SYNTHESIS AND NEUTROTROPIC ACTIVITY OF DIARYLPHOSPHORYL-ACETYLHYDRAZONES

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In continuation of investigations of psychotropic activity of derivatives of phosphorylated acetic acids [1] we have synthesized C-diarylphosphorylacetylhydrazones (I-XIV) (Table 1).

Hydrazones I-XIV were prepared by reaction of RCHO with hydrazides of diphenyl- and di(chlorophenyl)phosphorylacetic acids.

$(XC_6H_4)_2P(O)CH_2C(O)NHN{=}CHR$
I—XIV
R= CH=CHPh (I, IX), C_6H_4OH-2 (II, III)
$C_6H_3(OH)_2$-2,4 (IV, V), $C_6H_3(OME)_2$-3,4 (VI),
$C_6H_4NMe_2$-4 (VII), α-thienyl (VIII), $C_6H_4NO_2$-3 (X),
$CCl{=}CHC_6H_4NO_2$-3 (XI, XII), C_6H_4OH-4 (XIII),
C_6H_4OMe-4 (XIV); X=H (I, II, IV, VIII, XI, XIII, XIV),
Cl-4 (III, V—VII, IX, X, XII).

Composition and structure of compounds I-XIV were proven by elemental analyses and also by IR and NMR spectrometry.

In the IR spectra of hydrazones I-XIV the phosphoryl group gives a strong absorption band in the region 1170-1185 cm^{-1}, and the carbonyl group in the region 1665-1690 cm^{-1}. These two bands remain practically unchanged when going from the starting hydrazides to the corresponding hydrazones. A considerably larger change is undergone in the region of valence vibrations of the NH group. In contrast to the complex picture of the spectra of the starting hydrazides [4], the NH group in final hydrazones I-XIV gives one absorption band at 3180-3190 cm^{-1}.

^{31}P NMR spectra of hydrazones I-XIV are characterized by two series of resonance signals (see Table 1), which points to the presence of syn and anti isomers. For screening of the neurotropic activity of hydrazones I-VIII we used the orientation reaction of white mice and the test with subcutaneous administration of an absolutely lethal dose of corazole. To find out the disturbance of the myorelaxant nature we used the rotating rod method.

TABLE 1. Diarylphosphorylacetylhydraxones (I-XIV)

Compound	Yield %	mp, °C	Empirical formula	^{31}P NMR, δ, ppm
I	92	212	$C_{23}H_{21}N_2O_2P$	—
II	97	218	$C_{21}H_{19}N_2O_3P$	27,1; 26,1
III	94	228	$C_{21}H_{17}Cl_2N_2O_3P$	26,5; 25,0
IV	98	238	$C_{21}H_{19}N_2O_4P$	27,3; 26,0
V	99	236	$C_{21}H_{17}Cl_2N_2O_4P$	26,4; 25,1
VI	83	178—9	$C_{23}H_{21}Cl_2N_2O_4P$	26,7; 25,3
VII	95	210	$C_{23}H_{22}Cl_2N_3O_2P$	27,4; 26,1
VIII	95	218	$C_{20}H_{17}N_2O_2SP$	27,9; 26,4
IX	98	188—9	$C_{23}H_{19}Cl_2N_2O_2P$	—
X	92	183—5	$C_{21}H_{16}Cl_2N_3O_4P$	—
XI	94	174—5	$C_{23}H_{19}ClN_3O_4P$	25,9; 24,6
XII	95	230	$C_{23}H_{17}Cl_3N_3O_4P$	25,5; 24,0
XIII	93	151—2	$C_{21}H_{19}N_2O_3P$	27,6; 26,3
XIV	93	230—2	$C_{22}H_{21}N_2O_3P$	26,9; 25,6

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TABLE 2. Neurotropic Activity of Diarylphosphorylacetylhydrazones I-VIII (control 100%, differences significant)

Compound	Orientation reaction, number of approaches	Effect of corazole		Time of staying on the rotating rod, min
		duration of preconvulsive period, sec	life span, min	
I	2	330	180	19,4
II	51	180	110	20,5
III	38	112*	108*	18,3
IV	37	160	120*	30,9
V	18	190	120*	27,2
VI	22	120*	113*	22,0
VII	23	200	140*	21,3
VIII	24	110*	85*	—

*Difference uncertain.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a UR-20 spectrometer in the region 400-3600 cm^{-1} from films in paraffin oil. PMR spectra were recorded on a WP-80 spectrometer operating at 32,38 MHz. ^{31}P chemical shifts are reported relative to 85% H_3PO_4. Found and calculated values of elemental analyses were in agreement.

To a solution of 0.02 mole of hydrazide in 20 ml of ethanol is added at room temperature a solution of 0.02 mole of the appropriate aldehyde in 10 ml of ethanol. The reaction mixture is stirred at room temperature for 2-6 h. The precipitate is filtered off, washed with ethanol or $CHCl_3$, and dried. Hydrazones I-XIV are high-melting white or light-yellow powders, soluble in DMSO, poorly soluble in ethanol. The hydrazones are insoluble in water. Characteristics of compounds I-XIV are listed in Table 1.

EXPERIMENTAL (BIOLOGICAL)

The acute toxicity of hydrazones I-VIII was determined in white mice by intraperitoneal administration of a freshly prepared mixture of the compound with a 2% starch suspension in water (1:10).

Because of the low solubility and low toxicity we failed to determine the average lethal dose of the investigated hydrazones. The biological activity of the compounds was studied at the maximum high doses that could be given (5000 mg/kg). Introduction of an alkylidene substituent (=CHR) into the hydrazones leads to considerable lowering of the toxicity. Similar data are reported in [2, 3].

In the picture of the general action of hydrazones I-VIII against a depression background a distinct muscular relaxation is observed. That effect distinguishes hydrazones I-VIII from the starting hydrazides because the latter do not show disturbance of the myorelaxant character [1].

Compounds I-VIII showed a depressing effect on the orientation reaction of mice whereby introduction of a chlorine atom into the aryl group at the phosphorus leads to some increase in the depressing activity (compare compounds IV and V, Table 2). Most of the compounds under investigation showed weak anticorazole activity. In [2] it is mentioned that occurrence of anticonvulsive activity is not characteristic of hydrazine derivatives. In our experiments the presence of weak anticorazole activity in hydrazones I-VIII and also depression of the orientation reaction by them obviously may be connected with distinct muscle-relaxant activity. Compounds I-VIII lowered the time that the mice remained on the rotating rod (see Table 2).

Comparison of the effects of the starting hydrazides and the hydrazones obtained from them showed that change of the nature of the activity upon the whole depends on the attachment of an alkylidene group (=CHR) to the nitrogen atom. All the alkylidene derivatives of the hydrazones studied proved to be less toxic compounds, having central activity that is accompanied by distinct myorelaxation.

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