Russian Journal of Organic Chemistry, Vol. 41, No. 6, 2005, pp. 898–900. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 6, 2005, pp. 917–919.

Synthesis and Structure of Cytisinyl(β-chloro-β-phenylvinyl)phosphinic Esters

T. S. Zhivotova[1], A. M. Gazaliev[1], S. D. Fazylov[1], A. B. Karimova[1], D. M. Turdybekov[2], and K. M. Turdybekov[2]

[1] *Institute of Organic Synthesis and Coal Chemistry of Kazakhstan Republic, ul. Alikhanova 1, Karaganda, 470061 Kazakhstan*
e-mail: dfmuh@nursat.kz

[2] *Institute of Phytochemistry of Kazakhstan Republic, Karaganda, Kazakhstan*

Received July 9, 2004

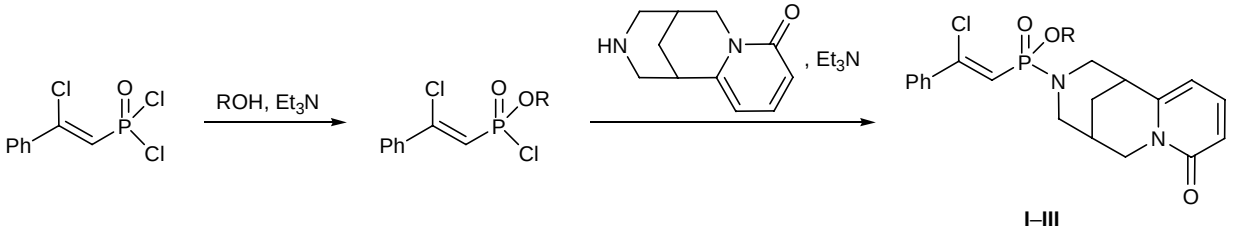
Abstract—2-Propynyl, ethyl, and isopropyl cytisinyl(β-chloro-β-phenylvinyl)phosphinates were synthesized, and their structure was determined by X-ray analysis.

An important line in the search for new pharmaceutical agents is synthesis of analogs of natural biologically active compounds, as well as modification of the latter. Studies on synthetic derivatives of cytisine showed that their biological activity strongly depends on the structure of the side chain attached to N^{12} [1] (for atom numbering, see figure).

With a view to examine the effect of various substituents on the biological activity of cytisine derivatives (7,11-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4-dien-6-one) we synthesized cytisinyl(β-chloro-β-phenylvinyl)-phosphinates **I**–**III** by reacting β-chloro-β-phenylvinylphosphonic dichloride in succession with the corresponding alcohols and cytisine. The reactions were carried out in benzene, and compounds **I**–**III** were isolated in fairly high yields.

Esters **I**–**III** are crystalline or oily substances soluble in common organic solvents. Their structure was confirmed by elemental analysis and IR and ^{1}H NMR spectroscopy. The IR spectra of **I**–**III** contained absorption bands typical of vibrations of C=C (1570–1565 cm^{-1}), P=O (1255–1235 cm^{-1}), P–O–C (990–960 cm^{-1}), and P–N groups (1350–1345 cm^{-1}). In the ^{1}H NMR spectra of **I**–**III**, signals from protons in the cytisine moiety appear in the expected regions [1]. The signals from 3-H, 4-H, and 5-H are split doublets at δ 6.3, 5.9, and 7.0 ppm, respectively. An unresolved multiplet at δ 3.8–4.4 ppm is assigned to the axial and equatorial protons on C^{10}. A number of lines in the region δ 2.9–3.1 ppm belong to protons on C^7 and C^9. Methylene protons on C^8 give rise to an unresolved multiplet centered at δ 1.9 ppm, and signals from protons on C^{11} and C^{13} are located at δ 2.4–2.8 ppm. The chemical shifts of the other protons are given in Experimental.

The steric structure of the products was determined by X-ray analysis of a single crystal of 2-propynyl ester **I** (see figure). The bond lengths and bond angles in the cytisine fragment are close to their usual values [2]. Exceptions are the bond angles at N^{12}. The N^{12} atom in *N*-methylcytisine [3] and *N*-cyanomethylcytisine [4] has a pyramidal configuration (the sum of the bond angles is 335.7 and 334.0°, respectively), whereas the same atom in *N*-(β-morpholinopropionyl)-



I–**III**

I, R = HC≡CCH$_2$; **II**, R = Et; **III**, R = *i*-Pr.

1070-4280/05/4106-0898

cytisine [5] and dimethyl cytisinylphosphonate [6], as well as in molecule **I**, is planar–trigonal (the sum of the bond angles is 359.8, 354.8, and 354.3°, respectively). The difference in the configuration of the nitrogen atoms in the above molecules originates from mesomeric effect in *N*-(β-morpholinopropionyl)cytisine, steric strains due to introduction of a bulky substituent, and effects of the lone electron pair on the nitrogen and douple $P^1{=}O^2$ bond. The dihydropyridine ring in molecule **I** is planar within ±0.005 Å, and the carbonyl oxygen atom (O^1) lies almost in that plane (the deviation is 0.2 Å). The tetrahydropyridine ring $N^1C^6C^7C^8C^9C^{10}$ adopts a distorted *sofa* conformation (ΔC_s^8 = 6.93 Å), the bridging C^8 atom deviating by 0.76 Å from the mean-square plane formed by the other atoms. The piperidine ring has an ideal *chair* conformation (ΔC_s^{12} = 1.39 Å). The N^{12} and C^8 atoms deviate from the plane formed by the other atoms by –0.62 and 0.74 Å, respectively. The $P^1C^{17}C^{18}Cl^1$ fragment is planar within ±0.002 Å. The torsion angles in the cytisine fragment differ from their usual values by no more than 9°.

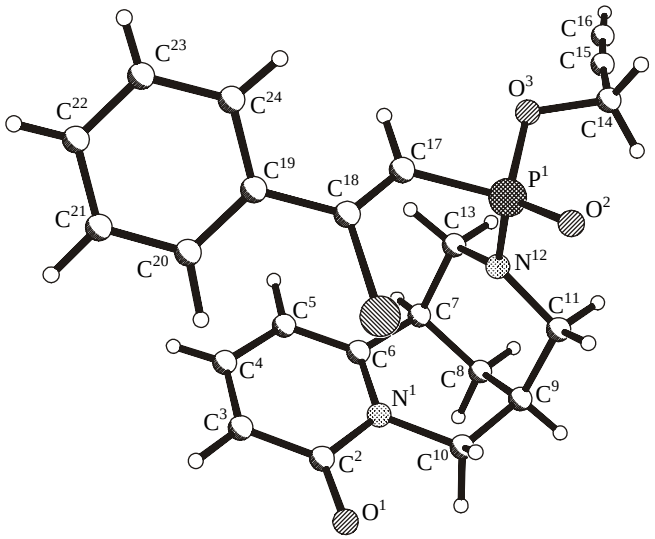
Thus the cytisine fragment in molecule **I** has a fairly rigid conformation. The tetrahydropyridine ring therein is affected by the substituent on N^{12} to a greater extent, and this effect is reflected in its symmetry. The symmetry of the piperidine ring remains almost unchanged, regardless of the size of the substituent on N^{12} (which is oriented equatorially). Nevertheless, the N^{12} atom is capable of changing its configuration due to mesomeric effect, as in the molecule of *N*-(β-morpholinopropionyl)cytisine [5].

EXPERIMENTAL

The IR spectra of compounds **I**–**III** were recorded on a UR-20 spectrometer from samples prepared as KBr pellets. The ^{1}H NMR spectra were obtained on a Varian Mercury-300 instrument (300 MHz) from solutions in C_6D_6; the chemical shifts were measured relative to HMDS.

β-Chloro-β-phenylvinylphosphonic dichloride was synthesized by reaction of phenylacetylene with phosphorus pentachloride [7].

2-Propynyl β-chloro-β-phenylvinyl(6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-11-yl)phosphinate (I). A mixture of 0.46 g (0.0052 mol) of 2-propynyl alcohol and 0.52 g (0.0052 mol) of triethylamine in 20 ml of benzene was added dropwise to a solution of 1.32 g (0.0052 mol) of β-chloro-β-phenylvinylphosphonic dichloride in 30 ml of benzene under stirring at 10–15°C in an argon atmosphere. The mixture was stirred for 2–3 h at room temperature until the first stage was complete. A mixture of 1.00 g (0.0052 mol) of cytisine and 0.52 g (0.0052 mol) of triethylamine was then added on cooling. The precipitate of triethylamine hydrochloride was filtered off, the solvent was removed from the filtrate, and the residue was subjected to chromatography on silica gel using benzene–ethanol (10:1). Compound **I** was isolated as an oily substance which crystallized on treatment with hexane. Recrystallization from benzene–acetone gave 1.96 g (88.2%) of the product with mp 208–209°C. IR spectrum, ν, cm^{-1}: 1570 (C=C), 1245 (P=O), 990 (P–O–C), 1350 (P–N). ^{1}H NMR spectrum, δ, ppm: 7.2 m (5H, C_6H_5), 5.5 s (1H, C=CH), 3.5 s (2H, OCH_2C), 2.3 s (1H, C≡CH). Found, %: C 61.64; H 5.15; N 6.51. $C_{22}H_{22}ClN_2O_3P$. Calculated, %: C 61.61; H 5.13; N 6.53.



Structure of the molecule of 2-propynyl β-chloro-β-phenylvinyl(6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-11-yl)phosphinate (**I**) according to the X-ray diffraction data.

Compounds **II** and **III** were synthesized by a similar procedure.

Ethyl β-chloro-β-phenylvinyl(6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-11-yl)phosphinate (II). Yield 2.05 g (94.3%), oily substance. IR spectrum, ν, cm^{-1}: 1565 (C=C), 1250 (P=O), 965 (P–O–C), 1345 (P–N). ^{1}H NMR spectrum, δ, ppm: 7.2 m (5H, C_6H_5), 5.6 s (1H, C=CH), 3.4 q (2H, OCH_2C), 0.9 t (3H, $CH_2C\mathbf{H}_3$). Found, %: C 60.18; H 5.76; N 6.65. $C_{21}H_{24}ClN_2O_3P$. Calculated, %: C 60.21; H 5.73; N 6.69.

Isopropyl β-chloro-β-phenylvinyl(6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-11-yl)phosphinate (III). Yield 1.90 g (87.0%), oily substance. IR spectrum, ν, cm^{-1}: 1565 (C=C), 1255 (P=O), 980 (P–O–C), 1345 (P–N). ^{1}H NMR spectrum, δ, ppm: 7.2 m (5H, C_6H_5), 5.6 s (1H, C=CH), 3.7 m (1H, OCHC), 1.7 d (6H, CHC**H**$_3$). Found, %: C 60.98; H 5.99; N 6.44. $C_{22}H_{26}ClN_2O_3P$. Calculated, %: C 61.04; H 6.01; N 6.47.

X-Ray analysis of compound I. The unit cell parameters and intensities of 2046 reflections were measured on a Bruker P4 automatic four-circle diffractometer (MoK_α irradiation, graphite monochromator). Orthorhombic crystals, $C_{22}H_{22}ClN_2O_3P$; a = 9.1750(10), b = 12.1070(10), c = 18.2180(10) Å; α = β = γ = 90°; V = 2023.7(3) Å^3; Z = 4; d_{calc} = 1.365 g/cm^3; space group $P2_12_12_1$. In the calculations, 2046 independent reflections with $I > 2\sigma$ were used. The structure was solved by the direct method and was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms. A correction for absorption by ψ-curves was introduced. The positions of hydrogen atoms were determined from the difference synthesis in anisotropic approximation. The final divergence factors were R = 0.0301 and wR = 0.0723. All calculations were performed using SHELXL-97 package. Additional information is available from the authors.

REFERENCES

1. Gazaliev, A.M., Zhurinov, M.Zh., and Fazylov, S.D., *Novye bioaktivnye proizvodnye alkaloidov* (New Biologically Active Derivatives of Alkaloids), Almaty: Gylym, 1992, p. 88.
2. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc., Perkin Trans. 1*, 1987, p. S1.
3. Freer, A.A., Robins, D.J., and Sheldrake, G.N., *Acta Crystallogr., Sect. C*, 1987, vol. 43, p. 1119.
4. Nurkenov, O.A., Gazaliev, A.M., Turdybekov, K.M., Shalbaeva, A.B., Aubakirova, A., and Zhurinov, M.Zh., *Russ. J. Gen. Chem*., 1999, vol. 69, p. 648.
5. Ibraev, M.K., Turdybekov, D.M., Fazylov, S.D., Turdybekov, K.M., Gazaliev, A.M., and Zhivotova, T.S., *Vestn. Kazan. Nats. Univ. Imeni Al'-Farabi*, 2003, vol. 31, p. 13.
6. Gazaliev, A.M., Turdybekov, K.M., Lindeman, S.V., Struchkov, Yu.T., Tuleuov, B.I., and Zhurinov, M.Zh., *Zh. Obshch. Khim*., 1992, vol. 62, p. 456.
7. Petrov, K.A., Raksha, M.A., and Vinogradov, V.L., *Zh. Obshch. Khim*., 1966, vol. 36, p. 715.