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INVESTIGATIONS IN THE FIELD OF ACYL GROUP CARRIERS

VIII. Synthesis of 4'-O-Phosphate Ester Derivatives of D-(+)-2'-O-Mesylpantothenonitrile

V. M. Kopelevich, E. S. Zhdanovich, and N. A. Preobrazhenskii

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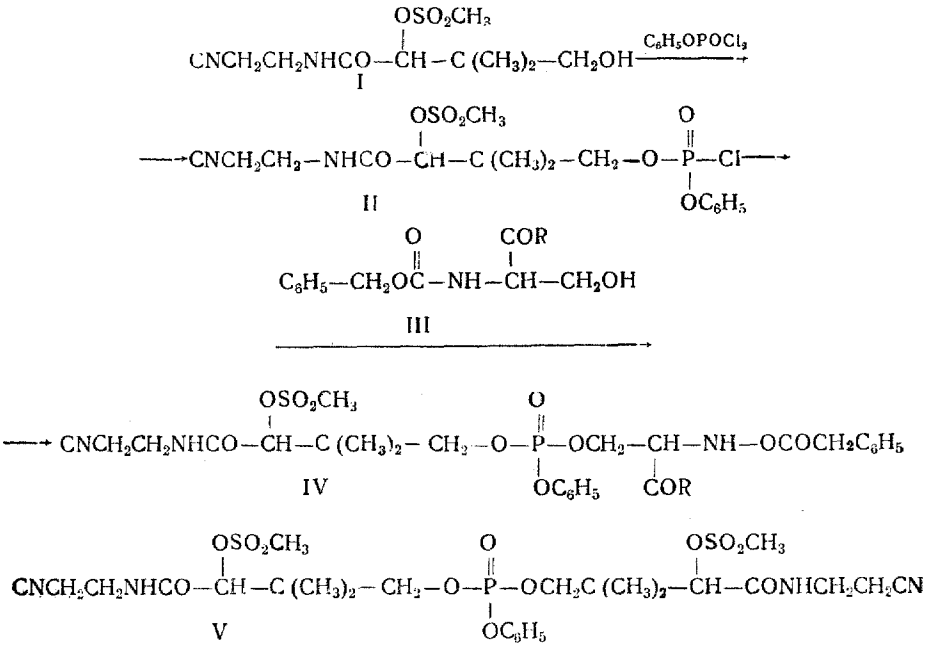
In a preceding part, we described the synthesis and properties of the starting materials for models of the acyl carrier protein (ACP) [1]. In this paper we consider a method of constructing the phosphate ester bond between the molecule of pantothenonitrile and serine derivatives. We have effected the synthesis of the methyl ester of D-(+)-4'-O-[2'-O-mesylpantothenonitrilyloxy(phenoxy)phosphoryl]-N-benzyloxycarbonylserine (IV, R = OCH_3) and the ethyl ester of D-(+)-4'-O-[2'-O-mesylpantothenonitrilyloxy(phenoxy)phosphoryl]-N-benzyloxycarbonylserylglycine (IV, R = $NHCH_2COOC_2H_5$) by the following route:



2'-O-Mesylpantothenonitrile (I) was phosphorylated with phenyl phosphorodichloridate in pyridine, and the resulting phenyl phosphorochloridate (II), without isolation, was caused to react with the methyl ester of benzyloxycarbonylserine (III, R = OCH_3) or with the ethyl ester of N-benzyloxycarbonylserylglycine (III, R = $NHCH_2H_5$). In addition to the formation of the unsymmetrical triesters (IV, R = OCH_3, and R = $NHCH_2COOC_2H_5$), the formation of a small amount of the symmetrical dialkyl phenyl phosphate (V) is possible.

To isolate the compounds IV (R = OCH_3 and R = $HCH_2COOC_2H_5$), the aqueous solution of the mixture of products was extracted with chloroform, which proved to be a selective solvent for the triesters.

The individuality of the substances obtained was established by paper chromatography. The structure of compounds IV (R = OCH_3 and R = $NHCH_2COOC_2H_5$) was shown by their IR and PMR spectra. The IR spectra have absorption bands showing the presence of a phosphate grouping: 1030 cm^{-1} (P—O—C), 1230 and 1280 cm^{-1} (P=O); there is no band corresponding to a P—OH grouping in the 2300-2700 cm^{-1} region. The PMR spectrum also lacks the signals of a hydroxyl group. The presence of a phenyl ring in the molecules of the triesters IV (R = OCH_3 and $NHCH_2COOC_2H_5$) is confirmed by the presence in the IR spectrum of bands of =C—H stretching vibrations at 3030 cm^{-1} and of C=C vibrations at 1600 and 1500 cm^{-1}; the signal from the protons of the phenyl ring in the PMR spectrum is in the 7.15 ppm region. A characteristic feature of the IR spectra of compound IV (R = OCH_3 and $NHCH_2COOC_2H_5$) in the presence of absorption bands in the following regions: 1180 and 1360 cm^{-1} (SO_2), 1530 (amide II), 1680 (amide I), and 1730 cm^{-1} (C=O). The PMR spectra of compounds IV (R = OCH_3 and R = $NHCH_2COOC_2H_5$) have a strong signal from the methyl protons (δ = 1 ppm), two triplets from the protons of the methylene groups of CH_2—CN (δ = 3.1 ppm) and CH_2—N (δ = 4.0 ppm), a signal of the methylene group of CH_2—O—P (δ = 4.1 ppm), a signal from the methine proton of CH—OSO_2 (shifted into the weak field, δ = 5.0 ppm), and the signal of the methine group of CH—COR (δ = 4.15 ppm). In addition, there is the singlet of the methylene group of the ring in the 5.2 ppm region.

Experimental

Methyl ester of D-(+)-4'-O-[2'-O-mesylpantothenonitrilyloxy(phenoxy)phosphoryl]-N-benzyloxycarbonylserine (IV, R = OCH_3). In drops at 1–3° C, 0.31 g of phenyl phosphorodichloridate in 2 ml of pyridine was added to 0.27 g of D-(+)-2'-O-mesylpantothenonitrile [1] with mp 102–103° C; $[\alpha]_D^{20}$ +17.8° (c 2; water). The mixture was stirred at 2–4° C for 30 min and at 20° C for 2 hr, and then 0.25 g of the methyl ester of N-benzyloxycarbonylserine was added. The reaction mixture was stirred for 4 hr, the pyridine was eliminated in vacuum, the residue was dissolved in 10 ml of chloroform, and the solution was washed with 0.5 N sulfuric acid (2 × 4 ml). The chloroform was evaporated off, the residue was taken up in methanol, the insoluble part was separated off, and the solvent was driven off. Yield 0.29 g (44.1%); $[\alpha]_D^{20}$ +18.3° (c 1.75; chloroform).

Found, %: C 49.86, 49.92; H 5.61, 5.63; P 4.22, 4.34. Calculated for $C_{28}H_{36}N_3O_{12}PS$, %: C 50.21; H 5.42; P 4.62.

Ethyl ester of D-(+)-4'-O-[2'-O-mesylpantothenonitrilyl(phenoxy)phosphonyl]-N-benzyloxycarbonylserylglycine (IV, R = $NHCH_2COOC_2H_5$). In drops at 1–3° C, 0.31 g of phenyl phosphorodichloridate in 2 ml of pyridine was added to 0.27 g of D-(+)-2'-O-mesylpantothenonitrile in 3 ml of pyridine. The mixture was stirred at 2–4° C for 30 min and at 20° C for 2 hr, and then 0.32 g of the ethyl ester of N-benzyloxycarbonylserylglycine was added and the mixture was treated further as in the preparation of compound IV (R = OCH_3). The yield was 0.40 g (54.1%); $[\alpha]_D^{20}$ +17.5° (c 1.75; chloroform).

Found, %: C 50.22, 50.35; H 5.68, 5.77; P 3.66, 3.87. Calculated for $C_{31}H_{41}N_4O_{13}PS$, %: C 50.25; H 5.58; P 4.18.

The PMR spectra were taken on a "Hitachi" H-60 instrument.

Conclusions

Two representatives of phosphate ester derivatives of pantothenonitrile have been obtained: the methyl ester of D-(+)-4'-O-[2'-O-mesylpantothenonitrilyloxy(phenoxy)phosphonyl]-N-benzyloxycarbonylserine and the ethyl ester of D-(+)-4'-O-[2'-O-mesylpantothenonitrilyl(phenoxy)phosphonyl]-N-benzyloxycarbonylserylglycine.

REFERENCES

1. V. M. Kopelevich, L. M. Shmuilovich, E. S. Zhdanovich, and N. A. Preobrazhenskii, KhPS [Chemistry of Natural Compounds], **5**, p. 170, 1969.

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