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Synthesis and Some Reactions of 3-Methyl-4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiols

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3-Methyl-4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine-6-thiols(*II*) were synthesised by the raction of thiourea with 3-methyl--1-phenyl-4-arylidene-2-pyrazolin-5-ones(*I*) in ethanolic solution of potassium hydroxide. The mechanism of this reaction is discussed and further transformation of the products with different reagents (S-methylation, substitution of SH-group by arylamines, hydrazine, and azide) was carried out.

The literature reveals that the reactions of 3-metyl-1-phenyl-4-arylidene--2-pyrazolin-5-ones with thiourea[1–3] have not been reported. This led us to attempt the above reactions in order to get the pyrazole nucleus fused with a pyrimidine ring, a combination which is expected to possess high biological activities. Interaction of 3-methyl-1-phenyl-4-arylidene-2-pyrazolin-5-ones (*I*) with thiourea in ethanolic potassium hydroxide gives the corresponding 3-methyl-4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiols(*II*). The reaction proceeds by addition of thiourea on arylidene double bond, this process, also could be assigned as Michael type addition on α,β-unsaturated amide[4–8], followed by cyclisation of the intermediate *1* to *2*. The latter undergoes dehydration and aromatisation to yield the final product (*II*). The force for such elimination reactions is the resonance stabilisation energy in (*II*). We were not able to isolate the intermediate and the reaction can be represented by Scheme 1.

The structure of derivatives (*II*) was established using physical and chemical methods (cf. Table I).

The IR spectra show the absorption band at 2700—2800 cm^{-1} characteristic of SH group and no absorption can be detected for thio carbonyl group. These products can be alkylated or aminated using an appropriate reagent. Thus, the reaction with methyl iodide in dry acetone and in the presence of basic catalyst yields S-methyl derivative (cf. Table II).

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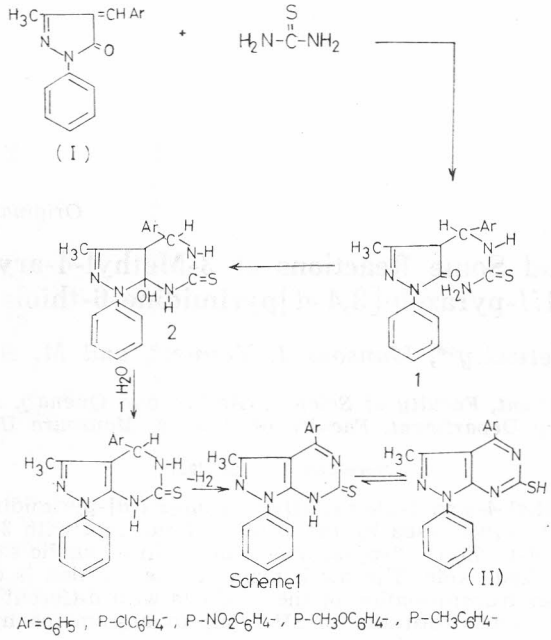


Ar=C_6H_5 , P-ClC_6H_4- , P-$NO_2C_6H_4$- , P-$CH_3OC_6H_4$- , P-$CH_3C_6H_4$-

TABLE I

*3-Methyl-4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiol(II)*

Compd* No.	Ar	M. p./°C**	Yield (%)	Molecular Formula	Analysis Calc'd./Found			
					C	H	N	S
IIa	C_6H_5	142	68	$C_{18}H_{14}N_4S$	67.92	4.43	17.72	10.12
					68.20	4.30	17.4	10.3
IIb	p-ClC_6H_4	145	79	$C_{18}H_{13}N_4SCl$	61.27	3.68	15.88	9.07
					61.52	3.7	15.4	8.9
IIc	p-$NO_2C_6H_4$	162	62	$C_{18}H_{13}N_5O_2S$	59.50	3.58	19.28	8.81
					59.50	3.70	18.95	8.5
IId	p-$CH_3OC_6H_4$	118	84	$C_{19}H_{16}N_4SO$	65.51	4.59	16.09	9.19
					65.3	4.90	15.9	9.4
IIe	p-$CH_3C_6H_4$	192	93	$C_{19}H_{16}N_4S$	68.67	4.81	16.86	9.63
					68.3	5.0	16.4	9.2

* IR spectra exhibited the characteristic absorption bands for SH at 2700—2800 cm^{-1} and > C=N at ~ 1580.

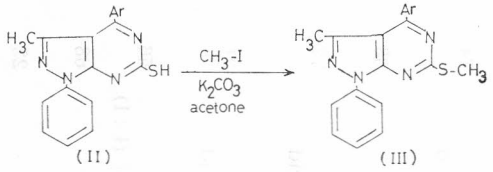
** Crystallised from benzene.

TABLE II

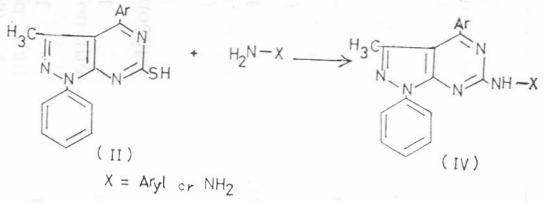
6-Methylthio-3-methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (III)

Compd. No.	Ar	M. p./°C*	Yield (%)	Molecular Formula	Analysis Calc'd./Found			
					C	H	N	S
IIIa	C_6H_5	125—1	78	$C_{19}H_{16}N_4S$	68.67	4.81	16.86	9.63
					68.7	4.9	16.6	9.50
IIIb	p-ClC_6H_4	100—1	72	$C_{19}H_{15}N_4SCl$	62.21	4.09	15.27	8.73
					61.8	4.1	14.9	8.45
IIIc	p-$CH_3OC_6H_4$	110	80	$C_{20}H_{18}N_4OS$	66.29	4.97	15.46	8.83
					65.9	5.2	15.2	8.70

* Crystallised from benzene/light petroleum (40—60 °C)



Amination of (*II*) using aromatic amines or hydrazine resulted in substitution of sulphydryl group, affording *IV*.



The structural assignments of (*IV*) were based on elemental and spectral analyses (cf. Table III).

Treatment of 6-hydrazino-3-methyl-4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (*IV*, X = NH_2) with nitrous acid gave the corresponding tetrazolo derivatives (*VI*), which may take place *via* 6-azido intermediate (*Va*). The reaction can be represented by Scheme 2.

The angular tetrazolo derivative (*VI*) is more likely than the plannar one (*VII*) as it shows more conjugation and hence more aromatic character.

This is supported by analogy with previously mentioned tetrazole syntheses.[9–14] The chemical structure of compounds (*VI*) was elucidated from their analytical and spectral data (cf. Table IV).

TABLE III

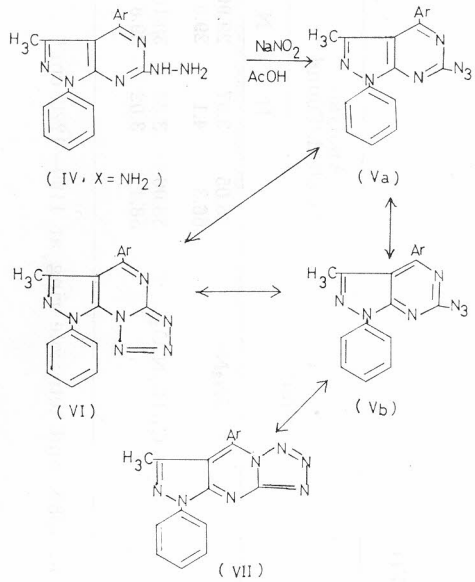
6-Substituted Amino-3-methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (IV)

Compd.*	X	Ar	m. p./°C and solvent of crystallisation	Yield (%)	Molecular Formula	Analysis Calc'd./Found		
						C	H	N
IVa	p-$CH_3OC_6H_4$	C_6H_5	202 aqueous acetic acid (1 : 1)	74	$C_{25}H_{21}N_5O$	73.71 73.60	5.15 5.3	17.19 17.40
IVb	p-$CH_3OC_6H_4$	p-Cl—C_6H_4	208 acetic acid	68	$C_{25}H_{20}N_5OCl$	67.95 68.4	4.53 4.6	15.85 15.4
IVc	p-$CH_3OC_6H_4$	p-$NO_2C_6H_4$	222—1 aqueous acetic acid (1 : 1)	77	$C_{25}H_{20}N_6O_3$	66.37 66.40	4.42 4.8	18.58 18.8
IVd	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	167 aqueous acetic acid (1 : 1)	81	$C_{26}H_{23}N_5O_2$	71.39 71.70	5.26 5.40	16.01 16.2
IVe	NH_2	C_6H_5	138 aqueous methanol (1 : 1)	56	$C_{18}H_{16}N_6$	68.35 67.91	5.06 5.4	26.58 26.2
IVf	NH_2	p-$NO_2C_6H_4$	145—1 ethanol	68	$C_{18}H_{15}N_7O$	62.50 62.72	3.34 4.5	28.40 28.72
IVg	NH_2	p-$CH_3C_6H_4$	105 light petroleum (60—80°)	22	$C_{19}H_{18}N_6$	69.09 69.3	4.45 5.60	25.45 25.40

* IR spectra exhibited the characteristic absorption bands for $\geq C=N$ at ~ 1580; NH at ~ 3220; and NH_2 at 3340—3450 cm^{-1}.

The PMR spectrum of (*IVf*) in DMSO showed a singlet at δ 2.45 (3H, CH_3); at δ 72—7.8 (m, 9H, Ar-H); at δ 6.66 (S, 2H, NH_2) and at δ 9.8 (S, 1H, NH).

The PMR spectrum of (*IVg*) in $CDCl_3$ showed at δ 1.29 (S, 3H, p-CH_3-Ar); at δ 2.45 (S, 3H, CH_3); at δ 7.2—7.7 (m, 9H, Ar-H); at δ 7.1 (S, 2H, NH_2) and at δ 9.9 (S, 1H, NH).



Scheme 2

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance spectra were measured on varian XL-100 spectrophotometer. Infrared spectra were measured on a Perkin-Elmer model 21 spectrophotometer.

3-Methyl-1-phenyl-4-arylidine-2-pyrazolin-5-ones were prepared according to the litrature procedure.[15-17]

3-Methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-6-thiol(II)
Model procedure

A mixture of (0.01 mole) of the 3-methyl-1-phenyl-4-arylidene-2-pyrazolin-5--ones (*Ia-e*); (0.011 mole) of thiourea and 1 g of potassium hydroxide in 30 ml of ethanol was refluxed for 3 hours then cooled and filtered off. The filtrate was acidified with dilute acetic acid and the solid formed was collected, washed with water and crystallised (cf. Table I).

Reaction of Methyl Iodide with II. Formation of (III)

3-Methyl-4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiol (0.01 mole) and anhydrous potassium carbonate (2.07 g, 0.015 mole) were dissolved in dry acetone (30 ml) and heated under efficient reflux for 30 minutes. Methyl iodide (0.61 ml, 0.01 mole) was added to the refluxing solution and the mixture heated for 5 hours on the water bath. The excess solvent was removed and the residue was crystallised (cf. Table II).

5-Amino-3-methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (IVa-d)
General procedure

A mixture of *II* (0.001 mole) and *p*-anisidine (0.0011 mole) was heated in an oil bath at 170—180 °C for 4 hours. On cooling and tituration with ethanol the product separated out and crystallised from the proper solvent. The results are summarized in Table III.

TABLE IV

Tetrazolo Derivatives (VI)

Compd.*	Ar	m. p./°C and solvent of crystallization	Yield (%)	Molecular Formula	Analysis Calc'd./Found		
					C	H	N
VIa	C_6H_5	85 benzene/methanol	55	$C_{18}H_{13}N_7$	66.05 66.3	3.97 4.1	29.96 29.6
VIc	*p*-$NO_2C_6H_4$	110 aqueous ethanol (1 : 1)	62	$C_{18}H_{12}N_8O_2$	58.06 58.4	3.22 3.02	30.10 29.8

* IR spectra exhibited the characteristic absorption bands for $>C=N$ at 1580; and tetrazole ring at 1180—1220 cm^{-1}.

6-Hydrazino-3-methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (IVe-g)
Model procedure

A mixture of *II* (0.03 mole) and excess hydrazin hydrate (10 ml, 98%) was heated at 100 °C for 5 hours, after which hydrogen sulfide ceased to evolve. The mixture was concentrated, left at room temperature for one weak, whereby the product was formed, collected and crystallised (cf. Table III).

To a solution of *IV*, $X=NH_2$ (0.02 moles) in acetic acid (15 ml) was added sodium nitrite solution (0.022 moles in 3 ml water) at 0—5 °C during 30 minutes with stirring. The mixture was kept over night at room temperature, diluted with water and filtered. The product was crystallised from the proper solvent (cf. Table IV).

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SAŽETAK

Priprava i neke reakcije 3-metil-4-aril-1-fenil-1*H*-pirazolo 3,4-*d* pirimidin-6-tiola

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3-retil-4-aril-1-fenil-1*H*-pirazolo 3,4-*d* -pirimidin-6-tioli (*II*) pripravljeni su reakcijom tioureje s 3-metil-3-fenil-4-ariliden-2-pirazolin-5-onima (*I*) u etanolnoj otopini kalijeva hidroksida. Diskutira se o mehanizmu te reakcije; dobiveni produkti dalje su transformirani u reakcijama S-metilacije, supstitucije sulfhidrilne skupine arilaminima, hidrazinom i azid-ionom.