Short Communication

One-pot Synthesis of (*R*)-(−)-Xanthinol Nicotinate, a Peripheral Vasodilator, Using (*S*)-(Chloromethyl)oxirane as Chiral Synthon

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Xanthinol nicotinate (Complamin®), a drug used in the treatment of peripheral and cerebral vascular diseases, consists of the salt of the basic, racemic theophylline derivative xanthinol (*1*,(±)-3,7-dihydro-7-[2-hydroxy-3-[(2-hydroxyethyl)-methylamino]propyl]-1,3-dimethyl-1*H*-purine-2,6-dione) and nicotinic acid.[1-3] Recently, we reported on the optical resolution and absolute configuration of xanthinol.[4] (−)-Xanthinol (*1a*) was considered to possess (*R*)- configuration on the basis of its CD curve being similar to that of the structurally closely related (*R*)-(−)-proxyphylline.[4-6] This assignment has now been confirmed by preparing (*R*)-(−)-xanthinol (*1a*) using (*S*)-(chloromethyl)oxirane as the chiral building block.

Theophylline (*2*) was reacted with (*S*)-(chloromethyl)oxirane (*3*)[7-9] in the presence of puridine as catalyst to yield (*S*)-7-(3-chloro-2-hydroxypropyl)theophylline (*4*) as described by Roth[10] for racemic *4*. The chlorohydrin *4* was, without isolation, subsequently reacted with 2-(methylamino)ethanol (*5*) furnishing (*R*)-xanthinol (*1a*) which was readily purified as the crystalline nicotinate salt; overall yield, 67 %. The latter step which is similar to reactions between *4* and various amines described by Yoshida and Fukuda,[11] is considered advantageous compared to the procedure of Korbonits *et al.*[12] who successively treated *4* with sodium hydroxide and 2-(methylamino)ethanol (*5*). In our hands, this treatment resulted in a discoloured product which, on chromatography, gave xanthinol nicotinate at a lower yield.

The (*R*)-(−)-xanthinol (*1a*) thus prepared was regarded as optically pure judging from its optical activity, $[\alpha]_D^{22}-77.35°$, which agrees well with the rotation calculated, $[\alpha]_D-77.07°$, on the basis of the optical activity of a 93:7 mixture of (*R*)- and (*S*)-xanthinol (*1a* and *1b*) which was examined using ^{1}H NMR and a chiral solvating agent.[4,13,14]

The synthesis of (*S*)-(+)-xanthinol (*1b*) using the same chiral synthon *3* was envisaged applying the synthetic route described in the patent for this drug.[1] However, the modest optical activity for the final product ($[\alpha]_D$ varied between +2° and +18° for the nicotinate salt) indicated that both the oxirane ring and the chloromethyl group of *3* had been attacked by the amine *5*.

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Optical rotations, IR spectra, and mass spectra were recorded on Carl Zeiss, Perkin Elmer 597, and Jeol JMS-DX303 instruments, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol JNM GX270 instrument. TMS, TSP-d_4, or

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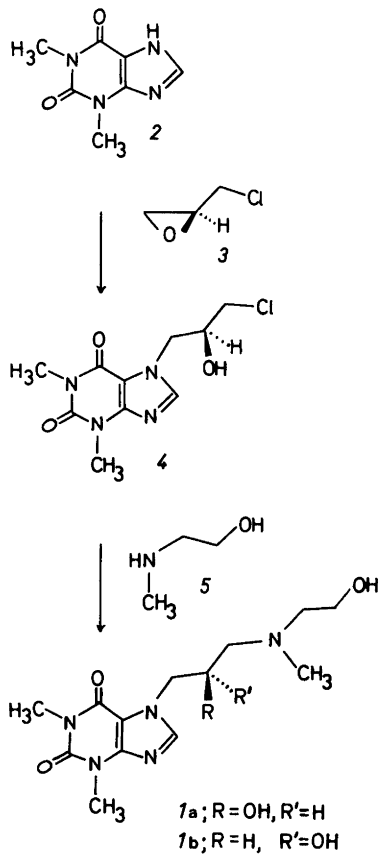

Fig. One-pot synthetic route to (*R*)-(−)-xanthinol (*1a*).

the solvent peak of $CDCl_3$ at δ 77.08 (^{13}C) were used as internal references unless otherwise stated.

(S)-(*Chloromethyl*)*oxirane* (3). Compound *3* was prepared as described by Baldwin *et al.*[7] $[\alpha]_D^{23}$ 31.9° (*c* 1.12; CH_3OH), lit.[7] $[\alpha]_D^{23}$ 33.0° (*c* 1.126; CH_3OH).

(R)-(−)-*Xanthinol nicotinate.* A stirred mixture of (*S*)-(chloromethyl)oxirane (*3*, 507 mg of a fraction containing ~15 % (^1H NMR) of an unknown impurity; 4.66 mmol) theophylline hydrate (*2*; 916 mg; 4.63 mmol; Norsk Medisinaldepot), pyridine (0.1 ml), and 2-propanol (4 ml) was refluxed for 1 h. Dissolution of the poorly soluble theophylline (*2*) indicated complete reaction. 2-(Methylamino)ethanol (*5*; 960 mg; 12.78 mmol; Fluka) was added to the reaction mixture which was stirred and refluxed for 3 h 15 min and subsequently stirred at ambient temperature for 2 h 15 min. Nicotinic acid (1006 mg; 8.17 mmol; Merck), and 2-propanol (10 ml) was added to the solution and (*R*)-(−)-xanthinol nicotinate (1353 mg; 67 %) crystallized at room temperature overnight. The product was recrystallized thrice from water/2-propanol (ratio ~1:9; 5–10 ml). M.p. 183–186 °C, lit.[1] m.p. 181 °C for the racemate; $[\alpha]_D^{25}$ −45.16° (*c* 3.48; H_2O); ^1H NMR (D_2O): δ 3.01 (3H, s), 3.31 (3H, s), 3.3–3.6 (4H, m), 3.49 (3H, s), 3.97 (2H, t), 4.28 (1H, dd), 4.53 (2H, m), 7.48 (1H, m), 7.99 (1H, s), 8.18 (1H, m), 8.56 (1H, m), 8.86 (1H, m), ^{13}C NMR (D_2O): δ 175.16 (s), 158.59 (s), 155.03 (s), 152.84 (d), 151.52 (d), 151.28 (s), 146.56 (d), 140.33 (d), 134.93 (s), 126.51 (d), 109.65 (s), 67.07 (d), 60.41 (t), 60.33 (t), 57.87 (t), 52.91 (t), 43.74 (q), 32.54 (q), 30.62 (q), (reference: CH_3CN; CH_3-signal at δ 3.53), and IR (KBr): 1088 (s), 1020 (s), 970 (s), 745 (s), 685 (s), 618 (m), 495 (m) cm^{-1} were in close agreement with corresponding data for (±)-xanthinol nicotinate.

(*R*)-(−)-*Xanthinol* (1a). Compound *1a* was obtained in quantitative yield by passing an aqueous solution of (*R*)-(−)-xanthinol nicotinate (710 mg) through an anion exchange column, CG-400, followed by removal of the water *in vacuo*. *1a* Crystallized on standing at room temperature. M.p. 131 °C, lit.[15] m.p. 133 °C for (−)-xanthinol obtained on optical resolution via its mandelate salt. Our previously reported[4] m.p. 87–88 °C should be corrected. Lit.[15] m.p. 99 °C for (±)-xanthinol (*1*); $[\alpha]_D^{22}$ −77.35° (*c* 8.50; EtOH), calculated[4] (^1H NMR and chiral solvating agent[4,13,14]): $[\alpha]_D$ −77.07°; lit.[4] $[\alpha]_D^{20}$ −76.54° (*c* 8.1; EtOH); lit.[15] $[\alpha]_D$ −75.8° (solvent?) for (−)-xanthinol obtained on optical resolution; ^1H NMR and MS: as previously described for (±)- and (*R*)-(−)-xanthinol.[4] ^{13}C NMR was nearly identical to that of (±)-xanthinol (*1*). (*R*)-(−)- and (±)-xanthinol could not be separated when cochromatographed on silica gel (TLC, MeOH/$CHCl_3$ = 1:2).

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