A New Route to DL-*threo-1-p-Nitrophenyl-2-amino-1, 3-propanediol*

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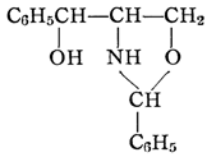
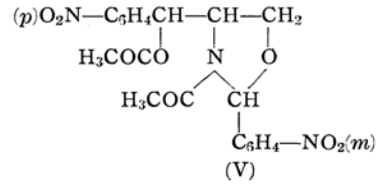
During the course of synthetic investigations of E. Erlenmeyer's *threo* phenylserine[1], we have reduced the latter with a modified Raney nickel catalyst, and obtained a new oxazolidine derivative which appears to be 2-phenyl-4-(α-hydroxybenzyl) oxazolidine (I). Starting from this oxazolidine derivative, we have



(I)

now synthesized DL-chlorampphenicol, an important antibiotic found by scientists of Parke, Davis and Company.

The *threo*-phenylserine ethyl ester was reduced in ethanol at about 50°C. with a modified Raney-nickel which was prepared by the ordinary digestion-procedure at 30°C. for one hour. After working up by evaporation and recrystallization, the above described oxazolidine (41%), m.p. 138–139°C. was obtained. *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.4; H, 6.67; N, 5.50. Found: C, 75.1; H, 6.58; N, 5.53%. Acetylation of the oxazolidine derivative (I) with acetic anhydride at room temperature



(V)

1) E. Erlenmeyer, *Ber.*, **25**, 3445 (1892).

yielded an N-acetyl derivative (II) (82%), m.p. 145–146°C. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: N, 4.72. Found: N, 4.64%. The failure of II to hydrolyze under Kunz's conditions[2] demonstrated that II is an N-acetyl derivative. Further acetylation of II with acetic anhydride in pyridine gave a viscous product (III), which on nitration with mixed acid (conc. H_2SO_4: conc. HNO_3=1:1) under ice-cooling for 30 minutes, finally at 15°C. for one hour, led to a viscous product (IV) containing a small quantity of crystals. The latter, after recrystallization, appeared to be 2-(*m*-nitrophenyl)-4-(α-hydroxy-*p*-nitrobenzyl)-oxazolidine (V) (12%), m.p. 192–193°C. *Anal.* Calcd. $C_{20}H_{19}O_8N_3$: N, 9.78. Found: N, 9.44%. V gave *m*-nitrobenzaldehyde on hydrolysis with dilute hydrochloric acid. The main part of IV usually remained viscous and oily. Hydrolysis with dilute hydrochloric acid, followed by neutralization with dilute sodium hydroxide, led to DL-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol, pale yellow crystals (49%), m.p. 143.5–145°C., which did not depress the melting point of an authentic sample obtoined by the synthetic route through *p*-nitroacetophenone[3] and, acylation with methyl dichloroacetate converted the product to DL-chloramphenicol.

It was also shown that the oxazolidine derivative (I) could be directly hydrolysed with dilute hydrochloric acid to DL-*threo*-1-phenyl-2-amino-1,3-propanediol (84%), m.p. 85–86°C., which led to the DL-chloramphenicol by the synthetic route described by Controulis and his coworkers.[4]

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2) A. Kunz and C. S. Hudson, *J. Am. Chem. Soc.*, **48**, 1982 (1926); M. L. Wolfrom, M. Königsberg, and S. Soltzberg, ibid., **58**, 409 (1936).
3) L. M. Long and H. D. Troutman. ibid., **71**. 2473(1949).
4) J. Controulis, M. C. Rebstock and H. M. Crooks, ibid., **71**, 2463 (1949).