Synthesis of Certain Heteroaryl-fused 1,3,5-triazine Ring Systems As Potential Antimicrobial Agents

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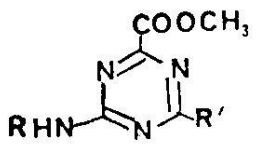
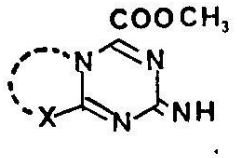
Summary: 2-Imino-4-carbomethoxy-s-triazino[2,1-b]benzothiazoles, benzoxazoles, and thiazoles (VI), and XIII were synthesized in combination with their 4-carboxylic acid derivatives (VII) & (XIV), via the cyclization reaction of their corresponding 2-guanidine salts with diethyl oxalate. Reaction of 4-carbomethoxy-s-triazines with hydrazine hydrate gave the corresponding hydrazides (VIII), from which hydrazones (IX) were prepared. Cyclization of 2-guanidine heterocyclic salts with ethyl chloroacetate afforded 2-imino-4-chloromethyl-s-triazines (V & XII) in fair yields. Some of the synthesized compounds were studied through their ir, nmr spectra.

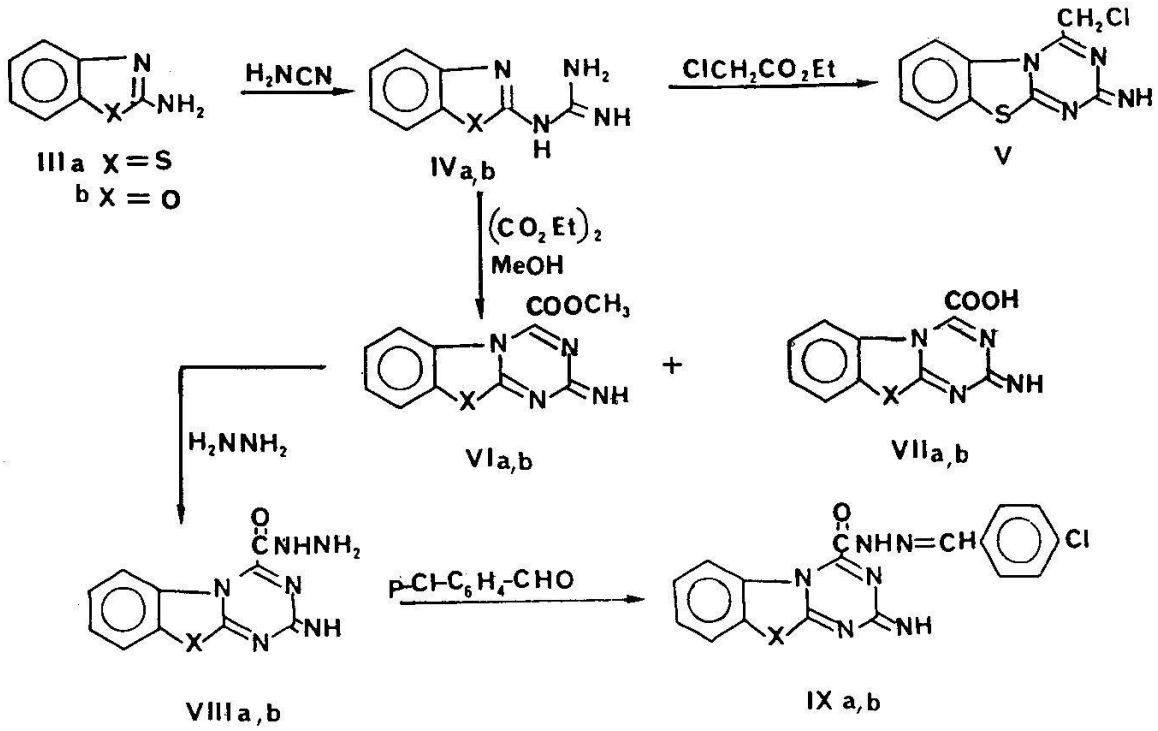
Substituted monocyclic s-triazines (1) are reported to possess a variety of biological activities such as virostatic [1], tumor inhibitors [2], antimicrobial and antiviral [3], and muscle relaxant [4] activities. These observations prompted us to undertake the synthesis of several new 2-imino-4-substituted-s-triazines fused with biologically active heterocyclic moieties (II). Specifically, we undertook the synthesis of several derivatives of 2-imino-4-substituted-s-triazino[2,1-b]benzoxazole (of which one example is known [3]), and of the new ring system 2-imino-4-substituted-s-triazino[2,1-b]benzothiazole and thiazoles.

The synthesis of the designed compounds were accompalished by application of the method established for the synthesis of monocyclic s-triazines (1) via the cyclization of the appropriately substituted biguanides [5-7]. Consequently, when 2-guanidino-heterocyclic salts (IV & XI) reacted with diethyl oxalate in absolute methanol and in the presence of sodium methylate, underwent cyclization to afford 2-imino-s-triazino[2,1-b] benzothiazole, benzoxazol, and thiazoles-4-carboxylic acids (VII & XIV) in combination with their methyl esters (VI & XII). The reaction mechanism is considered as an N-Mannich base type in which aminomethinylation

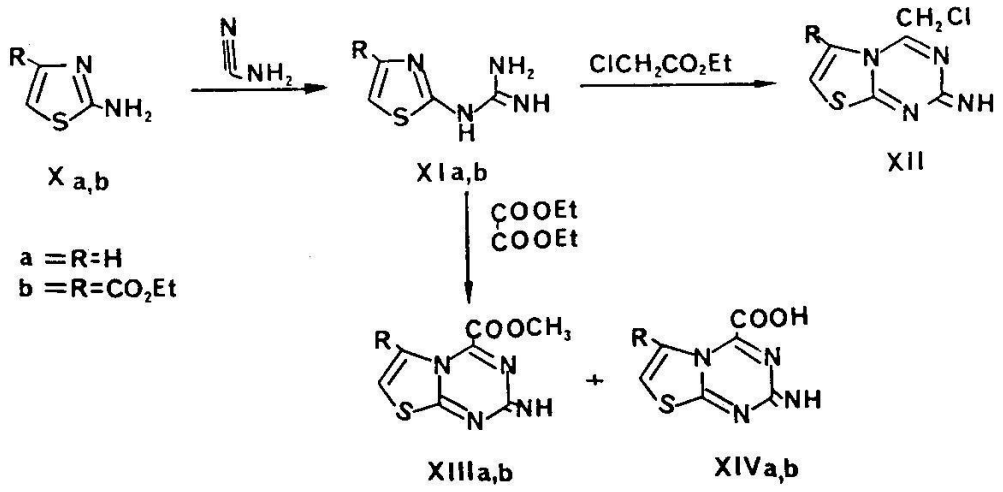




II X=O, S



Scheme 1



Scheme 2

Table-1: Physical and analaytical data of 2-Guanidine heterocyclic Salts.

Comp. No.	R	X	M.P. °C	Yield %	Molecular Formula		Analysis C	H	N
IVa	-	S	128-30[a]	65	$C_8H_8N_4S.HNO_3$	Calcd.	37.64	3.33	27.30
						Fd.	37.58	3.58	27.43
IVb	-	O	230[a]	70	$C_8H_8N_4O.HNO_3$	Calcd.	40.12	3.76	29.28
						Fd.	40.33	3.00	29.40
XIa	H	S	250[a]	41	$C_4H_6N_4S.HCl$	Calcd.	28.89	3.92	31.37
						Fd.	28.55	3.71	31.44
XIb	CO_2Et	S	170-2[a]	46	$C_7H_{10}N_4O_2S.HCl$	Calcd.	33.53	4.39	22.35
						Fd.	33.55	4.43	22.29

a = Crystallization from methanol/water.

process is passed first followed by ring closure [8]. Where the cyclization of the 2-guanidino-heterocyclic salts using ethyl chloroacetate in basic medium affords in an electrophilic attack which is followed by ring closure the corresponding 2-imino-4-chloromethyl-s-triazines (V & XII) in fair yields, (Scheme 1 & 2, Table 2). The 2-guanidino-heterocyclic salts (IV & XI) starting materials were prepared by heating equimolar amounts of 2-aminoheterocycle (III & X) and cyanamide in ethanolic hydrochloric acid. The obtained guanidine hydrochloride salts were converted into their stable nitrate salts, (see experimental).

2-Imino-4-carbomethoxy-s-triazines (V & XII) were subjected to react with hydrazine hydrate in boiling ethanol to give the corresponding 2-imino-s-triazine-4-carboxylic acid hydrazides (VIII) in good yields. The hydrazides were reacted with p-chlorobenzaldehyde to afford their hydrazones (IX) in fair yields.

The IR., ^{1}H-NMR and elemental analysis of the synthesized compounds were consistant with the assigned structures.

Experimental

^{1}H-NMR spectra were determined with Hitachi R-22 spectrometer (90 MHz), with TMS as internal standard. IR spectra were recorded with a Hitachi EP-G2 spectrometer.

2-Guanidino-benzothiazole nitrate (IIIa):

A solution of 2-aminobenzothiazole (0.02 moles) in ethanol (20 ml) was added to a solution of cyanamide (0.02 moles) and hydrochloric acid (10 mg) and the mixture was refluxed for 2 hrs. The insoluble product was collected by filtration and air dried. The hydrochloride salt was dissolved in the least amount of hot water and treated while hot with ammonium nitrate (0.04 moles) to yield IIIa, Table 1.

2-Guanidino-benzoxazole nitrate (IIIb):

A solution of 2-aminophenol (0.02 moles) in ethanol (20 ml), was added to a solution of dicyandiamide (0.02 moles) in ethanol (20 ml) containing concentrated hydrochloric acid (10 gm), and the mixture was refluxed

Table-2: 2-Imino-4-substituted-s-triazino[2,1-b]heterocycles.

Comp. No.	R	R	X	M.P. C°	Yield %	Molecular Formula		Analysis % C	H	N
V	CH_2Cl	-	S	122[a]	30	$C_{10}H_7ClN_4S$	Calcd.	47.90	2.79	22.35
							Fd.	47.70	2.55	22.00
VIa	$COOCH_3$	-	S	190-193[a]	50	$C_{11}H_8N_4O_2S$	Calcd.	50.76	3.07	21.53
							Fd.	50.40	3.15	21.39
VIb	$COOCH_3$	-	O	188-190[a]	70	$C_{11}H_8N_4O_5$	Calcd.	54.10	3.28	19.67
							Fd.	54.22	3.33	19.70
VIIa	COOH	-	S	235[a]	25	$C_{10}H_6N_4O_2S$	Calcd.	48.78	2.44	22.76
							Fd.	48.43	2.33	22.52
VIIb	COOH	-	O	230[b]	15	$C_{10}H_6N_4O_3$	Calcd.	52.17	2.61	24.34
							Fd.	52.39	2.64	24.44
VIIIa	$CONHNH_2$	-	S	120-122[b]	80	$C_{10}H_8N_6OS$	Calcd.	46.15	3.08	32.31
							Fd.	46.25	3.64	32.52
VIIIb	$CONHNH_2$	-	O	170-171[b]	70	$C_{10}H_8N_6O_2$	Calcd.	49.18	3.28	34.42
							Fd.	49.19	3.42	34.56
IXa	$CONHN{=}CHC_6H_4$ -(p-Cl)	-	S	250-253[b]	60	$C_{17}H_{11}ClN_6OS$	Calcd.	53.33	2.87	21.96
							Fd.	53.31	2.77	21.81
IXb	$CONHN{=}CHC_6H4$ -(p-Cl)	-	O	231-233[b]	50	$C_{17}H_{11}ClN_6O_2$	Calcd.	55.66	3.01	22.92
							Fd.	55.61	3.00	22.66
XII	CH_2Cl	COOET	S	155[b]	40	$C_9H_9ClN_4O_2S$	Calcd.	39.63	3.30	20.55
							Fd.	39.50	3.80	20.40
XIIIa	$COOCH_3$	H	S	190[a]	40	$C_7H_6N_4O_2S$	Calcd.	40.00	2.86	26.66
							Fd.	40.12	2.58	26.65
XIIIb	$COOCH_3$	COOET	S	230[a]	55	$C_{10}H_{10}N_4O_4S$	Calcd.	42.55	3.55	19.86
							Fd.	42.43	3.67	19.71
XIVa	COOH	H	S	255[b]	20	$C_6H_4N_4O_2S$	Calcd.	36.73	2.04	28.33
							Fd.	36.57	2.01	28.33
XIVb	COOH	COOET	S	240[a]	10	$C_9H_8N_4O_4S$	Calcd.	40.29	2.98	20.89
							Fd.	40.99	2.99	20.81

a = Crystallization from methanol/water.
b = Crystallization from acetic acid/water.

gently for 2 hrs. After cooling, the separated hydrochloride salt [3] was converted into the nitrate salt as described for IIIa.

^{1}H-NMR (DMSO-d): δ 6.20-6.80 (m, 4H, aromatic protons), 8.50 (m, 5H, H of the protonated guanidine side chain, which disappeared by addition of D_2O).

Compounds Xa and Xb were obtained similarly as described under the preparation of IIIa.

2-Imino-s-triazino[2,1-b]benzothiazoles (VIa & VIIa):

This procedure fcr the synthesis of (VIa & VIIa) was given as a general method for the synthesis of VIb,

XIIIa,b, and XIVa,b. To a solution of sodium methylate (0.01 moles) in methanol (30 ml), the guanidine salt (0.01 mole) was added and the mixture was stirred for 5 min. at room temperature. Diethyl oxalate (0.01 mole) was added and stirring was continued for another 10 min. then setaside in dark for 2 hrs. The separated crystals were removed by filtration to give (VIIa) Table 2. IR (KBr) cm^{-1}: 3100, 1645, 1550, 1510, and 1310. The filtrate was evaporated in vacuo, and the residue was treated with cold water and the insoluble ester (VIa) was collected and air dried (Table 2).

2-Imino-2-chloromethyl-s-triazino [2,1-b]benzothiazole (V):

The guanidine benzothiazole (IVa), was added to a solution of absolute methanol containing sodium methylate (0.01 mole), and the mixture was colled to 10°C in ice-bath. Ethyl chloroacetate (0.01 mole) was added dropwise with stirring (about 15 min.), then the reaction mixture was left overnight. The solvent was removed in vacuo and the residue was triturated with small portion of water and the solid given was collected by filtration and air dried.

2-Imino-s-triazino[2,1-b]benzothiazole-4-carbohydrazide (VIIIa):

Hydrazine hydrate (0.02 mole) was added to a solution of methyl ester s-triazine (VIa) (0.01 mole) in ethanol (25 ml) and the mixture was refluxed for 1 hr. The solvent was evaporated in vacuo and the oily residue was solidified on addition of small amount of cold water. The solid was filtered off, air dried, and then recrystallized from acetic acid-water. IR (KBr) cm^{-1}: 3300, 3070, 1570 and 1500. Similarly, compound (VIIIb) was prepared.

2-Imino-s-triazino[2,1-b]benzothiazole-4-p-(chlorobenzylidene)-carbohydrazide (IX):

To a solution of compound (VIIIa) (0.01 mole) in ethanol (25 ml) p-chlorobenzaldhyde (0.01 mole) was added and the mixture was refluxed for 2 hrs. The solvent was evaporated in vacuo, and the solid residue was treated with cold water and collected by filtration, washed with water and air dried to give (IXa). ^{1}H-NMR of compound (IV)(DMSO-d_6): δ 11.28-10.75 (m, 2H,=NH and -CONH), 8.10 (s, 1H, -N=CH-), 6.70-6.00 (m, 8H, aromatic protons) ppm.

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