ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 1, pp. 153–156. © Pleiades Publishing, Ltd., 2012.
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Synthesis and Tuberculocidic Activity of Some 4-Arylaminomethylene-3-methyl-1-(pyrimidin-2-yl)pyrazol-5(4*H*)-ones

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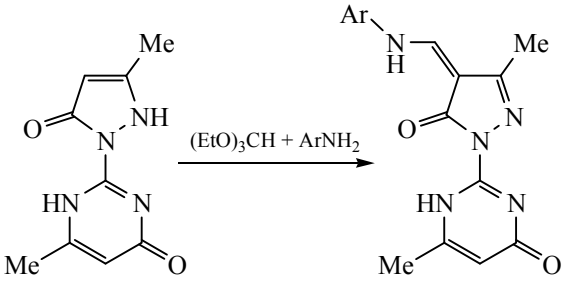
Received April 26, 2011

Abstract—4-Arylaminomethylene-3-methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)pyrazol-5(4*H*)-ones were synthesized by a three-component reaction between the 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)pyrimidin-4(1*H*)-one, triethoxymethane, and an aromatic amine. These compounds were found to exist as aminomethyleneketones regardless of the electronic effects of substituents in the aromatic fragments. The resulting compounds showed pronounced tuberculocidic activity.

DOI: 10.1134/S1070363212010252

The detected ability of some 4-arylidene-3-methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)pyrazol-5(4*H*)-ones (**I**) to inhibit the *Mycobacterium tuberculosis* cell growth [1] stimulates a search for the substances with similar effects among the structurally similar compounds. The modification of arylidene-pyrazolones **I** through fusing pyrimidine and cyclopentane rings led to the loss of tuberculocidic properties in the obtained 4-arylidene-3-methyl-1-(4-oxo-3,4-dihydrocyclopenta[*d*]pyrimidin-2-yl)-pyrazol-5(4*H*)-ones [2]. The extension of the series of compounds **I** by varying the substituents in the aromatic ring was found to be hindered because the condensation of the initial ethyl acetoacetate (6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)ethyl hydrazone [3] or 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl) pyrimidin-4(1*H*)-one **III** [4] with aromatic aldehydes leds to the products of the desired structure only with the reagents containing an auxochromic substituent in the *para*-position of the ring. The arylidenepyrazolone analogs of **I** with the minimally transformed structure are 4-arylaminomethylene-3-methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)pyrazol-5(4*H*)-ones (**IVa–IVk**). In order to study their tuberculocidic action we have synthesised these compounds by a three-component reaction between the pyrazolone (**III**), triethoxymethane, and aromatic amines.



III **IVa–IVk**

The reaction was performed by heating the equimolar mixture of reagents at 70–80°C without a solvent till the solidification of the reaction mixture. When the mixture did not solidify despite an increase in the time of contact of the initial compounds, the formed thick oil was treated with benzene to cause the product crystallization. To purify arylaminomethylene-pyrazolones **IVa–IVk** obtained they were crystallized once or twice from a suitable solvent or solvent mixture, to reach chromatographic purity of the target compound (Table 1).

Structure of arylaminomethylenepyrazolones **IV** is confirmed by the data of the ^{1}H NMR spectra, which contain multiplets of aromatic protons in the region of 7.2–7.9 ppm, as well as the characteristic doublets of protons of exocyclic CH groups near 8.5 ppm and NH about 11.0 ppm. In some cases the signals of secondary exocyclic amino groups appear as an unresolved singlet. Table 2 lists more detailed spectral parameters of compounds **IVa–IVk**.

Table 1. Yields, melting points, TLC,and elemental analyses of 4-arylaminomethylene-3-methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)pyrazol-5(4*H*)-ones **IVa–IVk**

Comp. no.	Ar	Yield,[a] %	mp, °C	R_f	Found, %			Formula	Calculated, %		
					C	H	N		C	H	N
IVa	Ph	50	277	0.43	61.82	4.56	22.51	$C_{16}H_{15}N_5O_2$	62.13	4.89	22.64
IVb	4-MeC_6H_4	54	263	0.42	62.75	5.05	21.46	$C_{17}H_{17}N_5O_2$	63.15	5.30	21.66
IVc	4-EtC_6H_4	63	240	0.42	63.88	5.56	20.62	$C_{18}H_{19}N_5O_2$	64.08	5.68	20.76
IVd	4-*i*-PrC_6H_4	15	211	0.42	64.76	5.89	19.82	$C_{19}H_{21}N_5O_2$	64.94	6.02	19.93
IVe	4-FC_6H_4	23	275	0.43	58.53	4.30	21.07	$C_{16}H_{14}FN_5O_2$	58.71	4.31	21.40
IVf	4-ClC_6H_4	42	258	0.43	55.61	4.23	20.13	$C_{16}H_{14}ClN_5O_2$	55.90	4.10	20.37
IVg	4-BrC_6H_4	38	262	0.43	49.57	3.54	17.78	$C_{16}H_{14}BrN_5O_2$	49.50	3.63	18.04
IVh	4-IC_6H_4	15	260	0.44	44.05	3.34	15.78	$C_{16}H_{14}IN_5O_2$	44.16	3.24	16.09
IVi	3,4-$Cl_2C_6H_3$	24	291	0.44	50.51	3.05	18.34	$C_{16}H_{13}Cl_2N_5O_2$	50.81	3.46	18.52
IVj	3-Me-4-BrC_6H_3	41	248	0.44	50.42	4.08	17.13	$C_{17}H_{16}BrN_5O_2$	50.76	4.01	17.41
IVk	3-Cl-4-$MeOC_6H_3$	37	227	0.43	54.61	4.27	18.67	$C_{17}H_{16}ClN_5O_3$	54.63	4.31	18.74

[a] After purification by recrystallization.

The arylaminomethylenepyrazolones **IV** exist preferably as β-amino-α,β-unsaturated ketones, as seen from their IR spectra, and virtually the same is correct for the whole series despite the difference in the directions of the inductive effects of substituents in the *para*-position of the aromatic ring. Thus, the frequency of the stretching vibrations of C=O and C=C bonds, which are in conjugation, are 1682 and 1558, 1685 and 1564 cm^{-1} for compounds **IVb, IVe**, respectively, indicating the dominant influence of the resonance effect of the halogen atom in the molecule of fluorophenylaminomethylenepyrazolone **IVe**. At the same time, a significant decrease in the frequency of stretching vibrations (Δν 100 cm^{-1}) of the exocyclic NH bond of compound **IVd** compared with that of the methylphenylaminomethylenepyrazolone **IVb** (νNH 3512 cm^{-1}) indicates its weakening caused by the inductive effects of substituents, and shows some disturbance of total conjugation in this structure resulting from it. Such a conclusion follows from the analysis of UV spectra of compounds **IVb, IVe**, which contain an absorption band corresponding to the π→π* transitions in the conjugation chains involving the aryl fragments, therewith for the peaks a blue shift is observed (Δλ = 11 nm) in the case of fluorophenylaminomethylenepyrazolone **IVe** and a red shift (Δλ = 10 nm), in the case of methylphenylaminomethylenepyrazolone **IVb** relative to the maximum (λ_{max} 344 nm) of the absorption bands of unsubstituted arylaminomethylenepyrazolone **IVa** (see the figure). However, a significant (Δε ~ 1000 l mol^{-1} cm^{-1}) increase in the molar absorption coefficient of compound **IVe** compared to the same characteristic absorption bands of compounds **IVb** provides additional evidence that the former is not involved in tautomeric rearrangement, which would lead to a significant change in its structure.

The biological screening of arylaminomethylenepyrazolones **IVa–IVk** *in vitro* showed a marked inhibitory effect of the some compounds on the cells of *Mycobacterium tuberculosis* strain $H37R_v$. Compounds **IVa, IVb, IVe, IVf,** and **IVh** show 100% inhibition of reproduction of a biological object at a concentration IC_{100} = 0.0125 g l^{-1}, compound **IVg**, at IC_{100} = 0.05 g l^{-1}. The IC_{100} values indicate a low sensitivity of this strain to the nature of the substituent in *para* position of the ring. The arylaminomethylenepyrazolones **IVi–IVk** containing a disubstituted

Table 2. [1]H NMR spectra of 4-arylaminomethylene-3-methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl) pyrazol-5(4*H*)-ones **IV**

Comp. no.	δ,[a] ppm							
	Me	Me	CH	Ar	–CH=	NH_e	NH	others groups
IVa	2.19 s	2.30 s	5.92 s	7.24–7.62 m	8.59 d	11.10 d	11.92	
IVb	2.18 s	2.32 s	5.92 s	7.22, 7.24 d; 7.48, 7.50 d	8.55 d	11.08 d	11.96	2.24 s (Me)
IVc	2.19 s	2.28 s	5.91 s	7.24, 7.26 d; 7.50, 7.52 d	8.56 d	11.09 d	11.98	1.20 t ($\underline{CH_3}CH_2$), 2.62 q ($CH_3\underline{CH_2}$)[c]
IVd	2.19 s	2.29 s	5.92 s	7.27, 7.29 d; 7.50, 7.52 d	8.54, 8.57 d	11.10, 11.13 d	11.96	1.22 s (Me), 1.23 s (Me), 2.91 m (CH)[c]
IVe	2.21 s	2.34 s	5.90 s	7.19–7.66 m	8.51, 8.54 d	11.14 br.s	–[b]	
IVf	2.21 s	2.31 s	5.90 s	7.42, 7.44 d; 7.65, 7.66 d	8.55, 8.58 d	11.14 br.s	–[b]	
IVg	2.19 s	2.29 s	5.95 s	7.61 s	8.54, 8.57 d	11.09, 11.13 d	11.90	
IVh	2.20 s	2.29 s	5.89 s	7.44, 7.46 d; 7.72, 7.74 d	8.55, 8.58 d	11.06, 11.09 d	11.85	
IVi	2.19 s	2.30 s	5.98 s	7.67–8.06 m	8.54, 8.57 d	11.08 br.s	–[b]	
IVj	2.20 s	2.30 s	5.89 s	7.37–7.60 m	8.56, 8.58 d	11.06 br.s	–[b]	2.40 s (Me)
IVk	2.17 s	2.27 s	5.94 s	7.16–7.85 m	8.47, 8.50 d	11.03, 11.06 d	11.96	3.87 s (MeO)

[a] Integral intensity of the signals corresponds to the number of proton groups. [b] Do not appear due to deuterium exchange. [c] The signal center.

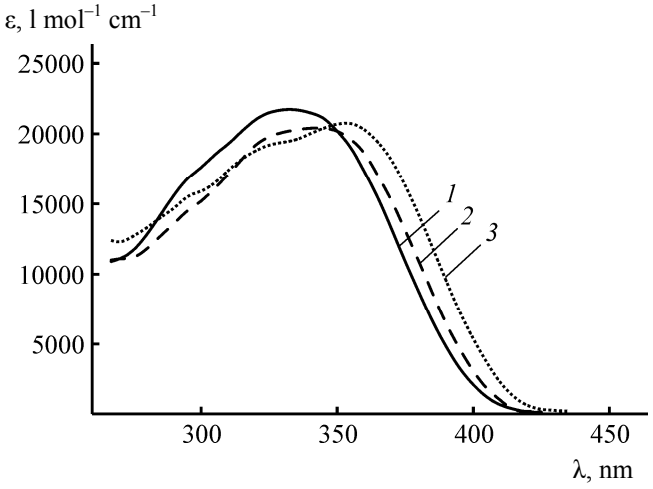
aromatic fragment were unable to inhibit the growth of the mycobacterial cells even at increasing the IC_{100} values to 0.1 g l^{-1}. The results obtained suggest that the structural transformation of arylidene pyrazolones **I** at the introduction of exocyclic amino group leads to an increased level of their tuberculocidic activity.

EXPERIMENTAL

The [1]H NMR spectra were recorded on a Bruker WM-400 spectrometer (operating frequency 400.13 MHz) in DMSO-d_6, as internal reference were used the signals of the residual protons of the solvent. The IR spectra were recorded on an FSM-1201 IR-Fourier spectrometer in KBr tablets. The UV spectra were recorded on an SF-26 spectrophotometer, solvent DMF, the concentration of a substance 0.3×10^{-4} M. The individuality of compounds was monitored by TLC on Silufol UV-254 plates in the system of 2-propanol–25% aqueous ammonia, 3:1, development of the spots was performed under UV light. Elemental analyses were carried out on a Hewlett Packard B-185 CHN-analyzer.

6-Methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)pyrimidin-4(1*H*)-one III was prepared according to [5].

4-Arylaminomethylene-3-methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)pyrazol-5(4*H*)-ones



UV spectra: (*1*) compound **IVe**, (*2*) **IVa**, and (*3*) **IVb**.

(IV). A mixture of 0.0015 mol of pyrimidylpyrazolone **III**, 0.0015 mol of triethoxymethane, and 0.0015 mol of an aromatic amine was heated at 70–80°C until solidification. After cooling, the reaction product was ground and recrystallized. The oily products were triturated with 10 ml of benzene, the precipitates formed were filtered off and purified by recrystallization. Compounds **IVa–IVc** were recrystallized from ethanol–water, 8:2, **IVd**, from ethanol–water mixture, 1:1, **IVe**, from acetic acid–water mixture, 4:6, **IVf**, from acetic acid–water mixture, 7:3, **IVg, IVj**, from DMF, **IVh, IVk**, from acetic acid–water, 1:1, **IVi**, from acetic acid. Purified products were washed with ethanol and dried at 80°C.

ACKNOWLEDGMENTS

The authors express their deep gratitude to Proffessor Tets V.V. and his colleagues (St. Petersburg Pavlov State Medical University) for performing the microbiological research, and to I.V. Klaptyuk (Scientific Research Institute of the Fire Defence, Ministry of Emergency Situations of Russia) for recording the IR spectra.

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