A New Approach to Semisynthetic Penicillins by the Mixed Anhydride Method

V. Škarić and V. Turjak-Zebić

Laboratory of Stereochemistry and Natural Products, »Ruder Bošković« Institute, 41001 Zagreb, Croatia, Yugoslavia

Received February 4, 1980

Aminoacylation of methyl 6-aminopenicillanate by energy-rich N-protected glycyl dibenzylphosphate in the presence of dicyclohexylcarbodi-imide is described.

An improvement of the efficiency of organic chemical synthesis was attempted by the imitation of natural reactions. Phosphorylated amino acid derivatives and the rupture of thus obtained high energy phosphates was used for aminoacylations of 6-aminopenicillanic acid (6-APA). Namely, the energy-rich mixed anhydrides, formed from adenosine triphosphate (ATP) and amino acids were shown to be the most efficient biosynthetic aminoacylating agents for the formation of the terminal 3'-O-aminoacyl-adenosine of the transfer ribonucleic acids. To our knowledge only a French patent1 superficially described mixed anhydrides as acylating agents in the semi-synthetic approach to penicillins.

In our quest for a new method for the preparation of semisynthetic β-lactam antibiotics the aminoacylation of methyl 6-aminopenicillanate by mixed high-energy phosphates was shown to be an efficient one. A mixed anhydride such as N-phthaloylglcyldibenzylphosphate anhydride was prepared from phthaloylglycyl chloride and the silver salt of dibenzylphosphate2 according to the Sheehan and Frank method3. It exhibited signals at δ 2.02—2.36 (4H, m, Ph protons), 2.63 (10H, s, Ph protons), 4.77 and 4.91 (2 × 2H, 2 × s, 2 × OCH2) and 5.57 (2H, s, N-CH2) in the 1H NMR spectrum and absorptions at \( \nu_{\text{max}} \) 1792, 1773, 1720, 1735, 735, 713, and 697 cm\(^{-1}\) in the IR spectrum.

\[
\begin{align*}
\text{(I)} & \quad R = \text{Pht-CH2} \\
\text{(II)} & \quad R = \text{Ph-CH2}
\end{align*}
\]

The prepared anhydride was allowed to react with methyl 6-aminopenicillanate in anhydrous dioxane solution at room temperature in the presence...
of dicyclohexylcarbodiimide. After 16 h a precipitate separated and the dioxane solution was lyophilized to the hitherto unknown methyl ester of phthalimido-methylpenicillin (I); it was efficiently purified by preparative TLC (developed and eluted with ether), 77% yield, m. p. 86–87 °C (ether — n-hexane), [α]D24 + 258° (c 1, MeOH).

**Anal. C11H19N3O5S** (417.43) calcd.: C 54.67; H 4.59; N 10.07%; found: C 55.02; H 4.92; N 10.08%.

UV spectrum: (in EtOH) λmax 219, 223 sh, 232 sh, and 240 nm (log ε 4.65, 4.58, 4.11, and 3.94). IR spectrum: νmax 3350, 2970, 1770, 1754, 1556, 1425, 1399, 1217, 797, and 719 cm⁻¹. 1H NMR spectrum (in CDCl₃): r 2.05–2.30 (4H, m, aromatic protons), 3.27 (1H, d, NH; JNH 8.78 Hz), 4.29 (1H, q, 6-H; J 6, 5 3.91 and JNH 8.78 Hz), 4.45 (1H, d, 5-H; J 5, 6 3.91 Hz), 5.56 (3H, s, 3-H and N-CH₂), 6.22 (3H, s, OCH₃), 8.36 and 8.51 (6H, 2 × s, 2 × 2-CH₃). The coupling constant for the protons at C-5 and C-6 (J 3.91 Hz) indicated the desired cis-configuration.

It is worth noting that treatment of the methyl ester of 6-APA with the amino acid phosphate in the absence of DCC afforded the corresponding penicillin derivative in remarkably lower yields. The smooth aminoacylation in the presence of DCC could be explained by its susceptibility to react with the dibenzylphosphoric acid formed, which otherwise could hydrolyze methyl 6-aminopenicillanate and thus lower the yield of the desired product. This assumption was based on our earlier dinucleoside phosphate syntheses and isolation of intermediary adducts the latter being masked at the anionic (phosphoric) sites by DCC.

In a similar attempt the methyl ester of 6-APA was converted into the methyl ester of benzylpenicillin 6 (II) by acylation with phenylacetyldibenzyl-phosphate, the latter being prepared from phenylacetyl chloride and the silver salt of dibenzylphosphoric acid. The mixed anhydride showed r values (in CDCl₃) at 2.67 (15 H, aromatic protons), 4.99 (4H, m, OCH₂), and 6.5 (2H, m, C—CH₂), while the IR spectrum exhibited absorption at νmax 1820, 1780, 1730, 742, and 700 cm⁻¹. The penicillin (II) was isolated in 55.4% yield and showed the 1H NMR spectrum (in CDCl₃): r 2.68 (5H, s, aromatic protons), 3.87 (1H, d, NH), 4.34 (1H, d, 5-H); J 5, 6 4 Hz), 4.54 (1H, d, 6-H); J 5, 6 4 Hz), 5.65 (1H, s, 3-H), 6.24 (3H, s, OCH₃), 6.38 and 8.51 (6H, 2 × s, 2 × 2-CH₃). The 1H NMR as well as the IR spectra were identical to those earlier reported for penicillin 7.

**REFERENCES**

Novi pristupi semisintetnim penicilinima metodom miješanih anhidrida

V. Škarić i V. Turjak-Zebić

Opisano je aminoaciliranje metil 6-aminopenicilanata s pomoću energijom bogatoga N-zaštićenog glicil dibenzilfosfata u nazočnosti dicikloheksilkarbodiimida.