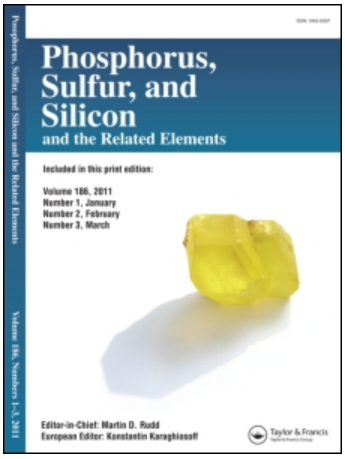

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REACTIONS WITH PYRIDINETHIONE DERIVATIVES: SYNTHESIS AND CHARACTERIZATION OF THIENYL[2,3-b]PYRIDINE, PYRIDO[2',3':4,5] THIENO[2,3-b]PYRIDAZINE, PYRIDO[2',3':4,5] THIENO[2,3-b]-PYRIMIDINONE, PYRAZOLINO [3',4':4,5] THIENO[2,3-b]PYRIDINE AND AMINOPYRAZOLO[3,4-b]PYRIDINE DERIVATIVES

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Thieno[2,3-b]pyridines **5a,b,** 2-S-methylacetyl pyridine derivative **7a,** 2-S-methyldiaetyl pyridine derivative **7b,** 2-S-methylethoxycarbonyl pyridine derivative **12a,** 2-S-methylacetylethoxycarbonyl pyridine derivative **12b** and 2-S-methyl pyridine derivative **28,** had been obtained via the reaction of pyridinethione **3** with phenacyl bromide derivatives, chloroacetone, α-chloroacetylacetone, chloroethylacetone, α-chloroethylacetoacetate and methyl iodide respectively.

Several cyclization reactions were performed with 10 % KOH, nitrous acid, hydrazine hydrate, formic acid, acetic anhydride and acetic acid to give an additional ring on the previously obtained new ring system.

Keywords: Pyridothienopyridazine; Pyrazo[3,4-b]pyridine; thieno[2,3-b]pyridine; 2-S-methyl pyridine; 2-S-methylacetyl pyridine.

INTRODUCTION

The reported biological activities of pyridines and fused pyridine heterocycles as antihypertensive agents[1], hypoglycenic agents[2,3], antibacterial[4], antidepressant[5] and antiarrhythmic[6]. In addition to the biological activities of both pyrazoles[7]

and pyridazines[8] stimulated our interest in chemistry of pyridinethione and its derivatives[9-16]. The newly synthesized pyridinethione derivative **3** reacted with several halogeno-ketones and halogenoesters to represent a direct and easy route for the synthesis of several newly synthesized thienopyridine derivatives, 2-S-acetyl and 2-diacetylmethylpyridines, pyridothienopyridazine and pyrazolothienopyridine derivatives

RESULTS AND DISCUSSION

It has been found that the α-thiocarboxamido-β-(3'-indolyl)-acrylonitrile (**1**) reacted with ethylbenzoylacetate (**2**) in ethanol in the presence of triethylamine and pyridine to afford the corresponding dihydropyridinethione derivative **3** which was taken as the starting material owing to the presence of more than one active center in best positions for substitution followed by cyclization reactions. 3-Cyano-4(3'-indolyl)5-ethoxycarbonyl-6-phenylpyridine-2-thione (**3**) reacted with ω-bromoacetophenone derivatives **4a,b** to afford a reaction products corresponded to equimolecular addition of **3** to each of **4a,b** followed by the loss of hydrogen bromide. Surprisingly, the IR spectra of these reaction products were entirely free from the bonds of the nitrile function. Instead, the bands of the newly born amino group were clearly detected in both IR and ^{1}H-NMR spectra. Based on the above facts these reaction products were formulated as thieno[2,3-b]pyridine derivatives **5a,b.** The formation of **5a,b** most likely proceeded via the formation of non-isolable 2-S-aroylmethyl pyridine intermediate which underwent cyclization via addition to the nitrile function to afford the final isolable **5a,b** (cf. Chart 1, Tables I and II). The synthetic potential of **3** was investigated via its reaction with chloroacetone **6a** and α-chloroacetylacetone **6b**. Thus, it has been found that **3** reacted with **6a,b** in methanolic sodium methoxide to give product of chemical formula corresponding to the addition of equimolecular amounts of **3** and **6a,b** with the loss of hydrogen chloride in each case. The IR spectra of the reaction products showed the presence of CN, ester CO and acetonyl CO groups in each case. The reaction products were formulated as 2-S-acetonylpyridine derivative **7a** and 2-S-diacetylmethylpyridine derivative **7b.** Compounds **7a,b** could be cyclized via treatment with boiling 10 % KOH in ethanol to afford one and the same compound **8**. The IR spectrum of **8** showed the absence of CN and instead the newly born bands of NH_2 were detected. Moreover, the signals of the acetonyl-CH_2 and diacetyl-CH groups of **7a,b** were entirely absent in the ^{1}H-NMR spectra of **8** (cf. Tables I and II). Collecting the above data together it could be concluded that the reaction product could be for-

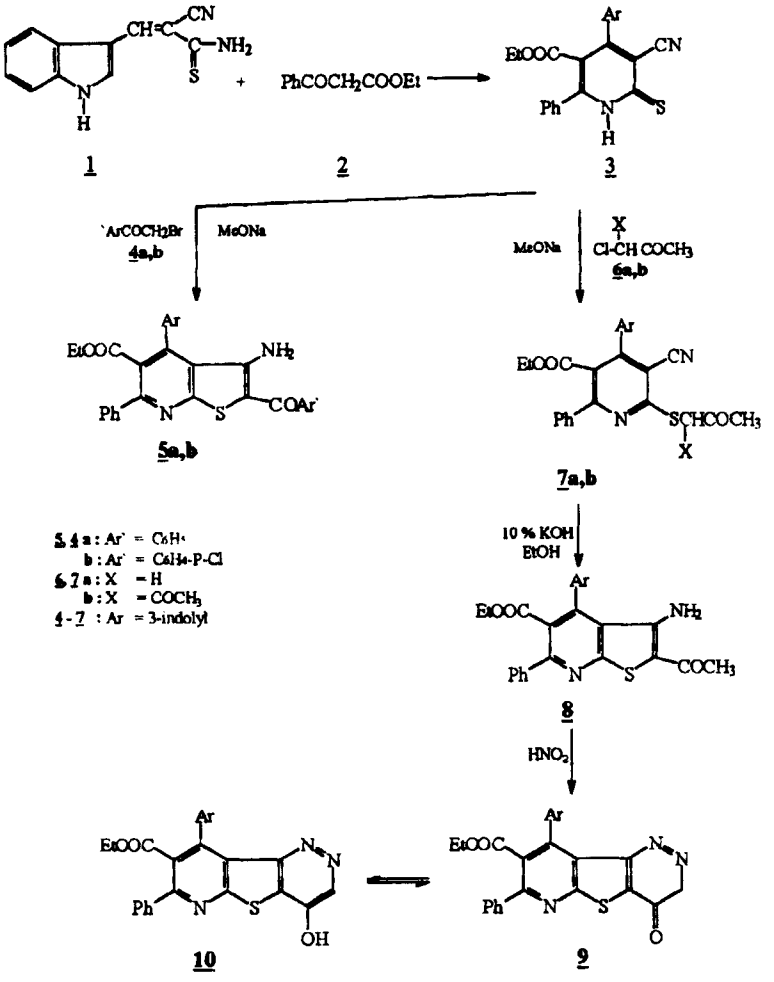


CHART 1

mulated as thieno[2,3-b]pyridine derivative **8**. The formation of **8** involved the addition of the two hydrogens of the acetonyl-CH_2 and one hydrogen of the diacetyl-CH in **7a,b** respectively, to the nitrile function to afford **8** directly in case of **7a** while in case of **7b** gave the non-isolable diacetyliminothieno[2,3-b]pyridine which add one molecule of water to give acetic acid and **8**. A solid evidence ofthe structure **8** was obtained via its reaction with nitrous acid (cold solution of sodium nitrite and HCl) to give product free from the bands of NH_2 in its IR spectrum. Moreover, this spectrum showed clearly the presence of an OH group and this more established by the intense blue colouration developed in the treatment of its ethanolic solution with $FeCl_3$. Based on the above facts the

reaction product could be formulated as the pyrido[2',3' :4,5]thieno[2,3-b]pyridazine derivative **10** rather than pyridazinone derivative **9** (cf. Chart 1).

A further demonstration of the **3** activity was achieved by its reaction with some other halogenated ester. Thus, it has been found that **3** reacted with ethyl chloroacetate and α-chloroacetoacetate **11a,b** respectively in boiling methanolic sodium methoxide to give 2-S-ethoxycarbonyl methyl pyridine and 2-S-(acetyl ethoxycarbonyl)methyl pyridine derivatives **12a,b** respectively. The structures of **12a,b** was established via its cyclization with boiling ethanolic KOH to afford one and the same reaction product **13.** The IR spectrum of **13** showed the absence of CN and acetonyl CO groups. Also, the ^{1}H-NMR spectrum revealed no signals corresponding to $COCH_3$, CH or CH_2 protons in **12a,b.** Based on the above data the reaction product could be formulated as thieno[2,3-b]pyridine derivative **13.** The formation of **13** involved initial addition of one hydrogen (S-CH) and two hydrogens ($S-CH_2$) to the nitrile function of **12a,b** to give directly **13** in case of **12a** while in case of **12b** give non-isolable iminothienopyridine intermediate which can add one molecule of water to eliminate one acetic acid molecule and the final isolable product **13** (cf. Chart 2). The activity of the ethoxycarbonyl group in each of **13** and **12b** was confirmed by their reaction with hydrazine hydrate. Thus, the reaction of both **13** and **12b** with hydrazine hydrate gave one and the same reaction product **14**. The IR and ^{1}H-NMR spectrum confirm the presence of one NH and two NH_2 groups (cf. Table II) in the reaction product **14**. Collecting the above data together, this reaction product could be formulated as acid hydrazidethieno[2,3-b]pyridine derivative **14**. The activity of hydrazide group in **14** could be demonstrated via its reaction with acetylacetone, cinnamonitrile derivatives, aromatic aldhydes, anhydrous formic acid and glacial acetic acid. Thus, it has been found that **14** reacted with acetylacetone (**15**) in pyridine to afford product corresponded to addition of one molecule of **15** to one molecule of **14** followed by loss of two water molecules. The mass spectrum of the reaction product gave m / e = 534 which corresponded to molecular formula $C_{30}H_{24}N_5SO_3$, based on elemental analysis, IR and ^{1}H-NMR spectral data the reaction product could be formulated as 2-(3',5'-dimethylpyrazolo-l'-oyl)thieno[2,3-b]pyridine derivative **16** (cf. Tables I and II).

Compound **14** reacted also with either α-cyanocinnamonitriles **17a,b** or aromatic aldhydes **18a,b** in pyridine to yield one and the same reaction product **19a,b** which could be formulated as the ylidene group exchange reaction product. The IR spectra of **19a,b** indicate the presence of only one NH and one NH_2 group. Also three exchangeable protons of NH and NH_2 groups were revealed in its ^{1}H-NMR spectra. The mass spectrum of **19a** gave m / e - 559.

A final proof of **14** structure came from its reaction with both anhydrous formic acid and glacial acetic acid to yield pyrido[2',3':4,5]-thieno[3,2-d]pyridinone derivative **20** and the deaminative cyclization reaction product **21** respectively. The IR spectrum of **21** showed the absence of NH_2 group and its ^{1}H-NMR spectrum revealed the presence of only two exchangeable protons (NH and OH).

Based on the above data the deaminative cyclization reaction product could be formulated as pyrazolino[3',4': 4,5]thieno[2,3-b]pyridine derivative **21** (cf. Chart 2).

The interest in the chemistry of **3** was also continued to shed more light on its chemical reactivity and its utility in the synthesis of an additional number of new heterocycles. Thus, it has been found that **3** reacted with chloroacetamide (**22**) in methanolic sodium methoxide to yield the corresponding 2-S-(carboxamido)methyl pyridine derivative **23** whose structure was established based on correct elemental analysis, IR and ^{1}H-NMR spectral data gave the expected values as required for the assigned structure. Compound **23** could be cyclized by boiling their ethanolic solutions with 10 % KOH proceeded via addition of the active CH_2 group to the CN to give the corresponding thieno[2,3-b]pyridine derivative **24** (cf. Tables I and II).

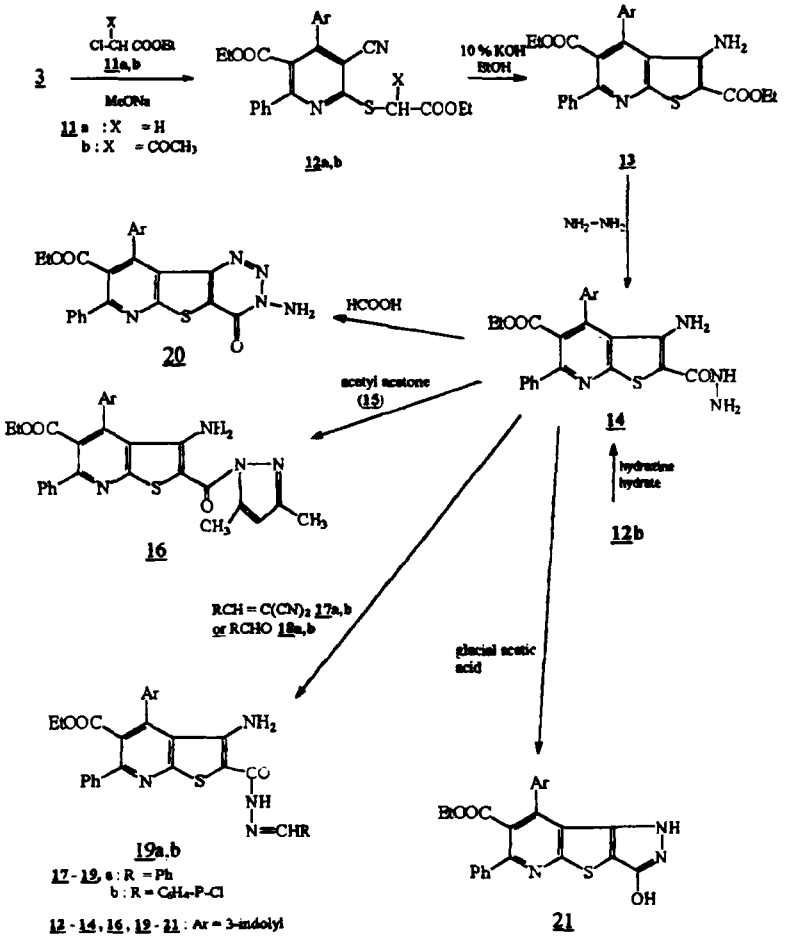
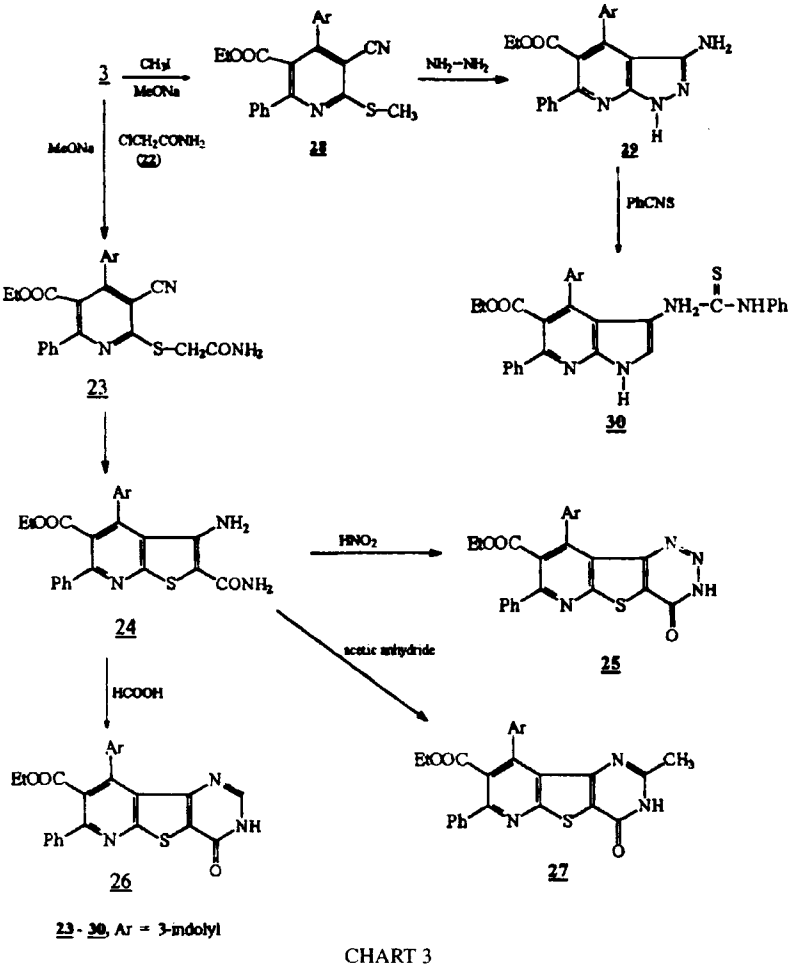


CHART 2

The enaminoamidic moiety in **24** seemed to be an excellent candidate for the synthesis of other heterocyclic derivatives which are expected to be difficulty obtained via other routes. Thus, it has been found that **24** reacted with nitrous acid to give the corresponding pyrido[2',3';5,4]thieno[3,2-b]-1,2,3-triazin-4-one **25** which most likely proceeded via the initial diazotization of the NH_2 group followed by dehydrochlorination to give **25.** On the other hand, compound **24** reacted with anhydrous formic acid to give the corresponding pyrido[2',3':5,4]-thieno[3,2-d]pyrimidin-4-one derivative **26** its mass spectrum gave m/e = 466 which corresponds to molecular formula $C_{26}H_{18}N_4SO_3$. An interesting acetylative cyclization reaction of **24** took place via its reaction with acetic anhydride to give compound **27**. The structures of **25, 26, 27** were confirmed based on elemental analysis, IR and ^{1}H-NMR spectral data (cf. Chart 3, Tables I and II).



23 - 30, Ar = 3-indolyl

CHART 3

TABLE I Characterization Data of the Newly Synthesized Compounds

Comp.	*solvent of crystall.*	*mp°C*	*Yield (%)*	*Molecular formula*	*% Analysis (calcd. / found)*				
					C	*H*	*N*	*S*	*Cl*
3	Acetic acid	220	82	$C_{23}N_{17}N_3SO_2$	69.17 69.2	4.26 4.3	10.52 10.6	8.02 8.1	– –
5a	Ethanol	170	85	$C_{31}H_{23}N_3SO_3$	71.95 72.0	4.45 4.5	8.12 8.2	6.19 6.2	– –
5b	Ethanol	150-2	80	$C_{31}H_{22}N_3SO_3Cl$	67.45 67.5	3.99 4.0	7.62 7.7	5.80 5.90	6.44 6.5
7 a	Ethanol	110-3	78	$C_{26}H_{32}N_3SO_3$	68.57 68.6	4.62 4.7	9.23 9.3	7.03 7.1	– –
7 b	Ethanol	122-2	83	$C_{28}H_{23}N_3SO_4$	67.47 67.5	4.82 4.9	8.43 8.5	6.43 6.5	– –
8	Acetic acid	150	87	$C_{26}H_{21}N_3SO_3$	68.57 68.6	4.62 4.7	9.23 9.3	7.03 7.1	– –
10	Ethanol	80 dec.	82	$C_{26}H_{18}N_4SO_3$	66.95 67.0	3.86 3.9	12.02 12.1	6.87 7.0	– –
12 a	Ethanol	210	85	$C_{27}H_{23}N_3SO_4$	66.8 66.9	4.74 4.8	8.66 8.7	6.6 6.7	– –
12 b	Ethanol	118	79	$C_{29}H_{25}N_3SO_4$	68.10 68.2	4.89 4.9	8.22 8.3	6.26 6.3	– –
13	Acetic acid	185	80	$C_{27}H_{23}N_3SO_4$	66.8 66.9	4.74 4.8	8.66 8.7	6.60 6.7	– –
14	Ethanol	201	83	$C_{25}H_{21}N_5SO_3$	63.69 63.7	4.46 4.5	14.86 15.0	6.79 7.0	– –
16	Acetic acid	160	85	$C_{30}H_{25}N_5SO_3$	67.42 67.5	4.49 4.5	13.11 13.2	5.99 6.0	– –
19 a	Acetic acid	250	73	$C_{32}H_{25}N_5SO_3$	68.69 68.7	4.47 4.5	12.52 12.6	5.72 5.8	– –
19 b	Acetic acid	275	87	$C_{32}H_{24}N_5SO_3Cl$	64.7 64.8	4.04 4.1	11.79 11.8	5.39 5.4	5.98 6.0
20	Ethanol	235	72	$C_{26}H_{19}N_5SO_3$	64.86 64.9	3.95 4.0	14.55 14.6	6.65 6.7	– –
21	Acetic acid	310	70	$C_{25}H_{18}N_4SO_3$	66.08 66.1	3.96 4.0	12.33 12.4	7.05 7.1	– –
23	Ethanol	188-9	79	$C_{25}H_{20}H_4SO_3$	65.79 65.8	4.39 4.4	12.28 12.3	7.02 7.0	– –
24	Acetic acid	200-1	87	$C_{25}H_{20}N_4SO_3$	65.79 65.8	4.39 4.4	12.28 12.3	7.02 7.0	– –
25	Ethanol	160 dec.	82	$C_{25}H_{17}N_5SO_3$	64.24 64.3	3.64 3.7	14.99 15.0	6.85 6.9	– –
26	Ethanol	305	74	$C_{26}H_{18}N_4SO_3$	66.95 67.0	3.86 3.9	12.01 12.0	6.87 6.9	– –
27	Acetic acid	280	79	$C_{27}H_{20}N_4SO_3$	67.5 67.6	4.17 4.2	11.67 11.7	6.67 6.7	– –
28	Ethanol	150	85	$C_{24}H_{19}N_3SO_2$	69.73 69.7	4.60 4.6	10.17 10.1	7.75 7.8	– –
29	Ethanol	180	84	$C_{23}H_{19}N_5SO_2$	69.52 69.5	4.79 4.8	17.63 17.6	8.06 8.1	– –
30	Ethanol	270	82	$C_{30}H_{24}N_6SO_2$	67.67 67.7	4.51 4.5	4.51 4.5	15.79 15.8	– –

TABLE II IR and ^{1}H-NMR Spectral Data

Compound	*IR (KBr, cm^{-1})*	*1H-NMR (δ ppm)*
3	3479, 3200 (two NH); 3040 (aromatic C-H); 2940 (sat. C-H); 2225 (CN); 1720 (ester CO) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 3.4 (q, 2H, $\underline{CH_2}CH_3$); 4.4 (s, 1H, CH-indolyl); 4.8 (s, br., 1H, NH indolyl), 6.3 (s, br., 1H, NH pyridine) and 7.1 - 8.2 (m, 9H, ArH'S).
5a	3470, 3320, 3180 (NH_2 and NH); 3070 (aromatic C-H); 2940 (sat. C-H); 1725 (ester CO), 1710 (ketone CO) and 1600 (C=C).	1.1 (t, 3H, $CH_2\underline{CH_3}$); 3.5 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (s, 1H, CH-indolyl); 4.7 (s, br., 1H, NH, indolyl), 6.5 (s, br., 2H, NH_2) and 7.1 - 8.2 (m, 14H, ArH'S).
7b	3180 (NH); 3060 (aromatic C-H); 2980 (aliphatic C-H); 2220 (CN); 1725 (ester C=O) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 2.3 (s, 6H, $CH(CO\underline{CH_3})_2$); 3.1 (s, 1H, $\underline{CH}$-$(COCH_3)_2$); 3.7 (q, 2H, $\underline{CH_2}CH_3$); 4.5 (s, 1H, CH-indolyl); 5.1 (s, br., 1H, NH-indolyl); and 7.0 - 8.3 (m, 9H, ArH'S).
8	3470, 3330, 3200 (NH_2 and NH); 3070 (aromatic C-H); 2980 (aliphatic C-H); 1715 (CO acetyl) and 1600 (C=C).	1.1 (t, 3H, $CH_2\underline{CH_3}$); 2.6 (s, 3H, $CO\underline{CH_3}$); 3.5 (q, 2H, $\underline{CH_2}CH_3$); 4.2 (s, 1H, CH-indolyl); 4.8 (s, br., 1H, indolyl-NH), 6.2 (s, br., 2H, NH_2) and 7.1 - 8.5 (m, 9H, ArH'S).
10	3220 (OH); 3180 (NH); 3050 (aromatic C-H); 2980 (aliphatic C-H); 1720 (ester CO), 1625 (N=N) and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 3.1 (s, 1H, CH-pyridazine); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (s, 1H, CH-indolyl); 4.9 (s, br., 1H, indolyl-NH), 7.0 - 8.1 (m, 9H, ArH's) and 12.1 (s, br., 1H, OH).
12a	3185 (NH); 3060 (aromatic C-H); 2980 (aliphatic C-H); 2220 (CN); 1740 (ester CO); 1720 (ester CO at pyridine) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$ at pyridine); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 3.5 (q, 2H, $\underline{CH_2}CH_3$ at pyridine); 3.8 (s, 2H, S-CH_2); 4.5 (q, 2H, $\underline{CH_2}CH_3$); 4.7 (s, 1H, CH-indolyl); 5.2 (s, 1H, indolyl-NH) and 7.2 - 8.5 (m, 9H, ArH'S).
13	3460, 3335, 3190 (NH_2 and NH); 3060 (aromatic C-H); 2985 (aliphatic C-H); 1725 (ester CO at pyridine); 1670 (ester CO at thiophene) and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$ at pyridine); 1.2 (t, 3H, $CH_2\underline{CH_3}$ at thiophene); 3.5 (q, 2H, $\underline{CH_2}CH_3$ at pyridine); 3.9 (q, 2H, $\underline{CH_2}CH_3$ at thiophene); 4.5 (s, 1H, CH-indolyl); 5.1 (s, br., 1H, indolyl-NH); 5.9 (s, br., 2H, NH_2) and 7.1 - 8.3 (m, 9H, ArH'S).
14	3480, 3360, 3230, 3200 (two NH_2 and NH); 3030 (aromatic C-H); 2975 (aliphatic C-H); 1720 (ester CO); 1635 (CO hydrazide) and 1600 (C=C).	0.95 (t, 3H, $CH_2\underline{CH_3}$); 3.0 (s, br., 2H, NH_2 at thiophene); 4.2 (q, 2H, $\underline{CH_2}CH_3$); 4.6 (s, br., 1H, CH-indolyl); 5.1 (s, br., 1H, indolyl-NH); 5.9 (s, br., 2H, $CONH\underline{NH_2}$); 6.6 (s, br., 1H, $CO\underline{NH}NH_2$); and 7.3 - 8.5 -(m, 9H, ArH'S).
16	3490, 3340, 3200 (NH_2 and NH); 3050 (aromatic C-H); 2980 (aliphatic C-H); 1730 (ester CO); 1680 (CO at thiophene); 1635 (C=N) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3 at 3-pyrazole); 2.8 (s, 3H, CH_3 at 5-pyrazole); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.5 (s, 1H, CH-indolyl); 4.9 (s, br., 1H, indolyl-NH); 5.9 (s, 1H, pyrazole H-4); 6.4 (s, br., 2H, NH_2) and 7.0 - 8.2 (m, 9H, ArH'S).
19 b	3485, 3340, 3200, 3160 (NH_2 and two NH); 3050 (aromatic C-H); 2985 (aliphatic C-H); 1730 (ester CO); 1640 (CO hydrazide); 1620 (C=N) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 3.8 (q, 2H, $\underline{CH_2}CH_3$); 4.4 (s, 1H, CH-indolyl); 4.9 (s, br., 1H, NH-indolyl); 5.8 (s, br., 2H, NH_2); 6.9 (s, br., 1H, -NH-N=CHR) and 7.2-8.5 (m, 10H, ArH'S and -N=CHR).

TABLE II (Continued).

Compound	*IR (KBr, cm^{-1}*	*1H-NMR (δ ppm)*
20	3340, 3250, 3201, (NH_2 and NH); 3050 (C-H aromatic); 2970 (C-H aliphatic); 1725 (CO ester); 1680 (CO pyrimidinone); 1620 (C=N) and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.5 (s, 1H, CH-indolyl); 4.9 (s, br., 1H, indolyl-NH); 6.4 (s, br., 2H, NH_2) and 7.2 - 8.4 (m, 10H, ArH'S and pyrimidinone H-2).
21	3470 (OH); 3215, 3200 (two NH); 3050 (C-H aromatic); 2985 (C-H aliphatic); 1725 (CO ester); 1725 (CO ester); 1625 (C=N) and 1600 (C=C).	0.97 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.5 (s, 1H, indolyl CH); 5.6 (s, br., 2H, two NH); 7.0 - 8.2 (m, 9H, ArH's) and 12.2 (s, br., 1H, OH).
23	3340, 3280, 3190 (NH_2 and NH); 3070 (aromatic C-H); 2980 (aliphatic C-H); 2220 (CN); 1715 (ester CO); 1690 (amidic CO); and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 3.8 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (s, 2H, S-CH_2); 4.6 (s, 1H, indolyl-CH); 5.8 (s, br., 3H, NH_2 and NH) and 7.0 - 8.2 (m, 9H, ArH's).
24	3480, 3390, 3340, 3220, 3150 (two NH_2 and NH); 3060 (aromatic C-H); 2980 (aliphatic C-H); 1725 (ester CO); 1670 (amidic CO) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.4 (s, 1H, indolyl-CH); 4.9 (s, 1H, indolyl-NH); 5.4 (s, br., 2H, $\underline{NH_2}$); 5.9 (s, br., 2H, $CO\underline{NH_2}$) and 7.2 - 8.2 (m, 9H, ArH's).
25	3205, 3150 (two NH); 3080 (aromatic C-H); 2970 (aliphatic C-H); 1735 (ester CO); 1695 (triazin-one CO) and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 3.5 (q, 2H, $\underline{CH_2}CH_3$); 4.4 (s, 1H, indolyl-CH); 4.9 (s, br., 1H, indolyl-NH); 6.3 (s, br., 1H, triazinone-NH) and 7.2 - 8.4 (m, 9H, ArH'S).
26	3208, 3180 (two NH); 3060 (aromatic C-H); 2980 (aliphatic C-H); 1730 (ester CO); 1670 (pyrimidinone CO) and 1600 (C=C).	0.98 (t, 3H, $CH_2\underline{CH_3}$); 3.8 (q, 2H, $\underline{CH_2}CH_3$); 4.5 (s, 1H, indolyl-CH); 5.1 (s, br., 1H, indolyl-NH); 6.6 (s, br., 1H, pyrimidinone-NH) and 7.0 - 8.2 (m, 10H, ArH'S and pyrimidinone H-2).
27	3200, 3170 (two NH); 3070 (aromatic C-H); 2985 (aliphatic C-H); 1728 (ester CO); 1660 (pyrimidinone CO) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 1.4 (s, 3H, pyrimidinone CH_3); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (s, 1H, indolyl-CH); 4.9 (s, br., 1H, indolyl-NH); 6.4 (s, br., 1H, pyrimidinone-NH) and 7.0 - 8.3 (m, 9H, ArH'S).
28	3080 (aromatic C-H); 2985 (aliphatic C-H); 2225 (CN); 1730 (ester CO) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 1.5 (s, 3H, S-$\underline{CH_3}$); 3.7 (q, 2H, $\underline{CH_2}CH_3$); 4.2 (s, 1H, indolyl-CH); 4.9 (s, br., 1H, indolyl-NH) and 7.0 - 8.2 (m, 9H, ArH'S).
29	3470, 3290, 3200, 3180 (two NH_2 and two NH); 3050 (aromatic C-H); 2970 (aliphatic C-H); 1730 (ester CO) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 3.6 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (s, 1H, indolyl-CH); 4.8 (s, br., 1H, indolyl-NH); 5.4 (s, br., 2H, NH_2); 6.2 (s, br., 1H, pyrazole-NH) and 7.1 - 8.4 (m, 9H, ArH'S).
30	3400, 3220, 3200, 3160 (four NH); 3060 (aromatic C-H); 2975 (aliphatic C-H); 1725 (ester CO); 1630 (CN); 1600 (C=C) and 1550 (CS).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 3.7 (q, 2H, $\underline{CH_2}CH_3$); 4.4 (s, 1H, indolyl-CH); 4.8 (s, 1H, indolyl-NH); 6.0 - 6.5 (m, 3H, three NH for pyrazole and phenyl-thiourea) and 7.1 - 8.3 (m, 14H, ArH'S).

A further and last demonstration of the activity of **3** was achieved via its reaction with methyl iodide in methanolic sodium methoxide to give the corresponding 2-S-methylpyridine derivative **28**. The IR spectrum of **28** was found free from the band of NH group and this more confirmed from the singlet signal of S-$\underline{CH_3}$ proton in the ^{1}H-NMR spectrum (cf. Table II). An equivocal support for the structure of **28** came from its reaction with hydrazine hydrate to give the sulfur free reaction product. The IR of this reaction product showed no CN group and newly born NH_2 group will be detected. Based on both the above data and elemental analysis data this reaction product could be formulated as aminopyrazolo[3,4-b]pyridine derivative **29**. Compound **29** was thus involved into interesting chemical reaction to confirm the presence of NH_2 group. Thus, it has been found that **29** reacted with phenyl isothiocyanate in pyridine to afford the corresponding pyrazolo[3,4-b]pyridin-3-yl phenyl thiourea derivative **30**. The IR spectrum of **30** showed the presence of three NH (also in ^{1}H-NMR spectrum) in addition to C=S groups (cf. Tables I and II). Also the mass spectrum of **30** gave m/e = 532 which represent the exact molecular weight of formula $C_{30}H_{24}N_6SO_2$ in addition to the base peak at m/e = 397 due to the loss of PhNCS moiety.

EXPERIMENTAL

All melting points are **uncorrected.** IR spectra were recorded (KBr disc) on a Pye Unicam SP-1100 and Perkin-Elmer FT-IR type 4 spectrophotometers. ^{1}H-NMR spectra were recorded on Gemini 200 Hz and Brucker WP-80 spectrometers using TMS as internal standard and chemical shifts are expressed as δ ppm units using $DMSOd_6$, $CDCl_3$ and $(CD_3)_2CO$ as solvents. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using DIP technique at 15 eV and 70 eV. Microanalyses were performed by microanalytical center at Cairo University using Perkin-Elmer 2400 CHN Elemental analyzer.

SYNTHESIS OF THE STARTING MATERIAL 3

A mixture of 2-thiocarboxamido-3-(3'-indolyl)propionitrile (**1**) (0.01 mole) and ethylbenzoyl acetate (0.01 mole) in absolute ethanol (50 ml) containing the catalytic amounts of triethylamine (0.5 ml) and pyridine (5 ml) was heated under reflux for 6 hours. The reaction mixture was then evaporated till dryness and then cooled, acidified with acetic acid. The product formed was collected by filtration, washed with water and then crystallized from acetic acid to give **3**.

SYNTHESIS OF 5a,b, 7a,b, 12a,b, 23a,b and 28

A solution of **3** (0.01 mole) and each of ω-bromoacetophemone (**4a**), p-chloro-ω-bromoacetophenone (**4b**), chloroacetone (**6a**), chloro-acetylacetone (**6b**), chloroethylacetate (**11a**), chloroethylacetoacetate (**11b**), chloroacetamide (**22**) and methyl iodide (0.01 mole) was heated under reflux in methanolic sodium methoxide (0.01 atom of sodium in 30 ml methanol) for 3-5 hours. The reaction products obtained on hot or after cooling were filtered off and crystallized from ethanol to yield **5a,b, 7a,b, 12a,b, 23a,b** and **28** respectively (cf. Tables I and II).

SYNTHESIS OF 8, 13 and 24

A solution of each of **7a,b, 12a,b,** and **23a,b** in ethanol (30 ml) was heated under reflux for 5 hours with potassium hydroxide (0.01 mole). The reaction mixture was then cooled, acidified with dilute HCl. The solid products were filtered off, washed with water then crystallized from acetic acid to yield the cyclized products **8, 13,** and **24** respectively.

SYNTHESIS OF 10, and 25

A cold solution of each of **8** and **24** (0.01 mole) in concentrated HCl (1 ml) was treated with a cold saturated solution of sodium nitrile (0.015 mole) then stirred in ice-cold bath for one hour. The solid products obtained were filtered off, washed with water and crystallized from ethanol to yield **10,** and **25** respectively (cf. Tables I and II).

SYNTHESIS OF 20, and 26

A solution of each of **14** and **24** (0.01 mole) and formic acid (30 ml) was heated under reflux for 5 hours. The solid products obtained after cooling were filtered off and crystallized from ethanol to yield **20** and **26** respectively (cf. Tables I and II).

SYNTHESIS OF 16, and 19a,b

A solution of **14** (0.01 mole) in ethanol (30 ml) containing triethylamine (0.5 ml) / pyridine (5 ml) was heated with acetylacetone, cinnamonitrile derivatives **17a,b** or aromatic aldhydes **18a,b** (0.01 mole) for 4 hours. The solids obtained on hot or after cooling were filtered off and crystallized from acetic acid to yield **16**, and **19a,b** respectively (cf. Tables I and II).

SYNTHESIS OF 14, and 29

A solution of each **13** (or **12b**) and **28** (0.01 mole) in ethanol (30 ml) was treated with hydrazine (10 ml) and then heated under reflux for 8 hours. The solid products obtained on hot or after cooling were filtered off and crystallized from ethanol to yield **14**, and **29** respectively (cf. Tables I and II).

SYNTHESIS OF 21 and 27

A solution of **14** (0.01 mole) in glacial acetic acid (30 ml) and a solution of **24** (0.01 mole) in acetic anhydride (30 ml) were heated under reflux for 5 hours. The solid products obtained after cooling were filtered off and crystallized from acetic acid to yield **21** and **27** respectively (cf. Tables I and II).

SYNTHESIS OF 30

A solution of **29** (0.01 mole) in pyridine (30 ml) was treated with phenyl isothiocynate (0.01 mole). The reaction mixture was heated under reflux for 5 hours then cooled, poured onto ice-cold water and acidified by dilute HCl. The solid product obtained was filtered off, washed with water and crystallized from ethanol to yield **30** (cf. Tables I and II).

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