13] can be observed by heating the 3.4-dihydroisoquinoline up to 170° without the quinone methide precursor. Using isoquinoline as educt, compound 4a was obtained in good yield (fig. 3), too.

Starting with 4-hydroxybenzyl alcohol isoquinoline 7 (m.p. found 234°, lit.[14] 238°C) was synthesized analogously to 4. In contrast to

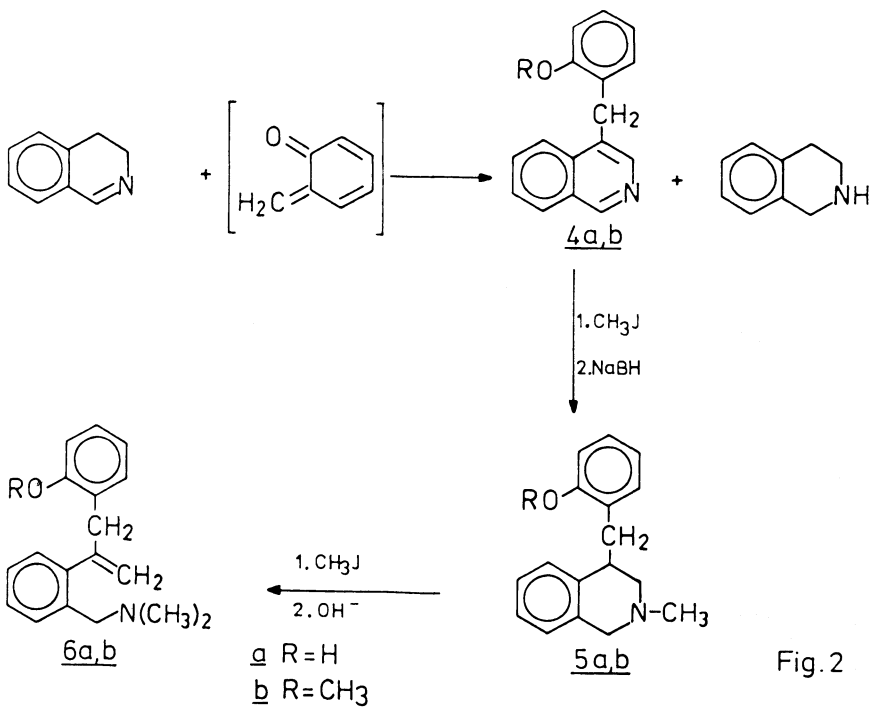
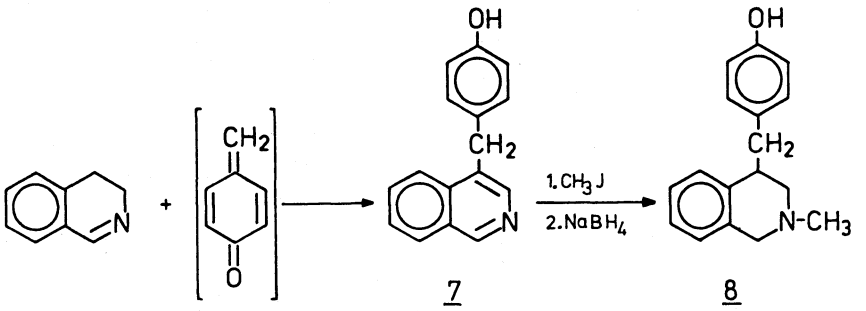


Fig. 2

‡ A detailed mechanistic study on o-substituted benzyl-quinolines, isoquinolines and naphthalines and their tetrahydro-derivatives is under work.

4a no $[M-C_7H_6O]$-ion was found in the mass spectrum of 7, whereas the ion at m/z = 234 $[M-H]^+$ gives rise to the base peak. The additional spectroscopic data of the tetrahydroisoquinolines 5 and 8 resemble each other closely and are given in detail in the experimental section. These results point out, that quinone methides, which can be generated in situ, are suitable compounds for benzylation of CH-acidic ketimines at the exo- or endocyclic α-C-Atom[4] or of isoquinolines at position C-4, thus making available a convenient synthesis for 1-β-phenethyl or 4-benzylisoquinoline derivatives.



7 8

Fig. 3

Table 1: ^{1}H-NMR, 250 MHz, $CDCl_3$, T = 297 K

	H1	H3	H4	CH_2	NCH_3	$N(CH_3)_2$	OCH_3
4a	9.15	8.41		4.41			
5a	δ_A = 4.14 δ_B = 3.42 δ_{AB} = 15.62 Hz	2.98 - (A B C D E - system)		2.32	2.43		
4b	9.16	8.36		4.36			3.89
5b	δ_A = 3.75 δ_B = 3.37 δ_{AB} = 14.82 Hz	3.19 - (A B C D E - system)		2.29			3.87
6b	3.44	δ_A = 4.89 δ_B = 4.84 J_{AB} = 2.02 Hz $^4J_{cis}$ = 1.93 Hz $^4J_{trans}$ = 1.23 Hz		3.60 (broad)		2.21	3.76

Table 2: ^{13}C-NMR, 22.63 MHz, $CDCl_3$, T = 308 K

	C1	C3	C4	CH_2	C2'	NCH_3	$N(CH_3)_2$	OCH_3
4a (DMSO-d_6)	151.09 d	143.08 d	*	29.08 t	154.80 s			
5a	57.42 t	53.94 t	40.46 d	37.66 t	156.65 t	46.25 q		
4b	151.44 d	143.71 d	*	29.71 t	157.01 s			55.27 q
5b	58.69 t°	56.56 t°	38.73 d	37.64 t	157.87 s	46.24 q		55.21 q
6b	60.74 t	114.29 t	*	38.91 t	157.61 s		45.36 q	54.98 q

*not assigned; °assignments are uncertain and could be reversed.

Experimental

Apparatus: Mp (Tottoli apparatus, uncorr.); IR spectra: Beckman Acculab III; UV spectra: Kontron 810; NMR spectra: ^{1}H-NMR spectra (compounds 4, 5, 6) were obtained at 24°C in the PFT mode using 32 K data points for the Bruker WM 250 spectrometer, operating at 250.13 MHz. The digit resolution was 0.134 to 0.196 Hz/data point. ^{13}C-NMR measurements were performed with a sweep of 4800 Hz at 36°C in the PFT mode on a Bruker WH 90 spectrometer. under noise and off-resonance decoupling, operating at 22.63 MHz. For the FID 8 K data points were used by zero filling with 8 K. Chemical shifts in all cases are reported in δ units from the internal standard TMS in $CDCl_3$ or DMSO-d_6. NMR spectra of compounds 7, 8 were obtained using the Varian EM 390 (90 MHz) spectrometer. Mass spectra: Varian MAT CH 5 and 311 A, 70 eV, direct insertion-probe. Microanalyses: Microanalytical laboratory, Universität Regensburg.

4-(o-Hydroxybenzyl)-isoquinoline 4a

10 mmol 3.4-dihydroisoquinoline and 2 mmol o-hydroxybenzyl alcohol were heated in a sealed tube at 170°C for 8 h.

The excess imine is distilled off with a Kugelrohr apparatus, the residue can be purified by column chromatography (SiO_2, ether, R_f = 0.6), yield 55 %, mp 220° ($CHCl_3$/ethyl acetate 1 : 2). $C_{16}H_{13}NO$ (235.3) Calc.: C 81.7 H 5.57 N 5.9, Found: C 81.8 H 5.55 N 5.9. IR (KBR): 3420 cm^{-1} (OH). UV (MeOH): λ_{max} (log ε) = 322 (3.68), 309 (3.55), 284 (sh), 274 (3.78), 218 (4.75), 203 (sh). MS: m/z (rel. int.) = 235 (100 % $M^{+\cdot}$), 234 (35 % $M^{+\cdot}$-H), 218 (43 % $M^{+\cdot}$-OH), *202.23), 129 (93 % C_9H_7N). ^{1}H-NMR ($CDCl_3$): δ = 4.41 (s, 2H, CH_2), 6.76-7.12 (m, 4H, H3'-H6'), 7.57-8.11 (m, 4H, H5-H8), 6.5-8.5 (br., 1H, OH), 8.41 (s, 1H, H3), 9.15 (s, 1H, H1). ^{13}C-NMR (DMSO-d_6): δ = 29.08 (t, CH_2), 115.14, 119.03, 123.25, 127.03, 127.27, 128.02, 129.86, 130.33 (d, $C_{arom.}$, not assigned), 125.90, 128.02, 130.05, 134.19 (s, $C_{arom.}$, not assigned), 143.08 (d, C3), 151.09 (d, C1), 154.80 (s, C2').

4-(o-Methoxybenzyl)-isoquinoline 4b

4a dissolved in MeOH was methylated with a 5 fold excess of CH_2N_2. 4b was separated from unreacted 4a by column chromatography (SiO_2, ether, R_f = 0.6), yield 67 %, mp. 84°C (MeOH). $C_{17}H_{15}NO$ (249.3) MS (high resolution) Calc. 249.11536, Found: 249.11544. UV (MeOH) λ_{max} (log ε) = 323 (3.51), 310 (3.39), 273 (3.62), 217 nm (4.60). MS: m/z (rel. Int.) = 249 (86 % $M^{+\cdot}$) 234 (22 % $M^{+\cdot}$-CH_3), 218 (100 % $M^{+\cdot}$-OCH_3, *190.86), 217 (30 %, 218-H), 143 (25 % $C_{10}H_9N$), 130 (27 % C_9H_8N). ^{1}H-NMR ($CDCl_3$): δ = 3.89 (s, 3H, OCH_3), 4.36 (s, 2H, CH_2), 6.76-7.23 (m, 4H, H3'-H6'), 7.54-7.99 (m, 4H, H5-H8), 8.36 (s, 1H, H3), 9.16 (s, 1H, H1). ^{13}C-NMR ($CDCl_3$): δ = 29.71 (t, CH_2), 55.27 (q, OCH_3), 110.25 (d, C3'), 120.28, 123.44, 126.68, 127.54, 128.00, 129.82, 130.08 (d, $C_{arom.}$, not assigned), 127.92, 128.42, 129.71, 134.98 (s, $C_{arom.}$, not assigned), 143.71 (d, C3), 151.44 (d, C1), 157.01 (s, C2').

N-Methyl-4-(o-hydroxybenzyl)-1.2.3.4-tetrahydroisoquinoline 5a

80 mg (0.34 mmol) 4a are refluxed in 1 ml CH_3J for 15 h. The precipitated unpurified salt was reduced with a ten fold excess $NaBH_4$ in 90 % ethanol. The excess of $NaBH_4$ was destroyed by 2 N CH_3COOH; after adding water the reaction mixture was extracted with $CHCl_3$ at p_H 8 - 9. Yield 75 % (65 mg) 5, mp 154°C (ether/ethyl acetate 1 : 1).

$C_{17}H_{19}NO$ (253.3) IR (KBr): 3430 cm^{-1} (OH). UV (MeOH): λ_{max} (log ε) = 281 (sh), 273 (3.53), 214 (sh), 204 nm (4.48). MS: m/z (rel. int.) = 253 (100 % $M^{+\cdot}$), 252 (30 % $M^{+\cdot}$-H), 236 (8 % $M^{+\cdot}$-OH, *220.14), 210 (6 % $M^{+\cdot}$-$CH_3N{=}CH_2$, RDA), 209 (7 %), 195 (36 % $C_{14}H_{11}O$), 159 (28 % $M^{+\cdot}$-C_6H_5OH, *99.92), 147 (70 % $M^{+\cdot}$-C_7H_6O, *25.41), 146 (32 %), 145 (42 %), 144 (86 %). ^{1}H-NMR ($CDCl_3$): δ = 2.32-2.98 (m, 5H, CH_2, H_3, H4, ABCDE-system, not analyzed), 3.42, 4.16 (AB-system, 2H, J = 15.6 Hz, H1A, H1B), 6.82-7.24 (m, 8H, $H_{arom.}$), 8.6-9.6 (br, 1H, OH). ^{13}C-NMR ($CDCl_3$): δ = 37.66 (t, CH_2), 40.46 (d, C4), 46.24 (q, NCH_3), 53.94 (t, C3), 57.42 (t, C1), 117.09, 119.99, 126.29, 126.42, 126.42, 127.67, 127.90, 130.31 (d, $C_{arom.}$, not assigned), 126.29, 132.64, 138.50 (s, $C_{arom.}$, not assigned), 156.65 (s, C2').

N-Methyl-4-(o-methoxybenzyl)-1.2.3.4-tetrahydroisoquinoline 5b

According to 5a compound 5b was synthesized from 4b. 5b was obtained with 67 % as pale yellow oil after column chromatography (SiO_2, CH_2Cl_2, followed by ether, R_f (ether) = 0.7) and Kugelrohr distillation (10^{-2} Torr, 200°). $C_{18}H_{21}NO$ (267.3). UV (MeOH): λ_{max} (log ε) =

272 (3.54), 247 (3.31), 209 nm (4.31). MS: m/z (rel. int.) = 267 (66 % $M^{+\cdot}$) 266 (36 % $M^{+\cdot}$-H), 252 (12 % $M^{+\cdot}$-CH_3), 236 (20 % $M^{+\cdot}$-OCH_3, *208.60), 224 (6 % $M^{+\cdot}$-$H_3CN{=}CH_2$, RDA, *187.93), 209 (34 %, 224-CH_3), 159 (71 % $M^{+\cdot}$-$C_6H_5OCH_3$, *94.69), 146 (33 % $M^{+\cdot}$-C_8H_9O), 145 (58 % 146-H), 144 (100 % 146-2H, *142.03). ^{1}H-NMR ($CDCl_3$): δ =2.29-3.19 (m; 5H, CH_2, H3, H4, ABCDE-system, not analyzed), 2.39 (s, NCH_3), 3.37, 3.75 (AB-system, 2H, J = 14.82 Hz, H1A, A1B), 3.87 (s, OCH_3), 6.87-7.31 (m, 8H, $H_{arom.}$). ^{13}C-NMR ($CDCl_3$): δ = 37.64 (t, CH_2), 38.73 (d, C4), 46.24 (q, NCH_3), 55.21 (q, OCH_3), 56.56, 58.69 (t, C1 and C3, not assigned), 110.32 (d, C3'), 120.23, 125.57, 126.03, 126.14, 127.33, 128.52, 131.32 (d, $C_{arom.}$, not assigned), 129.46, 134.85, 138.68 (s, $C_{arom.}$, not assigned), 157.86 (s, C2').

N.N-Dimethyl-2[1-(2-hydroxybenzyl)-ethen-1-yl]-benzylamine 6a

0.44g (1.74 mmol) 5a were heated with 0.57g (4 mmol) CH_3J in 15 ml dry acetone. After 8 h CH_3J and acetone were distilled off; the oily residue was dissolved in 80 % ethanol and then stirred with 1 g basic ion-exchange resin (Merck 4767) for 48 h. The solvent was evaporated and the remaining powder recrystallized from ethylacetate/ethanol (5 : 1); yield 0.34 g (73 %), m.p. 138° (decomp.).

$C_{18}H_{21}NO$ (267.2) MS (high resolution) Calc.: 267.16231, Found 267.16228. IR (KBr): 3380 cm^{-1} (OH). UV (MeOH): λ_{max} (log ε) = 275 (3.43), 207 nm(4.20). MS: m/z (rel. int.) = 267 (96 % $M^{+\cdot}$), 252 (10 % $M^{+\cdot}$-CH_3), 222 (100 % $M^{+\cdot}$-C_2H_7N), 207 (25 % 222-CH_3).

N.N-Dimethyl-2-[1-(2-methoxybenzyl)-ethen-1-yl]-amine 6b

The method given for 6a was used to prepare 6b; yield 74 %, pale yellow oil, purified by column chromatography (Al_2O_3 neutrale, activity II, ether; R_f = 0.9).

$C_{19}H_{23}NO$ (281.2) MS (high resolution) Calc.: 281.17796, Found: 281.17802. IR (mull): 1610 cm^{-1} (C=C). UV (MeOH): λ_{max} (log ε) = 278 (3.39), 272 (3.44), 205 nm (4.46). MS: m/z (rel. int.) = 281 (90 % $M^{+\cdot}$), 266 (45 % $M^{+\cdot}$-CH_3), 250 (15 % $M^{+\cdot}$-OCH_3), 237 (66 % $M^{+\cdot}$-$NHMe_2$, *198.21), 129 (69 % $C_{10}H_9$), 121 (92 % C_8H_9O). ^{1}H-NMR ($CDCl_3$): δ = 2.21 (s, 6H, $N(CH_3)_2$), 3.44 (s, 2H, H4), 3.60 (broad), 4.84, 4.89 (ABX_2-system, 4H, J = 2.02 Hz, $^4J_{cis}$ = 1.93 Hz, $^4J_{trans}$ = 1.23 Hz, CH_2, H3A, H3B; decoupling at δ = 3.60 leads to an AB-system for the C3-protons), 6.83, 7.49 (m, 8H, $H_{arom.}$). ^{13}C-NMR ($CDCl_3$): δ = 38.91 (t, CH_2). 45.36 (q, $N(CH_3)_2$), 54.98 (q, OCH_3), 60.74 (t, C1), 110.43 (d, C3'), 114.29 (t, C3), 120.88, 126.06, 126.63, 127.48, 128.37, 128.94, 131.14 (d, $C_{arom.}$, not assigned), 127.33, 136.22, 143.32, 148.27 (s, 3 $C_{arom.}$ and C4, not assigned), 157.61 (s, C2').

4-(p-Hydroxybenzyl)-isoquinoline 7

Analogous to 4 compound 7 was prepared; yield 43 %, mp. 234°C (lit. 238°C[14]; n-pentyl alcohol).

$C_{16}H_{13}NO$ (235.3). Calc.: 81.7 H 5.57 N 5.9; Found: C 81.5 H 5.66 N 5.7. IR (KBr): 3410 cm^{-1} (OH). UV (MeOH): λ_{max} (log ε) = 322.5 (3.62), 309 (3.51), 285 (sh), 272.5 (3.73), 217.5 nm (4.70). MS: m/z (rel. int.) = 235 (94 % $M^{+\cdot}$), 234 (100 % $M^{+\cdot}$-H). ^{1}H-NMR (DMSO-d_6, 90 MHz): δ(ppm) = 4.32 (s, 2H, CH_2), 6.73, 7.11 (AB-system, J_{AB} = 9.0Hz, 4 $H_{arom.}$) 7.63-8.36 (m, H5-H8), 8.47 (s, 1H, H3), 9.26 (s, 1H, H1).

N-Methyl-4-(p-hydroxybenzyl)-1.2.3.4-tetrahydroisoquinoline 8

8 was synthesized as described for 5. Yield 70 %, mp. 159° (ethyl acetate).

$C_{17}H_{19}NO$ (253.3) IR (KBr): 3380 cm^{-1} (OH). UV (MeOH): λ_{max} (log ε) = 279.5 (sh), 272.5 (3.03), 225 (sh), 204 nm (4.38). MS: m/z (rel. int.) = 253 (47 % $M^{+\cdot}$), 252 (28 % $M^{+\cdot}$-H), 210 (6 % $M^{+\cdot}$-$CH_3N{=}CH_2$, RDA), 209 (9 %), 195 (34 % 210-CH_3, *99.92), 158 (20 % 159-H), 146 (34 % $M^{+\cdot}$-$CH_2C_6H_4OH$), 145 (77 %), 144 (100 % 146-H, *142.03), 116 (31 %), 107 (17 %). ^{1}H-NMR ($CDCl_3$, 90 MHz): δ (ppm) = 2.39 (s, 3H, CH_3), 2.46-3.14 (m, 5H, $2CH_2$, CH), 3.50, 3.71 (AB-system, J_{AB} = 14.5 Hz, 2H, C1), 6.68, 7.03 (AB-system, J_{AB} = 8.5 Hz, 4$H_{arom.}$), 7.00-7.72 (m, 4H, H5-H8).

1-o-Chlorobenzyl-naphthalene 9 and 1-o-Methoxybenzyl-naphthalene 10

Both compounds were prepared analogous to [15] starting with naphthalene, o-chlorobenzylchloride and o-methoxybenzylbromide, resp.

9 $C_{17}H_{13}Cl$ (252.74) MS: m/z (rel. int.) = 252 (69 % $M^{+\cdot}$); 217 (100 % $M^{+\cdot}$-Cl, *186.86), 216 (30 %), 215 (55 %), 213 (13 %), 202 (33 % 217-CH_3, *188.04).

10 $C_{18}H_{16}O$ (248.31) MS: m/z (rel. int.) = 248 (100 % $M^{+\cdot}$), 247 (14 % $M^{+\cdot}$-H), 217 (40 % $M^{+\cdot}$-OCH_3), 216 (14 %), 215 (42 %), 213 (9 %), 202 (22 %, 217-CH_3).

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