SYNTHESIS AND BIOLOGICAL ACTIVITY OF ESTERS AND HYDRAZIDES OF PHOSPHORYLATED PHENYLACETIC ACIDS

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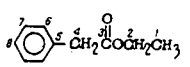
In continuation of our studies in the field of hydrazides of phosphorylated carboxylic acids [1], we paid attention to the study of the synthesis and properties of esters and hydrazides of phosphorylated phenylacetic acids.

To synthesize esters of diethyl(diphenyl)phosphinylphenylacetic acid, we used the Arbuzov rearrangement of ethyl esters of diethyl- and diphenylphosphinous acids under the action of ethyl α-chloro(bromo)phenylacetates.

$$R_2POC_2H_5+C_6H_5CHXCOOC_2H_5 \longrightarrow \underset{\displaystyle C_6H_5}{\overset{\displaystyle R_2P(O)CHCOOC_2H_5}{|}} + C_2H_5X$$

$X = Cl, Br;\ R = C_2H_5(I),\ C_6H_5\ (II).$

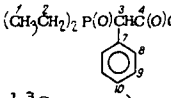
The Arbuzov rearrangement of ethyl diethylphosphinite under the action of ethyl α-bromophenylacetate is accompanied by an attack of the trivalent phosphorus atom of the phosphinite on the positive bromine atom, in analogy with data in [2]. This is indicated by the fact that besides ethyl diethylphosphinylphenylacetate (I; yield 23%), the normal product of the Arbuzov rearrangement ethyl phenylacetate was isolated in considerable amounts; its structure was confirmed by the data of [^{13}C]-NMR spectroscopy. Each nucleus of the [^{13}C]-carbon atom of the molecule of



is characterized by an individual chemical shift (δ ^{13}C, ppm): C^1, 14.0; C^2, 60.4; C^3, 170.9; C^4, 41.1; C^5, 134.9; C^6, 129.5; C^7, 129.8; C^8, 128.5.

The rearrangement of ethyl diethylphosphinite under the action of ethyl α-chlorophenylacetate leads to the formation of the end product I in a yield of 61%. The reaction mixture was studied by [^{31}P]-NMR spectroscopy, one and two hours after the beginning of the reaction. After 1 h of heating at 80°C, compounds are observed in the reaction mixture with chemical shifts at 144.5, 60, 58, and 46.8 ppm, corresponding to the initial trivalent phosphorus ester, an unidentified compound with a phosphate structure, ethyl diethylphosphinite, and the end product I. After 2 h of heating at 80-100°C, the 144.5 ppm peak disappears completely, the peak at 46.8 ppm increases, and the other peaks remain unchanged.

The structure of I was determined from ^{1}H, [^{13}C]-NMR spectra, shown in Fig. 1. In the PMR spectrum, a complex multiplet of the protons of ethyl radicals is observed, attached to the phosphorus atom and methyl radical at δ 1.25, a quartet of methylene protons at δ 4.00, a doublet of methylene protons at 4.18 ppm, J_{PCH} 12.5 Hz, and resonance signals of the aromatic protons at δ 7.25 ppm. The data of the [^{13}C]-NMR spectrum also correspond to the formula



The individual chemical shifts (δ ^{13}C, ppm) and spin–spin interaction constants are as follows: C^1, 6.28 (J_{P-C} 5.5 Hz); C^2, 20.25 (J_{P-C} 75 Hz); C^2, 20.25 (J_{P-C} 74.5 Hz); C^3, 58.3 (J_{P-C} 47.6 Hz); C^4, 169.0; C^5, 61.7; C^6, 14.6; C^8, 133.3 (J_{P-C} 6.7 Hz); C^9, 130 (J_{P-C} 5.5 Hz); C^{10}, 128.8.

The multiplicity of the C^1-carbon signal at 6.28 ppm and the presence of two doublets at δ 20.25 ppm and δ 20.75 ppm of the P-CH_2 groups indicate nonequivalence of the ethyl radicals attached to the phosphorus atom.

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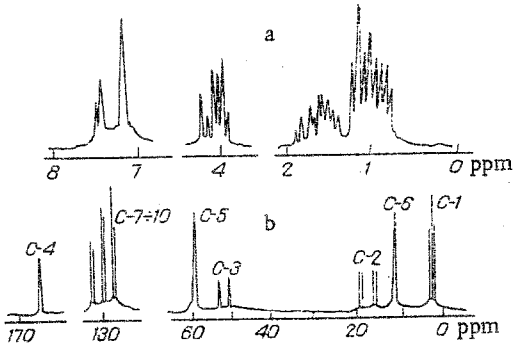

Fig. 1. [^{13}C]-NMR spectrum (a) and PMR spectrum (b).

Ethyl ester I is a very viscous, light-lemon colored liquid, which distills without decomposition and is soluble in organic solvents.

The rearrangement of the ethyl ester of diphenylphosphinous acid under the action of α-chloro(bromo)phenylacetic acid esters proceeds very smoothly to give high yields of the end product, ethyl α-diphenylphosphinylphenylacetate (II).

The conditions of the synthesis of hydrazides of phosphorylated phenylacetic acids depend on the structure of the esters.

$$R_2P(O)\underset{\displaystyle C_6H_5}{\underset{|}{C}}HCOOC_2H_5 + NH_2NH_2\cdot H_2O \longrightarrow R_2P(O)\underset{\displaystyle C_6H_5}{\underset{|}{C}}HC(O)NHNH_2 + C_2H_5OH$$

$R = C_2H_5$ (III), C_6H_5 (IV).

To synthesize the hydrazide of diethylphosphinylphenylacetic acid it is sufficient to boil the ester for 3 h with an excess of hydrazine hydrate in ethanol, while to prepare the hydrazide of diphenylphosphinylphenylacetic acid, 5-h boiling in an excess of hydrazine hydrate in a higher-boiling n-amyl alcohol is necessary. The hydrazides are colorless, crystalline substances, soluble in polar organic solvents.

To confirm the structure of the hydrazides, we studied their reaction with m-nitrobenzaldehyde. The reaction proceeds with boiling of alcoholic solutions of the components in the presence of a catalytic amounts of hydrochloric acid with the formation of the corresponding hydrazones, which are high-melting light-yellow crystalline compounds.

The structure of the compounds obtained is confirmed by the data of IR spectroscopy. In the IR spectra of the phosphorylated phenylacetic acids, stretching vibration bands are observed at P=O (1150-1200 cm^{-1}), C_6H_5 (1600-1610 cm^{-1}), C=O (1730-1740 cm^{-1}); in the IR spectra of hydrazides: P=O (1150-1180 cm^{-1}), C_6H_5 (1610-1620 cm^{-1}), C=O (1670-1690 cm^{-1}, amide I), NH (3200-3380 cm^{-1}); in the IR spectra of hydrazones: P=O (1150 cm^{-1}), NO_2 (1360, 1540 cm^{-1}), C=N (1640 cm^{-1}), C=O (1690 cm^{-1}), NH (3180 cm^{-1}).

To study the biological activity of hydrazides III and IV, we used methods that can reveal sedative, antispasmodic, and myorelaxant effects. The experiments were carried out on 60 white mice.

Studies on the influence of compounds III and IV on the orientational reaction of the mice showed that compound IV has an appreciable suppressing action. Mice which receive this compound inspected many less holes (13.1 ± 5.6) than the control mice (19.5 ± 5.1; $P = 0.05$). In a one-time experiment, nearly equal numbers of holes were inspected by the experimental and control group animals (9.2 ± 2.2 and 11.2 ± 2.4; $P > 0.1$), respectively. However, in a repeated experiment, animals of the experimental group inspected considerably less holes (3.9 ± 2.9) than the control group mice (8.1 ± 3.6; $P = 0.05$). Compound III does not influence the orientational reaction of mice.

Compounds III and IV do not have any noticeable antispasmodic action. Compound III had a protective action in 1 of 10 animals only.

Thirty minutes after administration of compounds III and IV, the muscular force significantly decreased, compared with that of the control (159.5 ± 13.4), in animals which received IV (136.4 ± 17.7 g; $P < 0.05$); after 60 min, the muscular force was nearly the same in animals of all the groups studied.

Our studies show that compound IV suppresses the orientational reaction and decreases the muscular force in mice but has no antispasmodic action; compound III does not influence the orientational reaction and the muscular force in mice and has no antispasmodic action.

EXPERIMENTAL PHARMACOLOGICAL PART

To study the psychotropic properties of the preparations, we used the method of "orientational reaction" [3] which can reveal the sedative properties of the preparation. The degree of expression of the orientational reaction was judged from the number of holes inspected by the animals in the course of 5 min.

The antispasmodic action of the preparations was studied by the "maximal electric shock" method [4]. The electric shock was induced by passing an alternate current at a voltage of 50 V and current strength of 50 mA by electrodes attached to the cornea through the surface of the eyeballs of the mice (at a frequency of 1 pulse per second, pulse duration 0.2 sec). The protective action was estimated from the absence of the tonic-extensor phase of the electroconvulsive fit.

To estimate the myorelaxant effect, we used the method of determination of muscular force [5], based on the prehensile reflex of the mice, and determined by a dynamometer.

Compounds III and IV were administered intraperitoneally in a dose of 100 mg/kg; III in the form of an aqueous solution; and IV in the form of a suspension in 2% starch mucilage.

The orientational reaction and antispasmodic action were evaluated 1 h after administration of the preparations, and the muscular force 30 and 60 min after administration. The results were processed statistically [6].

EXPERIMENTAL CHEMICAL PART

The IR spectra were run on the UR-10 spectrophotometer (GDR); the compounds were determined in a crystalline state in the form of a paste with Vaseline. The NMR spectra were run on the WP-80 spectrometer (Bruker, GFR). The chemical shifts of the H and ^{13}C nuclei are shown with reference to tetramethylsilane, and the phosphorus nuclei with reference to 85% H_3PO_4.

Decrease in the P nuclear magnetic screening constant corresponds to the shift of the signal of the phosphorus nucleus in the direction of positive values of chemical shifts.

All the operations with trivalent phosphorus esters were carried out in an argon current.

Ethyl α-diethylphosphinylphenylacetate (I). A mixture of 11.8 g (0.088 mole) of ethyl diethylphosphinite and 17.6 g (0.088 mole) of ethyl α-chlorophenylacetate was heated at 80°C for 3 h until the liberation of ethyl chloride ceased. As the result of several distillations, 14.2 g (61%) of a product (I) (δ_{31P} 46.8 ppm) were obtained; bp 146-148°C (0.1 mm); d_4^{20} 1.1160; n_D^{20} 1.5255; MR_{found} 73.70; MR_{calc} 73.53. IR spectrum, ν, cm^{-1}: 1735 (C=O), 1610, 1500, 770 (C_6H_5), 1170 (P=O). Found, %: C 63.02, 63.87; H 8.02, 8.12; P 11.67. $C_{14}H_{21}O_3P$. Calculated, %: C 62.75; H 7.88; P 11.52.

The reaction between 13.4 g (0.1 mole) of ethyl diethylphosphinite and 24.3 g (0.1 mole) of ethyl α-bromophenylacetate proceeds with strong exothermal effect. After 3 h of heating at 60-70°C, 5.5 g of ethyl phenylacetate were isolated by several distillations; bp 99-102°C (12 mm); d_4^{20} 1.0334; n_D^{20} 1.4922 (according to literature data, bp 120-125°C (17-18 mm); d_4^{20} 1.0333; n_D^{20} 1.4992) and 6.4 g (23%) of a product (I), bp 140-145°C (0.06 mm), d_4^{20} 1.1204, n_D^{20} 1.5325, MR_{found} 74.25, MR_{calc} 73.53.

Ethyl α-diphenylphosphinylphenylacetate (II). A mixture of 12.2 g (0.05 mole) of ethyl diphenylphosphinite and 10.0 g (0.05 mole) of ethyl α-chlorophenylacetate was heated at 100-130°C for 3 h until liberation of ethyl chloride ceased. When cool, the reaction mixture crystallized. By reprecipitation from benzene into hexane, 15.6 g (80%) of II were isolated; mp 165-168°C (alcohol–water). IR spectrum, ν, cm^{-1}: 1730 (C=O), 1600, 1500, 790, 710 (C_6H_5), 1170 (P=O). Found, %: P 8.20, 8.39. $C_{22}H_{20}O_3P$. Calculated, %: P 8.53.

The reaction between 7.7 g (0.033 mole) of ethyl diphenylphosphinite and 8.4 g (0.034 mole) of ethyl α-bromophenylacetate proceeds exothermally and with crystallization of the product in the course of the reaction. After the mixture was heated at 80°C for 3 h, 10.0 g (83%) of II were isolated, mp 170-171°C (from aqueous alcohol).

Hydrazide of α-diethylphosphinylphenylacetic acid (III). A mixture of 8.9 g (0.033 mole) of ester (I), 4 ml (0.08 mole) of hydrazine hydrate and 5 ml of ethanol was boiled for 3 h. When cool, 5.7 g (67%) of (III) were isolated, mp 171-172.5°C (alcohol). IR spectrum, ν, cm^{-1}: 3370 (NH), 1690 (C=O), 1600 (C_6H_5), 1150 (P=O). Found, %: N 11.17, 11.06; P 11.87, 11.84. $C_{12}H_{19}O_2N_2P$. Calculated, %: N 11.00; P 12.20.

Hydrazide of α-diphenylphosphinylphenylacetic acid (IV). A solution of 3.6 g (0.01 mole) of ester II and 2 ml (0.04 mole) of hydrazine hydrate in 20 ml of n-amyl alcohol was boiled for 5 h. The yield was 2.5 g (71%) of hydrazide IV, mp 249-251°C (n-amyl alcohol). IR spectrum, ν, cm^{-1}: 3300 (NH), 1670 (C=O), 1620, 730, 700 (C_6H_5), 1180 (P=O). Found, %: N 8.05, 7.85; P 8.83, 8.67. $C_{20}H_{19}O_2N_2P$. Calculated, %: N 8.02; P 8.88.

m-Nitrobenzylidenehydrazide of α-diethylphosphinylphenylacetic acid. A mixture of 0.25 g (0.001 mole) of hydrazide III, 0.15 g (0.001 mole) of m-nitrobenzaldehyde, 5 ml of ethanol, and a few drops of 1 N HCl was boiled for $2^1/_2$ h. The yield of the product was 0.25 g (64%), mp 226-228°C (from aqueous DMFA). IR spectrum, ν, cm^{-1}: 3180 (NH), 1690 (C=O), 6140 (C=N), 1540, 1370 (NO_2), 1150 (P=O). Found, %: N 10.70, 10.56; P 3.20. $C_{19}H_{22}O_4N_3P$. Calculated, %: N 10.75; P 8.03.

m-Nitrobenzylidenehydrazide of α-diphenylphosphinylphenylacetic acid. Similarly, from 0.18 g (0.0005 mole) of hydrazide IV and 0.08 g (0.0005 mole) of m-nitrobenzaldehyde, 0.15 g (63%) of a product was obtained, mp 261-263°C (from aqueous DMFA). Found, %: N 6.40, 6.31; P 9.27. $C_{27}H_{22}O_4N_3P$. Calculated, %: N 6.42; P 8.70.

Mixed probes of the hydrazones with initial hydrazides show a considerable depression of the melting point.

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EFFECTS OF CERTAIN FLAVONOIDS ON THE ULCEROGENIC ACTION OF RESERPINE IN MICE

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According to data of S. V. Anichkov et al. [1, 2], one of the leading mechanisms of the formation of neurogenic dystrophies of the stomach is exhaustion of the catecholamine depots in its tissues and an inhibition of the trophic function of the sympathetic nervous system. There is also information on the ability of flavonoids to inhibit catechol ortho-methyl transferase (COMT) — one of the enzymes responsible for the inactivation of epinephrine and norepinephrine — and thus to prolong the action of catecholamines [3, 4]. Data on antiulcer activity of flavonoids [5, 6, 7] and preparations containing them [8, 9] agree with this information. The purpose of the present work was a comparative estimation of the effects of 11 flavonoids and a COMT inhibitor, depaverine [10], on the formation of destruction of the gastric mucosa, induced by reserpine in mice. The selection of reserpine as the ulcerogenic agent was due to the fact that it labilizes norepinephrine and epinephrine in the sympathetic ter-

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