SYNTHESIS OF PHOSPHORYLATED PYRAZOLONES

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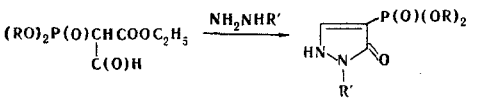
Methods are proposed for the synthesis of phosphorylated pyrazolones by condensation of phosphonates of β-keto(formyl) esters with hydrazine and its derivatives. The IR spectra are presented, and the fine structures of the compounds are discussed.

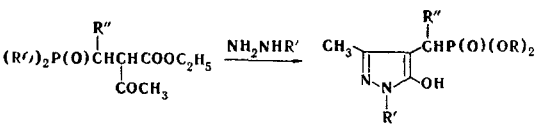
Carbon-phosphorylated heterocycles have recently been the subject of extensive study [1] in connection with data on their high physiological activity. At the same time, extremely limited consideration has been given to the synthesis of such substances that have an additional function, for example, phosphorylated pyrazolones. The usual method for the preparation of pyrazolones is condensation of β-keto(formyl) esters with hydrazine and its derivatives. Thus a pyrazolone whose structure has not been proved was obtained from phospho keto ester $(C_2H_5O)_2P(O)C(O)CH_2COOC_2H_5$ [2].

We have synthesized ethyl dialkoxyphosphonylformylacetates I-III (Table 1). According to the PMR spectral data, these compounds do not contain an aldehyde group, and this indicates that they have enol structures. 4-Phospho-5-pyrazolones IV-VII were obtained by condensation of II and III with hydrazine and phenylhydrazine (see Table 2).



I-III IV

Compounds IX-XI (Table 3) were similarly obtained from phosphorylated derivatives of acetoacetic ester.



IX-XI

The ^{31}P NMR spectra prove the phosphonate nature of the pyrazolones.

The literature contains data according to which pyrazolones of this type have been obtained by reaction of 4-arylidene-1-aryl-3-methyl-5-pyrazolones with dialkyl phosphites [3, 4]; however, the reaction is not of general importance [5]. One of our pyrazalones (IX, Table 3) has been previously described [3]. Analysis of the IR spectra makes it possible to assume that pyrazolones containing phosphorus directly bonded to the ring exist in various tautomeric forms. The spectra of IV-VI are characterized by the presence of an intense absorption band at 3250 cm^{-1} (associated NH) and a carbonyl band at 1670-1675 cm^{-1}. Pyrazolones IV-VI probably have a structure similar to that of amides in the crystalline state.

An absorption band at 3150 cm^{-1}, which cap also be assigned to an associated NH group, and an intense band of complex structure at 1800-2800 cm^{-1}, which was assigned to the OH group [6], are observed in the spectra of VII and VIII. All of this indicates the formation of strong intermolecular hydrogen bonds. Thus the spectral data constitute evidence in favor of an enol structure for VII and VIII in the crystalline state.

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TABLE 1. Characteristics of the Formyl Derivatives

Compound	R	n_D^{20}	Emperical formula	P found %	P calculated, %	R_f (system)*	PMR spectrum (CCl_4), δ, ppm C=CH	PMR spectrum (CCl_4), δ, ppm OH	Yield, %
I	C_2H_5	1,4515	$C_9H_{17}O_6P$	12,4	12,8	0,33(Г)	8,30	12,80	20
II	C_3H_7	1,4522	$C_{11}H_{21}O_6P$	11,4	11,7	0,83(Б)	8,60	12,70	20
III	$CH_2CH_2CH_2(CH_3)$	1,4660	$C_9H_{15}O_6P$	11,9	12,4	0,66(Б)	7,90	9,50	18

*Silufol.

TABLE 2. 4-Dialkoxyphospho-5-pyrazolones

Compound	R	R′	mp. °C	Found, % C	Found, % H	Found, % P	Emperical formula	Calc., % C	Calc., % H	Calc., % P	R_f (system)	^{31}P NMR, δ, ppm	Yield, %
IV	C_2H_5	C_6H_5	92—93	52,8	5,9	10,1	$C_{13}H_{17}N_2O_4P$	52,7	5,7	10,5	0,41 (C)*	−39,5	52
V	C_3H_7	C_6H_5	96—97	56,0	6,8	9,1	$C_{15}H_{21}N_2O_4P$	55,5	6,5	9,6	0,62 (C)*	—	45
VI	$CH_2CH_2CH(CH_3)$	C_6H_5	87—88	53,4	5,4	10,3	$C_{13}H_{15}N_2O_4P$	53,0	5,1	10,5	0,50 (B)*	−37,3	34
VII	C_2H_5	H	154—155	37,6	6,2	13,8	$C_8H_{13}N_2O_4P$	38,2	6,0	14,1	0,55 (A)†	−30,2	44
VIII	C_3H_7	H	162—163	43,7	6,2	12,2	$C_9H_{17}N_2O_4P$	43,5	5,9	12,5	0,60 (A)†	—	45

*Aluminum oxide.
†Silufol.

TABLE 3. 4-Dialkoxyphosphoalkyl-5-pyrazolones

Compound	R	R′	R″	mp, °C	Found, % C	Found, % H	Found, % P	Emperical formula	Calc., % C	Calc., % H	Calc., % P	R_f*	^{31}P NMR, δ, ppm	Yield, %
IX	CH_3	C_6H_5	C_6H_5	163—164†	61,5	5,9	7,9	$C_{19}H_{21}N_2O_4P$	61,3	5,6	8,3	0,63	−22,7	78
X	C_2H_5	C_6H_5	CH_3	159—160	56,5	6,6	9,0	$C_{16}H_{23}N_2O_4P$	56,8	6,8	9,2	0,60	−27,0	70
XI	C_2H_5	H	CH_3	222—223	46,2	7,6	11,7	$C_{10}H_{19}N_2O_4P$	45,8	7,4	11,8	0,45	−35,4	80

*Silufol, system E.
†According to the data in [3], this compound has mp 115-116°.

Pyrazolones IX and X are also represented by an enol form in the crystalline state. A broad band at 2500-2650 cm^{-1} (OH) is observed in their IR spectra. In chloroform solution these pyrazolones also exist in the enol form. Dilution of the solutions to 0.004 M does not affect the character of the absorption of the hydroxy group, and this indicates that it participates in the formation of an intramolecular hydrogen bond. The presence of absorption at 3200 (associated NH) and 2500-2800 cm^{-1} (OH) is characteristic for pyrazolone XI.

EXPERIMENTAL

The syntheses were carried out in an inert gas atmosphere. Chemapol 100/250 μ silica gel and activity II aluminum oxide were used for column chromatography. Silufol UV-254 and aluminum oxide were used for thin-layer chromatography (TLC). The following systems were used for chromatography: A) benzene–dioxane (3:1), B) hexane–dioxane (2:1), C) ethyl acetate, D) benzene–diozane; (2:1), and E) benzene–methanol (4:1). The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The NMR spectra were recorded with a Varian XL-100 spectrometer. The standard for NMR was 85% phosphoric acid, and the standard for PMR was tetramethylsilane.

1,3-Butylenephosphoacetic Ester. A 90-g (0.5 mole) sample of ethyl bromoacetate was added at 60° to 66 g (0.44 mole) of methyl 1,3-butylenephosphite [7]. The reaction was accompanied by spontaneous heating, and methyl bromide distilled into a cooled receiver. The temperature in the reaction mixture was maintained at 80-90°. Traces of methyl bromide were removed in vacuo (water aspirator), and the residue was fractionated

to give 49 g (50%) of a product with bp 150-155° (1 mm), R_f 0.55 (system D, Al_2O_3), n_D^{20} 1.4560, and d_4^{20} 1.1978. PMR spectrum (CCl_4): 1.22 (t, ester CH_3), 1.32 (t, CH_3 butylene), 1.90 (m, CH_2), 2.83 (d, CH_2, $J_{P,H}$=22.7 Hz), 4.16 (m, CH_2 ester), 4.45 (m, butylene CH_2), and 4.75 ppm (m CH). The integral intensities are in agreement with the number of protons included in the composition of the molecule. Found: C 43.3; H 6.7; P 13.9%. $C_8H_{15}O_5P$. Calculated: C 43.6; H 7.1; P 13.5%.

Formyl Derivatives (I-III). A mixture of 56.2 g (0.25 mole) of 1,3-butylenephosphoacetic ester, 17.7 g (0.25 mole) of ethyl formate, and 14 ml of absolute ethanol was added at 0° to a suspension of 5.7 g (0.25 g-atom) of sodium metal in 250 ml of absolute ether, and the mixture was allowed to stand at room temperature for 24 h. The resulting salt was dissolved in 400 ml of water, organic layer was separated, and the aqueous lyer was cooled and acidified to pH 1 with 25 ml of concentrated HCl. The formylation product was extracted with three 100-ml portions of chloroform, and the extract was dried with sodium sulfate. The chloroform was evaporated to 20 ml, and the desired product was purified by chromatography in a column filled with silica gel (elution with mixture B). The yield of III was 11.5 g (20%) (Table 1).

Compounds I and II were similarly obtained from the corresponding diethoxyphosphoacetic ester [8] and dipropoxy phosphoacetate [9].

1-Phenyl-4-diethoxyphospho-5-pyrazolone (IV). A 2.15-g sample of freshly distilled phenylhydrazine was added at room temperature to 5 g (0.02 mole) of formyl derivative I, and the mixture was stirred with a stream of argon. The low-molecular-weight substances (H_2O and C_2H_5OH) formed in the reaction were removed immediately in vacuo (water aspirator) at 30 mm and 80°. The cyclization product was maintained at this temperature for 3 h, after which it was dissolved in ethyl acetate, and the solution was passed through a column filled with Al_2O_3. The eluate was poured into a fivefold excess of petroleum ether. The oil crystallized after a few hours, and the powery product was removed by filtration, washed with warm hexane, dried, and recrystallized from benzene-petroleum ether. The yield of IV was 3 g (52%).

Compounds V and VI were obtained by a similar method.

4-Diethoxyphospho-5-pyrazolone (VII). A 0.8-g sample of hydrazine hydrate was added to 4 g (0.016 mole) of derivative I in 10 ml of alcohol, and the mixture was heated on a boiling-water bath for 5 h. The low-molecular-weight product were removed by vacuum distillation, and the residual oil was washed with chloroform until it began to crystallize. The solid was removed by filtration, washed with chloroform and ether, and crystallized from alcohol. The yield of VII was 1.5 g (44%).

Compounds VIII and XI were obtained by a similar method.

1-Phenyl-3-methyl-4-dimethoxyphosphobenzyl-5-pyrazolone (IX). A 15.5-g (0.046 mole) sample of meso-dimethylphosphobenzylacetoacetic ester [10] was heated in a benzene–acetic acid medium with 4.9 g of phenylhydrazine at 90° for 8 h. The low-molecular-weight products were removed by vacuum evaporation (water aspirator), and the residue was triturated in hexane. The colorless crystals were removed by filtration and crystallized from benzene–methanol. The yield was 12 g (78%).

Pyrazolone X was similarly obtained from the appropriate keto ester [10].

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