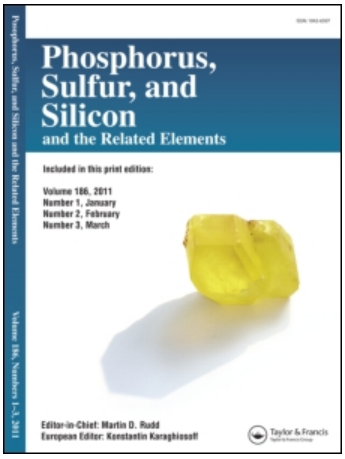

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SYNTHESIS AND SOME REACTIONS OF 3-METHYL-4-ARYL-1-PHENYL-1H-PYRAZOLO[3,4-d]PYRIMIDINE-6-THIOLS

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SYNTHESIS AND SOME REACTIONS OF 3-METHYL-4-ARYL-1-PHENYL-1H-PYRAZOLO[3,4-d]PYRIMIDINE-6-THIOLS

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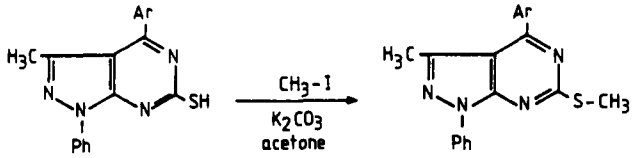
3-Methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-6-thiols(II) were synthesised by the interaction of thiourea with 3-methyl-1-phenyl-4-arylidene-2-pyrazolin-5-ones (I) in ethanolic potassium hydroxide. The mechanism of this synthesis is discussed and the reaction of the products with different reagents was carried out.

The literature revealed that the reactions of 3-methyl-1-phenyl-4-arylidene-2-pyrazolin-5-ones[1-3] with thiourea 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-1H-pyrazolo[3,4-d]pyrimidine-6-thiols(II). The reaction can proceed by either two routes: (i) addition on arylidene double bond (Michael type addition). (ii) addition on carbonyl group of derivative (I), followed by cyclisation of the intermediates 1 or 2 to 3. 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 any intermediates and the reaction can be represented by Scheme 1.



(II) (III)

The Michael type addition (route i) seems to be more likely by analogy to the reaction of nitrogen compounds with α,β-unsaturated carbonyl compounds.[4-8]

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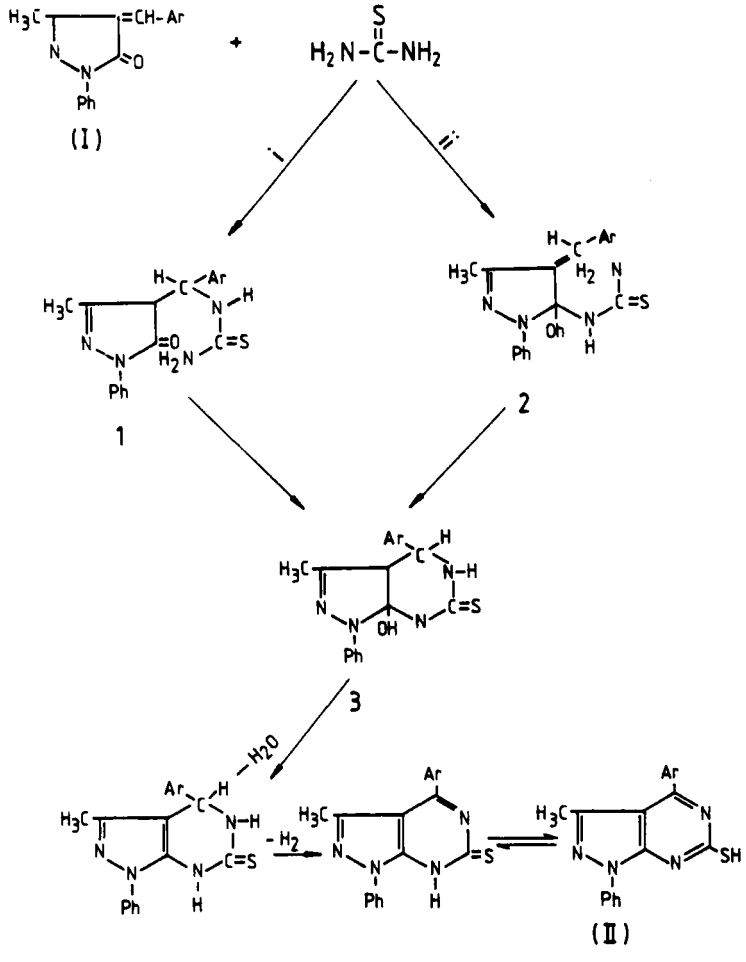
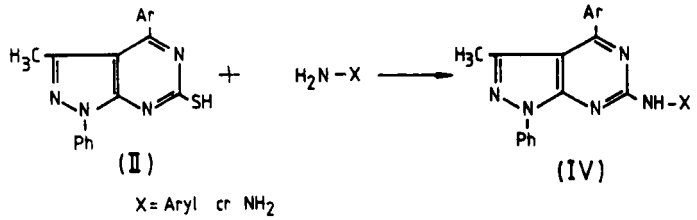


SCHEME 1

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

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

The IR spectra show the absorption band at 2800 cm^{-1} characteristic of SH group and no absorption can be detected for the carbonyl group. Chemically, these



X = Aryl or NH_2

TABLE I

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

Compd. No.	Ar	Mp.C° *	Yield	Molecular Formula	Analysis Calcd./Found C	H	N	S	Infrared (Cm^{-1})
IIa	C_6H_5	142	68	$C_{18}H_{14}N_4S$	67.92	4.43	17.72	10.12	2800 (SH)
					68.20	4.30	17.4	10.3	1580 (C=N)
IIb	ClC_6H_4(p)	145	79	$C_{18}H_{13}N_4SCl$	61.27	3.68	15.88	9.07	2800 (SH)
					61.52	3.7	15.4	8.9	1584 (C=N)
IIc	$NO_2C_6H_4$(p)	162	62	$C_{18}H_{13}N_5O_2S$	59.50	3.58	19.28	8.81	2820 (SH)
					59.50	3.70	18.95	8.5	1590 (C=N)
IId	$CH_3OC_6H_4$(p)	118	84	$C_{19}H_{16}N_4SO$	65.51	4.59	16.09	9.19	2800 (SH)
					65.3	4.90	15.9	9.4	1584 (C=N)
IIe	$CH_3C_6H_4$(p)	192	93	$C_{19}H_{16}N_4S$	68.67	4.81	16.86	9.63	2800 (SH)
					68.3	5.0	16.4	9.2	2585 (C=N)

* Crystallised from benzene.

TABLE II

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

Compd.	Ar	Mp.C° *	Yield	Molecular Formula	Analysis Calcd./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	ClC_6H_4(p)	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	$CH_3OC_6H_4$(p)	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/pet.ether (40–60).

products can be alkylated or aminated using the appropriate reagent. Thus reaction with methyl iodide in dry acetone and in presence of basic catalyst yields S-methyl derivative (cf. Table II).

Amination of (11) using aliphatic (not ammonia) or aromatic amines resulted in the elimination of sulphohydryl group which is substituted with the amino radical.

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-1H-pyrazolo[3,4-d]pyrimidine (IV, X = NH_2) with nitrous acid gave the corresponding tetrazolo derivatives (VI) which may occur through the 6-azido intermediate (V_a). The reaction can be represented by Scheme 2.

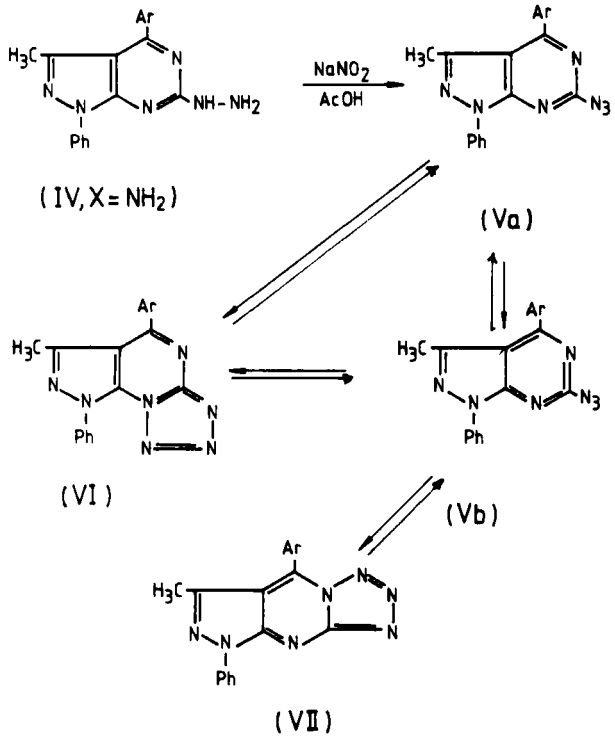
The angular tetrazolo derivative (VI) is more likely than the plannar one (VII) as it shows more conjugation and hence more aromatic character. This is supported by analogy with previously mentioned tetrazole syntheses.[9–14] The chemical structure of compounds VI was elucidated from their analytical 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	Mp.°C & solvent of crystallisation	Yield	Molecular Formula	Analysis Calcd./Found C	H	N	Infrared (CM^{-1})
IVa	$CH_3OC_6H_4$(p)	C_6H_5	202 dil.acetic acid	74	$C_{25}H_{21}N_5O$	73.71 73.60	5.15 5.3	17.19 17.40	1580 (C=N) 3200 (NH)
IVb	$CH_3OC_6H_4$(p)	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	1585 (C=N) 3220 (NH)
IVc	$CH_3OC_6H_4$(p)	P-$NO_2C_6H_4$	222-1 dil.acetic acid	77	$C_{25}H_{20}N_6O_3$	66.37 66.40	4.42 4.8	18.58 18.8	1580 (C=N) 3220 (NH)
IVd	$CH_3OC_6H_4$(p)	P-$CH_3OC_6H_4$	167 dil.acetic acid	81	$C_{26}H_{23}N_5O_2$	71.39 71.70	5.26 5.40	16.01 16.2	1590 (C=N) 3210 (NH)
IVe	NH_2	C_6H_5	138 dil.methanol	56	$C_{18}H_{16}N_6$	68.35 67.91	5.06 5.4	26.58 26.2	1580 (C=N) 3220 (NH) 3450 (NH_2)
IVf	NH_2	$NO_2C_6H_4$(p)	145-1 ethanol	68	$C_{18}H_{15}N_7O$	62.60 62.72	4.34 4.5	28.40 28.72	1585 (C=N) 3200 (NH) 3440 (NH_2)
IVg	NH_2	$CH_3C_6H_4$(p)	105 pet.ether (60-80)	22	$C_{19}H_{18}N_6$	69.09 69.3	5.45 5.60	25.45 25.40	1580 (C=N) 3200 (NH) 3450 (NH_2)

The pmr spectrum of (IVf) in DMSO showed a singlet at δ 2.45 (3 H, CH_3); at δ 7.2-7.8 (m, 9 H, Ar—H); at δ 6.66 (S, 2 H, NH_2) and at δ 9.8 (S, 1 H, NH). The pmr spectrum of (IVg) in $CDCl_3$ showed at δ 1.29 (S, 3 H, P—CH_3-Ar); at δ 2.45 (S, 3 H, CH_3); at δ 7.2-7.7 (m, 9 H, Ar—H); at δ 7.1 (S, 2 H, NH_2) and at δ 9.9 (S, 1 H, NH).



SCHEME 2

TABLE IV

Tetrazolo derivatives (VI)

Compd.	Ar	Mp.°C and solvent of crystallisation	Yield	Moleculer Formula	Analysis Calcd./Found C	H	N	Infrared (Cm^{-1})
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	1580 (C=N) 1180–1200 (tetrazole ring)
VIc	$NO_2C_6H_4$(p)	110 dil.ethanol	62	$C_{18}H_{12}N_8O_2$	58.06 58.4	3.22 3.02	30.10 29.8	1585 (C=N) 1180–1220 (tetrazole ring)

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 literature procedure.[1-3]

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 acidifed 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-1H-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).

6-Amino-3-methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine(IV a–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.

6-Hydrazino-3-methyl-4-aryl-1-phenyl-1H-pyrazolo[3,4-d]-pyrimidine (IV e–g). Model procedure. A mixture of II (0.03 mole) and excess hydrazine 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 week, whereby the product was formed, collected and crystallised (cf. Table III).

6-Methyl-8-phenyl-8H-pyrazolo[3,4-e]tetrazolo[5,1-c]pyrimidine(VI a–c). 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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