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A CONVENIENT SYNTHESIS OF OPTICALLY PURE (S,S)-NORPSEUDOEPHEDRINE

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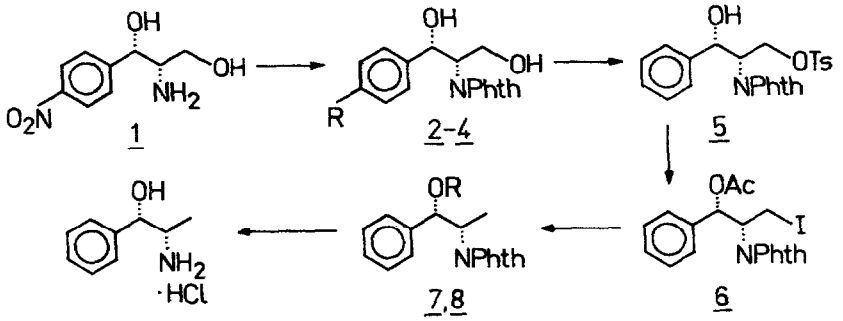
The synthesis of optically pure (S,S)-norpseudoephedrine starting from (1S,2S)-2-amino-1(4-nitrophenyl)propan-1,3-diol is described.

We describe a convenient synthesis of the title compound which in rac. form is used in appetite suppressors and administered as a special antiepilepticum starting from an intermediate of the chloramphenicol synthesis (L-base 1). The chemistry of chloramphenicol intermediates is still of interest and recently several papers have been published with regard to photooxidation of the N-acyl-L-base[1] and further conversion reactions of the D-base intermediate[2]. Furthermore, some amendments of the Meerwein-Ponndorf-Verley reduction have been demanded recently by Czech authors[3]. Early investigations were performed by Fodor et al.[4]. During the structural elucidation of chloramphenicol they obtained norpseudoephedrine, but only in very small yield (0.1 %). Obviously, the main difficulties depend on the proper choice of the N-protection group important for the adjoining substitution of the nitro and primary OH-group by hydrogen to obtain the 1,2-aminoalcohol moiety.

Treatment of the N-phthaloyl derivative[5] 2 ($R=NO_2$, Scheme 1) with isopropanol and Raney-nickel yielded the amine 3 ($R=NH_2$, mp 136-7 °C, 80 %). Under the mild condition of the transfer hydrogenation neither the phthalimido nor the benzylic hydroxyl group were attacked affording a rather pure intermediate suitable for diazotization which efficiently proceeded in aqueous H_2SO_4 with $NaNO_2$. Although the diazotization procedure required 3 hours to be nearly complete, no phthaloyl loss was observed. This underlines the advantage of the phthaloyl group in contrast to acyl groups migrating under these conditions to a rather high degree[6]. Therefore, the reported yields for 2-benzamido[7] 3 seem to be overestimated. The addition of Cu-powder and ethanol rapidly led to the evolution of N_2 giving 4 (R=H, mp 162-6 °C, 75 %). Reaction of 4 with 1.1 equivalent p-TsCl in pyridine (0 °C) provided the 3-O-tosyl-ester 5 (mp 170-4 °C, 75 %) without forming the corresponding 1,3-di-O-tosylate under these conditions, however, rising the temperature to 80 °C and enhancing the molar ratio of p-TsCl to 3 the 1,3-ditosylate becomes the main product. Replacement of the tosyl group by iodide in 5

was performed with NaI in boiling acetic anhydride, thus highly increasing the reaction rate in contrast to DMSO or HMPA. Simultaneously, acylation of the hydroxyl group occurs to give 6 (mp 179-83 °C, 90 %), the structure of which became evident from the spectra[8]. Reduction of 6 with Pd/C and H_2 afforded the amino alcohol 7 (R=Ac, mp 98-100.5 °C, 80 %). Preliminary experiments revealed that the hydrogenation of the nitro group combined with the simultaneous reductive dehalogenation of the corresponding iodide of 1 proceeds disadvantageously, thus indicating the synthetic pathway cited. Treatment of 7 by potassium methoxide resulted only in ester bond cleavage to give 8 (R=H, mp 156-8 °C, 80 %), which after hydrazinolysis yielded L-norpseudoephedrine hydrochloride ($[\alpha]_D^{20}$ +42.6°, c=7, H_2O; lit.[9] $[\alpha]_D^{20}$ +42.5°).

Scheme 1



Among the different N-protected groups investigated (alkyl, acetyl, benzoyl, cbo) only the phthaloyl group turned out to be useful in the norpseudoephedrine synthesis starting with L-base. It proved to be stable under transfer hydrogenation or other catalytic hydrogenation processes, inert against treatment with pyridine, and suitable for halogen incorporation (Br instead of I was also practised).

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