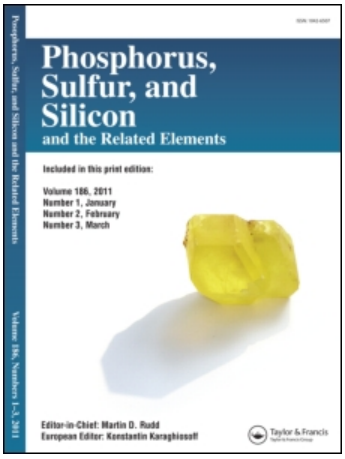

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REACTIONS WITH CYANOTHIOACETAMIDE DERIVATIVE: SYNTHESIS AND REACTIONS OF SOME THIENO[2,3-B]PYRIDINE, PYRIDOTHIENOPYRIDAZINE, PYRAZOLO[3,4-B]PYRIDINE AND PYRIDOPYRAZOLO-1,2,4-TRIAZINE DERIVATIVES

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Thiocarboxamidocinnamonitrile derivatives **3a,b** reacted with ethyl-benzoylacetate (**4**) to give pyridinethione derivatives **5a,b** which were used as starting materials for synthesis of several heterocyclic compounds. Reactions with phenacyl bromides **6a,b**, chloroacetone (**8**), α-chloroacetylacetone and methyl iodide gave thieno[2,3-b]pyridines **7a–d**; 2-S-methylacetylpyridine derivatives **9a,b**; 2-S-methyldiacetyl pyridine derivatives **11a,b** and 2-S-methyl pyridine derivatives **14a,b** respectively. Several cyclization reactions were performed with 10% KOH, nitrous acid and hydrazine hydrate to give an additional ring on **9a,b**, **10a,b**, **11a,b** and **14a,b**.

Keywords: Dihydropyridinethione; 2-S-methylacetylpyridine; 2-S-diacetylpyridine; thieno[2;3-b]pyridine; pyridothienopyridazine; pyrazolo[3,4-b]pyridine and pyridopyrazolo-1,2,4-triazine

INTRODUCTION

In continuation of the work[1–8] in the chemistry of thiocyanoacetamide (**1**), the present paper deals with the synthesis of several new heterocyclic compounds which exhibit biological activities as well as several chemical transformations.

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The reported biological activities of both pyridines as antimycotic[9], antidepressant[10], fungicidal agents[11] and antilipemic agents[12] and pyrazoles as inhibitors and deactivators of liver alcohol dehydrogenase[13,14] stimulated our interest in the use of the dihydropyridinethione derivatives **5a,b** as excellent starting materials for the synthesis of thieno[2,3-b]pyridines **7a,b**, **10a,b**, pyridothienopyridazines **13a,b**, pyrazolo[3,4-b]pyridines **15a,b**, **16a,b**, **17a,b**, **21a,b** and pyridopyrazolo-1,2,4-triazines **19a,b**, **24a,b**, **26a,b**, **29a,b**.

RESULTS AND DISCUSSION

It has been found that α-thiocarboxyamidocinnamonitrile derivatives **3a,b** (obtained from the reaction of **1** with the corresponding aldehydes **2a,b**) reacted with ethyl benzoylacetate **4** in ethanol in the presence of triethylamine and pyridine (one step reaction) to afford the corresponding dihydropyridinethione derivatives **5a,b** respectively, in a better yields than the multistep reaction reported by *Soto et al*[15].

The reaction products **5a,b** were taken as a good starting materials for the synthesis of other heterocyclic derivatives. Thus, it has been found that **5a,b** reacted with phenacyl bromide **6a** to afford a reaction product of molecular formula $C_{30}H_{24}N_2O_4S$. This formula corresponds to the equimolecular addition of **5a** to **6a** followed by the loss of hydrogen bromide. Surprisingly, the IR spectrum of this reaction product was entirely free from the bands of the nitrile functions and instead, the bands of the newly formed amino group were clearly detected, which was also confirmed by the ^{1}H-NMR spectrum. Based on the above facts this product was formulated as the thieno[2,3-b]pyridine derivative **7a**. Similarly, **5a** reacted with the phenacyl bromide derivative (**6b**) to afford the corresponding thieno[2,3-b]pyridine derivative **7b**. Following the same steps the dihydropyridinethione derivative **5b** reacted with each of **6a,b** to yield the corresponding thieno[2,3-b]pyridine derivatives **7c,d** respectively. The structure of **7c,d** was also confirmed based on elemental and spectral data studies (cf. Tables I and II).

Furthermore, the synthetic potential of **5a,b** was investigated via their reaction with a variety of halogenated ketones and esters. Thus, it has been found that **5a** reacted with chloroacetone (**8**) in methanolic sodium methoxide to give a product of molecular formula corresponding to the addition of equimolecular amounts of **5a** and **8**. The IR spectrum of the reaction product showed the presence of a nitrile function in addition to the ester CO and acetonyl CO groups. The reaction products could thus be formulated as 2-S-acetonylpyridine derivative **9a**. **5b** reacted

TABLE I Characterization data of the newly synthesized compounds

Comp. (colour)	*solvent of crystall.*	*mp °C*	*Yield (%)*	*Molecular formula*	*% Analysis (calcd./found)*				
					C	*H*	*N*	*S*	*Cl*
7 a (yellow)	Acetic	138–40	85	$C_{30}H_{24}N_2O_4S$	70.87	4.72	5.51	6.3	—
					70.8	4.6	5.5	6.2	—
7 b (yellow)	Ethanol	158	62	$C_{30}H_{23}ClN_2O_4S$	66.36	4.24	5.16	5.89	6.54
					66.4	4.1	5.3	5.6	6.5
7 c (orange)	Acetic	210–2	80	$C_{29}H_{21}ClN_2O_3S$	67.90	4.09	5.46	6.24	6.93
					67.8	4.1	5.3	6.1	6.9
7 d (yellow)	Ethanol	170	68	$C_{29}H_{20}Cl_2N_2O_3S$	63.61	3.66	5.12	5.85	12.97
					63.6	3.5	5.2	5.6	12.8
9 a (white)	Ethanol	116–8	70	$C_{25}H_{22}N_2O_4S$	67.42	4.93	6.28	7.17	—
					67.4	4.8	6.4	7.1	—
9 b (white)	Ethanol	120	81	$C_{24}H_{19}ClN_2O_3S$	63.39	4.22	6.22	7.1	7.88
					63.4	4.3	6.2	7.1	7.7
10 a (yellow)	Acetic	166–8	65	$C_{25}H_{22}N_2O_4S$	67.42	4.93	6.28	7.17	—
					67.5	4.9	6.3	7.1	—
10 b (orange)	Acetic	196–8	60	$C_{24}H_{19}ClN_2O_3S$	63.93	4.22	6.22	7.10	7.88
					63.9	4.2	6.2	6.9	7.8
11 a (white)	Ethanol	98–100	58	$C_{27}H_{24}N_2O_5S$	66.39	4.92	5.47	6.56	—
					66.3	5.0	5.6	6.5	—
11 b (white)	Ethanol	142	67	$C_{26}H_{21}ClN_2O_4S$	63.35	4.26	5.69	6.46	7.21
					63.2	4.3	5.5	6.5	7.2
13 a (yellow)	Ethanol	70 (decomp.)	63	$C_{25}H_{19}N_3O_4S$	65.65	4.16	9.19	7.00	—
					65.5	4.2	8.9	7.1	—
13 b (yellow)	Ethanol	90 (decomp.)	80	$C_{24}H_{16}ClN_3O_3S$	62.41	3.47	9.10	6.93	7.69
					62.5	3.4	8.9	6.9	7.5
15 a (green)	Acetic	160	75	$C_{22}H_{20}N_4O_3$	68.04	5.15	14.43	—	—
					68.2	5.2	14.5	—	—
15 b (green)	Acetic	212–4	62	$C_{21}H_{17}ClN_4O_2$	64.20	4.33	14.27	—	9.04
					64.1	4.4	14.1	—	9.1
16 a (white)	Acetic	226–8	68	$C_{29}H_{25}N_5O_3S$	66.54	4.78	13.38	6.12	—
					66.5	4.7	13.1	6.2	—
16 b (white)	Acetic	230–2	79	$C_{28}H_{22}ClN_2O_5S$	63.69	4.17	13.27	6.07	6.73
					63.7	4.1	13.3	6.0	6.8
17 a (white)	Ethanol	150 (decomp.)	70	$C_{22}H_{18}ClN_5O_3$	60.62	4.13	16.07	—	8.15
					60.4	4.1	15.9	—	8.1
17 b (yellow)	Ethanol	136–8	60	$C_{21}H_{15}Cl_2N_5O_2$	57.27	3.14	15.91	—	16.14
					57.3	3.4	15.8	—	16.3
19 a (yellow)	Ethanol	265–7	79	$C_{25}H_{19}N_7O_3$	64.52	4.09	21.08	—	—
					64.5	4.0	21.0	—	—
19 b (yellow)	Ethanol	252–4	55	$C_{24}H_{16}ClN_7O_2$	61.34	3.41	20.87	—	7.56
					61.1	3.5	20.7	—	7.4
21 a (yellow)	Ethanol	194–6	70	$C_{27}H_{24}N_6O_5$	63.28	4.69	16.41	—	—
					36.3	4.6	16.5	—	—
21 b (orange)	Ethanol	>300	80	$C_{31}H_{23}N_7O_3S$	64.92	4.01	17.1	5.58	—
					64.8	4.0	17.2	5.3	—
21 c (yellow)	Ethanol	120	67	$C_{25}H_{21}N_7O_3S$	60.12	4.21	19.64	6.41	—
					60.2	4.1	19.5	6.5	—

TABLE I Continued

Comp. (colour)	*solvent of crystall.*	*mp °C*	*Yield (%)*	*Molecular formula*	*% Analysis (calcd./found)*				
					C	*H*	*N*	*S*	*Cl*
21 d	Ethanol	196–8	81	$C_{26}H_{21}ClN_6O_4$	60.41	4.07	16.26	—	6.87
(yellow)					60.3	4.1	16.1	—	6.7
21 e	Ethanol	>300	70	$C_{30}H_{20}ClN_7O_2S$	62.34	3.46	16.96	5.54	6.15
(orange)					62.1	3.4	16.8	5.5	6.2
21 f	Ethanol	140	63	$C_{24}H_{18}ClN_7O_2S$	57.2	3.75	19.46	6.36	7.05
(yellow)					57.1	3.5	19.3	6.4	7.0
22 a	Acetic	286–8	86	$C_{27}H_{24}N_6O_5$	63.28	4.69	16.41	—	—
(yellow)					63.2	4.6	16.2	—	—
22 b	Acetic	>300	79	$C_{31}H_{23}N_7O_3S$	64.92	4.01	17.1	5.58	—
(yellow)					64.7	4.0	16.9	5.5	—
22 c	Acetic	280–2	58	$C_{25}H_{21}N_7O_3S$	60.12	4.21	19.64	6.41	—
(brown)					60.20	4.10	19.50	6.40	—
22 d	Acetic	270-2	84	$C_{26}H_{21}ClN_6O_4$	60.41	4.07	16.26	—	6.87
(yellow)					60.30	4.00	16.30	—	6.80
22 e	Acetic	>300	80	$C_{30}H_{20}ClN_7O_2S$	62.34	3.46	16.96	5.54	6.15
(yellow)					62.20	3.50	16.90	5.50	6.10
22 f	Ethanol	310-2	64	$C_{24}H_{18}ClN_7O_3S$	57.2	3.57	19.46	6.36	7.05
(orange)					57.1	3.50	19.30	6.40	7.00
24 a	Ethanol	228	65	$C_{27}H_{23}N_5O_4$	67.36	4.57	14.55	—	—
(yellow)					67.40	4.70	14.30	—	—
24 b	Ethanol	184-6	70	$C_{28}H_{25}N_5O_5$	65.75	4.89	13.69	—	—
(white)					65.50	4.80	13.50	—	—
24 c	Ethanol	190	75	$C_{26}H_{20}ClN_5O_3$	64.26	4.12	14.42	—	7.31
(yellow)					64.30	4.10	14.20	—	7.20
24 d	Ethanol	170	80	$C_{27}H_{22}ClN_5O_4$	62.85	4.27	13.58	—	6.89
(yellow)					62.70	4.30	13.50	—	6.70
25 a	Ethanol	120	68	$C_{33}H_{29}N_5O_6$	67.01	4.91	11.84	—	—
(yellow)					67.00	4.80	11.60	—	—
25 b	Ethanol	130	63	$C_{32}H_{26}ClN_5O_5$	64.48	4.37	11.75	—	5.96
(yellow)					64.4	4.5	11.5	—	5.9
26 a	Ethanol	148	69	$C_{33}H_{27}N_5O_5$	69.11	4.71	12.22	—	—
(yellow)					69.11	4.60	12.00	—	—
26 b	Ethanol	194-6	70	$C_{32}H_{24}ClN_5O_2$	66.49	4.16	12.12	—	6.15
(yellow)					66.30	4.00	12.00	—	6.20
28 a	Ethanol	129-1	60	$C_{29}H_{29}N_5O_7$	62.25	5.19	12.52	—	—
(yellow)					62.30	5.10	12.4	—	—
29 a	Acetic	258–260	62	$C_{27}H_{23}N_5O_6$	63.16	4.48	13.56	—	—
(yellow)					63.20	4.40	13.50	—	—
29 b	Acetic	240-2	64	$C_{26}H_{20}ClN_5O_5$	60.29	3.86	13.53	—	6.86
(yellow)					60.30	3.70	13.40	—	6.60

TABLE II IR and ^{1}H-NMR spectral data

Compound	*IR (KBr, cm^{-1})*	*^{1}H-NMr (δ ppm)*
7a	3470, 3319 (NH_2); 3036 (aromatic CH); 2976 (aliphatic CH); 1721 (ester CO) and 1603 (C=C)	0.9 (t, 3H, $CH_2\underline{CH_3}$); 3.7 (q, 2H, $\underline{CH_2}CH_3$); 3.9 (s, 3H, OCH_3); 6.9 (broad, 2H, NH_2) lost after D_2O exchange and 7 – 8.3 (m, 14H, ArH'S).
7c	3460,3320 (NH_2); 3040 (aromatic CH); 2970 (aliphatic CH);1720 (ester CO) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (s, 3H,OCH_3); 4.0 (q, 2H, $\underline{CH_2}CH_3$); 6.5 (broad, 2H, NH_2) lost after D_2O exchange and 7.0–8 (m, 13H, ArH'S).
9a	3062 (aromatic CH); 2979 (sat. CH);2220 (CN); 1724 (ester C=O); 1710 (S-acetonyl C=O); 1620 (CN) and 1600 (C=C).	0.92 (t, 3H, $CH_2\underline{CH_3}$); 2.1 (s, 3H, $COCH_3$); 3.1 (s, 2H, CH_2); 3.8(s, 3H, OCH_3); 4.1 (q, 2H,$\underline{CH_2}$ CH_3) and 6.8–7.5 (m, 9H, ArH's).
10b	3480, 3350 (NH_2); 3040 (aromatic CH); 2950 (sat. CH); 1719 (ester C=O); 1635 (CO acetyl at thiophene with H-bonding) and 1620 (C=C).	0.99 (t, 3H, $CH_2\underline{CH_3}$); 2.5 (s, 3H, $COCH_3$); 4.05 (q, 2H, $\underline{CH_2}CH_3$); 4.7 (s, 2H, NH_2) lost after D_2O-exchange and 7.0–8.0 (m, 9H, ArH's).
11a	3010 (aromatic CH); 2968 (sat. CH); 2220 (CN); 1725 (ester C=O); 1711 (C=N) and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 2.3 (s, 6H, - CH $(CO\underline{CH_3})_2$); 3.2 (s, 1H, -CH$(CO\underline{CH_3})_2$); 3.6 (s, 3H, OCH_3); 4.05 (q, 2H, $\underline{CH_2}CH_3$) and 7–8 (m, 9H, ArH's).
13a	3220 (OH); 3050 (aromatic CH); 2940 (sat. CH); 1720 (ester C=O); 1710 (CO pyridazinone); 1625 (N=N) and 1608 (C=C).	0.97 (t, 3H, $CH_2\underline{CH_3}$); 3.1 (s, 1H, CH-pyridazine); 3.5 (s, 3H, OCH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 6.9–7.8 (m, 9H, ArH's) and 11.1 (s, 1H, OH).
15a	3463, 3288, 3192 (NH_2, NH); 3037 (aromatic CH); 1712 (ester C=O); 1620 (C=N) and 1600 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 3.8 (s, 3H, OCH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 5.4 (S, 2H, NH_2) lost after D_2O exchange and 6.8–7.6 (m, 9H, ArH's).
16b	3389, 3281, 3209 (three NH); 3051 (aromatic CH); 2940 (sat. CH); 1724 (ester C=O); 1635 (C=N) and 1598 (C=C) and 1560 (C=S).	0.9 (t, 3H, $CH_2\underline{CH_3}$); 4.0 (q, 2H, $\underline{CH_2}CH_3$); 6.1–6.5 (m, 3H, three NH). lost after D_2O exchange and 7.1–8.2 (m, 14H, ArH's).
17a	3180 (NH); 3053 (aromatic CH); 2907(sat. CH); 2154 ($N{=}N^+$); 1720 (ester C=O); 1620 (C=N) and 1600 (C=C).	1.1 (t, 3H,$CH_2\underline{CH_3}$); 3.7 (s, 3H, OCH_3); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 5.9 (s, 1H, NH) lost after D_2O exchange and 7.1–7.9 (m, 9H, ArH's).
19a	3423, 3269 (NH_2); 3020 (aromatic CH); 2962 (sat. CH); 2227 (CN); 1720 (ester C=O); 1634 (C=N) and 1600 (C=C).	1.1 (t, 3H, $CH_2\underline{CH_3}$); 3.7 (s, 3H, OCH_3); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 6.2 (s, 2H, NH_2) lost after D_2O exchange and 7.2–8.0 (m, 9H, ArH's).
21a	3134 (two NH); 2977 (sat. CH); 2219 (C=N); 1723, 1694 (two ester C=O) and 1607 (C=C).	1.1 (t, 3H,$CH_2\underline{CH_3}$); 1.6 (t, 3H, $CH_2\underline{CH_3}$); 3.7 (s, 3H, OCH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 4.5 (q, 2H, $\underline{CH_2}CH_3$); 7.2–8 (m, 9H, ArH's) and 13.5 (s, 2H, two NH_2) lost after D_2O exchange.
21c	3412, 3301, 3256, 3207 (NH_2 and two NH); 3054 (aromatic CH); 2936 (sat. CH); 2210 (C=N); 1720 (ester C=O) and 1600 (C=C).	0.95 (t, 3H, $CH_2\underline{CH_3}$); 3.8 (s, 3H, OCH_3); 4.0 (q, 2H, $\underline{CH_2}CH_3$); 7.4–8.0 (m, 9H, ArH's); 9.2 (broad, 2H, NH_2) lost after D_2O-excgange; 9.9 (broad, 1H, NH) lost after D_2O-exchange. and 11.1 (b, 1H, NH) lost after D_2O-exchange.

TABLE II Continued

Compound	*IR (KBr, cm^{-1})*	*^{1}H-NMr (δ ppm)*
22b	3303, 3250 (NH_2); 2974 (sat. CH); 1726 (ester CO); 1631 (C=N) and 1590 (C=C).	0.95 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (s, 3H, OCH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 5.5 (broad, 2H, NH_2) lost after D_2O-exchange and 7.2 –8.0 (m, 13H, ArH's).
22e	3303, 3200 (NH_2); 2974 (sat. CH); 1726 (ester CO); 1631 (C=H) and 1590 (C=C).	0.98 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 5.5 (s, 2H, NH_2) lost after D_2O -exchange and 7.3–8.1 (m, 13H, ArH's).
24a	3050 (aromatic CH); 2974 (sat. CH); 1734 (ester CO); 1697 (acetyl CO) and 1605 (C=C).	0.96 (t, 3H, $CH_2\underline{CH_3}$); 2.9 (s, 3H, CH_3); 3.4 (s, 3H, $COCH_3$); 3.9 (s, 3H, OCH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$) and 7.1–7.9 (m, 9H, ArH's).
24c	3050 (aromatic CH); 2980, 2974 (sat. CH); 1730 (ester CO); 1697 (acetyl CO) and 1600 (C=C).	0.98 (t, 3H, $CH_2\underline{CH_3}$); 2.9 (s, 3H, CH_3); 3.4 (s, 3H, $COCH_3$); 4.1 (q, 2H, $\underline{CH_2}CH_3$) and 7.1–7.8 (m, 9H, ArH's).
25a	3125 (two NH); 2978 (sat. CH); 1726 (ester CO); 1684 (benzoyl CO) and 1587 (C=C).	1.0 (t, 3H, $CH_2\underline{CH_3}$); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 3.5 (s, 3H, OCH_3); 4.0 (q, 2H, $\underline{CH_2}CH_3$); 4.7 (q, 2H, $\underline{CH_2}CH_3$); 7.1–8.0 (m, 14H, ArH's), 9.2 (broad, 1H, NH) lost after D_2O-exchange and 11.1 (broad, 1H, NH) lost after D_2O-exchange.
26a	3058 (aromatic CH); 2977, 2933 (sat. CH); 1725 (two ester CO) and 1596 (C=C).	0.99 (t, 3H, $CH_2\underline{CH_3}$) at pyridine ring; 1.6 (t, 3H, $CH_2\underline{CH_3}$) at triazine ring; 3.7 (s, 3H, OCH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$) at pyridine ring; 4.7 (q, 2H, $\underline{CH_2}CH_3$) at triazine ring and 7.2–8.0 (m, 14H, ArH's).
26b	3050 (aromatic CH); 2952 (sat. CH); 1725 (two ester CO) and 1598 (C=C).	0.95 (t, 3H, $CH_2\underline{CH_3}$) at pyridine ring; 1.6 (t, 3H, $CH_2\underline{CH_3}$) at triazine ring; 4.1 (q, 2H, $\underline{CH_2}CH_3$) at pyridine ring; 4.7 (q, 2H, $\underline{CH_2}CH_3$) at triazine ring and 7.1 – 8.0 (m, 14H, ArH's).
28a	3419, 3183 (two NH); 2936 (sat. CH); 1726 (two ester CO); 1709 (ester CO); 1625 (C=N) and 1589 (C=C).	0.89 (t, 3H, $CH_2\underline{CH_3}$) at pyridine ring; 1.3 (t, 6H, two $CH_2\underline{CH_3}$) 3.6 (s, 3H, OCH_3); 3.9 (q, 2H, $\underline{CH_2}CH_3$) at pyridine ring; 4.2 (q, 4H, two $\underline{CH_2}CH_3$); 7.1 – 7.9 (m, 9H, ArH's); 9.4 (broad, 1H, NH) lost after D_2O-exchange and 11.2 (broad, 1H, NH) lost after D_2O-exchange.
29a	3212 (two NH); 2957 (sat. CH); 1717 (two ester CO); 1690 (CO endocyclic at triazinone ring); 1633 (C=N) and 1590 (C=C).	0.8 (t, 3H, $CH_2\underline{CH_3}$) at pyridine ring; 1.2 (t, 3H, $CH_2\underline{CH_3}$); 3.7 (s, 3H, OCH_3); 3.8 (q, 2H, $\underline{CH_2}CH_3$) at pyridine ring; 4.0 (q, 2H, $\underline{CH_2}CH_3$) at triazinone ring; 5.2 (broad, 1H, NH) lost after D_2O-exchange; 7.3 – 7.7 (m, 9H, ArH's).
29b	3200 (NH); 2970 (sat. CH); 1720 (two ester CO); 1690 (CO endocyclic at triazinone ring); 1630 (C=N) and 1600 (C=C).	0.9 (t, 3H, $CH_2\underline{CH_3}$) at pyridine ring; 1.3 (t, 3H, $CH_2\underline{CH_3}$); 3.8 (q, 2H, $\underline{CH_2}CH_3$) at pyridine ring; 4.0 (q, 2H, $\underline{CH_2}CH_3$) at triazinone ring; 5.3 (broad, 1H, NH) lost after D_2O-exchange; 7.4 – 7.8 (m, 9H, ArH's).

with the same reagent to afford the corresponding 2-S-acetonyl pyridine derivative **9b**.

The structures of both **9a,b** could also be confirmed via their cyclization on treatment with boiling 10% potassium hydroxide in ethanol to afford compounds with exactly the same molecular weights as **10a,b**. The structure of **10a,b** was confirmed based on both physical (IR and ^{1}H-NMR) and chemical evidence compounds **10a,b** could also be synthesized by another route through the reaction of **5a,b** with α-chloroacetylacetone in methanolic sodium methoxide followed by loss of hydrogen chloride to give the corresponding 2-S-(diacetyl)-methyl pyridine derivatives **11a,b** respectively. Compounds **11a,b** were cyclized to the corresponding **10a,b** by boiling their ethanolic solutions with 10% KOH. This represents evidence for the structures of **9a,b**, **11a,b** and **10a,b**. Solid evidence for the structure of **10a,b** was obtained by their treatment with nitrous acid to give products free from the bands of amino groups in their IR spectra. Moreover, these spectra showed clearly the presence of an OH group in each case. This fact was established by the intense coloration of their ethanol solutions developed on treatment with ferric chloride solutions. According to the above facts these reaction products could be formulated as theinopyrido-pyridazine derivatives **13a,b** rather than the pyridazinone derivatives **12a,b** (cf. Chart 1, Table II and Experimental part).

A further demonstration of the reactivity of **5a,b** was achieved via their reaction with methyl iodide in methanolic sodium methoxide to give the corresponding 2-S-methylpyridine derivatives **14a,b** respectively. The IR spectra of **14a,b** were found free from the band of the NH group in each case. Moreover, a singlet of the S-CH_3 protons was revealed in their ^{1}H-NMR spectra (cf. Experimental part).

An unequivocal support for structures **14a,b** came from their reaction with hydrazine hydrate in ethanol which was accompanied by evolution of methyl mercaptan and the formation of reaction products free from the absorption band of the nitrile function in each case. In addition, the bands of a new NH_2 group were shown in their IR spectra. Based on the above data, these reaction products could be formulated as the aminopyrazolo[3,4-b]pyridine derivatives **15a,b** respectively. Compounds **15a,b** were thus involved into two interesting chemical reactions. Compounds **15a,b** each reacted with phenyl isothiocyanate in pyridine to afford their pyrazolopyridylphenyl thiourea derivatives **16a,b** respectively. The IR spectra of **16a,b** showed the presence of bands of three NH and C=S groups in their proper positions (cf. Experimental part).

In addition **15a,b** were each tested for the presence of the NH_2 group via the reaction with nitrous acid which gave the corresponding diazonium salts **17a,b** these compounds were isolated in a pure crystalline form and kept for further chemical reactions to establish their activity and synthetic potential. Thus, it has

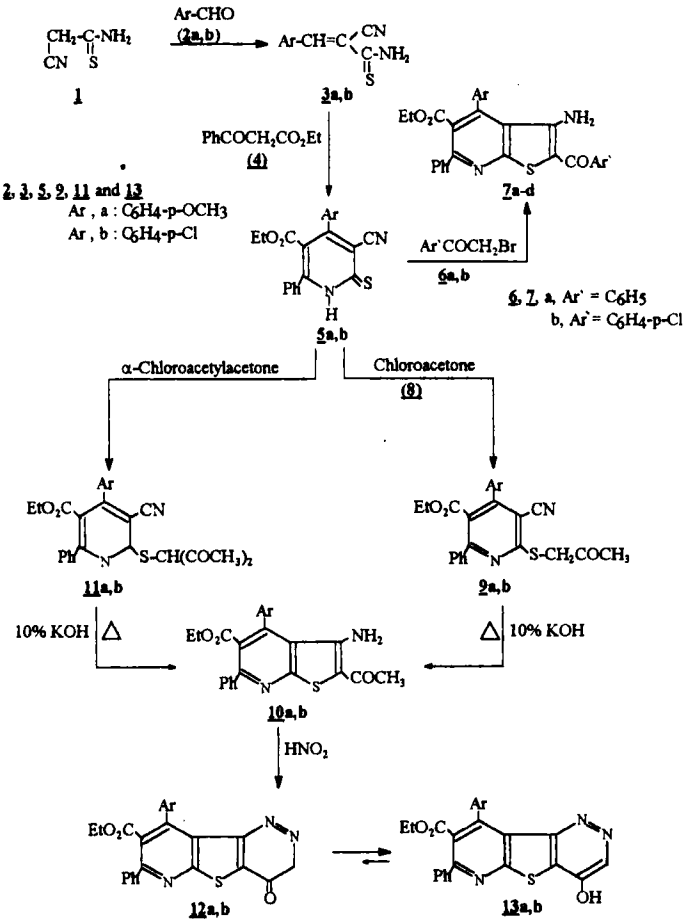

CHART 1

been found that **17a,b** reacted with malononitrile (**18**) in ethanol in the presence of sodium acetate to give products **19a,b** showing absorption bands of one CN and one NH_2 group in their respective IR spectra. These compounds could thus be formulated as the corresponding pyrido[2,3:3′,4′]pyrazolo[5,1-c]-1,2,4-triazine derivatives **19a,b**, respectively.

In contrast to their behavior towards malononitrile (**18**), compounds **17a,b** reacted with ethyl cyanoacetate (**20a**), with benzothiazoloacetonitrile (**20b**) and with cyanothioacetamide (**1**) in cold ethanol in the presence of sodium acetate to afford the separable intermediate condensation products **21a–f**, respectively. These compounds showed bands for two NH groups in their IR spectra indicating the compounds to be in the hydrazo rather than the azo form. This conclusion was also supported by the ^{1}H-NMR spectral data of the reaction products

which revealed the presence of two D_2O exchangeable NH groups and the absence of any signals which may be attributed to the presence of a methine CH proton (cf. Experimental part, Table II and Chart 2).

Structures of **21a–f** were further confirmed via their cyclization into the corresponding pyridopyrazolo-1,2,4-triazine derivatives **22a–f**, respectively. Compound **22a–f** could also be obtained via another route by conducting the reaction between each of **17a,b** and each of **20a,b** and **1** in boiling ethanol containing a catalytic amount of triethylamine. Compounds **22a–f** prepared via this route were found to be completely identical in elemental and spectral data to **22a–f** prepared via cyclization of the corresponding **21a–f**, respectively (cf. Chart 2). The mass spectrum of compound **22c** gave m/z = M^+ = 573 (100 %) which is exactly the same molecular weight required for a compound with molecular

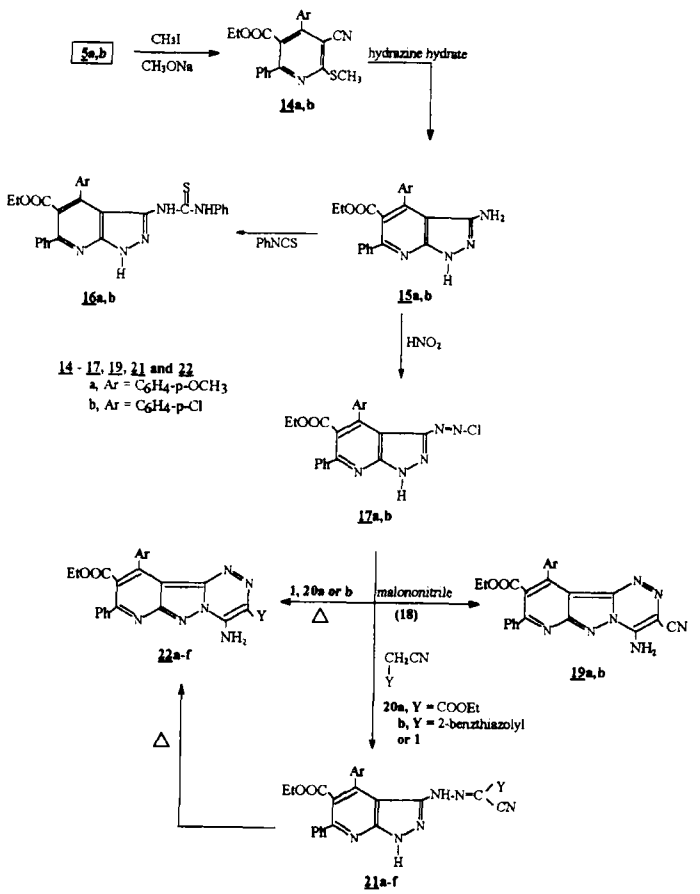

CHART 2

formula $C_{31}H_{23}N_7O_3S$. The activity of the diazonium salts **17a,b** towards some active methylene ketones and esters was also studied. It has been found that **17a,b** reacted with ethyl acetoacetate **23a** and with acetylacetone (**23b**) in cold ethanol in the presence of sodium acetate to afford directly the corresponding pyrido[2,3:3′,4′]pyrazolo[5,1-c]-1,2,4-triazine derivatives **24a–d** respectively. The structures of **24a–d** were confirmed by elemental analyses and spectral data (cf. Experimental part). It is remarkable that attempts to isolate the corresponding simple condensation reaction products (formed via loss of HCl) were unsuccessful under a variety reaction conditions.

In contrast to their behavior towards **23a,b**, compounds **17a,b** reacted with ethyl benzoyl acetate (**4**) under the same experimental conditions to afford the corresponding substituted hydrazinopyrazolo[3,4-b]pyridine derivatives **25a,b**, respectively. The IR spectra of **25a,b** showed the presence of bands of two NH groups in each case. Moreover, their ^{1}H-NMR spectra revealed the absence of signals for methine CH protons (cf. Experimental part, Tables 2).

Further confirmation of the structures **25a,b** was achieved via their cyclization in boiling ethanolic triethyl amine which afforded the corresponding pyrido[2,3:3′,4′]pyrazolo[5,1-c]-1,2,4-triazine derivatives **26a,b**, respectively via loss of water. Again the structures of **26a,b** were confirmed via ^{1}H-NMR spectral data which revealed only the triplets and quartets of the two $COOCH_2CH_3$ groups in addition to the aromatic protons in each case. The mass spectrum of compound **26b** gave m/z = M^+ = 577 (100%) which is the exact molecular weight required for a compound with molecular formula $C_{32}H_{24}N_5O_4Cl$.

The study was also extended to investigate the behavior of **17a,b** towards diethyl malonate (**27**). Cold mixtures of **17a,b** were allowed to react with **27** in ethanol in the presence of sodium acetate. The reaction products showed the presence of bands for two NH groups. Accordingly these reaction products could be formulated as the substituted hydrazinopyrazolo[3,4-b]pyridine derivatives **28a**. The cyclization reaction of **28a** was taken also as a further confirmation of the assigned structure. Thus, when **28a** was heated under reflux in the presence of ethanol and triethyl amine it underwent loss of ethanol and gave pyrido[2,3:3′,4′]pyrazolo[5,1-c]-1,2,4-triazin-5-one **29a**. The ^{1}H-NMR spectrum of **29a** revealed only signals due to NH, two COOEt groups and aromatic protons (cf. Experimental part and Table II).

In contrast to the behavior of **17a** towards the action of diethyl malonate (**27**), compound **17b** reacted with the same reagent under the same reaction conditions to give pyrazolo[3,4-b]pyridine derivative **29b** directly. Attempts to obtain the corresponding **28b** were unsuccessful under a variety of reaction conditions. The

structure of **29b** was based on a correct elemental analysis and spectral data (cf. Experimental part).

Moreover, compounds **29a,b** could also be directly synthesized via another route by conducting the reaction of **17a,b** and **27** in boiling ethanol in the presence of sodium acetate. Compounds **29a,b** prepared via this route were found to be identical in all aspects with **29a,b** obtained via cyclization of **28a,b**, respectively (cf. Chart 3).

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 MHz and Brucker WP-80 spectrometers using TMS as an internal standard. Chemical shifts are expressed as ppm using DMSO-d_6, $CDCl_3$ and $(CD_3)_2CO$ as solvents.

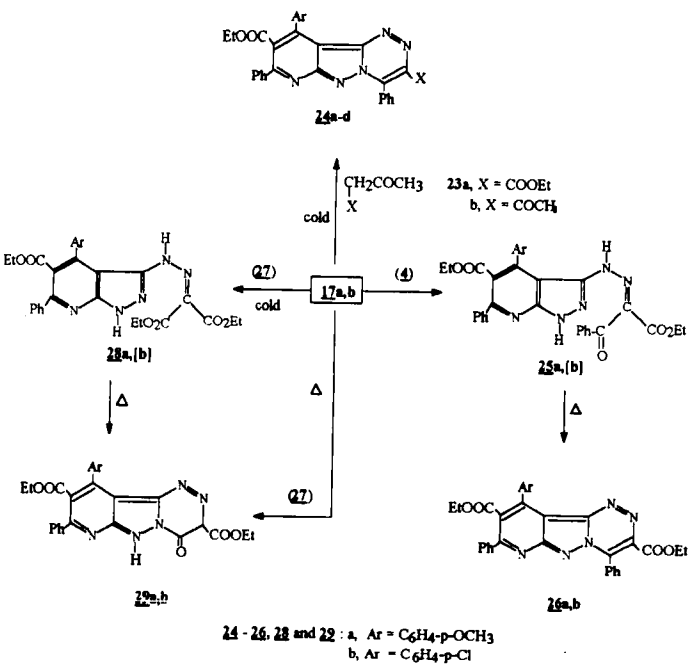

CHART 3

Mass spectra were recorded on a Hewlett-Packard GC-MS, type 2988, series A using DIP technique at 15 eV and 70 eV.

Microanalyses were performed by the Microanalytical Center at Cairo University using a Perkin-Elmer 2400 CHN analyzer.

Synthesis of 7a,b, 9a,b, 11a,b and 14a,b (General Procedure)

A solution of **5a,b** (0.01 mole) and each of the phenacyl bromides (**6a,b**), chloroacetone (**8**), α-chloroacetylacetone and methyl iodide (0.01 mole) was heated under reflux in methanolic sodium methoxide (prepared from 0.01 atom of sodium metal in 30 mL of methanol) for 1–5 hours (TLC). The reaction products obtained hot or after cooling were filtered and recrystallized from the proper solvents to yield the reaction products **7a–d**, **9a,b**, **11a,b** and **14a,b**, respectively (cf. Tables I and II).

Synthesis of 19a,b, 21a–f 24a–d, 25a and 28a

A solution of each of **17a,b** (0.01 mole) in ethanol (30 mL) in the presence of sodium acetate (1g) with each of (**18**), **1**, **20a,b**, **23a,b**, **4** and **27** (0.01 mole) and the whole was stirred in an ice-cold bath for one hour. The solid products obtained were filtered, washed with water, recrystallized from the proper solvents, and identified as **19a,b**, **21a–f**, **24a–d**, **25a** and **28a**, respectively (cf. Tables I and II).

Synthesis of 10a,b (Cyclization of each of 9a,b and 11a,b)

A solution of each of **9a,b** and **11a,b** in ethanol (30 mL) was heated under reflux for 3–5 hours with potassium hydroxide (0.01 mole). The reaction mixture was then cooled, acidified with dilute hydrochloric acid and the precipitated solid products were filtered, washed with water and then recrystallized from the proper solvents to yield the cyclized products **10a,b** (cf. Tables I and II).

Synthesis of 22a–f and 29a,b

A solution of each of **17a,b** (0.01 mole) in ethanol (30 mL) in the presence of triethylamine (0.5 mL) was treated with each of **1**, **20a,b** and **27** (0.01 mole) and then heated under reflux for 2–3 hours. The solids obtained hot or after cooling were filtered and recrystallized from the proper solvents to yield the reaction products **22a–f** and **29a,b**, respectively (cf. Tables I and II).

Synthesis of 22a–f; 26a and 29a

A solution of each of **21a–f**; **25a** and **28a** (0.01 mole) in ethanol (30 mL) in the presence of triethylamine (0.5 mL) was heated under reflux for 2–3 hours. The solids formed hot or after cooling were filtered and recrystallized from the proper solvents to yield the reaction products **22a–f**; **26a** and **29a** respectively (cf. Tables I and II).

Synthesis of 13a,b and 17a,b (Reaction with Nitrous Acid)

A cold solution of each of **10a,b** and **15a,b** (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 an ice-cold bath for one hour. The solid products obtained were filtered, washed with water and recrystallized from the proper solvents to yield the reaction products **13a,b** and **17a,b**, respectively (cf. Tables I and II).

Synthesis of 16a,b

A solution of each of **15a,b** (0.01 mole) in pyridine (30 mL) was treated with phenylisothiocyanate (0.01 mole). The reaction mixture was heated under reflux for 4 hours then cooled, poured into ice-cold water and acidified by dilute hydrochloric acid. The solid products obtained were filtered, washed with water and recrystallized from the proper solvents to yield the reaction products **16a,b**, respectively (cf. Tables I and II).

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