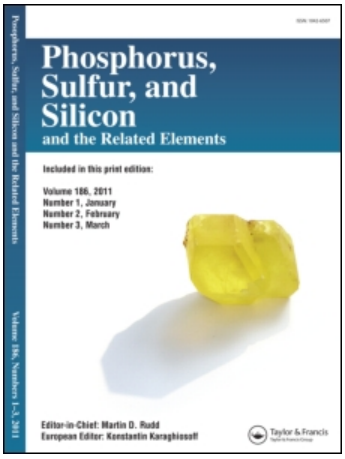

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Fawzy A. Attaby[a]; M. A. A. Elneairy[a]; M. S. Elsayed[a]
[a] Chemistry Department, Faculty Of Science, Cairo University, Giza, Egypt

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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SEVERAL NEW PYRIDINE, THIENOPYRIDINE AND PYRIDOTHIENOPYRAZOLE DERIVATIVES

FAWZY A. ATTABY*, M. A. A. ELNEAIRY and M. S. ELSAYED

Chemistry Department, Faculty Of Science, Cairo University, Giza, Egypt

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The reaction of thiocyanoacetamide **(1)** with α,β-unsaturated ketones **2a,b** resulted in the formation of the corresponding newly synthesized 1(H)pyridinethione derivatives **3a,b.** Compounds **3a,b** were used as synthons for the preparation of 2-S-alkyl-, 2-S-aryl-, 2-S-acetamidopyridine, thieno[2,3-b]pyridine and pyrazolo[3,4-b]pyridine derivatives via a wide range of reactions with different reagents. The antimicrobial activity of some of the newly synthesized compounds was tested. Compounds **3a, 11a, 15a,** and **19a,b** were found to be the most active ones.

Keywords: Pyridinethione; 2-S-alkylpyridine; 2-S-acetamidopyridine; thieno[2,3-b]pyridine and pyrazolo[3,4-b]pyridine

INTRODUCTION

Chemistry of thiocyanoacetamide **(1)** and its utility in heterocyclic synthesis were the main objectives in most of our recent publications.[1–5] The newly synthesized compounds **3a,b** reacted with several halogenated ketones, halogenated esters and chloroacetamide to give the newly synthesized 2-S-alkyl derivatives **5a-d, 9a-d, 14a,b** and **17a,b.** The above mentioned compounds were cyclized using ethanolic potassium hydroxide solution to afford the thieno[2,3-b]pyridines **6a,b, 10a,b, 15a,b** and **18a,b.** On the other hand, **3a,b** reacted with methyl iodide to give the corresponding 2-S-methylpyridines **19a,b** which were cyclized by hydrazine hydrate to

* To whom any correspondence to be sends.

afford the pyrazolo[3,4-b]pyridines **20a,b.** The reported biological activities of pyridines,[6–9] pyrazolo[3,4-b]pyridines[10] and thieno[2,3-b]pyridines[11] stimulated our interest to synthesize a variety of these heterocycles. The reactions of the pyridinethiones with active reagents seemed to be an easy and logic route for the synthesis of these derivatives, which are required for our medicinal chemistry program.

RESULTS AND DISCUSSION

It has been found that thiocyanoacetamide **(1)** reacted with 4-aryl-but-3-en-2-one **2a,b** in absolute ethanol containing the catalytic amount of triethylamine to afford the 1(H)pyridinethiones **3a,b.** The structures of **3a,b** were established based on elemental analyses, IR and ^{1}H-NMR spectral data (cf. Tables I, II and Chart 1). Moreover, the mass spectra of **3a,b** gave m/z = 260 and 216 respectively which corresponded to the exact molecular weights of the molecular formulae $C_{13}H_9N_2SCl$ and $C_{11}H_8N_2SO$ of the assigned structures (cf. Chart 1).

3-Cyano-4-(4′-chlorophenyl)-6-methyl-1(H)pyridinethione **(3a)** reacted with chloroacetone **(4a)** in sodium ethoxide to give a reaction product formed via the loss of hydrogen chloride. The IR of this reaction product showed the bands for CN and acetonyl CO groups. Its ^{1}H-NMR spectrum revealed the signals corresponded to -CH_2CO-, -$COCH_3$, pyridine H-5, pyridine-CH_3, and aromatic protons. Moreover, its mass spectrum gave m/z = 316 which corresponded to the exact molecular weight of a molecular formula $C_{16}H_{13}N_2SOCl$ of the assigned structure (cf. Chart 1). Considering all the above data, this reaction product was formulated as the 2-S-acetonylpyridinethione derivative **5a.**

In a similar manner, compound **3a** reacted with α-chloroacetylacetone **(4b)** in sodium ethoxide to afford the 2-S-diacetylmethylpyridinethione derivative **(5b).** The mass spectrum of **5b** gave m/z = 359 which corresponded to the exact molecular weight of a molecular formula $C_{18}H_{15}N_2SO_2Cl$ of the assigned structure (cf. Chart 1). The structure of **5b** was further confirmed by considering the data of elemental analyses, IR, and ^{1}H-NMR spectra (cf. Tables I and II). On the other hand, **3b** reacted also, with each of **4a,b** under the same experimental conditions to afford **5c,d** respectively. The structure of **5c,d** was established based on elemental analyses, IR and ^{1}H-NMR spectral data (cf. Tables I, II and

Chart 1). Compounds **5a-d** were cyclized in absolute ethanol containing the catalytic amount of triethylamine to afford the corresponding thieno[2,3-b]pyridine derivatives **6a,b** respectively. The IR spectra of each of **6a,b** showed the absence of the CN group and instead the bands of the newly born NH_2 group were detected. Their ^{1}H-NMR revealed no signals of -CH_2CO- protons while the NH_2 protons were detected. Based on both IR and ^{1}H-NMR spectral data it could be concluded that both the-CH_2CO- protons and the CN group were involved in the cyclization step in case of **5c,d** while the addition of the anions from the -$CH(COCH_3)_2$ to the CN group to afford the non-isolable 3-iminothienopyridine intermediates of **5b,d.** These intermediates, in turn, added water molecule in each case to give the 3-aminothieno[2,3-b]pyridine derivatives **6a,b.** The mass spectra of **6a,b** gave m/z = 316 and 272 which corresponded to the exact molecular weights of the molecular formulas $C_{16}H_{13}N_2SOCl$ and $C_{14}H_{12}N_2SO_2$ of the assigned structures (cf. Chart 1). A further elucidation of **6a,b** structures were given from their reaction with hydrazine hydrate. The reaction products were formulated as pyridothienopyrazole derivatives **7a,b,** respectively, whose structures were confirmed based on IR, ^{1}H-NMR, and elemental analyses (cf. Tables I and II).

The synthetic potentialities of **3a,b** were further demonstrated via their reactions with ethyl chloroacetate (**8a**) in sodium methoxide to give a reaction products formed via dehydrochlorination. The IR spectra of these reaction products showed the bands corresponded to CN group and ester CO. Their ^{1}H-NMR spectra revealed the signals corresponded to CH_3 at pyridine, pyridine H-5, CH_3CH_2-, and aromatic protons (cf. Table II). Moreover, their mass spectra gave m/z = 347 and 302 which corresponded to the exact molecular weight of the molecular formulae $C_{17}H_{15}N_2SO_2Cl$ and $C_{15}H_{14}N_2SO_3$ of the assigned structures. Considering all the above data, these reaction products were formulated as the 2-S-ethoxycarbonylmethylpyridine derivatives **9a,b** respectively. A further confirmation of the structure of **9a,b** was given through their cyclization in absolute ethanol containing triethylamine to afford the corresponded thieno[2,3-b]pyridine derivatives **10a,b** respectively (cf. Chart 1). The IR spectrum of each of **10a,b** showed no bands for the CN group while the newly born NH_2 group was detected, and this proved that both the S-CH_2- and the CN group were involved in the cyclization step. The above results were confirmed also by the fact that the signals of the S-CH_2- protons were absent while those of the NH_2 protons were detected in the ^{1}H-NMR spectra (Table II).

TABLE I Characterization of the newly synthesized compounds

Comp.	*M.P. (°C)*	*Yield (%)*	*Solvent of Cryst.*	*Molecular Formula*	*% Of Analysis Calcd./Found*				
					C	*H*	*N*	*S*	*Cl*
3a	260	69	Ethanol	$C_{13}H_9N_2SCl$	59.88 60.1	3.45 3.5	10.75 10.9	12.28 12.5	13.63 13.4
3b	275	66	Acetic acid	$C_{11}H_8N_2SO$	61.11 61.1	3.70 3.2	12.96 13.3	14.81 14.4	- -
5a	120	81	Ethanol	$C_{16}H_{13}N_2SOCl$	60.66 60.3	4.11 4.5	8.85 8.9	10.11 10.5	11.22 11.6
5b	150	79	Dil. DMF	$C_{18}H_{15}N_2SO_2Cl$	61.76 61.8	4.41 4.2	10.29 10.4	11.76 11.3	- -
5c	145	59	Ethanol	$C_{14}H_{12}N_2SO_2$	60.25 60.5	4.18 4.3	7.81 7.9	8.93 9.0	9.90 10.0
5d	122	55	DMF	$C_{16}H_{14}N_2SO_3$	61.15 61.4	4.46 4.3	8.92 9.0	10.19 10.2	- -
6a	165	82	Ethanol	$C_{16}H_{13}N_2SOCl$	60.66 60.7	4.1 1 4.1	8.85 8.4	10.1 1 10.4	11.22 11.5
6b	185	61	DMF	$C_{14}H_{12}N_2SO_2$	61.76 61.5	4.41 4.1	10.29 10.5	11.76 11.2	- -
7a	187	65	Ethanol	$C_{16}H_{12}N_3SCl$	61.24 61.5	3.83 3.7	13.40 13.4	10.21 10.5	11.32 11.5
7b	239	73	DMF	$C_{14}H_{11}N_3SO$	62.45 62.6	4.09 4.2	15.61 15.6	11.90 12.0	- -
9a	220	65	Ethanol	$C_{17}H_{15}N_2SO_2Cl$	58. 87 58. 7	4.33 4.4	8.08 8.4	9.24 9.5	10.25 10.0

Comp.	M.P. (°C)	Yield (%)	Solvent of Cryst.	Molecular Formula	% Of Analysis Calcd./Found				
					C	H	N	S	Cl
9b	140	82	Ethanol	$C_{15}H_{14}N_2SO_3$	59.60 59.4	4.64 4.2	9.27 9.6	10.60 10.3	- -
9c	120	67	Ethanol	$C_{19}H_{17}N_2SO_3Cl$	58.69 58.3	4.38 4.1	7.21 7.0	8.24 8.5	9.14 9.3
9d	180	86	Ethanol	$C_{17}H_{16}N_2SO_4$	59.30 59.0	4.65 4.2	8.14 8.4	9.30 9.1	- -
10a	180	66	Ethanol	$C_{17}H_{15}N_2SO_2Cl$	58.87 58.4	4.33 4.5	8.08 8.3	9.24 9.5	10.25 10.6
10b	200	56	Ethanol	$C_{15}H_{14}N_2SO_3$	59.60 59.9	4.64 4.8	9.27 9.0	10.60 10.4	- -
11a	197	69	Ethanol	$C_{15}H_{13}N_4SOCl$	54.14 54.3	3.91 4.0	16.84 16.8	9.62 9.5	10.68 10.8
11b	228	74	Ethanol	$C_{13}H_{12}N_4SO_2$	54.17 54.3	4.17 4.3	19.44 19.6	11.11 11.1	- -
12a	286	81	Ethanol	$C_{15}H_{10}N_3SOCl$	57.05 57.0	3.17 3.1	13.31 13.3	10.14 10.2	11.25 11.4
12b	300	78	DMF	$C_{13}H_9N_3SO_2$	57.56 57.7	3.32 3.3	15.50 15.6	11.81 11.9	- -
14a	150	78	Ethanol	$C_{15}H_{12}N_3SOCl$	56.69 56.4	3.78 3.6	13.23 13.2	10.08 10.2	11.18 11.3
14b	250	91	Ethanol-DMF	$C_{13}H_{11}N_3SO_2$	57.14 57.1	4.03 4.2	15.38 15.6	11.72 11.9	- -
15a	220	87	Ethanol	$C_{15}H_{12}N_3SOCl$	56.69 56.9	3.78 3.9	13.23 13.2	10.08 10.3	11.18 11.4

Comp.	*M.P. (°C)*	*Yield (%)*	*Solvent of Cryst.*	*Molecular Formula*	*% Of Analysis Calcd./Found*				
					C	*H*	*N*	*S*	*Cl*
15b	300	69	Ethanol-DMf	$C_{13}H_{11}N_3SO_2$	57.14 57.4	4.03 4.0	15.38 15.1	11.72 12.0	- -
17a	100	81	Ethanol	$C_{21}H_{15}N_2SOCl$	66.58 66.8	3.96 4.1	7.40 7.2	8.45 8.6	9.38 9.3
17b	160	79	Ethanol	$C_{19}H_{14}N_2SO_2$	68.26 68.6	4.19 4.0	8.38 8.6	9.58 9.6	- -
18a	300	84	DMF	$C_{21}H_{15}N_2SOCl$	66.58 66.2	3.96 3.6	7.40 7.5	8.45 8.6	9.38 9.5
18b	300	73	Ethanol	$C_{19}H_{14}N_2SO_2$	68.26 68.0	4.19 4.3	8.38 8.1	9.58 9.5	- -
19a	140	66	Ethanol	$C_{14}H_{11}N_2SCl$	61.20 61.40	4.01 4.3	10.20 10.0	11.66 11.3	12.93 13.1
19b	130	69	Ethanol	$C_{12}H_{10}N_2SO$	62.61 62.9	4.35 4.5	12.17 12.3	13.91 14.2	- -
20a	157	75	Ethanol	$C_{13}H_{11}N_4Cl$	60.35 60.5	4.26 4.1	21.66 21.9	- -	13.73 14.0
20b	181	82	Ethanol	$C_{11}H_{10}N_4O$	61.68 62.0	4.67 4.3	26.17 26.4	- -	- -
21a	162	72	DMF	$C_{13}H_9N_5Cl_2$	50.98 51.1	2.94 3.2	22.88 22.6	- -	23.20 23.5
21b	272	69	DMF	$C_{11}H_8N_5OCl$	50.48 50.6	3.06 3.2	26.77 26.9	- -	13.58 13.7

In a similar manner, compounds **3a,b** reacted with ethyl-α-chloroacetoacetate **(8b)** to give the 2-S-ethoxycarbonylacetylmethylpyridine derivatives **9c,d** respectively. The structures of **9c,d** were cyclized also, in absolute ethanol containing triethylamine to afford **10a,b** respectively. It is remarkable to report here that these reaction products were identical in all aspects with that obtained from cyclization of **9a,b.** These reaction products were most probably formed via the addition of the anions from $-CH(COOEt)COCH_3$ to the CN group to give the non-isolable 3-iminothienopyridine intermediates. These intermediates then added water to liberate acetic acid and gave the final isolable **10a,b,** respectively (cf. Chart 1). The structures of **10a,b** were further confirmed via their reaction with hydrazine hydrate to give the corresponding acid hydrazide derivatives **11a,b.** The acid hydrazides **11a,b** were cyclized in boiled acetic acid to give the corresponding pyridothienopyrazole derivatives **12a,b,** respectively. The structures of **10a,b, 11a,b** and **12a,b** were established based on IR, ^{1}H-NMR, and elemental analyses (cf. Tables I and II). Moreover, the mass spectra of **10a, 11a** and **12a** as selective examples gave m/z = 346, 332 and 315 respectively, which represented the exact molecular weights of the molecular formulas $C_{17}H_{15}N_2O_2SCl$, $C_{15}H_{13}N_4OSCl$ and $C_{15}H_{10}N_3OSCl$ of the assigned structures (cf. Chart 1).

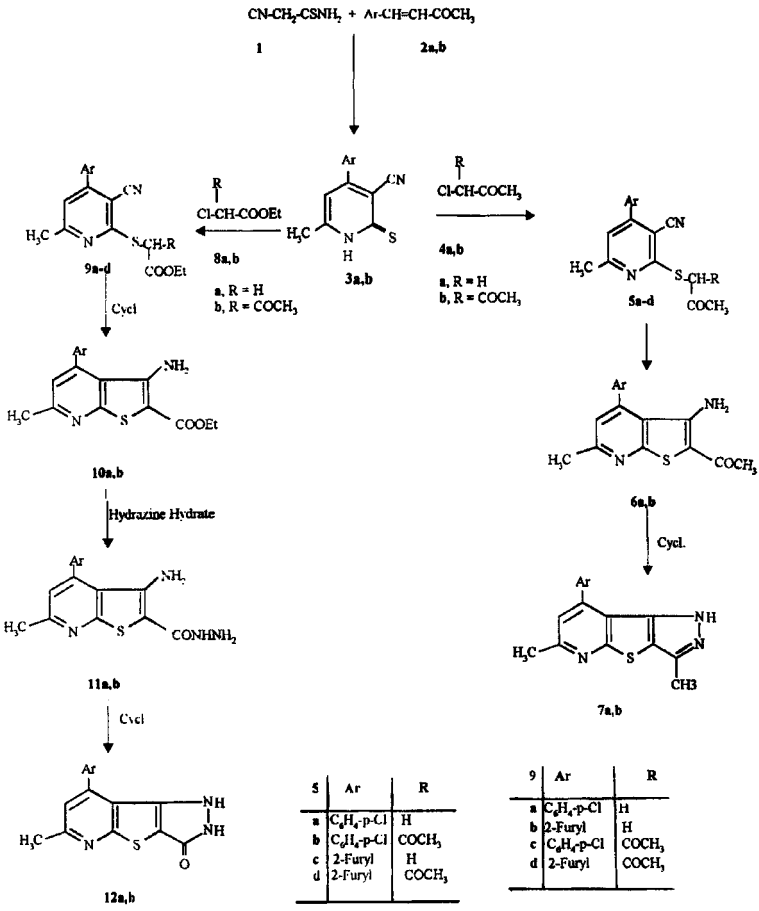
Work was also extended to shed more light on the activity of **3a,b.** Thus, **3a,b** reacted with both chloroacetamide **(13)** and phenacyl bromide **(16)** to afford **14a,b** and **17a,b** via the loss of hydrogen chloride and hydrogen bromide respectively (cf. Chart 2). The structures of **14a,b** and **17a,b** were established based on the elemental analyses, IR, and ^{1}H-NMR spectra (cf. Tables I, II and Chart 2). The mass spectra of **14a** and **17a** as typical examples gave m/z = 317 and 378 which corresponded to the exact molecular weights of the molecular formulas $C_{15}H_{12}N_3SOCl$ and $C_{21}H_{15}N_2SOCl$ of the assigned structures (cf. Chart 2). More evidence for the structures **14a,b** and **17a,b** was given through their cyclization in an ethanolic potassium hydroxide solution. The IR spectrum of each of these cyclization products showed no bands for the CN group while the bands of the newly born NH_2 were detected. Their ^{1}H-NMR spectra had no signals of the S-CH_2 protons and this proved that both the CN group and S-CH_2 protons were involved in the cyclization step. Considering all the above mentioned data, these cyclization products were formulated as the thieno[2,3-b]pyridine derivatives **15a,b** and **18a,b,** respectively (cf. Tables I, II and Chart 2).

TABLE II IR and ^{1}H-NMR spectral data of the newly synthesized compounds

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δ ppm)*
3a	3300 (NH), 3050 (CH aromatic), 2985 (sat. CH), 2217 (CN), 1600 (C=C) and 1540 (C=S)	1.7 (s, 3 H, CH_3), 4.1 (s, br. 1 H, NH), 5.2 (s, 1 H, Pyridine H-5) and 6.8–7.9 (m, 4 H, ArH's).
3b	3250 (NH), 3073 (CH aromatic), 2980 (sat. CH), 2222 (CN), 1600 (C=C) and 1550 (C=S).	1.4 (s, 3 H, CH_3), 4.3 (s, br. 1 H, NH), 5. 1 (s, 1 H, Pyridine H-5) and 6.2–7.8 (m, 3 H, Furyl H's).
5a	3070 (CH aromatic), 2985 (sat. CH), 2218 (CN), 1715 (CO) and 1600 (C=C).	1.5 (s, 3 H, CH_3), 2.5 (s, 3 H, $CO\underline{CH_3}$), 3.1 (s, 2 H, -$\underline{CH_2}$CO-), 4.9 (s, 1 H, Pyridine H-5) and 6.9–8. 1 (m, 4 H, ArH's).
5b	3067 (CH aromatic), 2982 (sat. CH), 2213 (CN), 1720 (CO) and 1600 (C=C).	1.3 (s, 3 H, CH_3), 2.3 (s, 6 H, $CH(CO\underline{CH_3})_2$), 3.5 (s, 1 H, -$\underline{CH}(COCH_3)_2$, 5.1 (s, 1 H, Pyridine H-5) and 7.1–8.0 (m, 4 H, ArH's).
5c	3079 (CH aromatic), 2979 (sat. CH), 2209 (CN), 1718 (CO) and 1600 (C=C).	1.2 (s, 3 H, CH_3), 2.5 (s, 3 H, $CO\underline{CH_3}$), 3.2 (s, 2 H, -$\underline{CH_2}$CO-, 5.2 (s, 1 H, Pyridine H-5) and 6.9–8.1 (m, 3 H, ArH's).
5d	3082 (CH aromatic), 2982 (sat. CH), 2222 (CN), 1720 (CO) and 1604 (C=C).	1.5 (s, 3 H, CH_3), 2.7 (s, 6 H, $CH(CO\underline{CH_3})_2$), 3.41 (s, 1 H, $\underline{CH}(COCH_3)_2$), 5.0 (s, 1 H, Pyridine H-5) and 6.9–8. 1 (m, 3 H, Furyl H's).
6a	3331, 3256 (NH_2), 3073 (CH aromatic), 1682 (CO) and 1605 (C=C).	1.1 (s, 3 H, CH_3), 1.9 (s, 3 H, $COCH_3$), 4.6 (s,br., 2 H, NH_2), 5.1 (s, 1 H, Pyridine H-5) and 7.0–7.8 (m, 4 H, ArH's).
6b	3324, 3287 (NH_2), 3079 (CH aromatic), 1675 (CO) and 1601 (C=C).	1.4 (s, 3 H, CH_3), 2.0 (s, 3 H, $COCH_3$), 4.9 (s,br., 2 H, NH_2) 5.3 (s, 1 H, Pyridine H-5) and 6.9–7.8 (m, 3 H, ArH's).
7a	3234 (NH), 3068 (aromatic CH), 1617 C=N) and 1600 (C=C).	1.3 (s, 6 H, two CH_3), 4.9 (s, 1 H, pyridine H- 5), 6.0 (s,br., 1 H, NH of pyrazole) and 7.2–8. 1 (m, 4 H, ArH's).
9a	3080 (CH aromatic), 2987 (sat. CH), 2219 (CN), 1728 (CO) and 1602 (C=C).	1.0 (s, 3 H, CH_3), 1.7 (t, 3 H, $CH_2\underline{CH_3}$), 2.9 (s, 2 H, $\underline{CH_2}$CO-), 3.4 (q, 2 H, $\underline{CH_2}CH_3$). 5.3 (s, 1 H, Pyridine H-5) and 7.3–7.8 (m, 4 H, ArH's).
9b	3073 (CH aromatic), 2982 (sat. CH), 2213 (CN), 1710 (CO acetyl), 1734 (CO ester) and 1600 (C=C).	0.95 (s, 3 H, CH_3), 1.6 (t, 3 H, $CH_2\underline{CH_3}$), 2.8 (s, 2 H, $S\underline{CH_2}$), 3.5 (q, 2 H, $\underline{CH_2}CH_3$), 5.1 (s, 1 H, Pyridine H-5) and 7.0–7.9 (m, 4 H, Furyl H's).

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δ ppm)*
9c	3078 (CH aromatic), 2978 (sat. CH), 2219 (CN), 1729 (CO ester), 1709 (CO acetyl) and 1601 (C=C).	1.1 (s, 3 H, CH_3), 1.5 (t, 3 H, $CH_2\underline{CH_3}$), 2.8 (s, 1 H, -S$\underline{CH}$-), 3.4 (q, 2 H, $\underline{CH_2}CH_3$), 2.3 (s, 3 H, $COCH_3$, 5.2 (s, 1 H, Pyridine H-5) and 7.2–7.7 (m, 4 H, ArH's).
9d	2989 (sat. CH), 2211 (CN), 1715 (CO acetyl), 1728 (CO ester) and 1602 (C=C).	1.0 (s, 3 H, CH_3), 1.5 (t, 3 H, $CH_2\underline{CH_3}$), 2.1 (s, 3 H, CH_3CO-), 2.9 (s, 1 H, S$\underline{CH}$), 3.6 (q, 2 H, $\underline{CH_2}CH_3$), 5.3 (s, 1 H, Pyridine H-5) and 7.0–7.9 (m, 3 H, Furyl H's).
10a	3330, 3289 (NH_2), 3079 (CH aromatic), 2982 (sat. CH), 1693 (CO) and 1601 (C=C).	1.1 (s, 3 H, CH_3), 1.6 (s, 3 H, $CH_2\underline{CH_3}$), 3.4 (q, 2 H, $CH_3\underline{CH_2}$), 4.7 (s, br., 2 H, NH_2), 5.0 (s, 1 H, Pyridine H-5) and 7.1–7.9 (m, 4 H, ArH's).
10b	3321, 3258 (NH_2), 2978 (CH sat), 1687(CO) and 1601 (C=C).	1.0 (s, 3 H, CH_3), 1.5 (s, 3 H, $CH_2\underline{CH_3}$), 3.3 (q, 2 H, $CH_3\underline{CH_2}$), 4.4 (s,br., 2 H, NH_2), 4.8 (s, 1 H, Pyridine H-5) and 6.8–8.2 (m, 4 H, Furyl H's).
11a	3452, 3342, 3218 (twoNH_2 and NH), 3078 (aromatic CH), 2890 (sat, CH), 1648 (CO hydrazide), 1615 (C=N) and (C=C).	1.2 (s, 3 H, CH_3 at pyridine), 4.7 (s,1 H, pyridine H-5), 5.5 (s, br., 2 H, NH_2 at thiophene), 6. (s, br., 2 H, CONH$\underline{NH_2}$), 7.0–7.6 (m, 4 H, Ar.H's) and 8.7 (s, br., 1 H, CO$\underline{NH}NH_2$
12b	3228 (NH), 2879,2837 (sat. CH), 1708 (CO of pyrazolone), 1617 (C=N), and 1602 (C=C).	1.3 (s,3 H, CH_3 at pyridine), 5. (s, 1 H, pyridine H-5), 6.4–7. 1 (m, 3 H, Furyl H's), 7.8 (s, br., 1 H, NH of pyrazole at 3-position) and 8.4 (s, br., 1 H, pyrazole adjacent to C=O).
14a	3330, 3195 (NH_2), 3065 (CH aromatic), 2987 (Sat. CH), 2217 (CN), 1690(CO) and 1605 (C=C).	1.1 (s, 3 H, CH_3), 2.7 (s, 2 H, -S$\underline{CH_2}$CO-), 4.2 (s,br., 2 H, NH_2), 5.1 (s. 1 H, Pyridine H-5) and 7.0–8.1 (m, 4 H, ArH's).
14b	3335, 3248 (NH_2), 2978 (Sat. CH), 1669 (CO) and 1604 (C=C).	1.3 (s, 3 H, CH_3), 2.4 (s, 2 H, -S$\underline{CH_2}$CO-), 4.8 (s,br., 2 H, NH_2). 5.3 (s, 1 H, Pyridine H-5) and 6.9–8.0 (m, 3 H, Furyl H's).
15a	3412, 3348, 3277, 3148 (two NH_2), 3050 (CH aromatic), 2985 (Sat. CH), 1679 (CO) and 1600 (C=C).	1.2 (s, 3 H, CH_3), 4.4 (s,br., 4 H, two NH_2), 5.1 (s, 1 H, Pyridine H-5) and 7.0–8.1 (m, 4 H, ArH's).
15b	3387, 3338, 3265, 3183 (two NH_2), 2985 (Sat. CH), 1682 (CO) and 1603 (C=C).	1.2 (s, 3 H, CH_3), 4.8 (s,br., 4 H, two NH_2), 5.4 (s, 1 H, Pyridine H-5) and 6.4–7.9 (m, 3 H, Furyl H's).
17a	3078 (CH aromatic), 2975 (Sat. CH), 2217 (CN), 1682 (CO) and 1603 (C=C).	1.3 (s, 3 H, CH_3), 2.5 (s, 2 H, -S$\underline{CH_2}$CO-), 5. 1 (s, 1 H, Pyridine H-5) and 7.1–8.2 (m, 9 H, ArH's).

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δ ppm)*
17b	3069 (Aromatic CH), 2986 (Sat. CH), 2221 (CN), 1689 (CO) and 1600 (C=C).	1.1 1 (s, 3 H, CH_3), 2.3 (s, 2 H, -S$\underline{CH_2}$CO-), 4.9 (s, 1 H, Pyridine H-5) and 7.0–8.2 (m, 8 H, Aromatic and Furyl H's).
18a	3379, 3298 (NH_2), 3079 (CH aromatic), 2968 (Sat. CH), 1689 (CO) and 1601 (C=C).	1.3 (s, 3 H, CH_3), 4.8 (s,br., 2 H, NH_2), 5.1 (s, 1 H, Pyridine H-5) and 7.0–8. 1 (m, 9 H, Furyl and Aromatic H's).
18b	3375, 3287 (NH_2), 3067 (Aromatic CH), 2979 (Sat. CH), 1676 (CO) and 1600 (C=C).	1.1 (s, 3 H, CH_3), 4.9 (s.br., 2 H, NH_2), 5.3 (s, 1 H, Pyridine H-5) and 6.9–8.2 (m, 8 H, Furyl and Aromatic H's).
19a	3069 (Aromatic CH), 2975 (Sat. CH), 2219 (CN) and 1600 (C=C).	1.3 (s, 3 H, CH_3), 1.9 (s, 3 H, -S$\underline{CH_3}$), 4.8 (s, 1 H, Pyridine H-5) and 7.1–7.9 (m, 4 H, ArH's).
19b	2987 (Sat. CH), 2214 (CN) and 1602 (C=C).	1.1 (s, 3 H, CH_3), 2.0 (s, 3 H, -S$\underline{CH_3}$), 5.2 (s, 1H, Pyridine H-5) and 6.9–7.8 (m, 3 H, Furyl H's).
20a	3286, 3228, 3177 (NH_2 and NH), 3069 (Aromatic CH), 2978 (Sat. CH) and 1600 (C=C).	1.2 (s, 3 H, CH_3), 4.6 (s,br., 2 H, NH_2), 5. 1 (s, 1 H, Pyridine H-5) and 7.0–8. 1 (m, 4 H, ArH's).
20b	3295, 3239, 3192 (NH_2 and NH), 3069 (Aromatic CH), 2978 (Sat. CH) and 1600 (C=C).	1.2 (s, 3 H, CH_3), 4.6 (s,br., 2 H, NH_2), 5. 1 (s, 1 H, Pyridine H-5) and 7.0–8.1 (m, 3 H, Furyl H's).
21a	3187 (NH), 3079 (aromatic CH), 2982 (sat. CH), 2152 ($^+$N=N), 1613 (C=N) and 1598 (C=C).	1. 1 (s, 3 H, CH_3), 5.0 (s, 1 H, pyridine H-5), 5.7 (s, br., 1 H, NH) and 7.5–8.1 (m, 4 H, ArH's).



5	Ar	R
a	C_6H_4-p-Cl	H
b	C_6H_4-p-Cl	$COCH_3$
c	2-Furyl	H
d	2-Furyl	$COCH_3$

9	Ar	R
a	C_6H_4-p-Cl	H
b	2-Furyl	H
c	C_6H_4-p-Cl	$COCH_3$
d	2-Furyl	$COCH_3$

CHART 1

The synthons **3a,b** reacted also, with methyl iodide in sodium methoxide to give the corresponding 2-S-methylpyridine **19a,b** whose structures were elucidated based on elemental analyses, IR, and ^{1}H-NMR data (cf. Tables I, II and Chart 2). A further confirmation of structure **19a,b** was given through their reaction with hydrazine hydrate to give the sulfur-free reaction products **20a,b**. Compounds **20a,b** were most probably formed via the

substitution of the S-CH_3 group to give the non-isolable 2-hydrazino pyridines. The hydrazino group was then, added to the CN group to afford the corresponded pyrazolo[3,4-b]pyridines **20a,b.** The structures of **20a,b** were established based on elemental analyses, IR, and ^{1}H-NMR data (cf. Tables I, II and Chart 2). Moreover, the mass spectrum of **20b** gave m/z = 214, which corresponded to the exact molecular weight of a molecular formula $C_{11}H_{10}N_4O$ of the assigned structure, (cf. Chart 2). Good evidence of structures **20a,b** was given through their synthesis via another route. Compounds **3a,b** reacted with hydrazine hydrate to give a reaction products which were found identical in all aspects with **20a,b** previously obtained from the reaction of **19a,b** with hydrazine hydrate.

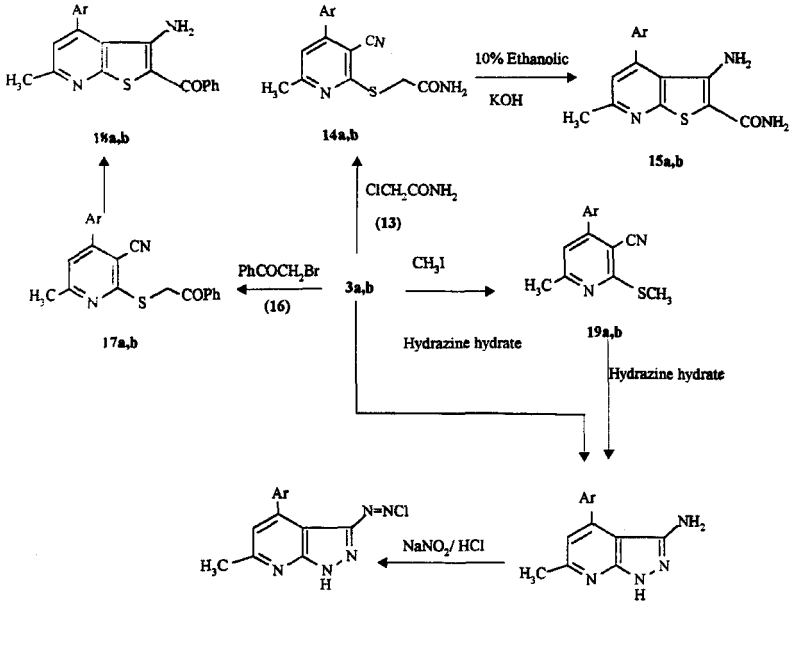
The nature and position of the NH_2 group in **20a,b** was elucidated through reaction with nitrous acid. The reaction proceeded through diazotization of the NH_2 group to give the corresponded diazonium chlorides **21a,b,** which will be used as basic starting materials for the next study. The structures **21a,b** were established based on elemental analyses, IR, and ^{1}H-NMR data (cf. Tables I, II and Chart 2).

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of some of the newly synthesized heterocyclic compounds was tested against six types of organisms (cf. Table III):

Bacteria Gr + ve Staphylococcus aureus, Bacteria Gr + ve Salmonilla Typhi, Yeast Candidralbicuns, Yeast Sacchuria Cerivi, Bacteria Gr + ve Esherichia Coli and Bacteria Gr + ve Bacillus Subtilis

Compounds **3a**, **11a**, **15a** and **19a,b** exhibited high activity (+++) against some of the tested organisms. On the other hand, compounds **3b, 10a,b, 11b** and **15b** exhibited moderate activity (++) against some of the tested organisms while compounds **6a, 12a, 14a** and **18a,b** showed slight activity towards such organisms. In all cases, compounds active against the microorganisms under investigation were determined according to the standard cupplate technique[12]. About 100 μgm concentrations of the tested compounds were used (cf. Table III).



	Ar
a	C_6H_4-p-Cl
b	2-Furyl
c	C_6H_4-p-Cl
d	2-Furyl

CHART 2

EXPERIMENTAL

All melting points are uncorrected. IR (KBr discs) were recorded on Pye Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM 390/90 MHz, Gemini 200 MHz, and Brucka WP-80 spectrometers using $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ as solvents and TMS as an internal standared. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using DIP techniques at 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University using a Perkin-Elmer 2400 CHN Elemental Analyzer.

TABLE III Antimicrobial activity of some of the newly synthesised compounds

Comp.	*Bacteria Gr+ve Staphylococcus aureus*	*Bacteria Gr +ve Salmonilla Typhi*	*Yeast Candidr albicuns*	*Yeast Sacchuria Cerivi*	*Bacteria Gr +ve Escherichia Coli*	*Bacteria Gr +ve Bacillus Subtilis*
3a	+++	++	+	-	+	+++
3b	++	-	-	+	++	-
6a	+	+	+	-	-	+
6b	-	-	-	+	-	-
7a	-	-	-	-	+	+
7b	+	-	-	-	-	-
10a	++	+	++	-	-	++
10b	-	++	+	++	-	+
11a	++	+	+++	-	+	++
11b	-	-	++	+	++	-
12a	+	+	+	-	+	-
12b	-	+	+	-	+	-
15a	++	+++	+	++	-	+
15b	-	+	+	++	-	+
18a	-	-	+	+	-	-
18b	-	-	-	-	+	-
19a	+	-	++	+++	+	++
19b	+++	+	+	-	++	++
20a	-	-	+	-	+	-
20b	-	-	-	-	-	+

(+++)= Highly active, (++) = Moderately active, (+) = Slightly active, (-) = Inactive.

Synthesis of 3a,b

A solution of thiocyanoacetamide (**1**) (0.01 mole) and each of **2a,b** (0.01 mole) in methanol (30 mL) containing the catalytic amounts of triethylamine (0.5 mL) was heated under reflux for 5 h. The solid products obtained after cooling were filtered off and recrystallized from the proper solvent to give **3a,b** respectively (cf. Tables I and II).

Synthesis of 5a-d, 9a-d, 14a,b, 17a,b and 19a,b

General Procedure

A solution of each of **3a,b** (0.01 mole) in methanolic sodium methoxide (0.01 mole) prepared from the equivalent amounts of sodium metal and methanol, was treated with each of chlororacetone (**4a**), α-chloroacetylacetone (**4b**), chloroethylacetate (**8a**), α-chloroethylacetoacetate (**8b**), chloroacetamide (**13**), phenylacylbromide (**16**) or methyl iodide (0.01 mole) and then was heated under reflux for 5 h. The solid products obtained, after pouring onto cold water and acidification with conc. HCl, were filtered off, washed with water and then recrystallized from the proper solvent to give **5a-d, 9a-d, 14a,b, 17a,b** and **19a,b** respectively (cf. Tables I and II).

Synthesis of 6a,b, 10a,b, 15a,b and 18a,b

General procedure

A solution of each of **5a-d, 9a-d, 14a,b,** and **17a,b** (0.01 mole) in ethanol (50 mL) was treated with 10% KOH (≅ 0.02 mole). The reaction mixture was heated under reflux for 5 h. The solid products obtained, after pouring onto ice-cold water and acidification with conc. HCl, were filtered off and washed with water and then recrystallized from the proper solvent to give **6a,b, 10a,b, 15a,b** and **18a,b,** respectively (cf. Tables I and II).

Synthesis of 20a,b

A solution of each of **19a,b** or **3a,b** (0.01 mole) was treated with an excess amount of hydrazine hydrate (≅ 4mL). The reaction mixture was heated under reflux for 5 h and the solid products obtained were filtered off and

recrystallized from the proper solvent to give **20a,b,** respectively (cf. Tables I and II).

Synthesis of 21a,b

A cold solution of each of **20a,b** (0.01 mole) in concentrated HCl (1mL) was treated with cold saturated solution of sodium nitrite (0.01 mole) and then stirred in an ice-bath for 2 h. The solid products obtained were filtered off, washed with water and recrystallized from to afford the corresponded **21a,b** respectively (cf. Tables I and II).

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