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Synthesis of Enantiopure Chiral Perhydrobenzimidazole and Hexahydroquinoxaline Derivatives

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Summary. Starting from 2-anilino-2-ethoxy-3-oxothiobutyric acid anilides and (*R*,*R*)-or (*S*,*S*)-*trans*-1,2-diaminocyclohexane, chiral C2-disubstituted perhydrobenzimidazole and *trans*-4a,5,6,7,8,8a-hexahydroquinoxaline derivatives were obtained depending on the polarity of the solvent.

Keywords. Perhydrobenzimidazole; Hexahydroquinoxaline; 1,2-Diaminocyclohexane.

Introduction

1,2-Diaminocyclohexane [1] has long been recognized as a reagent for the construction of cyclic compounds with C_2 chirality. The resulting strongly basic optically active C_2-chiral diamines, *e.g* 1,3-diacylbenzimidazoline-2-thione, 2-one [2], or -amidine [3], have served as auxiliary compounds for the NMR analysis of enantiomeric mixtures of weakly acidic compounds. Some chiral *Schiff* bases of 1,2-diaminocyclohexane are among the most effective chiral catalysts [4]. Moreover, these cyclic diamines are very attractive bifunctional auxiliaries for asymmetric syntheses.

Some of the compounds have found application due to their biological activity. In particular, some perhydrobenzimidazole derivatives show *anti*-HIV-1 activity [5, 6], whereas hexahydroquinoxaline derivatives show *DNA* strand breakage activity [7]. Moreover, they are used as components in photographic development [8]. These very interesting applications have increased our interest in their synthesis.

Results and Discussion

In this paper we report a novel methodology for the synthesis of hitherto unknown chiral C2-disubstituted, derivatives of perhydrobenzimidazole (**3**) and hexahydroquinoxaline (**4**) (Scheme 2) starting from 2-anilino-2-ethoxy-3-oxothiobutyric acid anilides **1a–d** and *trans*-1,2-diaminocyclohexane (**2**). The 3-oxoacid derivatives **1a–d** themselves were obtained from 3-oxothiobutyric acid anilides and nitroso-

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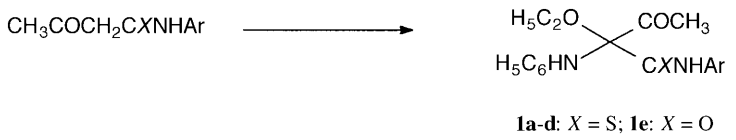
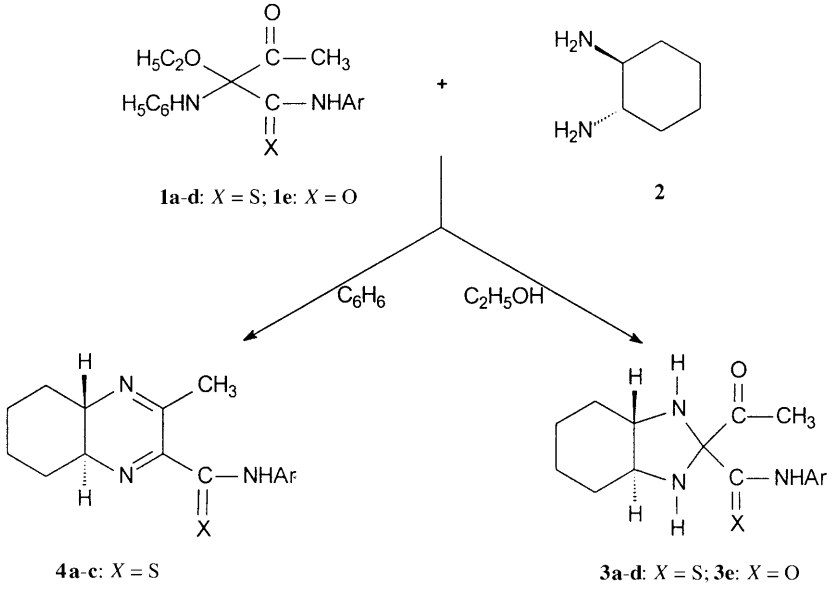


1a-d: X = S; **1e**: X = O

Scheme 1



1a-d: X = S; **1e**: X = O

2

4a-c: X = S

3a-d: X = S; **3e**: X = O

a: Ar = C_6H_5; **b**: Ar = 4-$C_6H_4CH_3$; **c**: Ar = 4-$C_6H_4OCH_3$; **d**: Ar = 4-C_6H_4Cl; **e**: Ar = C_6H_5

Scheme 2

benzene in ethanol at room temperature (Scheme 1) according to the procedure described for the **1e** [9].

The polyfunctional building block **1** offers several advantages including its stereoselectivity and chemoselectivity when undergoing cyclization with diamine **2**. We first examined the reaction of the readily available isomeric mixture of 1,2-diaminocyclohexane with **1**. In principle, this reaction could give a mixture of two possible products **3** and **4** (Scheme 2).

However, we found that the procedure is chemoselective and the outcome depends on the reaction conditions such as solvent and stoichiometry, giving exclusively *trans*-perhydrobenzimidazole as evidenced by H,H- and C,H-COSY experiments on compound **3a**. In the ^{13}C NMR spectra of **3a**, the presence of a carbonyl group is observed at 172.4 ppm, whereas the thiocarbonyl signal was observed at 200.5 ppm. The diagnostic C2 carbon of the imidazolidine ring appears at 68.22 ppm; aliphatic carbons are found at 23.63 (C6), 24.6 (C5), 30.9 (C7), 31.49 (C4), 56.29 (C3a), and 56.61 (C7a) ppm. Additional evidence came from the IR spectra which displayed a peak characteristic for the C=O group at 1684 cm^{-1} and for the NH moiety in the range of 3170–3360 cm^{-1}. EIMS confirmed the structure of

3a; the diagnostic peak at $m/z = MH^+$ is present in all spectra. The most intense (100%) peak is formed *via* loss of phenyl isothiocyanate $(M\text{-PhNCS})^+$.

The spectra for hexahydroquinoxaline **4a** indicated the difference in the structure compared to **3a**. The ^1H NMR spectra of this compound showed the specific features due to the presence of cyclohexane ring, whereas the two *trans* protons at positions 4a and 8a of **4a** appeared as a multiplet in the range of 2.62–2.74 ppm with $J_{HH} = 4.25$ Hz. The singlet of the CH_3 group at 2.37 ppm was shifted downfield relative to the perhydrobenzimidazole derivative **3a**. ^{13}C NMR data revealed differences in the range of aliphatic carbons; a signal characteristic for a sp^3 carbon (C2) of perhydrobenzimidazole at 68.22 ppm was not present as well as that of C=O of the acetyl moiety. C2 and C3 appeared at 157.76 and 157.97 ppm. In the IR spectra, two bands at 1605 and 1624 cm^{-1} corresponding to a vibration the C=N group of the quinoxaline skeleton were observed. A very important proof came from the mass spectra where a characteristic M^+ peak confirmed the presence of the hexahydroquinoxaline system.

In conclusion, it should be pointed out that the presented methodology for the synthesis of perhydrobenzimidazole derivatives **3a–e** and the hexahydroquinoxaline derivatives **4a–c** opens a new straightforward entry to a variety of heterocyclic compounds. Moreover, the products **3a–e** represent fundamental compounds which can be used for the construction of new chiral heterocyclic systems. The new chiral bases **3** and **4** can be conveniently converted into metal complexes. We have successfully prepared the Cu(II), Ni(II), Mn(III) complexes by reaction of the ligands with the corresponding metal salts. The investigation of their asymmetric catalytic properties is currently in progress.

Experimental

Melting points were determined on an electrothermal IA9000 digital melting point apparatus and are uncorrected. Column chromatographic separations were performed using Silica gel 60 (35–70 mesh ASTM). Rotatory chromatography was performed on a Chromatotron apparatus using a 2 mm sorbent layer (silica gel 60 PF-254) with visualization by UV light. The IR spectra were obtained on a Bruker IFS 48 spectrometer at room temperature. ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX 500 NMR spectrometer using *TMS* as internal standard. Chemical shifts are reported in ppm downfield from *TMS*. The elemental analyses (C, H, N, S) agreed favourably with the calculated values.

General procedure for the preparation of **3**

A solution of 0.55 cm^3 *trans*-(±)-1,2-diaminocyclohexane (**2**, 4.58 mmol) and 3.06 mmol of the corresponding anilide of 2-anilino-2-ethoxy-3-oxothiobutyric acid **1a–d** in 20 cm^3 anhydrous ethanol was refluxed for 5 min. Removal of the solvent gave a dark residue which was purified by crystallization from benzene.

(±)-2-Acetyl-2-phenylthiocarbamoyl-(3a,7a)-trans-perhydrobenzimidazole (**3a**; $C_{16}H_{21}N_3OS$)

Yield: 54%; m.p.: 220°C (white needles); IR (KBr): $\nu = 3366$ (NH amide), 3177 (NH amine), 1684 (C=O), 1110 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 11.86 (s, 1H, NH amide), 7.81 (d, 2H, CH aromat.), 7.41 (t, 2H, CH aromat.), 7.25 (t, 1H, CH aromat.) 6.08 (s, 1H, NH amine), 2.95 (d,

$J = 6.78$ Hz, 1H, NH amine), 3.03 (m, 1H, 7a-H), 2.75 (m, 1H, 3a-H), 2.01 (m, 1H, 4-H), 1.87 (m, 1H, 7-H), 1.86 (m, 1H, 5-H), 1.78 (m, 1H, 6-H), 1.38 (t, 2H, 5-H, 4-H), 1.26 (t, 2H, 6-H, 7-H), 1.78 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 29.12 (CH_3), 23.63, 24.6, 30.99, 31.49, 56.29, 56.61, 68.22 (C aliphat.) 122.28, 126.57, 128.86, 138.76 (C aromat.) 172.39 (C=O), 200.5 (C=S) ppm; MS:m/z (%) = 304 (MH^+, 0.96), 167 (M^+-PhNCS, 100), 135 (PhNCS, 4), 43 (CH_3CO, 3.3).

(+)-(3aR,7aR)-2-Acetyl-2-phenylthiocarbamoyl-(3a,7a)-trans-perhydrobenzimidazole (**3a′**)

Yield: 40%; m.p.: 186°C; $[\alpha]_{546}^{20} = +160$ ($c = 1$, ethanol).

(−)-(3aS,7aS)-2-Acetyl-2-phenylthiocarbamoyl-(3a-7a)-trans-perhydrobenzimidazole (**3a″**)

Yield: 40%; m.p.: 186°C; $[\alpha]_{546}^{20} = -160$ ($c = 1$, ethanol).

(±)-2-Acetyl-2-(4-methylphenylthiocarbamoyl)-(3a,7a)-trans-perhydrobenzimidazole
(**3b**; $C_{17}H_{23}N_3OS$)

Yield: 77%; m.p.: 223°C (white needles); IR (KBr): $\nu = 3366$ (NH amide), 3190 (NH amine), 1685 (C=O), 1112 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 11.76 (s, 1H, NH amide), 7.65 (d, 2H, CH aromat.), 7.20 (d, 2H, CH aromat.) 6.28 (s, 1H, NH amine), 2.96 (d, $J = 6.83$ Hz, 1H, NH amine), 3.01 (m, 1H, 7a-H), 2.74 (m, 1H, 3a-H), 2.01 (m, 1H, 4-H), 1.87 (m, 1H, 7-H), 1.82 (m, 1H, 5-H), 1.77 (m, 1H, 6-H), 1.37 (t, 2H, 5-H, 4-H), 1.27 (t, 2H, 6-H, 7-H), 1.77 (s, 3H, CH_3CO), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 29.07 (CH_3CO), 21.09 (CH_3), 23.63, 24.6, 30.97, 31.57, 56.24, 56.66, 68.06 (C aliphat.) 122.76, 129.38, 136.26, 136.49 (C aromat.), 172.46 (C=O), 200.3 (C=S) ppm.

(±)-2-Acetyl-2-(4-methoxyphenylthiocarbamoyl)-(3a,7a)-trans-perhydrobenzimidazole
(**3c**; $C_{17}H_{23}N_3O_2S$)

Yield: 13%; mp.: 222°C (white needles); IR (KBr): $\nu = 3362$ (NH amide), 3193 (NH amine), 1674 (C=O), 1110 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 11.71 (s, 1H, NH amide), 7.67 (d, 2H, CH aromat.), 6.91 (d, 2H, CH aromat.) 6.03 (s, 1H, NH amine), 2.96 (d, $J = 6.83$ Hz, 1H, NH amine), 3.02 (m, 1H, 7a-H), 2.75 (m, 1H, 3a-H), 2.01 (m, 1H, 4-H), 1.86 (m, 1H, 7-H), 1.83 (m, 1H, 5-H), 1.78 (m, 1H, 6-H), 1.37 (t, 2H, 5-H, 4-H), 1.28 (t, 2H, 6-H, 7-H), 1.78 (s, 3H, CH_3CO), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 29.21 (CH_3CO), 55.45 (OCH_3) 23.65, 24.6, 31.5, 32.11, 56.14, 56.87, 67.85 (7C aliphat.), 113.98, 124.53, 131.92, 157.9 (C aromat.) 172.49 (C=O), 200.09 (C=S) ppm.

(±)-2-Acetyl-2-(4-chlorophenylthiocarbamoyl)-(3a,7a)-trans-perhydrobenzimidazole
(**3d**; $C_{16}H_{20}N_3OSCl$)

Yield: 54%; mp.: 223°C (white needles); IR (KBr): $\nu = 3362$ (NH amide), 3180 (NH amine), 1687 (C=O), 1113 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 11.94 (s, 1H, NH amide), 7.77 (d, 2H, CH aromat.) 7.37 (d, 2H, CH aromat.), 6.29 (s, 1H, NH amine), 2.92 (d, $J = 6.83$ Hz, 1H, NH amine), 3.02 (m, 1H, 7a-H), 2.75 (m, 1H, 3a-H), 2.01 (m, 1H, 4-H), 1.87 (m, 1H, 7-H), 1.85 (m, 1H, 5-H), 1.77 (m, 1H, 6-H), 1.38 (t, 2H, 5-H, 4-H), 1.28 (t, 2H, 6-H, 7-H), 1.77 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 29.29 (CH_3), 23.63, 24.57, 30.9, 31.48, 56.05, 56.89, 68.08 (C aliphat.) 124.08, 128.92, 131.56, 137.27 (C aromat.) 172.38 (C=O), 200.85 (C=S) ppm.

(±)-2-Acetyl-2-phenylcarbamoyl-(3a,7a)-trans-perhydrobenzimidazole
(**3e**; $C_{16}H_{21}N_3O_2$)

A solution of 0.38 cm^3 *trans*-(±)-1,2-diaminocyclohexane (**2**, 3.21 mmol) and 1 g anilide of 2-anilino-2-ethoxy-3-oxobutyric acid **1e** (3.21 mmol) in 20 cm^3 anhydrous ethanol was refluxed for 15 min. Removal of the solvent gave an orange oil which was purified by rotatory chromatography eluting with a gradient solvent of $CHCl_3/CH_3COCH_3$ (1:1) through 60% $CH_3COCH_3/CHCl_3$. The last fraction was concentrated giving a white residue.

Yield: 12%; mp.: 245°C (white needles); IR (KBr): $\nu = 3287$ (NH amide), 3174 (NH amine), 1684 (C=O), 1645 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 9.86 (s, 1H, NH amide), 7.56 (d, 2H, CH aromat.), 7.31 (t, 2H, CH aromat.), 7.09 (t, 1H, CH aromat.), 6.31 (s, 1H, NH amine), 2.41 (s, 1H, NH amine), 3.03 (m, 1H, 7a-H), 2.67 (m, 1H, 3a-H), 1.93 (m, 1H, 4-H), 1.82 (m, 1H, 7-H), 1.78 (m, 1H, 5-H), 1.72 (m, 1H, 6-H), 1.39 (t, 2H, 5-H, 4-H), 1.30 (t, 2H, 6-H, 7-H), 1.74 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 26.87 (CH_3), 23.69, 24.7, 30.8, 31.11, 54.47, 58.37, 63.94 (C aliphat.), 119.76, 124.18, 128.9, 137.8 (C aromat.) 168.94 (C=O), 172.23 (C=O) ppm; MS: *m/z* (%); = 288 (MH^+, 16), 167 (M^+-PhNCS, 100), 119 (PhNCO, 5).

General procedure for the preparation of **4**

A solution of 0.35 g *trans*-(±)-1,2-diaminocyclohexane (**2**, 3.06 mmol) and 3.06 mmol of the corresponding anilide of 2-anilino-2-ethoxy-3-oxothiobutyric acid **1a–c** in 20 cm^3 benzene was refluxed for 1 min. Removal of the solvent gave a dark oil which was purified by column chromatography eluting with a gradient solvent of $CHCl_3$ through 40% $CH_3COCH_3/CHCl_3$. The last fraction gave a yellow oil on concentrating which was purified by rotatory chromatography eluting with a gradient solvent of $CHCl_3$ through 10% $CH_3COCH_3/CHCl_3$. The last fraction was concentrated giving yellow residue.

(±)-2-Methyl-3-phenylthiocarbamoyl-trans-4a,5,6,7,8,8a-hexahydroquinoxaline (**4a**; $C_{16}H_{19}N_3S$)

Yield: 14%; mp.: 89–90°C (yellow needles); IR (KBr): $\nu = 3469$ (NH amide), 2935, 2854 (CH aliphat), 1624, 1605 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 10.44 (1H, NH amide), 7.88 (d, 2H, CH aromat.), 7.39 (t, 2H, CH aromat.) 7.26 (t, 1H, CH aromat.) 2.62–2.74 (m, 2H, CHN), 2.27–2.4 (m, 2H, CH aliphat.), 1.86–1.88 (m, 2H, CH aliphat.), 1.47–1.57 (m, 2H, CH aliphat.), 1.32–1.39 (m, 2H, CH aliphat.), 2.37 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 23.34 (CH_3), 25.06, 25.38, 32.81, 33.21, 58.73, 59.69 (6C aliphat.), 122.23, 126.92, 128.98, 138.18 (6C aromat.) 157.76, 157.97 (C=N), 189.18 (C=S) ppm; MS: *m/z* (%) = 285 (M^+, 100%), 135 (PhNCS, 4.1%).

(−)-(4aR,8aR)-2-Methyl-3-phenylthiocarbamoyl-trans-4a,5,6,7,8,8a-hexahydroquinoxaline (**4a′**)

Yield: 20%; m.p.: 102°C; $[\alpha]_{546}^{20} = -563$ ($c = 1$, ethanol).

(+)-(4aS,8aS)-2-Methyl-3-phenylthiocarbamoyl-trans-4a,5,6,7,8,8a-hexahydroquinoxaline (**4a″**)

Yield: 20%; m.p.: 102°C; $[\alpha]_{546}^{20} = +563$ ($c = 1$, ethanol).

(±)-2-Methyl-3-(4-methylphenylthiocarbamoyl)-trans-4a,5,6,7,8,8a-hexahydroquinoxaline
(**4b**; $C_{17}H_{21}N_3S$)

Yield: 13%; mp.: 83°C (yellow needles); IR (KBr): $\nu = 3431$ (NH amide), 2929, 2854 (CH aliphat.), 1625, 1604 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 10.49 (1H, NH amide), 7.76 (d, 2H, CH

aromat.), 7.21 (d, 2H, CH aromat.), 2.63–2.68 (m, 2H, CHN), 2.29–2.32 (m, 2H, CH aliphat.), 1.85–1.86 (m, 2H, CH aliphat.), 1.49–1.5 (m, 2H, CH aliphat.) 1.35–1.37 (m, 2H, CH aliphat.), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 23.6 (CH_3), 21.13 (CH_3), 25.1, 25.42, 32.85, 33.25, 58.73, 59.76 (6C aliphat.), 122.38, 129.5, 135.65, 136.95 (6C aromat.), 157.77, 158 (C=N), 188.9 (C=S) ppm.

(±)-2-Methyl-3-(4-methoxyphenylthiocarbamoyl)-trans-4a,5,6,7,8,8a-hexahydroquinoxaline (**4c**; $C_{17}H_{21}N_3OS$)

Yield: 14%; mp.: 84°C (yellow needles); IR (KBr): $\nu = 3437$ (NH amide), 2929, 2854 (CH aliphat.), 1625, 1605 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$ δ, 500 MHz): 10.56 (1H, NH amide), 7.78 (d, 2H, CH aromat.) 7.67 (d, 2H, CH aromat.), 2.65–2.68 (m, 2H, CHN), 2.27–2.3 (m, 2H, CH aliphat.), 1.85–1.86 (m, 2H, CH aliphat.), 1.49–1.5 (m, 2H, CH aliphat.), 1.34–1.36 (m, 2H, CH aliphat.), 2.37 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 23.5 (CH_3), 55.47 (OCH_3), 25.1, 25.38, 32.82, 33.21, 58.69, 59.68 (6C aliphat.), 114.09, 124, 131.2, 157.77 (6C aromat.), 158.07, 158,15 (C=N), 188.6 (C=S) ppm.

References

[1] Bennani YL, Hannessian S (1997) Chem Rev **97**: 3161
[2] Davies SG, Evans GH, Mortlock AA (1994) Tetrahedron Asymm **5**: 585
[3] Dauwe C, Buddrus J (1995) Synthesis 171
[4] Jacobsen EN, Zhang W, Muci AR, Ecker JR, Deng L (1991) J Am Chem Soc **113**: 7063
[5] El-Ella DA (1997) Bull Far Pharm **35**: 1
[6] Young SD, Amblard MC, Brichter SF, Grey VE, Lumma WC, Tran LO, Huff JR, Schleif WA, Emini EE (1995) Bioorg Med Chem Lett **5**: 491
[7] Yamaguchi T, Kashige N, Mishiro N, Miake F, Watanabe K (1996) Biol Pharm Bull **19**: 1261
[8] Hayakawa H, Morimoto K, Fujimoto H (1994) JP 06, 148, 840 [94,148,840]; Chem Abstr (1995) **122**: 29700 s
[9] Mirek J, Moskal A, Moskal J (1972) Rocz Chem Ann Soc Chim Polonorum **46**: 2233

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