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A New Approach to Semisynthetic Penicillins by the Mixed Anhydride Method

V. Škarić and V. Turjak-Zebić

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

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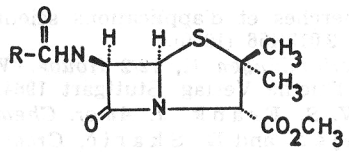
Aminoacylation of methyl 6-aminopenicillanate by energy-rich *N*-protected glycyl dibenzylphosphate in the presence of dicyclohexylcarbodi-imide is described.

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 patent[1] superficially described mixed anhydrides as acylating agents in the semisynthetic 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*-phthaloylglycyldibenzylphosphate anhydride was prepared from phthaloylglycyl chloride and the silver salt of dibenzylphosphate[2] according to the Sheehan and Frank method[3]. It exhibited signals at τ 2.02—2.36 (4H, m, Pht protons), 2.63 (10 H, s, Ph protons), 4.77 and 4.91 (2×2H, $2 \times$ s, $2 \times OCH_2$) and 5.57 (2H, s, N—CH_2) in the ^{1}H NMR spectrum and absorptions at ν_{max} 1792, 1773, 1720, 735, 713, and 697 cm^{-1} in the IR spectrum.



(I) R = Pht-CH_2
(II) R = Ph-CH_2

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 phthalimidomethylpenicillin (I); it was efficiently purified by preparative TLC (developed and eluted with ether), R_F ca. 0.67 (visible by starch-iodine-azide reagent and UV lamp), 77%, m. p. 86—87 °C (ether — *n*-hexane), $[\alpha]_D^{24}$ + 258° (c 1, MeOH).

Anal. $C_{19}H_{19}N_3O_6S$ (417.43) calc'd.: C 54.67; H 4.59; N 10.07%
found: C 55.02; H 4.92; N 10.08%

UV spectrum: (in EtOH) λ_{max} 219, 223 sh, 232 sh, and 240 nm (log ε 4.65, 4.58, 4.11, and 3.94). IR spectrum: ν_{max} 3350, 2970, 1779, 1754, 1724, 1536, 1425, 1399, 1217, 957, and 719 cm^{-1}. ^1H NMR spectrum (in $CDCl_3$): τ 2.05—2.30 (4H, m, aromatic protons), 3.27 (1H, d, NH; $J_{NH,6}$ 8.78 Hz), 4.29 (1H, q, 6-H; $J_{6,5}$ 3.91 and $J_{6,NH}$ 8.78 Hz), 4.45 (1H, d, 5-H; $J_{5,6}$ 3.91 Hz), 5.56 (3H, s, 3-H and N—CH_2), 6.22 (3H, s, OCH_3), 8.36 and 8.51 (6H, 2 × s, 2 × 2-CH_3). 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[4,5] 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 phenylacetyldibenzylphosphate, the latter being prepared from phenylacetyl chloride and the silver salt of dibenzylphosphoric acid. The mixed anhydride showed τ values (in $CDCl_3$) at 2.67 (15 H, s aromatic protons), 4.99 (4H, m, OCH_2), and 6.5 (2H, m, C—CH_2), while the IR spectrum exhibited absorption at ν_{max} 1820, 1780, 1730, 742, and 700 cm^{-1}. The penicillin (II) was isolated in 55.4% yield and showed the ^1H NMR spectrum (in $CDCl_3$): τ 2.68 (5H, s, aromatic protons), 3.87 (1H, d, NH), 4.34 (1H, d, 6-H); $J_{6,5}$ 4 Hz), 4.54 (1H, d, 5-H); $J_{5,6}$ 4 Hz), 5.65 (1H, s, 3-H), 6.24 (3H, s, OCH_3), 6.38 (2H, s, C—CH_2), 8.51 (6H, s, 2 × 2-CH_3). The ^1H NMR as well as the IR spectra were identical to those earlier reported for penicillin[7,8].

REFERENCES

1. Société d'études de recherches et d'applications scientifiques et médicales E. R. A. S. M. E., Fr. Demande 2 013 456 (1970).
2. F. Lynen, *Phosphorverbindungen II*, 12/2 *Houben-Weyl, Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart 1964.
3. J. C. Sheehan and V. S. Frank, *J. Amer. Chem. Soc.* **72** (1950) 1312.
4. V. Škarić, M. Hohnjec, and D. Škarić, *Croat. Chem. Acta* **49** (1977) 851.
5. V. Škarić and Z. Raza, *Croat. Chem. Acta* **52** (1979) 51.
6. H. T. Clarke, J. R. Johnson, and R. Robinson, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J. 1949, p. 93.
7. G. Yu. Pek, V. F. Bystrov, E. M. Kleiner, I. N. Blinova, and A. S. Khokhlov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **10** (1968) 2213.
8. J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach, and J. J. Ryan, *J. Amer. Chem. Soc.* **72** (1950) 3828.

SAŽETAK

Novi pristupi semisintetskim 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 diciklohekslkarbodiimida.

LABORATORIJ ZA STEREOKEMIJU
I PRIRODNE SPOJEVE
INSTITUT »RUĐER BOŠKOVIĆ«

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