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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SUBSTITUTED 4H-PYRANO- AND DIHYDROPYRANO[3,2-d]PYRAZOLES

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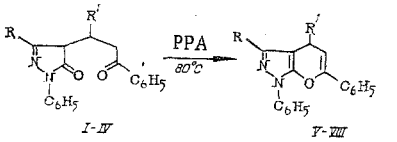
Many pyrazole derivatives possess a wide spectrum of pharmacological action [1], including antiinflammatory, antipyretic, analgesic, and antirheumatic activity. The vasodilating and hypotensive action of heterocyclic compounds containing condensed pyrazole and 6H-pyran rings has been reported [2]. Hence, the preparation and biological properties of new substituted 4H-pyrano- and 5,6-dihydropyrano[3,2-d]pyrazones are of interest.

We have found that the 4-(3-oxopropyl)pyrazolones-5 (I-IV) on reaction with polyphosphoric acid (PPA) readily cyclize to give the 4H-pyrano[3,2-d]pyrazoles V-VIII:



I-IV V-VIII

I, V: R = CH_3, R′ = C_6H_5; II, VI: R = CH_3, R′ = m-$NO_2C_6H_4$;
III, VII: R = R′ = C_6H_5; IV, VIII: R = C_6H_5; R′ = m-$NO_2C_6H_4$.

The structures of the pyrano[3,2-d]pyrazoles V-VIII were confirmed by elemental analysis, IR, and NMR spectroscopy (Table 1). The IR spectra of compounds V-VIII show strong absorption at 1660 cm^{-1} due to the double bonds of the 4H-pyran ring [3] but the band at 1690 cm^{-1} which is characteristic of the C=O group in compounds I-IV is absent. The NMR spectra of V-VIII contain doublets from the vinyl proton and the proton at position 4, confirming that the heterocycle has a 4H-pyran structure. The NMR spectrum of V (in carbon tetrachloride) has doublets due to the vinyl proton at δ 5.36 ppm and the C4 proton at δ 4.56 ppm with J = 3.8 Hz, and also a singlet from the three protons (δ 1.80 ppm) and a multiplet from the aromatic protons at δ 6.9-7.78 ppm.

TABLE 1. Yields and Physical Constants for 4H-Pyrano[3,2-d]-pyrazoles V-VIII

Compound	Yield, %	mp, °C*	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
V	82	124—5	82,48	5,97	7,71	$C_{25}H_{20}N_2O$	82,39	5,53	7,69
VI	65	168—9	73,15	4,65	9,83	$C_{25}H_{19}N_3O_3$	73,34	4,68	10,26
VII	70	167—8	84,53	5,12	6,75	$C_{30}H_{22}N_2O$	84,48	5,20	6,57
VIII	67	172—3	75,92	4,44	8,89	$C_{30}H_{21}N_3O_3$	76,42	4,49	8,91

* Compounds V-VIII were recrystallized from ethanol, VIII from acetone.

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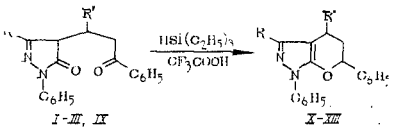
TABLE 2. The Antimicrobial Activity of the 4H-pyrano[3,2-dipyrazoles V-VIII and the dihydropyrano[3,2-d]-pyrazoles X-XIII

Compound	Minimum bacteriostatic concn., μg/ml				
	Staph. aureus 209 p	E. coli 675	Pr. vulgaris 38	Pr. aeruginosa 165	Candida ablicans 45
V	100	>100	100	100	100
VI	>100	50	100	100	100
VII	>100	>100	>100	>100	>100
VIII	>100	>100	>100	>100	>100
X	100	50	100	50	100
XI	100	100	100	100	100
XII	100	100	100	50	100
XIII	100	100	100	100	100

TABLE 3. The Antiphage Activity of the 4H-pyrano[3,2-d]pyrazoles V-VIII and the Dihydropyrano[3,2-d]pyrazoles X-XIII

Compound	% inactivation			
	phage T_6		phage MS-2	
	dose, μg/μl			
	1000	100	1000	100
V	24	10	22	20
VI	15	4	85	12
VII	29	13	98	49
VIII	76	69	85	33
X	19	42	20	13
XI	32	25	27	11
XII	50	30	26	7
XIII	46	42	50	39,2

To obtain new biologically active heterocycles containing a condensed pyrazole ring, we investigated the ionic hydrogenation of some propanonylpyrazolones. Compounds I-III and IX in trifluoroacetic acid and triethylsilane in the presence of a catalytic amount of boron trifluoride etherate were cyclized to the 5,6-dihydropyrano[3,2-d]pyrazole derivatives X-XIII [4]:



I-III, IX X-XIII

I, X: R = CH_3, R′ = Ph; II, XI: R = CH_3, R′ = m-$NO_2C_6H_4$;
III, XII: R = R′ = Ph; IX, XIII: R = CH_3, R′ = p-$OCH_3C_6H_4$.

The nature of the dihydropyranopyrazoles X-XIII was confirmed by NMR and IR spectroscopy. The IR spectra of compounds X-XIII contained bands at 1150–1000 cm^{-1} characteristic of the C–O–C bond but no carbonyl absorption bands. The NMR spectra of compounds of X-XIII show no vinyl proton signals, but the interaction of the protons at the 4 and 6 positions with the methylene group of the dihydropyran ring gives rise to two double doublets [4].

The results of a study of the antimicrobial and antiphage activity of the compounds prepared are presented in Tables 2 and 3.

From Table 2 it can be seen that the substituted 4H-pyrano- and dihydropyrano[3,2-d]pyrazoles exhibit moderate antimicrobial activity.

More interesting were the results of the study of antiphage activity (see Table 3). The 4H-pyrano[3,2-d]pyrazones, especially VII and VIII, were active against RNA-containing phage. Of the dihydropyrano[3,2-d]-pyrazoles, VIII showed the greatest effect.

The ability of the 4H-pyrano- and dihydropyrano[3,2-d]pyrazoles to suppress the propagation of phages makes them an extremely promising subject for future study of potential antiviral agents.

EXPERIMENTAL (CHEMICAL)

IR spectra of the compounds in mineral oil or hexachlorobutadiene were taken on a UR-20 spectrophotometer (GDR), NMR spectra on a Tesla BS-487 (ChSSR) (80 MHz), internal standard hexamethylenedisiloxane. The purity of the products and the course of the reaction were checked by TLC on Silufol UV-254 plates, solvent system ethyl acetate–hexane 12 : 27, developed in iodine vapor.

1-Phenyl-3-R-4-(1-R′-3-phenyl-3-oxopropyl)-2-pyrazoline-5-ones (I-IV, and (IX). These were prepared by the Michael condensation of 1-phenyl-3-methylpyrazolone-5 and the corresponding chalcones in the presence of an alkaline catalyst [4].

1,6-Diphenyl-3-R-4-R'-4H-pyrano[3,2-d]pyrazoles (V-VIII). A mixture of 5 mmoles of the oxopropylpyrazolone (I-IV) and 12 g of PPA was heated in the water bath at 80° for 1-2 h until no oxopropylpyrazolone was present (checked by TLC). The excess PPA was decomposed with water, the mixture extracted with ether, and the ether extracts washed with water and dried. The ether was evaporated at reduced pressure, and the residue recrystallized. Data on the pyranopyrazoles V-VIII are given in Table 1.

1,6-Diphenyl-3-R-4-R'-5,6-dihydropyrano[3,2-d]pyrazoles (X-XIII) were obtained by the ionic hydrogenation of oxopropylpyrazolones I-III, IX [4].

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the compounds was determined by the method of double serial dilution in meat–peptone broth (pH 7.2-7.4); activity against Staph. aureus 209 P., E. coli 675, Pr. vulgaris 38, Pr. aeruginosa 165, and Candida albicans 45 was determined. Antiphage activity of the compounds was studied on DNA-containing (T_6) and RNA-containing (MS-2) phages. E. coli type B and type Hfr C were used as indicator cultures. Quantity of surviving phage particles was determined by the Gratia agar layer method. Antiphage activity was expressed as percent inactivation according to the formula

$$1-\frac{c_0}{c_c}\cdot 100,$$

where C_0 is the quantity of surviving phage particles in the test; c_c is the quantity of phage particles in control.

The test substance was dissolved in DMFA and subsequently diluted with sterilized distilled water.

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