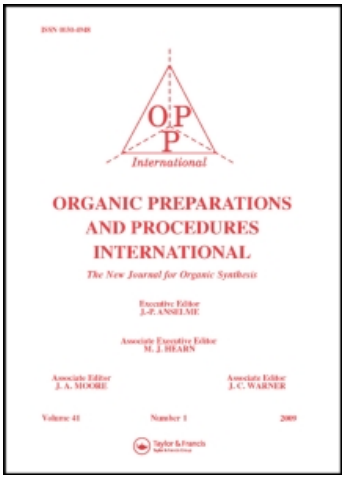


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# REGIOSELECTIVE DEOXYGENATION OF CHLORAMPHENICOL AND OF (1R,2R)-(+)-2-AMINO-1-PHENYL-1,3-PROPANEDIOL

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# REGIOSELECTIVE DEOXYGENATION OF CHLORAMPHENICOL AND OF (1R,2R)-(+)-2-AMINO-1-PHENYL-1,3-PROPANEDIOL†

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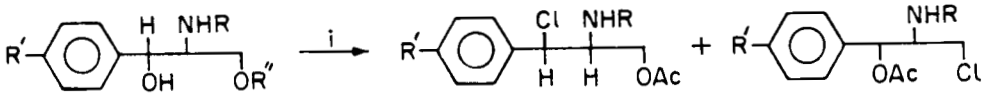
The removal of benzylic oxygen[1] from complex molecules[2] is of considerable interest in organic chemistry. Since (S)-(-)-2-amino-3-phenylpropanol[3] and other β-amino alcohols[4] exhibit interesting biological activity, we have studied the selective removal of benzylic hydroxyl from (1R,2R)-(+)-2-amino-phenyl-1,3-propanediol and from the drug chloramphenicol (2b). In the commercial synthesis of chloramphenicol (2b), racemic 2-amino-1-phenyl-1,3-propanediol is resolved and hence both enantiomers are readily available.

2-Acetoxybenzoyl chloride (1) is known to convert 1,3-diols to chloro acetates.[5] Amide 2a yielded the chloro acetate 3a when reacted with 1. Although chloramphenicol reacted readily with 1, the reaction was not regioselective and a 1:1 mixture of chloro acetates 3b and 4 was obtained.




2a) R = $COC_6H_5$, R' = R'' = H

2b) R = $COCHCl_2$, R' = $NO_2$, R''=H

3a) R = $COC_6H_5$, R' = H

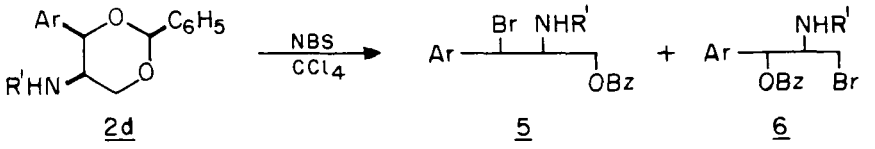
3b) R = $COCHCl_2$, R' = $NO_2$

4

R = $COCHCl_2$, R' = $NO_2$

i) 2-Acetoxybenzoyl Chloride (1), $CH_3CN$

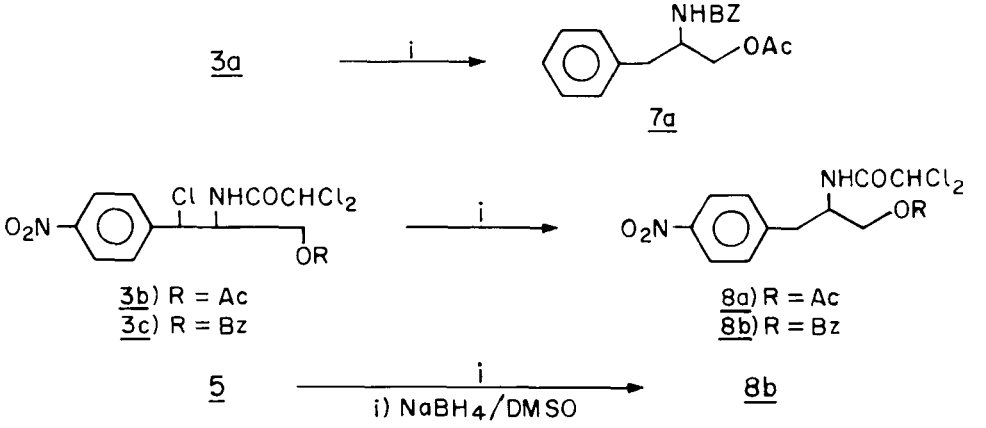
Reaction[6] of the benzylidene derivative 2d[7] with N-bromosuccinimide readily furnished a 1:1 mixture of the bromo benzoates 5 and 6.

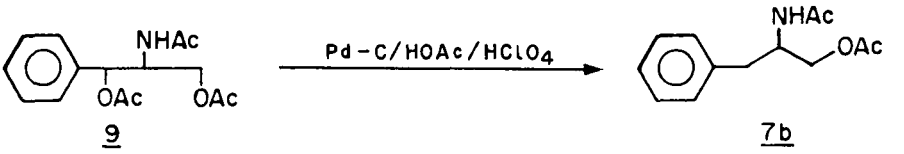



2d 5 6

$R' = COCHCl_2$ Ar = 4-$O_2NC_6H_4$

Compound 3a was reduced to 7a by heating with $NaBH_4$-DMSO.[8] Similarly, the mixture of chloro acetates 3b and 4 upon treatment with $NaBH_4$-DMSO, afforded 8a. $NaBH_4$-DMSO reduction of the mixture of 5 and 6 yielded the benzoate 8b. An alternative route for the preparation of the benzoate 8b from chloramphenicol involved the following steps: (i) selective benzoylation of 2b to the benzoate 2c (R = $COCHCl_2$; R' = $NO_2$; R'' = Bz); (ii) reaction of 2c with thionyl chloride to give the erythro chloro benzoate 3c[9] and (iii) reduction of 3c with $NaBH_4$-DMSO. Triacetate 9 could be smoothly hydrogenolysed to diacetate 7b by stirring under $H_2$ in acetic acid in the presence of Pd-C.






9 7b

## EXPERIMENTAL SECTION

(1S,2R)-(-)-Erythro-2-benzamido-1-chloro-1-phenyl-3-acetoxypropane (3a).- To a solution of 2-acetoxybenzoyl chloride (1) (3.3 g, 17 mmol) in anhydrous acetonitrile (30 ml) was added with stirring a solution of 2a[10] (2.5 g, 9.3 mmol) in acetonitrile (20 ml). The reaction mixture was heated under reflux for 2 hrs, cooled and the solvent was removed under vacuum. The residue was extracted with ether and the combined ethereal extracts were washed with cold $Na_2CO_3$ (50 ml, 5%) solution, water and saturated brine solution. The organic phase was dried over anhydrous $Na_2SO_4$, evaporated and the residue recrystallised from benzene-pet.ether to yield 2.5 g (80%) of white crystals, mp. 102-104°; $[\alpha]_D^{20}$ -57° (c = 1.4 EtOH).

Anal. Calcd. for $C_{18}H_{18}ClNO_3$: C, 65.47; H, 5.43

Found: C, 65.54; H, 5.66

$^1$H-NMR ($CDCl_3$): δ 2.09 (s, 3H, OCO-C<u>H</u>$_3$), 4.20 (m, 2H, C<u>H</u>$_2$-$OCOCH_3$), 4.88 (m, 1H, N-<u>CH</u>), 5.20 (d, 1H, $C_6H_5$-C<u>H</u>, J = 4 Hz), 7.19-7.53 (m, 5H, ArH), 7.75 (m, 3H, ArH), 7.95 (m,2H, ArH).

Reaction of 2-Acetoxybenzoyl Chloride with Chloramphenicol(2b). This reaction was carried out and the products worked up as described above to furnish a 1:1 mixture of (1S,2R)-erythro-1-chloro-2-dichloroacetamido-1-(4-nitrophenyl)-3-acetoxypropane (3b) and (1R,2R)-threo-3-chloro-2-dichloroacetamido-1-(4-nitro-

and then cooled to 0°. The succinimide was removed by filtration, the filtrate was evaporated in vacuo and the residue was extracted with ether. The ethereal extract was washed with $Na_2CO_3$ solution (10%, 2 x 20 ml), sodium thiosulphate solution (15%, 2 x 10 ml), water and saturated brine solution. The organic phase was dried ($Na_2SO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography [silica gel, solvent:pet.ether-ether (1:2)] to furnish a 1:1 mixture of (1S, 2R)-erythro-1-bromo-2-dichloroacetamido-1-(4-nitrophenyl)-3-benzoyloxypropane (5) and (1R, 2R)-threo-3-bromo-2-dichloroacetamido-1-(4-nitrophenyl)-1-benzoyloxypropane (6). Yield: 1.79 g (80%). $^1$H-NMR($CDCl_3$): δ 3.45 (m, 1H, $C\underline{H}_2$-Br), 4.53 (m, 1H, $C\underline{H}_2$-$OCOC_6H_5$), 4.73 (broad, m, 1H, N-C$\underline{H}$), 5.40 (d, J = 5 Hz, 0.5 H, C$\underline{H}$-Br), 5.89 (s, 1H, $C\underline{H}Cl_2$), 6.38 (d, J = 8 Hz, 0.5 H, C$\underline{H}$-$OCOC_6H_5$), 7.16 (m, 1H, $\underline{NH}$), 7.33 - 8.44 (m, 9H, ArH).

S-(-)-2-Benzamido-1-phenyl-3-acetoxypropane (7a).- To a solution of sodium borohydride (0.37 g, 9.8 mmol) in dry DMSO (10 ml) was added with stirring a solution of 3a (0.5 g, 1.5 mmol) in DMSO (10 ml). The reaction mixture was heated at 85° for 2 hrs, cooled and poured into cold water and extracted with ether. The ethereal extract was washed with water, saturated brine, dried ($Na_2SO_4$), the solvent evaporated and the residue recrystallized from benzene-pet.ether to yield 0.271g (60%) of white crystals, mp. 132-134°; $[\alpha]_D^{20}$ -40° (c=1 EtOH).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.17; H, 6.44

Found: C, 72.34; H, 6.54

$^1$H-NMR($CDCl_3$): δ 2.09 (s, 3H, OCOC$\underline{H}_3$), 3.00 (octet, 2H, $C_6H_5$-

phenyl)-1-acetoxypropane (4). Yield: 83%. $[\alpha]_D^{28}$ -30° (c = 10 $CHCl_3$).

3b: $^1$H-NMR($CDCl_3$): δ 2.08 (s, 3H, O-$COCH_3$), 4.20 (d, 2H, J = 6 Hz, $CH_2$-$OCOCH_3$), 4.60 (m, 1H, N-CH), 5.30 (d, J = 4 Hz, 1H, CH-Cl), 6.84 (m, 1H, NH), 7.55 (d, J = 10 Hz, 2H, ArH), 8.20 (d, J = 10 Hz, 2H, ArH).

4: $^1$H-NMR($CDCl_3$): δ 2.12 (s, 3H, $OCOCH_3$), 3.50 (m, 2H, $CH_2$-Cl) 4.60 (m, 1H, N-CH), 6.84 (m, 1H, NH), 7.55 (d, J = 10 Hz, 2H, ArH), 8.20 (d, J = 10 Hz, 2H, ArH).

(2S, 4R, 5R)-(+)-Threo-5-(2,2-dichloroacetamido)-4-(4-nitrophenyl)-2-phenyl-1,3-dioxane (2d).- A mixture of 2b (3 g, 9.2 mmol), benzaldehyde (2 g, 19 mmol) and p-toluenesulfonic acid (0.12 g) in dry benzene (200 ml) was heated under reflux and the water formed was removed as an azeotrope (3 hrs). The solvent was removed under vacuum and the residue was taken up in ether. The ethereal extract was washed with cold $Na_2CO_3$ (50 ml, 5%) solution, water and saturated brine (2 x 50 ml), dried ($Na_2SO_4$), filtered and concentrated to a white solid under reduced pressure. Recrystallization from benzene-pet. ether yielded 2.8 g (73%) of white crystals, mp. 98-100°, lit.[7] mp. 100.5°.

Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O_5$: C, 52.52; H, 3.89
Found : C, 52.65; H, 3.99

Reaction of N-bromosuccinimide with (2S, 4R, 5R)-(+)-threo-5-(2,2-dichloroacetamido)-4-(4-nitrophenyl)-2-phenyl-1,3-dioxane (2d).- A mixture of 2d (1.70 g, 4.2 mmol), N-bromosuccinimide (1g, 5 mmol), benzoyl peroxide) (0.1 g) and carbon tetrachloride (50 ml) was heated under reflux for 2 hrs.

$CH_2$), 4.20 (octet, 2H, $C\underline{H}_2$-$OCOCH_3$), 4.60 (m, 1H, N-C$\underline{H}$), 6.50 (d, 1H, N$\underline{H}$, J = 9 Hz), 7.30 (s, 5H, ArH), 7.5 (m, 3H, ArH), 7.8 (m, 2H, ArH).

S-(-)-2-Dichloroacetamido-1-(4-nitrophenyl)-3-acetoxypropane (8a) from reaction of $NaBH_4$ (0.526 g, 14 mmol) on a 1:1 mixture of 3b and 4 (2.65 g, 7 mmol) at room temperature for 12 hrs, followed by recrystallization of the reaction product from benzene-pet.ether yielded 0.8 g (66%) of light yellow crystals, mp. 143-145°, lit.[11] mp. 147°; $[\alpha]_D^{20}$ -9° (c = 1 EtOH) lit.[11] $[\alpha]_D^{20}$ -10°.

$^1$H-NMR($CDCl_3$): δ 2.09 (s, 3H, $OCOC\underline{H}_3$), 2.99 (d, J = 6 Hz, $C_6H_5$-$C\underline{H}_2$), 4.13 (d, J = 5 Hz, $C\underline{H}_2$-$OCOCH_3$), 4.33 (m, 1H, N-C$\underline{H}$), 5.8 (s, 1H, COC$\underline{H}$), 7.32 (d, J = 8 Hz, 2H, ArH), 8.11 (d, J = 8 Hz, 2H, ArH).

S-(+)-3-Benzoyloxy-2-dichloroacetamido-1-(4-nitrophenyl)-propane (8b) was obtained in 65% yield by reaction of 3c with $NaBH_4$ at 35° for 6 hrs, mp. 188-190°; $[\alpha]_D^{20}$ +27° (c = 3.8 EtOAc).

Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O_5$: C, 52.52; H, 3.89
Found: C, 52.32; H, 4.03

$^1$H-NMR($CDCl_3$): δ 3.13 (d, J = 7 Hz, 2H, $C_6H_5C\underline{H}_2$), 4.44 (m, 2H, $C\underline{H}_2$-O-), 4.53 (m, 1H, N-C$\underline{H}$), 5.90 (s, 1H, COC$\underline{H}$), 7.00 (m, 1H, NH, J = 9 Hz), 7.40 (d, J = 8 Hz, 2H, ArH), 7.49 (m, 3H, ArH), 8.00 (m, 2H, ArH), 8.16 (d, J = 8 Hz, 2H, ArH).

Reaction of $NaBH_4$ with a Mixture of (5) and (6).- The reaction of $NaBH_4$ (0.165 g, 4 mmol) with a 1:1 mixture of 5 and 6 (0.99 g, 2 mmol) at 35° for 6 hrs, gave 0.29 g (60%) of 8b, mp. 186-188°. NMR spectrum of 8b thus obtained was identical with

that of a sample prepared as described above.

S-(-)-Acetamido-1-phenyl-3-acetoxypropane (7b).- Compound 9[12] (1 g, 3.4 mmol) in glacial acetic acid (15 ml) was hydrogenated in the presence of 5% Pd/C and perchloric acid (Caution! 72%, 0.5 ml) for 2 hrs at 85-90°. After cooling, the catalyst was filtered, the solvent was removed in vacuo and the residue was extracted with ether. The ethereal extract was washed with $Na_2CO_3$ solution (5%, 20 ml), water and saturated brine solution. After drying ($Na_2SO_4$), the solvent was removed by distillation. Recrystallization from ether-pet.ether yielded 0.46 g, (60%) of white crystals, mp. 115-116°; $[\alpha]_D^{20}$ -21° (c = 1 $CHCl_3$).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28

Found: C, 65.98; H, 7.17

$^1$H-NMR($CDCl_3$): δ 1.96 (s, 3H, NHAc), 2.09 (s, 3H, $OCOCH_3$), 2.84 (m, 2H, $C_6H_5$-$CH_2$), 4.02 (d, J = 5 Hz, $CH_2$-$OCOCH_3$), 4.38 (m, 1H, -NCH), 5.67 (d, J = 7 Hz, 1H, NH), 7.20 (s, 5H, ArH).



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