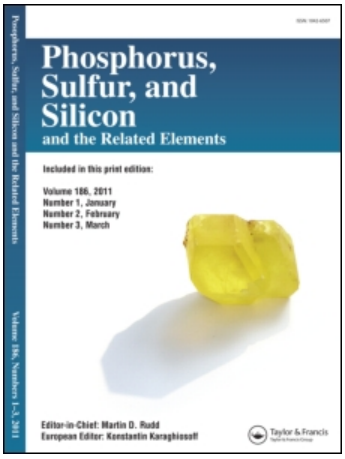

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REACTIONS OF α-THIOCARBOXAMIDOCINNA-MONITRILE DERIVATIVES WITH DIETHYL MALONATE: SYNTHESIS OF PYRAZOLO-[3,4-b]-α-PYRIDINONE, THIENO[2,3-b]-α-PYRIDINONE, PYRIDO[2,3:4',5']THIENO[2,3-c]PYRIDAZINE AND PYRIDO[2,3:4',5']-THIENO[2,3-d]PYRIMIDINONETHIONE DERIVATIVES

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REACTIONS OF α-THIOCARBOXAMIDOCINNAMONITRILE DERIVATIVES WITH DIETHYL MALONATE: SYNTHESIS OF PYRAZOLO-[3,4-b]-α-PYRIDINONE, THIENO[2,3-b]-α-PYRIDINONE, PYRIDO[2,3:4′,5′]THIENO[2,3-c]PYRIDAZINE AND PYRIDO[2,3:4′,5′]-THIENO[2,3-d]PYRIMIDINONETHIONE DERIVATIVES

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3-Cyano-4-aryl-5-ethoxycarbonyl-6-pyridinone-2-thione derivatives **3a–c** reacted with several halogen-containing compounds to give the corresponding 2-S-methylpyridinones **4a–c**, 2-S-acetonyl pyridinones **7a–c**, 2-S-benzoyl methyl pyridinones **12a–c**, 2-S-acetamidopyridinones **15a–c** and 2-S-ethoxycarbonyl methylpyridinones **20a–c**. The ethanolic solution of KOH used as a cyclization agent to give the corresponding thieno[2,3-b]pyridines **8a–c**, **13a–c**, **16a–c** and **21a–c**. Hydrazine hydrate, nitrous acid, carbon disulphide, acetic anhydride, formic acid, acetic acid and acetyl acetone gave further cyclization to construct an additional ring.

Keywords: pyridinonethiones; pyrazolo[3,4-b]pyridines; pyridothienopyridazines; pyridothienopyrimidinonethiones; pyridothienopyrazole; pyridothienopyrimidininoes

INTRODUCTION

In conjunction with our previous work[1–5] our research group had been interested in the chemistry of pyridines and its derivatives. The expected biological activities of pyridines as antidepressant,[6] fungicidal agents[7] and antimycotic

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agents[8] as well as thienopyridines as antithrombotic[9–11] agents against the platelet aggregation, stimulated our interest in the synthesis of several newly synthesized derivatives of these ring systems which are required for our medicinal chemistry program.

Geies et al[12] reported that the arylidenes of diethyl malonate reacted with cyanothioacetamide in basic medium to give the pyridinonethione derivative **3a**. In our laboratory the same reaction product **3a** resulted by the reaction of α-thiocarboxamidocinnamonitrile **1a** and diethyl malonate in ethyl alcohol containing the catalytic amounts of triethylamine in a better yield and in purer state than that given by Geies et al. It is important to report here that both our reaction product and the product of Geies et al are identical in all aspects (m.p., mixed mp., IR, ^{1}H-NMR and mass spectral data). Analogues of **3a** could be prepared and used as a basic starting materials of the present study.

The compounds **3a–c** reacted with methyl iodide, chloroacetone (**6a**), 3-chloro-2,4-pentanedione (**6b**) phenacyl bromide (**11**), chloroacetamide (**14**), ethyl chloroacetate (**19a**) and ethyl-α-chloroacetoacetate (**19b**) to give 2-S-methylpyridinone derivatives **4a–c**, 2-S-acetonyl pyridinone derivatives **7a–c**, thieno[2,3-b]pyridine derivatives **8a–c**, 2-S-benzoyl methyl pyridinone derivatives **12a–c**, 2-S-acetamidopyridinone derivatives **15a–c**, 2-S-ethoxycarbonyl methyl pyridinone derivatives **20a–c** and thieno[2,3-b]pyridinone derivatives **21a–c** respectively. Hydrazine hydrate reacted with **4a–c** to give the corresponded pyrazolo[3,4-b]pyridine derivatives **5a–c**. An ethanolic solution of KOH could be used to cyclize compound **7a–c**, **12a–c**, **15a–c** and **20a–c** to give the corresponded thieno[2,3-b]pyridine derivatives **8a–c**, **13a–c**, **16a–c** and **21a–c** respectively. An additional third ring was built via the use of nitrous acid, acetic anhydride, carbon disulphide, acetic acid, formic acid and acetylacetone. Elemental analyses, IR, ^{1}H-NMR and mass spectra were used as good tools for the structural establishment of the all newly synthesized compounds.

RESULTS AND DISCUSSION

It has been found that 3-cyano-4-phenyl-5-ethoxycarbonyl-6-pyridinone-2-thione (**3a**) reacted with methyl iodide in sodium methoxide to give product via the loss of hydrogen iodide. This reaction product could be formulated as the 2-S-methyl pyridinone derivatives **4a**. The structure of **4a** was established based on IR, ^{1}H-NMR and elemental analyses (cf. Tables I and II). A good structure proof of **4a** was given via its reaction with hydrazine hydrate. The reaction product was sulfur-free and in its IR (cm^{-1}) the CN group was absent and replaced by the newly born NH_2 group. Its ^{1}H-NMR spectrum has no signals

TABLE I Characterization data of the newly synthesized compounds.

Comp.	*M.P. (C°)*	*Yield (%)*	*Solvent of cryst.*	*Molecular formula*	*% of Analysis calcd./found*				
					C	*H*	*N*	*S*	*Cl*
3b	190	74	Acetic acid	$C_{15}H_{11}N_2SO_3Cl$	53.81	3.29	8.37	9.57	10.61
					53.9	3.3	8.4	9.6	10.6
3c	200	82	Ethanol	$C_{13}H_{10}N_2SO_4$	53.79	3.45	9.66	11.03	—
					53.8	3.5	9.7	11.1	—
4a	170	66	Ethanol	$C_{16}H_{14}N_2SO_3$	61.15	4.46	8.92	10.19	—
					61.2	4.5	8.9	10.2	—
4b	122	73	Ethanol	$C_{16}H_{13}N_2SO_3Cl$	60.66	4.11	8.85	10.11	11.22
					60.7	4.1	8.9	10.2	11.2
4c	110	80	Ethanol	$C_{14}H_{12}N_2SO_4$	55.26	3.95	9.21	10.53	—
					55.3	4.0	9.2	10.6	—
5a	300	60	Acetic acid	$C_{13}H_{10}N_6O$	58.65	3.76	31.58	—	—
					58.7	3.8	31.6	—	—
5b	230	75	Acetic acid	$C_{13}H_9N_6OCl$	51.91	3.00	27.95	—	11.81
					52.0	3.0	27.9	—	11.8
5c	275	82	Ethanol	$C_{11}H_8N_6O_2$	51.56	3.13	32.81	—	—
					51.6	3.2	32.8	—	—
7a	290	85	Ethanol	$C_{18}H_{16}N_2SO_4$	60.74	4.49	7.87	8.99	—
					60.7	4.5	7.9	9.0	—
7b	250	84	Ethanol	$C_{18}H_{15}N_2SO_4Cl$	55.31	3.84	7.17	8.19	9.09
					55.3	3.8	7.2	8.2	9.1
7c	230	80	Acetic acid	$C_{16}H_{14}N_2SO_5$	55.49	4.05	8.09	9.25	—
					55.5	4.1	8.1	9.2	—
8a	>300	76	DMF	$C_{18}H_{16}N_2SO_4$	60.64	4.49	7.87	8.99	—
					60.6	4.5	7.9	8.9	—
8b	290	82	Acetic acid	$C_{18}H_{15}N_2SO_4Cl$	55.31	3.84	7.17	8.19	9.09
					55.3	3.8	7.2	8.2	9.1
8c	305	86	DMF	$C_{16}H_{14}N_2SO_5$	55.49	4.05	8.09	9.25	—
					55.5	4.1	8.1	9.3	—
10a	105 dec.	82	Ethanol	$C_{18}H_{13}N_3SO_4$	58.86	3.54	11.44	8.72	—
					58.9	3.5	11.4	8.7	—
10b	78 dec.	87	Ethanol	$C_{18}H_{12}N_3SO_4Cl$	53.80	2.99	10.46	7.97	8.84
					53.8	3.0	10.5	8.0	8.8
10c	120 dec.	74	Ethanol	$C_{16}H_{11}N_3SO_5$	53.78	3.08	11.76	8.96	—
					53.8	3.1	11.8	9.0	—
12a	180	65	Ethanol	$C_{23}H_{18}N_2SO_4$	66.03	4.31	6.70	7.66	—
					66.1	4.3	6.7	7.7	—
12b	250	60	Ethanol	$C_{23}H_{17}N_2SO_4Cl$	60.99	3.77	6.19	7.07	7.85
					61.0	3.8	6.2	7.1	7.9
12c	230	67	Acetic acid	$C_{21}H_{16}N_2SO_5$	61.76	3.92	6.86	7.84	—
					61.8	3.9	6.9	7.9	—
13a	320	85	DMF	$C_{23}H_{18}N_2SO_4$	66.03	4.31	6.70	7.66	—
					66.0	4.3	6.7	7.7	—
13b	315	70	DMF	$C_{23}H_{17}N_2SO_4Cl$	60.99	3.77	6.19	7.07	7.85
					61.0	3.8	6.2	7.1	7.9
13c	>300	64	Acetic acid	$C_{21}H_{16}N_2SO_5$	61.76	3.92	6.86	7.84	—
					61.8	3.9	6.9	7.8	—
15a	230	84	Acetic acid	$C_{17}H_{15}N_3SO_4$	57.14	4.20	11.76	8.96	—
					57.1	4.2	11.8	9.0	—
15b	280	60	Acetic acid	$C_{17}H_{14}N_3SO_4Cl$	52.11	3.58	10.73	8.17	9.07

TABLE I *continued*

Comp.	*M.P. (C°)*	*Yield (%)*	*Solvent of cryst.*	*Molecular formula*	*% of Analysis calcd./found*				
					C	*H*	*N*	*S*	*Cl*
					52.1	3.6	10.8	8.1	9.0
15c	295	73	DMF	$C_{15}H_{13}N_3SO_5$	51.87	3.75	12.10	9.22	—
					51.8	3.8	12.1	9.2	—
16a	170	78	Ethanol	$C_{17}H_{15}N_3SO_4$	57.14	4.20	11.76	8.96	—
					57.2	4.2	11.8	8.9	—
16b	207	82	Ethanol	$C_{17}H_{14}N_3SO_4Cl$	52.11	3.58	10.73	8.17	9.07
					52.1	3.6	10.8	8.2	9.1
16c	225	88	Acetic acid	$C_{15}H_{13}N_3SO_5$	51.87	3.75	12.10	9.22	—
					51.9	3.7	12.1	9.3	—
17a	> 300	60	Ethanol	$C_{18}H_{13}N_3S_2O_4$	54.14	3.26	10.53	16.04	—
					54.2	3.2	10.5	16.1	—
17b	260	84	Ethanol	$C_{18}H_{12}N_3S_2O_4Cl$	49.88	2.77	9.69	14.76	8.19
					49.8	2.8	9.7	14.7	8.2
17c	315	70	DMF	$C_{16}H_{11}N_3S_2O_5Cl$	49.36	2.83	10.80	16.45	—
					49.4	2.9	10.8	16.5	—
18a	> 300	82	Ethanol	$C_{19}H_{15}N_3SO_4$	59.84	3.94	11.02	8.40	—
					60.0	4.0	11.1	8.4	—
18b	287	75	Acetic acid	$C_{19}H_{14}N_3SO_4Cl$	54.87	3.37	10.11	7.70	8.54
					54.9	3.4	10.2	7.7	8.6
18c	269	65	Acetic acid	$C_{17}H_{13}N_3SO_5$	54.99	3.50	11.32	8.63	—
					55.0	3.5	11.3	8.7	—
20a	180	66	Ethanol	$C_{19}H_{18}N_2SO_5$	59.07	4.66	7.25	8.29	—
					59.0	4.7	7.3	8.3	—
20b	150	75	Ethanol	$C_{19}H_{17}N_2SO_5Cl$	54.22	4.04	6.66	7.61	8.44
					54.2	4.1	6.7	7.6	8.5
20c	175	70	Athanol	$C_{17}H_{16}N_2SO_6$	54.26	4.26	7.45	8.51	—
					54.3	4.3	7.5	8.5	—
21a	220	68	Ethanol	$C_{19}H_{18}N_2SO_5$	59.07	4.66	7.25	8.29	—
					59.1	4.6	7.2	8.3	—
21b	210	86	Acetic acid	$C_{19}H_{17}N_2SO_5Cl$	54.22	4.04	6.66	7.61	8.44
					54.3	4.0	6.6	7.7	8.5
21c	260	66	DMF	$C_{17}H_{16}N_2SO_6$	54.26	4.26	7.45	8.51	—
					54.3	4.2	7.5	8.6	—
22a	283	70	Acetic acid	$C_{15}H_{12}N_6SO_2$	52.94	3.35	24.71	9.41	—
					52.9	3.4	24.8	9.4	—
22b	275	70	Ethanol	$C_{15}H_{11}N_6SO_2Cl$	48.06	2.94	22.43	8.54	9.48
					48.1	2.9	22.5	8.5	9.5
22c	290	82	DMF	$C_{13}H_{10}N_6SO_3$	47.27	3.03	25.45	9.70	-
					47.3	3.1	25.5	9.7	—

of SCH_3 protons while signals of NH and NH_2 protons were detected. Based on both the above data and elemental analyses this reaction product could be formulated as pyrazolo[3,4-b]pyridine derivative **5a**. Moreover, the mass spectrum of **5a** gave m/z = 266 (100%) which corresponded to the exact molecular weight of the molecular formula $C_{13}H_{10}N_6O$ of the assigned structure (Chart 1).

In a similar manner **3b,c** reacted under the same experimental conditions to give the 2-S-methylpyridinone derivatives **4b,c** which also, reacted with hydrazine hydrate to afford the corresponded pyrazolo[3,4-b]pyridine derivatives **5b,c**.

TABLE II IR (cm^{-1}) and ^{1}H-NMR (δppm) Spectral data

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δppm)*
3b	3185 (NH); 3040 (aromatic CH); 2950 (aliphatic CH); 2220 (CN); 1725 (ester CO), 1680 (amidic CO) and 1600 (C=C).	0.9 (t, 3H, CH_2CH_3); 3.6 (q, 2H, CH_2CH_3); 5.7 (s, br., 1H, NH) and 7.0–7.8 (m, 5H, Ar H's and pyridine H-5)
3c	3192 (NH); 2970 (alphatic CH); 2222 (CN), 1728 (ester CO); 1690 (amidic CO) and 1600 (C=C)	0.9 (t, 3H, CH_2CH_3); 3.8 (q, 2H, CH_2CH_3); 5.9 (s, br., 1H, NH) and 6.3–7.5 (m, 4H, Furyl and pyridine H-5 protons).
4a	3070 (aromatic CH); 2950 (aliphatic CH); 2227 (CN); 1728 (ester CO), 1670 (amidic CO) and 1600 (C=C)	0.9 (t, 3H, CH_2CH_3); 1.4 (s, 3H, SCH_3); 3.9 (q, 2H, CH_2 CH_3) and 7.0–7.9 (m, 6H, Ar H's and pyridine H-5).
4c	2960 (aliphatic CH), 2225 (CN); 1730 (ester COO, 1675 (amidic CO) and 1600 (C=C)	0.9 (t, 3H, CH_2 CH_3); 1.3 (s, 3H, SCH_3); 4.0 (q, 2H, CH_2 CH_3) and 6–2–7–5 (m, 4H furyl and pyridine H-5 protons)
5b	3470, 3290, 3185 (NH_2, NH); 3040 (aromatic CH); 1680 (amidic CO) and 1600 (C=C)	3.9 (s, br., 2H, NH_2); 5.3 (s, 1H, pyridine H-5); 6–2 (s, br., 2H, two NH) and 7.1–8.2 (m, 4H, Ar H's)
7a	3060 (aromatic CH); 2970 (aliphatic CH); 2220 (CN); 1728 (ester CO); 1708 (acetonyl CO); 1675 (amidic CO) and 1600 (C=C)	0.95 (t, 3H, CH_2CH_3); 2.2 (s, 3H, $COCH_3$); 3.0 (s, 2H, SCH_2); 4.1 (q, 2H, CH_2CH_3) and 6.9–7.7 (m, 6H, Ar H's and pyridine H-5)
8C	3460, 3320 (NH_2); 3060 (aromatic CH); 2970 (aliphatic CH); 1730 (ester CO); 1710 (acetyl CO); 1680 (amidic CO) and 1600 (C=C).	0.92 (t, 3H, CH_2CH_3); 2.1 (s, 3H, $COCH_3$); 3.9 (q, 2H, CH_2 CH_3); 4.3 (s, br., 2H, NH_2); 5.4 (s, br., 1H, pyridine H-5) and 6.2–7.3 (m, 3H, furyl protons).
10a	3225 (OH); 3055 (aromatic CH); 2978 (aliphatic CH); 1725 (CO ester), 1685 (amidic CO); 1625 (N=N) and 1600 (C=C).	0.95 (t, 3H, CH_2CH_3); 2.9 (s, 1H, pyridazine H-3); 4.1 (q, 2H, CH_2CH_3); 7.0–7.8 (m, 6H, Ar H's and pyridine H-5) and 12.4 (s, br., 1H, OH enolic).
10C	2223 (OH); 3068 (aromatic CH); 2975 (aliphatic CH); 1728 (ester CO); 1685 (CO amidic); 1627 (N=N) and 1602 (C=C).	0.95 (t, 3H, CH_2CH_3); 2.9 (s, 1H, pyridazine H-3); 4.1 (q, 2H, CH_2CH_3); 6.3–7.3 (m, 4H, furyl and pyridine H-5) and 12.1 (s,br.,1H,OH enolic).
12b	3075 (aromatic CH); 2975 (aliphatic CH); 1728 (ester CO); 1712 (ketone CO); 1684 (amide CO) and 1600 (C=C).	1.0 (t, 3H, CH_2 CH_3); 2.7 (s, 2H, SCH_2); 4.1 (q, 2H, CH_2 CH_3) and 7.0–8.2 (m, 10H, ArH's and pyridine H-5)
13a	3474, 3280 (NH_2); 3060 (aromatic CH);2950 (aliphatic CH); 1730 (ester CO); 1705 (Ketonic CO); 1680 (amidic CO) and 1600 (C=C).	0.85 (t, 3H, CH_2CH_3); 3.9 (q, 2H, CH_2CH_3); 4.4 (s, br., 2H, NH_2); 5.6 (s, 1H, pyridine H.5 and 6.9–7.8 (m, 10H, Ar H's).
15b	3364, 3165 (NH_2); 3055 (aromatic CH); 2985 (aliphatic CH); 2217 (CN); 1734 (ester CO); 1660 (amidic CO) and 1604 (C=C)	0.92 (t, 3H, CH_2CH_3); 3.9 (q, 2H, CH_2CH_3); 4.4 (s, 2H, S-CH_2); 5.3 (s, 1H, pyridine H-5); 5.8 (s, br., 2H, NH_2) and 7.1–7.9 (m, 4H, Ar H's).

TABLE II *continued*

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δppm)*
16a	3469, 3375, 3312, 3155 (two NH_2); 3050 (aromatic CH); 2975 (aliphatic CH); 1735 (ester CO); 1665 (amidic CO) and 1595 (C=C)	0.95 (t, 3H, CH_2CH_3); 3.8 (q, 2H, CH_2CH_3); 4.9 (s, br., 2H, NH_2); 5.4 (s, 1H, pyridine H-5); 5.9 (s, br., 2H, $CONH_2$) and 7.0–7.9 (m, 5H, Ar H's)
17b	3380, 3340 (two NH); 1730 (ester CO); 1690 (ring CO) and 1605 (C=C)	1.0 (t, 3H, CH_2CH_3); 3.9 (q, 2H, CH_2CH_3); 5.3 (s, 1H, pyridine H-5); 5.8 (s, br., 1H, NH); 7.0–7.8 (m, 4H, Ar H's) and 9.1 (s, br., 1H, NH).
18c	3168 (NH); 3070 (aromatic CH); 2955 (aliphatic CH); 1733 (ester CO); 1685 (ring CO) and 1600 (C=C)	0.87 (t, 3H, CH_2CH_3); 1.6 (s, 3H, CH_3 at pyrimidinone); 3.9 (q, 2H, CH_3CH_2); 5.3 (s, 1H, pyridine H-5); and 6.2–7.4 (m, 4H Furyl protons and NH).
20b	3078 (aromatic CH); 2955 (aliphatic CH); 2220 (CN); 1735 (ester CO); 1690 (amide CO) and 1600 (C=C)	0.92 (t,3H, CH_3CH_2, at pyridine); 1.3 (t, 3H, CH_3CH_2); 3.4 (s, 2H, SCH_2); 4.1 (q, 2H, CH_2CH_3, at pyridine); 4.7 (q, 2H, CH_2CH_3,); 5.4 (s, 1H., pyridine H-5 and 6.9–7.8 (m, 4H, Ar H's).
21a	3480, 3355 (NH_2); 3078 (aromatic CH); 2985 (aliphatic CH); 1732 (ester CO); 1685 (ring CO) and 1604 (C=C).	0.85 (t, 3H, CH_3 CH_2 at pyridine); 1.5 (t,3H, CH_3CH_2; 4.0 (q, 2H, CH_3CH_2 at pyridine); 4.8 (q,2H, CH_2CH_3); 5.2 (s, 1H, pyridine H-5); 5.8 (s, br., 2H, NH_2) and 7.1–7.9 (m, 5H, Ar H's).
22b	3475, 3300, 3210, 3158 (two NH_2 and two NH); 3048 (aromatic CH); 2958 aliphatic CH); 1680 (pyrazole CO); 1635 hydrazide CO and 1600 (C=C).	3.8 (s, br., 2H, NH_2 at thiophene); 5.1 (s, 1H, pyridine H-5); 5.8 (s, br., 2H, CONH-NH_2); 6.5 (s, br., 1H, CONH-NH_2); 7.0–7.8 (m, 4H, ArH's) and 8.7 (s, br. 1H, pyrazolone NH).
22c	3468, 3320, 3217, 3182 (two NH_2 and two NH); 1687 (pyrazole CO); 1643 hydrazide CO and 1600 (C=C).	3.4 (s, br., 2H, NH_2 at thiophene); 4.9 (s, 1H, pyridine H-5); 5.9 (s, br., 2H, CONH-NH_2); 6.2–6.9 (m, 4H, furyl and CO $NH$$NH_2$) and 8.5 (s, br. 1H, pyrazolone NH).

A chemical evidence of **5a–c** structures was given through their preparation via another route. Compounds **3a–c** reacted with hydrazine hydrate to give reaction products which were identical in all aspects (m.p., mixed m.p., IR, ^{1}H-NMR and elemental analyses) with that given through the reaction of **4a–c** with hydrazine hydrate. The structures of **4b,c** and **5b,c** were established based on both elemental analyses and IR, ^{1}H-NMR spectral data (cf. Tables I, II and Chart 1).

The synthetic potential of compounds **3a–c** was investigated via their reaction with both chloroacetone **6a** and 3-chloro-2,4-pentanedione **6b**. Thus, it has been

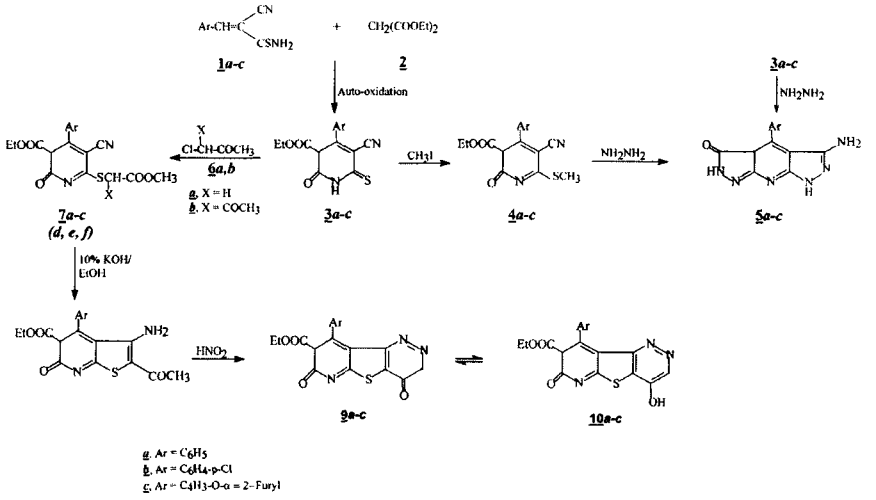


CHART 1

found that pyridinonethione derivatives **3a–c** reacted with chloroacetone **6a** in sodium methoxide to give reaction products via the loss of hydrogen chloride molecule. The IR of these reaction products showed the bands that corresponded to CO(ester), CO(ketone), CO(amide) and CN groups. Their ^{1}H-NMR revealed the signals of S-CH_2, $COCH_3$, $COOCH_2CH_3$, aryl and pyridine H-5 protons. Based on both elemental analyses and the above spectral data these reaction products could be formulated as 2-S-acetonyl pyridine derivatives **7a–c** respectively. Moreover, the mass spectrum of **7c** as a selective example gave m/z = 346 (100%) which corresponded to the exact molecular weight of the molecular formula $C_{16}H_{14}N_2SO_5$ of the assigned structures (cf. Tables I and II, Chart 1). Other peaks are detected at m/z = 257 (34%), 225 (82%), 212 (14%) and 180 (54%) due to the loss of CH_2COCH_3, SCH_2COCH_3 and OCH_2CH_3 fragments respectively either from the parent peak or from the base peak this in addition to other peaks at low % of abundance.

Further confirmation of the structure of **7a–c** could be given through cyclization in 10% ethanolic solution of potassium hydroxide to afford products via addition of the anions from S-CH_2 on the CN group. The IR (cm^{-1}) of these reaction products showed the absence of CN group while newly born NH_2 group was detected. Their ^{1}H-NMR (δ ppm) revealed the signals of NH_2 protons while the signals of SCH_2 protons were absent. In view of all the above data, these reaction products could be formulated as thieno[2,3-b]pyridine derivatives **8a–c** respectively (cf. Tables I and II).

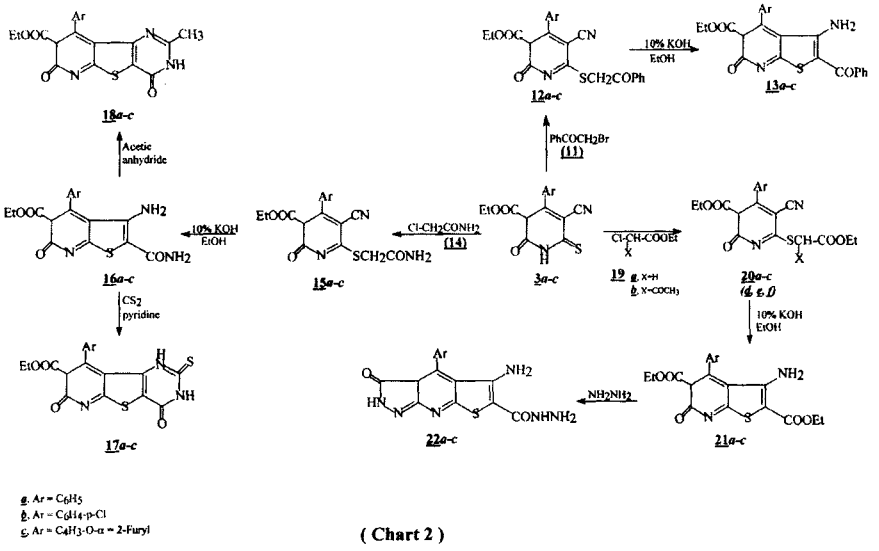
The positions of NH_2 and $COCH_3$ groups in each of **8a–c** were confirmed via their reaction with nitrous acid. The reaction with nitrous acid was probably proceeded through the diazotization of the NH_2 group then, coupled with the adjacent active CH_3 to give either pyridothienopyridazinone **9a–c** or pyridothienopyridazinol **10a–c**. The IR (cm^{-1}) of these reaction products showed the presence of an enolic OH group and their ^{1}H-NMR (δ ppm) revealed the signals of $COOCH_2CH_3$, aryl, pyridine H-5, pyridazine H-3 and enolic OH protons. Thus the reaction products were formulated as pyrido[2,3:4′,5′]thieno[3,2-c]pyridazinol derivatives **10a–c** respectively (cf. Tables I, II, Chart 1). Moreover, the mass spectra of both **8a** and **10a** gave m/z = 356 (100%) and 367 (100%) which represent the exact molecular weights of the molecular formulae $C_{18}H_{16}N_2SO_4$ and $C_{18}H_{13}N_3SO_4$ of the assigned structures (cf. Chart 1).

In a similar route, compounds **3a–c** reacted with 3-chloro-2,4-pentanedione under the same experimental conditions to give directly the thieno[2,3-b]pyridine derivatives **8a–c**. These reaction products are probably formed through the addition of the anion from $CH(COCH_3)_2$ on the CN group followed by addition of one water molecule and liberation of an acetic acid molecule; the thienopyridines **8a–c** which are reacted with nitrous acid under the above mentioned experimental conditions to give **10a–c** respectively. All trials for isolation of the 2-S-diacetyl methyl pyridine derivatives **7d–f** failed under several conditions.

It is remarkable to report here that the reaction products given from the cyclization of 2-S-acetonyl pyridine derivatives **7a–c** in 10% ethanolic KOH are identical with those given from the reaction of pyridinethiones **3a–c** with 3-chloro-2,4-pentanedione **(6b)** in all aspects (m.p., mixed m.p., IR and ^{1}H-NMR).

Furthermore, compounds **3a–c** reacted with phenacylbromide **(11)** in sodium ethoxide to give reaction products through the loss of hydrogen bromide. The structure of these reaction products were supported by elemental analyses, IR and ^{1}H-NMR spectra data (cf. Tables I and II); based on these data the reaction products was formulated as 2-S-benzoyl methyl pyridine derivatives **12a–c**. The structures of **12a–c** were finally proved through their cyclization in 10% ethanolic KOH to give the corresponding thieno[2,3-b]pyridine derivatives **13a–c** (cf. Chart 2). The IR (cm^{-1}) of **13a** showed CO (ketonic), CO (ester), CO (amide) and NH_2 groups. Its ^{1}H-NMR (δppm) revealed the signals of $COOCH_2CH_3$, pyridine H-5, aryl and NH_2 protons. Moreover, its mass spetrum gave m/z = 418 which corresponded to the molecular weight of the molecular formula $C_{23}H_{18}N_2SO_4$ of the assigned structures (cf. Tables I, II and Chart 2).

The synthetic potential of **3a–c** was further investigated through the reaction of chloroacetamide **(14)** in sodium methoxide to afford the corresponding 2-S-acetamidopyridine derivatives **15a–c** via the loss of a hydrogen chloride molecule. The 2-S-acetamidopyridines **15a–c** structure were supported by IR,



(Chart 2)

^{1}H-NMR and elemental analyses (cf. Tables I and II). The cyclization of **15a–c** in 10% ethanolic KOH to afford the corresponding thieno[2,3-b]pyridine derivatives **16a–c** was taken as evidence for **15a–c** structure (cf. Chart 2). The reactivity and position of NH_2 and $CONH_2$ in **16a–c** was used for building a third ring through the reaction of **16a–c** with carbon disulphide and acetic anhydride. Thus, it was found that each of **14a–c** reacted with CS_2 in pyridine to give pyrido[2,3:4′,5′]thieno[3,2-d]pyrimidinonthione derivatives **17a–c** respectively. The structures of **17a–c** were established based on IR, ^{1}H-NMR and elemental analyses (cf. Tables I and II). Moreover, the mass spectrum of **17c** as a selective example gave m/z = 389 (82%) which corresponded to the exact molecular weight of the molecular formula $C_{16}H_{11}N_3S_2O_5$ of the assigned structure (cf. Chart 2). Other peaks were detected at m/z = 315 (100%), 316 (45%), 344 (31%) and 270 (11%) due to the loss of NHCSNH, $COOCH_2CH_3$, CH_3CH_2O fragments either from the base peak or from the parent peak. Also, in a similar behavior compounds **16a–c** reacted with acetic anhydride to give pyrido [2,3:4′,5′]thieno[3,2-d]pyrimid-inone derivatives **18a–c** respectively. The structures of **18a–c** were established based on IR, ^{1}H-NMR, spectral data and elemental analyses (cf. Tables I and II).

The synthons **3a–c** also, reacted with both ethyl chloroacetate (**19a**) and ethyl-α-chloroacetoacetate (**19b**) in sodium ethoxide to give products via the loss of a hydrogen chloride molecule. Compounds **3a–c** reacted with ethylchloroacetate (**19a**) to give reaction products **20a–c**. The IR (cm^{-1}) of these reaction products

showed CO, CN groups, and their ^{1}H-NMR (δ ppm) revealed the signals of aryl, pyridine H-5, and two $COOCH_2CH_3$ protons. These reaction products were formulated as 2-S-ethoxycarbonylmethylpyridine derivatives **20a–c** respectively (cf. Tables I and II). Moreover, the mass spectrum of **20a–c** as a selective example gave m/z = 420 (49%) which corresponded to the exact molecular weight of a molecular formula $C_{19}H_{17}N_2SO_5Cl$ of the assigned structure (cf. Chart 2). Other peaks were detected at m/z = 333 (22%), 301 (100% base peak), 256 (15%), and 228 (65%) due to the loss of $CH_2COOCH_2CH_3$, $SCH_2COOCH_2CH_3$, $COOCH_2CH_3$ and OCH_2CH_3 fragments either from the parent peak or from the base peak.

Compounds **20a–c** were cyclized in 10% ethanolic KOH solution to give cyclized products. The IR (cm^{-1}) of these products surprisingly showed no CN group and instead the newly born NH_2 group was detected; this confirms the addition of the anions from the S-CH_2COOEt on the CN group. Their ^{1}H-NMR revealed the NH_2 protons in addition to the two $COOCH_2CH_3$, aryl and pyridine H-5 protons (cf. Tables I and II). In view of all the above data, these reaction products were formulated as thieno[2,3-b]pyridine derivatives **21a–c** respectively. Moreover, the mass spectrum of **21c** as a selective example gave m/z = 376 which corresponded to the exact molecular weight of a molecular formula of $C_{17}H_{16}N_2SO_6$ of the assigned structure (cf. Chart 2).

Compounds **21a–c** reacted with hydrazine hydrate to give the corresponding hydrazide derivatives **22a–c** respectively. Structures of **22a–c** were supported by elemental analyses, IR and ^{1}H-NMR spectral data. Moreover, the mass spectra of **22a–c** gave m/z = 340, 374 and 330 respectively which represented the exact molecular weights of molecular formulae $C_{15}H_{12}N_6SO_2$, $C_{15}H_{11}N_6SO_2Cl$ and $C_{13}H_{10}N_6SO_3$ of the assigned structures (cf. Tables I, II and Chart 2).

In a similar reaction, each of **3a–c** reacted with ethyl-α-chloroacetoacetate to afford the corresponded thieno[2,3-b]pyridine derivatives **21a–c** respectively. All attempts to isolate the noncyclized 2-S-ethoxy-carbonylacetyl methylpyridine derivatives **20d–f** were failed. The reaction was probably proceeded via the addition of the anion from SCH on the CN group to give the non-isolable 3-iminothieno[2,3-b]pyrimidine derivatives **20d–f** respectively and this followed by addition of one water molecule and liberation of acetic acid molecule; **21a–c** reacted with hydrazine hydrate to give **22a–c** respectively. It is remarkable to report here that the reaction products given through the reaction of each of **3a–c** with ethyl-α-chloroacetoacetate (**19b**) are identical in all aspects with those given from the reaction of 2-S-ethoxy-carbonyl methyl pyridine derivatives **18a–**

c with 10% ethanolic KOH solution. The above mentioned fact was supported by elemental analyses, IR and ^{1}H-NMR spectral data (cf. Tables I and II).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra in KBr discs were recorded on Perkin-Elmer FT-IR type 4 and Pye Unicam SP-1100 spectrophotometers. The ^{1}H-NMR spectra were recorded on Varian EM 390–90 MHz, Gemini 200, Varian NMR spectrophotometers (200 MHz) and Brucker WP-80 spectrometers using $CDCl_3$, DMSO-d6 a d $(D_3)_2CO$ as solvents and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using DIP technique at 70 eV. Microanalyses were performed at Microanalytical Center of Cairo University using a Perkin-Elmer 2400 CHN Elemental Analyzer.

Synthesis of 3a–c

A mixture of thiocarboxamidocinnamonitriles **1a–c** (0.01 mole) in absolute ethanol (50 mL) containing the catalytic amounts of triethylamine (0.5 mL) was heated under reflux for 5 h. The reaction mixture was then evaporated to dryness and then cooled and acidified with acetic acid. The solid products so formed were collected by filteration, washed with water and then crystallized from acetic acid to give the corresponding **3a–c** respectively (cf. Tables I and II).

Synthesis of 4a–c, 7a–c, 8a–c, 12a–c, 15a–c, 20a–c and 21a–c. (General Procedure)

A solution of each of **3a–c** (0.01 mole) and each of methyl iodide, chloroacetone (**6a**), 3-chloro-2,4-pentanedione (**6b**), phenacyl bromide (**11**), chloroacetamide (**14**), ethyl chloroacetate (**19a**) or ethyl-α-chloroacetoacetate (**19b**) (0.01 mole) was heated under reflux in methanolic sodium methoxide (prepared from 0.01 atom of sodium metal in 30 mL methanol) for 6 h. The reaction products obtained from hot solution or after cooling were filtered off and recrystallized from the proper solvent to yield **4a–c**, **7a–c**, **8a–c**, **12a–c**, **15a–c**, **20a–c** and **21a–c** respectively (cf. Tables I and II).

Synthesis of 5a–c and 22a–c. (General Procedure)

A solution of each of **3a–c** or **4a–c** or **21a–c** (0.01 mole) in methanol (30 mL) was treated with hydrazine hydrate (10 mL) and then heated under reflux for 6–8 h. The solid products obtained from hot solution or after cooling were filtered off and recrystallized from the proper solvent to yield **5a–c** or **22a–c** respectively (cf. Tables I and II).

Synthesis of 8a–c, 13a–c, 16a–c and 21a–c. (General Procedure)

A solution of each of **7a–c**, **12a–c**, **15a–c** or **20a–c** (0.01 mole) in methanol (30 mL) was heated under reflux for 5–7 h with potassium hydroxide ($\simeq 0.02$ mole). The reaction mixture was then cooled and acidified with dilute hydrochloric acid and the precipitate was filtered off, washed with water and recrystallized from the proper solvent to yield **8a–c**, **13a–c**, **16a–c** or **21a–c** respectively (cf. Tables I and II).

Synthesis of 10a–c

A cold solution of **8a–c** (0.01 mole) in concentrated hydrochloric acid (1 mL) was treated with a cold saturated solution of sodium nitrite (0.015 mole) and then stirred in ice-cold bath for 1–2 h. The solid products obtained was filtered off, washed with water and recrystallized from the proper solvent to yield **10a–c** respectively (cf. Tables I and II).

Synthesis of 17a–c

A solution of each of **16a–c** (0.01 mole) in pyridine (30 mL) was treated with carbon disulphide (0.01 mole) and then heated under reflux for 4 h. The reaction mixture was cooled, poured onto ice-cold water and acidified by dilute hydrochloric acid. The solid products obtained were filtered off and then recrystallized from the proper solvent to yield **17a–c** respectively (cf. Tables I and II).

Synthesis of 18a–c

A solution of each of **16a–c** (0.01 mole) in acetic anhydride (30 mL) was heated under reflux for 5 h. The solid products obtained after cooling were filtered off and recrystallized from the proper solvent to yield **17a–c** respectively (cf. Tables I and II).

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