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AN EFFICIENT SYNTHESIS OF S-(+)-AMPHETAMINE

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Abstract: Optically active *(S)*-(+)-amphetamine hydrochloride (**5**·HCl) was prepared from *(1S,2S)*-2-amino-1-phenyl-1,3-propanediol (**1**) via its 3-iodo intermediate (**3**). A phthaloyl group was used for protecting the amine function.

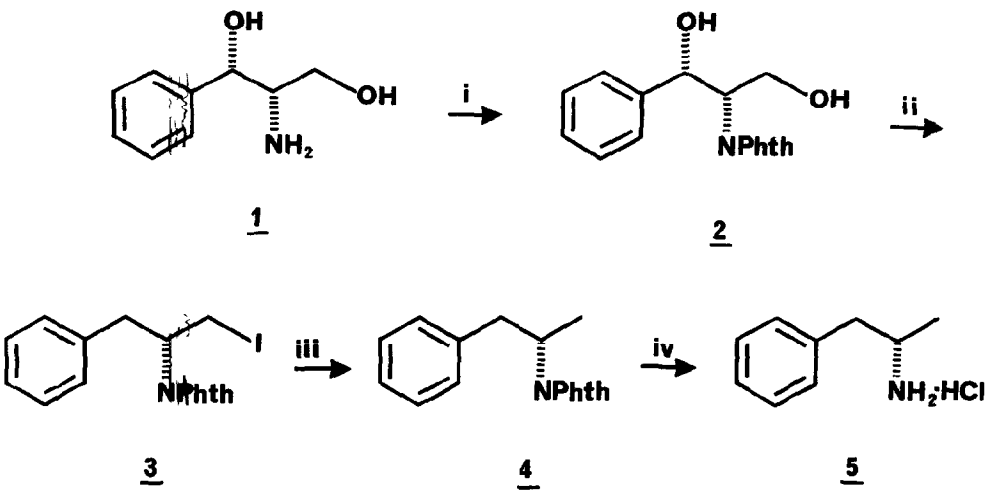
2-Amino-1-aryl-1,3-propanediols are the key intermediates in the synthesis of chloramphenicol-type antibiotics. Only the *(1R,2R)* isomers are biologically active, while their *(1S,2S)* enantiomers are devoid of such activity. In contrast to the recently reported enantioselective synthesis of chloramphenicol[1], the industrial syntheses of the aminodiols involve an optical resolution of racemic intermediate supplying both enantiomers with equal chemical and optical purity. Attempts at utilizing the undesired stereoisomers have been made in many laboratories, resulting in a variety of interesting applications as well as chemical transformations.

From a practical point of view, a conversion of the inactive *(1S,2S)* enantiomers into the active *(1R,2R)* ones is an important problem. As yet, it has been solved by applying two strategies. One of them involves a racemization[2,3], which again necessitates a resolution, the other one deals with a stereoselective transformation of one enantiomer into the other without racemization[4]. An example of inversion of configuration at only one stereogenic center was also described[5].

As optically active amines, both enantiomers of 2-amino-1-aryl-1,3-propanediols have been used as resolving agents for the optical resolution of racemic organic acids[6-8]. They have also found broad application as a chiral auxiliary in asymmetric synthesis, e.g. in Strecker aminoacids synthesis[9,10], Michael addition[11,12], reduction[13], C-alkylation[14,15] and in the famous Meyers' oxazoline chemistry[16]. There are also reports on asymmetric reactions mediated by these aminodiols used as chelating ligands or catalysts[17-19]. They serve as chiral starting material in the synthesis of various optically active molecules. Apart from the above mentioned oxazolines[16,20,21] other heterocycles[20-23] as well as important aminoalcohols : *(S,S)*-norpseudoephedrine[24,25] and *(R)*-phenylalaninol[26] have been prepared.

In this paper we report an efficient method for converting *(1S,2S)*-2-amino-1-phenyl-1,3-propanediol (**1**) into homochiral *(S)*-(+)-amphetamine (**5**). The sequence of synthetic transformations is shown in **Scheme 1**.

Scheme 1



Phth = phthaloyl

i, phthalic anhydride, ii, PPh_3,I_2,toluene, iii, H_2/Pd-C, Et_3N, ethyl acetate, iv, $NH_2NH_2 \cdot H_2O$, n-butanol

In order to realize the outlined strategy, selection of a proper amine protecting group was essential. As it followed from our experience and was proven by others[24–28], the phthaloyl group turned out to be superior to acyl or alkoxycarbonyl ones. Thus, treatment of **1** with freshly sublimed phthalic anhydride at 160°C under atmospheric pressure resulted in N-phthaloyl derivative **2** (88%), which crystallized persistently with 1/3 of a molecule of water of crystallization melting at 180-180.5°C and showing $[\alpha]_D^{20}$ +40.6, while the corresponding data reported[27] for anhydrous **2** were 164-168°C, $[\alpha]_D^{20}$ +41.1, respectively. In the next step the substitution of both hydroxyl groups by hydrogen via the corresponding diiodo intermediate was planned. The well known triphenylphosphine/iodine/imidazole in boiling toluene system seemed to be the reagent of choice for direct replacement of

hydroxyls by iodine. When the reaction was run in the absence of imidazole, however, the monoiodide **3** was obtained in 86% yield (m.p. 141-142 °C, $[\alpha]_D^{20}$ +99.1). Apparently it results from a diiodo intermediate in which the benzylic iodine was reduced by hydriodide formed as a by-product in this process[29]. The reductive dehalogenation of iodide **3** with hydrogen under pressure (1.5 atmosphere) in the presence of 10% Pd/C and triethylamine afforded N-phthaloylamphetamine (**4**) in 94% yield (m.p. 78-79°C , $[\alpha]_D^{20}$ +183.0). The N-phthaloyl protecting group was then removed by hydrazinolysis in boiling n-butanol. As a result, *(S)*-(+)-amphetamine hydrochloride (**5**·HCl) was obtained in 61% yield (m.p. 156.5-158.5°C , $[\alpha]_D^{20}$ +27.5). The physical data of so prepared **5**·HCl are identical, within experimental error, with those reported in the literature for a sample prepared from racemic amphetamine by chemical resolution with D-tartaric acid (m.p. 156°C , $[\alpha]_D^{15}$ +24.8)[30]. Amphetamine hydrochloride (**5**·HCl) turned out to be difficult to handle when anhydrous. It was characterized by ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H NMR spectrum the six aliphatic protons form a $ABMX_3$ splitting pattern in which the methyl protons are evidenced as a doublet located at 1.39 ppm ($J = 6.6$ Hz) and the two nonequivalent benzylic protons appear as a pair of doublets of doublets at 2.86 ppm ($J_{AB} = 13.3$, $J_{AM} = 14.4$ Hz) and at 3.26 ppm ($J_{BA} = 13.3$, $J_{BM} = 13.4$ Hz), respectively. The H-2 methine proton can be found as an unresolved multiplet centered at 3.59 ppm. The ^{13}C-NMR spectrum clearly shows the presence of three sp^3 hybridized carbons located at 18.21 ppm (CH_3), 41.13 ppm (CH_2) and 49.80 ppm (CH), respectively. The five protonated aromatic carbons are located at 127.14, 128.74 and 129.19 ppm, whereas the quaternary one at 135.61 ppm.

This short and efficient synthesis of *(S)*-(+)-amphetamine (**5**) from *(1S,2S)*-2-amino-1-phenyl-1,3-propanediol (**1**) in 44% overall yield demonstrates another possibility of making use of the waste isomers formed in the production of chloramphenicol antibiotics.

Acknowledgements

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Experimental Section

General

Melting points: determined on a Koffler block. IR spectra: Pekrin-Elmer 180 in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra: Varian Gemini 300, TMS as internal standard. Mass spectra, chemical ionization: Finnigan 1015D. Specific rotation: Perkin Elmer Polarimeter 243B. Macherey-Nagel silica gel 60 (200-300 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60 F_{254} for TLC. *(1S,2S)*-2-amino-1-phenyl-1,3-propanediol was purchased

from Fluka AG.

(1S,2S)-1-Phenyl-2-phthalimido-1,3-propanediol (2)

(1S,2S)-2-amino-1-phenyl-1,3-propanediol (1) (3.34 g, 20 mmol) and phthalic anhydride (2.96 g, 20 mmol) were melted together at 160°C and stirred for few minutes until the mixture turned into a solid. After cooling it was dissolved in hot methanol and left for crystallization. The crystals were filtered off to give 5.22 g (88%) of 2. m.p. 180-180.5° (lit.[27] 164-168°C) and $[\alpha]_D^{20}$ +40.6 (c = 1, acetone) (lit.[27] $[\alpha]_D^{20}$ +41.1 (c = 1, acetone)).
IR cm^{-1}: 3430 (OH), 1775 and 1705 (imide C = O). ^1H NMR (d_6-acetone) δ: 3.40 (dd, J = 4.0 and 11.3 Hz, 1H, H-3), 4.10 (dd, J = 10.0 and 11.3 Hz, 1H, H-3'), 4.58 (ddd, J = 4.0 and 10.0 and 9.2 Hz, 1H, H-2), 5.23 (d, J = 9.2 Hz, 1H, H-1), 7.27-7.52 (m, 5H, Ar-H), 7.87 (s, 4H, Ar-H). CI MS (NH_3) m/e (%): 289 $(M+1)^+$ (42), 280 $(M-17)^+$ (80), 250 (100), 173 (23). Found: C 67.34, H 4.92, N 4.40; $C_{17}H_{15}NO_4 \cdot 1/3\ H_2O$ req.: C 67.33, H 4.99, N 4.62%.

(R)-3-Iodo-1-phenyl-2-phthalimidopropane (3)

To a refluxing solution of compound 2 (1.48 g, 5 mmol) and triphenylphosphine (3.41 g, 13 mmol) in toluene (25 ml), iodine (3.30 g, 13 mmol) was added portionwise. The mixture was heated at reflux for 1h, then anhydrous ethanol (0.5 ml) was added in two portions at ca. 1/2 h intervals. The mixture was then cooled to R.T., decanted and the residue was washed with toluene (2 x 20 ml). The combined organic extracts were washed with saturated $Na_2S_2O_3$ sol., then with water, dried and the solvent was evaporated. The oily residue, dissolved in methanol, deposited crystalline 3 in 86% yield: m.p. 141-142°C (lit.[31] m.p. 138-140°C for ent-3), $[\alpha]_D^{20}$ +99.1 (c = 1, acetone).
IR cm^{-1}: 1770 and 1705 (imide C = O), ^1H NMR ($CDCl_3$) δ: 3.30 (dd, J = 1.8 and 7.8 Hz, 2H, H-1), 3.55 (dd, J = 4.9 and 10.4 Hz, 1H, H-3), 3.97 (dd, J = 10.6 and 10.4 Hz, 1H, H-3'), 4.68-4.79 (m,1H, H-2), 7.14-7.24 (m, 5H, ArH), 7.67-7.83 (m, 4H, ArH). CI MS (NH_3) m/e (%): 409 $(M+18)^+$ (100), 392 $(M+1)^+$ (25), 283 (20), 264 (12). Found: C 52.09, H 3.67, N 3.46; $C_{17}H_{14}NO_2I$ req.: C 52.19, H 3.61, N 3.58%.

(S)-N-Phthaloylamphetamine (4)

A solution of compound 3 (1.13 g, 2.97 mmol) in ethyl acetate (45 ml) in the presence of triethylamine (1.88 ml) and 10% Pd/C catalyst (226 mg) was hydrogenated under the pressure of 1,5 atmosphere of hydrogen for 20 h. The catalyst was then filtered off and the filtrate was washed with 5% aqeous hydrochloric acid. The organic phase was dried and the solvent was evaporated to give (0.72 g (94%) of crystalline residue, which after crystallization from ether/hexane showed m.p. 78-79°C (lit.[32] m.p. 78-78.5°C) and $[\alpha]_D^{20}$ +183.0 (c = 1, acetone), (lit.[32] $[\alpha]_D^{20}$ +156.6 (c = 0.89, $CHCl_3$)).
IR cm^{-1}: 1765 and 1705 (imide C = O), ^1H NMR ($CDCl_3$) δ: 1.53 (d, J = 6.9 Hz, 3H, CH_3), 3.10 (dd,

J = 6.8 and 13.7 Hz, 1H, H-1), 3.32 (dd, J = 9.2 and 13.7 Hz, 1H, H-1'), 4.65 (m, 1H, H-2), 7.12-7.23 (m, 5H, Ar-H), 7.64-7.77 (m, 4H, Ar-H). CI MS (NH_3) m/e (%): 265 M^+ (5), 174 (100), 130 (15), 118 (10), 68 (45). Found: C 76.90, H 5.73, N 5.20; $C_{17}H_{15}NO_2$ req.: C 76.96, H 5.70, N 5.28%.

(S)-(+)-Amphetamine hydrochloride (5·HCl)

N-Phthaloylamphetamine (4) (0.94 g, 3.55 mmol) in n-butanol (50 ml) and 80% aqueous hydrazine (1 ml) were heated at reflux for 2 h. The mixture was left at R.T. for 18 h and then the precipitate was filtered off and washed with n-butanol (10 ml). After addition of 6N hydrochloric acid (2.5 ml) the filtrate was concentrated to half of its volume, the precipitate was filtered off and the filtrate concentrated again. It yielded a solid which was recrystallized from ethanol/ ethyl ether to give 0.31 g (61%) of pure *(S)*-(+)-amphetamine hydrochloride (5·HCl). M.p.156.5-158.5°C (lit.[30] m.p. 156°C), $[\alpha]_D^{20}$ +27.5 (c = 1, H_2O) (lit.[30] $[\alpha]_D^{15}$ +24.8 (c = 9, H_2O)).
IR cm^{-1}: 3700-2300 (NH_3^+). ^1H NMR ($CDCl_3$) δ: 1.39 (d, J = 6.6 Hz, 3H, H-3), 2.86 (dd, J = 13.3 and 14.4 Hz, 1H, H-1), 3.26 (dd, J = 13.3 and 13.4 Hz, 1H, H-1'), 3.59 (m, 1H, H-2). ^{13}C NMR ($CDCl_3$) δ: 18.21 (CH_3), 41.13 (CH_2), 49.80 (CH), 127.14, 128.74, 129.19 (Ar-CH), 135.61 (Ar-C). EI MS m/z (%): 135 M^+ (10), 119 (50), 91 (100), 77 (40). Found: C 62.21, H 8.30, N 8.42; $C_9H_{14}NCl$ req.: C 62.96, H 8.22, N 8.19%.

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