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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1239–1244

Chiral drugs related to guaifenesin: synthesis and phase properties of methocarbamol and mephenoxalone

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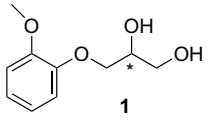
Received 19 April 2007; accepted 21 May 2007

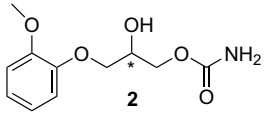
Abstract—The muscle relaxant methocarbamol **2** and tranquilizer mephenoxalone **3**, as well as intermediate cyclic carbonate **4**, have been prepared in enantiopure form by starting from enantiopure guaifenesin **1** easily available by an entrainment resolution procedure. Thermal investigations reveal that **2** is probably a conglomerate forming substance, **3** forms a stable racemic compound, and **4** occupies an intermediate position. The enantiomeric excess of a binary phase eutectic point for these substances comprises 0%, 85%, and 10%, respectively.

1. Introduction

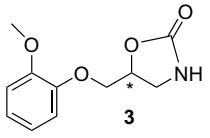
Recently we have described[1] a very practical entrainment procedure for the direct resolution of 3-(2-methoxyphenoxy)-1,2-propanediol **1**, the chiral drug guaifenesin.[2a,3a] This compound can be treated as a typical New Chiral Pool representative taking into account the easiness of both enantiomer production and wide possibilities to transform the framework of guaifenesin to other useful substances. In the previous paper we reported the conversion of scalemic **1** to single enantiomer β-blockers levomoprolol and levotensin.[1] The obvious structural similarity is also present between guaifenesin and the skeletal muscle relaxant and spasmolytic methocarbamol **2**[2b,3b] and tranquilizer mephenoxalone **3**.[2c,3c]



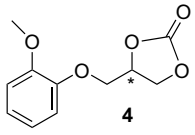
Guaifenesin



Methocarbamol



Mephenoxalone



Methocarbamol is a popular remedy for different health disorders. Recent investigations have shown that two thirds of the prescriptions for muscle relaxants among individuals with back pain in the United States were attributable to methocarbamol (along with cyclobenzaprine and carisoprodol).[4] Until now methocarbamol was used as a racemate, yet rather different activities for racemic and the individual (+)-**2** enantiomer have been demonstrated in experiments in mice.[5] Bearing in mind a general tendency for the replacement of racemic drugs by their single enantiomer analogues, we wanted to represent herein the synthesis and properties of scalemic **2** and **3**, as well as a valuable intermediate in the synthesis of **2** and undesirable side product in the synthesis of **3** cyclic carbonate **4**.

A chiral compound, due to the very fact of its chirality, requires some additional characteristics for its description. Data for the latter include the customary sign and value of optical rotation power and the measure of enantiomeric composition, the ee value. An important quantity in determining the method of resolution of such a compound and/or the possibilities for its further enantioenrichment is the composition of its eutectic point.[6] The last is the special

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doi:10.1016/j.tetasy.2007.05.019

point on the binary or ternary phase diagram where the three phases, liquid (melt or solution) and two solid (either two individual enantiomers or enantiomer and racemic compound) exist in equilibrium. If the enantiomeric excess of the eutectic point (eutectic ee, ee_{eu}) is exactly equal to zero, we are dealing with a conglomerate forming compound. For this compound, the direct resolution approaches could be realized and the enantiomeric composition of any scalemic (non-racemic) sample could be enriched to any desirable degree by fractional crystallization. If the eutectic ee lies between 0 and 1 (0–100%), we are dealing with a racemic compound forming substance. For this system, the direct resolution is impossible, but if the ee of the starting sample is lower than the eutectic ee, the predominant enantiomer can be enriched in the liquid phase (mother liquor) to the eutectic ee extent, whereas the precipitate will tend to be aracemate. If the solution of the starting material has an ee higher than the eutectic ee, a pure predominant enantiomer or mixtures of enantiomers with an ee higher than the eutectic ee can be crystallized out. Equilibrium crystallization of the sample with eutectic ee could not change its enantiomeric composition neither in the precipitate nor in the filtrate form. The non-equilibrium crystallization method reminds us that the well known 'resolution by entrainment' can be used for enantioseparation in this case.[7]

Until now, there are no firmly established interdependences between binary and ternary phase diagram eutectic point compositions. On the one hand, theoretical treatment shows that the ternary eutectic ee is independent of the nature of achiral solvent(s) in dilute solution if no solvates are formed.[8] The same treatment also shows that eutectic ee must vary with temperature: increasing the crystallization temperature will decrease the eutectic ee. Although the experimental evidence for the last statement remains very scarce,[8,9] Wang et al. have reported that it is misleading to use a calculated or measured eutectic composition at the binary eutectic temperature in place of the eutectic ee at the temperature of interest.[8] On the other hand, a thorough investigation of the phase behavior for mandelic acid has shown practical constancy of the eutectic composition in the broad temperature range (0–115 °C) and coincidence of binary and ternary (water as a solvent) eutectics.[10] The close agreement between the melting and solubility (in ethanol and water system) phase diagram eutectics have been shown for chiral drug ketoprofen.[11]

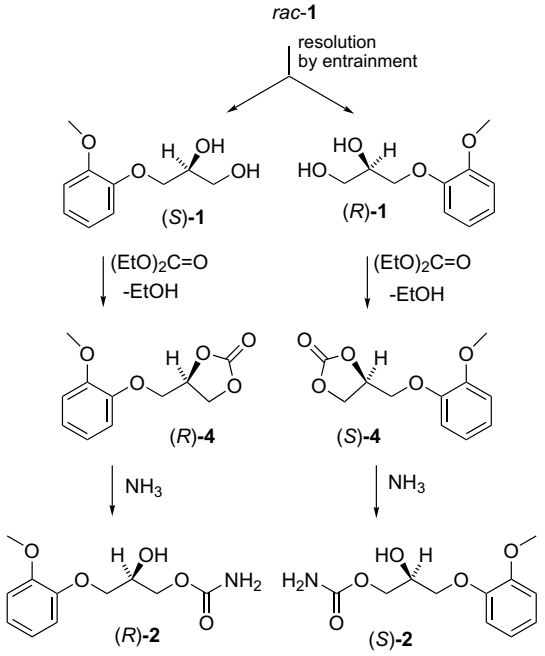
The building of a solubility (ternary) phase diagram and the determination by this means of the eutectic ee is a tedious and time consuming procedure. In addition, the so-obtained quantities conserve their validity only for this solvent and vary with temperature. Conversely, the construction of a melting (binary) phase diagram by means of differential scanning calorimetry (d.s.c.) is a relatively straightforward and rapid procedure. The thus obtained eutectic is characterized by a well-defined composition and is ascribed to the definite temperature. As a result we believe that a binary phase diagram eutectic ee of the chiral substance can serve as a very useful starting point for those concerned with the substance resolution and/or purification.

2. Results and discussion

2.1. Chemistry

Guaifenesin enantiomers are easily available through our previously described direct resolution procedure[1] and were used as starting materials for all the investigated products.

For the synthesis of racemate and both enantiomers of the methocarbamol **2**, we followed the scheme of Baizer et al.[12] The synthesis the existing guaifenesin chiral center is bound to conserve its configuration, meaning (*R*)-**4** and (*R*)-**2** have to be obtained from (*S*)-**1** and vice versa (configuration descriptors are changing for formal reasons, because $C(O)NH_2$ group has higher rank than substituted phenyl group in the CIP system).

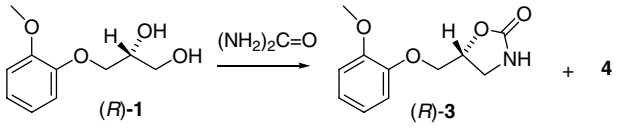


We are unaware of any published data for the chiroptical properties of cyclic carbonate **4**, and some uncertainties concerning the absolute configuration and the sign of the specific rotation for methocarbamol **2** existing in the available literature. Souri et al. have reported that the (*R*)-(+)-enantiomer of methocarbamol is more biologically active.[5] The authors did not mention the conditions for rotary power determinations, but we know from our experience that at least in alcohols and water, (*R*)-**2** has a negative specific rotation. Demian[13] reported that the signs of the specific rotation and the configuration descriptors (*R* or *S*) for **1** and **2** have not been combined in the unified name for methocarbamol enantiomer. However on the sketched chromatograms the author has used the same elution order [namely, (*S*) after (*R*)] for enantiomers **1** and **2** under the same conditions. Moreover, judging from the phrase 'the optical rotations of the methocarbamol enantiomers are even lower (than that for guaifenesin enantiomers)' the author believes that the isomers of **1** and **2** which have the same specific rotation signs, have the same spatial organization as well as CIP descriptors for their stereogenic

centers. We found that the enantiomers of guaifenesin and methocarbamol that have the same spatial organization of their stereogenic centers have opposite specific rotation signs. As a result (*S*)-(+)-guaifenesin corresponds to (*R*)-(−)-methocarbamol and vice versa.

The enantiomeric purities of products **2** and **4** were usually equal to the enantiomeric purity of initial guaifenesin, although there was no need to use an enantiopure starting material to obtain highly enantioenriched methocarbamol. As will become clear from the subsequent material, the low value of the eutectic ee for intermediate carbonate **4** makes it possible to obtain enantiopure product via simple crystallization of the crude material. Moreover, methocarbamol **2** itself is most likely a conglomerate forming compound and could be purified by subsequent crystallizations to any desirable enantioenrichment from any starting one.

For the synthesis of the racemic and enantiomeric forms of mephenoxalone **3** we followed the scheme reported by Lunsford et al.[14] (*R*)-Mephenoxalone was obtained from (*R*)-guaifenesin, but the product was always contaminated with carbonate **4**.



In contrast to the case of **2**, the eutectic ee for compound **3** is rather high, so almost enantiopure **1** must be used from the start in order to obtain enantiopure **3**.

2.2. IR spectroscopy

To investigate the type of crystallization for our compounds, we compared the IR spectra of the racemic and highly enantiomerically enriched crystalline samples of **2**–**4** in KBr pellets, since the IR spectra of the optically active and the racemic form should be identical for the conglomerate formation and different for the racemic compounds.

To substantiate this comparison, the spectra were subjected to a procedure of normalization and baseline correction. For this purpose, coefficients that minimize the difference $A_s - [a_0 + a_1\nu + A_r(a_2 + a_3\nu)]$, where A_s and A_r are the molar absorption coefficients of the scalemic and racemic samples, respectively, ν is the IR radiation frequency corresponding to A, and a_n are the desired regression coefficients, were selected by the least-squares method. It was reasonable to introduce the regression $a_1\nu$ and $A_r a_3\nu$ terms to correct the spectral differences caused by the non-specific (not related to particular absorption bands) interaction of IR radiation with matter (probably by radiation scatter on heterogeneities of the sample). It should be noted that the use of polynomials of higher powers (quadratic and cubic) for the generation of differential spectra does not improve the statistical parameters characterizing regression. The ratio between mean-square deviation of differential curves and mean-square deviation of spectral curves for racemate, that is, the ratio of error to variation (%), was used as a quantitative characteristic for differential curves.

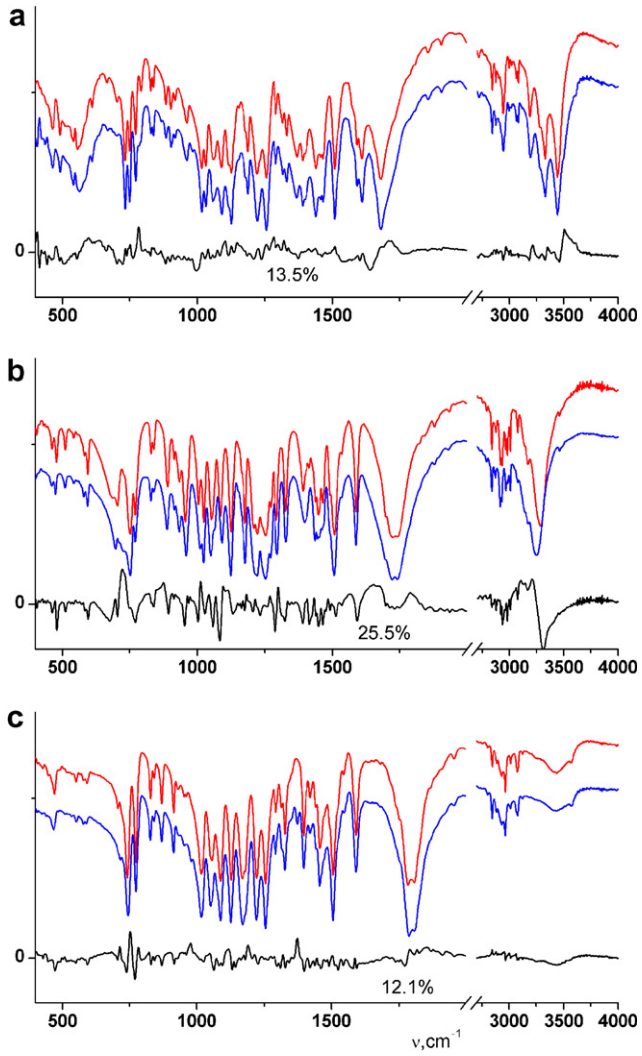


Figure 1. IR spectra of the crystalline samples of **2** (a), **3** (b), and **4** (c). Red curves—racemates, blue curves—scalemates, black curves are differential curves.

Figure 1 shows a good coincidence between the pairs of spectra for compounds **2** and **4** under visual comparison, whereas the spectra of racemic and enantiopure crystalline samples for **3** differ noticeably. A similar pattern was observed for the differential curves: for compounds **2** and **4**, differences between the spectra of the racemate and enantioenriched sample are slightly above the level of instrumental background, while they are rather substantial for compound **3**. This is in agreement with the assumption that a racemic compound is formed upon crystallization of racemic mephenoxalone, and the probability exists that racemic conglomerates are formed by cyclic carbonate **4** and methocarbamol, although the latter cannot be considered as a conclusive decision.

2.3. Thermochemical investigations

This part of the work deals with binary mixtures of (*R*)- and (*S*)-compounds **2**–**4** using differential scanning calorimetry (d.s.c.) as a research method. The temperature

data were determined according to the method reported by Höhne et al.,[15] and were treated as previously described.[16]

The results obtained for the temperature and enthalpy of fusion of the pure enantiomers and the pure racemates, as well as the calculated[6,17] values of entropy of mixing for liquid enantiomeric compounds, ΔS_l^m, and free energy of formation for racemic compounds in the solid state, ΔG^0, are presented in Table 1. The calculated and experimentally obtained eutectic melting temperatures and eutectic compositions are presented in the same table.

The entropy of mixing for enantiomeric **2** in the liquid state is equal to 5.23 J K^{-1} mol^{-1}, which is slightly less but close to the ideal value of 5.75 J K^{-1} mol^{-1} ($R\ln 2$) for conglomerates. The near zero value for ΔG^0 also points on the same peculiarity of chiral **2**.[17] The high negative value for ΔG^0 for mephenoxalone **3** is a good diagnostic for stable racemic compound formation in the crystalline state.[17] The intermediate ΔS_l^m and ΔG^0 values for compound **4** are compatible with the assumption of unstable racemic compound formation.

From the d.s.c. data, the melting temperature against composition diagrams were reconstructed and are depicted in Figure 2. The binary phase diagram for compound **2** has an obvious single eutectic V-shape typical to a racemic conglomerate.[6] If the last is true, the eutectic ee for methocarbamol is equal to zero. The phase diagram for **3** is very typical for a racemic compound. The eutectic ee for this case found as mutual point(s) for Schröder–Van Laar and Prigogine–Defay curves branches is equal to 85%, that is, a sample with about 93% or more of one enantiomer initial content could only be enantioenriched by crystallization (see however Wang et al.[8]). The phase diagram for **4** represents a rather conglomerate-like curve with a very shallow plateau in the racemate region. The theoretical eutectic ee for carbonate **4** is about 10%.

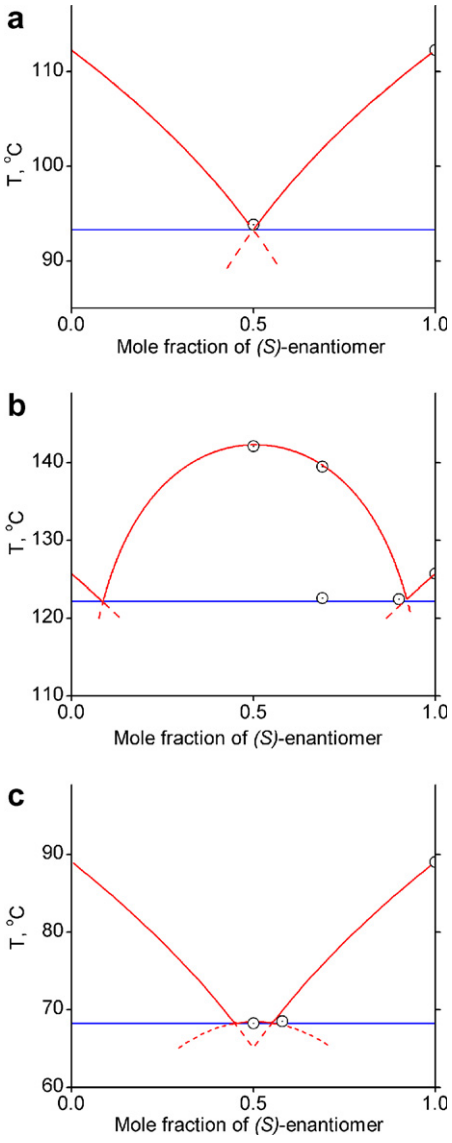


Figure 2. Experimental (circles) points and calculated (solid lines) binary melting phase diagrams for compounds **2** (a), **3** (b), and **4** (c).

3. Conclusion

In conclusion, we are able to say that discovering the conglomerate nature and developing on this basis an effective procedure for the direct resolution of guaifenesin enables easy access to some other single enantiomer drugs. Thermochemical investigations paying special attention to eutectic enantiomeric composition make clear that only the enantiopure starting material allows enantiopure mephenoxalone to be obtained, whereas the demands to enantioenrichment of raw material are not so critical for single enantiomer methocarbamol production. Moreover, the plausible assumption about the conglomerate forming nature of methocarbamol opens up the possibilities of the direct resolution of this popular drug itself.

Table 1. d.s.c. measured melting point and enthalpy of fusion of racemic (low index *R*) and enantiopure (low index *A*) compounds **2**–**4** and calculated thermodynamic characteristics for these substances along with calculated and measured eutectic fusion temperature and eutectic enantiomeric composition

Compound	**2**	**3**	**4**
T_A^f (°C)	112.3	125.7	89.1
T_R^f (°C)	93.8	142.1	68.3
ΔH_A^f (J mol^{-1})	42,800	35,190	29,420
ΔH_R^f (J mol^{-1})	37,450	39,120	26,900
T_{eu}^f, calcd (°C)	93.3	122.5	68.3
T_{eu}^f, exp. (°C)	93.8	122.7	68.5
ee_{eu} (%)	~0	85	~10
ΔS_l^m (J K^{-1} mol^{-1})	5.23	−3.68	4.73
ΔG^0 (J mol^{-1})	−65	−3844	−279

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker Avance-600 spectrometer in either $CDCl_3$ or DMSO-d_6 with TMS or

the signals of the solvent as the internal standard. The IR spectra of the polycrystalline samples of *rac*- and *scal*-compounds under investigations in KBr pellets were recorded on a Bruker IFS-66v Fourier-transform spectrometer. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration c is given as g/100 mL). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected.

Melting curves were measured on a Perkin–Elmer Diamond DSC differential scanning calorimeter in aluminum pans with a rate of heating of 10 °C min^{-1}. Mass of the samples amounted to approximately 2.5 mg. Temperature scale and heat flux were calibrated against the data for indium, phenol, and naphthalene.

HPLC analyses were performed on a Shimadzu LC-20AD system controller, and UV monitor 275 nm was used as a detector. The column used, from Daicel, Inc., was Chiralcel OD (0.46 × 25 cm). All experiments were run with a column temperature of 40 °C.

4.2. Synthesis

Racemic guaifenesin, 3-(2-methoxyphenoxy)-propane-1,2-diol, *rac*-**1** is commercially available (Alfa Aesar, A16827). (*R*)- and (*S*)-3-(2-methoxyphenoxy)-propane-1,2-diol were prepared from the racemate by an entrainment resolution method according to a previously described protocol without modifications.[1]

4.2.1. (*R*)-3-(2-Methoxyphenoxy)-propane-1,2-diol, (*R*)-1. Mp 97–99 °C; $[\alpha]_D^{20} = -9.4$ (c 1.0, MeOH); 99.5% ee (HPLC; hexane/isopropanol/diethylamine = 80/20/0.1; flow rate 1.0 ml/min; $t_R = 9.9$ min).

4.2.2. (*S*)-3-(2-Methoxyphenoxy)-propane-1,2-diol, (*S*)-1. Mp 97–99 °C; $[\alpha]_D^{20} = +9.5$ (c 1.0, MeOH); 99.9% ee (HPLC; hexane/isopropanol/diethylamine = 80/20/0.1; flow rate 1.0 ml/min; $t_R = 17.4$ min).

4.2.3. *rac*-1-Carbamoyloxy-2-hydroxy-3-(2-methoxyphenoxy)propane, *rac*-methocarbamol, *rac*-2. Mp 94–95 °C (lit.[12] mp 95–96.5 °C); ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.33$ (br s, 1H, OH), 3.87 (s, 3H, CH_3), 4.04 (dd, $^2J = 9.9$, $^3J = 6.3$ Hz, 1H, OCH_2), 4.11 (dd, $^2J = 9.9$, $^3J = 4.7$ Hz, 1H, OCH_2), 4.23–4.28 (m, 2H, CH, $1CH_2O$), 4.32 (dd, $^2J = 11.0$, $^3J = 3.7$ Hz, 1H, $1OCH_2$), 4.77 (br s, 2H, NH_2), 6.92–7.01 (m, 4H, Ar).

4.2.4. *rac*-4-(2-Methoxyphenoxymethyl)-[1,3]dioxolan-2-one, *rac*-4. This [mp 68–69 °C (lit.[12] mp 68.4–69.0 °C); ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.86$ (s, 3H, CH_3), 4.24 (d, $^3J = 3.8$ Hz, 2H, CH_2), 4.60–4.65 (m, 2H, CH_2), 4.50–5.03 (m, 1H, CH), 6.90–7.05 (m, 3H, Ar), 7.27–7.30 (m, 1H, Ar)] was prepared according to Baizer et al. without modifications.[12]

4.2.5. (*S*)-4-(2-Methoxyphenoxymethyl)-[1,3]dioxolan-2-one, (*S*)-4. To 5.0 g (25 mmol) of molten (100 °C) (*R*)-3-(2-methoxyphenoxy)-propane-1,2-diol (*R*)-**1** was added, with stirring, 0.07 g (1.3 mmol) of sodium methylate and 5.95 g (50 mmol) of diethyl carbonate. The mixture was heated with stirring and the ethanol formed was distilled at 79–84 °C. When the internal temperature was 130 °C, heating was stopped, and 0.07 g (1.3 mmol) of ammonium chloride added. The remainder of the ethanol and the excess diethyl carbonate were distilled in vacuo. The residue, crude (*S*)-**4** (5.92 g) was used without purification for the next step. For analytical purposes, a small amount (1.03 g) of the obtained crude product was crystallized from ethyl acetate to yield 0.81 g (*S*)-**4**; mp 88–89 °C (EtOAc); 99.2% ee (HPLC; hexane/isopropanol = 60/40; flow rate 0.4 ml/min; $t_R = 37.3$ min); $[\alpha]_D^{20} = -17.3$ (c 1.0, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 3.80$ (s, 3H, CH_3), 4.13 (dd, $^2J = 11.0$, $^3J = 3.8$ Hz, 1H, OCH_2), 4.19 (dd, $^2J = 11.0$, $^3J = 3.9$ Hz, 1H, OCH_2), 4.54 (d, $^3J = 7.3$ Hz, 2H, CH_2), 4.94–5.00 (m, 1H, CH), 6.84–7.01 (m, 4H, Ar). ^{13}C NMR (150.864 MHz, $CDCl_3$) $\delta = 55.81$ (CH_3), 66.13 (CH_2), 69.25 (CH_2), 74.66 (CH), 112.63 (C^3_{Ar}), 116.50 (C^6_{Ar}), 120.92 (C^4_{Ar}), 123.19 (C^5_{Ar}), 147.51 (C^1_{Ar}), 150.29 (C^2_{Ar}), 154.85 (C=O).

4.2.6. (*R*)-4-(2-Methoxyphenoxymethyl)-[1,3]dioxolan-2-one, (*R*)-4. This was obtained by analogy with (*S*)-**4** starting from (*S*)-**1**; mp 88–89 °C (EtOAc); $[\alpha]_D^{20} = +17.7$ (c 1.0, EtOH); 99.8% ee (HPLC; hexane/isopropanol = 60/40; flow rate 0.4 ml/min; $t_R = 38.9$ min).

4.2.7. (*S*)-1-Carbamoyloxy-2-hydroxy-3-(2-methoxyphenoxy)propane, (*S*)-Methocarbamol, (*S*)-2. A solution of 0.86 g (50 mmol) of ammonia in 30 ml isopropyl alcohol was added to a mixture of 10 ml isopropyl alcohol and 4.89 g of crude (*S*)-**4** with stirring at room temperature. The mixture was stirred overnight at room temperature in a tightly stopped flask. At first, a dense almost unstirrable precipitate formed, which dissolved and then re-precipitated. The isopropyl alcohol and excess ammonia were removed in vacuo. The residue was recrystallized from ethyl acetate and gave 2.64 g (53%) of (*S*)-**2**; mp 113–114 °C (EtOAc); 99.9% ee (HPLC; hexane/isopropanol = 60/40; flow rate 0.4 ml/min; $t_R = 16.6$ min); $[\alpha]_D^{20} = +0.8$ (c 1.1, MeOH); (lit.[13] $[\alpha]_D^{22} = +0.5$ (c 1, MeOH)). ^{1}H NMR (600 MHz, DMSO-d_6) $\delta = 3.42$ (br s, 1H, OH), 3.76 (s, 3H, CH_3), 3.87–4.04 (m, 5H, CH_2OAr, CH_2OCO, CH), 6.48 (br s, 2H, NH_2), 6.83–6.91 (m, 3H, Ar), 6.96–6.99 (m, 1H, Ar). ^{13}C NMR (150.864 MHz, DMSO-d_6) $\delta = 56.09$ (CH_3), 65.39 (CH_2), 67.81 (CH_2), 70.78 (CH), 113.05 (C^6_{Ar}), 114.43 (C^3_{Ar}), 121.26 (C^4_{Ar}), 121.72 (C^5_{Ar}), 148.66 (C^1_{Ar}), 149.76 (C^2_{Ar}), 157.21 (C=O).

4.2.8. (*R*)-1-Carbamoyloxy-2-hydroxy-3-(2-methoxyphenoxy)propane, (*R*)-Methocarbamol, (*R*)-2. This was prepared from (*S*)-**1** (9.91 g, 50 mmol) as described for (*S*)-**2**; yield 7.45 g (68%); mp 113–114 °C (EtOAc); 99.8% ee (chiral HPLC analysis; hexane/isopropanol = 60/40; flow rate 0.4 ml/min; $t_R = 28.8$ min); $[\alpha]_D^{20} = -0.6$ (c 1.0, MeOH) {lit.[13] $[\alpha]_D^{22} = -0.8$ (c 1, MeOH)}.

4.2.9. (*rac*)-5-(2-Methoxyphenoxymethyl)-oxazolidin-2-one, (*rac*)-Mephenoxalone, (*rac*)-3. This was prepared from 8.0 g (40 mmol) of *rac*-**1** and 4.85 g (80 mmol) of urea according to Lunsford et al., method A without modifications.[14] Yield 6.61 g (67%); mp 141–142 °C (ethanol)

(lit.[14] mp 143–145 °C). ^{1}H NMR (600 MHz, DMSO-d_6) $\delta = 3.36$ (dd, $^2J = 8.8$, $^3J = 7.7$ Hz, 1H, NCH_2), 3.61 (dd, $^2J = 8.8$, $^3J = 8.8$ Hz, 1H, NCH_2), 3.76 (s, 3H, CH_3), 4.07 (dd, $^2J = 11.0$, $^3J = 6.0$ Hz, 1H, OCH_2), 4.12 (dd, $^2J = 11.0$, $^3J = 3.2$ Hz, 1H, OCH_2), 4.98–5.05 (m, 1H, CHO), 6.98–7.03 (m, 1H, Ar), 7.04–7.13 (m, 3H, Ar), 7.56 (s, 1H, NH). ^{13}C NMR (150.864 MHz, DMSO-d_6) $\delta = 41.54$ (CH_2N), 55.67 (CH_3), 69.81 (CH_2O), 73.76 (CH), 112.75 (C^3_{Ar}), 114.56 (C^6_{Ar}), 120.82 (C^4_{Ar}), 121.86 (C^5_{Ar}), 147.80 (C^1_{Ar}), 149.41 (C^2_{Ar}), 158.68 (C═O).

4.2.10. (*R*)-5-(2-Methoxyphenoxymethyl)-2-oxazolidinone, (*R*)-Mephenoxalone, (*R*)-3. A mixture of 8 g (40 mmol) (*R*)-**1** and 4.85 g (80 mmol) of urea was heated in a flask equipped with a thermometer and an air condenser. The mixture was heated rapidly to the range of 180–200 °C by immersing the flask in a Wood's metal-bath, which had previously been heated to 190 °C. Heating in this temperature range was continued for 5 h and then the reaction mixture was poured into 50 ml of water and extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and concentrated. The residue was crystallized from ethanol, and 5.3 g of (*R*)-**3** collected. Yield 59%; mp 125–127 °C ($CHCl_3$); $[\alpha]^{20}_D = -34.4$ (*c* 1.3, EtOH); $[\alpha]^{20}_D = -37.2$ (*c* 1.1, MeOH); ee >99.9% (HPLC; hexane/isopropanol = 60/40; flow rate 0.4 ml/min; $t_R = 22.4$ min). ^{1}H NMR (600 MHz, $CDCl_3$) 3.63 (dd, $^2J = 8.5$, $^3J = 7.6$ Hz, 1H, NCH_2), 3.75 (dd, $^2J = 8.5$, $^3J = 8.8$ Hz, 1H, NCH_2), 3.83 (s, 3H, CH_3), 4.14 (dd, $^2J = 10.5$, $^3J = 5.7$ Hz, 1H, OCH_2), 4.20 (dd, $^2J = 10.5$, $^3J = 4.8$ Hz, 1H, OCH_2), 4.94–5.00 (m, 1H, CHO), 6.31 (s, 1H, NH), 6.87–7.01 (m, 4H, Ar).

4.2.11. (*S*)-5-(2-Methoxyphenoxymethyl)-oxazolidin-2-one, (*S*)-Mephenoxalone, (*S*)-3. This was obtained from 0.8 g (4 mmol) of (*S*)-**1** by analogy with the (*R*)-isomer of (*S*)-**3** was collected. Yield 0.43 g (47.4 %); mp 124–126 °C ($CHCl_3$); $[\alpha]^{20}_D = +33.7$ (*c* 1.0, EtOH); 99.8% ee (HPLC; hexane/isopropanol = 60/40; flow rate 0.4 ml/min; $t_R = 36.6$ min). NMR spectra were close to the above described for enantiomer and racemate.

Acknowledgements

The authors thank the Russian Fund of Basic Research for financial support (Grant Nos. 06-03-32508 and 07-03-12070).

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