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A Convenient Synthesis of Thiazolo[3,2-a]- and Triazolo[4,3-a]- Pyrimidines and Pyrimido[2,l-c] Triazine Derivatives

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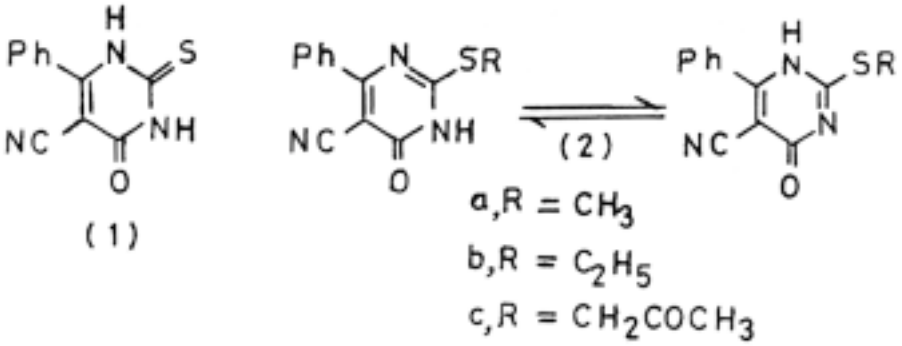
ABSTRACT. Alkylation of 4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (1) gave the S-alkyl derivatives (2b,c). Compound (2c) could be cyclised into 3-methyl-5-oxo-5H-7- phenyl-thiazolo[3,2-a] pyrimidine-6-carboxamide (3). Further substitution of compounds (2a,b) yielded the N_3-Substituted pyrimidine derivatives (7a-e). Desulphunisation of each of compounds (2a,b) with benzhydrazide resulted in the formation of 2-(2-benzoylhydrazino)- pyrimidine derivative (9) , which could be converted into the triazolo[4,3-a] pyrimidine (11). Each of compounds (2a,b) reacted with semicarbazide to produce directly the dioxotriazolopyrimidine derivative (14). Treatment of the 2-hydrazinopyrimidine derivative (10) with chloroacetyl chloride afforded the pyrimido[2,1-c]triazine derivative (16). Its isomeric compound (17) could be also prepared. The structures of the newly synthesized compounds were proved by chemical routes and spectral studies.

Introduction

Diverse pharmacological properties of pyrimidine derivatives as anticancer[1-3], antiinflammatory[4,5], antimalarial[6], antiviral[7], and antidepressant[8] and fused pyrimidines as antimicrobial[9-11], antibacterial[12], antifungal[13] and antihypertensive[14] have aroused our recent interest to synthesize several new derivatives of these ring systems in anticipation that compounds would exhibit medicinal activities[15,16]. This paper describes the strategy to synthesize poly-substituted pyrimidines, thiazolo[3,2-a]-, triazolo[4,3-a]pyrimidines and pyrimido- [2,1-c] triazine derivatives from 4-oxo-6-phenyl-2-thioxo-1,2,3,4- tetrahydropyrimidine-5- carbonitrile(1)[17].

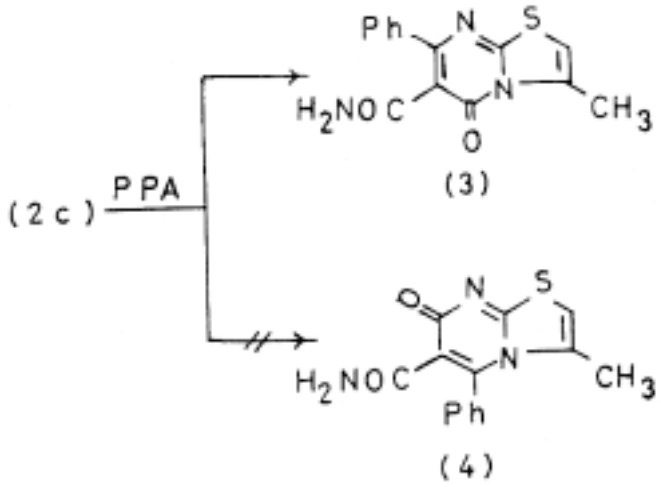
Results and Discussion

It has been found that the pyrimidine derivative (1) reacted with each of ethyl bromide and chloroacetone in ethanol in the presence of potassium carbonate to give the 2-alkylthiopyrimidine derivatives (2b,c), similar to compound (2a)[18]. That alkylation took place at the sulphur atom was recently proved in our previous publications[15,16].



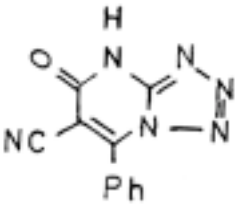
The ^{1}H-nmr spectrum (DMSO-d_6) of compound (2c), as an example, showed signals at δ 2.22 (3H, s, CH_3), 3.73 (1H, broad s, disappeared after D_2O exchange, NH), 4.25 (2H,s,CH_2), 7.57 (3H, m, ArH) and 7.87ppm (2H,m,ArH) and its infrared spectrum (KBr) displayed absorption bands at 3250 (NH), 2221 (CN), 1715 and 1665 cm^{-1} (2CO).

Heating compound (2c) at 100-120ºC with polyphosphoric acid resulted in cyclisation besides partial hydrolysis of the cyano group. The reaction product could be formulated as 3-methyl-5-oxo-5H-7-phenyl-thiazolo[3,2-a] pyrimidine-6-carboxamide (3) rather than the isomeric structure (4).



It appeared that the structure of compound (3) might be elucidated by physical tools rather than chemical ones. Thus the ^{1}H-nmr spectrum (DMSO-d_6) of compound (3) showed signals at δ 2.74 (3H,s,CH_3), 3.58 (2H,broad s, disappeared after D_2O exchange, NH_2), 7.14 (1H, s, ethylenic proton), 7.48 (3H,m,ArH) and 7.83 ppm (2H,m,ArH) and its infrared spectrum revealed no absorption in the CN region, furthermore, it displayed absorption bands at 3150 (NH), 1690 and 1670 cm^{-1}(2CO).

The product of this reaction has two possible structures (3) and (4) but (3) is favourable than (4) for the following facts. It can be seen that the phenyl group in compound (4), like that in compound (5)[18], must be twisted out of plane of the pyrimidine ring because of steric interference. This phenyl group would be expected to give a compact signal in the nmr spectrum. However, the phenyl group in compound (3) should be coplanar with the pyrimidine ring, and in agreement there is a complex two-protons signal at low field. Since the nmr spectrum data of the reaction product show that the ortho phenyl protons are deshielded by 0.35 ppm relative to the meta- and para-protons, similar to the non-subsitituted N-1 pyrimidine compound (6)[18], this indicates that structure (3) is the correct one for the reaction product. This is in agreement with the reported nmr spectrum data for other compounds with similar system[19-21].



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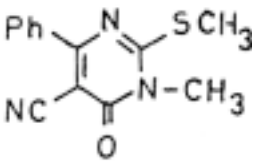


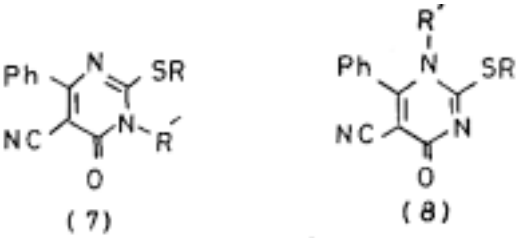
(6)

When the 2-alkylthio-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitriles (2a,b) were subjected to react with acetyl chloride, benzoyl chloride and ethyl chloroacetate the product was 2-alkylthio-4-oxo-6- phenyl-3-substituted-3,4-dihydropyrimidine-5-carbonitriles (7) rather than the isomeric structure (8).

The ^{1}H-nmr spectrum (DMSO-d_6) of compound (7a), as an example, exhibited signals at δ 2.70 (3H,s,-SCH_3), 3.25 (3H,s,-$COCH_3$), 7.52 (3H,m,ArH) and 7.99 ppm (2H,m,ArH). The infrared spectrum (KBr) of compounds (7a-e) revealed absorption bands characteristic for CN and two CO groups.

The structure (7) was established on the study of the nmr spectral data. Thus, as we mentioned before, since the ortho phenyl protons in compounds (7a-e) are deshielded by about 0.45 ppm relative to the meta- and para-protons, similar to

the non-substituted N-1 pyrimidine derivative (6),this indicates that structure (7) is favoured for the reaction products[18-21] .



a, $R = CH_3$; $R' = COCH_3$

b, $R = CH_3$; $R' = CO C_6H_5$

c, $R = CH_3$; $R' = CH_2 COO C_2H_5$

d, $R = C_2H_5$; $R' = COCH_3$

e, $R = C_2H_5$; $R' = CO C_6H_5$

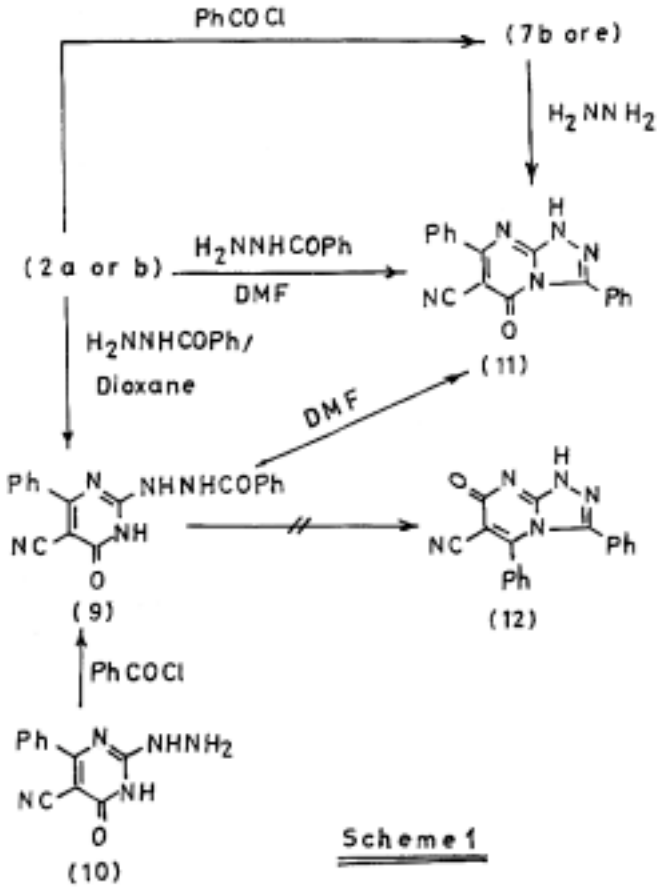
Desulphunisation of each of compounds (2a,b) with benzhydrazide in refluxing dioxane led to the formation of one and the same product formulated as 2-(2-benzoylhydrazino)-4-oxo-6-phenyl-3,4- dihydropyrimidine-5- carbonitrile (9). The latter compound could also be prepared by an alternative route via the reaction of the 2-hydrazinopyrimidine derivative(10)[18] with benzoyl chloride in anhydrous dioxane.

The ^{1}H-nmr spectrum (DMSO-d_6) of compound (9) showed signals at δ 3.42 (1H, broad s, disappeared after D_2O exchange, NH), 7.55 (6H, m, ArH), 8.01 (5H,m,4H ArH+NH, exchangeable with D_2O) and 10.56 ppm (1H,s, disappeared after D_2O exchange, NH). Its infrared spectrum displayed absorption bands at 3320 (NH), 2219 (CN), 1670 and 1660 cm^1 (2CO).

Refluxing compound (9) with dimethylformamide underwent ring closure to give a product which could be formulated as 5-oxo-3,7- diphenyl-1,5-dihydro-s-triazolo[4,3-a]pyrimidine-6-carbonitrile (11) or the isomeric structure (12). However, compound (11) could also be obtained by two other different alternative routes: (a) Heating either compound (2a) or (2b) with benzhydrazide in dimethylformamide, (b) Treatment of each of compounds (7b,e) with hydrazine hydrate in refluxing dioxane (Scheme 1).

The ^{1}H-nmr spectrum (DMSO-d_6) of compound (11) exhibited signals at δ 7.52 (6H,m, ArH), 7.92 (4H, m, ArH) and 11.79 ppm (1H, broad s, disappeared after D_2O exchange, NH) and its infrared spectrum (KBr) displayed absorption bands at 3330 (NH),2220 (CN) and 1690 cm^{-1} (CO). The assignment of structure (11) to the reaction product is based on chemical and physical evidences: (a) Compound

(11) could be synthesized by three different methods (Scheme 1), (b) The deshielding of the ortho pheny1 protons in compound (11) by 0.40 ppm relative to the meta- and para- protons, similar to the non-substituted N-1 pyrimidine derivative (6) reveals that structure (11) is favoured for the reaction product[18-21].



Scheme 1

Similarly, compound (7a) or (7d) reacted with hydrazine hydrate in refluxing dioxane to give the 3-methyltriazolo[4,3-a]pyrimidine derivative (13) whose structure was based on analytical and spectral data (*cf.* Tables 1 and 2).

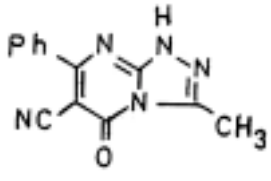


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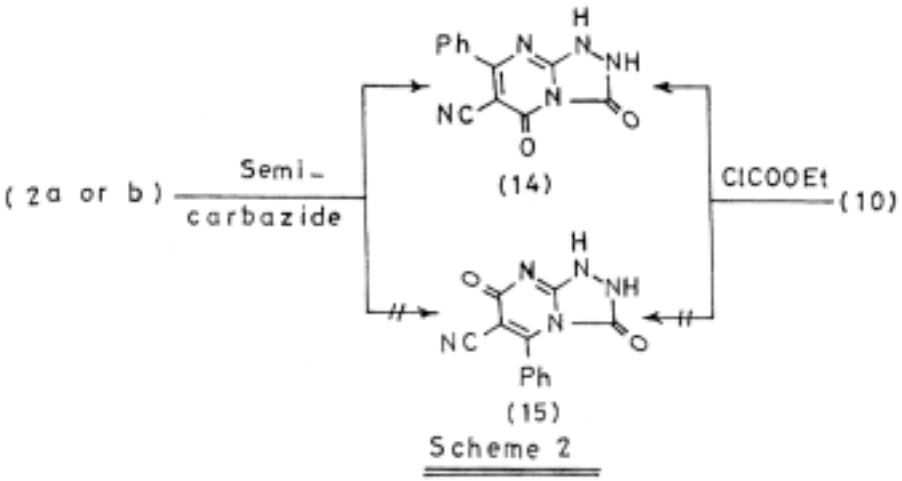
TABLE 1. Characterization data of products 2-20.

Comp.	M.P. (ºC)	Yield (%)	Formula (M.W.)	Analysis		Calcd. / Found	
				C	H	N	S
2b	260	78	$C_{13}H_{11}N_3OS$ (257.3)	60.69 60.70	4.31 4.20	16.33 16.30	12.46 12.50
2c	190	80	$C_{14}H_{11}N_3O_2S$ (285.3)	58.94 59.00	3.89 3.80	14.73 14.70	11.24 11.30
3	229	75	$C_{14}H_{11}N_3O_2S$ (285.3)	58.94 59.10	3.89 3.90	14.73 14.80	11.24 11.20
7a	174	72	$C_{14}H_{11}N_3O_2S$ (285.3)	58.94 58.90	3.89 3.80	14.73 14.70	11.24 11.30
7b	168	77	$C_{19}H_{13}N_3O_2S$ (347.4)	65.69 65.70	3.77 3.70	12.10 12.10	9.23 9.30
7c	90	63	$C_{16}H_{15}N_3O_3S$ (329.4)	58.34 58.30	4.59 4.50	12.76 12.80	9.73 9.70
7d	239	70	$C_{15}H_{13}N_3O_2S$ (299.4)	60.18 60.20	4.38 4.30	14.04 14.10	10.71 10.70
7e	230	68	$C_{20}H_{15}N_3O_2S$ (361.4)	66.47 66.40	4.18 4.20	11.63 11.60	8.87 8.90
9	220	63(A) 65(B)	$C_{18}H_{13}N_5O_2$ (331.3)	65.26 65.20	3.96 3.90	21.14 21.20	– –
11	284	71 (A) 63 (B) 65 (C)	$C_{18}H_{11}N_5O$ (313.3)	69.01 69.00	3.54 3.60	22.35 22.30	– –
13	229	63	$C_{13}H_9N_5O$ (251.3)	62.13 62.10	3.61 3.70	27.87 27.90	– –
14	> 300	61 (A) 63 (B)	$C_{12}H_7N_5O_2$ (253.2)	56.92 56.98	2.79 2.80	27.66 27.70	– –
16	> 300	67 (A) 64 (B)	$C_{13}H_9N_5O_2$ (267.3)	58.41 58.40	3.39 3.30	26.20 26.20	– –
17	> 300	70	$C_{13}H_9N_5O_2$ (267.3)	58.41 58.50	3.39 3.40	26.20 26.20	– –
20	290	85	$C_{22}H_{12}N_6O_2S_2$ (456.5)	57.88 57.90	2.65 2.70	18.41 18.50	14.05 14.0

TABLE 2. IR and ^{1}H-nmr spectra of products in Table 1.

Comp.	IR (Cm^{-1})	^{1}H-nmr δ ppm
2b	3300 (NH), 2220 (CN), 1660 (CO).	2.00 (3H, t, CH_3), 4.15 (2H, q, CH_2), 6.31 (1H, broad s, disappeared after D_2O exchange, NH), 7.65 (3H, m, ArH), 7.95 (2H, m, ArH).
2c	3250 (NH), 2221 (CN), 1715, 1665 (2CO).	2.22 (3H, s, CH_3), 3.73 (1H, broad s, disappeared after D_2O exchange, NH), 4.25 (2H, s, CH_2), 7.57 (3H, m, ArH), 7.87 (2H, m, ArH).
3	3150 (NH), 1690, 1670 (2CO).	2.74 (3H, s, CH_3), 3.58 (2H, broad, s, disappeared after D_2O exchange, NH_2), 7.14 (1H, s, ethylenic proton), 7.48 (3H, m, ArH), 7.83 (2H, m, ArH).
7a	2220 (CN), 1690, 1675 (2CO).	2.70 (3H, s, CH_3), 3.25 (3H, s, CH_3), 7.52 (3H, m, ArH), 7.99 (2H, m, ArH).
7b	2220 (CN), 1695, 1680 (2CO)	2.63 (3H, s, CH_3), 7.54 (6H, m, ArH), 7.99 (4H, m, ArH).
7c	2223 (CN), 1755, 1691 (2CO).	1.45 (3H, t, CH_3), 2.60 (3H, s, CH_3), 4.05 (2H, s, CH_2), 4.35 (2H, q, CH_2), 7.63 (3H, m, ArH), 7.95 (2H, m, ArH).
7d	2220 (CN), 1695, 1670 (2CO).	2.05 (3H, t, CH_3), 3.20 (3H, s, CH_3), 4.10 (2H, q, CH_2), 7.50 (3H, m, ArH), 7.97 (2H, m, ArH).
7e	2221 (CN), 1690, 1680 (2CO).	2.10 (3H, t, CH_3), 4.10 (2H, q, CH_2), 7.52 (6H, m, ArH), 7.98 (4H, m, ArH).
9	3320 (NH), 2219 (CN), 1670, 1660 (2CO).	3.42 (1H, broad, s, disappeared after D_20 exchange, NH) 7.55 (6H, mArH), 8.01 (5H, m, 4H ArH + NH exchangeable with D_2O), 10.56 (1H, s, disappeared after D_2O exchange, NH).
11	3330 (NH), 2220 (CN), 1690 (CO).	7.52 (6H, M, ArH), 7.92 (4H, m, ArH), 11.79 (1H, broad s, disappeared after D_2O exchange, NH).
13	3300 (NH), 2221 (CN), 1695 (CO).	2.51 (3H, s, CH_3), 3.45 (1H, broad, s, disappeared after D_2O exchange, NH), 7.47 (3H, m, ArH), 7.93 (2H, m, ArH).
14	3340 (NH), 2223 (CN), 1700, 1690 (2CO).	7.49 (3H, m, ArH), 7.94 (2H, m, ArH), 10.71 (1H, broad s, disappeared after D_2O exchange, NH), 11.72 (1H, broad, s, disappeared after D_2O exchange, NH).
16	3400, 3100 (broad OH and NH), 2220 (CN), 1660 (CO).	6.34 (1H, s, triazine proton), 7.53 (3H, m, ArH), 7.87 (2H, m, ArH), 10.61 (2H, s, disappeared after D_2O exchange, 2NH), 13.51 (1H, broad s, disappeared after D_2O exchange, enolic OH).
17	3270 (NH), 222 (CN), 1697, 1680 (2CO).	4.22 (2H, s, CH_2), 7.46 (3H, m, ArH), 7.92 (2H, m, ArH), 10.07 (2H, broad, s, disappeared after D_2O exchange, 2NH).
20	3200 (NH), 2220 (CN), 1665 (CO).	7.58-7.71 (10H, M, ARH), 11.23 (2H, broad s, disappeared after D_2O exchange, 2NH).

On the other hand, the reaction of each of compounds (2a,b) with semicarbazide hydrochloride in refluxing dioxane and in the presence of sodium acetate directly afforded 3,5-dioxo-7-phenyl-1,2,3,5-tetrahydro-s-triazolo[4,3-a] pyrimidine-6-carbonitrile (14) and not the isomeric structure (15). Compound (14) could be again obtained through the reaction of compound (10) with ethyl chloroformate in diaxone, (Scheme 2). The ^{1}H-nmr spectrum (DMSO-d_6) of compound (14) showed signals at δ 7.49 (3H,m, ArH), 7.94 (2H,m, ArH), 10.71 (1H,broad s, disappeared after D_2O exchange, NH) and 11.72 ppm (1H, broad s, disappeared after D_2O exchange, NH) and its infrared spectrum (KBr) displayed absorption bands at 3340 (NH), 2223 (CN), 1700 and 1690 cm^{-1} (2CO).



Scheme 2

The structure (14) was confirmed based on the fact that the ortho phenyl protons in its nmr spectrum are deshielded by 0.45 ppm relative to the meta- and para-protons indicating that the pyrimidine N-1 nearby the phenyl group is non-substituted, this proves structure (14)[18-21].

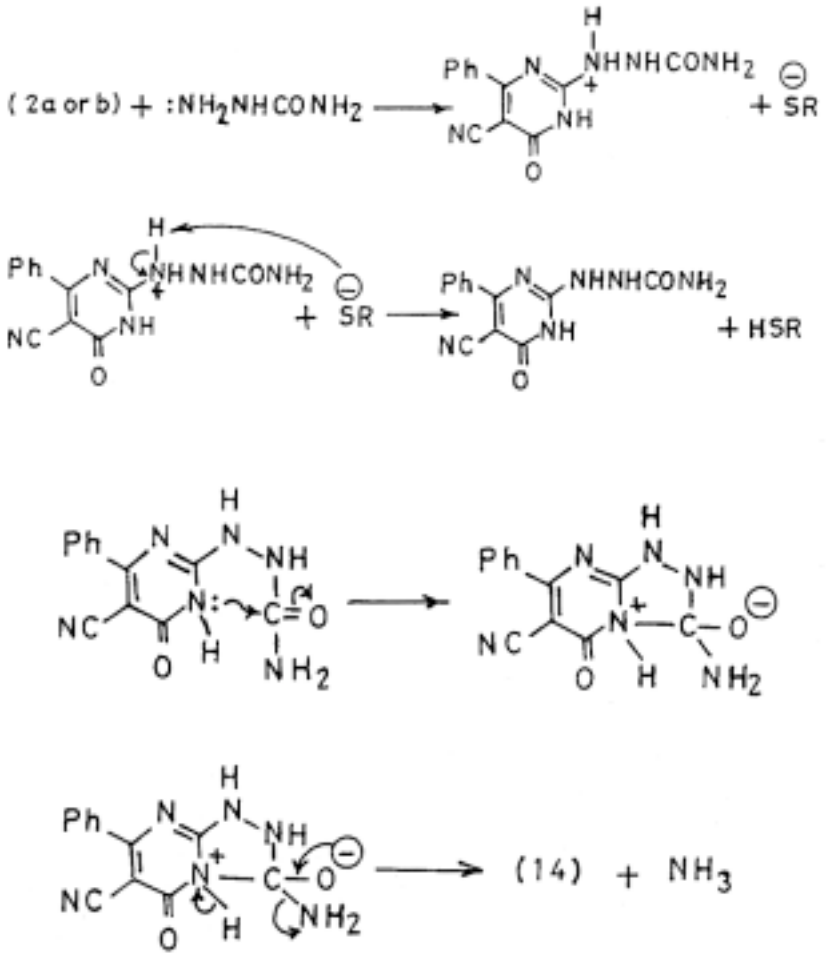
A mechanism of this reaction may be suggested as follows:

(a) The reaction of (2a or b) with semicarbazide :

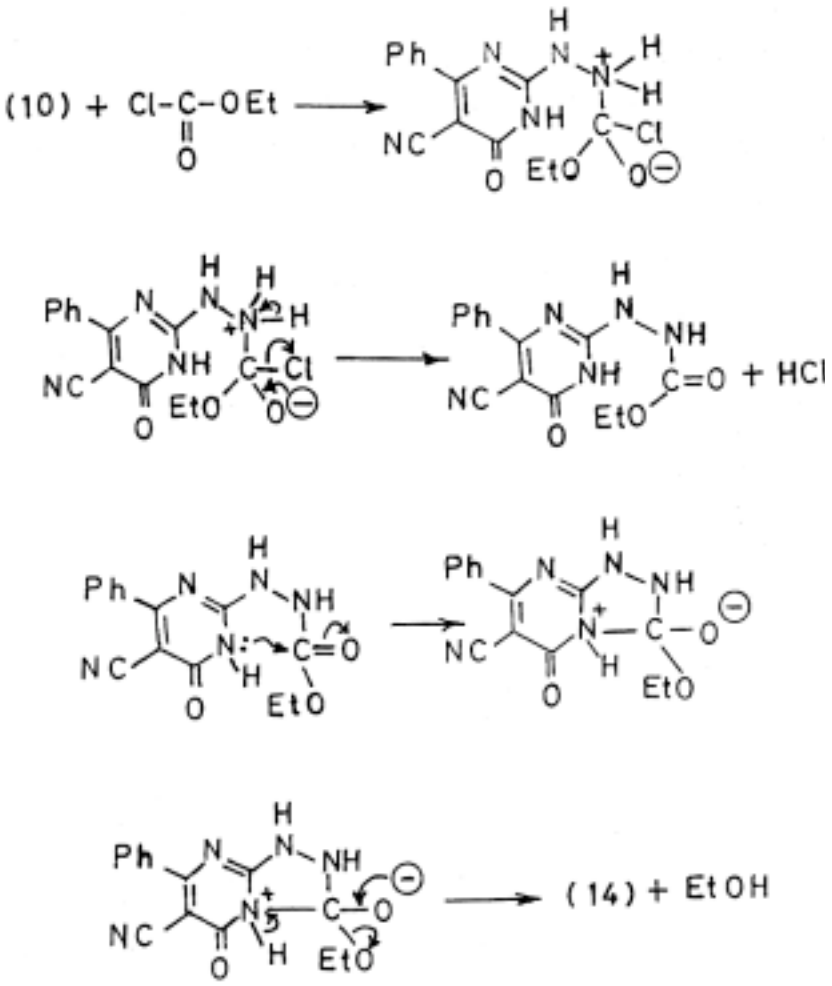
(b) The reaction of (10) with ethyl chloroformate :

When the 2-hydrazinopyrimidine derivative (10) was treated, in anhydrous dioxane, with chloroacetyl chloride, at room temperature, 4-hydroxy-6-oxo-6H-8-phenyl-1,2-dihydropyrimido[2,1-c]-as-triazine-7- carbonitrile (16) was obtained as hydrochloride salt. The free base could be separated on treatment with sodium acetate solution. It is worth to mention that other isomeric structures (17), (18) and (19) seem possible for the reaction product. The same compound could be again obtained via the reaction of compound (10) with ethyl

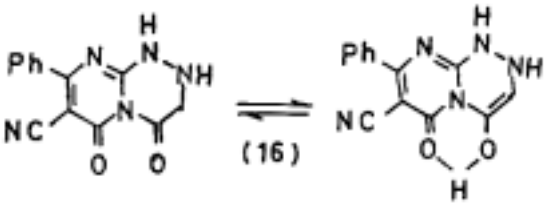
chloroacetate in refluxing dioxane. The ^{1}H-nmr spectrum (DMSO-d_6) of the reaction product showed signals at δ 6.34 (1H,s, triazine proton), 7.53 (3H,m, ArH), 7.87 (2H,m, ArH), 10.61 (2H,s, disappeared after D_2O exchange, 2NH) and 13.51 ppm (1H, broad s, disappeared after D2O exchange, enolic OH) and its infrared spectrum (KBr) revealed absorption bands at 3400, 3100 (broad, OH and NH), 2220 (CN) and 1660 cm^{-1} (CO).



The structure (16) was inferred from the following facts : (a) Once again, as we reported before, that the phenyl group in compounds (18) and (19) like that in compound (5)[18], must be twisted out of the pyrimidine plane due to steric interference. This phenyl group would be expected to appear as a compact signal in the ^{1}H-nmr spectrum. However, the phenyl group in compounds (16) and (17), similar to the non-substituted N-1 pyrimidine derivative (6)[18], should be



coplanar with the pyrimidine ring, and in agreement there is a complex two-protons signal at low field[18-21]. Since the ^{1}H-nmr spectrum data of the reaction product reveal that the ortho phenyl protons are deshielded by 0.34 ppm relative to the meta- and para- protons, this indicated that structures (16) or (17) are preferred over (18) and (19). (b) The infrared pyrimidine carbonyl frequency of compound (16) (1660 cm^{-1}) is lower than that of compounds (3), (11), (13) and (14) (around 1690 cm^{-1}) (Table 2) indicating hydrogen bonding as expected for compound (16) where the C = O and the OH groups may interact intramolecularly. This confirms the structure (16) over (17). (c) Moreover, the isomeric compound (17) could be also synthesized through the reaction of compound (7c) with hydrazine hydrate in dioxane.



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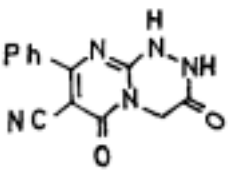

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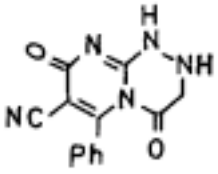

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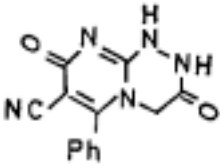
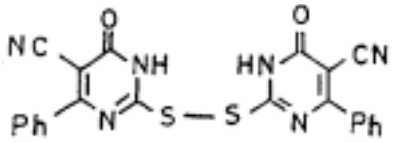


(19)

The ^{1}H-nmr spectrum (DMSO-d_6) of compound (17) showed signals at δ 4.22 (2H,s, CH_2), 7.46 (3H,m,ArH), 7.92 (2H,m, ArH) and 10.07 ppm (2H, broad s, disappeared after D_2O exchange, 2NH) and its infrared spectrum (KBr) displayed absorption bands at 3270 (NH), 2223 (CN), 1697 and 1680 cm^{-1} (2CO).

Finally, oxidation of compound (1) with bromine in acetic acid afforded the disulphide (20) in good yield. Elemental analysis, infrared and ^{1}H-nmr spectral data were consistent with the assigned structure.



(20)

Experimental

General Methods

Melting points were determined with Kofler apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded at 25ºC on a Perkin-Elmer R12A spectrometer, in deuterodimethylsulphoxide using tetramethyl silane as standard. Infrared spectra were recorded, for potassium bromide disc, with a Perkin-Elmer spectrophotometer.

Microanalytical data were processed by Cairo University Microanalytical Center.

2-Alkylthio-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitriles (2b,c)

General Procedure

A mixture of compound (1) (2.29 g; 1×10^{-2} mole), ethyl bromide (1.09 ; 1×10^{-2} mole) or chloroacetone (0.93 g; 1×10^{-2} mole) and potassium carbonate (1.38 g; 1×10^{-2} mole) in ethanol (100 ml) was heated under reflux for 3h and then concentrated. The reaction mixture after cooling was poured into water (100 ml). The solid that separated was collected, washed with water, dried and recrystallised from dilute dimethylformamide to yield compounds (2b,c) (*cf.* Tables 1 and 2).

3-Methyl-5-oxo-5H-7-phenylthiazolo[3,2-a] pyrimidine-6-carboxamide (3)

A suspension of compound (2c) (2g; 7×10^{-3} mole) in polyphosphoric acid (10g) was heated at 100ºC for one hour and then at 120ºC for another hour. The solution was left to cool, poured into ice-water and stirred. The solid that precipitated was filtered off, well washed with water, dried and recrystallised from dioxane to produce (3) (*cf.* Tables 1 and 2).

2-Alkylthio-4-oxo-6-phenyl-3-substituted-3,4-dihydropyrimidine-5-carbonitriles (7a,b,d,e)

General Procedure

A mixture of either (2a) (2.43g; 1×10^{-2} mole) or (2b) (2.57g; 1×10^{-2} mole), each of acetyl chloride (0.79 g; 1×10^{-2} mole), benzoyl chloride (1.41g ; 1×10^{-2} mole) and anhydrous sodium acetate (2g) was refluxed in glacial acetic acid (100 ml) for 2 h. The reaction mixture was allowed to cool and then poured into water (150 ml). The solid that separated was collected, thoroughly washed with water, dried and recrystallised from dioxane to yield (7a, b, d, e) (*cf.* Tables 1 and 2).

3-Carbethoxymethyl-2-methylthio-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile (7c)

A mixture of (2a) (2.43g ; 1×10^{-2} mole), ethyl chloroacetate (1.23g; 1×10^{-2} mole) and potassium carbonate (1.38g ; 1×10^{-2} mole) in dimethylformamide (50 ml) was stirred at room temperature for 4 h. The solid that precipitated after dilution with water (50 ml) was filtered off, washed with water, dried and recrystallised from dioxane to produce (7c) (*cf.* Tables 1 and 2).

2-(2-Benzoylhydrazino)-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile (9)

Method (A)

A solution of either (2a) (2.43g; 1×10^{-2} mole) or (2b) (2.57g; 1×10^{-2} mole) in anhydrous dioxane (100 ml) was treated with benzhydrazide (1.36 g; 1×10^{-2} mole). The solution was refluxed till evolution of alkanethiol ceased (about 5 h), left to cool and diluted with water (100 ml). The precipitate that formed was filtered off, dried and recrystallised from dioxane to produce (9).

Method (B)

A solution of (10) (1.14g; 5×10^{-3} mole) and benzoyl chloride (0.70g; 5×10^{-3} mole) in anhydrous dioxane (30 ml) was refluxed for 2 h. The reaction mixture was allowed to cool and diluted with water (30 ml). The solid that separated was collected, washed with water, dried and recrystallised from dioxane to give (9) and to be identical with compound prepared in method (A), m.p. and m.m.p. determination (*cf.* Tables 1 and 2).

5-Oxo-3,7-diphenyl-1,5-dihydro-1,2,4-triazolo[4,3-a]-pyrimidine-6-carbonitrile (11)

Method (A)

One gram of (9) was heated under reflux in dimethylformamide (30 ml) for 2 h. The reaction mixture was allowed to cool and diluted with water (20 ml). The precipitate that precipitated was collected, dried and recrystallised from dimethylformamide to give (11) (Tables 1 and 2).

Method (B)

To a solution of either (2a) (2.43g; 1×10^{-2} mole) or (2b) (2.57g; 1×10^{-2} mole) in dimethylformamide (50 ml), benzhydrazide (1.36g; 1×10^{-2} mole) was added. The reaction mixture was refluxed for 4 h and then left to cool. The solid that obtained on diluting with water (50 ml) was filtered off, dried and recrystallised from dimethylformamide to produce (11), m.p. and m.m.p. determination.

Method (C)

General Procedure

A solution of 5×10^{-3} mole of each of (7a or d) and (7b or e) in anhydrous dioxane (30 ml) was treated with hydrazine hydrate (2 ml, 99%) and refluxed for 4 h. The reaction mixture was left to cool, the solid so formed was collected, dried and recrystallised from dioxane to give compound (13) or from dimethylformamide to yield compound (11). Identical m.p. and m.m.p. of (11) with each obtained in methods (A) and (B).

3,5-Dioxo-7-phenyl-1,2,3,5-tetrahydro-1,2,4-triazolo-[4,3-a]pyrimidine-6-carbonitrile (14)

Method (A)

A mixture of either (2a) (2.43g; 1×10^{-2} mole) or (2b) 2.57g; 1×10^{-2} mole), anhydrous fused sodium acetate (2g) and semicarbazide hydrochloride (1.23g; 11×10^{-3} mole) in anhydrous dioxane (100 ml) was heated under reflux for 10 h . The reaction mixture was left to cool, poured into water (100 ml). The solid that isolated was collected, thoroughly washed with water, dried and recrystallised from dilute dimethylformamide to give one and the same product (14), identical infrared spectra.

Method (B)

A mixture of (10) (1.14g; 5×10^{-3} mole), potassium carbonate (1 g) and ethyl chloroformate (0.55g; 5×10^{-3} mole) was refluxed in anhydrous dioxane (30 ml) for 4 h. The reaction mixture was left to cool and poured into water (50 ml). The precipitate so formed was filtered off, washed with water, dried and recrystallised from dimethylformamide to yield (14). Identical infrared spectra with that obtained in method (A).

4-Hydroxy-6-oxo-6H-8-phenyl-1,2-dihydropyrimido-[2,1-c]-as-triazine-7-carbo-nitrile (16)

Method (A)

The mixture of (10) (1.14g; 5×10^{-3} mole) and chloroacetyl chloride (0.57g; 5×10^{-3} mole) in anhydrous dioxane (50 ml) was allowed to stir, at room temperature, for 5 h. The reaction mixture was poured into water (50 ml) containing sodium acetate (1 g), the precipitate that isolated, was filtered off, washed with water, dried and recrystallised from dimethyl-formamide to give (16).

Method (B)

A solution of (10) (1.14g; 5×10^{-3} mole) and ethyl chloroacetate (0.62g; 5×10^{-3} mole) in dioxane (50 ml) was heated under reflux for 4 h. The reaction mixture was left to cool and poured into water (50 ml). The solid that separated, was collected, washed with water, dried and recrystallised from dimethylformamide to produce (16).

Identical infrared spectra with that obtained in method (A), (Tables 1 and 2).

6-Oxo-6H-8-phenyl-1,2,3,4-tetrahydropyrimido[2,1-c]- as - triazine-7-carbonitrile (17)

A mixture of (7c) (1.65g; 5×10^{-3} mole) and hydrazine hydrate (2 ml, 99%) was refluxed in dioxane (50 ml) for 5 h. The solid that precipitated, on cooling,

was collected, dried and recrystallised from dioxane to yield (17) (*cf.* Tables 1 and 2).

Bis-(5-cyano-3,4-dihydro-4-oxo-6-phenylpyrimid-2-yl) disulphide (20)

To a solution of (1) (2.29g; 1×10^{-2} mole) in glacial acetic acid (100 ml), bromine (0.26 ml, 5×10^{-3} mole) in acetic acid (20 ml) was gradually added with shaking. The reaction solution was heated on a water bath for 30 minutes, left to cool and poured into water (200 ml). The precipitate that precipitated was collected, thoroughly washed with water, dried and recrystallised from dimethylformamide to form (20) (Tables 1 and 2).

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تحضير ثيازولو [٣، ٢- أ] - وتريازولو [٤، ٣- أ] بيريميدينات ومشتقات بيريميدو [٢، ١- جـ] تريازين

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المستخلص . إن ألكلة ٤-أوكسو-٦-فينيل-٢-ثيوكسو-١، ٢، ٣، ٤ - رباعي هيدروبيريميدين-٥-كربونيتريل (1) أعطت مشتقات S - مستبدل (2b, c) . أمكن تخليق المشتق (2c) إلى ٣-ميثيل-٥-أكسو-٥ يد -٧-فينيل ثيازولو [٣، ٢- أ] بيريميدين-٦-كربونيتريل (3) . مزيد من الاستبدال للمركبات (2a, b) أنتجت المركبات (7a-e) . ثم نزع الكبريت من كل من (2a, b) بواسطة بنزهيدرازيد وكون مشتق N - بنزويل (9) الذي أمكن تحويله إلى تريازولو [٤، ٣- أ] بيريميدين (11) .

تفاعل كل من (2a, b) مع سيمي كاربازيد وأنتج المشتق (14) . بمعالجة مشتق ٢-هيدرازينو بيريميدين (10) بواسطة كلوريد كلورو أسيتيل نتج المشتق بيريميدو [٢، ١- جـ] تريازين (16) . كما أمكن كذلك تحضير صنوه الأيزومري المركب (17) .

تم إثبات البناء التركيبي للمركبات المحضرة حديثًا بالطرق الكيميائية والدراسات الطيفية .