Journal of the Korean Chemical Society
2011, *Vol. 55, No. 6*
Printed in the Republic of Korea
http://dx.doi.org/10.5012/jkcs.2011.55.6.988

Synthesis of Some New Condensed Pyrimidine Derivatives

Enaiat K. Mohamed and Wesam S. Shehab*
Chemistry Department, Faculty of Science, Zagazig University, Zagazig, 44519, Egypt.
**E-mail: enaiat50@gmail.com, dr_wesam123@yahoo.com*
(Received April 4, 2011; Accepted July 28, 2011)

ABSTRACT. Cyclodehydration of 6-amino-5-cyano pyrimidine derivative (2) afforded pyrimidoisoindole derivatives (3). Compound (3) reacted with carbethoxymethylene derivative to give pyridopyrimidine derivatives (5a,b). Compound (3) was also reacted with formamide to give the corresponding pyrimidopyrimdine derivatives (6) that condensed with benzaldehyde to give Schiff's base (7). Refluxing of compound (3) with triethyl orthoformate afforded compound (8) that cyclized with ammonium hydroxide giving the same compound (6). Compound (8) cyclized with hydrazine hydrate giving compound (9) which also cyclized with triethyl orthoformate affording compound (10). Diazotization of compound (3) led to the formation of triazinopyrimidine derivative (11). Cyclization of compound (11) upon treatment with hydrazine hydrate afforded compound (12). Compound (15) was prepared from reaction of compound (3) and ethylenediamine in presence of carbon disulfide. The behaviour of compound (15) toward benzoyl chloride, triethyl orthoformate, nitrous acid and/or carbon disulfide was also described. All proposed structures were supported by elemental analyses, spectroscopic data and some of the new products showed antimicrobial activity.

Key words: Pyrimidoisonidole, Pyridopyrimidoisoindole, Pyrimidopyrimidoisoindole, Imidazolyl pyrimidoisoindole, Triazinopyrimidoisoindole and triazolopyrimido pyrimdoisoindole

INTRODUCTION

Pyrimidoisoindole and imidazolyl pyrimidoisoindole derivatives have proved to be an interesting class of heterocycles compounds. They are very widely used as drugs[1] in treatment of parasitic diseases mainly protozoa (Ameba),[2] promote aortic ring vasodilatation[3] and have shown anti-HIV activity.[4] The pyrimidoisoindole antidepressants are very promising class of polycyclic indole derivatives, which have recently been synthesized and clinically tested. They provide inhibition of the ATP-dependent K^+ channels and, moreover, they are able to stimulate the secretion of insulin.[5,6] Their efficiency in alleviating depression or side effect depends upon their concentration and purity.

EXPERIMENTAL

General

All melting points were determined in an electrothermal IA 9000 digital melting-point apparatus. IR spectra were recorded with a perkin-Elmer model 1600 FTIR spectrometer as KBr discs. 1H-NMR spectra were determined on a Jeol Ex-300 NMR spectrometer and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal references. Elemental analysis were determined on a perkin Elmer 240 (microanalysis). The EITMS were obtained with ovarian MAT311. An instrument (Faculty of Science, Cairo University, Cairo, Egypt).

Chemistry

2-(6-amino-5-cyano-2-oxo-2,3-dihydropyrimidin-4-yl) benzoic acid (2): A mixture of 2-carboxy benzaldehyde (1) (0.01 mol.), malononitrile (0.01 mol) and urea (0.01 mol) in (20 ml) of absolute ethanol containing triethylamine (5-8 drops) was refluxed for 4 hrs. After cooling the reaction mixture was poured into acidified cold water and the solid so-formed was collected by filtration and crystallized from ethanol to give an white crystals (Yield: 50%); mp 124 °C. IR(KBr): 3450 (br, OH), 3420-3310 (NH_2, NH), 3050 (CH-arom.), 2220 (CN), 1700 (C=O), 1675 (NH-C=O) and 1610 (C=N). ^{1}H-NMR (DMSO): 13.39 (S, 1H, OH), 8.20 (S, 1H, NH), 8.14-7.59 (m, 4H, arom.) and 6.65 (S, 2H, NH_2). Anal. Calcd for $C_{12}H_8N_4O_3$ (256.22); C, 56.25; H, 3.15; N, 21.87 Found: C, 56.23; H, 3.11; N, 21.83.

3-amino-1, 9-dioxo-1,9-dihydropyrimido[6,1-a] isoindole-4-carbonitrite (3): A mixture of compound (2) (0.01 mole) and 1 g of phosphorus pentoxide was fused in

sand bath at 124 °C for 3 hrs. After cooling the reaction mixture was poured into cold water The solid product was filtered off and washed with water and crystallized from (benzene + p.e (40-60 °C) as yellow crystals (Yield: 60%); m.p 214 °C. IR(KBr): 3455-3332 (NH_2), 3083(CH-arom.), 2220 (CN), 1703, 1634 (2C=O), 1560 (C=N). ^{1}H-NMR (DMSO): 7.70-7.20 (m, 4H,arom.) and 5.86 (S, 2H, NH_2). Anal. Cald for $C_{12}H_6N_4O_2$ (238.05); C, 60.51; H, 2.54; N, 23.52. Found: C, 60, 49; H, 2.51.

1-amino-3,6,8-trioxo-3,4,6,8-tetrahydropyrido[2',3':4,5] -pyrimide[6,1-a] isoindole-2-carbonitride(5a) or ethyl 1-amino-3,6,8-trioxo-3,4,6,8-tetrahydropyrido [2',3':4,5] pyrimido[6,1-a] isoindole-2-carboxylate(5b): A mixture of compound (3) (0.01 mol), ethyl cyanoacetate (0.01 mol) or diethyl malonate (0.01 mol), ammonium acetate (3 g.) and acetic acid (5 ml) was refluxed for 4 hrs., then left to cool and triturated with ethanol. The solid product thus formed was collected by filtration. Compound (5a) (from ethyl cyanoacetate) was recrystallized from ethanol as brown needles (Yield: 62%); m.p. 270 °C. IR(KBr): 3420-3300 (NH_2), 3080 (CH-arom.), 3180 (NH), 2210 (CN). ^{1}H-NMR (DMSO): 8.20 (S, 1H, NH), 7.70-7.20 (m, 4H, arom.), 6.20-5.90 and (S, 2H, NH_2). Anal. Cald for $C_{15}H_7N_5O_3$ (305.25); C, 59.02; H, 2.31; N, 22.94, Found: C, 59.01; H, 2.30; N, 22.92.

Compound (5b) (from diethyl malonate) was recrystallized from ethanol as buff crystal (Yield: 63%); m.p 201 °C. IR(KBr): 3420-3320 (NH_2), 3075 (CH-arom.), 3190 (NH), 1735 (C=O, ester), 1703, 1680, 1665 (3C=O) 1610 (C=N). ^{1}H-NMR (DMSO): 8.22 (S, 1H, NH), 7.71-7.18 (m, 4H, arom.), 6.21-5.91 (S, 2H, NH_2), 4.3 (q, 2H, CH_2CH_3) and 1.2 (t, 3H, CH_2CH_3). Anal. Cald. for $C_{17}H_{12}N_4O_5$ (352.30); C, 57.96; H, 3.43; N, 15.90. Found: C, 57.95; H, 3.41; N, 15.89.

1-amino-pyrimido[4',5':4,5] pyrimido[6,1-a] isoindole-6,8-dione (6): A solution of compound (3) (0.01 mol) in formamide (10 ml) was refluxed for 2 hrs. The reaction mixture after cooling was poured into cold water (40 ml) and the solid so-formed was collected by filtration and crystallized from (benzene-p.e (60-80 °C) as pale brown crystals (Yield: 70%); m.p (290 °C). IR(KBr): 334-3330 (NH_2), 3080 (CH-arom.), 1710, 1666 (2, C=O) and 1620 (C=N). ^{1}H-NMR (DMSO): 8.40 (S, 1H, CH-pyrimidine, 7.70-7.20 (m, 4H, arom.), 6.20-5.50 (S, 2H, NH_2). Anal. Calcd. for $C_{13}H_7N_5O_2$ (265.23): C, 58.87; H, 2.66; N, 26.41. Found: C, 58.85; H, 2.64; N, 26.40.

1-(benzylideneamino)pyrimido[4',5': 4,5]pyrimido[6,1-a]isoindole-6,8-dione (7): A mixture of compound (3) (0.01 mol) and benzaldehyde (0.01 mol) was dissolved in ethanol (20 ml) in the presence of a few drops of piperidine. The reaction mixture was refluxed fro 3 hrs. and left to cool. The solid product was filtered off and recrystalized from ethanol to give a white crystals (Yield: 61%); m.p 230 °C. IR(KBr): 3085 (CH-arom.), 1703, 1634 (2, C=O) 1615 (C=N). ^{1}H-NMR (DMSO): 8.30 (S, 1H, CH-pyrimidine), 8.10 (N=CH) and 7.90-7.20 (m, 9H, arm.). Anal. Calcd. for $C_{20}H_{11}N_5O_2$ (353.33); C, 67.99; H, 3.14; N, 19.30. Found: C, 67.95; H, 3.11; N, 19.31.

Ethyl(4-cyano-1,9-dioxo-1,9-dihydropyrimido[6,1-a] isoindol-3-yl)imidoformate (8): A mixture of compound (3) (0.01 mol), triethyl orthoformate (3 ml) and acetic anhydride (20 ml) was heated under reflux for 4 hrs. After cooling the reaction mixture was poured into water and the solid so-formed was collected by filtration and crystallized from ethanol as brown crystals, (Yield: 53%) ; m.p 130 °C. To a solution of compound (8) (0.01 mol) in absolute ethanol (20 ml) ammonium hydroxide solution (5 ml, 25%) was added under stirring at 0 °C for 30 min, then left at room temperature for 4 hrs. The solvent was removed under reduced pressure a (the residue was recrystallized from benzene + p.e (40-60 °C) to give the same compound (6) which identical in all spectral data and physical properties. IR(KBr): 3075 (CH-arom.), 2210 (CN), 1703, 1660 (2, C=O), 1620 (C=N). ^{1}H-NMR (DMSO): 8.10 (N=CH), 7.70-7.10 (m, 4H, arom.), 4.3 (q, 2H, OCH_2CH_3) and 1.25 (t, 3H, CH_3). Anal.Calcd. for $C_{15}H_{10}N_4O_3$ (294.26): C, 61.22; H, 3.43; N, 19.04. Found: C, 61.21; H, 3.42; N, 19.01.

2-Amino-1-imino-1,2-dehydropyrimido[4',5': 4,5] pyrimido [6,1-a] isoindol-6,8-dione (9): Hydrazine hydrate (80%) (2 ml) was added to a solution of compound (8) (0.01 mol) in dioxane (40 ml). The reaction mixture was stirred at room temperature for 1 hr. The precipitate which formed was filtered off, washed with water and recrystallized from dioxane as white crystals (Yield: 52%); m.p 170 °C. IR(KBr): 3320-3220 (NH_2), 3200 (NH), 1704, 1660 (2C=O), 1610 (C=N). ^{1}H-NMR (DMSO): 8.20 (S, 1H, NH), 7.80 (S, 1H, CH-Pyrimidine) 7.70, 7.20 (m, 2H, arom.), 5.20 (S, 2H, NH_2). Anal. Calcd. for $C_{13}H_8N_6O_2$ (280.24): C, 55.72; H, 2.88; N, 29.99. Found: C, 55.70; H, 2.86; N, 29.97.

[1,2,4]Triazolo[1'',5'':1',6;] pyrimido[4',5':4,5]pyrimido[6,1-a]isoindole-8, 10-dione (10): Compound (9) (0.01 mol) in an excess of triethyl orthofromate (5 ml) was refluxed for 2 hrs. After cooling the precipitated produced was collected by filtration and recystallized from dioxane as brown crystals (Yield: 52%); m.p > 300 °C. IR(KBr): 3075 (CH-arom.), 1703, 1660 (2C=O) and 1600 (C=N). ^{1}H-NMR (DMSO): 8.40 (S, 1H, CH-pyrimidine) 8.10 (S,

1H, CH-triazole) and 7.50-7.10 (m, 4H, arm.). Anal. Calcd. for $C_{14}H_6N_6O_2$ (290.24): C, 57.94; H, 2.08; N, 28.96. Found: C, 57.91; H, 2.07; N, 28.95.

1-chloro-[1,2,3] trizino[4'5':4,5] pyrimido[6,1-a]isoindole-6,8-dione (11): A solution of (0.01 mol) sodium nitrite in 10 ml of water was added to cold solution of compound (3) (0.01 mol) in acetic acid (30 ml) and concentrated hydrochloric acid (1.5 ml). After completion of the addition, the ice bath was removed and stirring continued for an additional 2 hrs. The crude product obtained was recrystallized from ethanol as orange crystals (Yield: 62%); m.p 250 °C. IR(KBr): 3080 (CH-arom.), 1703, 1634 (2C=O) and 1610 (C=N). ^{1}H-NMR (DMSO): 7.90-7.32 (m, 4H, arom.). Anal.Calcd. for $C_{12}H_4ClN_5O_2$ (285.65): C, 50.46; H, 1.41; N, 24.52. Found: C, 50.45; H, 1.39; N, 24.50.

1-hydrazino[1,2,3]-triazino[4',5':4,5]pyrimido[6,1-a]isoindole-6,8-dione (12): A mixture of compound (11) (0.01 mol) and hydrazine hydrate (3 ml) in ethanol (20 ml) was refluxed for 2 hrs. The precipitate that separated after cooling was recystallized from ethanol as yellow crystals (Yield: 61%); m.p. 280 °C. IR(KBr): 3320-3270 (NH_2), 3080 (CH-arom.), 3180 (NH), 1703, 1660 (2C=O) and 1610 (C=N). ^{1}H-NMR (DMSO): 8.00 (S, 1H, NH), 7.80-7.20 (m, 4H, arom.) and 5.00 (S, 2H, NH_2). Anal. Calcd. for $C_{12}H_7N_7O_2$ (281.23): C, 51.25; H, 2.51; N, 34.86. Found: C, 51.24; H, 2.49; N, 34.85.

3-amino-4-(4,5-dihydro-1H, imidazol-2-yl)pyrimido [6,1-a]isoindole-1,9-dione (15): To a suspension of compound (3) (0.01 mol), ethylenediamine (1.5 ml) and carbon disulfide (0.5 ml) were added drop wise. The reaction mixture was heated on a water both for 2 hrs. The precipitated solid was triturated with ethanol (10 ml), filtered off and recystallized from ethanol to give yellow crystals (Yield: 53%); m.p 200 °C. IR(KBr): 3340-3260 (NH_2), 3070 (CH-arom.), 3200 (NH), 1710, 1660 (2C=O) and 1600 (C=N). ^{1}H-NMR (DMSO): 8.10 (S, 1H, NH), 7.70-7.10 (m,4H, arom.), 5.60 (S, 2H, NH_2) and 4.00-3.50 (m, 4H, $2CH_2$-imidazole). Anal. Calcd. for $C_{14}H_{11}N_5O_2$ (281.27): C, 59.78; H, 3.94; N, 24.90. Found: C, 59.75, H, 3.92, N, 24.88.

5-Phenyl-2,3-dihydroimidazo[1'',2'':1':6']pyrimido [4',5':4,5]pyrimido[6,1-a] isoindole-8,10-dione (16): A mixture of compound (15) (0.01 mol.), benzoyl chloride (0.01 mol) and dry pyridine (15 ml) was heated under refluxed for 5 hrs. The reaction mixture was cooled, poured onto water, the solid formed was filtered off and from recrystallized ethanol as pale brown crystals (Yield: 54%); m.p 310 °C. IR(KBr): 3080 (CH-arom.), 1703, 1660 (2C=O), 1620 (C=N). ^{1}H-NMR (DMSO): 7.90-7.10 (m, 9H, arom.) and 4.00-3.40 (m, 4H, $2CH_2$-imidazole). Anal. Calcd. for $C_{21}H_{13}N_5O_2$ (367.35): C, 68.66, H, 3.57; N, 19.07. Found: C, 68.64, H, 3.54, N, 19.04.

2,3-dihydroimidazo[1'',2'':1',6']pyrimido[4',5':4,5] pyrimido[6,1-a] isoindole-8,10-dione (17): Compound (15) (0.01 mol) in triethyl orthoformate (10 ml) was heated under reflux for 3 hrs. The precipitated solid was collected and crystallized from ethanol as yellow crystals (Yield: 61%); m.p. 140 °C. IR(KBr): 3075 (CH-arom.), 1703, 1662 (2C=O), 1610 (C=N). ^{1}H-NMR (DMSO): 8.50 (S, 1H, CH-pyrimidine), 7.70-7.20 (m, 4H, arom.) and 4.00-3.40 (m, 4H, $2CH_2$-imidazole). Anal. Calcd. for $C_{15}H_9N_5O_2$ (291.26): C, 61.85, H, 3.11, 24.04: Found: C, 61.83, H, 3.09, N, 24.02.

2,5-dihydroimidazo[1'',2'': 1',6'] [1,2,3] triazino [4',5': 4,5] pyrimido [6,1-a] isoindole-8,10-dione (18): To a solution of compound (15) (0.01 mol) in concentrated hydrochloric acid (5 ml) and glacial acetic acid (10 ml), sodium nitrite (0.01 mol) dissolved in 5 ml water was added dropwise with constant stirring during 10 min. The mixture was stirring without heating for additional 1 hr. and then diluted with water. The precipitate was filtered off and recrystallized from dioxane as brown crystals (Yield: 62%); m.p 165 °C. IR(KBr): 3050 (CH-arom.), 1703, 1660 (2C=O) and 1610 (C=N). ^{1}H-NMR (DMSO): 7.80-7.20 (m, 4H, arom.) and 4.00-3.55 (m, 1H, m $2CH_2$-imidazole). Anal. Calcd. for $C_{14}H_8N_6O_2$ (292.25): C, 57.54; H, 2.76; N, 2.518.76. Found: C, 57.51; H, 2.75; N, 28.74.

5-thioxo-2,3,5,6-tetrahydroimidazo[1'',2'':1',6]pyrimido[4',5':4,5]pyrimido [6,1-a] isoindole-8,10-odione (19): A mixture of compound (15) (0.01 mol) and 15 ml carbon disulfide in (50 ml) dry pyridine was heated under reflux for 10 hrs. The reaction mixture after cooling was poured into cold water and the solid formed was isolated by filtration, washed with water, dried and crystallized from ethanol as light brown crystals (Yield: 52%); m.p 110 °C. IR(KBr): 3180 (NH), 3083 (CH-arom.), 1703, 1653 (2, C=O), 1610 (C=N) and 1247 (C=S) ^{1}H-NMR (DMSO): 8.10 (S, 1H, NH), 7.70-7.20 (m, 4H, arom.), and 4.00-3.50 (m, 4H, $2CH_2$-imidazole). Anal. Calcd. for $C_{15}H_9N_5O_2S$ (323.33): C, 55.72; H, 2.81; N, 21.66; S, 9.92. Found: C, 55.70; H, 2.79; S, 9.89.

Antimicrobial testing

Preliminary biological activity screening of the synthesized compounds has been performed at 50 μg/ml against microorganisms representing Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*)

***Table* 1.** The antimicrobial activity of some synthesized compounds

Sample		Inhibition zone diameter (mm/mg sample)			
		Esherichia coli (G^-)	Staphylococus aureus (G^+)	Aspergillus flavus (Fungus)	Candida albican (Fungus)
Control: DMSO		0.0	0.0	0.0	0.0
Standard	Tetracycline antibacterial agent	33	31	--	--
	Amphotericing B antifungal agent	--	--	17	19
5b		12	13	0.0	0.0
6		0.0	0.0	0.0	0.0
8		14	16	0.0	11
15		13	13	11	13

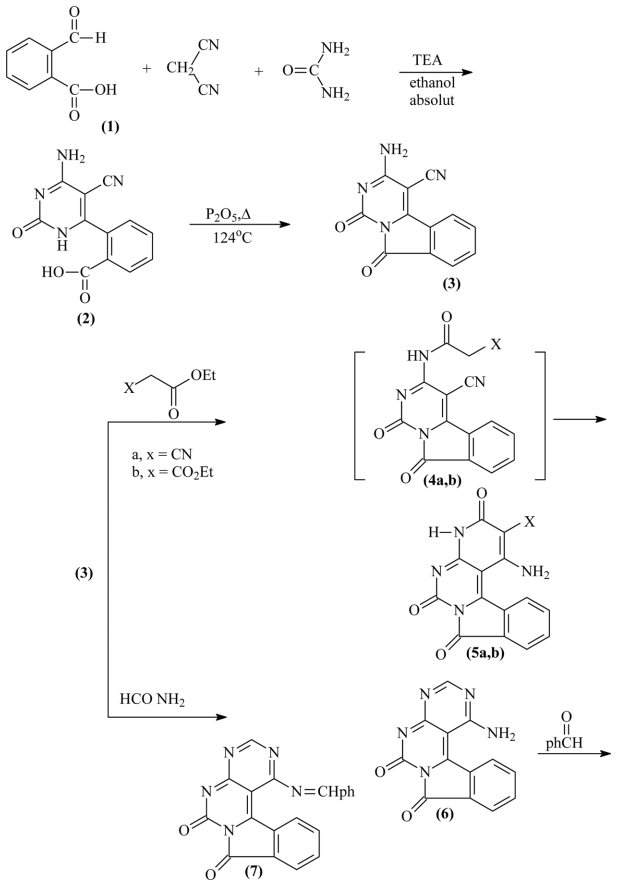
and fungi (*Candida albicans* and *Aspergillus flavus*), using the bioassay technique for antibiotics[7] specified in the US Pharmacopeia. From *Table* 1 it appears that imidazolyl pyrimidoisoindole 15 has significant antimicrobial activities. Among these compound 5b which has medium antimicrobial activities and compound 6 which completely inactive. Tetracycline and amphotericin B were used as antibacterial and antifungal reference drug, respectively.

RESULTS AND DISCUSSION

Chemistry

As a part of project directed toward the synthesis of condensed pyrimidine of suitable functionality for biological studies, the present paper describe the synthesis and biological activity of some new condensed pyrimidines. Thus, refluxing a ternary mixture of phthaladehydic acid, malononitrile and urea in the presence of triethylamine afforded aminocyanopyrimidine derivative (2). Intramolecular cyclodehydration of (2) was achieved by fusion with P_2O_5 producing isoindolpyrimidine derivative (3). Compound (3) appears of suitably located functionality for further heterocyclization. Thus pyridopyrimidine derivatives (5a,b) was prepared from the reaction of compound (3) and ester with activated methylene. The synthesetic strategy of compound (5a,b) depends upon the formation of the nonisolable acylated derivative (4a,b) which undergo intramolecular cycloaddition reaction via the addition of carbanion of activated methylene to cyano function affording final product (5a,b).

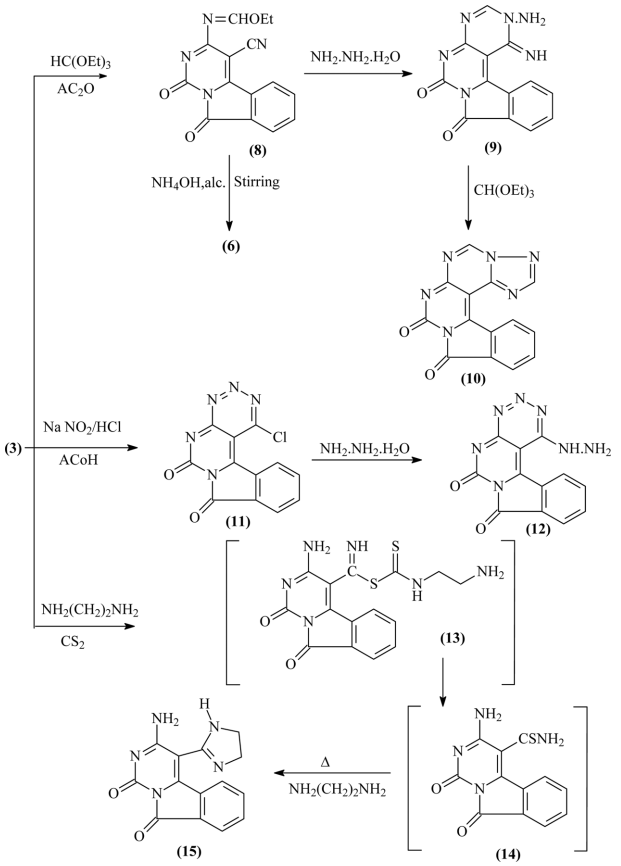
Also compound (3) was allowed to reacted with formamide to give the corresponding 1-aminopyrimido [4',5' : 4,5] pyrimido [6,1-a] isoindole-6,8-dione (6) which condensed with benzaldehyde to yield 1-(benzylideneamino) pyrimido [4',5' : 4,5] pyrimido [6,1-a] isoindole-6,8-dione (7) as Schiff's base *Scheme* 1.



***Scheme* 1.**

The condensation of compound (3) with triethyl orthoformate in refluxing acetic anhydride gave ethyl (4-cyano-1,9-dixo-1,9-dihydropyrimido [6,1-a] isoindol-3-yl) imidoformate (8). Treatment of compound (8) with nitrogen nucleophile resulted cyclization affording pyrimidopyrimidine derivatives (6).

Compound (8) was undergone further cyclization upon treatment with hydrazine hydrate affording 2-amino-1-imino-1,2-dihdyropyrimido [4',5':4,5] pyrimido [6,1-a] isoin-



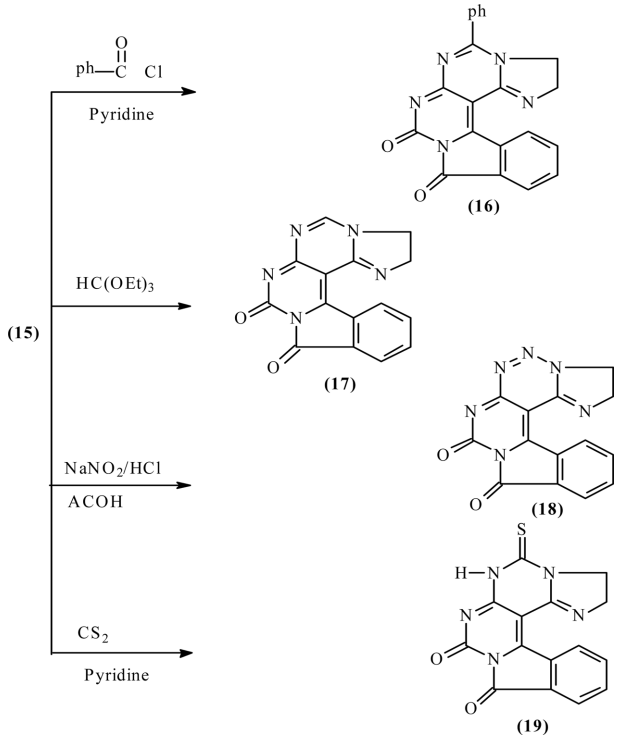
Scheme 2.

dole-6,8-dione (9) which reacted with triethy orthoformate giving [1,2,4] triazolo [1",5":1',6'] pyrimido [4',5':4,5] pyrimido [1, 6-a] isoindole-8, 10-dioen (10).

Diazotization of compound (3) with sodium nitrite and concentrated hydrochloric acid led to formation of 1-chloro [1,2,3] triazino [4',5':4,5] pyrimido [6,1-a] isoindole-6,8-dione (11) which in turn, was allowed to react with hydrazine hydrate to give 1-hydrazino [1,2,3] triazino [4',5': 4,5] pyrimido [6,1-a] isoindole-6,8-dione (12).

The reaction of compound (3) with 1,2-ethylenediamine in the presence of carbon disulfide was achieved by converting of nitrile group of compound into a dihydroimidazolyl residue giving 3-amino-4-(4,5-dihydro-1H-imidazol-2-yl) pyrimido [6,1-a] isoindole-1,9-dione (15), *Scheme* 2.

Finally treatment of compound (15) with benzoyl chloride, triethyl orthoformate, nitrous acid and/or carbon disulfide furnished the corresponding compounds (16-19) respectively *Scheme* 3. Analytical and spectral data of the newly synthesized compounds were in agreement with the proposed structures as shown.



Scheme 3.

Acknowledgement. The authors would like to thank Prof. Dr M. M. Assy for his support and useful discussions during the preparation of this paper.

REFERENCES

1. Stolc, S. *Life Sci*. **1999**, *65*, 1943.
2. Del Olma, E.; Garcia, M.; Lopez-Perez, J. L.; Munoz, V.; Deharo, E.; San Feliciano, A. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2123.
3. Del Olma, E.; Barboza, B.; Ybarra, M. I.; Lopez-Perez, J. L.; Carron, R.; Sevilla, M. A.; Boselli, C.; Samfeliciano, A. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2786
4. Wang, L. X.; Heredia, A.; Song, H.; Zhang, Z.; Yu, B.; Davis, C.; Redfield, R. J. *Pharm. Sci*. **2004**, *93*, 2448.
5. Lee, K.; Khan, R. N.; Rowe, I. C.; Ozanne, S. E.; Hall, A. C.; Papadakis, E.; Hales, C. N.; Ashford, M. L. *Mol. Pharmacol*. **1996**, *49*, 715.
6. Cliffe, I. A.; Lien, E. L.; Mansell, H. L.; Steiner, K. E.; Todd, R. S.; White, A. C.; Black, R. M. *J. Med. Chem.* **1992**, *35*, 1169.
7. Abou-Zeid, A. A.; Shehata, Y. M. *Indian J. Pharm*. **1969**, *31*, 72.
8. Shishoo, C. J.; Devani, M. B.; Ananthan, S.; Bhadti, V. S. *J. Heterocyclic Chem.* **1981**, *18*, 43.
9. Katritski, A. R.; Fu-Bao, J.; Fan, W.; Collas, J. K.; Greenhill, J. V.; King, R. W. *J. Org. Chem*. **1992**, *57*, 190.

10. Rashad, A. E.; Heikal, O. A.; El-Nezhawy, A. O. and Abdel-Megeid, F. M. E. *Heterocycl. Chem*. **2005**, *16*, 226.
11. El-Gazzar, A. B.; Hassan, N. A. *Molecules*. **2000**, *5*, 835-850.
12. Abdel Fattah, A. M.; Aly, A. S.; Gad, F. A.; Hassan, N. A.; El-Gassar, A. B. *Phosphorus sulfur*. **1998**, *141*, 263.
13. Khodairy, A.; Abdel-Ghany, H. *Phosphorus, sulfur silicon relat. Elem.* **2000**, *162*, 259.
14. Abdel-Ghany, H.; Khodairy, A. *Phosphorus, sulfur relat. Elem.* **2000**, *166,* 45.
15. El-Shafei, A. K.; El-Sagheir, A. M. M.; Ahmed, E. A. *Synthesis*. **1994**, 152.
16. Bakhite, E. A.; Radwan, S. M.; El-Saghier, A. M. M. *Indian J. Chem*. **1995**, *34B*, 97.
17. Al-Omran, F.; Abdel-Khalik, M. M.; Al-Awadhi, H.; Elnagdi, M. H. *Tetrahedron*. **1996**, *52*, 11915.
18. Nesmerak, K.; Pelouch, H.; Vstecha, V.; Nemec, I.; Gabriel, *J. Folia Microbial.* **1998**, *43*(1), 39.
19. Del Olmo, E.; Armas, M. G.; Ybarra, M. I.; Lopez, J. L.; Oporto, P.; Gimenez, A.; Dehara, E.; Feliciano, A. S. *Bioorg and Med. Chem. Lett*. **2003**, *13*, 2769.