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CHEMISTRY

Synthesis of Some New Pyrimidine and Fused Pyrimidine Derivatives

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Abstract. 2-Mercapto- and 2-hydroxy-3,4-dihydro-4-oxo-6-(4-tolyl)pyrimidine-5-carbonitriles (3a, b) were synthesized by two different routes. Compound 3a could be converted into 3b by the action of hydrogen peroxide. Alkylation of 3a with alkyl halides gave the S-alkyl derivatives 4a-c. Compound 4a could also be prepared by two other different methods. The reaction of 4a-c with phosphorus oxychloride yielded the 4-chloropyrimidine derivatives 6a-c. Compounds 6a-c reacted with ammonia, glycine, anthranilic acid and hydrazine hydrate to form the tetrasubstituted pyrimidine derivatives 7a-d. Compound 7a could also be produced via two other alternative routes. The reaction of 6a with phenyl hydrazine gave directly the pyrazolo[3,4-d] pyrimidine derivative 10. The 2,4-dihydrazino-pyrimidine derivative 7d reacted with nitrous acid to give ditetrazolo[1,5- a:1′, 5′-c] pyrimidine 11. It also reacted with carbon disulphide to form pyrazolo[3,4-d]-s-triazolo[3,4-b] pyrimidine 12. Compounds 7b,c could be cyclised into imidazo[1,2-c] pyrimidine 13 and pyrimido [6,1-b] quinazoline 14, respectively. Product 13 could be directly obtained by the reaction of 6c with glycine in acetic acid.

Introduction

Pyrimidine and its thione derivatives have found a wide range of application in medicine due to their pronounced biological activity. Many of these compounds have proved to be active antiviral [1,2], antimicrobial [3,4], anticancer [5], herbicides [6,7], fungicides [8,9] and phleomycin amplifiers [10]. This stimulated our interest for the synthesis of new 2-hydroxy-, 2-mercapto- and 2-alkylmercapto-pyrimidine derivatives via the reaction of aromatic aldehyde, ethyl cynoacetate with urea, thiourea and S-methylisothiourea, respectively. The reaction products were utilized for the synthesis of other new azolopyrimidines bearing latent functional substituents and pyrimido [6, 1-b] quinazoline derivative.

Experimental

2-Mercapto- and 2-hydroxy-3,4-dihydro-4-oxo-6-(4-tolyl) pyrimidine-5-carbonitriles (3a,b):

Method A:

A mixture of p-toulaldehyde (0.01 mole, 1.20 g), ethyl cyanoacetate (0.01 mole, 1.13 g), and thiourea (0.01 mole, 0.76 g) or urea (0.01 mole, 0.60 g) in ethanol (50 ml) containing potassium carbonate (0.01 mole, 1.38 g) was heated under reflux for 4h. The potassium salt of 3, which precipitated during the reaction, was collected, dried and crystallized. The salt was stirred in water and acidified with acetic acid. The deposited precipitate was collected, washed thoroughly with water, dried and recrystallized from dil. DMF to give 3a,b (Tables 1 and 2).

^{1}HNMR of 3a: δ 2.40 (s, 3H, CH_3), 3.20 (s, 1H disappeared after D_2O exchange, SH), 5.15 (s, 1H, disappeared after D_2O exchange, NH) and 7.25 (m, 4H, J = 8 Hz,arom.).

Method B:

A mixture of ethyl α-cyano-p-methylcinnamate (1) (0.01 mole, 2.15 g) and thiourea (0.01 mole, 0.76 g) or urea (0.01 mole, 0.60 g) in pyridine (30 ml) was refluxed for 4h. The reaction mixture was allowed to cool, then poured over ice cold water. The precipitate was collected, washed well with water, dried and recrystallized from dil. DMF to yield 3a, b, identical m.p. and m.m.p. with those obtained by method A above.

Method C: Action of H_2O_2 on 3a-Formation of 3b:

To a mixture of 3a (0.005 mole, 1.22 g) and potassium carbonate (0.005 mole, 0.69 g) in water (20 ml), H_2O_2 (30%, 8 ml) was drop-wisely stirred in. The reaction mixture was left overnight and the colourless solid, so obtained, was filtered off and crystallized from dil. DMF to produce 3b (Tables 1 and 2.).

2-Alkylthio-3,4-dihydro-4-oxo-6-(4-tolyl)-pyrimidine-5-carbonitriles (4a-c):

Method A:

A mixture of 3a (0.01 mole, 2.43 g), appropriate alkyl halide (0.012 mole) and potassium carbonate (0.01 mole, 1.38 g) in ethanol (50 ml) was heated under reflux for 3h, concentrated, allowed to cool and diluted with water. The separated solid was filtered off, dried and recrystallized from dil. DMF to form 4a-c (Tables 1 and 2).

^{1}HNMR of 4a: δ 2.35 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.47 (d, 2H, J=8 Hz,arom.) and 7.80 ppm (d, 2H, J = 8 Hz, arom.).

Method B:

Applying the same procedure described in method A for the preparation of 3a, using S-methylisothiourea sulphate (instead of thiourea) and an equivalent amount of sodium acetate (instead of potassium carbonate) gave directly a solid reaction product after cooling. Recrystallization from dil DMF gave 4a (Tables 1 and 2).

Method C:

Applying the same procedure reported in method B for the preparation of 3a, using S-methylisothiourea sulphate (instead of thiourea) and an equivalent amount of sodium acetate (instead of potassium carbonate) yielded a product which was recrystallized from dil. DMF. The product proved to be 4a (Tables 1 and 2).

Table 1. Characterization data of products 3a-14

Comp. No.	MP. (°C)	Yield %	Formula (M.W.)	Analysis Found/Requires			
				C	H	N	S
3a	285	70 (A) 68 (B)	$C_{12}H_9N_3OS$ (243.3)	59.30 59.24	3.60 3.73	17.10 17.27	13.20 13.18
3b	> 300	65 (A) 67 (B) 60 (C)	$C_{12}H_9N_3O_2$ (227.2)	63.40 63.43	4.00 3.99	18.40 18.50	-- --
4a	277	72 (A) 70 (B) 75 (C)	$C_{13}H_{11}N_3OS$ (257.3)	60.70 60.69	4.30 4.31	16.40 16.33	12.40 12.46
4b	267	68	$C_{14}H_{13}N_3OS$ (271.3)	62.00 61.98	4.90 4.83	15.40 15.49	11.80 11.82
4c	230	70	$C_{19}H_{15}N_3OS$ (333.4)	68.60 68.45	4.50 4.53	12.50 12.60	9.60 9.62
6a*	159	85	$C_{13}H_{10}ClN_3S$ (275.8)	56.60 56.61	3.60 3.65	15.30 15.24	11.60 11.63
6b*	114	73	$C_{14}H_{12}ClN_3S$ (289.8)	58.00 58.02	4.10 4.17	14.40 14.50	11.00 11.06
6c*	148	80	$C_{19}H_{14}ClN_3S$ (351.9)	64.90 64.85	4.10 4.01	11.90 11.94	9.10 9.11
7a	210	65 (A) 67 (B) 63 (C)	$C_{13}H_{12}N_4S$ (256.3)	60.90 60.92	4.70 4.72	21.90 21.86	12.50 12.51
7b	185	55	$C_{21}H_{18}N_4O_2S$ (390.5)	64.60 64.59	4.70 4.65	14.30 14.35	8.20 8.21

Table 1. Contd.

Comp. No.	MP. (°C)	Yield %	Formula (M.W.)	Analysis Found/Requires			
				C	H	N	S
7c	258	72	$C_{21}H_{18}N_4O_2S$	64.60	4.60	14.40	8.20
			(390.5)	64.59	4.65	14.35	8.21
7d	225	70 (A)	$C_{12}H_{13}N_7$	56.50	5.10	38.40	--
		66 (B)	(255.3)	56.46	5.13	38.41	--
10	274	58	$C_{19}H_{16}N_4OS$	65.40	4.70	16.10	9.20
			(348.4)	65.50	4.63	16.08	9.20
11	152	60	$C_{12}H_7N_9$	52.00	2.60	45.40	--
			(277.3)	51.98	2.54	45.46	--
12	> 300	53	$C_{13}H_{10}N_6OS$	52.30	4.00	28.20	10.80
			(298.3)	52.34	3.38	28.17	10.75
13	221	46 (A)	$C_{21}H_{16}N_4OS$	67.80	4.40	15.00	8.60
		53 (B)	(372.5)	67.71	4.33	15.04	8.61
14	225	55	$C_{21}H_{16}N_4OS$	67.70	4.30	15.10	8.60
			(372.5)	67.71	4.33	15.04	8.61

* **6a** = % Cl; Found: 12.90; Requires: 12.85
6b = % Cl; Found: 12.20; Requires: 12.23
6c = % Cl; Found: 10.10; Requires: 10.07

Table 2. IR data of products 3a -14

Compound No.	IR (Kbr, cm^{-1})
3a	3350, 3320 (NH), 3200 (SH), 2225 (CN), 1660 (CO) and 1640 (C = N)
3b	3300 (broad, OH and NH), 2222 (CN), 1665 (CO) and 1640 (C = N)
4a	3250 (NH), 2220 (CN), 1670 (CO) and 1640 (C = N)
4b	3275 (NH), 2220 (CN), 1670 (CO) and 1640 (C = N)
4c	3200 (NH), 2215 (CN), 1665 (CO) and 1640 (C = N)
6a	2220 (CN) and 1645 (C = N)
6b	2220 (CN) and 1645 (C = N)
6c	2220 (CN) and 1640 (C = N)
7a	3350, 3300 (NH), 2215 (CN) and 1650 (NH_2)
7b	3200 (broad, NH and OH), 2225 (CN) and 1720 (CO)
7c	3150 (broad, NH and OH), 2220 (CN) and 1690 (CO)
7d	3300, 3200 (NH) and 2218 (CN)
10	3250 (NH) and 1665 (CO)
11	2225 (CN)
12	3400, 3100 (NH) and 1663 (CO)
13	3020 (broad, OH), 2219 (CN) and 1740 (weak CO)
14	2220 (CN) and 1710 (CO)

2-Alkylthio-4-chloro-6-(4-tolyl) pyrimidine-5-carbonitriles (6a-c):

A solution of each of 4a-c (0.01 mole) in dioxane (50 ml) was treated with phosphorus oxychloride (25 ml) and heated under reflux for 3h. The solution was cooled and poured into ice water. The separated solid was collected, washed with water, dried and recrystallized from ethanol to give 6a-c.

^{1}HNMR of 6a: δ 2.42 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 7.50 (d, 2H, J = 8 Hz, arom.) and 8.00 ppm (d, 2H, J = 8 Hz, arom.).

4-Amino-2-methylthio-6-(4-tolyl) pyrimidine-5-carbonitrile (7a):

Method A:

A stream of dry ammonia gas was bubbled slowly through a solution of one gram of 6a in anhydrous dioxane (20 ml). The solution was warmed for 15 min., cooled and then poured into water. The collected precipitate was washed with water, dried and recrystallized from dioxane to yield 7a.

^{1}HNMR : δ 2.30 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.25 (d, 2H, J = 8 Hz, arom.), 7.78 (d, 2H, J = 8Hz,arom.) and 8.35 ppm (s, 2H, disappeared after D_2O exchange NH_2).

Method B:

A mixture of p-toualdehyde (0.005 mole, 0.60 g), malononitrile (0.005 mole, 0.33 g) and S-methylisothiourea sulphate (0.005 mole, 1.27 g) in pyridine (25 ml) containing fused sodium acetate (2 g), was heated for 4h. The reaction mixture was cooled, poured into water and then acidified with acetic acid. The solid, thus formed, was filtered off, washed thoroughly with water and recrystallized from dioxane to give 7a (Tables 1 and 2).

Method C:

A mixture of α-cyano-p-methylcinnamonitrile (8) (0.005 mole, 0.84 g), S-methylisothiourea sulphate (0.005 mole, 1.27 g) and fused sodium acetate (2 g) in pyridine (25 ml) was refluxed for 4h. The reaction mixture was cooled, poured into water and then acidified with acetic acid. The precipitate, so formed, was collected, washed with water and recrystallized from dioxane to produce 7a (Tables 1 and 2).

2-Benzylthio-4-carboxymethylamino-6-(4-tolyl) pyrimidine-5-carbonitrile (7b):

To a solution of 6c (0.01 mole, 3.52 g) in ethanol (50 ml), glycine (0.02 mole, 1.50 g) was added. The solution was heated, under reflux, for 2h then cooled and poured into

water. The separated solid was filtered off, washed with water, dried and recrystallized from dil. dioxane to give 7b.

^{1}HNMR: δ 2.40 (s, 3H, CH_3), 4.05 (broad s, 1H, disappeared after D_2O exchange, NH), 4.15 (s, 2H,CH_2), 4.30 (s, 2H, CH_2), 7.36 (m, 5H, J = 8 Hz, arom.), 7.78 (m, 4H, J = 8 Hz, arom.) and 8.78 ppm (s, 1H, disappeared after D_2O exchange, COOH).

4-(2-carboxyphenylamino)-2-ethylthio-6-(4-tolyl) pyrimidine-5-carbonitrile (7c):

To a solution of 6b (0.01 mole, 2.90 g) in acetic acid (50 ml), anthranilic acid (0.02 mole, 2.74 g) was added. The solution was refluxed for 5h. Compound 7c which precipitated during reflux was collected and recrystallized from DMF to yield 7c.

^{1}HNMR: δ 1.35 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.15 (q, 2H, CH_2), 3.55 (broad s, 1H, disappeared after D_2O exchange, NH), 7.17 (m, 2H, J = 8 Hz, arom.), 7.34 (m, 2H, J = 8 Hz, arom.), 7.64 (m, 4H, J = 8Hz,arom.), and 11.33 ppm (s, 1H, disappeared after D_2O exchange, COOH).

Reaction of 6a with each hydrazine hydrate and phenylhydrazine - Synthesis of 7d and 10:

Method A:

A solution of 6a (0.01 mole, 2.76 g) in anhydrous dioxane (50 ml) was treated with hydrazine hydrate (3 ml, 99%) or phenylhydrazine (0.01 mole, 1.08 g) and refluxed for 7h. In the case of hydrazine hydrate, methanethiol was detected. The solution was concentrated and cooled. The solid, so separated, was collected and recrystallized from dil. DMF to yield 7d and 10.

^{1}HNMR of 7d: δ 2.30 (s, 3H, CH_3), 4.50 (broad s, 4H, disappeared after D_2O exchange, 2 NH_2), 7.35 (d, 2H, J = 8 Hz,arom.), 7.55 (d, 2H, J = 8 Hz, arom.) and 8.80 ppm (broad s, 2H, disappeared after D_2O exchange, 2NH).

^{1}HNMR of 10: δ 2.43 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.65 (broad s, 1H, disappeared after D_2O exchange, NH), 7.40 (m, 5H, J = 8 Hz, arom.) and 7.80 ppm (m, 4H, J = 8 Hz, arom.).

Action of hydrazine hydrate on 6b - Preparation of 7d:

Method B:

Applying the procedure described above for the synthesis of 7d and 10, and using

6b (0.01 mole, 2.90 g) instead of 6a, resulted in the evolution of ethanethiol during heating, and the formation of a product which proved to be 7d (Tables 1 and 2).

Action of nitrous acid on 7d - Preparation of 11:

A solution of 7d (1 g) in acetic acid (50 ml) was cooled to 0°C and a cold solution of sodium nitrite (0.5 g) in water (10 ml) was gradually added. The reaction mixture was kept at 0-5°C while stirring for 2h. It was left overnight, when diluted with water, precipitation took place. The precipitated solid was collected, washed with water, dried and recrystallized from dil. DMF to yield 11.

^{1}HNMR: δ 2.45 (s, 3H, CH_3), 7.45 (d, 2H, J = 8 Hz, arom.) and 7.88 ppm (d, 2H, J = 8 Hz, arom.).

Action of carbon disulphide on 7d - Synthesis of 12:

A mixture of 7d (1 g), carbon disulphide (3 ml) and potassium hydroxide (0.3 g) in ethanol (30 ml) was refluxed for 4h. After removal of the ethanol, water was added and the alkaline solution was filtered. The clear filtrate was acidified with diluted hydrochloric acid. The formed precipitate was collected and recrystallized from DMF to give 12.

^{1}HNMR: δ 2.37 (s, 3H, CH_3), 5.97 (broad s, 1H, disappeared after D_2O exchange NH), 7.33 (d, 2H, J = 8 Hz, arom.), 7.65 (d, 2H, J = 8 Hz, arom.), 12.28 (broad s, 1H, disappeared after D_2O exchange, NH) and 14.00 ppm (broad s, 1H, disappeared after D_2O exchange, NH).

Cyclization of each of 7b,c - Formation of 13 and 14:

Method A:

A solution of each of 7b,c (1 g) in acetic anhydride (10 ml) was heated under reflux for 6h. The separated solid, while boiling (14) or after cooling (13), was collected and recrystallized from acetic acid to give 13 and 14.

^{1}HNMR of 13: δ 2.41 (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 7.41 (m, 6H, 5H arom + 1H ethylenic), 7.85 (m, 4H, J = 8 Hz, arom.) and 13.25 ppm (s, 1H disappeared after D_2O exchange, OH).

^{1}HNMR of 14: δ 1.40 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.30 (q, 2H, CH_2), 7.20 (m, 2H, J = 8 Hz, arom.), 7.40 (m, 2H, J = 8Hz, arom.) and 7.75 ppm (m, 4H, J = 8 Hz, arom.).

Method B:

A solution of 6c (0.005 mole, 1.76 g) and glycine (0.01 mole, 0.75 g) in acetic acid (30 ml) was refluxed for 2h. The solution was cooled, the resulting solid was collected and recrystallized from acetic acid to yield 13 (Tables 1 and 2).

Material:

The totality of the material used consisted of commercially available compounds.

Instruments:

^{1}HNMR spectra were measured at 25°C on a Perkin-Elmer R12A spectrometer, in DMSO-d_6 with TMS as internal standard and chemical shifts are expressed as δ (ppm) values.

IR spectra were recorded (KBr) on a Perkin-Elmer Infracrod 137 instrument. Microanalytical data was processed by Cairo University Microanalytical Center.

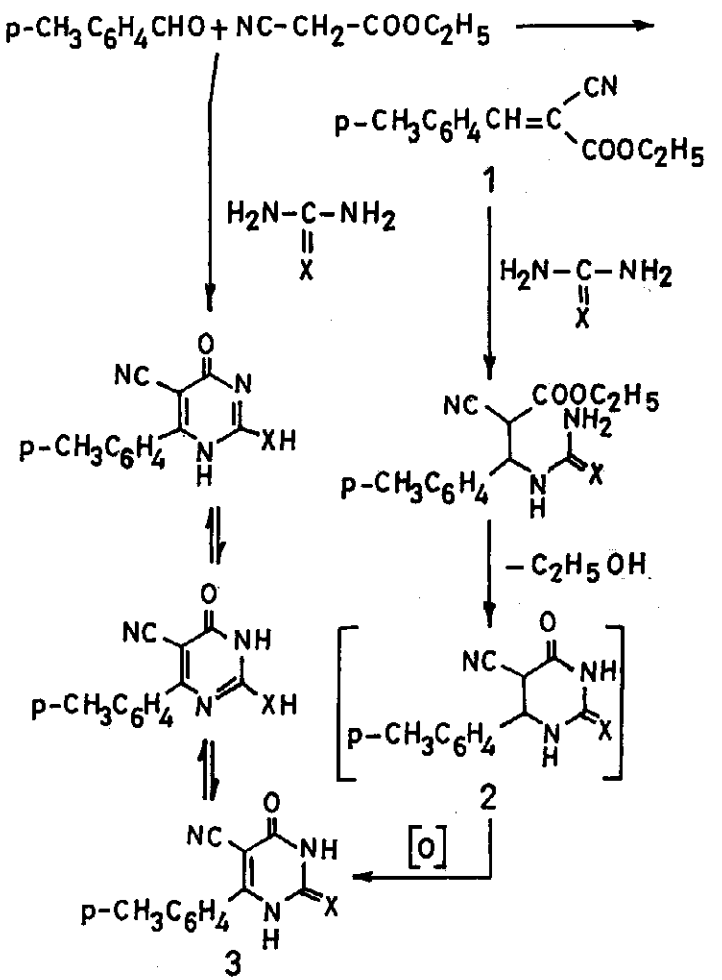
All melting points were taken on a Kofler apparatus and are uncorrected.

Results and Discussion

Heating under reflux, a ternary mixture of p-tolualdehyde, ethyl cyanoacetate and thiourea or urea in ethanol in the presence of potassium carbonate, the 3,4-dihydro-2-mercapto-4-oxo-6-(4-tolyl) pyrimidine-5-carbonitrile and 2-hydroxy analogue **(3a,b)** were obtained. The reaction proceeds probably via Michael addition, cyclisation with the loss of ethanol and the formation of the non-isolable intermediates **2** which then undergo autoxidation to give the final isolable **3a,b** (Scheme 1). A similar oxidation of comparable ring systems has been previously observed [11].

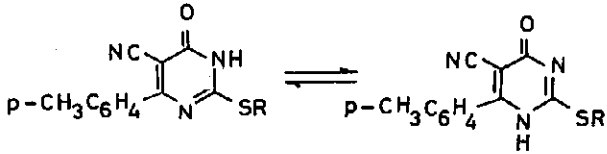
Scheme 1

Structure **3** was inferred from the following facts: (a) The mercapto-pyrimidine derivative **3a** could easily be converted into the oxygen counter analogue **3b** by simple treatment with hydrogen peroxide; (b) The ^{1}HNMR spectra (DMSO-d_6) of the reaction products indicated the absence of any signals corresponding to a proton at a lower field up to 7 (except for CH_3 protons and D_2O exchangeable protons) proves the autoxidation of the reaction intermediates **2** and hence the formation of **3** (cf. Experimental); (c) The IR spectra of **3a,b** displayed characteristic bands for NH, CN and SH **(3a)** or OH **(3b)** (cf. Table 2); and (d) Compounds **3a,b** could also be sythesized via the reaction of ethyl α-cyano-p-methylcinnamate **(1)** with thiourea or urea in boiling pyridine.


p-CH3C6H4CHO + NC-CH2-COOC2H5
p-CH3C6H4CH=C(CN)COOC2H5
1
H2N-C(=X)-NH2
H2N-C(=X)-NH2
NC
O
N
p-CH3C6H4
N
H
XH
NC
COOC2H5
NH2
p-CH3C6H4
N
H
X
- C2H5OH
NC
NH
p-CH3C6H4
N
XH
NC
NH
p-CH3C6H4
N
H
X
2
[O]
NC
NH
p-CH3C6H4
N
H
X
3
3a, X = S
3b, X = O

Scheme 1

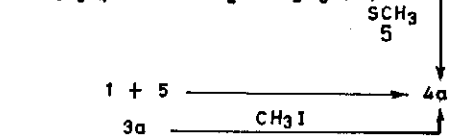
Alkylation of **3a** with alkyl halides in aqueous ethanolic potassium carbonate solution gave the S-alkyl derivatives **4a-c**.



4

a, R = CH_3
b, R = CH_2CH_3
c, R = $CH_2C_6H_5$

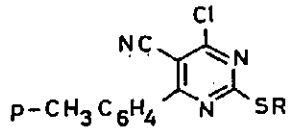
That alkylation took place at the sulphur atom level was proved by: (a) preparation of **4a** by two other different alternative routes via the reaction of S-methylisothiourea (**5**) with either **1** or a mixture of p-tolualdehyde and ethyl cyanoacetate (Scheme 2); (b) the treatment of either compounds **4a,b** with hydrazine hydrate and the separation of one and the same sulphur-free compound (see below).



Scheme 2

The ^{1}HNMR spectrum (DMSO-d_6) of **4a**, as an example, showed signals at δ 2.35 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.47 (d, 2H, H arom.), and 7.80 ppm (d, 2H, H arom.). The IR spectra of 4 displayed characteristic bands for NH, CN and amidic CO.

Heating compounds **4a-c** with phosphorus oxychloride in dioxane produced the 4-chloropyrimidine derivatives **6a-c**.



6

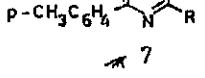
a, R = CH_3

b, R = CH_2CH_3

c, R = $CH_2C_6H_5$

The ^{1}HNMR spectrum (DMSO-d_6) of **6a**, as an example, showed signals at δ 2.42 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 7.50 (d, 2H, H. arom.) and 8.00 ppm (d, 2H, H arom.).The IR spectra of **6** revealed besides the absence of any absorption bands in the NH and CO regions, the presence of an absorption CN band (c.f.Table 2).

Position 4 in compounds **6a-c** showed distinct activity and the chlorine atom could be replaced by ammonia, glycine or hydrazine. Thus, compounds **6a-c** reacted with ammonia, glycine and hydrazine hydrate to give the corresponding 4-substituted pyrimidine derivatives **7a-d.**



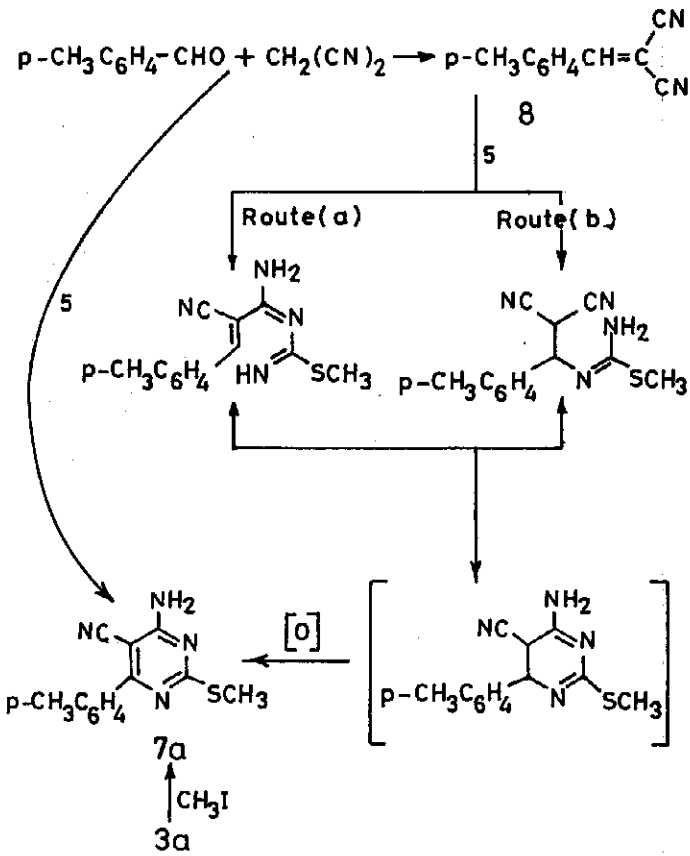
7

7	R	R
a	SCH_3	NH_2
b	$SCH_2C_6H_5$	$NHCH_2COOH$
c	SCH_2CH_3	HNC_6H_4COOH (o)
d	$NHNH_2$	$NHNH_2$

It is worth mentioning that the treatment of each of **6a,b** with hydrazine hydrate resulted in the evolution of methanethiol and ethanethiol, respectively and the production of one and the same desulphurised product **7d.**

As a continuation of this work, compound **7a** was also synthesized by the reaction

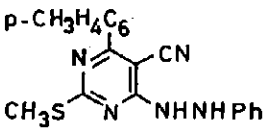
of **5** with either α-cyano-p-methylcinnamonitrile (**8**) or a mixture of p-toulaldehyde and malononitrile in boiling pyridine (Scheme 3).



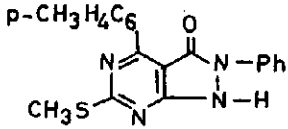
Scheme 3

As an example, the ^{1}HNMR spectrum (DMSO-d_6) of **7d** showed signals at δ 2.30 (s, 3H, CH_3), 4.50 (broad s, 4H, disappeared after D_2O exchange, 2 NH_2), 7.35 (d, 2H, H arom.), 7.55 (d, 2H, H arom.) and 8.80 ppm (broad s, 2H, disappeared after D_2O exchange, 2 NH). The IR spectra displayed characteristic bands (see Table 2).

In contrast to the action of hydrazine hydrate, phenylhydrazine reacted with **6a** under the same experimental conditions to directly yield 2,3-dihydro- 5-methylthio-1-oxo-2-phenyl-7-(4-tolyl)-1H-pyrazolo[3,4-d]pyrimidine(**10**). The formation of **10** may proceed via the non-isolable **9**.



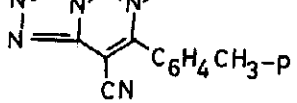
9



10

The assignment of structure **10** to the reaction product is based on analytical and spectral data. Thus, its ^{1}HNMR spectrum (DMSO-d_6) showed signals at δ 2.43 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.65 (broad s, 1H, disappeared after D_2O exchange, NH), 7.40 (m, 5H, H. arom.) and 7.80 ppm (m, 4H, H arom.). The IR spectrum of **10** indicated no absorption band in the cyano region, furthermore, it displayed a carbonyl absorption band at 1665 cm^{-1}.

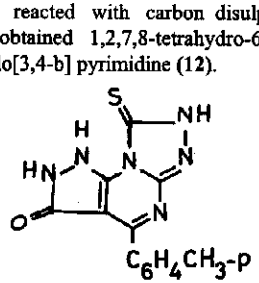
The treatment of compound **7d** with nitrous acid at 0°C resulted in the formation of 5-(4-tolyl)-ditetrazolo[1,5-a:1′,5′-c] pyrimidine-6-carbonitrile (**11**).



11

Structure **11** was inferred from analytical and spectral data. Thus, besides the correct values in the elemental analyses for the reaction product, its ^{1}HNMR spectrum (DMSO-d_6) showed signals at δ 2.45 (s, 3H, CH_3), 7.45 (d, 2H, H arom.), and 7.88 ppm (d, 2H, H arom.). The IR spectrum displayed an absorption band at 2225 cm^{-1} (CN) and revealed no absorption in the NH region.

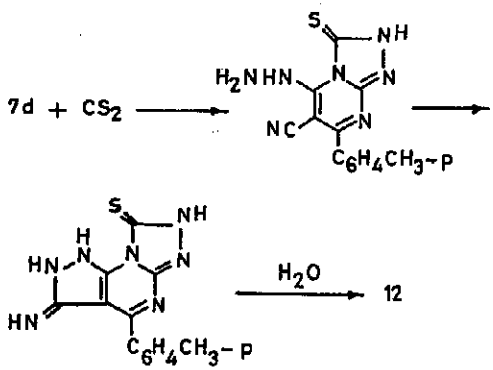
When compound **7d** reacted with carbon disulphide in ethanolic potassium hydroxide solution, we obtained 1,2,7,8-tetrahydro-6-oxo-1-thioxo-5-(4-tolyl)-6H-pyrazolo[3,4-d]-1,2,4-triazolo[3,4-b] pyrimidine (**12**).



12

The ^{1}HNMR spectrum (DMSO-d_6) of **12** showed signals at δ 2.37 (s, 3H, CH_3), 5.97 (broad s, 1H, disappeared after D_2O exchange, NH), 7.33 (d, 2H, H arom.), 7.65 (d, 2H, H arom.), 12.28 (broad s, 1H, disappeared after D_2O exchange, NH) and 14.00 ppm (broad s, 1H, disappeared after D_2O exchange, NH). Its IR spectrum revealed no absorption CN band, but it displayed absorption bands at 3400,3100 (NH) and 1663 cm^{-1} (CO).

The formation of **12** may be explained as shown in Scheme 4.



Scheme 4

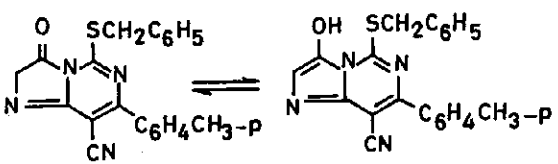
It is reported in the literature that the imino group is hydrolysed into carbonyl

group [12].

Compound **6c** reacted with glycine in boiling ethanol to yield 2-benzylthio-4-carboxymethylamino-6-(4-tolyl) pyrimidine-5-carbonitrile (**7b**). The ^{1}HNMR spectrum (DMSO-d_6) of **7b** showed signals at δ 2.40 (s, 3H, CH3), 4.05 (broad s, 1H, disappeared after D_2O exchange, NH), 4.15 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.36 (m, 5H, H. arom.), 7.78 (m, 4H, H arom.), and 8.78 ppm (s, 1H, disappeared after D_2O exchange, COOH). Its IR spectrum displayed bands at 3200 (broad, NH and OH), 2225 (CN) and 1720 cm^{-1} (CO).

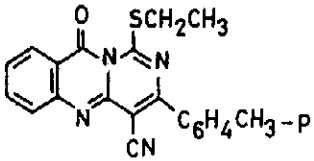
Similarly, the reaction of compound **6b** with anthranilic acid in refluxing acetic acid formed 4-(2-carboxyphenylamino)-2-ethylthio-6-(4-tolyl) pyrimidine-5-carbonitrile (**7c**). The ^{1}HNMR spectrum (DMSO-d_6) of **7c** showed signals at δ 1.35 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.15 (q, 2H, CH_2), 3.55 (broad s, 1H, disappeared after D_2O exchange, NH), 7.17 (m, 2H, H. arom.), 7.34 (m, 2H, H arom.), 7.64 (m, 4H, H arom.), and 11.33 ppm (s, 1H, disappeared after D_2O exchange, COOH). Its IR spectrum displayed bands at 3150 (broad, NH and OH), 2220 (CN) and 1690 cm^{-1} (CO).

Each of the compounds **7b,c** underwent cyclisation, when heated with acetic anhydride to yield the cyclised products **13'** and **14**, respectively. Compound **13'** may be present mainly in the enol from **13** as revealed by its spectra. Thus, ^{1}HNMR spectrum (DMSO-d_6) showed signals at δ 2.41 (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 7.41 (m, 6H, 5 H. arom. + 1H ethylenic), 7.85 (m, 4H, H arom.), and 13.25 ppm (s, 1H, disappeared after D_2O exchange, OH). Its IR spectrum displayed bands at 3020 (broad OH), 2219 (CN) and 1740 cm^{-1} (weak CO). The above data are consistent with the formulation of this compound as 1-benzylthio-7-hydroxy-3-(4-tolyl) imidazo[1,2-c] pyrimidine-4-carbonitrile (**13**).



13' 13

The ^{1}HNMR spectrum (DMSO-d_6) of **14** indicated that the signals corresponding to the NH and COOH in its precursor **7c** have disappeared. In addition, its IR spectrum displayed no absorption in the NH and OH regions. Compound **14** could be formulated as 1-ethylthio-10-oxo-3-(4-tolyl)-10H-pyrimido[6,1-b]quinazoline-4-carbonitrile (**14**).



14

When a mixture of **6c** and glycine was heated in acetic acid, compound **13** was directly obtained.

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تحضير بعض مشتقّات البيريميدين الجديدة

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(أستلم في ١٤١٨/٣/٢٩ هـ ، و قُبل للنشر في ١٤١٨/١٠/٢٠ هـ)

ملخص البحث. تم تحضير ٢- مركبتو-، ٢- هيدروكسي -٣، ٤- ثنائي هيدرو-٤ - أوكس - ٦ - (٤- طوليل) بيريميدين -٥- كاربونيتريل (3a,b) بطريقتين مختلفتين. المركب 3a حُول إلى 3b بواسطة فوق أكسيد الهيدروجين. ألكلة 3a بهاليدات ألكيل أعطت مشتقات S- ألكيل 4a-c . أمكن تحضير المشتق 4a بطريقتين مختلفتين. تفاعل 4a-c مع أوكسي كلوريد الفوسفور وأنتج المشتقات ٤-كلورو 6a-c التي تفاعلت مع كل من أمونيا، حليسين، حمض أنثرانيليك، والهيدرازين وكوّنت مشتقات البيريميدين 7a-d . أمكن الحصول على المشتق 7a بطريقتين مختلفتين. تفاعل 6a مع فينيل هيدرازين وأعطي مباشرة مشتق بيرازولو بيريميدين 10 . كما أن مشتق ٢، ٤- ثنائي هيدرازينوبيريميدين 7d تفاعل مع حمض نيتروز وانتج ثنائي تترازولوبيريميدين 11، ومع ثنائي كيريتيد الكربون وكوّن بيرازولو- تراي أزولو بيريميدين 12.

أمكن حلوقة كل من 7b,c إلى مشتقات إيميدازوبيريميدين 13 وبيريميد وكينازولين 14 على الترتيب، أمكن الحصول على المركب 13 مباشرة عن طريق تفاعل 6c مع الجليسين في حمض أسيتيك.