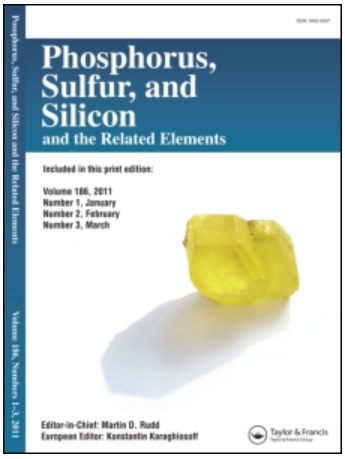

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REACTIONS WITH 2-METHYLTHIOPYRIMIDINES SYNTHESIS OF SOME NEW FUSED PYRIMIDINES

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REACTIONS WITH 2-METHYLTHIOPYRIMIDINES SYNTHESIS OF SOME NEW FUSED PYRIMIDINES

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4-Chloro-2-methylthio-6-phenylpyrimidine-5-carbonitrile (**II**) reacts with hydrazine hydrate to yield the 2,4-dihydrazino derivative (**IIId**). Compound **IIId** reacts with nitrous acid to give ditetrazolo[1,5-a:1′,5′-c]pyrimidine (**VI**) and with carbon disulphide to form pyrazolo[3,4-d]-s-triazolo[3,4-b]pyrimidine (**VII**). The reaction of **II** with phenylhydrazine affords directly the pyrazolo[4,3-d]-pyrimidine derivative (**IV**). Also, compound **II** reacts with anthranilic acid to form 2-methylthio-4-phenyl-6-(o-carboxyphenylamino)pyrimidine-5-carbonitrile (**IIIe**) which can be cyclised into 1-methylthio-10-oxo-3-phenyl-10-pyrimido[6,1-b]quinazoline-4-carbonitrile (**IX**) by heating with acetic anhydride.

Key words: Methylthiopyrimidine; chloropyrimidine; hydrazinopyrimidine; pyrimidoquinazolinone.

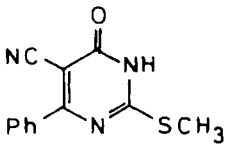
INTRODUCTION

In connection with a general program, directed to the chemistry of pyrimidines, we are concerned in the synthesis of pyrimidines[1,2] and fused pyrimidines,[3,4] since similar compounds are used in medicine due to their pronounced anticancer,[5] analgesics,[6] bactericides,[7] fungicides[8] and as phleomycin amplifiers.[9]

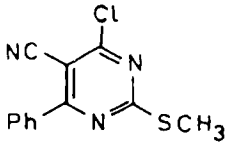
We describe here the syntheses of pyrazolo[4,3-d]-, ditetrazolo[1,5-a:1′,5′-c]- and pyrazolo[3,4-d]-s triazolo[3,4-b]pyrimidines. Also, we report a synthesis of the pyrimido[6,1-b]quinazoline derivative

DISCUSSIONS

Heating 3,4-dihydro-2-methylthio-4-oxo-6-phenyl-pyrimidine-5-carbonitrile (**I**)[10] with phosphorus oxychloride in dioxane gives the 4-chloropyrimidine derivative (**II**).



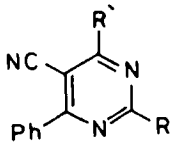
I



II

The ir spectrum of **II** displays no absorption in the carbonyl region and its ^{1}H-nmr spectrum (DMSO-d_6) shows characteristic peaks.

The reactivity of chlorine atom in position 4 is proved by its substitution with ammonia, aniline, thiophenol and hydrazine. Thus compound **II** reacts with ammonia, aniline, thiophenol or hydrazine hydrate to yield the corresponding 4-substituted pyrimidine derivatives (**IIIa–d**).

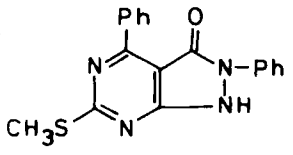


III

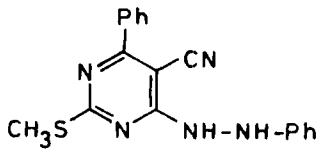
	R	R`
a	SCH_3	NH_2
b	SCH_3	NHC_6H_5
c	SCH_3	SC_6H_5
d	$NHNH_2$	$NHNH_2$
e	SCH_3	$NHC_6H_4CO_2H$ (o)

Compound **IIIa** is identical with an authentic sample prepared by an alternative route.[1] The ir spectra of **IIIb–d** display characteristic bands. The ^{1}H-nmr spectra (DMSO-d_6) of III are agreed with the proposed structure. (See Table II).

In contrast to the action of hydrazine hydrate, phenylhydrazine reacts with **II** under the same experimental conditions to afford directly by 2,3-dihydro-2,7-diphenyl-5-methylthio-1-oxo-1H-pyrazolo[4,3-d]pyrimidine (**IV**). Formation of **IV** may be proceeded via the non-isolable intermediate **V**.



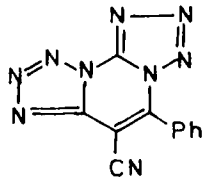
IV



V

The assignment of structure **IV** to the reaction product is based on analytical and spectral data. Thus, the ir spectrum of **IV** displays no bands for CN group and its ^{1}H-nmr spectrum (DMSO-d_6) shows characteristic peaks. (See Experimental).

When compound **IIId** is treated with nitrous acid at 0°C, there is obtained 5-phenylditetrazolo[1,5-a:1′,5′-c]-pyrimidine-6-carbonitrile (**VI**).

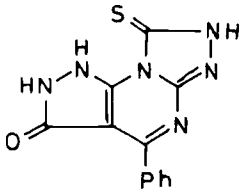


VI

The mass spectrum of **VI** is helpful in elucidating its structure. Thus, the appearance of a peak at m/e 263 (70%) supports the structure **VI**, which also supported by analytical and spectral data.

The reaction of compound IIId with carbon disulphide in ethanolic potassium

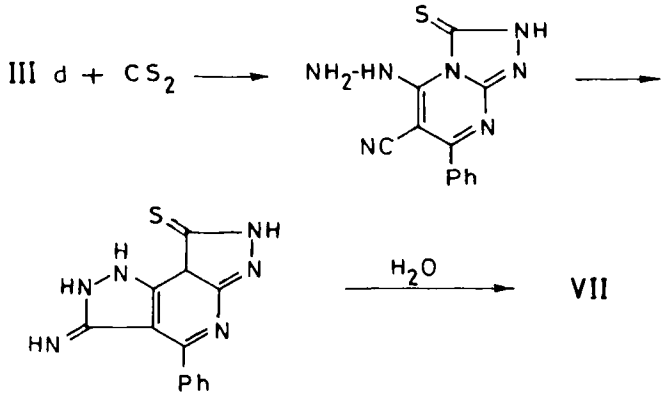
hydroxide solution results in the formation of 6-oxo-5-phenyl-1,2,7,8-tetrahydro-1-thioxo-6H-pyrazolo[3,4-d]-1,2,4-triazolo[3,4-b]pyrimidine (**VII**).



VII

The assignment of structure **VII** to the reaction product is based on: The ir spectrum of **VII** displays no absorption in the cyano region and its ^{1}H-nmr spectrum (DMSO-d_6) shows characteristic peaks. It is reported in literature that the imino group is hydrolysed into carbonyl group.[11]

The formation of **VII** may be explained as shown in Scheme A:

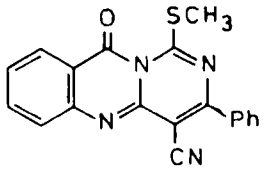


SCHEME A

Compound **II** reacts with anthranilic acid in boiling acetic acid to give 2-methylthio-4-phenyl-6-(o-carboxylphenylamino)pyrimidine-5-carbonitrile (**IIIe**).

The ir and ^{1}H-nmr spectra of **IIIe** are compatible with the given structure.

Compound **IIIe** undergoes cyclisation on heating with acetic anhydride to yield 1-methylthio-10-oxo-3-phenyl-10H-pyrimido[6,1-b]quinazoline-4-carbonitrile (**IX**).



IX

The ir spectrum of **IX** displays no absorption in the NH region and the signals corresponding to the NH and COOH in its precursor **IIIe** are disappeared in the ^{1}H-nmr spectrum (DMSO-d_6).

TABLE I

2,4-Disubstituted-6-phenylpyrimidine-5-carbomotriles (**III**)

Comp. no.	M.P °C	Yield %	Solvent	R	R′	Formula (M.W.)	Analysis calcd/found C	H	N	S
IIIb	221	79	Dioxane	SCH_3	NHC_6H_5	$C_{18}H_{14}N_4S$	67.90	4.43	17.60	10.07
						(318)	67.79	4.38	17.61	10.10
IIIc	132	73	Ethanol	SCH_3	SC_6H_5	$C_{18}H_{13}N_3S_2$	64.45	3.91	12.53	19.12
						(335)	64.53	4.00	12.48	19.02
IIId	217	75	Dioxane	$NHNH_2$	$NHNH_2$	$C_{11}H_{11}N_7$	54.74	4.59	40.67	
						(241)	54.67	4.61	40.72	
IIIe	273–4	85	Dioxane	SCH_3	$NHC_6H_4CO_2H(o)$	$C_{19}H_{14}N_4O_2S$	62.97	3.89	15.46	8.85
						(362)	62.87	3.91	15.50	8.92

EXPERIMENTAL

All melting points are taken on a Kofler apparatus and are uncorrected. ir spectra are determined (KBr) with a Perkin–Elmer Infracrod 137 instrument. ^{1}H-nmr spectra are obtained in $(CD_3)_2SO$ with a Perkin–Elmer R12A instrument with $SiMe_4$ as internal standard, and chemical shifts are expressed as δ values. Microanalytical data are performed by the Microanalytical Center at Cairo University. 3,4-Dihydro-2-methylthio-4-oxo-6-phenylpyrimidine-5-carbonitrile (I) is prepared by the method of Hussain *et al.*[10]

4-Chloro-2-methylthio-6-phenylpyrimidine-5-carbonitrile (**II**). A mixture of **I** (2.43 g, 0.01 mol), phosphorus oxychloride (25 ml) and dioxane (50 ml) is heated under reflux for 3 h. The solution is cooled and poured into ice water. The solid separated is collected, washed with water, dried and crystallised from ethanol to give 1.76 g (67%), of **II**, m.p. 147°C.—ir (KBr): 2220 cm^{-1} (CN), —^{1}H—nmr spectrum (DMSO-d_6): δ 2.65 (s, 3H, SCH_3), δ 7.61 (m, 3H, aromatic protons), δ 7.92 (m, 2H, aromatic protons). Anal. Found (Calcd): C, 55.13 (55.05); H, 3.14 (3.08); Cl. 13.47 (13.55); N, 161.0 (16.09); S, 12.19 (12.23).

2,4-Disubstituted-6-phenylpyrimidine-5-carbonitriles (**IIIb–d**). A mixture of II (2.61 g, 0.01 mol), 0.02 mol of aniline, thiophenol or hydrazine hydrate and 50 ml of glacial acetic acid (or 50 ml of dioxane in case of hydrazine hydrate) is refluxed for 5 h. The reaction mixture is cooled and poured into water. The solid separated is collected and crystallised from the proper solvent (c.f. Tables I and II).

2,3-Dihydro-2,7-diphenyl-5-methylthio-1-oxo-1H-pyrazolo[4,3-d]pyrimidine (**IV**). A solution of II (1.31 g, 0.05 mol) in dioxane (30 ml) is treated with phenylhydrazine (0.54 g, 0.005 mol) is refluxed for 10 h. The solution is left to cool, poured into water. The solid separated is collected and crystallized from ethanol to yield 1.06 g (63%) of IV; m.p. 217°C.—ir (KBr): 3300, 3200 (NH), 1660 cm^{-1} (CO); ^{1}H-nmr spectrum (DMSO-d_6): δ 2.63 (s, 3H, SCH_3), δ 5.35 (s, 1H, disappears after D_2O exchange, NH), δ 7.20–7.61 (m, 6H, aromatic protons), δ 7.80 (m, 2H, aromatic protons), δ 8.15 (m, 2H, aromatic protons). Anal. Found (calcd): C, 64.70 (64.66); H, 4.12 (4.22); N, 16.69 (16.76); S, 9.60 (9.58).

5-Phenylditetrazolo[1,5-a:1',5'-c]pyrimidine-6-carbonitrile (**VI**). A solution of 1 g of IIId in 50 ml of acetic acid is cooled to 0°C and a cold solution of 0.5 g of sodium nitrite in 10 ml of water is gradually added. The reaction mixture is kept at 0–5°C with stirring for 2 h, left overnight and diluted with water whereupon precipitation takes place. The solid, that precipitated, is collected and crystallised from ethanol to give 0.68 g (62%) of **VI**; m.p. 158°C.—^{1}H-nmr spectrum (DMSO-d_6): δ 7.65 (m, 3H, aromatic protons), δ 8.00 (m, 2H, aromatic protons). Anal. Found (calcd.): C, 49.99 (50.19); H, 2.00 (1.91); N, 47.87 (47.90).

TABLE II

ir and ^{1}H-nmr of Products in Table I

Comp. no.	ir (cm^{-1})	^{1}H-nmr δ ppm
IIIb	3300, 3150 (NH), 220 (CN)	2.51(s, 3H, SCH_3), 7.10–7.60 (m, 8H, aromatic protons), 7.85 (m, 2H, aromatic protons), 9.57 (s, 1H, disappears after D_2O exchange, NH).
IIIc	2220 (CN)	2.15 (s, 3H, SCH_3), 7.62 (m, 8H, aromatic protons), 7.92 (m, 2H, aromatic protons)
IIId	3320, 3200 (NH), 2220 (CN)	4.42 (broad s, 4H, disappears after D_2O exchange, $2NH_2$), 7.37 (m, 3H, aromatic protons), 7.69 (m, 2H, aromatic protons), 8.58 (broad s, 2H, disappears after D_2O exchange, 2NH).
IIIe	3150 (broad, NH + OH), 2220 (CN), 1665 (CO)	2.68 (s, 3H, SCH_3), 7.23 (m, 2H, aromatic protons), 7.61 (m, 4H, aromatic protons), 7.97 (m, 3H, aromatic protons), 8.66 (s, 1H, disappears after D_2O exchange, NH), 11.95 (s, 1H, disappears after D_2O exchange, COOH).

6-Oxo-5-phenyl-1,2,7,8-tetrahydro-1-thioxo-6H-pyrazolo-[3,4-d]-1,2,4-triazolo[3,4-b]pyrimidine (**VII**). A mixture of 1 g of IIId, 50 ml ethanol, 0.3 g of potassium hydroxide and 3 ml of carbon disulphide is refluxed for 5 h. After removal of ethanol, water is added and the alkaline solution is filtered. The clear filtrate is acidified with dilute hydrochloric acid and the formed precipitate is collected and crystallised from dimethylformamide-ethanol to give 0.70 g (59%) of **VII**; mp.p. > 300°C.—ir (KBr): 3400, 3100 (NH), 1660 cm^{-1} (CO); ^{1}H-Nmr spectrum (DMSO-d_6): δ 5.70 (s, 1H, disappears after D_2O exchange, NH), δ 7.45–7.93 (m, 6H,5 5-aromatic protons + NH, exchanges after D_2O), 12.24 (s, 1H, disappears after D_2O exchange, NH). Anal-Found (calcd.): C, 50.81 (50.70); H, 2.76 (2.84); N, 29.71 (29.57); S, 11.32 (11.26).

2-Methylthio-4-phenyl-6-(o-carboxyphenylamino)pyrimidine-5-carbonitrile (**IIIe**). To a solution of **II** (2.61 g, 0.01 mol) in acetic acid (50 ml), anthranilic acid (1.37 g, 0.01 mol) is added. The solution is heated under reflux for 4 h. Compound **IIIe** which precipitated during reflux is collected and crystallised to give IIIe.

Cyclisation of IIIe-Formation of IX. A solution of 1 g of IIIe in 10 ml of acetic anhydride is refluxed for 4 h. The solid that separated while boiling is collect and crystallized from ethyl acetate to give 0.6 g (63%) of **IX**; m.p. 247–8°C.—ir (KBr): 2210 (CN), 1680 cm^{-1} (CO); ^{1}H-nmr spectrum (DMSO-d_6): δ 2.77 (s, 3H, SCH_3), δ 7.76 (m, 5H, aromatic proton), δ 8.22 (m, 4H, aromatic protons). Anal. Found (calcd.): C, 66.30 (66.26); H, 3.61 (3.50); N, 16.15 (16.28); S, 9.21 (9.30)

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