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Modified Synthesis of Some 1-(Pyrimidin-2-yl)-3-methyl-4-arylidenepyrazol-5(4*H*)-ones

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Abstract — 2-[3-Methyl-4(4-dialkylaminobenzylidene)-5-oxo-4,5-dihydropyrazol-1-yl]cyclopenta[*d*]pyrimidin-4(3*H*)-ones were synthesized by consecutive transformation of 2-hydrazinocyclopenta[*d*]pyrimidin-4(3*H*)-one prepared from benzylideneaminoguanidine and ethyl 2-oxocyclopentanoate.
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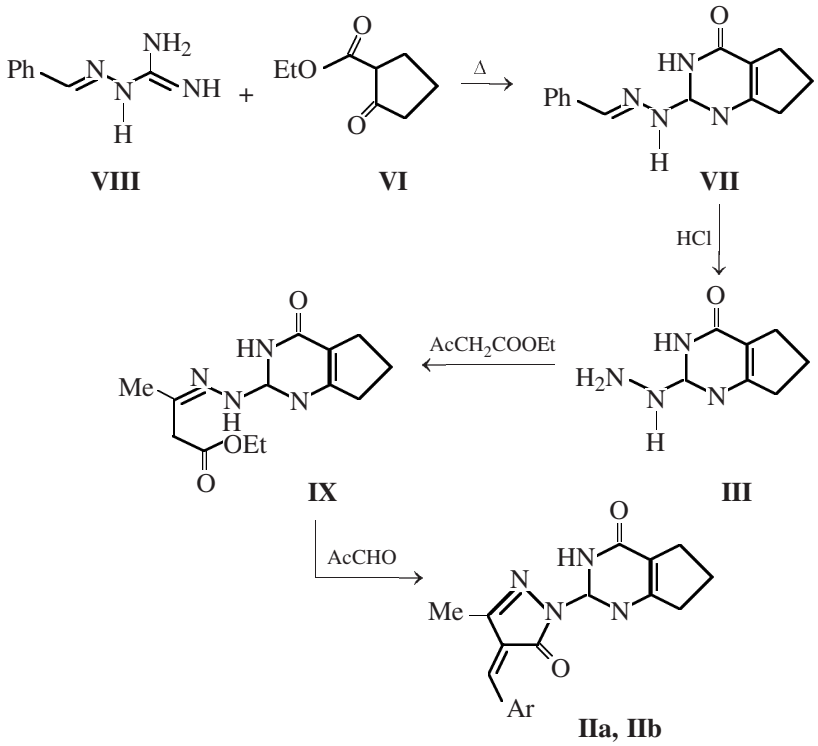
The establishing of general rules of cyclization of ethyl acetoacetate (6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone and aromatic aldehydes allowed synthesis of a series of 2-(3-methyl-4-arylidene-5-oxo-4,5-dihydropyrazol-1-yl)-6-methylpyrimidin-4(3*H*)-ones [1] which proved to be suitable objects for design of new antitubercular agents. The highest activity in vitro was shown by 2-[4-(4-diethylaminobenzylidene)-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl]-6-methylpyrimidin-4(3*H*)-one (**I**) [2] which inhibited growth of *Mycobacterium tuberculosis* bacilliculture by 100% at a concentration of 0.05 g l^{-1}.

With the purpose to obtain potentially biologically active analogs of compound **I** we synthesized 2-[4-(4-dialkylaminobenzylidene)-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl]cyclopenta[*d*]pyrimidin-4(3*H*)ones **IIa, IIb** according to the scheme presented below.



IIa, IIb

Ar = $Me_2NC_6H_4$ (**a**), $Et_2NC_6H_4$ (**b**).

The synthesis of the key product, 2-hydrazinocyclopenta[*d*]pyrimidin-4(3*H*)-one (**III**) by the reaction of 2-thioxo-1,2-dihydrocyclopenta[*d*]pyrimidin-4(3*H*)-one (**IV**) [3] or 2-(methylsulfanyl)cyclopenta[*d*]-pyrimidin-4(3*H*)-one with hydrazine is associated with significant difficulties. According to published data [4], the synthesis of thioxoketone **IV** by cyclization of thiourea with ethyl 2-oxocyclopentanoate proceeds unsatisfactorily due to cleavage of the latter under the conditions used, but it can be carried out through the stage of preparation of an intermediate product, ethyl 2-ureidocyclopentanoate, with the total yield of compound **IV** not exceeding 30–40%. In addition to that, hydrazinolysis of thioether **V** instead of the expect ed hydrazine gives an abnormal reaction product, cyclopenta[*c*]pyrazol-5(4*H*)-one [5].

With the above data in mind, we prepared compound **III** by an alternative procedure involving acid hydrolysis of 2-(benzylidenehydrazino)cyclopenta[*d*]-pyrimidin-4(3*H*)-one (**VII**) which, in its turn, was obtained by cyclocondensation of benzylideneaminoguanidine (**VIII**) with keto ester **VI**. Benzoylaminoguanidine is less suitable for this purpose, because it reacts with a suitable tricarbon component to form by-product triazolo[4,3-*a*]pyrimidines through intramolecular dehydration of initially formed 2-(benzoylhydrazino)pyrimidines [6]. Unsubstituted aminoguanidine is absolutely unsuitable due to its tendency for cyclization with various β-keto esters, leading to derivatives of 1-carbamimidoylpyrazol-5(4*H*)-one, 2,3-diaminopyrimidin-4(3*H*)-one, or 3-amino-1,2,4-triazole depending on reaction conditions [7].

Cyclocondensation of substituted guanidine **VIII** and keto ester**VI** proceeds on heating under rigid conditions in the absence of solvents. Subsequent hydrolysis of benzylidenehydrazine **VII** with HCl with simultaneous removal of liberated benzaldehyde from the reaction zone gives hydrazine **III**. Note that attempted preparation of compound **III** by boiling benzylidenehydrazine **VII** with hydrazine hydrate in ethanol according to the procedure in [8] failed: The compound isolated from the reaction mixture was chromatographically identical to starting compound **VII**, and their mixed sample gave no melting point depression.

Hydrazine **III** when reacted with ethyl acetoacetate without a solvent forms ethyl acetoacetate (4-oxo-3,4-dihydrocyclopenta[*d*]pyrimidin-2-yl)hydrazone (**IX**) whose treatment with 4-(dialkylamino)benzaldehydes in ethanol in the presence of potassium hydroxide gives target heterocycles **IIa, IIb**. The synthesis of compounds **IIa, IIb** by the three-component condensation of hydrazine **III**, ethyl acetoacetate, and aromatic aldehydes failed because of the strong tarring of the reaction mixture. Heterocycles **IIa, IIb** are easily identified by means of ^{1}H NMR and UV spectroscopy. The ^{1}H NMR spectra contain characteristic proton signals of the cyclopentane fragment (2.0–2.8 ppm), aromatic ring (6.0–9.0 ppm), and ylidene bond (7.6 ppm). In the visible part of the electronic absorption spectra, there is a strong band at 495 nm (log ε 4.40–4.80) related to electron transitions in the branched conjugation system.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WM-400 spectrometer (400.13 MHz) in DMSO-d_6 against residual DMSO protons. The UV spectra were recorded on an SF-26 spectrophotometer in DMF (c ~0.5×10^{-4} M). The individuality of the compounds was controlled by TLC on Silufol UV-254 plates, eluents 1 : 1 : 1 butanol-1–acetic acid–water (system A) and 2 : 1 acetone–hexane (system B), development in the UV and visible light. Elemental analysis was carried out on Hewlett–Packard B-185 and Leco CHNS-932 analyzers.

Ethyl 2-oxocyclopentanoate (**VI**) was obtained by cyclization of diethyl adipinate according to [9], and diethyl adipinate was obtained by esterification of adipic acid according to [10].

2-[4-(4-Dimethylaminobenzylidene)-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl]cyclopenta[*d*]pyrimidin-4(3*H*)-one (IIa). A mixture of 0.5 g of hydrazone **IX**, 0.26 g of 4-(dimethylamino)benzaldehyde and 0.1 g of potassium hydroxide was refluxed in 15 ml of ethanol for 2 h. The suspension obtained was cooled to room temperature, neutralized with acetic acid, stirred for 15 min, and left for 2 days. The precipitate formed was filtered off, washed with ethanol, and crystallized from DMF. After washing with diethyl ether and drying in a vacuum 0.35 g (54%) of compound **IIa** was obtained, mp 270°C (decomp.), R_f 0.73(A). ^{1}H NMR spectrum, δ, ppm: 2.01 m (2H, CH_2), 2.30 s (3H, Me), 2.65 t (2H, CH_2), 2.75 t (2H, CH_2), 3.13 s (6H, NMe_2), 6.84 d (2H, Ar), 7.64 s (1H, CH), 8.53 d (2H, Ar), 11.96 br.s (1H, NH). UV spectrum, λ_{max}, nm (log ε): 595 (4.41). Found, %: C 66.84; H 5.37; N 19.62. $C_{20}H_{21}N_5O_2$. Calculated, %: C 66.10; H 5,82; N 19.27.

2-[4-(4-Diethylaminobenzylidene)-3-methyl-5-oxo-4,5-dihydropyrazol-1-yl]cyclopenta[*d*]pyrimidin-4(3*H*)-one (IIb). A mixture of 0.5 g of hydrazone **IX**, 0.32 g of 4-(diethylamino)benzaldehyde, and 0.1 g of potassium hydroxide was refluxed for 2 h in 15 ml of ethanol. The suspension obtained was cooled

to room temperature, neutralized with acetic acid, stirred for 15 min, and left for 2 days. The suspension obtained was evaporated in a vacuum to dryness, the residue was triturated with 20 ml of water, and the precipitate was filtered off and dried in a vacuum over phosphorus pentoxide. The dry product was crystallized from DMF, washed with diethyl ether, and dried in a vacuum to give 0.19 g (27%) of compound **IIb**, mp 229°C (decomp.), R_f 0.80 (A). ^{1}H NMR spectrum, δ, ppm: 1.22 t (6H, Me), 2.03 m (2H, CH_3), 2.12 s (3H, Me), 2.62 t (2H, CH_2), 2.77 t (2H, CH_2), 3.57 m (4H, CH_2), 6.82 d (2H, Ar), 7.60 s (1H, CH), 8.53 d (2H, Ar), 12.02 br.s (1H, NH). UV spectrum, λ_{max}, nm (log ε): 495 (4.74). Found, %: C 67.31; H 5.93; N 17.95. $C_{22}H_{25}N_5O_2$. Calculated, %: C 67.50; H 6.44; N 17.89.

2-Hydrazinocyclopenta[*d*]pyrimidin-4(3*H*)-one (III)). Through a suspension of 5.08 g of benzylidenehydrazine **VII** in dilute (1 : 1) hydrochloric acid heated to 90°C, a stream of steam until a solution formed. It was filtered hot and evaporated to dryness in a vacuum. The residue was triturated with 30 ml of absolute ethanol, and the precipitate was filtered off and washed with ethanol. Drying in a vacuum over phosphorus pentoxide gave 2.36 g (58%) of compound **III**, mp > 230°C (decomp.), R_f 0.53 (A). An analytical sample was prepared by crystallization from ethanol. ^{1}H NMR spectrum, δ, ppm: 1.97 m (2H, CH_3), 2.54 t (2H, CH_2), 2.79 t (2H, CH_2), 8.89 br.s (5H, NH_2, 2NH, N^+H). Found, %: C 42.59; H 5.75; N 28.72. $C_7H_{10}N_4O$ HCl. Calculated, %: C 41.48; H 5.43; N 27.65. Isolated as hydrochloride.

2-(Benzylidenehydrazino)cyclopenta[*d*]pyrimidin-4(3*H*)-one (VIII). A mixture of 22.2 g of guanidine **VIII** and 23.6 g of ethyl 2-oxocyclopentanoate (**VI**) was heated at 150°C under vigorous stirring for 30 min. The semicrystalline material was cooled and triturated with 500 ml of water, the precipitate was filtered off, washed with water, and dried in a stream of warm air for 10 h. The dry product was crystallized from acetic acid, washed with water, and dried at 70°C for 10 h to give 13.3 g (52%) of compound **VIII**, mp 245°C (decomp.), R_f 0.55 (B). ^{1}H NMR spectrum, δ, ppm: 1.93 m (2H, CH_2), 2.54 s (2H, CH_2), 2.63 s (2H, CH_2), 7.37 m (3H, Ph), 7.90 s (2H, Ph), 8.00 s (1H, NH), 11.22 br.s (2H, NH, N=CH). Found, %: C 65.19; H 6.72; N 18.82. $C_{14}H_{14}N_4O$. Calculated, %: C 66.14; H 5.51; N 22.05.

1-(Benzylideneamino)guanidine (VIII). To a solution of 20 g of sodium hydroxide in 180 ml of water, 55.2 g of aminoguanidine hydrochloride was added with under vigorous stirring. The solution obtained was filtered, and 53 g of freshly distilled benzaldehyde dissolved in 50 ml of ethanol was added dropwise to the filtrate under vigorous stirring. After the addition was complete, the mixture was stirred additionally for 1 h, and the precipitate the formed was filtered off, crystallized from water, and dried at 70°C for 10 h to give 51.5 g (64%) of compound **VIII**, mp 182°C (published data: 178°C [11]), R_f 0.77 (A).

Ethyl acetoacetate (4-oxo-3,4-dihydrocyclopenta[*d*]pyrimidin-2-yl)hydrazone (IX). Hydrazine **III** hydrochloride, 1.6 g, was added to a solution of 0.44 g of potassium hydroxide in 25 ml of absolute ethanol. The mixture was refluxed for 30 min and evaporated in a vacuum to dryness. The residue was triturated with 15 ml of water, the precipitate was filtered off, washed with water, and dried in a vacuum over phosphorus pentoxide to give 0.92 g (70%) of hydrazine **III** as a free base which was used in the next step without additional purification. A mixture of 0.92 g of hydrazine **III** and 0.79 g of ethyl acetoacetate was kept at 100°C for 30 min. The precipitate was crystallized from acetonitrile and dried in a vacuum over phosphorus pentoxide to give 0.85 g (55%) of compound **IX**, mp 147°C, R_f 0.81 (A). ^{1}H NMR spectrum, δ, ppm: 1.25 m (3H, OCH_2*Me*0), 1.89 s (2H, CH_2), 1.96 s (3H, Me), 2.54 t (2H, CH_2), 2.64 t (2H, CH_2), 3.35 s (2H, CH_2), 4.11 m (2H, OCH_2Me), 9.85 br.s (1H, NH), 11.07 br.s (1H, NH). Found, %: C 55.88; H 6.36; N 20.04. $C_{13}H_{18}N_4O_3$. Calculated, %: C 56.11, H 6.47; N 20.14.

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