Semi-synthetic Antibiotics: Organometallic Derivatives of 6-amino Penicillinic Acid

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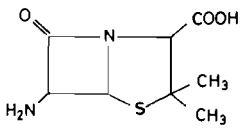
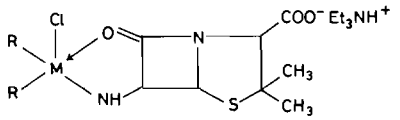
The semi-synthetic penicillins, derived from 6-amino penicillinic acid (*I*), constitute an important group of antibiotics. The introduction of substituents into the penicillin nucleus effects changes in antibiotic activity and β-lactamase susceptibility. Since the introduction of penicillins into chemical practice a continual problem has been the emergence of drug resistant strains of bacteria. In many cases this resistance arises from the production of β-lactamases, enzymes which degrade these antibiotics. The synthesis of new penicillins is important to keep pace with the appearance of these resistant bacteria strains. With this aim, we carried out the synthesis and characterisation of a few organometallic derivatives of penicillins of the type $(\eta^5\text{-R})_2M(Cl)L^-Et_3NH^+$ (II) [where R = cyclopentadienyl (C_5H_5), indenyl (C_9H_7); M = Ti(IV), Zr(IV), Hf(IV); LH = 6- amino penicillinic acid]. The compounds have been characterised as triethylamine salts. This is the first report on organometallic substituted semi-synthetic antibiotics, in which the penicillin moiety is directly bound to the metal ion.



(I)



(II)

R = C_5H_5 , C_9H_7

M = Ti(IV), Zr(IV), Hf(IV)

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The compounds (II) are yellow or brown in colour. They are soluble in THF, acetone and water. Conductance values indicate that these are 1:1 electrolytes. With ninhydrin reagent, these give the violet coloration characteristic of the amino acids. From TLC and elemental analyses, it is concluded that the compounds are pure.

The IR study of penicillin and its derivatives and possible models of penicillin has been extensive [1]. In the case of 6-amino penicillinic acid, the carbonyl absorption of the lactam ring is centered at 1765 cm^{-1}. However, for the metal complexes, it is shifted to 1650 cm^{-1}, indicating that the carbonyl group is bound to the metal ion. Thus the penicillin moiety is bidentate. The strong bands at ~1600 cm^{-1} and ~1330 cm^{-1} indicate the presence of an ionic carboxylic group. This is supported by the fact that the OH deformation vibration of the carboxylic group, which is expected to occur at ~935 cm^{-1} [2], is absent in the present complexes.

The appearance of a band at ~2715 cm^{-1} is indicative of the presence of the Et_3NH^+ group [3]. The C–H aromatic stretching frequency of the cyclopentadienyl or indenyl group absorbs at ~2930 cm^{-1}. Two prominent bands are also observed at ~2660 cm^{-1} and ~2480 cm^{-1}.

The C–N stretching frequency in the complexes absorbs at ~1040 cm^{-1}. In the case of 6-amino penicillinic acid, the corresponding absorption occurs at ~1015 cm^{-1}. The higher frequency observed in the case of metal complexes is due to the transfer of charge from the ligand to the metal. The C–S stretching frequency absorbs at ~580 cm^{-1}.

The ^1H NMR spectra of the complexes recorded in D_2O showed the following signals for the penicillin moiety: δ 5.30 (2H, s, methine at C_5, C_6); δ 4.20 (1H, s, methine at C_3); δ 1.62(3H, s,methyl); δ 1.48 (3H, s, methyl). In addition, the cyclopentadienyl protons absorb on a singlet at δ 6.0, the indenyl protons absorb on a singlet at δ 6.0 and the indenyl protons as a multiplet at δ 6.8–7.3, similar to the values observed for other ionic chelates involving these groups [4].

The UV spectra of 6-amino penicillinic acid showed a very intense band at 210 nm (log $\epsilon \sim 4.8$) due to the $\pi-\pi^*$ absorptions of the chromophoric C⋯⋯O group. In the case of metal complexes, this band is shifted to 224 nm, although its intensity remains almost the same. The shift is attributed to the involvement of the chromophoric C⋯⋯O group in the complexation.

The compounds have been found to be biologically active against various strains of drug resistant bacteria. The activities were measured *in vitro*. The details are under investigation.

0020-1693/84/$3.00

References

1 P. V. Demarco and R. Nagarajan, 'Cephalosporins and Penicillins', Academic Press, New York, 1972.
2 R. G. Sinclair, A. F. Mckay and R. N. Jones, *J. Am. Chem. Soc., 74,* 2578 (1952).
3 L. J. Bellamy, 'The Infrared Spectra of Complex Molecules, Third Edition', Chapman and Hall Ltd., London, 1975.
4 G. S. Sodhi, A. K. Sharma and N. K. Kaushik, *J. Organomet. Chem., 238,* 177 (1982).