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Synthesis of 2-(Pyrazol-1-yl)pyrimidine Derivatives by Cyclocondensation of Ethyl Acetoacetate (6-Methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone with Aromatic Aldehydes

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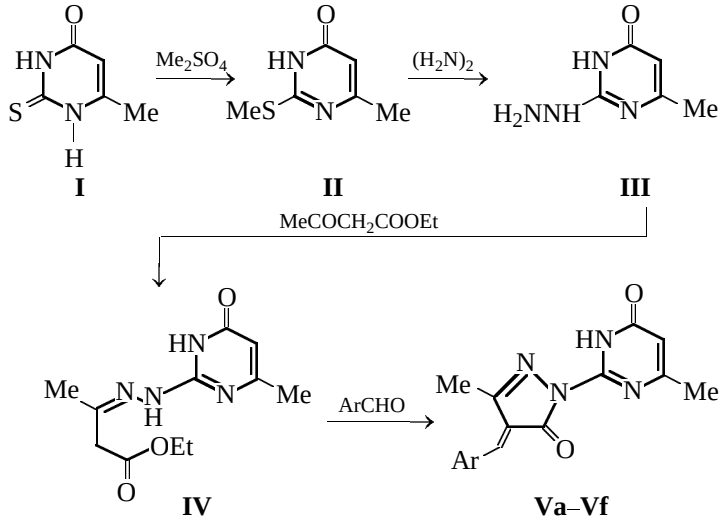
Abstract — 2-(4-Arylidene-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-6-methylpyrimidin-4(3*H*)-ones were obtained by reaction of ethyl acetoacetate (6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone with aromatic aldehydes. Successful cyclization occurs with aldehydes containing an auxochromic substituent in the *para* position.

2-(Pyrazol-1-yl)pyrimidines form an abundant class of heterocyclic compounds possessing antitubercular [1], antibacterial and antiviral [2], as well as antitumor properties [3]. The best known medicinal of this series is Mebron (Mepyryzol) [4-methoxy-6-methyl-2-(5-methoxy-3-methylpyrazol-1-yl)pyrimidine] used in treatment of acute inflammatory infections [4]. At the same time, the strong but short-term effect of Mebron necessitates search for its more effective analogs.

To this end, we undertook a modification of the synthetic precursor of Mebron, 6-methyl-2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)pyrimidin-4(3*H*)-one (**VI**) whose reactions with aromatic [5] or heterocyclic [6] aldehydes are known to provide the corresponding 4-ylidene derivatives. It was found that 2-(4-arylidene-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-6-methylpyrimidin-4(3*H*)-ones **Va**–**Vf** are readily formed by condensation of ethyl acetoacetonate (6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone (**IV**) with aromatic aldehydes in the presence of alkali by Scheme 1.

Scheme 1.



Ar = 4-$Me_2NC_6H_4$ (**a**), 4-$Et_2NC_6H_4$ (**b**), 3-MeO-4-HOC_6H_3 (**c**), 3-EtO-4-HOC_6H_3 (**d**), 3-MeO-4-HO-5-ClC_6H_2 (**e**), 3-MeO-4-HO-5-BrC_6H_2 (**f**).

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Table 1. Yields, melting points, TLC data, and elemental analyses of arylidenepyrazolones **Va**–**Vf**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	R_f (I^-)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
Va	32	255 (decomp.) (DMF)	0.47	63.37	5.82	20.47	$C_{18}H_{19}N_5O_2$	64.09	5.64	20.77
Vb	37	202 (decomp.) (MeCOMe)	0.49	65.36	6.03	18.95	$C_{20}H_{23}N_5O_2$	65.75	6.30	19.17
Vc	66	>300 (DMF–MeOH)	0.19	59.80	4.59	16.21	$C_{17}H_{16}N_4O_4$	60.00	4.71	16.47
Vd	28	>300 (DMF–MeOH)	0.23	60.73	4.93	15.65	$C_{18}H_{18}N_4O_4$	61.01	5.08	15.82
Ve	55	>300 (DMF)	0.21	54.27	3.85	14.81	$C_{17}H_{15}ClN_4O_4$	54.47	4.01	14.95
Vf	47	>300 (EtOH)	0.24	48.45	3.39	13.19	$C_{17}H_{15}BrN_4O_4$	48.69	3.58	13.37

Hydrazone **IV** was prepared by S-methylation of 6-methylthiouracil **I** with dimethyl sulfate, followed by hydrazinolysis of 6-methyl-2-(methylsulfanyl)-pyrimidin-4(3*H*)-one (**II**) and treatment of 2-hydrazino-6-methylpyrimidin-4(3*H*)-one (**III**) with ethyl acetoacetate. Direct hydrazinolysis of thioxoketone **I** in boiling ethanol provides little hydrazine **III** [7], whereas heating of thoether **II** with hydrazine hydrate for 6–60 h in ethanol [8, 9] provides compound **III** in reasonable yields. We found that reasonable (up to 45%) yields of hydrazine **III** can be attained by refluxing thioether **II** with excess hydrazine hydrate in 2-propanol for 2 h (method *a*). At shorter reaction times, a low (no higher than 14%) conversion of thioether **II** is observed, whereas at longer reaction times, much by-products are formed.

Baumbach *et al.* [10] have reported the reaction of thioether **II** with hydrazine hydrate in the absence of solvent. The reaction involved no recyclization of the pyrimidine ring into pyrazole, and compound **II** smoothly converted into hydrazine **III**. Actually, upon heating of thioether **II** with excess hydrazine hydrate at 100°C for no more than 30 min (method *b*) we isolated hydrazine **III** in a yield higher than 70%. The product was chromatographically identical to the sample of hydrazine **III**, synthesized by method *a*, and was identified as a benzylidene derivative.

The condensation of hydrazine **III** with ethyl acetoacetate we also performed in the absence of solvent by short heating of the reaction mixture at 100°C.

Of the published conditions for pyrazole ring closure in hydrazine **IV** and related compounds [11] we considered the most appropriate alkaline catalysis which prevents hydrolysis of the target products to 6-methyluracil. We found that when heated with equimolar amounts of aldehydes and potassium hydroxide in absolute methanol hydrazone **IV** undergoes cyclization to form arylidenepyrazolones **Va**–**Vf**. The products are colored high-melting compounds. Their physicochemical properties are given in Table 1.

Structural assessment of arylidenepyrazolones **Va**–**Vf** was made on the basis of a characteristic ylidene proton signal at 6.9–7.7 ppm in their ^{1}H NMR spectra (Table 2).

It should be noted that the cyclization of hydrazone **IV** into arylidenepyrazolones **Va**–**Vf** is successful only if an auxochromic substituent is present in the *para* position of the aldehyde to stabilize the target products via conjugation of its lone electron pairs with aromatic π electrons. With aldehydes containing no such a substituent, 4,4'-bispyrazolylmethanes are formed. Thus, the reaction of hydrazone **IV** with benzaldehyde gives, according to ^{1}H NMR data, bis-[5-hydroxy-3-methyl-1-(6-methyl-4-oxo-3,4-dihydropyrimiden-2-yl)pyrazol-4-yl]phenylmethane (**VII**).

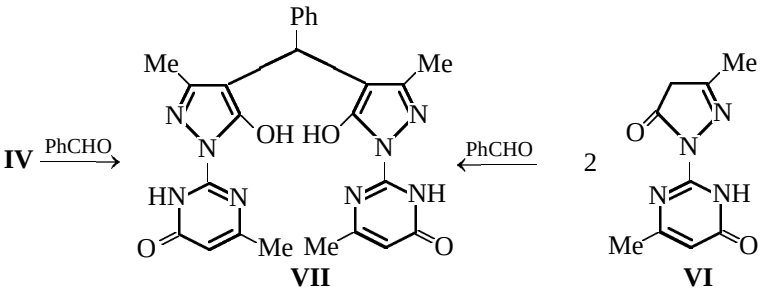


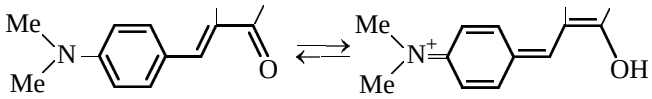
Table 2. ^{1}H NMR spectra of arylidenepyrazolones **Va**–**Vf**

Comp.	δ, ppm
Va	2.21 s (3H, Me), 2.31 s (3H, Me), 3.18 s (6H, NMe_2), 5.94 s (1H, CH),[a] 6.82, 6.87 d (2H, Ar), 7.63 s (1H, CH), 8.51, 8.55 d (2H, Ar)
Vb	1.17, 1.21, 1.25 t (6H, NCH_2*Me*), 2.20 s (3H, Me), 2.32 s (3H, Me), 3.51, 3.55, 3.59, 4.01 q (4H, NCH_2Me), 6.03 (1H, CH),[a] 6.83, 6.87 d (2H, Ar), 7.65 s (1H, CH), 8.51, 8.55 d (2H, Ar)
Vc	2.19 s (3H, Me), 2.21 s (3H, Me), 3.73 s (3H, OMe), 5.84 s (1H, CH),[a] 6.14, 6.19 d (1H, Ar), 6.97 s (1H, CH), 7.62, 8.38 d (2H, Ar), 13.05 s (1H, OH)
Vd	1.36, 1.40, 1.43 t (3H, OCH_2*Me*), 2.20 s (3H, Me), 2.21 s (3H, Me), 3.96, 3.98, 4.01, 4.05 q (4H, OCH_2Me), 5.82 s (1H, CH),[a] 6.18, 6.22 d (1H, Ar), 6.97 s (1H, CH), 7.63, 8.35 d (2H, Ar), 12.99 s (1H, OH)
Ve	2.20 s (3H, Me), 2.23 s (3H, Me), 3.76 s (3H, OMe), 5.83 s (1H, CH),[a] 7.09 s (1H, CH), 8.21 br.s (2H, Ar), 12.78 s (1H, OH)
Vf	2.20 s (3H, Me), 2.22 s (3H, Me), 3.74 s (3H, OMe), 5.85 s (1H, CH),[a] 7.10 s (1H, CH), 8.24 br.s (2H, Ar), 12.81 s (1H, OH)

[a] Pyrimidine methine proton signals.

The spectrum of phenylmethane **VII** contains a signal of the exocyclic methine proton at 5.04 ppm, and the integral intensity ratio of the methyl and phenyl proton signals is 12 : 5. The structure of compound **VII** was confirmed by its independent synthesis from pyrazolone **VI** and benzaldehyde at a 2 : 1 molar ratio.

The role the auxochromic substituent plays in stabilization of arylidenepyrazolones **Va**–**Vf** is illustrated by the UV spectra of 6-methyl-2-[4-(4-dimethylaminobenzylidene)-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl]pyrimidin-4(3*H*)-one (**Va**) (Fig. 1). The spectra of neutral (curve *2*) and alkaline (curve *3*) solutions of compound **Va** contains a broad strong band at 430–520 nm (ε_{max} ~27000) and a weak band at 350–400 nm (ε_{max} ~3000). Taking into account that pyrazolone **VI** is incapable of absorbing visible light [12] we can assign the first band to the $\pi\rightarrow\pi^*$ transition on the direct conjugation chain, whereas the fact that the second band is weak and smoothens in acidic solution (curve *1*) relates it to the $n\rightarrow\pi$ transition from the nitrogen lone electron pair to the aromatic ring. In combination with the enhanced intensity of the $\pi\rightarrow\pi^*$ band, the smoothening of the $n\rightarrow\pi^*$ band of pyrazolone **Va** in acidic solution can be explained in terms of formation of protonated form **A**.



A

The vibrational structure of the $\pi\rightarrow\pi^*$ band, which is preserved in the spectra of acidic, neutral, and alkaline solutions of compound **Va**, points to a weak overlap of the electronic clouds of its chromophores and thus to nonplanarity of the molecule. Actually, the Fletcher–Reeves quantum-chemical geometry optimization of molecule **Va** showed that the phenyl ring plane is drawn out of the pyrazole ring plane by 40.8°, and the angle between the pyrazole and pyrimidine ring planes is 54.5° (Fig. 2).

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker AC-200 instrument (200.13 MHz) in DMSO-d_6, the chemical shifts were measured relative to residual DMSO proton signals.

The UV spectra were recorded on an SF-26 spectrophotometer in methanol solutions (c 1×10^{-4} M).

The purity of the compounds was proved by TLC on Silufol UV-254 plates in the following systems: acetone–hexane, 2 : 1 (A); acetone–hexane, 2 : 1, plus 2 drops of conc. HCl (B); chloroform–methanol, 9 : 1 (C); and chloroform–methanol, 5 : 1 (D); development in UV light.

The Fletcher–Reeves quantum-chemical geometry optimization was performed using the HYPERCHEM program package (Ver. 6.03).

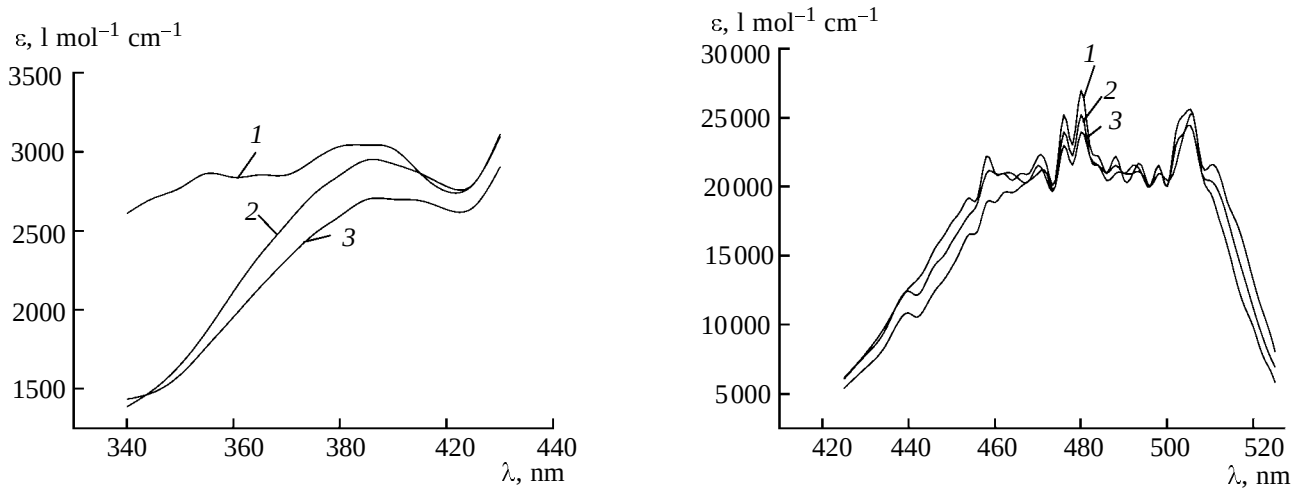


Fig. 1. Visible electronic absorption spectra of arylidenepyrazolone **Va** in mixed solvents. (*1*) MeOH–HCl, 1:1; (*2*) MeOH; and (*3*) MeOH–KOH, 1:1.

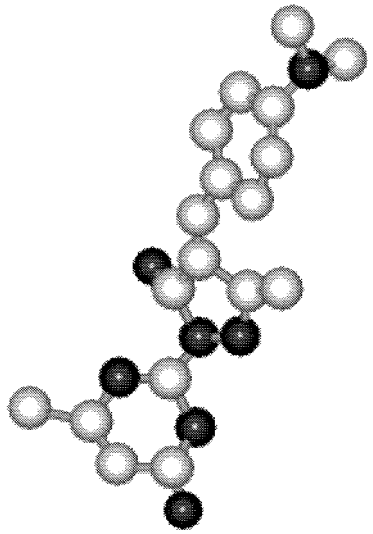


Fig. 2. Molecular geometry of arylidenepyrazolone **Va**, optimized by the Fletcher–Reeves method (carbon atoms are gray-colored, hydrogen atoms are not shown).

6-Methyl-2-thiouracil (I). Freshly distilled ethyl acetoacetate, 36.4 g, was added to a solution of sodium ethoxide, prepared from 6.5 g of sodium and 100 ml of 96% ethanol. The resulting solution was heated to 60°C, and 21.6 g of crystalline thiourea was added at that temperature with vigorous stirring. A suspension formed and was refluxed for 3 h. After cooling, the precipitate was filtered off, dissolved in 200 ml of water, and acidified with conc. HCl to pH 2. The precipitate was filtered off, washed with cold water, and dried at 100°C for 6 h. Yield 20.5 g (51%), R_f 0.54 (A), mp >300°C. ^{1}H NMR spectrum, δ, ppm: 2.06 s (3H, Me), 5.60 s (1H, CH), 12.15 s (2H, NH). Found N, %: 19.47. $C_5H_6N_2OS$. Calculated N, %: 19.71.

6-Methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one (II). Dimethyl sulfate, 7.1 g, was added to a solution of 8.0 g of thioxoketone **I** in 45 ml of water containing 5 g of NaOH. The mixture was heated on a boiling water bath for 3 h and then cooled to room temperature and acidified with dilute (1:1) hydrochloric acid to a stable weakly acidic reaction. The precipitate that formed was filtered off and purified by reprecipitation with dilute (1:1) HCl from 10% aqueous NaOH. The precipitate was washed with cold water and dried in a vacuum over P_2O_5. Yield 7.2 g (82%), R_f 0.47 (A), mp 228°C (published data: mp 225°C [13]).

2-Hydrazino-6-methylpyrimidin-4(3*H*)-one (III). *a*. A mixture of 1.56 g of thioester **II** and 1.5 g of hydrazine hydrate in 50 ml of 2-propanol was refluxed for 2 h. After cooling, the precipitate was filtered off, recrystallized from water, and dried in a vacuum over P_2O_5. Yield 0.62 g (45%).

b. A mixture of 1.56 g of thioether **II** and 1.5 g of hydrazine hydrate was heated on a boiling water bath for 30 min. After cooling, the suspension was diluted with 5 ml of water, the precipitate was filtered off, recrystallized from water, and dried in a vacuum over P_2O_5. Yield 1 g (71%), R_f 0.14 (B), mp >235°C (decomp.).

2-(Benzylidenehydrazino)-6-methylpyrimidin-4(3*H*)-one was prepared from hydrazine **III** and benzaldehyde. Yield 0.77 g (68%), R_f 0.39 (C), mp 237°C (*i*-PrOH) (published data: mp 228–229 [9],

235–237°C [14]). ^{1}H NMR spectrum, δ, ppm: 2.09 s (3H, Me), 5.48 s (1H, CH), 7.36, 7.87, 7.89 m (5H, Ph), 8.03 s (1H, NHe), 11.20 br.s (2H, CH + NH).

Ethyl acetoacetate (6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone (IV). A mixture of 0.7 g of hydrazine **III** and 0.78 g of ethyl acetoacetate was heated on a boiling water bath for 10 min. After cooling, the reaction mixture solidified and was ground, recrystallized from 2-propanol, and dried in a vacuum over P_2O_5. Yield 58 g (46%), R_f 0.19 (B), mp 147°C (published data: mp 148°C [15]).

2-[4-(4-Dimethylaminobenzylidene)-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl]-6-methylpyrimidin-4(3*H*)-one (Va). A mixture of 0.76 g of hydrazone **IV**, 0.45 g of 4-(dimethylamino)benzaldehyde and 0.17 g of KOH in 10 ml of absolute methanol was refluxed for 3 h, neutralized with glacial acetic acid, and cooled to 0°C. The precipitate that formed was filtered off, recrystallized from absolute DMF, and dried in a vacuum over P_2O_5.

Compounds **Vb**–**Vf** were prepared in a similar way and isolated by reduction of the reaction mixture by half, dilution of the residue with three volumes of water (**Vb**) or filtration after acidification (**Vc**–**Vf**), recrystallization from appropriate absolute solvent (Table 1), and drying over P_2O_5.

6-Methyl-2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)pyrimidin-4(3*H*)-one (VI). A mixture of 1.26 g of hydrazone **IV** and 0.28 g of KOH in 15 ml of absolute methanol was refluxed for 3 h. After cooling, the reaction mixture was neutralized with glacial acetic acid, the precipitate was filtered off, and the filtrate was reduced in a vacuum until crystallization began. The precipitates were combined, recrystallized from water, and dried in a vacuum over P_2O_5. Yield 0.67 g (65%), R_f 0.39 (D), mp 204°C (published data: mp 203°C [15]).

Bis[5-hydroxy-3-methyl-1-(6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)pyrazol-1-yl]phenylmethane (VII) *(independent synthesis).* A mixture of 0.62 g of pyrazolone **VI**, 0.16 g of benzaldehyde, and 0.08 g of KOH in 10 ml of absolute methanol was refluxed for 3 h. After cooling, the reaction mixture was neutralized with glacial acetic acid, methanol was evaporated by half, and the residue was diluted with two volumes of water and triturated until crystallized. The precipitate was filtered off, reprecipitated with acetic acid from 10% aqueous NaOH, washed with water, and dried in a vacuum over P_2O_5. Yield 0.19 g (25%), R_f 0.19 (D), mp > 290°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.09 s (6H, Me), 2.21 s (6H, Me), 4.79 s (1H, CH_e), 5.86 s (2H, CH), 7.22 m (5H, Ph). Found, %: C 59.47; H 4.61; N 22.05. $C_{25}H_{24}N_8O_4$. Calculated, %: C 60.00; H 4.80; N 22.40.

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