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Electron Impact Induced Fragmentation of Aromatic Alkoxyimines II [5]. Formation and Transformation of Heterocyclic Radical Cations in the Gas Phase[a]

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Summary. The molecular ion **1** of *N*-(*n*-propoxy)benzaldimine **I** rearranges by an 1,5-H-shift to the δ-distonic ion **2** which subsequently cyclizes to the α-distonic ion **3**. Homolytic cleavage of the N–O bond in **3** results in the δ-distonic ion **4** which expels CH_2O leading to the β-distonic ion **5**. Ion **5** is also formed from the molecular ions of tetrahydrooxazines **II** and **III** and from $M^{+\bullet}$ of phenylazetidine **IVa**. In a subsequent step, ion **5** cyclizes to the *N*-protonated 3,4-dihydroisoquinolinium ion **6**. The syntheses of **II**–**IV** and their derivatives are described.

Keywords. Alkoxybenzaldimines; Tetrahydrooxazines; 2-Phenylazetidines; Mass spectrometry; *Longevialle* migration.

Introduction

Many *N*-alkoxyimines are pharmacologically active. Fluvoxamine, a selective serotonin reuptake inhibitor (see *e.g.* Ref. [1a]), comprises a $C{=}N{-}O{-}(CH_2)_2{-}NH_2$ increment, and the antibacterial cephalosporins cefuroxime, cefotaxime, ceftizoxime, *e.g.* [1a, 1b] are *N*-methoxyimines. In 1971, *Cooks et al.* [2] studied the fragmentations of alkoxybenzaldimine radical cations. Methoxy derivatives lose 27 mu (HCN) after migration of OCH_3 and 31 mu ($^{\bullet}OCH_3$) directly from $M^{+\bullet}$, whereas in the homologous ethyl ether, a neutral loss of C_2H_4 occurs. More important, the authors discovered that $M^{+\bullet}$ (**1**) of *N*-(*n*-propoxy)benzaldimine (**I**) shows a 1,5-H-shift of one of the γ-CH_3 hydrogen atoms, thus affording the δ-distonic ion[1] **2**

[a] Dedicated to Prof. Dr. *J. Knabe*, Saarbrücken, Germany

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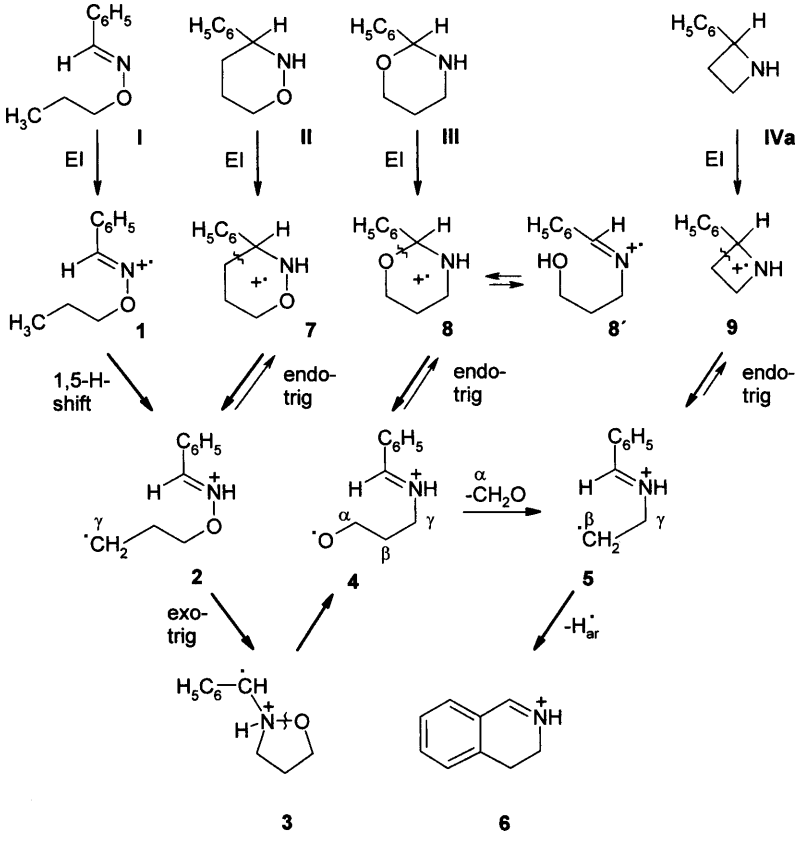
[1] Distonic radical ions are ions with separated radical and charge sites (Radom L, Bouma WJ, Nobes RH, Yates BF (1984) Pure Appl Chem **56**: 1831)

which expels formaldehyde (30 mu) and furnishes the β-distonic ion **5**, presumably *via* a four-membered transition state or intermediate. *Grützmacher et al.* [3] have shown that *Longevialle* migration [4] along the propoxy chain of the benzaldimine moiety within ion **2** takes place, thus affording the δ-distonic ion **4** which in turn leads to the β-distonic ion **5** by loss of CH_2O. Ion **5** was verified by *ab initio* calculations of the stationary points of the minimum energy reaction path [3] and proved to be the corner stone of subsequent reactions leading to the fragment $[M^{+\bullet}–CH_2O–H^{\bullet}]^+$, which in contrast to *Cooks* [2] was identified by us as the *N*-protonated 3,4-dihydroisoquinolinium ion **6** [5]. The $[M–CH_2O–H^{\bullet}]^+$ ion does not arise by loss of $H^{\bullet}$ from the γ-CH_2 increment [2, 5] of ion **5**, but by elimination of $H^{\bullet}$ from the aromatic ring. If this aromatic group is deuterated or halogenated (Cl, Br, I), deuterium or halogen atoms are lost [5].

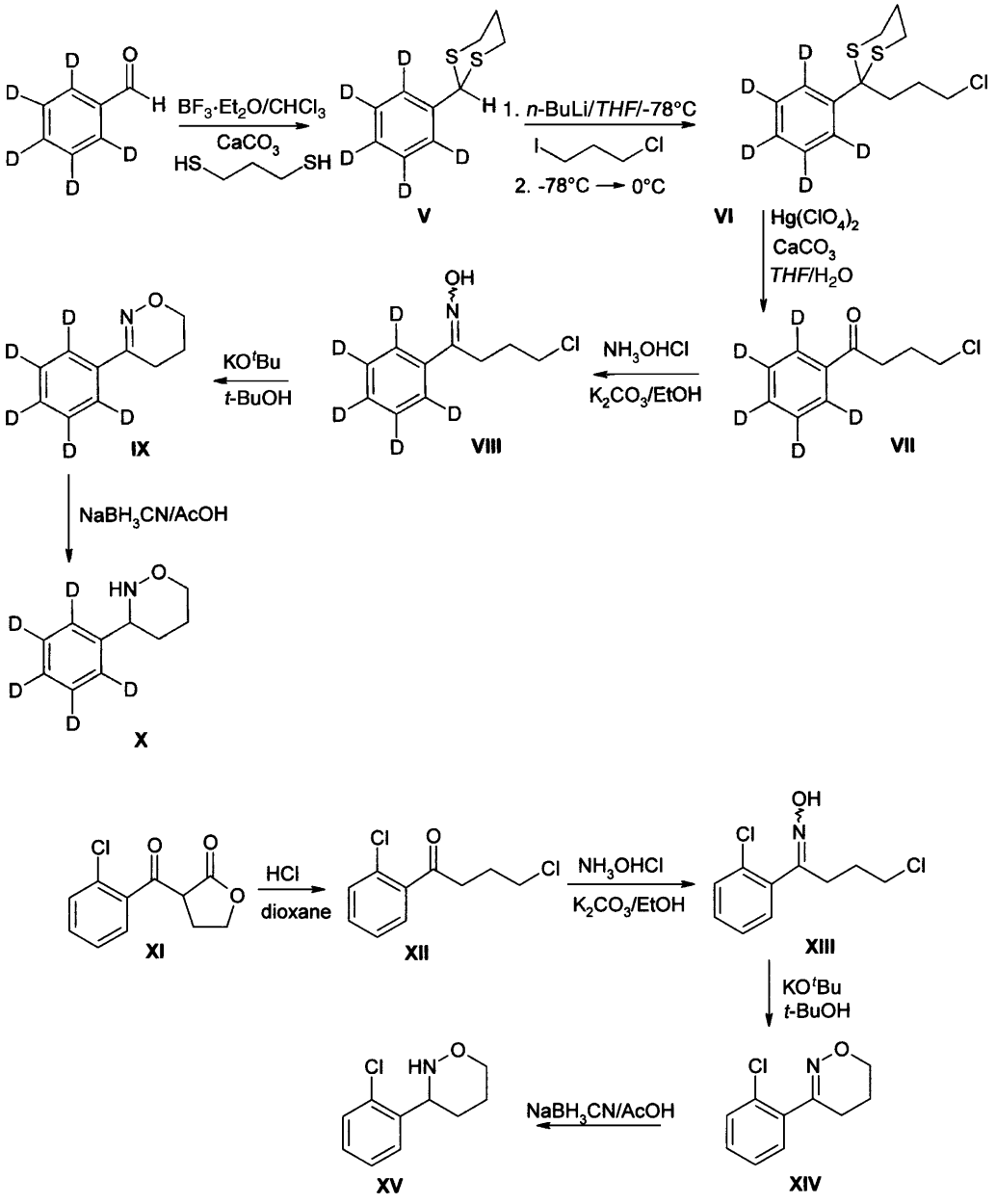
Results and Discussion

Cooks' proposal [2] includes the connection of the outside parts of **2** after loss of CH_2O, affording the β-distonic ion **5**. This interesting mechanistic concept motivated us to consider whether transformation of ion **2** into **4** could start by attack of the terminal $CH_2^{\bullet}$ group of **2** onto its $C{=}NH^+$ double bond in the course of an *endo-trig* radical cyclization leading to 3-phenyl-3,4,5,6-tetrahydro-1,2-oxazine



Scheme 1. Isomerization and reaction of the molecular ions **1**, **7**, **8**, and **9**

radical cation **7**. Formation of the isomeric 2-phenyl-3,4,5,6-tetrahydro-1,3-oxazine radical cation **8**, however, might proceed stepwise, starting with an *exo-trig* attack of the terminal $CH_2^{\bullet}$ group of **2** onto the $C{=}NH^+$ increment creating the α-distonic ion **3** [3], followed by N–O cleavage to ion **4**. At this stage, the terminal $CH_2{-}O^{\bullet}$ group of **4** attacks the C-atom of its $C{=}NH^+$ increment affording **8**. As stated by *Vainiotalo et al.* [6], **8** and its open chain tautomer *N*-(3-hydroxypropyl)-benzaldimine radical cation **8′** equilibrate in the gas phase. Therefore, we compared



Scheme 2. Synthesis of 3-phenyl-tetrahydro-1,2-oxazines

the EI mass spectra of **8** (as a source of **8′**) and **7** and that of the azetidine radical cation **9**, because these ions are potential sources of ion **5**.

For this purpose, the tetrahydro-1,2-oxazine **II**, its pentadeuterophenyl and its 2-chlorophenyl derivatives, the 1,3-oxazine **III**, the azetidine **IVa**, and its deuterated and chlorinated derivatives were synthesized.

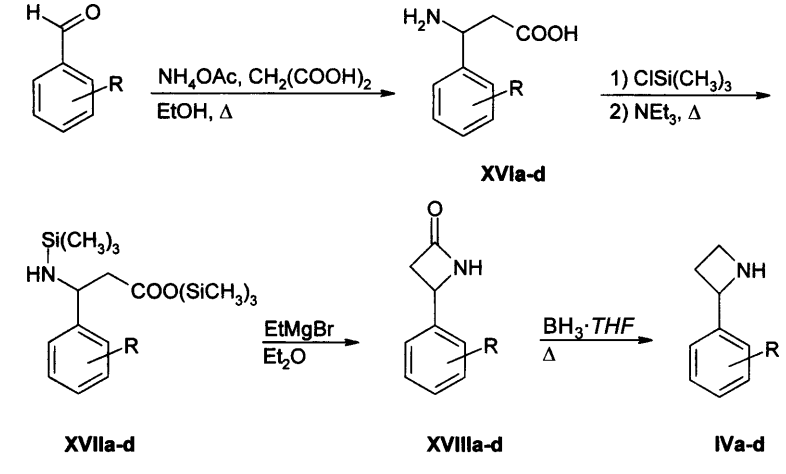
Syntheses of tetrahydrooxazines

3-Phenyl-5,6-dihydro-4*H*-1,2-oxazine was prepared according to *Ellames et al*. [7] and reduced to 3-phenyl-3,4,5,6-tetrahydro-1,2-oxazine (**II**) by $NaBH_3CN$ following a method of *Reissig* [8]. For the synthesis of 2-phenyl-3,4,5,6-tetrahydro-1,3-oxazine (**III**), see Ref. [6] and the literature cited there.

Pentadeuterobenzaldehyde was converted to its dithiane derivative **V** for *umpolung*, which gave dithiane **VI** with 3-chloropropyl-1-iodide after deprotonation. This dithiane was cleaved with $Hg(ClO_4)_2$ [9], and the resulting butyroketone **VII** was converted into its oxime **VIII**. Ring closure afforded the corresponding dihydro-1,2-oxazine **IX** which was reduced to **X** (*vide supra*). For the synthesis of 3-(2-chlorophenyl)-3,4,5,6-tetrahydro-1,2-oxazine (**XV**), 3-(2-chlorobenzoyl)-2,3,4,5-tetrahydrofuran-2-one (**XI**) [10] was converted to 4-chloro-1-(2-chlorophenyl)butan-1-one (**XII**) [11] by heating with HCl. For the further steps to product **XV**, see above.

Syntheses of 2-phenylazetidines

2-Phenylazetidine (**IVa**), its pentadeuterophenyl (**IVb**), its 2-chlorophenyl (**IVc**), and its 4-chlorophenyl derivative (**IVd**) were synthesized according to Scheme 3. Benzaldehyde, pentadeuterobenzaldehyde (obtained according to *Schlosser* [12]),



R	H	d_5	2-Cl	4-Cl
IV; XVI-XVIII	a	b	c	d

Scheme 3. Synthesis of 2-phenylazetidines

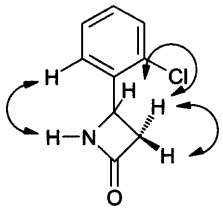


Fig. 1. ^{1}H, ^{1}H–NOE NMR spectrum of 4-(2-chlorophenyl)-2-azetidone (**XVIIIc**)

2-chloro, and 4-chlorobenzaldehyde, were converted to the corresponding racemic *β*-phenyl-*β*-aminopropionic acids **XVI**. Carboxyl- and *N*-trimethylsilylation (cf. **XVII**) [13], deprotonation by EtMgBr, and cyclization to the corresponding 4-phenyl-2-azetidinones **XVIII** were performed using Birkofer's procedure [13]. The structure of **XVIIIc** was additionally ascertained by ^{1}H, ^{1}H NOE spectroscopy (Fig. 1), because the analytical data – especially ^{1}H NMR – significantly differ from those described in Ref. [14]. The lactams **XVIII** were reduced to the azetidines **IV** by $BH_3 \cdot THF$ according to *Wells* [15].

Mass spectrometry

As expected, the isomeric phenyltetrahydrooxazines **II** and **III** (Scheme 1) gave different EI mass spectra, indicating that there is no (or only partial) isomerization in the ion source prior to fragmentation. On the other hand, both isomers lose CH_2O upon electron impact, and – more conclusive – the MIKE and the CAD spectra of the $(M–CH_2O)^{+\bullet}$ ions of **7** and **8** and the pertinent spectra of fragment ion **5** are virtually identical [3]. Moreover, the 3,4-dihydroisoquinolinium ion **6** is generated from both phenyloxazines by radical attack within ion **5** and subsequent

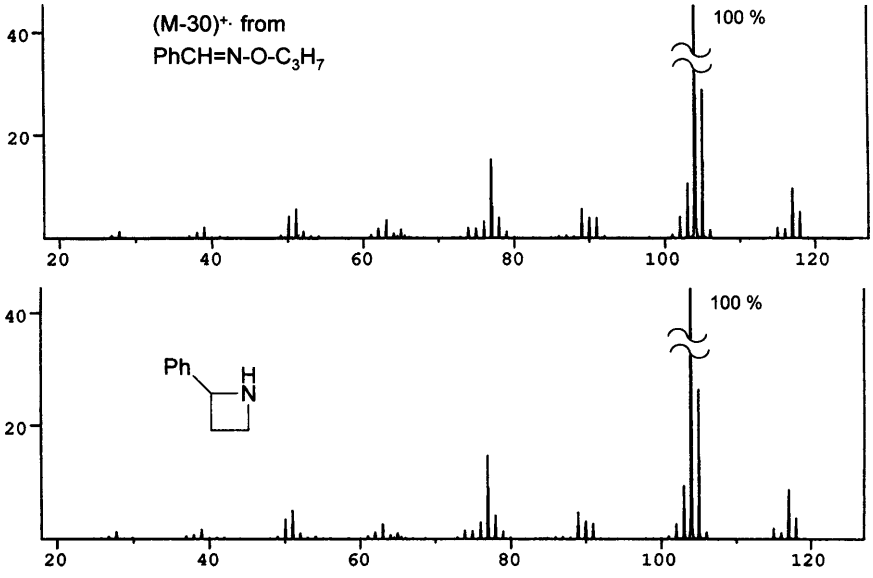


Fig. 2. CAD MS of $(M–CH_2O)^{+\bullet}$ ions from *N*-(*n*-propoxy)benzaldimine (**1**) and of 2-phenylazetidine (**9**) radical cations

loss of $H^{\bullet}$ (or $D^{\bullet}$, $Cl^{\bullet}$, respectively, if the phenyl increment of **5** carries these substituents) [5] as has been shown for the oxime ether **I** [5].

In the EI-MS (70 eV) of oxime ether **I**, a small but reproducible part of the ions at $m/z = 104$ was identified as C_8H_8 (styrene) by HRMS. This can be explained by cyclization of ion **5** to the 2-phenylazetidine radical cation **9** and subsequent 2 + 2-cycloreversion, forming a styrene radical cation and methyleneimine [16]. However, as indicated by computational data [3], only high energy species of ions **5** are able to cyclize to **9**.

In competition with 2 + 2-cycloreversion, the molecular ions **9** of **IVa** and those of its derivatives (Scheme 3) isomerize by ring cleavage to the (analogously substituted) distonic ions **5** (Scheme 1), which eliminate a $H^{\bullet}$ atom (or $D^{\bullet}$, $Cl^{\bullet}$, respectively, if appropriately substituted), thus forming **6**. Furthermore, the CAD spectra of the molecular ion **9** and of the $(M–CH_2O)^{\bullet+}$ ion from propoxybenzaldimine radical cation **1** are identical and verify an identical structure (or identical mixture of structures) of these ions shown as **5** (Fig. 2).

Experimental

Melting points were determined with a Reichert Thermovar melting point table and are not corrected. IR spectra were recorded with a Nicolet 510 FT-IR Spectrometer (KBr; films for liquids). ^{1}H NMR spectroscopy was performed with a Bruker NMR spectrometer WM 250 (250 MHz), using *TMS* as an internal standard. The δ-values of AB-systems were determined according to the rules of zero order spectra. Mass spectra were taken with a Varian MAT 95 MS (70 eV). Chromatography was performed on SiO_2 Merck No. 7734 Kieselgel 60 (70–230 mesh ASTM). The results of elemental analyses agreed favourably with the calculated values.

3-Phenyl-3,4,5,6-tetrahydro-2H-1,2-oxazine (**II**; $C_{10}H_{13}NO$)

To a solution of 3-phenyl-5,6-dihydro-4*H*-1,2-oxazine ([7]; 0.806 g, 5 mmol) in 15 cm^3 of AcOH, $NaBH_3CN$ (1.0 g, 15.9 mmol) was added with stirring. Stirring was continued for 6 h at room temperature. Then, 130 cm^3 of saturated Na_2CO_3 solution were added, and the mixture was extracted with EtOAc (2×100 cm^3). The combined organic phases were washed with saturated NaCl solution (2×50 cm^3), dried, and evaporated *in vacuo*. *Kugelrohr* distillation (oven temperature 70°C, 3.5 torr) afforded **II** (0.59 g, 72%) as a colourless oil.

EI-MS (70 eV) m/z (%) = 163 (57), 162 (9), 145 (8), 133 (11), 132 (41), 131 (13), 121 (10), 120 (15), 118 (14), 117 (25), 116 (9), 115 (14), 105 (33), 104 (100), 91 (30), 84 (24), 78 (23), 77 (34); EI-MS (12 eV): m/z (%) = 163 (100), 162 (12), 145 (9), 133 (21), 132 (52), 121 (9), 120 (7), 118 (11), 117 (8), 105 (22), 104 (49), 91 (4); HRMS: $m/z = 133$ ($C_9H_{11}N$); B/E ($M^{+\bullet} = 163$, 1st ffr[2]): m/z (%) = 162 (51), 133 (100), 132 (70), 121 (4), 120 (5), 119 (6), 118 (7), 105 (1), 104 (8); B/E ($(M–CH_2O)^{+\bullet} = 133$): m/z (%) = 132 (100), 118 (1), 105 (1), 104 (6); IR (film): $\nu = 3280$ (N–H) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.23–7.40$ (m, 5H, aromat.), 5.34 (s, 1H, NH, exch.), 4.00–4.15 and 3.80–3.92 (2 m, 3H, CHN and CH_2O), 1.70–2.00 (m, 4H, CH–C*H*$_2$–C*H*$_2$) ppm.

[2] 1st ffr: first field free region; *B*: magnetic field strength; *E*: electrostatic sector voltage; B/E linked scan gives all daugther cations from a selected cation (Chapman JR (1985) Practical Organic Mass Spectrometry, John Wiley & Sons, Chichester, p 145)

2-Pentadeuterophenyl-1,3-dithiane (**V**; $C_{10}H_7D_5S_2$)

Benzaldehyde-d_5 ([12]; 0.55 g, 5 mmol) was stirred with 1,3-propanedithiol (0.54 g, 5 mmol) and $CaCO_3$ (0.5 g, 5 mmol) in 5 cm^3 of $CHCl_3$ for 1 h in an ice/NaCl bath. $BF_3 \cdot Et_2O$ (0.2 cm^3, 1.6 mmol) was added, and stirring was continued for 15 min in the ice/NaCl bath and for 4 h at room temperature. Addition of $BF_3 \cdot Et_2O$ (0.2 cm^3, 1.6 mmol) and stirring at room temperature for 9 h were repeated. The mixture was diluted with 5 cm^3 of $CHCl_3$ and washed with H_2O (3×5 cm^3), 10% NaOH (3×5 cm^3), and again with H_2O (3×5 cm^3). After drying (K_2CO_3) and removing the solvent *in vacuo*, colourless crystals (0.86 g, 85%) were obtained.

M.p.: 72°C; IR (film): $\nu = 2275$ (=C–D) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 5.17$ (s, 1H, S_2CH), 2.88–3.15 (m, 4H, 2 SCH_2), 2.13–2.25 (m, 1H, CH_2–CH*H*–CH_2), 1.85–2.05 (m, 1H, CH_2–C*H*H–CH_2) ppm.

2-(3-Chloropropyl)-2-(pentadeuterophenyl)-1,3-dithiane (**VI**; $C_{13}H_{12}ClD_5S_2$)

To the solution of **V** (0.81 g, 4 mmol) in 20 cm^3 of absolute *THF*, *n*-BuLi (3.8 cm^3 of a 1.6 *M* solution in hexane) was added dropwise under N_2 at -78°C. After 1 h, a solution of 3-chloropropyl-1-iodide (0.82 g, 4 mmol) in 8 cm^3 of absolute *THF* was added. The cooling bath was allowed to reach 0°C, half saturated NH_4Cl solution (8 cm^3) was added, the organic phase was separated, and the aqueous phase was extracted with EtOAc (2×20 cm^3). The combined organic phases were washed with saturated NaCl solution (2×20 cm^3), dried (Na_2SO_4), and evaporated *in vacuo*. Column chromatography (CC; SiO_2; Et_2O:petroleum ether 40–60°C = 1:4) afforded **VI** (0.63 g, 56%) as a weakly yellow oil.

IR (film): $\nu = 2275$ (=C–D) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.40$ (t, $^3J = 6.5$ Hz, 2H, CH_2Cl), 2.65–2.78 (m, 4H, 2 SCH_2), 2.13–2.23 (m, 2H, CH_2), 1.90–2.02 (m, 2H, CH_2), 1.69–1.84 (m, 2H, CH_2–C*H*$_2$–CH_2) ppm.

4-Chloro-1-(pentadeuterophenyl)butan-1-one (**VII**; $C_{10}H_6ClD_5O$)

A suspension of **VI** (0.60 g, 2.16 mmol) and $CaCO_3$ (1.1 g, 11 mmol) in 9 cm^3 of *THF* and 1.2 cm^3 of H_2O was stirred with $Hg(ClO_4)_2$ (1.30 g, 3.25 mmol) for 5 min. Stirring was continued with additional $Hg(ClO_4)_2$ (0.20 g, 0.5 mmol) for 5 min. After addition of Et_2O (35 cm^3), the suspension was filtered through celite, the filter cake was washed thoroughly with Et_2O, the combined filtrates were washed with a saturated solution of $NaHCO_3$ (20 cm^3), H_2O (2×20 cm^3), and saturated NaCl solution (10 cm^3), dried (Na_2SO_4), and evaporated *in vacuo*. CC (SiO_2; Et_2O:petroleum ether 40–60°C = 1:1) afforded **VII** (0.3 g, 75%) as a colourless oil.

IR (film): $\nu = 2279$ (=C–D), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.69$ (t, $^3J = 6.2$ Hz, 2H, CH_2Cl) 3.19 (t, $^3J = 7.0$ Hz, 2H, O=C–CH_2), 2.19–2.30 (m, 2H, CH_2–C*H*$_2$–CH_2) ppm.

4-Chloro-1-(pentadeuterophenyl)butan-1-one oxime (**VIII**; $C_{10}H_7ClD_5NO$)

VIII was prepared from **VII** (0.28 g, 1.5 mmol) analogously to the non-deuterated compound [7] and further processed without purification.

3-(Pentadeuterophenyl)-5,6-dihydro-4H-1,2-oxazine (**IX**; $C_{10}H_6D_5NO$)

IX was prepared from crude **VIII** analogously to the non-deuterated compound [7]. Recrystallization from diisopropyl ether afforded **IX** (0.18 g, 72%) as colourless crystals.

M.p.: 71°C; IR (KBr): 2362, 2271 (=C–D) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.07$ (t, $^3J = 5.0$ Hz, 2H, OCH_2), 2.60 (t, $^3J = 6.8$ Hz, 2H, N=CCH_2), 2.07–2.18 (m, 2H, CH_2–C*H*$_2$–CH_2) ppm.

3-(Pentadeuterophenyl)-3,4,5,6-tetrahydro-2H-1,2-oxazine (**X**; $C_{10}H_8D_5NO$)

X was prepared analogously to the non-deuterated compound **II** starting from **IX** (0.166 g, 1.0 mmol). CC (SiO_2; CH_2Cl_2:EtOAc = 95:5) afforded **X** (0.081 g, 48%) as a colourless oil.

EI-MS (70 eV): m/z (%) = 168 (52), 167 (8), 150 (7), 138 (6), 137 (8), 136 (36), 126 (7), 124 (11), 122 (24), 121 (7), 120 (6), 119 (7), 110 (29), 109 (100), 96 (16), 86 (11), 83 (19), 82 (30); EI-MS (12 eV): m/z (%) = 168 (100), 150 (5), 138 (9), 137 (6), 136 (31), 126 (4), 124 (2), 123 (4), 122 (4), 110 (11), 109 (31); B/E ($M^{+\bullet}$ = 168, 1st ffr): m/z (%) = 167 (63), 138 (100), 137 (3), 136 (24), 126 (2), 125 (4), 124 (6), 123 (7), 110 (1), 109 (6); B/E ($(M–CH_2O)^{+\bullet}$ = 138): m/z (%) = 137 (11), 136 (100), 123 (1), 110 (1), 109 (19); IR (film): ν = 3278, 3115 (N–H), 2400, 2254 (=C–D) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.45 (br s, 1H, NH, exch.), 4.02–4.18 (m, 2H, OCH*H* and NCH), 3.80–3.94 (m, 1H, OC*H*H), 1.73–2.05 (m, 4H, OCH_2–CH_2–CH_2) ppm.

4-Chloro-1-(2-chlorophenyl)butan-1-one (**XII**; $C_{10}H_{10}Cl_2O$)

A solution of 3-(2-chlorobenzoyl)-2,3,4,5-tetrahydrofuran-2-one (**XI** [10]; 0.9 g, 4 mmol) in 4 cm^3 of dioxane was mixed with 8 cm^3 of concentrated HCl and refluxed for 1 h. The solution was diluted with H_2O (50 cm^3), extracted with Et_2O (4 × 20 cm^3), and the organic phase was washed with saturated $NaHCO_3$ solution (2 × 15 cm^3) and saturated NaCl solution (2 × 15 cm^3), dried, and evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2) afforded **XII** ([11]; 0.73 g, 84%) as a colourless oil.

^1H NMR ($CDCl_3$): δ = 7.30–7.52 (m, 4H, aromat.), 3.66 (t, ^3J = 6.3 Hz, 2H, CH_2Cl), 3.14 (t, ^3J = 7.0 Hz, 2H, O=CCH_2), 2.17–2.30 (m, 2H, CH_2–CH_2–CH_2) ppm.

*4-Chloro-1-(2-chlorophenyl)butane-1-one oxime (***XIII**; $C_{10}H_{11}Cl_2NO$)

XIII was prepared analogously to compound **VIII** from 0.54 g (2.5 mmol) **XII** and 0.52 g (7.5 mmol) hydroxylammonium chloride (reaction time: 24 h) and further used without purification.

3-(2-Chlorophenyl)-5,6-dihydro-4H-1,2-oxazine (**XIV**; $C_{10}H_{10}ClNO$)

XIV was prepared from crude **XIII** analogously to compound **IX** (reaction time: 50 min). CC (SiO_2; CH_2Cl_2:Et_2O = 9:1) led to 0.30 g (62%) of **XIV** as yellowish crystals.

M.p.: 69°C; IR (KBr): 1594 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.25–7.45 (m, 4H, aromat.), 4.13 (t, ^3J = 5.3 Hz, 2H, OCH_2), 2.54 (t, ^3J = 6.8 Hz, 2H, N=C–CH_2), 2.05–2.17 (m, 2H, CH_2–CH_2–CH_2) ppm.

3-(2-Chlorophenyl)-3,4,5,6-tetrahydro-2H-1,2-oxazine (**XV**; $C_{10}H_{12}ClNO$)

XV was prepared analogously to compound **X** from 0.195 g (1 mmol) of **XIV**. CC (SiO_2; CH_2Cl_2: Et_2O = 9:1) afforded **XV** (0.090 g, 45%) as a colourless oil.

EI-MS (70 eV): m/z (%) = 199 (16), 198 (9), 197 (53), 196 (10), 181 (1), 179 (2), 169 (5), 168 (9), 167 (16), 166 (23), 157 (2), 156 (3), 155 (6), 154 (7), 153 (3), 152 (8), 151 (5), 140 (35), 139 (38), 138 (100), 132 (16), 131 (3), 130 (14), 129 (9), 128 (6), 127 (8), 125 (15), 114 (4), 113 (3), 112 (11), 111 (5); EI-MS (12 eV): m/z (%) = 199 (32), 198 (14), 197 (100), 196 (12), 181 (1), 179 (3), 169 (8), 168 (11), 167 (26), 166 (28), 157 (1), 155 (5), 154 (3), 152 (6), 141 (9), 140 (21), 139 (30), 138 (56), 132 (21); B/E ($M^{+\bullet}$ (^{35}Cl) = 197, 1st ffr): m/z (%) = 196 (14), 167 (100), 166 (6), 156 (2), 155 (1), 154 (6), 153 (3), 140 (1), 138 (3), 132 (2); B/E ($(M–CH_2O)^{+\bullet}$, ^{35}Cl = 167): m/z (%) = 166 (100), 152 (1), 139 (1), 138 (24), 132 (28); IR (film): ν = 3276 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.17–7.50 (m, 4H, aromat.), 5.55 (s, 1H, NH, exch.), 4.52–4.63 (m, 1H, NCH), 4.02–4.13 (m, 1H, OCH*H*), 3.83–3.96 (m, 1H, OC*H*H), 1.70–2.10 (m, 4H, OCH_2–CH_2–CH_2) ppm.

(±)-β-Phenyl-β-aminopropionic acid (**XVIa**): Ref. [17]

(±)-β-Pentadeuterophenyl-β-aminopropionic acid (**XVIb**; $C_9H_6D_5NO_2$)

A solution of pentadeuterobenzaldehyde ([12]; 2.3 g, 15.4 mmol), malonic acid (1.63 g, 15.4 mmol), and ammonium acetate (1.18 g, 15.4 mmol) in EtOH (4.0 cm^3) was refluxed for 5 h. After 1 h, **XVIb** began to precipitate as white crystals. It was filtered off from the cold solution and washed with a small amount of ice-cold EtOH.

Yield: 1.13 g (43%); m.p.: 242–243°C (decomp.); IR (KBr): $\nu = 3431$ (N–H), 3000–2500 (O–H), 2273 (=C–D), 2205 (=C–D), 1625 (C=O $\cdots$ HN) cm^{-1}; ^1H NMR (D_2O): $\delta = 4.52$ (dd, $^3J = 6.7$ Hz, $^3J = 7.9$ Hz, 1H, CH-phen), 2.78 (dd, $^3J = 7.9$ Hz, $^2J = 16.2$ Hz, 1H, C*H*H), 2.68 (dd, $^3J = 6.7$ Hz, $^2J = 16.2$ Hz, 1H, CH*H*) ppm.

(±)-β-Phenyl-β-aminopropionic acids **XVIc** *and* **XVId**: Ref. [18]

(±)-Trimethylsilyl β-(N-trimethylsilylamino)-β-phenylpropionates **XVII**; *general procedure according to Birkofer* [13]

To 25 mmol of the corresponding β-aminopropionic acid **XVI** suspended in dry benzene (25 cm^3), a solution of trimethylsilyl chloride (50 mmol) was added under N_2. After stirring at room temperature (30 min), the mixture was heated for 15 min, and a solution of triethylamine (52 mmol) in benzene (20 cm^3) was added. The solution was heated on a steam bath for 2 h, cooled to room temperature, and triethylammonium chloride was filtered off. The solvent was removed under reduced pressure, and the colourless product was distilled *in vacuo*. The known compound (±)-trimethylsilyl β-(*N*-trimethylsilylamino)-β-phenylpropionate (**XVIIa**) was prepared from **XVIa** according to this procedure [13].

(±)-Trimethylsilyl β-(N-trimethylsilylamino)-β-(pentadeuterophenyl)propionate (**XVIIb**; $C_{15}H_{22}D_5NO_2Si_2$)

Preparation from **XVIb** (1.34 g, 7.87 mmol); yield: 1.52 g (63%); b.p. (0.4 torr): 102°C; IR: $\nu = 3381$ (N–H), 2954 (C–H), 2897 (C–H), 2271 (=C–D), 1717 (C=O) cm^{-1}.

(±)-Trimethylsilyl β-(N-trimethylsilylamino)-β-(2-chlorophenyl)propionate (**XVIIc**; $C_{15}H_{26}ClNO_2Si_2$)

Preparation from **XVIc** (4.80 g, 24.04 mmol); yield: 7.17 g (87%); b.p. (0.1 torr): 108–109°C; IR: $\nu = 3394$ (N–H), 2958 (C–H), 2902 (C–H), 1717 (C=O) cm^{-1}.

(±)-Trimethylsilyl β-(N-trimethylsilylamino)-β-(4-chlorophenyl)propionate (**XVIId**; $C_{15}H_{26}ClNO_2Si_2$)

Preparation from **XVId** (5.00 g, 25.0 mmol); yield: 5.25 g (61%); b.p. (0.1 torr): 99°C; IR: $\nu = 3381$ (N–H), 2954 (C–H), 1709 (C=O) cm^{-1}.

4-Phenyl-2-azetidinones **XVIII**; *general procedure according to Birkofer* [13]

To 20 mmol of the corresponding trimethylsilyl β-(trimethylsilylamino)-β-phenylpropionate **XVII** in Et_2O (20 cm^3), 1.2 equivalents of EtMgBr in Et_2O (20 cm^3) were added at 0°C under N_2. Vigorous development of ethane occured. After 2 h, the mixture was allowed to reach room temperature and then stirred for 12 h. The solution was cooled to − 18°C, hydrolyzed with 2*N* HCl, and saturated with NH_4Cl to reach *pH* 3–4. The mixture was extracted with Et_2O (5×50 cm^3), the combined organic

layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. CC (SiO_2; CH_2Cl_2:$Et_2O = 2:1$) and recrystallization from Et_2O afforded colourless crystals. The known compound 4-phenyl-2-azetidinone (**XVIIIa**) was prepared according to this procedure [13].

(±)-4-(Pentadeuterophenyl)-2-azetidinone (**XVIIIb**; $C_9H_4D_5NO$)

Preparation from **XVIIb** (1.52 g, 4.93 mmol). The mixture was hydrolyzed with saturated NH_4Cl solution without addition of HCl; yield: 0.31 g (41%); degree of deuteration according to ^{1}H NMR: >96%; m.p.: 105°C; EI-MS (70 eV): $m/z = 152$ ($M^{+\bullet}$, 9), 109 ([M–HNCO]$^{+\bullet}$, 100); IR (KBr): $\nu = 3210$ (N–H), 2947 (C–H), 2278 (=C–D), 1745 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 6.52$ (br s, 1H, NH, exch.), 4.71 (dd, $^3J = 5.3$ Hz, $^3J = 2.5$ Hz, 1H, CH-phen), 3.42 (ddd, $^3J = 5.3$ Hz, $^2J = 14.9$ Hz, $^4J_{NH} = 2.4$ Hz, 1H, C*H*H); 2.85 (ddd, $^3J = 2.5$ Hz, $^2J = 14.9$ Hz, $^4J_{NH} = 1.0$ Hz, 1H, CH*H*) ppm.

(±)-4-(2-Chlorophenyl)-2-azetidinone (**XVIIIc**; C_9H_8ClNO)

Preparation from **XVIIc** (6.59 g; 19.2 mmol); yield: 1.23 g (35%); m.p.: 121–122°C (decomp.; Ref. [14]: 110°C); EI-MS (70 eV): $m/z = 183$ ($M^{+\bullet}$, 2), 181 ($M^{+\bullet}$, 7), 146 ([M–Cl]$^{+\bullet}$, 0.5), 140 ([M–HNCO]$^{+\bullet}$, 35), 138 ([M–HNCO]$^{+\bullet}$, 100), 103 ([138–Cl$^\bullet$]$^+$, 27); IR (KBr): $\nu = 3456$ (N–H), 3166 (C–H), 1798 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.49$–7.23 (m, 4H, aromat.), 6.46 (br s, 1H, NH), 5.06 (dd, $^3J = 5.4$ Hz, $^3J = 2.7$ Hz, 1H, CH-phen), 3.55 (ddd, $^3J = 5.4$ Hz, $^2J = 15.0$ Hz, $^4J_{NH} = 2.9$ Hz, 1H, CH*H*), 2.83 (ddd, $^3J = 2.7$ Hz, $^2J = 15.0$ Hz, $^4J_{NH} = 0.6$ Hz, 1H, C*H*H) ppm.

(±)-4-(4-Chlorophenyl)-2-azetidinone (**XVIIId**; C_9H_8ClNO)

Preparation from **XVIId** (5.00 g, 15.5 mmol); yield: 1.02 g (36%); m.p.: 95°C (Ref. [19]: 98–99°C (MeOH/H_2O)); EI-MS (70 eV): $m/z = 183$ ($M^{+\bullet}$,7), 181 ($M^{+\bullet}$,19), 146 ([M–Cl$^\bullet$]$^+$, 8), 140 ([M–HNCO]$^{+\bullet}$, 37), 138 ([M–HNCO]$^{+\bullet}$, 100), 103 ([138–Cl$^\bullet$]$^+$, 20); IR (KBr): $\nu = 3438$ (N–H), 3218 (N–H), 2919 (C–H), 1787 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.36$–7.27 (m, 4H, aromat.), 6.19 (br s, 1H, NH), 4.64 (dd, $^3J = 5.3$ Hz, $^3J = 2.5$ Hz, 1H, CH-phen), 3.39 (ddd, $^3J = 5.3$ Hz, $^2J = 14.9$ Hz, $^4J_{NH} = 2.6$ Hz, 1H, C*H*H), 2.78 (ddd, $^3J = 2.5$ Hz, $^2J = 14.9$ Hz, $^4J_{NH} = 0.9$ Hz, 1H, CH*H*) ppm.

Phenylazetidines **IV**; *general procedure according to Wells* [15]

To 3.3 mmol of the corresponding lactam in *THF* (10.0 cm^3), $BH_3 \cdot THF$ (1.0 *M* in *THF*, 5.5 equivalents) was added under N_2 at 0°C. The mixture was allowed to reach room temperature and then refluxed for 16 h, followed by cooling to 0°C and addition of 6 *N* HCl (30 cm^3). The mixture was refluxed (30 min) to complete hydrolysis, and the solvent was removed under reduced pressure. The solution was rendered basic with 6 *N* NaOH ($pH = 9$), and the aqueous phase was extracted with Et_2O (3×30 cm^3). The combined organic layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the product was distilled *in vacuo* yielding colourless oils.

2-Phenylazetidine (**IVa**)

IVa was prepared according to *Testa* [20]. EI-MS (70 eV) m/z (%) = 133 (14), 132 (26), 118 (1), 105 (8), 104 (100), 103 (17), 78 (19), 77 (16), 51 (8); EI-MS (12 eV): m/z (%) = 133 (7), 132 (100), 118 (1), 105 (13), 104 (71); *B*/*E* ($M^{+\bullet} = 133$, 1st ffr): m/z (%) = 132 (100), 118 (1), 105 (1), 104 (8).

(±)-2-(Pentadeuterophenyl)azetidine (**IVb**; $C_9H_6D_5N$)

Preparation from **XVIIIb** (0.17 g, 1.12 mmol). Hydrolysis of the borane adduct was performed with 6 *N* NaOH (not HCl !) by heating to reflux for 30 min. **IVb** was distilled from a water bath at 50–80°C bath temperature (0.3 torr).

Yield: 0.098 g (63%); degree of deuteration: >95% (^{1}H NMR); EI-MS (70 eV): m/z (%) = 138 (15), 137 (6), 136 (17), 123 (1), 110 (16), 109 (100), 83 (10), 82 (13), 54 (7); EI-MS (12 eV): m/z (%) = 138 (74), 137 (20), 136 (73), 123 (1), 110 (26), 109 (100); B/E ($M^{+\bullet}$ = 138, 1st ffr): m/z (%) = 137 (18), 136 (100), 123 (1), 110 (1), 109 (19); IR (film): ν = 3274 (N–H), 2869 (C–H), 2271 (C–D, aromat.) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 4.93 (dd, ^3J = 7.8 Hz, ^3J = 8.3 Hz, 1H, CH-phen), 3.72 (ddd, ^3J = 7.9 Hz, ^3J = 8.9 Hz, ^2J = 7.1 Hz, 1H, NH–C*H*H), 3.35 (dddd, ^3J = 3.4 Hz, ^3J = 8.7 Hz, ^2J = 7.1 Hz, $^3J_{NH}$ = 0.7 Hz, 1H, NH–CH*H*), 2.53 (dddd, ^2J = 10.7 Hz, ^3J = 7.9 Hz, $^3J_{CH\text{-}phen}$ = 7.8 Hz, ^3J = 3.4 Hz, 1H, CH–C*H*H), 2.35 (dddd, ^2J = 10.7 Hz, ^3J = 8.9 Hz, $^3J_{CH\text{-}phen}$ = 8.3 Hz, ^3J = 8.7 Hz, 1H, CH–CH*H*), 2.35 (br s, 1H, NH) ppm.

(±)-2-(2-Chlorophenyl)azetidine (**IVc**; $C_9H_{10}ClN$)

Preparation from **XVIIIc** (0.60 g, 3.31 mmol); yield: 0.37 g (69%); b.p. (0.07 torr): 49°C; EI-MS (70 eV): m/z (%) = 169 (5), 168 (8), 167 (17), 166 (19), 141 (6), 140 (33), 139 (22), 138 (100), 132 (19), 114 (3), 112 (9), 103 (31), 102 (17), 77 (16), 51 (7); EI-MS (12 eV): m/z (%) = 169 (27), 168 (19), 167 (95), 166 (37), 141 (7), 140 (32), 139 (26), 138 (100), 132 (33), 112 (2); B/E ($M^{+\bullet}$ (^{35}Cl) = 167, 1st ffr): m/z (%) = 166 (100), 152 (1), 138 (13), 139 (1), 132 (45); IR (film): ν = 3324 (N–H), 3274 (N–H), 2865 (C–H) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.73–7.13 (m, 4H, aromat.), 5.22 (dd, ^3J = 7.9 Hz, ^3J = 8.5 Hz, 1H, CH-phen), 3.80 (ddd, ^3J = 7.9 Hz, ^3J = 9.2 Hz, ^2J = 6.9 Hz, 1H, NH–C*H*H), 3.32 (dddd, ^3J = 3.0 Hz, ^3J = 8.7 Hz, ^2J = 6.9 Hz, $^3J_{NH}$ = 0.8 Hz, 1H, NH–CH*H*), 2.68 (dddd, ^2J = 10.7 Hz, ^3J = 7.9 Hz, $^3J_{CH\text{-}phen}$ = 7.9 Hz, ^3J = 3.0 Hz, 1H, CH–C*H*H), 2.28 (dddd, ^2J = 10.7 Hz, ^3J = 9.2 Hz, $^3J_{CH\text{-}phen}$ = 8.5 Hz, ^3J = 8.7 Hz, 1H, CH–CH*H*), 2.20 (s, 1H, NH) ppm.

(±)-2-(4-Chlorophenyl)azetidine (**IVd**; $C_9H_{10}ClN$)

Preparation from **XVIIId** (0.35 g; 1.93 mmol); yield: 0.17 g (53%); b.p. (0.3 torr): 62°C; EI-MS (70 eV): m/z (%) = 169 (4), 168 (6), 167 (14), 166 (15), 141 (7), 140 (32), 139 (24), 138 (100), 132 (8), 114 (3), 113 (2), 112 (9), 111 (5), 103 (29), 77 (17); EI-MS (12 eV): m/z (%) = 169 (20), 168 (19), 167 (64), 166 (44), 141 (7), 140 (33), 139 (24), 138 (100), 132 (24); B/E ($M^{+\bullet}$ (^{35}Cl) = 167, 1st ffr): m/z (%) = 166 (100), 152 (1), 139 (1), 138 (12), 132 (23); IR (film): ν = 3320 (N–H), 3280 (N–H), 2869 (C–H) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.46–7.26 (m, 4H, aromat.), 4.86 (dd, ^3J = 7.9 Hz, ^3J = 8.5 Hz, 1H, CH-phen), 3.68 (ddd, ^3J = 7.9 Hz, ^3J = 9.1 Hz, ^2J = 7.0 Hz, 1H, NH–C*H*H), 3.29 (dddd, ^3J = 3.2 Hz, ^3J = 8.7 Hz, ^2J = 7.0 Hz, $^3J_{NH}$ = 0.8 Hz, 1H, NH–CH*H*), 2.48 (dddd, ^2J = 10.7 Hz, ^3J = 7.9 Hz, $^3J_{CH\text{-}phen}$ = 7.9 Hz, ^3J = 3.2 Hz, 1H, CH-phen–C*H*H), 2.25 (dddd, ^2J = 10.7 Hz, ^3J = 9.1 Hz, $^3J_{CH\text{-}phen}$ = 8.5 Hz, ^3J = 8.7 Hz, 1H, CH–CH*H*), 2.06 (s, 1H, NH) ppm.

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