Syntheses of (*R*)- and (*S*)-Proxyphylline

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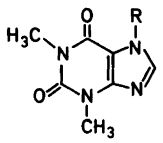
Proxyphylline [(±)-3,7-dihydro-7-(2-hydroxypropyl)-1,3-dimethyl-1*H*-purine-2,6-dione; *1*], a bronchodilator derived from theophylline (*2*) is currently being used in the racemic form.[1]

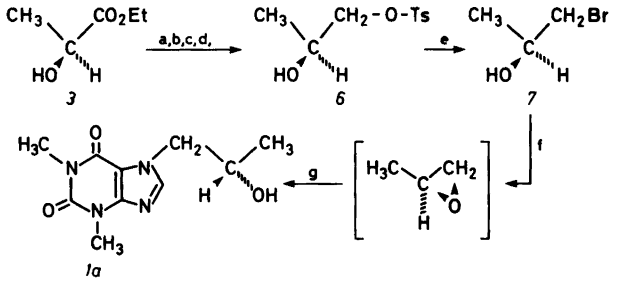


1: R = -CH_2-CHOH-CH_3
2: R = H

Recently we reported on the optical resolution, absolute configuration, and *in vitro* activity of the enantiomers of proxyphylline.[2] More comprehensive *in vivo* studies on activity, side effects, and metabolism require larger quantities of (*R*)- and (*S*)-proxyphylline, and the present communication describes the synthesis of the two enantiomers from theophylline and inexpensive, chiral starting materials.

The synthesis of (*S*)-proxyphylline (*1a*) is outlined in Scheme 1. Protection of the secondary hydroxyl group of (*S*)-ethyl lactate (=L-ethyl lactate, *3*), followed by hydride reduction, tosylation and removal of the tetrahydropyranyl group furnished (2*S*)-1-tosyloxypropane-2-ol (*6*) in good yield. The present route to this tosylate is considered advantageous compared to that of Gombos *et al.*[3] who had to perform chromatographic separation of *6* from the corresponding ditosylate. The tosylate *6* was reacted with LiBr in acetone to (2*S*)-1-bromopropane-2-ol (*7*). Treatment of the bromide *7* with KOH yielded (*S*)-propylene oxide which was distilled directly into the reaction vessel containing theophylline and catalytic amounts of pyridine.[2,4] The optical purity of (*S*)-proxyphylline (*1a*) was determined by HPLC-separation of the corresponding camphanates.[2] The ratio of (*S*)-proxyphylline to (*R*)-proxyphylline was found to be 98:2.

The preparation of (*R*)-proxyphylline (*1b*) is depicted in Scheme 2. In agreement with the results of Fu and co-workers[5] L-alanine (*8*) was converted to (2*S*)-2-chloropropionic acid (*9*) by nitrous acid in the presence of HCl. Winstein *et al.*[6,7] have suggested a mechanism for this reaction involving an intermediary α-lactone which is subsequently ring-opened by chloride ion. Thus, the retention of configuration is the net result of two inversions. The acid *9* was converted to the corresponding acyl chloride *10* in an exchange reaction with benzoyl chloride, and subsequently reduced with $LiAlH_4$ to (2*S*)-2-chloropropane-1-ol (*11*) as described by Fickett *et al.*[8] Neither the alcohol *11*, nor the acyl chloride *10*, were obtained in satisfactory yields by treating the acid *9* with $LiAlH_4$ or $SOCl_2$, respectively. KOH-treatment of (2*S*)-2-chloropropane-2-ol (*11*) gave (*R*)-propylene oxide which on reaction with theophylline in the usual manner, yielded (*R*)-proxyphylline (*1b*) of high optical purity. The product was esterified with (−)-camphanoyl chloride. TLC revealed the presence of traces of the diastereoisomeric (*S*)-proxyphylline camphanate. The two camphanates exhibit distinct



Scheme 1. Synthesis of (*S*)-proxyphylline (*1a*). a. Dihydropyran/H^+; b. $LiAlH_4$; c. TsCl; d. CH_3OH-water/H^+; e. LiBr; f. KOH; g. theophylline/pyridine.

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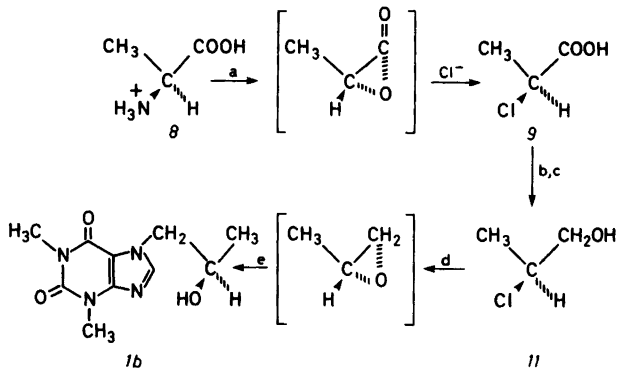

Scheme 2. Synthesis of (*R*)-proxyphylline (*1b*). a. $NaNO_2$–HCl; b. C_6H_5COCl; c. $LiAlH_4$; d. KOH; e. theophylline/pyridine.

differences in their ^1H NMR spectra[2] and, on the basis of integrals of CH_3-singlets in the 400 MHz spectrum of the mixture, the ratio of (*R*)-proxyphylline to (*S*)-proxyphylline was assessed to be 98.2:1.8.

Alternative syntheses of (*R*)- and (*S*)-propylene oxide have been reported by Hillis *et al.*[9] and Johnston *et al.*,[10] respectively.

Experimental. General. Melting points were determined on a Reichert melting point apparatus and are uncorrected. Analyses were performed by *Ilse Beetz Mikroanalytisches Laboratorium,* Kronach, West Germany. Optical rotations, infrared spectra, and mass spectra were recorded on Perkin-Elmer 141, Beckman Acculab 2, and Micromass 7070F instruments, respectively. Chemical ionization mass spectra were obtained by the direct-inlet method employing isobutane as ionizing gas. ^1H NMR spectra were recorded on Jeol JNM–PMX 60SI and Bruker WM-400 spectrometers, respectively. Analytical thin-layer chromatography was performed on Merck's HPTLC Kieselgel 60 F_{254}. Preparative thin-layer chromatography was accomplished on Merck's Kieselgel 60 F_{254}, 20×20×0.025 cm, with 2 % CH_3OH in $CHCl_3$ as the mobil phase. The esters were eluted from the silica gel with 50 % CH_3OH in $CHCl_3$.

(2S)-Ethyl 2-tetrahydropyranyloxypropionate (=(2*S*)-ethyl 2-THP-oxypropionate; two diastereoisomers; *4*). A mixture of (*S*)-ethyl lactate (29.9 g; 0.253 mol; *3*), dihydropyran (21.9 g; 0.26 mol), and two drops of concentrated HCl was stirred at room temperature for 3 h. CH_2Cl_2 (200 ml) was added and the solution washed with 10 % NaOH (75 ml) and 10 % NaCl (50 ml). Removal of the solvent left *4* as a colourless oil (47.7 g; 93 %). B.p. 97–105 °C (11 mm); $[\alpha]_D^{20}$ −41.1° (*c* 2.1; $CHCl_3$); R_f 0.70 and 0.76 (0.4 % CH_3OH in $CHCl_3$); ^1H NMR (60 MHz, $CDCl_3$): δ 1.1–2.0 (12H), 3.3–4.9 (6H); *m/z* (EI, %): 201 (M^+−1, 0.2), 85 (100). Anal. $C_{10}H_{18}O_4$:C,H.

(2S)-2-THP-oxypropane-1-ol (*5*); (two diastereoisomers). (2*S*)-Ethyl 2-THP-oxypropionate (5.63 g; 27.9 mmol; *4*) in diethyl ether (15 ml) was slowly (15 min) added to a suspension of $LiAlH_4$ (1.01 g; 26.6 mmol) in diethyl ether (100 ml) and the mixture was stirred at ambient temperature for 3 h. Excess $LiAlH_4$ was destroyed with water (9 ml). The mixture was filtered and the solution washed with 10 % NaCl and dried over Na_2SO_4. The solvent was removed leaving *5* as a colourless oil (3.99 g; 91 %). B.p. 100–105 °C (11 mm); $[\alpha]_D^{20}$ +17.0° (*c* 2.3; $CHCl_3$); R_f 0.14 and 0.19 (0.2 % CH_3OH in $CHCl_3$); ^1H NMR (60 MHz, $CDCl_3$): δ 1.1–2.5 (9H), 3.3–4.9 (7H). Anal. $C_8H_{16}O_3$: C,H.

(2S)-1-Tosyloxypropane-2-ol (*6*). *p*-Toluenesulfonyl chloride (21.8 g; 115 mmol) was added to a solution of (2*S*)-2-THP-oxypropane-1-ol (16.5 g; 103 mmol; *5*) in pyridine (60 ml) and the mixture was kept at room temperature for 24 h. CH_2Cl_2 (350 ml) was added and the solution successively washed with 2N HCl (100 ml), water (80 ml), 10 % $NaHCO_3$ (80 ml), and water (80 ml). Removal of the solvent yielded an oil (31.8 g; R_f 0.29 (0.4 % CH_3OH in $CHCl_3$)). A mixture of CH_3OH (60 ml), water (30 ml) and conc. HCl (6 ml) was added to the oil which slowly (in *ca.* 10 min) dissolved. After 20 min at room temperature, water (30 ml) was added and the solution extracted with CH_2Cl_2 (3×150 ml). The solvent was removed *in vacuo* leaving an oil (23.9 g) which crystallized from diethyl ether (40 ml)-pentane (25 ml). Yield: 14 g (59 %); m.p. 33–35 °C; lit.[3] m.p. 48–50 °C; $[\alpha]_D^{20}$ +10.6° (*c* 4.7; $CHCl_3$); lit.[3] $[\alpha]_D^{20}$ +9.8° (*c* 4.72; $CHCl_3$); R_f 0.37 (0.4 % CH_3OH in $CHCl_3$); ^1H NMR agreed

with data given in Ref. 3. Anal. $C_{10}H_{14}O_4S$: C, H, S.

(2S)-1-Bromopropane-2-ol (*7*). (2*S*)-1-Tosyloxypropane-2-ol (*6*) was converted to *7* essentially as described by Gombos *et al.*[3] Yield: 55 %; lit.[3] yield: 61 %; $[\alpha]_D^{20}$ +18.2° (*c* 8.2; $CHCl_3$); lit.[3] $[\alpha]_D^{20}$ +15.3° (*c* 8.2; $CHCl_3$); ^1H NMR agreed with data given in Ref. 3.

(S)-Proxyphylline (1a). *1a* was prepared as previously described.[2,4] Yield after recrystallization from absolute C_2H_5OH: 72 %, $[\alpha]_D^{20}$ +62.5° (*c* 2.8; $CHCl_3$); lit.[2] $[\alpha]_D^{20}$ +64.8° (*c* 4.5; $CHCl_3$); m.p. R_f, ^1H NMR, and MS agreed with data previously reported.[2] An aliquot (98 mg) of the product was esterified with (−)-camphanoyl chloride as described in Ref. 2 and the esters separated by HPLC. The ratio between the esters derived from (*R*)- and (*S*)-proxyphylline was found to be 98:2.

(2S)-2-Chloropropionic acid (*9*). The method of preparation followed that of Fu *et al.*[5] except for minor modifications. $NaNO_2$ (50.5 g; 0.73 mol) was added during 5 h to a chilled (0 °C) solution of L-alanine (*8*) (40.2 g; 0.45 mol) in 6 N HCl (400 ml). The mixture was strirred for a total of 20 h and then extracted with ether (4×250 ml). The extract was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Yield: 34.6 g (71 %); b.p. 77−82 °C (10 mm); lit.[5] b.p. 77 °C (10 mm); $[\alpha]_D^{20}$ −12.4° (*c* 2.7; water); lit.[5] $[\alpha]_D^{25}$ −14.6 (neat); ^1H NMR (60 MHz, $CDCl_3$): δ 1.75 (3H, d, *J*=7 Hz), 4.5 (1H, q, *J*=7 Hz); *m/z* (CI, %): 109 (M^++1, 100), 111(M^++1, 31).

(2S)-2-Chloropropionyl chloride (*10*). *10* was prepared from *9* in an exchange reaction with benzoyl chloride as described by Fickett *et al.*[8] Yield: 56 %; lit.[8] yield: 72 %; $[\alpha]_D^{20}$ −14.0° (*c* 2.0; $CHCl_3$); lit.[8] $[\alpha]_D^{25}$ +4.3° (neat); ^1H NMR (60 MHz, $CDCl_3$): δ 1.8 (3H, d, *J*=7 Hz), 4.7 (1H, q, *J*=7 Hz).

(2S)-2-Chloropropane-1-ol (*11*). *10* was reduced with $LiAlH_4$ in dry ether as described by Fickett *et al.*[8] The yield of *11* was 61 % according to ^1H NMR of the crude product which also contained some 2-chloropropionic acid. Yield after distillation: 46 %; lit.[8] yield: 67−72 %; $[\alpha]_D^{20}$ +21.8° (*c* 2.0; $CHCl_3$); lit.[8] $[\alpha]_D^{25}$ +17.16° (neat); ^1H NMR (60 MHz, $CDCl_3$): δ 1.5 (3H, d, *J*=7 Hz), 2.55 (1H, broad s, *OH*), 3.5−3.7 (2H, m), 3.8−4.4 (1H, m); *m/z* (EI, %): 94 (M^+, 6), 96 (M^+, 2).

(R)-Proxyphylline (1b). *1b* was prepared as previously described. Yield after recrystallization from C_2H_5OH: 65 %; m.p. 142−150 °C; lit.[2] m.p. 151−151.5 °C; $[\alpha]_D^{20}$ −58.3° (*c* 2.0; $CHCl_3$); lit.[2] $[\alpha]_D^{20}$ −63.8° (*c* 0.42; $CHCl_3$); R_f, ^1H NMR and MS agreed with data previously reported.[2] An aliquot (107 mg) of the product was esterified with (−)-camphanoyl chloride as previously described.[2] TLC (4 % CH_3OH in $CHCl_3$) and UV-detection at 254 nm, indicated the presence of traces (R_f 0.58) of the corresponding ester of (*S*)-proxyphylline; R_f 0.52 for the ester of (*R*)-proxyphylline. The camphanates were purified by preparative TLC, and the esters eluted together (19 mg). The ^1H NMR spectrum (400 MHz, $CDCl_3$) of the mixture allowed an assessment of the ratio of the two esters. A comparison of the integrals of the CH_3-singlets at δ 0.78 (major; *cf.* Ref. 2) and δ 0.92 indicated a ratio (*R*)-proxyphylline camphanate to (*S*)-proxyphylline camphanate of 98.2:1.8.

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