Synthesis and Structural Characterization of the Two Epimeric O-Cholesteryl-O-phenyl-N-phenylphosphoramidates

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Summary. O-Cholesteryl-O-phenyl-N-phenylphosphoramidate was synthesized as intermediate for the stereoselective synthesis of organophosphates and phosphorothioates. Single crystal X-ray diffraction discerned four independent P-epimeric phosphoramidates cocrystallizing in the triclinic P1 space group. They were found to be selectively paired in the crystal forming pseudo-centrosymmetric dimers via hydrogen bonds between the amide group of one epimer and the phosphinoyl group of the other.

Keywords. P-Epimeric phosphoramidates; O-Cholesteryl derivatives; X-Ray structure determination.

Introduction

Phosphoramidates have found considerable biological interest as anticancer agents [1]. Besides, they have been widely used in organic synthesis as the key intermediate in the Wadsworth-Emmons reaction [2], and their treatment with base followed by CO₂, CS₂, or CSe₂ provides a general method to synthesize organophosphates and phosphorothioates. Stec et al. [3] have shown that replacement of the anilino group by O, S, or Se proceeds with retention of configuration, thus allowing the stereospecific synthesis of phosphates and phosphorothioates containing chiral phosphor atoms [4]. With this aim in mind we present in this
work the synthesis and structure characterization of O-Cholesteryl-O-phenyl-N-phenylphosphoramidate.

**Results and Discussion**

*Spectroscopy*

The mass spectrum confirms the formula proposed for compound 3 by observation of the molecular ion at \( m/z = 617 \) (M⁺). Beside the resonance signals ascribed to the cholesteryl moiety (0.67–2.6, 4.4, and 5.3 ppm) and to phenyl groups (6.8–7.3 ppm), the most striking feature in the ¹H NMR spectrum was the couple of doublets at \( \delta = 5.8 \) ppm \( (2J_{PH} = 9.6 \text{ Hz}) \) whose total area accounts for a single hydrogen. It is assigned to the amide proton from its coupling with the phosphorous atom and suggest the presence of an equimolecular mixture of epimers at P. On trying to solve this ambiguity, the ³¹P NMR spectrum was of limited utility, since it showed a single signal at \(-3.11 \text{ ppm}, \) although diastereoisomeric phosphates display ³¹P shift differences in the order of 0.06 ppm [5, 6]. In order to clarify this point we decided to perform a single crystal structure determination of 3.

*Structure*

The solid state structure agrees with conclusions obtained from NMR data in solution, indicating the presence of both diastereoisomeric phosphoramides of 3. The crystal used for the X-ray measurement was found to contain four crystallographically independent molecules, *i.e.* the two pairs of epimers at the P-atom which differ in some conformational features as well as in bond lengths and, to some lesser extent, bond angles. The ORTEP view of the molecules showing also the absolute configuration is displayed in Fig. 1. Selected bond lengths, angles, and other significant data are listed in Table 1.

The geometry of the phosphoramidate group is similar to that observed in related compounds [7–9]. The four values of the P=O bond lengths are not significantly different (within experimental error) from the mean value of 1.459(4) Å. The P1–O2 (phenyl) bonds are significantly shorter than those of the typical single bond P1–O3 (cholesteryl), possible due to some resonance effect. The phosphorus tetrahedron in all four molecules is deformed as usually observed showing increased O1–P1–O2 and O1–P1–O3 angles and compressed O2–P1–O3 angles.