

Synthesis and Antibacterial Activities of Novel Pyrimidines Derived from 2-Oxo (or Thioxo)-4-Phenyl-5-Carboethoxy-6-Methyl-1,2,3,4-Tetrahydropyrimidine

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The 2-oxo (or thioxo)-4-phenyl-5-carboethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine (**1a-c**) were prepared. Heating a mixture of (**1a-c**, X=S) in 1,2-dibromoethane or chloroacetylchloride gave the thiazolopyrimidines (**2a-c**) and (**3a-c**) respectively. Acetylation of (**1a-c**, X=S) with acetic anhydride and acetic acid yielded the products (**3a-c**). Alkylation of (**1a-c**, X=S) with alkyl halide in alkaline medium in 1:2 and 1:1 ratios gave only monoalkyl derivatives (**4a-c**). Additional proof for the site of substitution was obtained by alternative synthesis of product (**6a-c**) through methylation of (**5a-c**). Product (**1a**, X=O) on acylation and alkylation in (**1a-c**, X=S) conditions gave structures **7** and **8** respectively, and reaction with POCl₃ afforded 3-formyl-2-oxopyrimidine (**9**) in good yield. Some of these products were screened for antibacterial activity.

Key Words: Synthesis, Antibacterial, Activity, Pyrimidines.

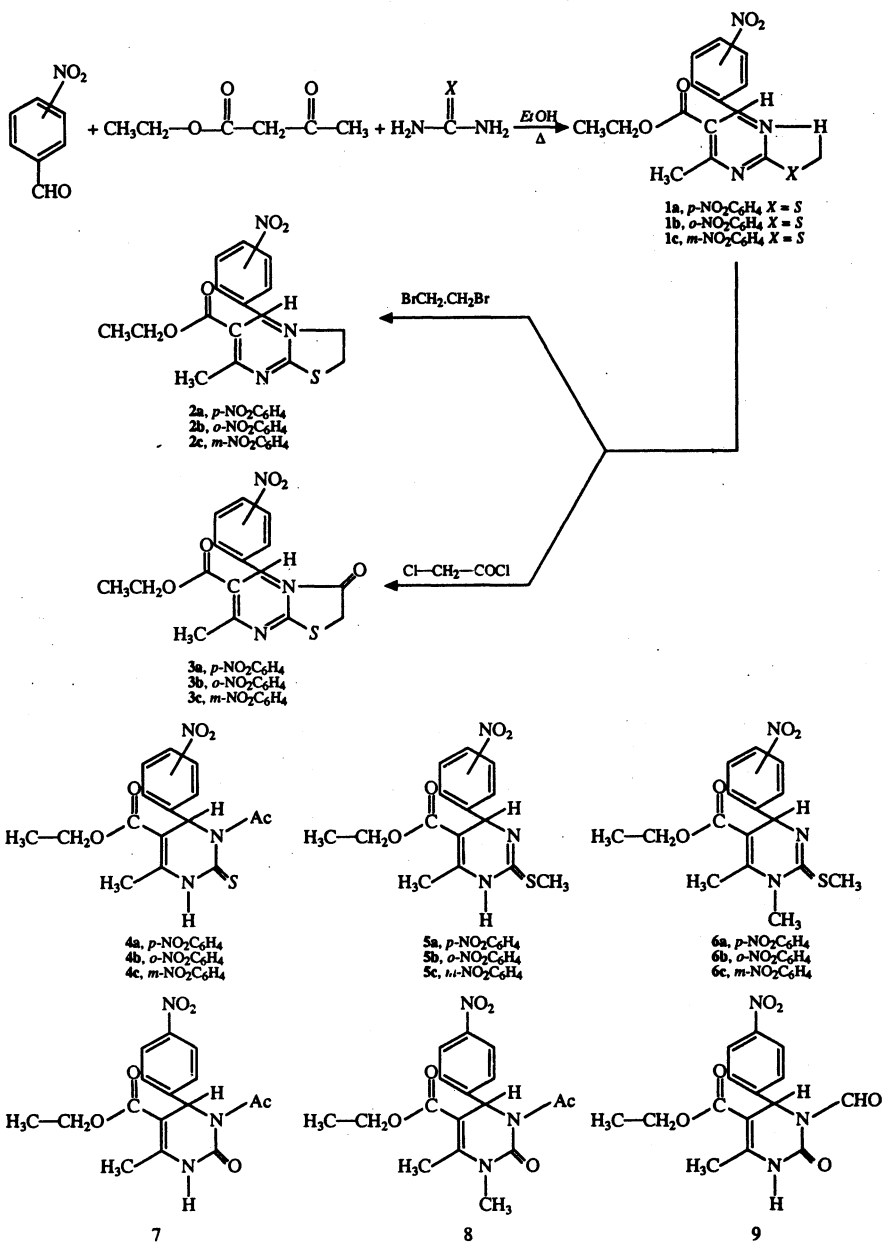
INTRODUCTION

Previous work in our research group has demonstrated that Biginelli reaction is a versatile and reliable synthesis of heterocyclic compounds^{1,2}. Pyrimidines have occupied a unique place and have remarkably contributed to biological and medicinal chemistry.

Various analogues of thiopyrimidines possess effective antibacterial, antifungal, antiviral, insecticidal and mitocidal activities^{3,4}.

EXPERIMENTAL

The versatile biological properties of thiopyrimidines prompted us to take up this project for synthesizing novel derivatives by introducing known biologically active substituents into the pyrimidine structure. Since nitro substituents in heterocyclic systems increase in anticipation to be very effective antimicrobial agents^{5,6}, for example, *p*-nitrobenzaldehyde (0.1 mole) with a mixture of β -ketoester (0.1 mol) and thiourea (0.14 mol) in some boiling ethanol to form structure (**1a**), which undergoes subsequent reactions to give thiazolopyrimidine (**2a**). Thus when (**1a-c**, X=S) were refluxed with 1,2-dibromoethane in DMF, products (**2a-c**) were obtained as a hydrobromide. Treatment with sodium



carbonate solution yielded the free base as oil. Reaction of (1a-c, X=S) with chloroacetylchloride and acetic acid under reflux afforded the product 3a.

The reaction of acetic anhydrides on (1a-c, X=S) led to the corresponding 3-acetyl derivatives (4a-c, X=S). The reaction of (1a-c) with methyl iodide in methanol under reflux gave the 5-methylated compound (5a-c) in excellent yield.

TABLE-1
SOME OF THE SPECTROSCOPIC DATA OF PRODUCTS

Cmpd.	¹ H-NMR (ppm)	¹³ C-NMR (ppm)	IR (cm ⁻¹)	MS	Elemental analysis (%) found (Calcd.)
1a	1.1 (t, 3H, CH ₃),	14.0 (CH ₃),	3250-3150 ν(NH),	M ⁺ • (321)	C 52.33 (52.27) H 4.68 (4.53) N 13.08 (13.47)
	2.3 (s, 3H, CH ₃),	17.0 (CH ₃),	3100-2900		
	4.0 (q, 2H, CH ₂),	52.0 (CH),	(CH aliphatic and		
	5.9 (d, 1H, H-4),	59.0 (CH ₂),	aromatic),		
	7.6-8.2 (m, 4H, aromatic protons),	100.0, 128.0, 129.0, 129.5, 132.0, 141.0,	1720 ν(C=O), 1345, 1530		
	9.7 (s, 1H, NH), 10.5 (s, 1H, NH)	145.0, 164.0, (aromatic and olefin), 174.0 (C=S), 184.0 (C=O)	ν(N=O), 1190- 1274 ν(C-O) ester		
1b	0.9 (t, 3H, CH ₃),	14.0 (CH ₃),	3235-3140 ν(NH),	M ⁺ • (321)	C 52.33 (52.31) H 4.68 (4.61) N 13.08 (13.51)
	2.2 (s, 3H, CH ₃),	17.0 (CH ₃),	3110-2950 (CH		
	3.8 (q, 2H, CH ₂),	49.0 (CH),	aliphatic and		
	5.9 (d, 1H, H-4),	60.0 (CH ₂),	aromatic),		
	7.4-7.9 (aromatic protons),	100.0, 124.0, 129.0, 130.0, 134.0, 136.0,	1705 ν(C=O), 1340, 1525		
	9.4 (s, 1H, NH), 10.3 (s, 1H, NH)	146.0, 147.0, (aromatic and olefin), 165.5 (C=S), 174.0 (C=O)	ν(N=O), 1190-1270 ν(C-O) ester		
1c	1.1 (t, 3H, CH ₃),	14.0 (CH ₃), 1	3250-3150 ν(NH),	M ⁺ • (321)	C 52.33 (55.08) H 4.68 (4.91) N 13.08 (13.77)
	2.3 (s, 3H, CH ₃),	7.0 (CH ₃), 53.0	3100-2900		
	4.0 (q, 2H, CH ₂),	(CH),	(CH aliphatic and		
	5.3 (d, 1H, H-4),	60.0 (CH ₂),	aromatic),		
	7.65-8.2 (m, 4H, aromatic protons),	100.0, 121.0, 122.0, 130.0, 133.0, 145.0,	1710 ν(C=O), 1345, 1530		
	9.7 (s, 1H, NH), 10.5 (s, 1H, NH)	146.0, 148.0, (aromatic and olefin), 165.0 (C=S), 175.0 (C=O)	ν(N=O), 1190-1274 ν(C-O) ester		

RESULTS AND DISCUSSION

The signal due to acetylation in (4a-c) was determined from the $^1\text{H-NMR}$ spectrum. The signal for the C-4 proton collapsed from a doublet in (1a, X=S) to singlet in (4a, X=S) due to the anisotropic effect of the carbonyl group at (4a, X=S) (Table-1).

Additional proof for the site of substitution was obtained by alternative synthesis of product (6a-c) through methylation of (5a-c). The reaction of acetic anhydride on (1a, X=O) led to the corresponding 3-acetyl derivative (7) and not to acetyl derivatives as previously assumed^{1,2}. This was confirmed not only by spectroscopic data (singlet for the C-4 proton for 7), but also by derivation. Thus, when (7) was refluxed with trimethylphosphate in the presence of potassium carbonate the 1-methyl-3-acetyltetrahydropyrimidine (8) was obtained. From the above acylation reactions it is quite obvious that the N-3 nitrogen in compounds (1a-c) and N-3 is more reactive towards electrophiles than the N-1 nitrogen which is part of a push-pull system with the ester group in 5-position of the pyrimidine ring. By heating (1a, X=O) with POCl_3 in DMF at 70°C , 3-formyl-2-oxypyrimidine (9) was obtained in good yield. The microanalysis and spectroscopic data for all products confirmed their structures and some of those summarized in Table-1.

The biological effect (Antibacterial activity): The product was screened for antibacterial activity by both dilutions in basic culture (Muller-Hinton broth)⁷. Microorganisms employed were *Staphylococcus aureus* and *Escherichia coli* using DMSO as a solvent at a concentration of $256\ \mu\text{g/mL}$ ⁸. The research shows that these compounds have some influence on the positive gram bacteria and they can stop the growth of this group of bacteria (Table-2).

TABLE-2
ANTIMICROBIAL ACTIVITY OF PRODUCTS

Inhibition zone of compounds	<i>Escherichia coli</i> ($\mu\text{g/mL}$)		<i>Staphylococcus</i>
	X=O	X=S	
1a	18	28	—
1b	17	24	—
1c	16	22	—
1d	12	18	—
3a	4	12	—
3b	2	9	—
3c	0.5	6	—

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