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Reactions with Cyanothioacetamide Derivatives: Synthesis of Several New Pyridine and Annelated Pyridine Derivatives

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Abstract□Several new pyridine, pyridinethione, pyrazole[3,4-b]-pyridine, pyrido [1,2-a]-1,3-thiazine and pyrido[1,2-a]pyridine thione derivatives have be synthesised via the reactions of 2-methyl-3-ethoxycarbonyl-4-phenyl-5-cyano-1,4,5,6-tetrahydro-pyridine-6-one 2 with different reagents. The structures of the newly synthesised derivatives were established on the basis of elemental analyses and spectal data studies.

Keywords□Cyanothioacetamide, pyridines, annelated pyridines,1,3-thiazine, cinnamonitriles.

The considerable biological activities of pyridine and its derivatives as antimycotic[1], antidepressant[3], fungicidal agents[4], antiarrhythmic[5] and antioipemic[5] agents stimulated our interest for the synthesis of several new derivatives of these ring systems which are required for a medicinal chemistry program. The reaction of the 2-thiocarboxyamido-cinnamonitrile derivaties[6-8] (benzalcyanothioacetamide) **1** with ethyl acetoacetate yielded 2-methyl-3-ethoxycarbonyl-4-phenyl-5-cyanotetra-hydrophridine-6-thione (**2**)[9] which was taken as the starting material for the present investigations. The reactions of **2** with different reagents resulted in the synthesis of several new pyridine and annelated derivatives bearing latent functional substituents and thus appear highly promising for biological activity studies.

It has been found that **2** reacted with methyl iodide in the presence of sodium ethoxide to afford a product of molecular formula $C_{18}H_{20}N_2SO_2$ corresponding to the addition of one molecule of **2** to two molecules of methyl iodide followed by dehydro-halogenation. The reaction product could, however, be formulated as the 1-methyl-6-methylmercapto tetra-hydropyridine derivative **3a**. The formation of this dimethyl derivative is infavour of the tetrahydropyridine structure of the key compound 2. The structure of **3a** was established on the basis of correct elemental analysis and spectral data studies. The IR spectrum of **3a** (cm^{-1}) showed absorption bands at 2980 (CH_3), 2225 (CN) and 1735 (ester C=O). The ^{1}H-NMR spectrum (δ ppm) of **3a** revealed signals at 1.2 (s, 9H, three CH_3); 1.7 (t, 3H, $\underline{CH_3}$ CH_2); 2.4 (q, 2H, $CH_3\underline{CH_2}$); 4.3 (s, 1H, pyridine H-4) and 7.2-7.9 (m, 5H, ArH's).

Similar to its behaviour towards methyl iodide, compound 2 reacted with ethyl iodide to afford the corresponding 1-ethyl-6-ethylmercapto-tetrahydro pyridine derivative **3b** whose structure was established also by elemental analysis and spectral data studies. (cf. Experimental Part.) It is remarkable to report here that the corresponding monoalkyl derivatives namely, 6-alkyl tetrahydropyridines could not, however, be obtained even on using a molecular ratio of 1:1. The S-alkyl derivatives **3a,b** reacted with hydrazine hydrate in ethanol to afford the corresponding pyrazolo-[3,4-b]pyridine derivatives **5a,b** most likely formed via the intermediacy of the corresponding 6-hydrazino derivatives **4a,b** respectively. The structural elucidations of **5a,b** were based on both elemental analyses and spectral data. The IR spectra of **5a,b** showed absorption bands related to the presence of NH_2, NH, saturated CH_2, CH_3 and C=O groups in each case (cf. Experimental Part). The ^{1}H-NMR spectrum of **5a** revealed singnals (δ ppm) at 1.4 (s, 6H, two CH_3); 4.5 (s, 1H, pyridine H-4); 7.5-8.0 (m, 5H, ArH's) and 8.5 (s, br, 6H) corresponding to two NH_2 and two NH groups respectively, on the other hand, the ^{1}H-NMR spectrum of **5b** revealed signals (δ ppm) at 1.2 (s, 3H, CH_3); 1.7 (t, 3H, $\underline{CH_3}$ CH_2); 2.7 (q, 2H, CH_3 $\underline{CH_2}$); 4.5 (s, 1H, pyridine H-4); 7.3-8.0 (m, 5H, ArH's) and 8.7 (s, br, 6H, two NH_2 and two NH).

The activity of the methyl group in both **5a,b** was demonstrated via their reaction with benzaldehyde. Thus, it has been found that each of **5a,b** reacted with benzaldehyde to afford the corresponding ylidene derivatives **6a,b** respectively most likely formed via the

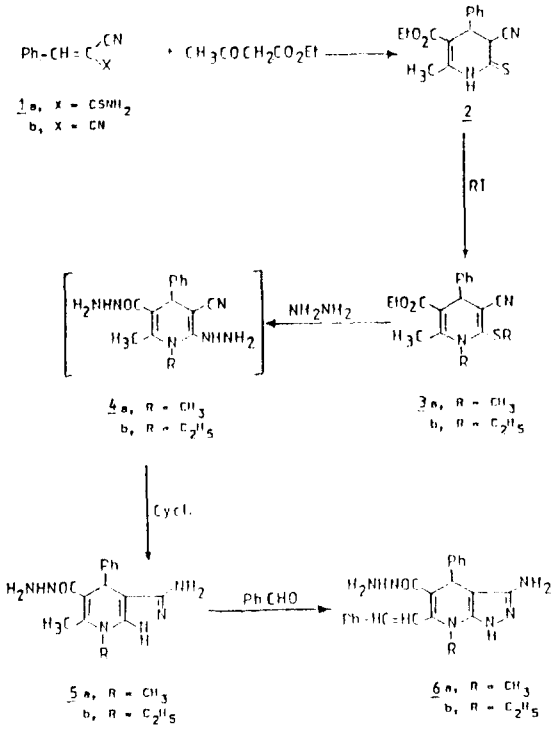

Chart 1

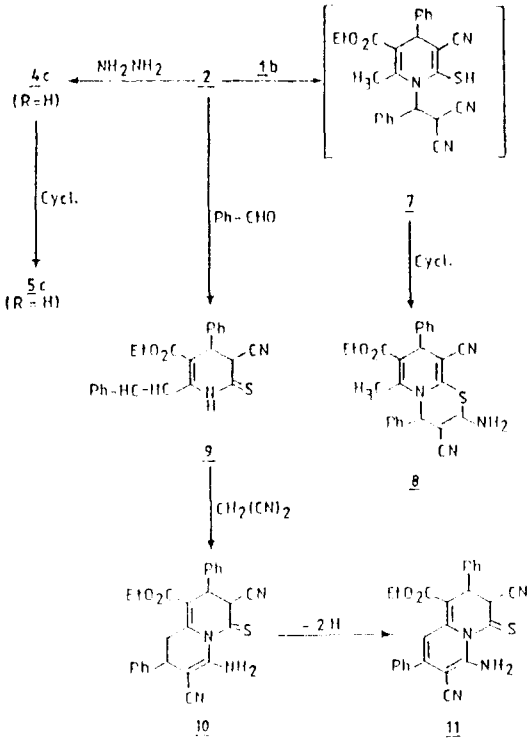

Chart 2

addition of one molecule of benzaldehyde to one molecule of each of **5a,b** followed by the loss of one molecule of water. The structure of **6a,b** was established by elemental analyses and spectral data studies (cf. Experimental Part). The synthetic potential of **2** was further demonstrated via other reactions. Thus, it has been found that **2** reacted with benzalmalononitrile (**1b**) to afford a product which could be formulated as the pyrido-[2,1-b]-1,3-thiazine derivative **8** on the basis of elemental analysis and spectral data. The IR spectrum of **8** revealed absorption bands corresponding to the presence of NH_2, sat. CH_3, two CN and ester C=O groups. The ^{1}H-NMR spectrum of **8** revealed among its signals those corresponding to the presence of pyridine H-4 (4.2 ppm) and thiazine H-4 (5.1 ppm) protons (cf. Experimental Part). The formation of **8** in this reaction is assumed to proceed most likely via the addition ofthe NH proton to the ylidenic double bond in **1b** to yield the corresponding Michael adduct **7** which could be cyclized via addition to the cyano function to afford the final isolable **8**. Furthermore, compound **2** reacted with benzaldehyde to yield the corresponding ylidene derivative **9** whose structure was established based on elemental as well as spectral back grounds (cf. Experimental Part).

The synthetic potential of **9** was, in turn, demonstrated via its reaction with malononitrile. Thus, it has been found that **9** reacted with malononitrile in absolute ethanol in the presence of catalytic amounts of triethylamine to afford a product corresponding to the addition of one molecule of **9** to one molecule of malononitrile and the loss of one molecule of hydrogen. The reaction product could, however, be formulated as the pyrido[1,2-a]pyridine derivative **11**. The structure of **11** was established via elemental analysis, IR and ^{1}H-NMR spectral data. The IR spectrum of **11** was in a good agreement with the assigned structure, while its ^{1}H-NMR spectrum revealed among its signals those corresponding to the presence of pyridine H-4 (3.6 ppm) and pyridine H-3 (3.6 ppm) and no triplets were observed indicating that the reaction product suffered dehydrogenation under the applied reaction conditions (cf. Chart 2).

Compound 2 reacted with hydrazine hydrate to afford a product corresponding to the addition of two molecules of hydrazine hydrate to one molecule of **2** followed by the loss of one molecule of ethanol and one molecule of hydrogen sulphide. The reaction product could, however, be formulated as the pyrazolo

Table 1.

Comp*	mp.(°C)	Yield (%)	Mol. formula	% Analysis Calcd./Found			
				C	H	N	S
2	240-1	72	$C_{16}H_{16}N_2SO_2$	64.00 63.9	5.33 5.3	9.33 9.3	10.66 10.6
3a	85	83	$C_{18}H_{20}N_2SO_2$	65.85 65.8	6.09 6.1	8.53 8.5	9.75 9.7
3b	70	80	$C_{20}H_{24}N_2SO_2$	67.41 67.3	6.74 6.7	7.86 7.8	8.98 8.9
5a	180-1	66	$C_{15}H_{18}N_6O$	60.40 60.1	6.04 6.0	28.18 28.2	
5b	270-2	71	$C_{16}H_{20}N_6O$	61.53 61.5	6.41 6.4	26.92 26.8	
5c	255-6	87	$C_{14}H_{16}N_6O$	56.00 56.1	5.33 5.3	28.00 28.2	
6a	165	86	$C_{22}H_{22}N_6O$	68.39 68.4	5.69 5.7	21.76 21.8	
6b	255-7	82	$C_{23}H_{24}N_6O$	69.00 69.1	6.00 6.2	21.00 20.9	
8	160	88	$C_{26}H_{22}N_4SO_2$	68.72 68.7	4.84 4.8	12.33 12.4	7.04 7.1
9	265-6	78	$C_{23}H_{20}N_2SO_2$	71.13 71.1	5.15 5.1	7.21 7.3	8.24 8.2
11	295-7	79	$C_{26}H_{20}N_4SO_2$	69.02 69.2	4.42 4.4	12.38 12.4	7.07 7.2

*All compounds are yellow in colour except **5a** and **8**, brown.

[3,4-b]pyridine derivative **5c** whose structure was established based on elemental analysis and spectral data studies. The IR of **5c** revealed the absence of any absorption bands related to the presence of the cyano function indicating that this was involved in the cyclization step of the intermediate **4c**. The ^{1}H-NMR spectrum of **5c** revealed the presence of signals corresponding to NH_2, three NH, CH_3 in addition to the aromatic protons (cf. Experimental Part).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer using KBr discs. ^{1}H-NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer. The microanalyses were performed by the Microanalytical Center at Cario University.

Synthesis of 2-methyl-3-ethoxycarbonyl-4-phenyl-5-cyano-4,5-dihydropyridine-6-thione (2)

A solution of ethyl acetoacetate (0.01 mole) and β-phenyl- α -cyano-thioacrylamide (0.01 mole) were refluxed in absolute ethanol (30 m*l*) containing the catalytic amount of triethylamine for 5 h. The reaction mixture was then concentrated by evaporation and the solid which formed was collected, washed with ethanol and then recrystallized from ethanol to give **2.**

General procedure for the preparation of 3a,b

A solution of **2** (0.01 mole) and either ethyl iodide (0.01 mole) or methyl iodide (0.01 mole) were refluxed in ethanolic sodium ethoxide solution (prepared by the equivalent amounts of sodium metal and ethanol) for 3 h. The reaction mixture was poured onto cold water. The solid so formed was collected and crystallized from the proper solvent to give **3a,b** respectively.

General procedure for preparation of 5a,b

A solution of **3a,b** (0.01 mole) and hydrazine hydrate (0.02 mole) was refluxed in ethanol till the odour of alkyl mercaptan ceased. The reaction mixture was poured onto cold water and the solid so formed was collected and crystallized from the proper solvent to give **5a,b** respectively.

General procedure for proparation of 6a,b

A solution of **5a,b** (0.01 mole) and benzyaldehyde (0.01 mole) was refluxed in absolute ethanol (20 m*l*) triethylamine (0.5 m*l*) for 5 h. The reaction mixture was poured onto cold water and the solid was collected then crystallized from the proper solvent to give

Table II.

Comp.	IR (cm^{-1})	^{1}H-NMR δ ppm
2	3350 (NH); 3050 (aromatic C-H); 2990-2985 (Aliphatic C-H), 2227 (CN), 1740 (ester C=O) and 1550 (C=S)	1.3 (s, 3H, CH_3); 1.9 (t, 3H, $\underline{CH_3}CH_2$); 2.4 (q, 2H, $CH_3\underline{CH_2}$); 4.5 (dd, 2H, pyridinethione H-3 and H-4); 7.5-8.0 (m, 5H, Aromatic protons); 8.7 (s, br, 1H, NH)
3a	3040 (Aromatic C-H); 2990-2985 (Aliphatic C-H); 2225 (CN); 1735 (ester C=O) and 1550 (C=S)	1.2 (s, 9H, three CH_3); 1.7 (t, 3H, $\underline{CH_3}CH_2$); 2.4 (q, 2H, $CH_3\underline{CH_2}$); 4.3 (s, 1H, pyridine H-4) and 7.2-7.9 (m, 5H, Aromatic protons)
3b	3060 (Aromatic C-H); 2995-2985 (Aliphatic C-H); 2223 (CN); 1739 (ester C=O) and 1550 (C=S)	1.3 (s, 3H, CH_3); 1.8 (t, 6H, two $\underline{CH_3}CH_2$); 2.6 (q, 4H, two $CH_3\underline{CH_2}$); 4.5 (s, 1H, pyridinethione-H_4) and 7.2-8.0 (Aromatic protons)
5a	3370, 3400 (NH_2, NH); 3070 (Aromatic C-H); 2950-2860 (Aliphaytic C-H) and 1690 (C=O)	1.4 (s, 6H, two CH_3); 4.5 (s, 1H, pyridine H-4); 7.5-8.0 (m, 5H, Aromatic protons) and 8.5 (s, br, 6H, two NH_2 and two NH)
5b	3375, 3400 (NH_2, NH); 3060 (Aromatic C-H); 2990-2885 (Aliphatic C-H) and 1690 (C=O)	1.2 (s, 3H, CH_3); 1.7 (3H, t, $\underline{CH_3}CH_2$); 2.7 (2H, q, $CH_3\underline{CH_2}$); 4.5 (s, 1H, pyridine H-4); 7.3-8.0 (m, 5H, Aromatic protons) and 8.7 (s, br, 6H, two NH_2 and two NH)
5c	3380, 3400 (NH_2 and NH); 3070 (Aromatic C-H), 2990-2980 (Aliphatic C-H) and 1690 (C=O)	1.4 (s, 3H, CH_3); 4.6 (s, 1H, pyridine H-4); 7.5-8.0 (m, 5H, Aromatic protons) and 8.7 (s, br., 7H, two NH_2 and three NH).
6a	3350, 3400 (NH_2, NH); 3070 (Aromatic C-H); 2950-2850 (Aliphatic C-H) and 1690 (C=O)	1.5 (s, 3H, CH_3); 3.5 (s, 1H, pyridine H-4); 4.7 (d, 2H, PhCH=CH-); 7.0-7.5 (m, 10H, Aromatic protons) and 8.5 (s, br, 6H, two NH_2 and two NH)
6b	3370-3400 (NH_2, NH); 3050 (Aromatic C-H); 2960-2870 (Aliphatic C-H) and 1685 (C=O)	1.7 (t, 3H, $\underline{CH_3}CH_2$); 3.9 (q, 2H, $CH_3\underline{CH_2}$); 3.6 (s,,1H, pyridine H-4); 4.9 (d, 2H, Ph CH=CH-); 7.0-7.5 (m, 10H, Aromatic protons) and 8.7 (s, br, 6H, two NH_2 an two NH)
8	3350, 3400 (NH_2); 3050 (Aromatic C-H); 2950-2890 (Aliphatic C-H); 2227, 2225 (two CN) and 1735 (ester C=O)	1.3 (s, 3H, CH_3); 1.6 (t, 3H, $\underline{CH_3}CH_2$); 2.7 (q, 2H, $CH_3\underline{CH_2}$); 4.2 (s, 1H, pyridine H-4); 5.1 (s, 1H, thiazine H-4); 7.0-7.5 (m, 10H, Aromatic protons) and 8.3 (s, br, 2H, NH_2)
9	3370 (CN); 3050 (aromatic C-H); 2950-2870 (Aliphatic C-H); 2225 (CN); 1737 (ester C=O); 1600 (sryryl C=C) and 1550 (C=S)	1.4 (t, 3H, $\underline{CH_3}CH_2$); 2.5 (q, 2H, $CH_3\underline{CH_2}$); 3.7 (d, 2H, pyridine H-3 and pyridine H-4); 4.5 (d, 2H, Ph, CH=CH); 7.0-7.5 (m, 10H, Aromatic protons) and 8.7 (s, br, 1H, NH)
11	3380, 3400 (NH_2), 3060 (Aromatic C-H); 2950-2870 (Aliphatic C-H); 2227, 2225 (two CN); 1735 (ester C=O) and 1550 (C=S)	1.5 (t, 3H, $\underline{CH_3}CH_2$); 3.9 (q, 2H, $CH_3\underline{CH_2}$); 3.6 (d, 2H, pyridine H-3 and pyridine H-4); 7.0-7.9 (m, 10H, Aromatic protons) and 8.7 (s, br, 2H, NH_2)

6a,b respectively.

Syntheis of the pyrido[1,2-b]thiazine derivative 8

A solution of **2** (0.01 mole) and benzalmalonitrile **1b** (0.01 mole) was refluxed in absolute ethanol (20 m*l*) containing triethyl amine (0.5 m*l*) for 3 h. The reaction mixture was poured onto cold water, the solid was collected and crystallized from ethanol to give **8**.

Synthesis of the pyrido[1,2-a]pyridine derivative 11

A solution of **2** (0.01 mole) and benzaldehyde (0.01 mole) was refluxed for 5 h in absolute ethanol (20 m*l*) containing triethylamine (0.5 m*l*). The reaction mixture was poured onto cold water, the solid was collected and then crystallized from ethanol to give **9**. The isolated solid compound **9** was in turn refluxed with malononitrile in absolute ethanol (20 m*l*) containing triethylamine (0.5 m*l*) for 5 h. The reaction mixture was poured onto cold water, the solid was collected and crystallized from ethanol to give **11**.

Synthesis of the pyrazolo[3,4-b]pyridine derivative 5c

A solution of **2** (0.01 mole) and hydrazine hydrate (0.02 mole) was refluxed till the odour of hydrogen sulfide ceased. The reaction mixture was poured onto cold water and the solid so formed was collected and recrystallized from ethanol to give **5c**.

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