SULFONES OF 7-SILYL- AND 7-GERMYLCEPHALOSPORANATES

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7-Silyl- and 7-germylcephalosporanates in the form of a mixture of 7a and 7b stereoisomers were prepared by the interaction of hydrosilanes and a hydrogermane* with sulfones of tert-butyl esters of 7-diazocephalosporanic acid and 7-diazodesacetoxycephalosporanic acid in the presence of rhodium diacetate. Some of the synthesized substances manifest cytotoxic effects in relation to tumor cells in vitro, and also inhibit the catalytic activity of the enzyme elastase.

Structural modification of the side chain of cephalosporins is used extensively to obtain new structural analogs of these antibiotics with improved pharmacological properties. To this end, we undertook an investigation of the introduction of triorganosilyl and triorganylgermyl groups into position 7 of the sulfones of tert-butyl esters of cephalosporin and desacetoxycephalosporin, with the synthesized products to be used in a study of the influence of Group IVA elements on the biological properties of the synthesized substances.

The planned transformation was accomplished on the basis of methodology for the introduction of rhodium-containing carbenoids into the Si–H bond [1-3]. The application of this technique to the synthesis of the target compounds Ia-g included the diazotization of the sulfones of tert-butyl esters of 7-aminocephalosporanic acids (IIa, b) by means of isopropyl nitrite, followed by replacement of the diazo group in IIa, b, by hydroxyls to obtain IVa-c or to obtain the hydrogermane IVd, in the presence of Rh2(OAc)4.

The tendency of the cephalosporin rhodium-carbenoid intermediate V to form by-products in the absence of hydrosilanes (or hydrogermane) determined the order of mixing the reactants. Maximum yields were obtained when the 7-diazocephalosporanates III were added to a dichloromethane solution of the hydrosilane (or hydrogermane) IV and the catalyst at 20°C. After completing the reaction, the sulfones of the 7-silyl- and 7-germylcephalosporanates Ia-g were separated from the reaction mixture by means of column chromatography, in the form of a mixture of 7α and 7β stereoisomers (Table 1). The ratio of isomers was established by means of HPLC, and their identity by the PMR spectra, which contained characteristic signals of the protons C6-H and C7-H with spin–spin coupling constants J = 5 Hz for the cis or 7-β stereoisomer and J = 2 Hz for the trans or 7α stereoisomer (Table 2).

It is known that in the process of replacing the diazo group, the nonplanarity of the condensed cephem ring of the cephalosporin favors preferential formation of the 7α isomers as a result of stereoselectivity in the approach of the carbanions from the α-side of the β-lactam ring. However, analysis of the ratios of 7α and 7β isomers indicates that this is not a significant factor; also, there is no significant influence of substituent size or the nature of the M–H bond in compounds IVa-d on the stereoselectivity of this reaction (see Table 1).

When the 7-silylcephalosporanates Ib and If are treated briefly with trifluoroacetic acid, the ester protective group is split off. From the reaction medium, by means of preparative column chromatography, we isolated the corresponding cephalosporanic acids VI, characterized as individual 7α stereoisomers by their PMR spectra (see Table 2).

The cytotoxic properties of the synthesized compounds were tested on two standard lines of tumor cells: HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma). We also investigated the influence of these substances on the

*Generic terms for compounds with the general formula HSiX3 or HGeX3—Translator.
amidolytic activity of Porcine Pancreas Elastase (Type III) in relation to the p-nitroanilide of the standard tetrapeptide N-methoxysuccinyl-ala-ala-pro-val as the substrate. The results of these studies are presented in Table 3.

From an analysis of the relation between structure and activity for these substances, we can draw the following conclusions: Cephalosporins containing an acetoxy group manifest higher activity as cytotoxic substances and inhibitors of elastase in comparison with the corresponding desacetoxycephalosporins; triethylsilyl and triethylgermyl groups are effective in suppressing the growth of tumor cells in vitro at lower concentrations than are required with other 7-substituted cephalosporanates.

EXPERIMENTAL

PMR spectra were obtained in a Bruker WH-90/DS spectrometer (90 MHz) in CDCl₃, internal standard TMS; the IR spectra were obtained in a Perkin-Elmer 580B spectrometer, in white mineral oil. Elemental analyses were performed in a Carlo Erba 1108 analyzer. The HPLC data were obtained in a Du Pont Model 8800 instrument equipped with a UV detector (λ = 254 nm) and a column (4.6×250 mm) packed with Supelcosil LC-Si phase (Symmetry C₁₈), in a system of hexane–ethyl acetate 4:1, throughput rate 1.5-2.0 ml/min. The course of the reaction was monitored by TLC on Merck Kieselgel plates with UV development. The preparative column chromatography employed Merck Kieselgel silica gel (0.063-0.230 mm). In these experiments, we used reagents and materials from Aldrich, Acros, and Sigma.

The ratio of stereoisomers, the empirical formulas, elemental analyses, and values of υC=O of the β-lactam carbonyl in the IR spectrum are listed in Table 1.

The sulfone of the tert-butyl ester of 7-diazoacetoxyccephalosporanic acid (IIla) and the sulfone of the tert-butyl ester of 7-diazocephalosporanic acid (IIlb) were synthesized by means of a procedure described in [4].

**Sulfone of tert-Butyl Ester of 7-Triethylsilylacetoxyccephalosporanic Acid (Ia).** To a solution of triethylsilane (453 μl, 2.8 mmoles) in 5 ml of dry CH₂Cl₂, a catalytic quantity of Rh₂(OAc)₄ was added; then, over the course of 1 h, there was added the sulfone of the tert-butyl ester of 7-diazoacetoxyccephalosporanic acid (300 mg, 0.95 mmole) dissolved in 2 ml of dry CH₂Cl₂. The mixture was stirred 3 h at room temperature, after which the solvent