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1-(Pyrimidin-4-yl)pyrazol-5(4*H*)-one Derivatives: I. Synthesis of 3-Methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-pyrazol-5-ol and Specificity of Its Knoevenagel Reaction

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Abstract—3-Methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-1*H*-pyrazol-5-ol available via cyclocondensation of 6-methyl-2-methylsulfanylpyrimidin-4-ylhydrazine with ethyl acetoacetate reacted with aromatic aldehydes to give two kinds of products, 4-arylmethylidene-5-oxo-4,5-dihydropyrazole and arylbis(5-hydroxypyrazol-4-yl)methane derivatives , depending on the substituent in the aromatic aldehyde.

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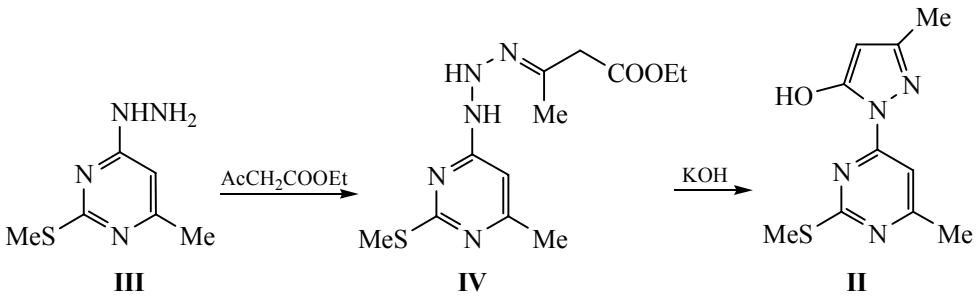
1-Aryl-1*H*-pyrazol-5(4*H*)-ones products of their condensation with aromatic aldehydes have been extensively studied [1], whereas structurally related 1-pyrimidinyl-1*H*-pyrazol-5(4*H*)-ones and their 4-arylmethylidene derivatives have been studied only in part. Transformations of 1-(pyrimidin-2-yl)-1*H*-pyrazol-5(4*H*)-ones in the Knoevenagel condensation have been reported [2–5], while there are no analogous data for isomeric 1-(pyrimidin-4-yl)-1*H*-pyrazol-5(4*H*)-ones **I**.

The goal of the present work was to synthesize one of pyrimidinylpyrazolones **I**, 3-methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-1*H*-pyrazol-5-ol (**II**), and to determine the structure of products of its reaction with aromatic aldehydes having typical electron-donating and electron-withdrawing substituents. Compound **II** was synthesized by conventional cyclocondensation of 6-methyl-2-methylsulfanylpyrimidin-4-ylhydrazine (**III**) with ethyl acetoacetate through intermediate ethyl 3-[2-(6-methyl-2-methylsulfanylpyrimidin-4-yl)hydrazono]butanoate (**IV**) (Scheme 1). Chromatographically pure hydrazone **IV** may be isolated as crystalline substance by reaction of hydrazine **III** with ethyl acetoacetate in butan-1-ol with simultaneous removal of liberated water as azeotrope. However, to avoid the loss of an appreciable amount of compound **IV**, its further purification is unreasonable, despite considerable difference in the melting points of the crude product and analytical sample.

Treatment of hydrazone **IV** with potassium hydroxide in aqueous ethanol at 50°C gave potassium salt of compound **II**, and neutralization of an aqueous solution of that salt with acetic acid afforded target pyrazole **II**. To improve the yield of **II**, the cyclization of hydrazone **IV** should be carried out at a temperature not exceeding 50°C; otherwise, the reaction is accompanied by considerable tarring.

Scheme 1.



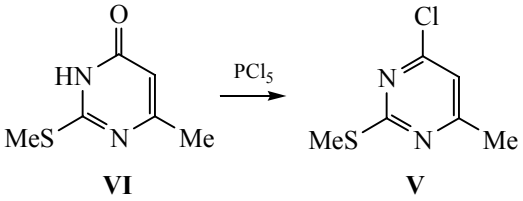
III **IV** **II**

Hydrazine **III** used as starting compound in the synthesis of pyrazole **II** was prepared in turn by reaction of 4-chloro-6-methyl-2-methylsulfanylpyrimidine (**V**) with excess hydrazine hydrate in boiling ethanol [6]. Hydrazinolysis of chloropyrimidine **V** at 80–90°C under solvent-free conditions was not successful. After cooling to 0–5°C, a product identical to initial pyrimidine **V** (according to the TLC data) separated from the reaction mixture.

The presence in molecule **V** of a sulfide moiety, which may also be replaced by the action of hydrazine hydrate, creates some difficulties in the purification of hydrazine **III** from the potential exhaustive hydrazinolysis product, 2,4-dihydrazino-6-methylpyrimidine [6]. Taking into account formation of trace amount of methanethiol during the synthesis of compound **III** and the absence in the ^{1}H NMR spectrum of **III** of a split signal assignable to 5-H, the contribution of exhaustive hydrazinolysis may be regarded as insignificant.

According to published data, intermediate chloride **V** is obtained by chlorination of 6-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**VI**) with phosphoryl chloride [7] or a mixture of phosphoryl chloride with phosphorus pentachloride [8]. However, we failed to reproduce these procedures, and we synthesized compound **V** by treatment of pyrimidinone **VI** with phosphorus pentachloride in the temperature range from 75 to 130°C (Scheme 2). The reaction mixture was heated until hydrogen chloride no longer evolved, and the product was isolated by extraction with methylene chloride (after preliminary removal of phosphoryl chloride and decomposition of its residual amount with ice). Our attempt to reproduce the procedure for chlorination of **VI** reported in [7] resulted in the isolation of a small amount of an unidentified hygroscopic substance with an R_f value of 0.89 (A); this substance was very poorly soluble in methylene chloride, diethyl ether, and benzene, and it melted in the temperature range from 120 to 140°C.

Scheme 2.

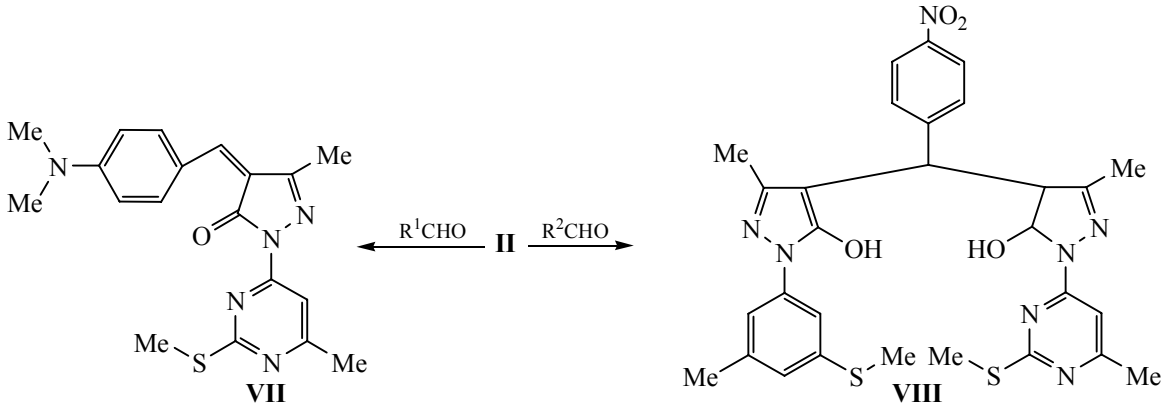


VI **V**

Pyrazole **II** reacted with aromatic aldehydes under the Knoevenagel reaction conditions to give two kinds of products whose structure was determined by the substituent in the aldehyde component. The condensation of compound **II** with 4-dimethylamino-benzaldehyde in ethanol in the presence of diethylamine afforded 4-(4-dimethylaminobenzyl-idene)-3-methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-pyrazol-5-(4*H*)-one (**VII**) (Scheme 3).

The ^{1}H NMR spectrum of pyrazolone **VII** contains a characteristic [2, 9] singlet from proton in the exocyclic –CH= group at δ 7.8 ppm, and a strong absorption band is observed in its UV spectrum at about λ 465 nm; the latter corresponds to π–π*-electron transitions in the direct conjugation chain. The reaction of pyrazole **II** with 4-nitrobenzaldehyde under analogous conditions resulted in the formation of bis-[5-hydroxy-3-methyl-1-(6-methyl-2-methylsulfanyl-pyrimidin-4-yl)-1*H*-pyrazol-4-yl](4-nitrophenyl)methane diethylammonium salt (**VIII**) even when equimolar

Scheme 3.

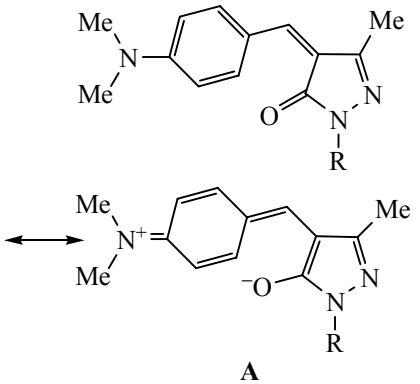


VII **VIII**

R^1 = 4-$Me_2NC_6H_4$, R^2 = 4-$O_2NC_6H_4$.

amounts of the reactants were used. Compound **VIII** displayed in the ^{1}H NMR spectrum a singlet at about δ 4.7 ppm from the exocyclic methine proton, which is typical of aldehyde addition products to two pyrazol-5(4*H*)-one molecules [10]. The intensity ratio of the CH and aromatic protons was 1:6. By neutralization of diethylammonium salt **VIII** with acetic acid we isolated arylbispyrazolylmethane **IX** as free base. Unlike diethylammonium salt **VIII**, the ^{1}H NMR spectrum of **IX** contained no signals from ethyl protons at δ 1.1 and 2.9 ppm. In the UV spectrum of bispyrazolylmethane **IX** we observed absorption bands with their maxima at λ 255 (log ε = 4.73) and 300 nm (log ε = 4.40), whose positions are similar to those typical of isolated chromophores of pyrazole **II**. Considerable increase in the intensity of these bands as compared to the spectrum of **II** is related to the contribution of substituted benzene ring.

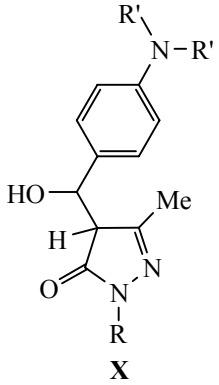
The formation of benzylidenepyrazolone **VII** may be interpreted on the basis of our previous assumption [9] that such compounds are stabilized due to participation of *n* electrons of the substituent in the overall conjugation system (zwitterionic canonical structure **A**). Taking into account the opposite electronic effect of nitro group, such stabilization of hypothetical 3-methyl-1-(6-methyl-2-methyl-sulfanyl-pyrimidin-4-yl)-4-(4-nitrobenzylidene)-1*H*-pyrazol-5-(4*H*)-one is hardly probable, and deficit of electron density on the exocyclic carbon atom may be compensated only by addition of the second pyrazole **II** molecule with the formation of arylbispyrazolyl-methane **VIII**. In some cases, the electron-donor effect of *p*-dialkylamino-substituted benzene ring is so strong that it hampers dehydration of intermediate 4-(α-hydroxy-4-dialkylaminobenzyl)-3-methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-1*H*-pyrazol-5(4*H*)-ones **X** to compounds like **VII**.



A

R = 6-Methyl-2-methylsulfanylpyrimidin-4-yl.

A mixture of benzylidenepyrazolone **VII** and intermediate **X** (R′ = Me) can be separated by single crystallization from appropriate solvent. The mixture obtained by reaction of pyrazole **II** with 4-diethyl-aminobenzaldehyde and consisting of α-hydroxyl-benzylpyrazolone **X** (R′ = Et) [R_f 0.83 (B)] and 4-(4-diethylaminobenzylidene)-3-methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-1*H*-pyrazol-5(4*H*)-one (**XI**) [a bright spot with R_f 0.63 (B) under visible light] cannot be separated in such a way. Moreover, neither heating of product mixture **X** (R′ = Et)/**XI** at 100°C under reduced pressure over a potent dehydrating agent, phosphoric anhydride, nor heating in benzene in the presence of a catalytic amount of concentrated sulfuric acid with simultaneous removal of water as azeotrope was efficient. Although the presence of α-hydroxybenzylpyrazolone **X** (R′ = Et) in the initial mixture followed from the observed separation of water in the Dean–Stark trap, its transformation into pyrazolone **XI** was not complete.



X

R = 6-Methyl-2-methylsulfanylpyrimidin-4-yl.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer at 400.13 MHz using $CDCl_3$ and DMSO-d_6 as solvents and references. The UV spectra were measured on an SF-26 spectrophotometer from solutions in ethanol with concentrations of 9.52×10^{-5} (compound **II**), 9.79×10^{-5} (**VII**), and 2.016×10^{-5} M (**IX**). The purity of the isolated compounds was checked by thin-layer chromatography on Silufol UV-254 plates using the following solvent systems as eluents: acetone–hexane (2:1) (A), butan-1-ol–acetic acid–water (1:1:1) (B), acetone–heptane (1:1) (C), and acetone–hexane (1:1) (D); spots were detected under UV light. The elemental compositions were determined on a Leco CHNS-932 analyzer.

6-Methyl-2-methylsulfanylpirimidin-4(3*H*)-one (**VI**) was synthesized according to the procedure described in [11].

3-Methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)pyrazol-5-ol (II). A solution of 1 g of hydrazine **III** in 30 ml of anhydrous butan-1-ol was heated to 120°C, 0.76 g of ethyl acetoacetate was added, and the mixture was heated for 1 h under reflux in a flask equipped with a Dean–Stark trap. The mixture was then evaporated under reduced pressure, the residue was left to stand until it crystallized completely, the crystalline material was ground with 15 ml of hexane, and the precipitate was filtered off, washed with hexane, and dried in air. We thus isolated 1.11 g (67%) of hydrazone **IV** with mp 87°C, R_f 0.45 (C), which was brought into further transformations without additional purification. A solution of 0.26 g of potassium hydroxide in 5 ml of water was added to a solution of 1.11 g of hydrazone **IV** in 15 ml of ethanol, the mixture was heated for 1 h at 50°C and evaporated to dryness under reduced pressure, the residue was dissolved in 10 ml of water, the aqueous solution was filtered and acidified with acetic acid, and the precipitate was filtered off, washed with cold water, dried over phosphorus pentaoxide under reduced pressure, recrystallized from cyclohexane, and dried in a high vacuum. Yield of pyrazole **II** 0.51 g (55%), mp 123°C, R_f 0.79 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.22 s (3H, Me), 2.46 s (3H, Me), 2.54 s (3H, Me), 5.40 s (1H, CH), 7.26 s (1H, CH), 11.80 br.s (1H, OH). UV spectrum, λ_{max}, nm (log ε): 248 (4.42), 310 (4.07). Found, %: C 50.28; H 5.37; N 23.55. $C_{10}H_{12}N_4OS$. Calculated, %: C 50.83; H 5.12; N 23.71.

6-Methyl-2-methylsulfanylpyrimidin-4-ylhydrazine (III). A mixture of 4 g of 4-chloropyrimidine **V** and 3.42 g of hydrazine hydrate in 30 ml of ethanol was heated for 1 h under reflux, and the solvent was distilled off under reduced pressure. The residue was treated with 20 ml of benzene, and the undissolved material was filtered off and dried in air. This procedure was repeated with the use of water instead of benzene. The dry product was recrystallized from benzene and dried for 3 h at 70°C. Yield 1.93 g (48%), mp 146°C, R_f 0.42 (B); published data [6]: mp 142–143°C.

Ethyl 3-[(6-methyl-2-methylsulfanylpyrimidin-4-yl)hydrazono]butanoate (IV) was synthesized as described above. An analytical sample was obtained by recrystallization from heptane, followed by drying in a high vacuum. mp 90°C, R_f 0.45 (C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 t (3H, CH_2CH_3), 1.96 s (3H, Me), 2.34 s (3H, Me), 2.49 s (3H, Me), 3.34 s (2H, CH_2), 4.17 q (2H, OCH_2), 6.67 s (1H, CH), 7.92 s (1H, NH). Found, %: C 50.77; H 6.21; N 19.39. $C_{12}H_{18}N_4O_2S$. Calculated, %: C 51.04; H 6.43; N 19.84.

4-Chloro-6-methyl-2-methylsulfanylpyrimidine (V). A mixture of 7.8 g of pyrimidinone **VI** and 10.4 g of phosphorus pentachloride was heated to 75–80°C, the temperature was then gradually raised to 125–130°C, and the mixture was kept until hydrogen chloride no longer evolved. Phosphoryl chloride was distilled off under reduced pressure from the resulting thick solution, the residue was cooled to 0–5°C, and finely crushed ice and 30 ml of methylene chloride were added. The organic phase was separated, the aqueous phase was extracted with methylene chloride (2×30 ml), the extracts were combined with the organic phase, dried over anhydrous sodium sulfate over a period of 24 h, and filtered, the solvent was distilled off completely under atmospheric pressure, and the residue was distilled under reduced pressure, a fraction with bp 110–115°C (8–10 mm) being collected. Yield 6.19 g (71%), mp 37°C, R_f 0.71 (D); published data [7]: mp 38°C.

4-(4-Dimethylaminobenzylidene)-3-methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-1*H*-pyrazol-5(4*H*)-one (VII). Diethylamine, 0.15 g, was added to a solution of 0.5 g of pyrazole **II** in 10 ml of ethanol, the mixture was stirred for a short time, a solution of 0.32 g of 4-dimethylaminobenzaldehyde in 5 ml of ethanol was added, and the mixture was stirred for 1 h at room temperature, heated for 2 h at 40–50°C, and left to stand for 24 h. The resulting suspension was evaporated to dryness under reduced pressure, the residue was treated with 5 ml of cold ethanol under stirring over a period of 2 h, and the precipitate was filtered off. The product was recrystallized from ethanol containing a small amount of dimethylformamide to ensure complete dissolution, washed with a minimal amount of cold ethanol, and dried under reduced pressure over phosphoric anhydride. Yield 0.15 g (19%), mp 202°C, R_f 0.78 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.36 s (3H, Me), 2.46 s (3H, Me), 2.61 s (3H, Me), 3.15 s (6H, NMe), 6.72 d (2H, H_{arom}), 7.27 s (1H, CH), 7.80 s (1H, CH), 8.50 d (2H, H_{arom}). UV spectrum, λ_{max}, nm (log ε): 250 (4.44), ~465 (4.4). Found, %: C 61.80; H 5.57; N 19.16. $C_{19}H_{21}N_5OS$. Calculated, %: C 62.10; H 5.76; N 19.06.

4,4′-(4-Nitrobenzylidene)bis[3-methyl-1-(6-methyl-2-methylsulfanylpyrimidin-4-yl)-1*H*-pyrazol-5-ol] (IX). Diethylamine, 0.15 g, was added to a solution of 0.5 g of pyrazole **II** in 10 ml of ethanol, the mixture was stirred for a short time, a solution of 0.32 g of 4-nitrobenzaldehyde in 5 ml of ethanol was added, and the mixture was stirred for 1 h at room temperature, heated for 1 h at 40–50°C, and left to stand for 24 h. The precipitate was filtered off, washed with a minimal amount of cold ethanol, recrystallized from acetonitrile containing a small amount of dimethylformamide to ensure complete dissolution, and dried under reduced pressure to obtain 0.27 g (18%) of compound **VIII** as diethylammonium salt, mp 173°C, R_f 0.91 (B). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.16 s (6H, NCH_2CH_3), 2.17 s (6H, Me), 2.38 s (6H, Me), 2.49 (SMe, obscured by the solvent), 2.92 d (4H, NCH_2), 4.69 s (1H, CH), 7.51 d (2H, H_{arom}), 7.65 s (2H, CH), 8.05 d (2H, H_{arom}). Found, %: C 54.11; H 5.82; N 20.17. $C_{27}H_{27}N_9O_4S_2 \cdot C_4H_{11}N$. Calculated, %: C 54.80; H 5.60; N 20.62. Diethylammonium salt of **VIII**, 0.27 g, was dissolved in 5 ml of acetic acid, and 15 ml of water was gradually added under stirring to the solution. The precipitate was filtered off, washed with water, dried in air, recrystallized from cyclohexane, and dried in a high vacuum. Yield 58 mg (24%, calculated on the diaethylammonium salt), mp >120°C (decomp.), R_f 0.23 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.10 s (6H, Me), 2.40 s (6H, Me), 2.54 s (6H, Me), 5.11 s (1H, CH), 7.50 d (2H, H_{arom}), 7.92 s (2H, CH), 8.12 d (2H, H_{arom}), 11.56 br.s (2H, OH).

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REFERENCES

1. *Heterocyclic Compounds*, Elderfield, R.C., Ed., New York: Wiley, 1957, vol. 5.
2. Cristea, I., *Stud. Univ. Babes-Bolyai, Chem*., 1988, vol. 33, no. 2, p. 61.
3. Cristea, I. and Panea, I., *Stud. Univ. Babes-Bolyai, Chem*., 1995, vol. 40, nos. 1–2, p. 171.
4. Panea, I. and Cristea, I., *Stud. Univ. Babes-Bolyai, Chem*., 1996, vol. 41, no. 1, p. 9.
5. Lovasz, T., Paizs, C., Cristea, I., and Irimie, F.D., *Stud. Univ. Babes-Bolyai, Chem*., 1998, vol. 43, no. 2, p. 145; *Chem. Abstr*., 2002, vol. 137, no. 247640h.
6. Vanderhaeghe, H. and Claesen, M., *Bull. Soc. Chim. Belg*., 1959, vol. 68, no. 3, p. 30.
7. Matsukawa, S. and Ohta, B., *J. Pharm. Soc. Jpn*., 1949, vol. 69, no. 4, p. 489; *Chem. Abstr*., 1950, vol. 44, p. 3455i.
8. Wheeler, H.L. and McFarland, D.F., *Am. Chem. J*., 1909, vol. 42, no. 5, p. 431.
9. Erkin, A.V., Krutikov, V.I., and Chubraev, M.A., *Russ. J. Gen. Chem*., 2004, vol. 74, no. 3, p. 423.
10. Pavlov, P.T., Goleneva, A.F., Lesnov, A.E., and Prokhorova, T.S., *Khim.-Farm. Zh*., 1998, vol. 32, no. 7, p. 28.
11. Erkin, A.V., Krutikov, V.I., and Pavlovich, N.I., *Russ. J. Gen. Chem*., 2003, vol. 73, no. 3, p. 463.