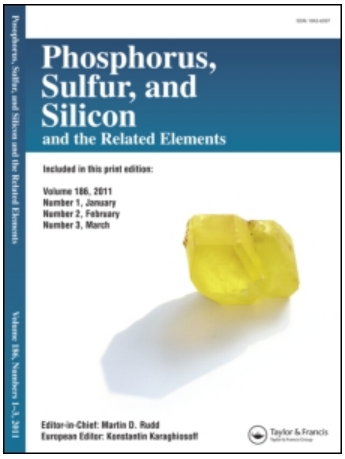

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SOME REACTIONS WITH 6-BENZOYL-3-AMINO-2-IMINO-2,3-DIHYDROTHIAZOLO[4,5-b]QUINOXALINE: SYNTHESIS OF (1,2,4) TRIAZOLO[3',2':2,3]THIAZOLO[4,5-b] QUINOXALINE AND (1,3,4)THIADIAZINO [5,6-b]QUINOXALINE DERIVATIVES

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SOME REACTIONS WITH 6-BENZOYL-3-AMINO-2-IMINO-2,3-DIHYDROTHIAZOLO[4,5-b]QUINOXALINE: SYNTHESIS OF (1,2,4) TRIAZOLO[3′,2′:2,3]THIAZOLO[4,5-b] QUINOXALINE AND (1,3,4)THIADIAZINO [5,6-b]QUINOXALINE DERIVATIVES

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Condensation of 6-benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-b]quinoxaline **(IV)** with aldehydes, formic acid and acetyl chloride yielded the corresponding Schiff bases **(VI)**, N-formyl **(VIII)** and triacetyl **(IX)** derivatives, respectively. While, interaction of **(IV)** with benzoyl chloride and ethyl cyanoacetate produced the (1,2,4) triazolo[3′,2′:3,2] thiazolo[4,5-b]quinoxaline derivatives **(X)** and **(XI)**, respectively. Also, interaction of **(IV)** with carbon disulphide caused ring expansion to give (1,3,4) thiadiazino[5,6-b]quinoxaline **(XII)** and **(XV)** was also prepared in one pot reaction on condensation of 6-benzoyl-2,3-dichloroquinoxaline with thiocarbohydrazide.

Keywords: Thiazoloquinoxaline; triazolothiazoloquinoxaline and thiadiazinoquinoxaline

INTRODUCTION

Quinoxaline derivatives have been found to exhibit interesting biological activities[1]. Some of these activities include antimicrobial[2], fungicidal[3], herbicidal[4], anticancer[5], antiinflammatory[6], tranquillizing[7] and antide-

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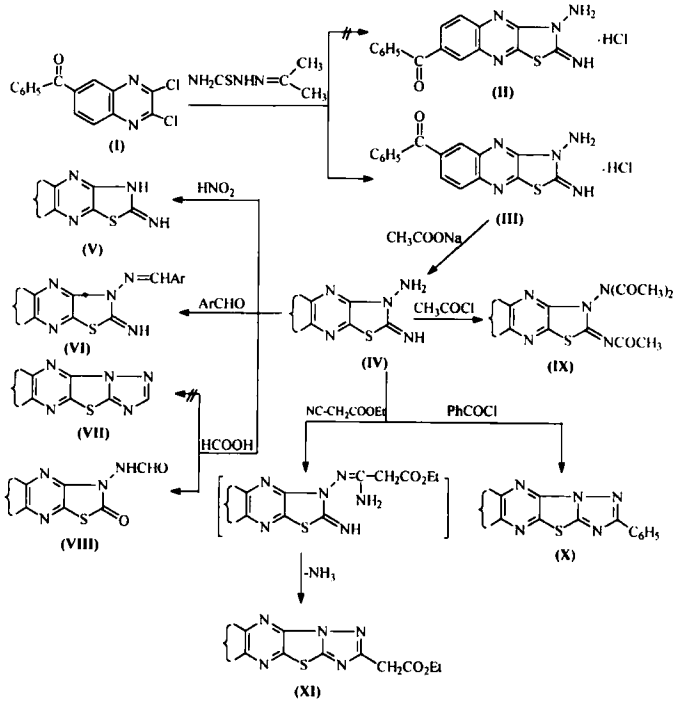
pressant properties[8]. With this in mind and in continuation of our previous work[9–12] for the synthesis of heterocyclic system containing quinoxaline moiety, we report herein the synthesis of thiazolo[4,5-b]quinoxaline, triazolo[3′,2′:2,3]thiazolo[4,5-b] quinoxaline and thiadiazino [5,6-b] quinoxaline derivatives.

RESULTS AND DISCUSSION

6-Benzoyl-2,3-dichloroquinoxaline (I) was synthesized in good yield by oxalylation of 4-benzoyl-1,2-phenylenediamine followed by chlorination of the formed 6-benzoyl-2,3-dihydroxyquinoxaline using thionyl chloride[13]. 6-Benzoyl-2,3-dichlroquinoxaline was reacted with acetone-thiosemicarbazone as a binucleophile in ethanol furnishing a product with analytical and spectral data in agreement with 3-amino-2-imino-2,3-dihydro-thiazolo[4,5-b]quinoxaline hydrochloride **(III)**. Two isomers are possible for the product either 6-benzoyl or 7-benzoyl thiazoloquinoxaline **(II)** and **(III)**, respectively. According to the effect of benzoyl group the authors favour isomer **(III)**. The 2-position is presumed to be preferentially substituted from the consideration of the (-R) effect of the benzoyl group in structure **(I)** which is the factor responsible for the formation of **(III)**. This mean that, the 2-carbon will be more susceptible to nucleophilic attack and the reaction proceed according to nucleophilic substitution through addition elimination mechanism. The free base **(IV)** was released from **(III)** through its decomposition with sodium acetate solution. Interaction of **(IV)** with nitrous acid caused deamination to give 6-benzoyl-2-imino-2,3-dihydrathiazolo[4,5-b]quinoxaline **(V)**. The IR spectrum of **(V)** showed the absence of ν_{NH2} and the presence of ν_{NH} at 3140 and $\nu_{C=O}$ at 1650 cm^{-1}. Condensation of **(IV)** with aromatic aldehydes produced the Schiff's bases **(VI)**. The chemical reactivity of **(IV)** towards some carboxylic acid derivatives was investigated. Thus, treatment of **(IV)** with formic acid under reflux conditions, in the hope of obtaining the triazolo derivative **(VII)** was unsuccessful. Instead, formylation with hydrolysis of the imino group took place without cyclization to yield the N-formyl derivative **(VIII)**. Also, when compound **(IV)** was treated with either acetic anhydride or acetyl chloride, acetylation took place to give the triacetyl derivative **(IX)**. The IR spectrum of **(IX)** revealed the complete disappear-

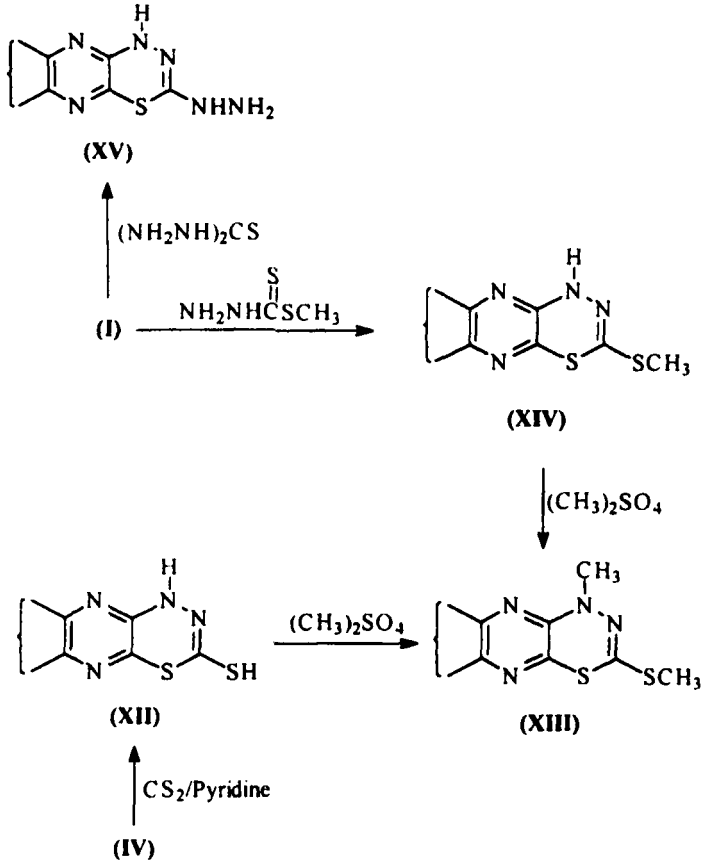
ance of ν_{NH2+NH} band which was present in the parent compound and the presence of $\nu_{C=O}$ at 1780, and 1690 cm^{-1}. On the other hand, cyclization of **(IV)** was accomplished upon its treatment with benzoyl chloride to furnish (1,2,4) triazolo[3′,2′:2,3]thiazolo[4,5-b]quinoxaline derivative **(X)**. Furthermore, cyclization of **(IV)** was achieved upon its treatment with ethyl cyanoacetate in DMF/TEA to yield the (1,2,4) triazolo[3′,2′:3,2]thiazolo[4,5-b]quinoxaline derivative **(XI)**. The formation of **(XI)** was proceeding via the addition of amino goup to cyano group followed by elimination of ammonia (scheme 1).



SCHEME 1

The authors planned to prepare some quinoxaline derivatives containing thiadiazine moiety, in order to evaluate the antibacterial activity (under investigation). Thus, refluxing of **(IV)** with CS_2 in pyridine, 7-benzoyl-2-mercapto-1,3,4-thiadiazino[5,6-b]quinoxaline **(XII)** was obtained.

The structure was confirmed by elemental analyses and analogy with previous work[10]. Methylation of **(XII)** with dimethyl sulphate in the presence of sodium hydroxide furnished 7-benzoyl-4-methyl-2-thiomethyl (1,3,4)thiadiazino[5,6-b]quinoxaline **(XIII)**. Condensation of **(I)** with methyl dithiocarbazate gave a single product with analytical and spectral data in agreement with 7-benzoyl-2-thiomethyl (1,2,4) thiadiazino [5,6-b] quinoxaline **(XIV)**. Alkylation of **(XIV)** with dimethyl sulphate gave **(XIII**; m.p. and m.m.p). In addition, interaction of **(I)** with thiocarbohydrazide gave the corresponding (1,2,4) thiadiazino[5,6-b]quinoxaline derivative **(XV)** (Scheme 2).



SCHEME 2

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried out by the Microanalytical unit, Faculty of Science, Cairo University. The IR spectra were performed on a Schimadzu IR 440 spectrophotometer using KBr pellet. ^{1}H-NMR spectra were recorded out on a Jeol FX, 90Q (90 MHz) spectrophotometer using TMS as an internal standard at Faculty of Pharmacy, Cairo University. The mass spectra were performed by Schimadzu-GC-MS-QP 100 EX using the direct inlet system, Cairo University.

6-Benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-b]quinoxaline hydrochloride (III)

A mixture of (**I**; 0.01 mol) and acetone thiosemicarbazone (0.01 mol) in ethanol/DMF (1:1; 50 ml) was refluxed for 1 h. The obtained solid was recrystallized from the appropriate solvent to give (**III**), (Table I).

TABLE I Physical data for the prepared compounds

Compd. No.	*M.P. (°C)*	*Yield (%)*	*Solvent Cryst.*	*Mol. Formula (Mol. wt.)*	*Analyses*			
					Required/Found %			
					C	*H*	*N*	*S*
III	>300	90	DMF	$C_{16}H_{12}ClN_5OS$	53.71	3.36	19.58	8.95
				(357.5)	53.70	3.30	19.40	9.00
IV	238	85	DMF/H_2O	$C_{16}H_{11}N_5OS$	59.81	3.43	21.81	9.97
				(321)	59.80	3.50	21.90	10.00
V	220	60	Ethanol	$C_{16}H_{10}N_4OS$	62.75	3.27	18.30	10.46
				(306)	62.80	3.10	18.40	10.50
VIa	234	67	Ethanol	$C_{23}H_{15}N_5OS$	67.48	3.67	17.12	7.82
				(409)	67.50	3.70	17.10	7.90
VIb	225	75	Ethanol	$C_{24}H_{17}N_5O_2S$	65.60	3.87	15.94	7.29
				(439)	65.70	3.90	16.00	7.10
VIc	165	66	Ethanol	$C_{26}H_{21}N_5O_4S$	62.53	4.21	14.03	6.41
				(499)	62.50	4.10	14.00	6.30
VId	210	72	Ethanol	$C_{23}H_{15}N_5O_2S$	64.94	3.53	16.47	7.53
				(425)	65.00	3.60	16.50	7.60

Compd. No.	*M.P. (°C)*	*Yield (%)*	*Solvent Cryst.*	*Mol. Formula (Mol. wt.)*	*Analyses*			
					Required/Found %			
					C	*H*	*N*	*S*
VIII	147	60	Ethanol	$C_{17}H_{10}N_4O_3S$	58.29	2.86	16.00	9.14
				(350)	58.10	2.80	16.10	9.00
IX	224	63	Acetic	$C_{22}H_{17}N_5O_4S$	59.06	3.83	15.66	7.16
			acid	(447)	59.00	3.90	15.70	7.00
×	>300	67	Ethanol/	$C_{23}H_{13}N_3OS$	67.81	3.19	17.10	7.86
			DMF	(407)	67.90	3.00	17.20	7.90
XI	182	73	Ethanol	$C_{21}H_{15}N_5O_3S$	60.43	3.60	16.79	7.76
				(417)	60.50	3.70	16.80	7.00
XII	>300	80	DMF	$C_{16}H_{10}N_4OS_2$	56.81	2.96	16.57	18.94
				(338)	56.90	3.00	16.70	18.80
XIII	140	69	Ethanol	$C_{18}H_{14}N_4OS_2$	59.02	3.83	15.30	17.49
				(366)	59.00	3.90	15.40	17.50
XIV	251	70	Ethanol	$C_{17}H_{12}N_4OS_2$	57.96	3.41	15.91	18.18
				(352)	57.90	3.50	16.00	18.20
XV	>300	80	DMF	$C_{16}H_{12}N_6OS$	57.14	3.57	25.29	9.52
				(336)	57.20	3.60	25.30	9.60

6-Benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-b]quinoxaline (IV)

The hydrochloride salt (**III**; 0.01 mol) was treated with aqueous sodium acetate (10%, 50 ml) at 50°C for 1h. The obtained solid was crystallized from proper solvent to give (**IV**); Table (I). IR ν_{max}/cm^{-1}, 3400, 3240 (NH_2 & NH), 1667(C=N). Mass spectrum of **IV**: 321 (M^+; 53.4%), 305 (5.7%), 294 (26.9%), 277 (2.2%), 244 (4.9%), 229 (70%), 201 (16.6%), 174 (2.2%), 145 (9.21%), 105 (100%) and 77 (22.6%).

6-Benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-b]quinoxaline (V)

$NaNO_2$ solution (5%; 50 ml) was added dropwise to a solution of (**IV**; 0.01 mol) in conc. HCl (20 ml) at 0 °C with stirring during 2 h. The reaction mixture was left to stand at room temperature for another 2 h., then added to crushed ice. The obtained solid was recrystallized from appropri-

ate solvent to give (**V**), Table (I). IR ν_{max}/cm^{-1} showed the absence of ν_{NH2} and the presence of ν_{NH} at 3140 and $\nu_{C=O}$ 1650.

The Schiff's bases (VI) a – d

To a solution of (**IV**; 0.01 mol) in DMF (20 ml), the aromatic aldehydes (0.01 mol) were added. The reaction mixture was refluxed for 4 h. and the obtained product was recrystallized from proper solvent to give (**VI**), Table (I).

IR ν_{max}/cm^{-1} 3235 (NH), 1675 (C=O). ^{1}H-NMR (**VIc**; DMSO-d_6) δ/ppm, 3.76, 3.83 and 3.9 (9H, 3 OCH_3), 7.2–8.0 (10H, m, Ar-H) 8.6 (1H, s, -N=CH-), 9.9 (1H, s, NH; eliminated by D_2O).

6-Benzoyl-3-formylamino-2-oxo-2,3-dihydrothiazolo[4,5-b]quinoxaline (VIII)

A solution of (**IV**; 0.01 mol) in formic acid (95%; 10 ml) was heated under reflux for 2 h. The separated solid after cooling was crystallized from proper solvent to give (**VIII**), Table (I). IRν_{max}/cm^{-1} 3140 (NH), 1780, 1710, 1640 (3 C=O). Mass spectrum of (**VIII**): 350 (M^+; 7.1%), 324 (4.3%), 307 (44.8%), 235 (9.3%), 230 (60.8%), 202 (14.4%), 185 (7.3%), 174 (2.9%) and 105 (100%; base peak).

6-Benzoyl-3-diacetylamino-2-acetylimino-2,3-dihydrothiazolo[4,5-b] quinoxaline (IX)

A solution of (**IV**; 0.01 mol) in acetyl chloride (10 ml) or acetic anhydride (10 ml) was refluxed for 4 h. After cooling the reaction mixture was poured into crushed ice, and the obtained product was crystallized from appropriate solvent to give (**IX**); Table (I). IR ν_{max}/cm^{-1}, which revealed the complete disappearance of $NH_2$and NH which were present in the parent compound and the presence of 1780, 1690 and 1650 (C=O). ^{1}H-NMR ($CDCl_3$), δ/ppm, 2.6 (9H, s, 3 $COCH_3$), 8.0–8.8 (8H, m, Ar-H).

8-Benzoyl-2-phenyl-(1,2,4)triazolo [3′,2′:2,3]thiazolo[4,5-b] quinoxaline (X)

A solution of (**IV**; 0.01 mol) in benzoyl chloride (10 ml) was refluxed for 5 h. The solid that was obtained and recrystallized from proper solvent to give (**X**), Table (I). IRν_{max}/cm^{-1}, which showed the complete disappearance of NH_2 and HN. Mass spectrum exhibited a molecular ion peak at m/z 407 (99.6%) together with a base peak at m/z 105 (100%).

(1,2,4) Triazolo [3′,2′:2,3]thiazolo[4,5-b]quinoxaline (XI)

A mixture of (**IV**; 0.01 mol), ethyl cyanoacetate (0.01 mol) and triethylamine (0.5 ml) in DMF/ethanol (1:1; 50 ml) was refluxed for 6 h. The obtained solid was recrystallized from proper solvent to give (**XI**), Table (I). IR spectrum which exhibited the absence of C≡N group. ^{1}H-NMR ($CDCl_3$), δ/ppm, 1.6 (3H, t, J= 6.9 Hz, CH_3), 4.4 (2H, q, J= 6.9 Hz, O-CH_2), 5.3 (2H, s, $COCH_2$) and 7.6–8.3 (8H, m, Ar-H). Mass spectrum: 417 (M^+, 16.6%), 418 (60.6%), 371 (49.0%), 266 (26.0%), 115 (16.3%), 105 (96.2%) and 77 (100%).

7-Benzoyl-2-mercapto-(1,3,4)thiadiazino[5,6-b]quinoxaline (XII)

Carbon disulphide (0.02 mol) was added to a solution of (**IV**; 0.01 mol) in anhydrous pyridine (30 ml). The reaction mixture was refluxed for 6 h. and the obtained product was recrystallized from proper solvent to give (**XII**), Table (I).

7-Benzoyl-4-methyl-2-thiomethyl-(1,3,4)-thiadiazino[5,6-b]quinoxaline (XIII)

Dimethyl sulphate (0.02 mol) was added to a solution of (**XII**; 0.01 mol) in aqueous sodium hydroxide (10%; 20 ml), the obtained product was recrystallized from appropriate solvent to give (**XIII**), Table (I). IR spectrum showed the disappearance of NH band present in the parent compound.

7-Benzoyl-2-thiomethyl-(1,3,4)-thiadiazino [5,6-b] quinoxaline (XIV)

To a solution of (**I**; 0.01 mol) in ethanol/DMF (1:1; 50 ml), was added methyl dithiocarbazate (0.01 mol). The reaction mixture was refluxed for 3 h. The obtained product was recrystallized from proper solvent to give (**XIV**), Table (I). IRν_{max}/cm^{-1}, 3301 (NH), 2916 (CH-aliphatic), 1654 (C=O). ^{1}H-NMR ($CDCl_3$), δ/ppm, 2.3 (1H, br, NH; eliminated by D_2O), 4.0 (3H, s, SCH_3), 7.2–8.4 (8H, m, Ar-H). Mass spectrum : 352 (M^+, 64.6%), 320 (10%), 174 (10.9%), 160 (9.6%), 147 (10.9%), 128 (8.3%), 105 (28.8%) and 73 (100%).

Alkylation of (XIV)

Dimethyl sulphate (0.01 mol) was added to a solution of (**XIV**; 0.01 mol) in sodium hydroxide (10%; 20 ml). The reaction mixture was stirred at 60 °C for 3 h. to give (**XIII**), Table (I).

Interaction of (I) with thiocarbohydrazide

A mixture of (**I**; 0.01 mol) and thiocarbohydrazide (0.01 mol) in DMF (50 ml) was heated under reflux for 4 h. to give (**XV**), Table (I).

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