Syntheses of (*S*)-(+)-Trihexyphenidyl Hydrochloride and (*S*)-(+)-Procyclidine Hydrochloride, two Anticholinergics, using (*S*)-(−)-3-Cyclohexyl-3-hydroxy-3-phenylpropanoic Acid as Chiral Synthon

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The absolute configuration of the more active (−)-enantiomer of the anticholinergic trihexyphenidyl hydrochloride has been established as (*R*) by syntheses of (*S*)-(+)-procyclidine hydrochloride, whose absolute configuration has been established previously, and (*S*)-(+)-trihexyphenidyl hydrochloride from the same chiral building block, viz. (*S*)-(−)-cyclohexyl-3-hydroxy-3-phenylpropanoic acid. Both enantiomers of this chiral synthon were prepared by optical resolution of the corresponding racemate, employing (*R*)- and (*S*)-1-phenylethylamine, respectively, as resolving agents.

Trihexyphenidyl hydrochloride [syn. benzhexol chloride; (±)-**1**] is an anticholinergic which has found a place in the treatment of parkinsonism.[1–3] Optical resolution of racemic trihexyphenidyl hydrochloride was reported some thirty years ago.[4,5] The absolute configuration of the physiologically more active (−)-enantiomer has subsequently been postulated as (*R*) by analogy with structurally closely related anticholinergics.[6,7]

Tacke *et al.*[7] recently established the absolute configuration of (−)-procyclidine [(−)-**7**] as (*R*) by carrying out an X-ray structural analysis of the corresponding (*R*)-methiodide [= (*R*)-tricyclamol iodide]. Since the antimuscarinic potencies of (*R*)-(−)-procyclidine hydrochloride and (−)-trihexyphenidyl hydrochloride have been found to be about 380 and 5.5 times, respectively, greater than those of the corresponding (+)-enantiomers,[5–7] Barlow,[6] and later Tacke and coworkers,[7] considered (*R*) as the plausible configuration for the (−)-enantiomer of trihexyphenidyl hydrochloride; all rotations were measured in chloroform. Their hypothesis is supported by the findings of Ellenbroek *et al.*,[8] Brimblecombe and co-workers,[9,10] and Barlow *et al.*,[11] who examined the antimuscarinic activity of a number of (1-cyclohexyl-1-hydroxy-1-phenyl)-methyl-derived compounds. Invariably, they found the compounds possessing the configuration depicted in Fig. 1 to display higher activity than their enantiomers. Consequently, Dahlbom concluded in a recent review article: "It is evident that the con-

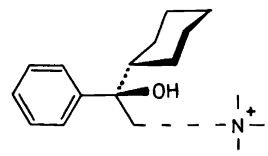

Fig. 1. Configuration of the benzylic centre of potent (1-cyclohexyl-1-hydroxy-1-phenyl)methyl-derived anticholinergics.

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figuration at the benzylic center is of greatest importance, having to be (*R*)".[12] The results described in the present communication demonstrate that trihexyphenidyl hydrochloride complies with this structure-activity relationship.

Results and discussion

As postulated by Barlow,[6] and Tacke and coworkers,[7] the (*R*)-configuration was considered plausible for the (−)-enantiomer of trihexyphenidyl hydrochloride. Supporting evidence for this assignment was anticipated to be found by comparing the CD curve of optically active trihexyphenidyl hydrochloride with that of the diol [(*S*)-(−)-**2**]; the latter compound was available by diborane reduction of (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid, whose absolute configuration was elucidated by Inch *et al.*[13] in 1968. Optical resolution of racemic trihexyphenidyl hydrochloride [(±)-**1**] was readily achieved by employing either (*S*)-mandelic acid, or (*R,R*)-tartaric acid as resolving agents. (+)-Trihexyphenidyl hydrochloride was obtained via the corresponding crystalline mandelate or tartrate.

The CD curves of (+)-trihexyphenidyl hydrochloride and the diol (*S*)-(−)-**2** are delineated in Fig. 2. The curves exhibit opposite extrema in the 210–230 nm region, suggesting, at first, (*R*)-configuration for the *less* potent (+)-enantiomer of trihexyphenidyl hydrochloride. However, the opposite assignment can be rationalized by adopting the aromatic quadrant rule devised by DeAngelis and Wildman,[14] who studied the CD spectra of rigid aromatic compounds containing an asymmetric centre adjacent to the aromatic ring. Assuming that (+)-trihexyphenidyl hydrochloride has a semi-rigid conformation stabilized by restricted rotation of the bulky substituents attached to the chiral benzylic C atom, and intramolecular hydrogen bonding between the HN^+ proton and the oxygen atom of the hydroxy group, the piperidinium moiety of the (*S*)-isomer of **1** is projected onto a negative quadrant, thus contributing to a negative Cotton effect. In such a conformation the cyclohexyl group is bisected by the dividing symmetry plane, and its contribution to the CD extremum is thought to be negligible. Assuming a similar conformation for the diol (*S*)-(−)-**2**, the hydroxymethyl group and the smaller hydroxy group occupy positive and negative quadrants, respectively.

Several rules, which unfortunately are not always consistent,[15] have been elaborated for the correlation of CD spectra of aromatic compounds with their absolute configuration.[16–19] Furthermore, interpretation of the spectra of the present type of compounds appears to be particularly difficult; e.g. (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid and the corresponding (*S*)-(+)-methyl ester display positive Cotton effects at 224–225 nm, while (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanal displays a negative CD peak at 225 nm.[20]

Since circular dichroism in the present case is prone to misinterpretation, chemical correlation with (*S*)-(+)-procyclidine hydrochloride [(*S*)-(+)-**7**][7] was carried out. Employing

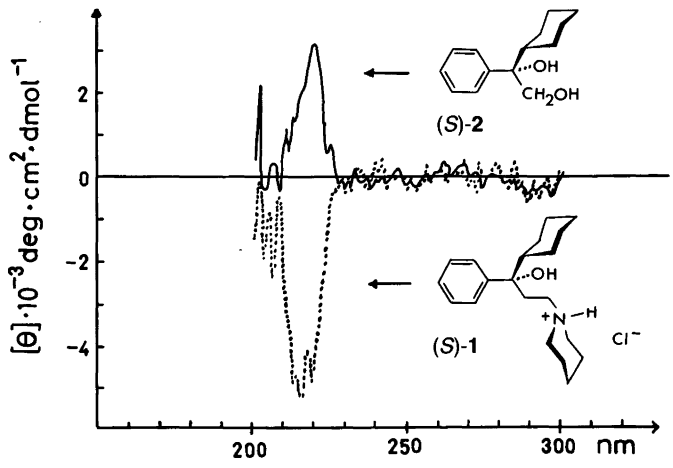

Fig. 2. CD curves of (*S*)-(+)-trihexyphenidyl hydrochloride [(*S*)-**1**] and (*S*)-(−)-1-cyclohexyl-1-phenyl-1,2-ethanediol [(*S*)-**2**] in EtOH.

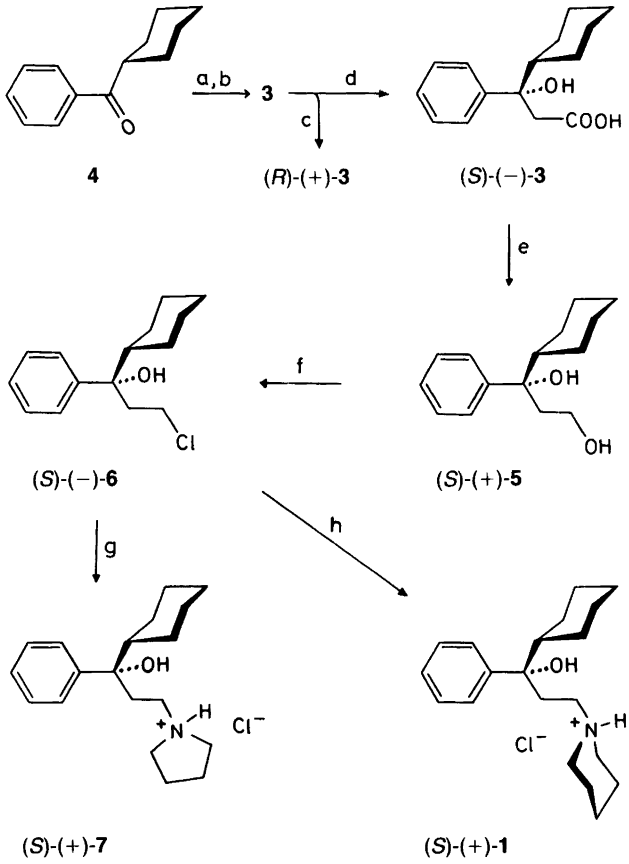

Fig. 3. Syntheses of (*S*)-(+)-trihexyphenidyl hydrochloride [(*S*)-(+)-**1**] and (*S*)-(+)-procyclidine hydrochloride [(*S*)-(+)-**7**]. a. $BrCH_2CO_2Et/Zn$; b. KOH; c. (*R*)-1-phenylethylamine; d. (*S*)-1-phenylethylamine; e. B_2H_6; f. $(C_6H_5)_3P/CCl_4$; g. Pyrrolidine; h. Piperidine.

(*S*)-(−)-3-cyclohexyl-3-hydroxy-3-phenylpropanoic acid [(*S*)-(−)-**3**] as chiral synthon, (*S*)-(+)-procyclidine hydrochloride and (*S*)-(+)-trihexyphenidyl hydrochloride were prepared as detailed in Fig. 3. Both enantiomers of the acid **3**[21,22] were obtained in nearly 50% yield and in high optical purity via a single fractional crystallization of the corresponding salts with (*R*)- and (*S*)-1-phenylethylamine, respectively. The acid (*S*)-(−)-**3** was reduced with diborane in excellent yield to the diol (*S*)-(+)-**5**, which was subsequently converted to the chloro-compound (*S*)-(−)-**6** using triphenylphosphine and tetrachloromethane.[23] The chloride (*S*)-(−)-**6** was reacted with pyrrolidine and piperidine, respectively, affording (*S*)-(+)-procyclidine hydrochloride [(*S*)-(+)-**7**] and (*S*)-(+)-trihexyphenidyl hydrochloride [(*S*)-(+)-**1**], thereby confirming the previously postulated (*R*)-configuration of the more potent (−)-enantiomer of trihexyphenidyl hydrochloride. The synthesis of (*S*)-(+)-procyclidine hydrochloride [(*S*)-(+)-**7**] implies configurational assignments of the intermediate acid **3**, the diol **5**, and the chloride **6** as specified in Fig. 3.

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Optical rotations and mass spectra were recorded on Carl Zeiss or Perkin-Elmer 241, and Jeol JMS-DX303 or Micromass 7070F instruments, respectively. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol JNM GX 270 instrument. TMS, or the central solvent peaks (^{13}C) of $CDCl_3$ (78.04 ppm) or CD_3OD (49.04 ppm) were used as internal references. CD spectra were recorded at

ambient temperature using a Jobin-Yvon Dichrograph IV (solvent EtOH, light-path 0.1 mm, concentration 1.3 mg ml^{-1}). Each spectrum was recorded ten times and the mean value of the circular dichroism at each wavelength was calculated; further details are given in Ref. 24.

Optical resolution of (±)-1-cyclohexyl-1-phenyl-3-(1-piperidyl)-1-propanol hydrochloride [(±)-trihexyphenidyl hydrochloride; (±)-**1**]. Optical resolution of racemic **1** was accomplished employing either (*R,R*)-(+)-tartaric acid or (*S*)-(+)-mandelic acid as resolving agents. Both acids furnished the (+)-enantiomer of **1** on fractional crystallization of the corresponding tartrates or mandelates, respectively, from EtOH. Adamson and Duffin,[4] and Duffin and Green[5] reported obtaining the (+)-enantiomer of **1** from the corresponding crystalline D-tartrate. "D-Tartaric acid" is, however, a misnomer for *d*-tartaric acid [= L-(+)-tartaric acid].[25]

(*S*)-(+)-Trihexyphenidyl (base): $[\alpha]_D^{20}$ +29.4° (*c* 1.47, EtOH); lit.[26] $[\alpha]_D^{25}$ +30.9° (*c* 0.4, EtOH); lit.[4] $[\alpha]_{546}^{20}$ −25° (*c* 0.4, EtOH) for the enantiomer.

(*S*)-(+)-Trihexyphenidyl hydrochloride [(*S*)-(+)-**1**]: $[\alpha]_D^{21}$ +36.3°, $[\alpha]_{578}^{21}$ + 38.0°, $[\alpha]_{546}^{21}$ +43.3°, $[\alpha]_{436}^{21}$ +75.4°, $[\alpha]_{365}^{21}$ +122.8° (*c* 0.92, $CHCl_3$); lit.,[26] $[\alpha]_D^{25}$ +38.3° (*c* 0.4, $CHCl_3$); lit.[27] $[\alpha]_{546}$ +42.9° ($CHCl_3$); based on the stereospecificity index of (−)- and (+)-trihexyphenidyl hydrochloride, Barlow[6] estimated $[\alpha]_{546}$ to be 44.9°; m.p. 258 °C; lit.[4] m.p. 264 °C; IR (KBr), ^1H NMR and ^{13}C NMR spectra were indistinguishable from those of (±)-**1**; the chemical shift of the HN^+ proton at 11.25 ppm (saturated $CDCl_3$ solution) showed little change on dilution; a 19-fold dilution effected an upfield shift of 0.04 ppm to 11.22 ppm. CD curve: see Fig. 2.

(S)-(−)-1-Cyclohexyl-1-phenyl-1,2-ethanediol [(*S*)-(−)-**2**]. Boron trifluoride etherate (262 mg, 1.85 mmol) was added to a solution of (*S*)-(+)-2-cyclohexyl-2-hydroxy-2-phenylethanoic acid[13,28,29] (187 mg, 0.799 mmol) and $NaBH_4$ (48 mg, 1.3 mmol) in dry THF (5 ml), and the mixture was stirred at room temperature for 16 h. Additional boron trifluoride etherate (262 mg, 1.85 mmol) and $NaBH_4$ (47 mg, 1.2 mmol) in dry THF (5 ml) were added and the stirring continued for 6.5 h at 50–60 °C. Water (20 ml) was added and the product extracted with CH_2Cl_2 (3×30 ml). Removal of the solvent left a semi-crystalline product which was subjected to chromatography on a silica gel column. The diol **2** (118 mg, 67 %) was eluted with 2 % MeOH in $CHCl_3$ and was recrystallized twice from diethyl ether and diethyl ether-hexane, respectively. $[\alpha]_D^{21}$ −7.1° (*c* 0.95, EtOH); lit.[20] $[\alpha]_D^{25}$ −5° (*c* 1, EtOH); m.p. 87–88 °C; lit.[20] 86–88 °C; ^{13}C NMR data were in good agreement with those given by Tambuté *et al.*[20] CD curve: see Fig. 2.

(±)-3-Cyclohexyl-3-hydroxy-3-phenylpropanoic acid [(±)-**3**]. Racemic **3** was prepared in 80 % overall yield from cyclohexyl phenyl ketone (**4**) in a Reformatsky reaction with ethyl bromoacetate followed by hydrolysis of the ester group as described by Gutsche and co-workers[21] and Nenitzescu *et al.*[22]

(R)-(+)-3-Cyclohexyl-3-hydroxy-3-phenylpropanoic acid [(*R*)-(+)-**3**]. Racemic acid **3** (408 mg, 1.65 mmol) and (*R*)-1-phenylethylamine (198 mg, 1.63 mmol; Fluka) were dissolved in EtOH (16 ml) and the solution left at +5 °C overnight. The crystalline precipitate (148 mg) was collected by filtration and washed twice with cold EtOH. The salt was dissolved in dilute HCl and extracted with EtOAc. Removal of the solvent furnished (*R*)-(+)-**3** (96 mg, 47 %) which was recrystallized from EtOAc. M.p. 170–172 °C; lit.[22] m.p. 175 °C for (±)-**3**; $[\alpha]_D^{22}$ +26.2° (*c* 1.60, EtOH); *m/z* (EI, %): 188 (18), 133 (9), 120 (5), 105 (100), 77 (27), 55 (10), 41 (11); ^1H NMR (270 MHz, $CDCl_3$): δ 0.9–1.3 (5H, m), 1.5–1.8 (6H, m), 2.92 (1H, A-part of AB-system, *J* 16.2 Hz), 3.06 (1H, B-part of AB-system, *J* 16.2 Hz), 3.9 (OH), 7.2–7.4 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 26.31, 26.56, 26.61, 26.94, 27.15, 41.88 (t), 48.89 (d), 77.25 (s), 125.67 (d), 126.91 (d), 127.96 (d), 144.47 (s), 178.38 (s).

(S)-(−)-3-Cyclohexyl-3-hydroxy-3-phenylpropanoic acid [(*S*)-(−)-**3**]. Racemic acid **3** (599 mg, 2.42 mmol) and (*S*)-1-phenylethylamine (289 mg, 2.38 mmol) were dissolved in EtOH (22 ml) and the solution kept at 5 °C overnight. The crystalline salt (217 mg) was harvested and decomposed as described above for (*R*)-(+)-**3**, yielding (*S*)-(−)-**3** (147 mg, 49 %) which was recrystallized from EtOAc. $[\alpha]_D^{20}$ −25.6° (*c* 1.92, EtOH). The acid (*S*)-(−)-**3** (1.41 g, 55 %) was also obtained from (±)-**3** (5.111 g, 20.6 mmol) employing cinchonine (6.079 g, 20.7 mmol; Fluka) and

fractional crystallization four times at ambient temperature from EtOH; $[\alpha]_D^{23}$ −26.8° (*c* 3.47, EtOH).

(S)-(+)-1-Cyclohexyl-1-phenyl-1,3-propanediol [(*S*)-(+)-**5**]. Boron trifluoride etherate (4.162 g, 29.3 mmol) was added to a mixture of (*S*)-(−)-3-cyclohexyl-3-hydroxy-3-phenylpropanoic acid [1.350 g, 5.44 mmol; $[\alpha]_D^{23}$ −26.8°; (*S*)-(−)-**3**] and $NaBH_4$ (930 mg, 24.6 mmol) in dry THF (25 ml), and the mixture was heated under reflux for 1 h. 1 M NaOH (50 ml) was added to the mixture, which was then extracted twice with CH_2Cl_2. A colourless oil (1.401 g) was obtained on removal of the solvent. The oil was passed through a silica gel column (eluted with 1–2% MeOH in $CHCl_3$) yielding an oil whose NMR spectra indicated the presence of boron trifluoride complexes (?). The oil was redissolved in CH_2Cl_2 and treated with aqueous 2 M NaOH, water, aqueous 1 M HCl and water, furnishing essentially pure (^{1}H NMR) diol **5** as a crystalline solid (1.207 mg, 95%). The diol (*S*)-(+)-**5** was recrystallized from *n*-hexane. M.p. 100–102 °C; lit.[30] m.p. 93–94 °C for racemic diol **5**; $[\alpha]_D^{23}$ +22.5° (*c* 3.60, EtOAc); *m/z* (EI, %): 189 (3), 152 (10), 151 (100), 133 (21), 105 (61), 77 (16); ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.9–1.4 (7H, m, 1.5–2.0 (6H, m), 2.27–2.38 (1H, m), 3.45–3.54 (1H, m), 3.66–3.73 (1H, m), 7.2–7.36 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 26.48, 26.67, 26.72, 27.07, 39.51 (t), 49.03 (d), 60.44 (t), 80.24 (s), 125.94 (d), 126.26 (d), 127.91 (d), 145.25 (s).

(S)-(−)-3-Chloro-1-cyclohexyl-1-phenyl-1-propanol [(*S*)-(−)-**6**]. A solution of (*S*)-(+)-1-cyclohexyl-1-phenyl-1,3-propanediol [613 mg, 2.62 mmol; (*S*)-(+)-**5**] and triphenylphosphine (730 mg, 2.78 mmol) in dry CCl_4 (6 ml)[23] was stirred for 6.5 h at 90 °C. A colourless precipitate [$(C_6H_5)_3PO$] appeared after ca. 2 h. The reaction mixture was transferred to a silica gel column and eluted with $CHCl_3$. Removal of the solvent left a colourless oil (520 mg, 74%). $[\alpha]_D^{21}$ −10.8° (*c* 4.50, EtOAc); *m/z* (EI, %): 189 (5), 171 (33), 169 (100), 133 (16), 105 (35), 91 (22); *m/z* (CI, %, isobutane): 237 (33), 236 (17), 235 (100), 175 (14), 169 (25), 153 (32); ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.8–1.4 (ca. 6H, m), 1.5–2.0 (ca. 6H, m), 2.26–2.46 (2H, m), 3.11–3.21 (1H, m), 3.42–3.52 (1H, m), 7.3–7.4 (5H, m); ^{13}C (67.8 MHz, $CDCl_3$): δ 26.34, 26.53, 26.94, 41.04 (t), 42.72 (t), 48.79 (d), 78.78 (s), 125.45 (d), 126.64 (d), 128.15 (d), 143.85 (s).

(S)-(+)-1-Cyclohexyl-1-phenyl-3-(1-pyrrolidinyl)-1-propanol hydrochloride [(*S*)-(+)-Procyclidine hydrochloride; (*S*)-(+)-**7**]. A solution of (*S*)-(−)-3-chloro-1-cyclohexyl-1-phenyl-1-propanol [308 mg, 1.22 mmol; (*S*)-(−)-**6**] and pyrrolidine (1.5 ml, 18 mmol) in 2-propanol (1 ml) was heated under reflux for 6.5 h. The solvent and excess pyrrolidine were removed *in vacuo*, leaving a solid residue which was redissolved in aqueous NaOH. The solution was extracted with EtOAc, and the extract was washed twice with water, dried over anhydrous Na_2SO_4, and concentrated to dryness. HCl in EtOH was added to the residue, and excess HCl and EtOH were removed *in vacuo*. Recrystallization from EtOH–diethyl ether (1:2) at −20 °C furnished (*S*)-(+)-**7** (248 mg, 63%). $[\alpha]_D^{20}$ +24.8°, $[\alpha]_{578}^{20}$ +26.0°, $[\alpha]_{546}^{20}$ +29.7°, $[\alpha]_{436}^{20}$ +51.3°, $[\alpha]_{365}^{20}$ +82.0° (*c* 0.40, $CHCl_3$); lit.[5] $[\alpha]_{546}^{20}$ +30° (*c* 0.4, $CHCl_3$); ^{1}H NMR and ^{13}C NMR spectra agreed with those of (±)-**7** (cf. Ref. 7).

(S)-(+)-1-Cyclohexyl-1-phenyl-3-(1-piperidyl)-1-propanol hydrochloride [(*S*)-(+)-**1**]. (*S*)-(−)-3-Chloro-1-cyclohexyl-1-phenyl-1-propanol [204 mg, 0.808 mmol; (*S*)-(−)-**6**] and piperidine (1 ml, 10 mmol) dissolved in 2-propanol (1 ml) were heated at reflux temperature for 4 h. The hydrochloride (*S*)-(+)-**1** was isolated as described above for (*S*)-(+)-**7**: yield 205 mg (75%); $[\alpha]_D^{20}$ +35.8°, $[\alpha]_{578}^{20}$ +37.5°, $[\alpha]_{546}^{20}$ +43.5°, $[\alpha]_{436}^{20}$ +76.5°, $[\alpha]_{365}^{20}$ +124.5° (*c* 0.4, $CHCl_3$); lit. values: see above; ^{1}H NMR and ^{13}C NMR spectra agreed with those of (±)-**1**.

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