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SHORT COMMUNICATIONS

Dithiophosphorylation of Quinine

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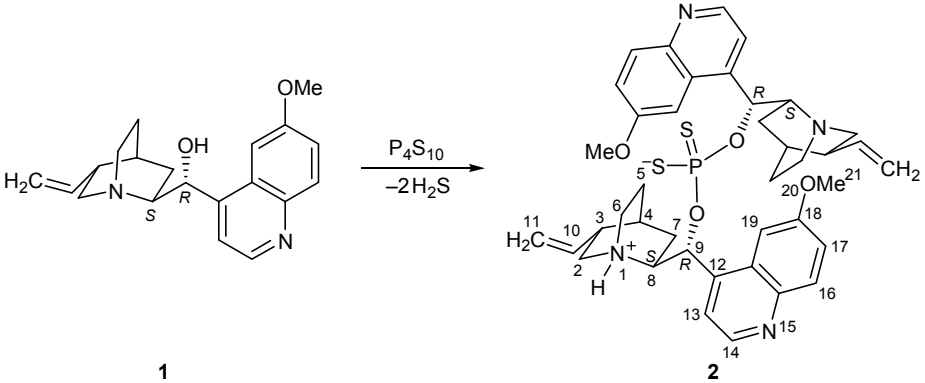
Natural compounds with asymmetric carbon atoms, in particular alkaloids, can be used as a source of chiral centers in their functionalization products. Promising synthons in the design of biologically active compounds are hydroxy-containing chiral alkaloids, such as quinine and cinchonine. Accessibility of these alkaloids has underlain their use as chiral P,N-bidentate ligands for metal complexes, catalysts for asymmetric syntheses, chromatographic selectors, and chiral NMR reagents [1–4]. Wide potential of their application for various purposes is determined by specific features of the molecular structure of quinine and cinchonine as major components of cinchona alkaloids, which consist of a quinoline fragment and vinyl-substituted bicyclic quinuclidine moiety with a tertiary nitrogen atom. Their molecules possess four chiral carbon atoms and one stereogenic nitrogen atom. Quinine alkaloids are represented by diastereoisomeric 8*R*,9*S*-quinidine and 8*S*,9*R*-quinine. Dithiophosphorylation products of quinine derivatives have not been reported so far. Dithiophosphates with quinine and cinchonidine fragments linked to the phosphorus through a sulfur atom have recently been synthesized by stereoselective functionalization of the corresponding *O*-methanesulfonyl derivatives with *O*,*O*-diethyl hydrogen phoshorodithioate in the presence of triethylamine [1]. In this work we used tetraphosphorus decasulfide P_4S_{10} as dithiophosphorylating agent whose reaction with alcohols is a traditional method of synthesis of dithiophosphoric acid derivatives [5]. By reaction of P_4S_{10} with quinine in benzene at 60°C (10 h) we obtained *O*,*O*-bis[(8*S*,9*S*)-quinin-9-yl] phosphorodithioate (**2**) which was isolated as inner ammonium salt.

The $^{31}P–\{^1H\}$ NMR spectrum of **2** in benzene contained two signals at δ_P 105.5 and 106.2 ppm at a ratio of 1 : 1. The downfield shift of the phosphorus signal from the region typical of dithiophosphoric acid derivatives (δ_P 83–86 ppm [6]) is likely to result from migration of the SH proton to the tertiary nitrogen atom of the quinuclidine fragment with formation of inner salt. In fact, compound **2** displayed in the IR spectrum (KBr) a broad absorption band at 3358 cm^{-1} due to stretching vibrations of the N^+–H bond. In the



1 **2**

^{1}H NMR spectrum of **2** in acetone-d_6 we observed a multiplet signal at δ 6.15 ppm, which belongs to the POCH proton and confirms the formation of P–O–C bond. The MALDI TOF mass spectrum of **2** contained the molecular ion peak with *m*/*z* 743.7.

Thus, smooth reaction of quinine with tetraphosphorus decasulfide opens a way to new dithiophosphates possessing pharmacophoric quinine fragments.

***O*,*O*-Bis{(*R*)-(6-methoxyquinolin-4-yl)[(2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl]methyl} phosphorodithioate (2).** Tetraphosphorus decasulfide, 0.34 g (0.77 mmol), was added in portions to a suspension of 2.0 g (6.2 mmol) of quinine (**1**) in 30 mL of anhydrous benzene under stirring at 20°C in a stream of dry argon. The mixture was stirred for 10 h at 60°C and left to stand for 12 h, and the precipitate was filtered off and dried under reduced pressure for 1 h at 40°C (0.5 mm) and for 1 h at 0.02 mm. Yield 1.7 g (74%), mp 213–215°C. IR spectrum (KBr), ν, cm^{-1}: 3358 m.br (N^+–H), 3071 w, 3031 w (C–H_{arom}), 2940 m, 2883 m, 2832 m (C–H_{aliph}), 2446 w.br, 2537 w (S–H), 1620 s (CH_2=CH), 1589 s, 1509 s (C=C_{arom}), 1429 m ($\delta_{as}CH_3$), 1358 m (δ_sCH_3), 1026 m [(P)O–C], 995 m, 985 m [O–C(C)], 683 m (P=S), 529 m (P–S). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.91 m (4H, 7-H), 2.21 d (4H, 5-H, $^3J_{HH}$ = 10.4 Hz), 2.23 (4H, 5-H, $^3J_{HH}$ = 10.9 Hz), 2.89 m (2H, 3-H), 3.32 m (4H, 2-H), 3.43 d (4H, 6-H, $^3J_{HH}$ = 10.1 Hz), 3.46 d (4H, 6-H, $^3J_{HH}$ = 10.2 Hz), 3.67 m (1H, 8-H), 3.92 s and 3.98 s (6H each, OCH_3), 5.00 m (4H, 11-H), 5.78 m (2H, 10-H), 6.15 m (2H, 9-H), 7.28 d ($^3J_{HH}$ = 9.4 Hz) and 7.29 d ($^3J_{HH}$ = 9.2 Hz) (2H each, 17-H), 7.46 d and 7.47 d (2H each, 13-H, $^3J_{HH}$ = 9.2 Hz), 7.69 m (2H, 19-H), 7.92 d ($^3J_{HH}$ = 9.1 Hz) and 8.06 d ($^3J_{HH}$ = 9.2 Hz) (2H each, 16-H), 8.72 d ($^3J_{HH}$ = 4.4 Hz) and 8.86 d ($^3J_{HH}$ = 4.5 Hz) (2H each, 14-H). ^{31}P–{^{1}H} NMR spectrum (C_6H_6), δ_P, ppm: 106.2, 105.5 (1:1). Mass spectrum MALDI TOF: *m*/*z* 743.7 $[M]^+$. Found, %: C 64.43; H 5.92; N 7.22; P 4.08; S 8.64. $C_{40}H_{47}N_4O_4PS_2$. Calculated, %: C 64.67; H 6.38; N 7.54; P 4.17; S 8.63. *M* 742.9.

The IR spectrum (400–4000 cm^{-1}) was recorded on a Bruker Tensor 27 spectrometer with Fourier transform. The ^{1}H NMR spectrum was taken on a Bruker Avance-600 spectrometer (600 MHz) using the residual proton signal of the solvent as reference. The ^{31}P NMR spectrum was measured on a Bruker Avance-400 instrument at 161.98 MHz relative to 85% H_3PO_4 as external standard. The mass spectrum (MALDI TOF) was obtained on a Bruker Ultraflex mass spectrometer using 4-nitroaniline as matrix and benzene as solvent; sample concentration 1 wt %.

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