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SYNTHESIS AND MASS SPECTROSCOPIC INVESTIGATION OF SOME 6-(PYRAZOL-1-YL)PYRIMIDINES

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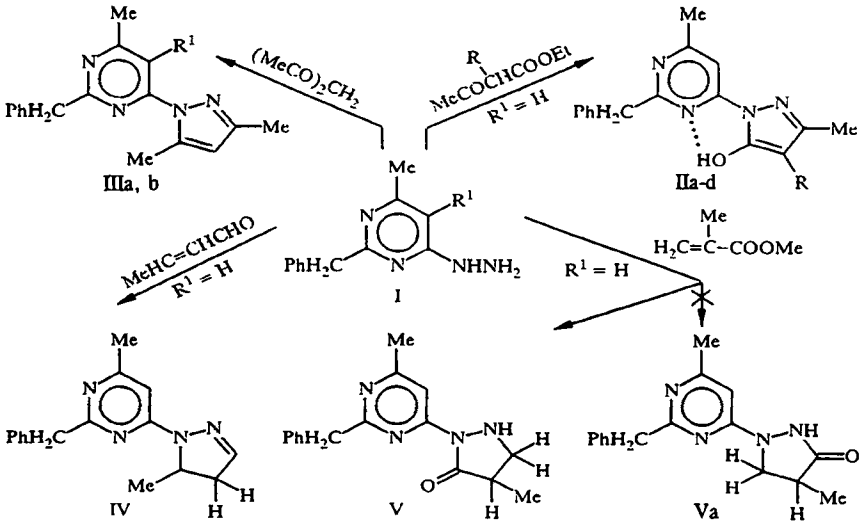
Condensation of 2-benzyl-4-hydrazino-6-methylpyrimidine with ethyl acetoacetate and its alkyl derivatives as well as with acetyl acetone, methyl methacrylate, and crotonaldehyde have given the corresponding 2-benzyl-4-methyl-6-(pyrazol-1-yl)pyrimidines which have been studied by PMR and mass spectrometry. Their biological activity has been investigated.

To continue our study of 2-benzyl-4-hydrazinopyrimidines [1-3] we have synthesized some substituted 2-benzyl-4-methyl-6-(pyrazol-1-yl)pyrimidines. It is known that pyrazolylpyrimidines shown high biological activity. Hence 2-(3-methyl-5-methoxypyrazol-1-yl)-4-methyl-6-methoxypyrimidine (compound DA-398, Merpirizole) shows antipyretic and antiinflammatory properties [4, 5] and a number of other 2- and 4-(substituted pyrazol-1-yl)pyrimidines have antitumor, antiviral, spasmolytic, and antitubercular activity [6-8]. The data reported warrants our interest in, and investigation of, this series of compounds.

The reaction of 2-benzyl-4-hydrazino-6-methylpyrimidine [1] with acetoacetic ester and its alkyl derivatives (R = C_3H_7, C_4H_9, $CH_2-CH=CH_2$) in alcoholic sodium ethylate solution gave the corresponding 2-benzyl-4-methyl-6-(3-methyl-4-alkyl-5-hydroxypyrazol-1-yl)pyrimidines IIa-d. Condensation of the same hydrazinopyrimidine and its 5-allyl derivative with acetyl acetone did not occur under the conditions quoted above. The reaction was brought about in high yield using benzene with azeotropic distillation of water.

Condensation of hydrazinopyrimidine I with crotonaldehyde and methyl methacrylate gave the corresponding hydrogenated pyrazolylpyrimidines IV and V.

Scheme 1



R = H, C_3H_7, C_4H_9, $CH_2-CH=CH_2$; R^1 = H, $CH_2-CH=CH_2$

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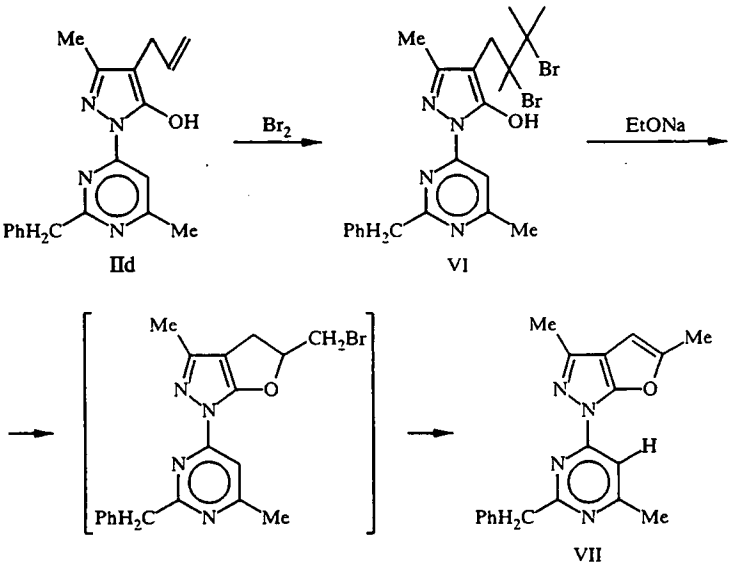
TABLE 1. Parameters for Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	R_f	PMR spectrum, δ, ppm	Yield, %
IIa	$C_{16}H_{16}N_4O$	68,37 / 68,55	5,54 / 5,75	20,24 / 19,99	118...121	0,49	2,05 (3H, s, 3'-CH_3); 2,43 (3H, s, 4-CH_3); 4,02 (2H, s, $CH_2C_6H_5$); 5,1 (1H, s, 4'-H); 7,15 (5H, s, C_6H_5); 7,23 (1H, s, 5-H)	60
IIb	$C_{19}H_{22}N_4O$	70,50 / 70,78	6,53 / 6,88	17,21 / 17,38	132...133	0,54	0,9...1,75 (5H, m, CH_2CH_3); 2,2 (3H, s, 3'-CH_3); 2,3 (2H, t, $CH_2CH_2CH_3$); 2,55 (3H, s, 4-CH_3); 4,22 (2H, s, $CH_2C_6H_5$); 7,36 (5H, s, C_6H_5); 7,4 (1H, s, 5-H)	48
IIc	$C_{20}H_{24}N_4O$	71,27 / 71,40	7,01 / 7,19	16,34 / 16,65	91...92	0,59	0,9...1,6 (9H, m, C_4H_9); 2,18 (3H, s, 3'-CH_3); 2,3 (2H, t, $CH_2-C_3H_7$); 2,31 (3H, s, 4-CH_3); 4,18 (2H, s, $CH_2C_6H_5$); 7,33 (5H, s, C_6H_5); 7,4 (1H, s, 5-H)	58
IId	$C_{19}H_{20}N_4O$	70,89 / 71,23	6,01 / 6,29	17,71 / 17,49	121...122	0,43	2,17 (3H, s, 3'-CH_3); 2,57 (3H, s, 4-CH_3); 3,08 (2H, d.t., $CH_2-CH=CH_2$); 4,23 (2H, s, $CH_2C_6H_5$); 4,8...5,2 (2H, m, $=CH_2$); 5,7...6,1 (1H, m, CH=); 7,36 (5H, s, C_6H_5); 7,5 (1H, s, 5-H)	53
IIIa	$C_{17}H_{18}N_4$	73,09 / 73,35	6,31 / 6,52	19,97 / 20,13	35...36	0,69	2,2 (3H, s, 3'-CH_3); 2,45 (3H, s, 5'-CH_3); 2,51 (3H, s, 4-CH_3); 4,25 (2H, s, $CH_2C_6H_5$); 5,96 (1H, s, 4'-H); 7,37 (5H, m, C_6H_5); 7,65 (1H, s, 5-H)	95
IIIb	$C_{20}H_{22}N_4$	75,21 / 75,44	6,69 / 6,96	17,84 / 17,60	46...47	0,71	2,07 (3H, s, 3'-CH_3); 2,14 (3H, s, 5'-CH_3); 2,52 (3H, s, 4-CH_3); 3,45 (2H, d, t, $CH_2CH=CH_2$); 4,2 (2H, s, $CH_2C_6H_5$); 4,8...5,0 (2H, m, $CH=CH_2$); 5,4...5,95 (1H, m, $CH=CH_2$); 5,9 (1H, s, 4'-H); 7,17...7,37 (5H, m, C_6H_5)	78
IV	$C_{16}H_{18}N_4$	71,84 / 72,15	6,57 / 6,81	20,81 / 21,04	74...76	0,57	1,57 (3H, d, 5'-CH_3); 1,77 (1H, m, 5'-H); 2,42 (2H, m, 4'-CH_2); 2,58 (3H, s, 4-CH_3); 4,27 (2H, s, $CH_2C_6H_5$); 5,25 (1H, t, 3'-H); 7,20...7,35 (5H, m, C_6H_5); 7,45 (1H, s, 5-H)	81
V	$C_{16}H_{18}N_4O$	67,84 / 68,06	6,21 / 6,43	19,58 / 19,85	145...147	0,51	1,3 (3H, d, 4'-CH_3, J = 7 Hz); 2,33 (3H, s, 4-CH_3); 3,04 (1H, m, 4'-H); 3,50 (1H, m, 3'-H); 4,10 (2H, s, $CH_2C_6H_5$); 4,30 (1H, m, 3'-H); 6,28 (1H, s, 5-H); 7,2...7,4 (5H, m, C_6H_5)	75
VI	$C_{19}H_{20}Br_2N_4O$	47,29 / 47,52	3,95 / 4,20	11,43 / 11,67	102...106	0,57	2,20 (3H, s, 3'-CH_3); 2,37 (2H, d, 4'-CH_2); 2,60 (3H, s, 4-CH_3); 3,25 (1H, m, CHBr); 3,65...3,80 (2H, d, CH_2Br); 4,25 (2H, s, $CH_2C_6H_5$); 7,1 (1H, s, 5-H); 7,2...7,4 (5H, m, C_6H_5)	96
VII	$C_{19}H_{18}N_4O$	71,35 / 71,68	5,44 / 5,70	17,35 / 17,60	162...165	0,64	2,55 (3H, s, 4'-CH_3); 2,68 (6H, s, 3'- and 5'-CH_3); 4,4 (2H, s, $CH_2C_6H_5$); 6,42 (1H, s, 4-H); 7,25...7,60 (6H, m, C_6H_5 and 5'-H)	52

*Spectra of IIb, c, d, IIIb, IV, V, VII recorded in $CDCl_3$, IIa in CCl_4, IIIa in CD_2Cl_2, VI in CD_3OH.

Bromination of the allyl derivative IId with an equimolar amount of bromine in chloroform gave 2-benzyl-4-methyl-6-[3-methyl-4-(2,3-dibromoprop-1-yl)-5-hydroxpyrazol-1-yl]pyrimidine (VI). In the presence of excess sodium ethylate solution and with subsequent neutralization, the latter gave 1-(2-benzyl-4-methylpyrimidin-6-yl)-3,5-dimethylfuro[3,2-d]pyrazole (VII, scheme 2). The reaction of the dibromo derivative VI to the furo[3,2-d]pyrazole VII also occurred upon prolonged standing.

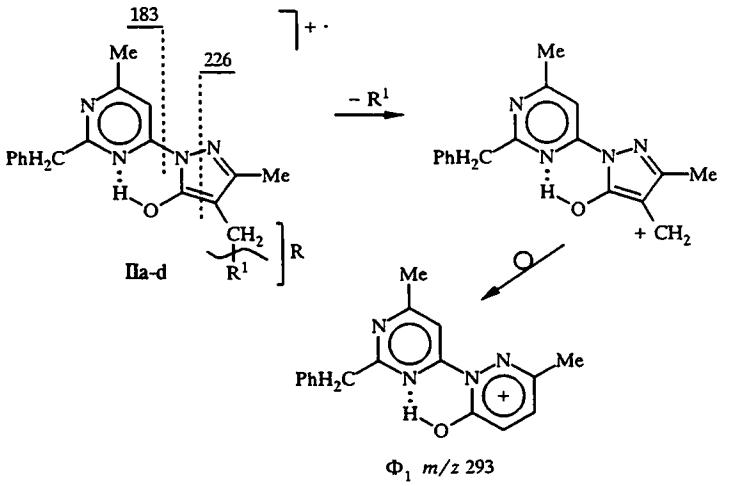
Scheme 2



Analysis of the spectral data leads to the conclusion that IIa-d occur almost wholly in the hydroxy tautomeric form as indicated by the low field signal for 4′ −H in the spectrum of IIa and by low field signals (and their multiplicities) for the "benzyl" methylene group protons in the R radicals of IIb-d. This probably promotes the fixing of the hydroxy tautomer via the formation of a hydrogen bond with the pyridine nitrogen N_1 atom (scheme 1).

Examination of the mass spectra of IIa-d also confirms the hydroxypyrazole form for these compounds in the gaseous phase since the fragmentation of their molecular ions (scheme 3) is markedly connected with a "benzyl" fission in the R radical to give the stable ions Φ_1 (evidently through rearrangement). This process is typical for the mass spectrometric breakdown of alkylpyrazoles [9]. At the same time, dissociation at the C−N bond joining the two heterocycles or fission of pyrazole ring fragments do not play an important part (the ion peaks at 183 and 226* are of low intensity). A strong peak for a Φ_1 ion (277) is also seen in the mass spectra of the pyrazolylpyrimidine IIIa.

Scheme 3



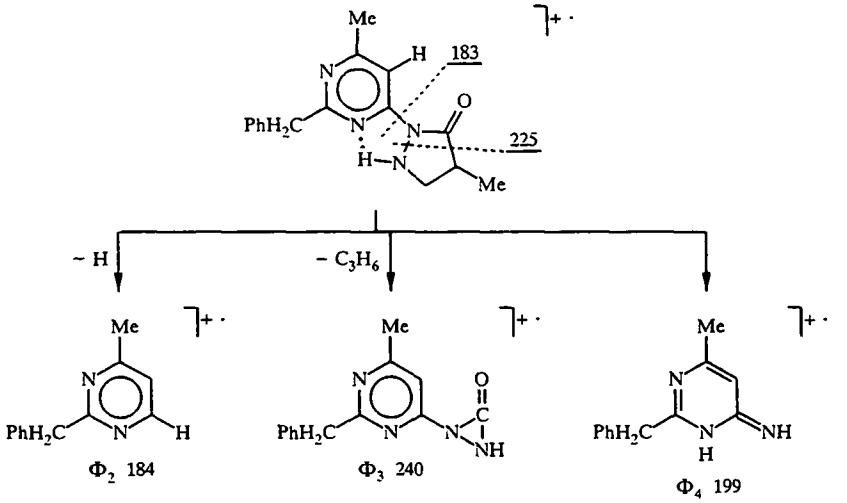
*From here mass spectral ion peaks are reported as m/z values.

The PMR spectrum of V shows signals for the 4'-CH_3 group seen as a doublet together with a multiplet for the 4'-H proton at 3.04 ppm and this unambiguously supports the pyrazolidone structure. The PMR spectra of IIa-d, III and IV show a pyrimidine 5-H proton signal at 7.23-7.65 ppm but, in V, the singlet for this proton is high field shifted to 6.28 ppm. In all probability in this case the alternative S-conformation is more stable (scheme 4) with the 5-H proton falling in the anisotropic cone of the neighboring carbonyl group. An analogous high field shift for the same proton signal in the case of compound VII is evidently due to the nearness of the heteroaromatic furan ring (scheme 2).

When in the gaseous phase, compound V retains the predominant amide tautomeric form since, in its molecular ion, there comparatively readily occur (scheme 4) both fission of the five membered ring (ions Φ_3 and Φ_4) and of the bond between the heterocycles (Φ_2 ion, 183).

The biological activity of the synthesized compounds have been studied at the All Russian Science Center for Nonhazardous Biologically Active Substances. The activity of V has been tested on the division of fertilized sea urchin cells. At a 10^{-5} molar concentration it blocks the first and second stages of subdivision by 50% and shows antitumor properties. Compound IIc is cytotoxic to human ovarian cancer cells and IId shows moderate activity towards classical fowl pest.

Scheme 4



EXPERIMENTAL

PMR Spectra were recorded on a Varian T-60 instrument and on a Bruker AC-200 (compound V) in CCl_4, $CDCl_3$, and CD_2Cl_2 with TMS internal standard. Mass spectra were taken on an IKB-2091 (Sweden) with an ionizing energy of 70 eV, direct introduction of sample into the ion source, and automatic processing of data on a computer. Silufol UV-254 plates were used for TLC with benzene-ethyl acetate 3:1 (IIa-c), or 1:1 (IId, IIIa, b, IV, and V) or with benzene-acetone 4:1 (VI, VII).

2-Benzyl-4-methyl-6-(3-methyl-4-R-5-hydroxypyrazol-1-yl)pyrimidines IIa-d. The ethyl acetoacetate (0.02 mole) was dissolved in ethanol (10 ml) containing sodium ethylate (0.02 mole). After heating for 15 min, 2-benzyl-4-hydrazino-6-methylpyrimidine (4.28 g, 0.02 mole) [1] in ethanol (40 ml) was added and refluxing continued for 18-20 h. At completion, alcohol was distilled off to dryness, water (50 ml) was added, the product neutralized with dilute hydrochloric acid, and extracted with chloroform. After drying with magnesium sulfate and distillation of solvent, hexane was added and the precipitated crystals were filtered and recrystallized from aqueous alcohol (see Table 1).

Mass spectrum, m/z (I_{rel}, %).

Compound IIa. 280 (100), 279 (9), 239 (3), 226 (3), 199 (3), 198 (8), 197 (3), 184 (4), 183 (5), 150 (5), 91 (18).

Compound IIb. 322 (34), 293 (100), 226 (2), 198 (1), 183 (2), 91 (30), 77 (4), 76 (3), 75 (2), 63 (2), 51 (4).

Compound IIc. 336 (31), 293 (100), 226 (1), 198 (1), 183 (1), 135 (1), 91 (20), 67 (3), 66 (2), 65 (2), 41 (4).

Compound IId. 320 (100), 319 (16), 305 (7), 293 (40), 279 (6), 278 (6), 250 (6), 226 (8), 198 (6), 147 (8), 91 (53).

2-Benzyl-4-methyl-6-(3,5-dimethylpyrazol-1-yl)pyrimidines IIIa, b. Hydrazinopyrimidine I or its 5-allyl derivative (0.25 mole), acetylacetone (2 g, 0.02 mole) and p-toluenesulfonic acid (0.1 g) were refluxed in benzene (100 ml) with a Dean and Stark separator until evolution of water ceased. Solvent was removed and hexane (20 ml) added. The product was filtered and hexane evaporated from the filtrate to give IIIa or IIIb (data in Table 1). Mass spectrum of IIIa, m/z ($I_{rel.}$, %): 278 (100), 277 (38), 263 (13), 237 (3), 236 (6), 187 (3), 183 (3), 182 (4), 95 (5), 91 (22), 65 (4).

2-Benzyl-4-methyl-6-(5-methyl-4,5-dihydropyrazol-1-yl)pyrimidine (IV). Similarly to the above, a mixture of hydrazinopyrimidine I (3.2 g, 0.015 mole), crotonaldehyde (1.4 g, 0.02 mole), p-toluenesulfonic acid (0.1 g), and hydroquinone (0.03 g) were refluxed for 6 h in absolute benzene (80 ml). After distillation of benzene, absolute ethanol (20 ml) was added to the residue followed by sodium ethylate (which had been prepared from sodium (0.345 g, 0.015 mole) and absolute ethanol (10 ml)) and then refluxed for a further 18 h. At the end, alcohol was distilled off, water (50 ml) added, and the product was neutralized with dilute HCl (1:1), extracted with chloroform, and the extracts dried over magnesium sulfate. After removal of solvent, hexane (15 ml) was added and the precipitated crystals filtered (see Table 1).

2-Benzyl-4-methyl-6-(4-methyl-5-hydroxy-2,3-dihydropyrazol-1-yl)pyrimidine (V). Sodium ethylate (0.02 mole), methyl methacrylate (2.2 g, 0.022 mole), and hydrazinopyrimidine I (3.2 g, 0.015 mole) were refluxed with stirring for 6 h in absolute ethanol (60 ml). At the end, the alcohol was distilled off, water (25 ml) added, and the product neutralized with HCl, extracted with chloroform, and the chloroform extracts dried over magnesium sulfate. After evaporation of solvent, hexane (20 ml) was added and the precipitated crystals filtered (see Table 1). Mass spectrum of V, m/z ($I_{rel.}$, %): 282 (100), 240 (12), 226 (5), 225 (2), 212 (3), 199 (9), 198 (13), 184 (35), 183 (18), 91 (50), 67 (28), 65 (10).

2-Benzyl-4-methyl-6-(3-methyl-4-(2,3-dibromoprop-1-yl)-5-hydroxypyrazol-1-yl)pyrimidine (VI). Bromine (0.8 g, 0.005 mole) was added dropwise with stirring to a solution of 2-benzyl-4-methyl-6-(4-allyl-3-methyl-5-hydroxypyrazol-1-yl)pyrimidine IId (1.6 g, 0.005 mole) in chloroform (30 ml). The product was then refluxed for 30 min, chloroform distilled off, and the product cooled, hexane added, and the precipitated crystals filtered to give VI (2.3 g, 96%) (see Table 1).

1-(2-Benzyl-4-methylpyrimidin-6-yl)-3,5-dimethylfuro[3,2-d]pyrazole (VII). A solution of the dibromo derivatives VI (1.44 g, 0.003 mole) in ethanol (20 ml) was added to an alcohol solution of sodium ethylate [prepared from sodium (0.46 g, 0.02 mole) and ethanol (30 ml)] and refluxed for 18 h. Alcohol was distilled off and the product neutralized with HCl, extracted with chloroform, and dried over magnesium sulfate. Solvent was distilled off, hexane added, and the product triturated. The crystals produced were filtered off and dried to give compound VII (0.5 g, 52%) (see Table 1).

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