SYNTHESIS OF 3-PHENYL-5-METHYL-4-ISOXAZOLYLHYDRAZINE AND SOME HYDRAZONES DERIVED FROM IT

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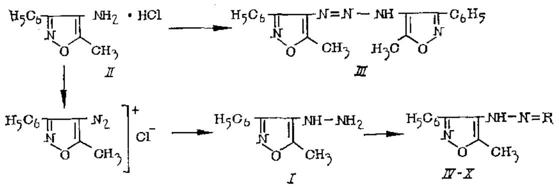
We have previously synthesized a series of 3-phenyl-5-methyl-4-isoxazolylhydrazines, which are of interest as biologically active compounds [1, 2]. Our intention in the work described here was to synthesize 3-phenyl-5-methyl-4-isoxazolylhydrazones and examine their biologic activity.

One of the methods for the synthesis of the starting 3-phenyl-5-methyl-4-isoxazolylhydrazine (I) is reduction of the product of diazotization of 3-phenyl-5-methyl-4-aminoisoxazole (II).



Aminoisoxazoles can be diazotized under normal conditions [3]. However diazotization of amine II in aqueous mineral acids formed the diazoamino compound, triazene (III), in quantitative yield. One of the reasons for the formation of the triazene is the low basicity of amine II (we determined its pK_a as 7.45 by potentiometric titration of its hydrochloride). We were able to prepare the diazo compound only by anhydrous diazotization with nitrosylsulfuric acid following [4]. However, the large quantity of sulfuric acid caused difficulty in the subsequent reduction and in the isolation of hydrazine I. We therefore developed a method for the diazotization based on that of Simon and Brodka [5]. However a small amount of the triazene was formed in this case.

We reduced the diazo compound with tin dichloride in hydrochloric acid. The base of hydrazine I decomposed in air; its hydrochloride was stable.

Reaction of hydrazine I with carbonyl compounds gave a series of hydrazones (IV-X).

We verified the structure of the hydrazones by UV and IR spectroscopy and polarography. The UV spectra of hydrazone IV-X have two maxima in the 225-270 and 302-370 nm regions. The IR spectra contain the characteristic $C=N$ stretching frequncies in the 1655-1620 cm^{-1} region, a broad band at 3380-3150 cm^{-1} (ν_{NH}), and a band at 1580 cm^{-1} ($\nu_{C=C}$).

We carried out the polarographic reduction of the hydrazones at the rotating platinum disk electrode in the aprotic solvent acetonitrile. In the working potential range (from 0 to -2 V) the polarograms of the synthetic compounds are one-step s-shaped curves, with the exception of the two-wave polarographic curves of reduction of hydrazones V and X, which contain a nitro group. The polarographic curves correspond to irreversible one-electron transfer with the formation of the radical anion [6, 7].

The polarographic process of all the compounds is diffusional, which is supported by the adherence to the linear dependence $i_\alpha = f(\omega^{1/2})$ derived from the Levich equation [8] for the diffusion process at a rotating disk electrode.

The reduction potentials of the hydrazones are summarized in Table 1.

We examined the antiviral activity of the hydrazones toward influenza viruses A2 and B in tests on developing chick embryos and mice. The protective index of the hydrazones are 33-46%.

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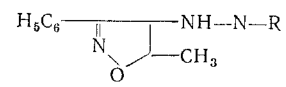
TABLE 1. Hydracones of 3-Phenyl-5-methyl-4-isoxazolylhydrazine



Compound	R	Yield, % (solvent)	mp, °C	Found, %			Formula	Calculated, %			R_f	$E_{1/2}$, B
				C	H	N		C	H	N		
IV	2-OH-C_6H_4-CH	33,0 (alcohol)	134—6	69,61	5,17	14,32	$C_{17}H_{15}N_3O_2$	69,72	5,43	14,48	0,78	—1,86
V	5-nitro-2-furyl-CH	30,1 (alcohol)	198—200	56,8	4,43	14,98	$C_{15}H_{17}N_4O_4 \cdot 1{,}5\ C_2H_5OH$	56,67	5,52	14,68	0,81	—1,48
VI	$C(CH_3)=CH=CH$-2-furyl	26,2 (chloroform)	108—9	70,9	5,46	13,68	$C_{18}H_{17}N_3O$	70,57	5,26	13,72	0,81	—1,71
VII	3-indolyl-CH	25,0 (dioxane)	162—4	72,42	5,19	17,76	$C_{19}H_{16}N_4O$	72,13	5,09	17,70	0,65	—1,77
VIII	4-diethylamino-C_6H_4-CH	31,0 (alcohol)	162—3	72,18	7,23	10,41	$C_{21}H_{26}N_4O$	72,06	7,48	10,29	0,83	—
IX	4-bis(2-chloroethyl)amino-C_6H_4-Cl	31,2 (alcohol)	132—5	60,67	5,33	13,98	$C_{21}H_{22}Cl_2N_4O$*	60,43	5,31	13,42	0,81	—
X	4-nitro-C_6H_4-CH	40,1 (alcohol)	143—5	63,47	4,23	17,8	$C_{17}H_{14}N_4O_3$	63,35	4,37	17,41	0,79	—1,46

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* Found, %: C 16.95. Calculated, %: C 16.99.

Note. Compounds IV, VIII, and IX were crystallized from alcohol; VII from dioxane; VI from aqueous alcohol; and V from alcohol–dioxane.

We assayed their antitumor effect in mongrel mice with the transplantable tumors sarcoma 37, adenocarcinoma AK-755, and Lewis's lung tumor. The compounds were administered in starch slurry. We found that some of the synthetic hydrazones stimulate the growth of adenocarcinoma AK-755 by 27-55%. The compounds had no substantial antitumor effect.

EXPERIMENTAL

The potentiometric titration of 3-phenyl-5-methyl-4-aminoisoxazole hydrochloride was carried out in 50% alcohol at concentration 0.01 M with a pH-340 millivoltmeter using 0.1 N sodium hydroxide; the titration curve was recorded on a PSR-01 recording potentiometer.

Polarography was carried out with a P-5827M potentiostat and a PDP-4-002 recorder. The reference electrode was the Ag/Ag^+ system in acetonitrile. The supporting electrolyte was tetrabutylammonium iodide.

The IR spectra were recorded on a UR-20 (East Germany) in Vaseline oil and the UV spectra on a Beckman M-26 spectrophotometer (West Germany) in ethanol.

Analytical thin-layer chromatograph was carried out on Silufol UV-254 plates in the solvent system chloroform–methanol (8 : 1). The chromatograms were visualized in UV light at 254 nm.

3-Phenyl-5-methyl-4-isoxazolylhydrazone (I). Diazotization. A. Amine II (1.74 g, 0.01 mole) was dissolved in hot acetic acid (21 ml). The solution was rapidly cooled to room temperature with ice and slowly added to a solution of nitrosylsulfuric acid. This was prepared by dissolving finely powdered sodium nitrite (0.78) in concentrated sulfuric acid (13.3 ml) at 70°C followed by cooling to room temperature. After the addition the mixture was stirred for 30 min.

B. The amine (1.74 g, 0.01 mole) was dissolved with warming in 7.2% hydrochloric acid (76 ml) and the solution was poured into a stirred water–ice mixture while the temperature was maintained at about 0°C. Dry sodium nitrite (0.69 g) was added and the mixture was kept for 30 min.

Reduction. To the resulting reaction mixture with stirring and cooling was added a solution of tin dichloride (6 g) in hydrochloric acid (60 ml). The mixture was kept at 0°C for 1 h and then 40% sodium hydroxide solution (40 ml) was added until alkaline while the temperature was maintained below 20°C. The hydrazine was extracted with ether (4 × 50 ml). The ethereal extracts were dried over sodium sulfate and ether was stripped off under an inert gas. The yield was 88% by method A and by 83% by method B.

3-Phenyl-5-methyl-4-isoxazolylhydrazine Hydrochloride. Hydrazine I (1.6 g) was treated with ethanol (20 ml) saturated with hydrogen chloride. Ether was added and the mixture was left overnight. The precipitate was filtered off and washed with ether. The yield was 92.5%, mp 193°C (from aqueous alcohol), R_f 0.423. Found, %: C 53.58; H 5.61; N 18.21; Cl 15.61. $C_{10}H_{11}N_3O \cdot HCl$. Calculated, %: C 53.22; H 5.35; N 18.64; Cl 15.71. IR spectrum, ν, cm^{-1}: 740, 1580, 1625, 2700, 2920, 3215. UV spectrum, nm, (log r): 236 (4.11), 390 (4.98).

2-Hydroxybenzaldehyde 3-Phenyl-5-methyl-4-isoxazolylhydrazone (IV). To a solution of the base of hydrazine I (1.89 g, 0.01 mole) in solvent (10 ml) was added 2-hydroxybenzaldehyde (1.05 ml, 0.01 mole). The solution was refluxed for 10 min and then cooled. The precipitate was filtered off and washed with alcohol. Compounds V-X were prepared in the same way. Some physical properties and the results of elemental analysis are summarized in Table 1.

1,3-Bis(3-phenyl-5-methyl-4-isoxazolyl)triazene (III). To the diazo compound prepared by method A from the amine (1.74 g, 0.01 mole) was added with stirring and cooling a solution of amine II (1.74 g, 0.01 mole) in ethyl alcohol (5 ml). The mixture was left for 30 min and then neutralized with 30% sodium hydroxide solution and extracted with ether (2 × 100 ml). The ethereal extracts were dried over sodium sulfate. The ether was stripped off and the reaction mixture was treated with ethanol saturated with hydrogen chloride. The precipitate was filtered off. The yield was 14.5%, mp 175°C (from alcohol), R_f 0.596. Found, %: C 55.31; H 4.3; N 16.25; Cl 16.40. $C_{20}H_{17}N_5O_2 \cdot HCl$. Calculated, %: C 55.56; H 4.43; N 16.10; Cl 16.40.. IR spectrum, ν, cm^{-1}: 780, 1465, 1565, 1615, 1650, 2170, 2800, 3270, 3430.

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