Synthesis of Penicillin V

**Significance:** The penicillins constitute a family of β-lactam antibiotics which were first discovered in 1928 by Alexander Fleming. The lability of the amide bond is responsible for their remarkable bioactivity. The formation of this bond posed a major challenge in early synthetic studies towards penicillins. Having previously invented carbodiimide coupling agents, Sheehan and co-workers achieved the first total synthesis of penicillin V in 1957.

**Comment:** Racemic valine was efficiently transformed into N-acetylpenicillamine (D). Resolution of formamide rac-F using brucine followed by hydrolysis afforded (−)-penicillamine hydrochloride (G). Condensation with aldehyde H afforded thiazolidine I; side-product epi-I could be converted into I employing pyridine-induced epimerization. Removal of protecting groups and installation of the phenoxycetyl side chain furnished penicilloic acid L. Subsequent construction of the central amide bond was achieved with DCC under basic conditions to give the potassium salt of penicillin V.

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- β-lactam antibiotic
- penicillamine
- penicilloic acid
- penicillin V
- modified Erlenmeyer–Plöchl azlactone synthesis
- carbodiimide coupling