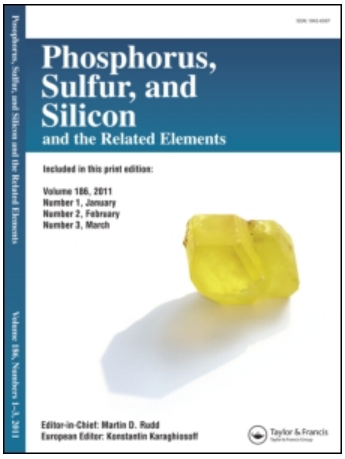

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REACTIONS WITH CYANOTHIOACETAMIDE AND ITS DERIVATIVES: SYNTHESIS AND CHARACTERIZATION OF SEVERAL NEW PYRIDINE AND ANNELATED PYRIDINE DERIVATIVES

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REACTIONS WITH CYANOTHIOACETAMIDE AND ITS DERIVATIVES: SYNTHESIS AND CHARACTERIZATION OF SEVERAL NEW PYRIDINE AND ANNELATED PYRIDINE DERIVATIVES

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Several new pyridines and annelated pyridines were synthesised via the reactions of some pyridinethiones with a variety of activated halogenomethyl containing reagents and hydrazines. Structures were established on the basis of elemental analysis and spectral data.

Key words: Cyanothioacetamides, chloroacetyl derivatives, chloro-ketones, pyridines, annelated pyridines.

INTRODUCTION

Cyanothionacetamide (1) and its derivatives (3) are versatile reagents and their utility in heterocyclic synthesis has gained considerable recent attention.[1-9] The reported biological activities of pyridines and annelated pyridines as antimycotic,[10] antidepressant,[11] fungicidal,[12] antiarrhythmic,[13] and antilipemic[14] agents stimulated our interest to synthesize a variety of these heterocycles. The arylidene cyanothioacetamides 3a,b seemed to be excellent and unique starting materials to fulfill this objective.

RESULTS AND DISCUSSION

It has been found that the arylidene derivative 3a reacted, base catalysed, with acetylacetone (4) for 3 h to yield a product of molecular formula $C_{13}H_{12}N_2S_2O$ and m.p. 188°C. This formula corresponded to the addition of 3a to 4 followed by the loss of water. The IR (cm^{-1}) spectrum of this product showed the presence of NH (2350), CN (2210), acetyl CO (1700), C=S (1540) and saturated CH_2, CH_3 (2980) groups. Its mass spectrum gave m/e = 276. Moreover, its ^{1}H-NMR spectrum (δ ppm) revealed among its signals those of pyridine H-4 (d, 4.1) and pyridine H-3 (d, 4.4). Based on

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the above data, this reaction product was formulated as 5-acetyl-3-cyano-6-methyl-4-(2′-thienyl)tetrahydro(1H)pyridine-2-thione (5a).

Conducting the reaction between 3a and 4 for 5 h resulted in the formation of another reaction product with m.p. 266°C as the sole product. This reaction product could, be formulated based on analytical and spectral data as 5-acetyl-3-cyano-6-methyl-4-(2′-thienyl)dihydro2(1H)pyridine-2-thione (6a) (cf. Experimental Part).

The structure of 5a was further confirmed either by boiling its solution in ethanol for 2 h in the presence of TEA to yield 6a or its independent synthesis via the reaction of 1 with the ylidene derivatives of acetylacetone 7a (cf. Chart 1) as previously reported[15] for similar ring systems. In contrast to its behavior towards 3a, acetylacetone (4) reacted with the furfurylidene derivative 3b either for 3 h or 5 h to yield *the same product* in each case which was formulated, based on elemental analysis and spectral data, as 5-acetyl-3-cyano-6-methyl-4-(2′-furyl)-tetrahydro-2(1H)-pyridine-2-thione 5b (cf. Experimental Part). Attempts to obtain the corresponding 6b were unsuccessful under a variety of reaction conditions. Compounds 5a,b and 6a were chosen as the starting materials for the product study owing to the presence of more than one active site. Thus, each of 5a,b and 6a reacted with hydrazine hydrate to afford sulfur-free reaction products. The IR spectra of these products were free from the nitrile absorption bands. Their ^{1}H-NMR spectra revealed the presence of NH and NH_2 signals at about 4.8–5.0 δ ppm. On shaking compounds 10a and 10b with deutrium oxide (D_2O) the singlet broad signal at δ 4.8–5.0 ppm which corresponds to the 3H of both NH and NH_2 groups disappeared and two new signals appeared: The first is the singlet signal at δ 4.5 ppm for 1H of DOH due to the exchanging proton at NH with D_2O and the second is the singlet signal at δ 4.7 ppm for 2H of H_2O due to the exchanging protons at NH_2 with D_2O.

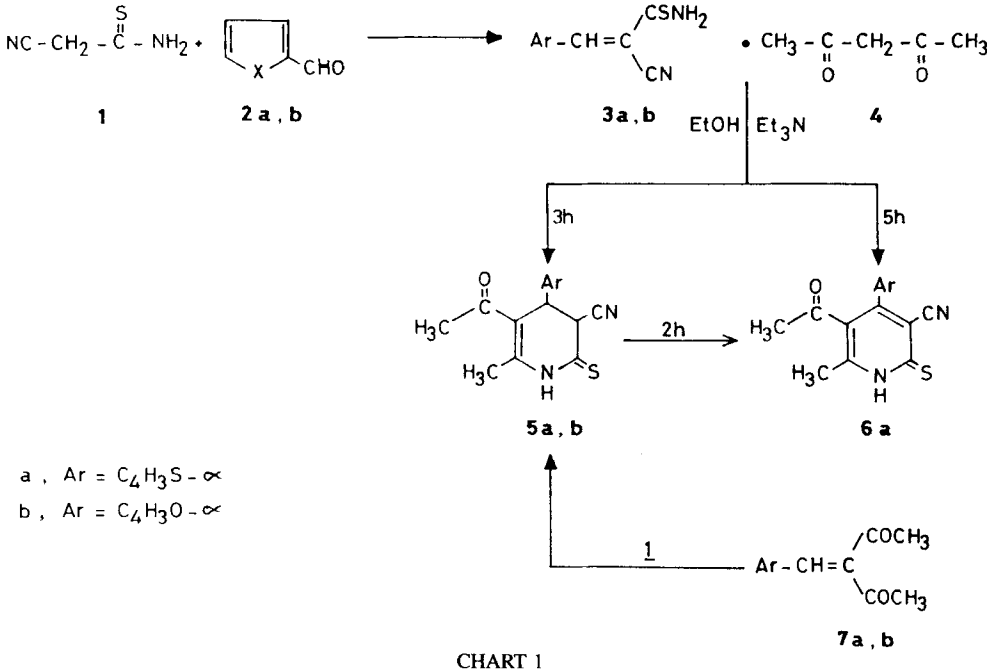

CHART 1

These reaction products were formulated as the pyrazolo[3,4-b]pyridines 10a,b and 11a respectively, most likely formed via the intermediacy of the non-isolated hydrazides 8a,b and 9a respectively.

An unequivocal support for the structure of each of 10a,b and 11a was achieved via their synthesis by first formation of the corresponding 2-S-ethylpyridinethiones 12a,b and 13a respectively by the reaction of each of 5a,b and 6a respectively with ethyl iodide. Compounds 12a,b and 13a then reacted with hydrazine hydrate with the loss of ethyl mercaptan and cyclization under the applied reaction conditions to yield the corresponding 10a,b and 11a respectively (cf. Chart 2).

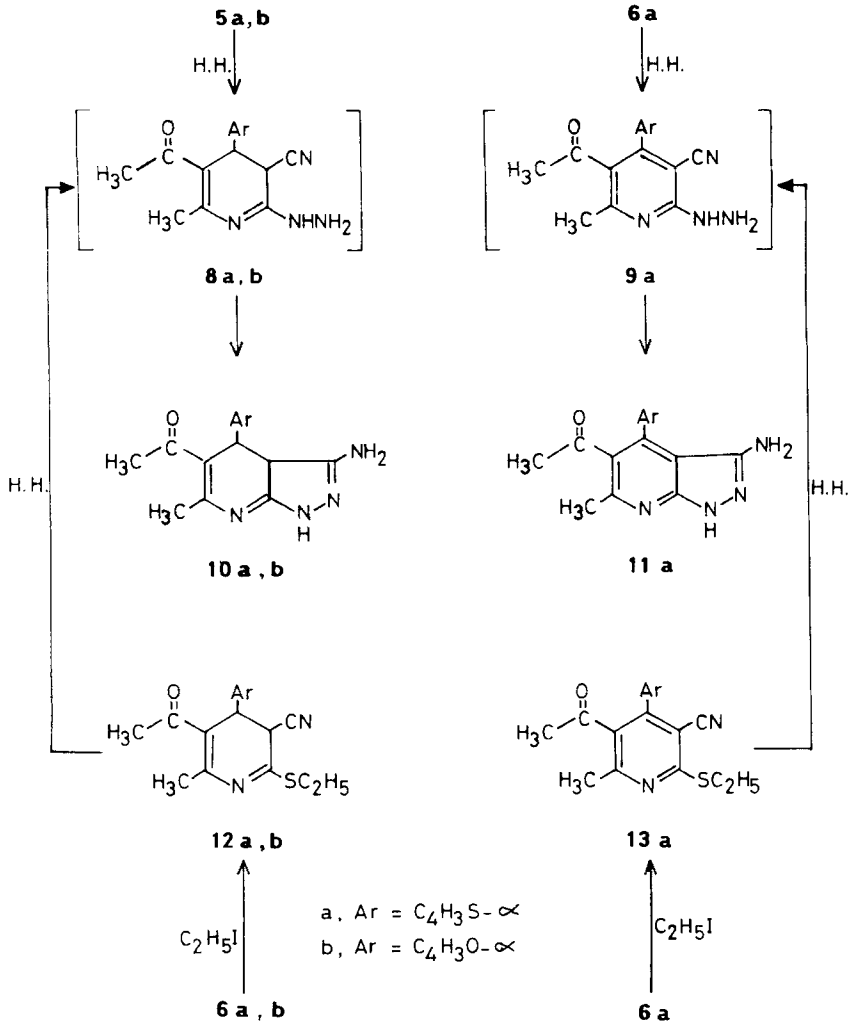

CHART 2

Structures of 12a,b and 13a were, in turn, established by elemental analysis and spectral data (cf. Experimental Part). Furthermore, the synthetic potential of each of 5a,b was demonstrated via their reactions with a variety of chloroacids, esters and

amides 14a–d. Thus, it has been found that 5a reacted with chloroacetic acid (14a) to afford a product of molecular formula $C_{15}H_{14}N_2S_2O_3$ corresponding to equimolecular, addition and a loss of HCl. Its IR spectrum showed OH, two CO and CN groups while its ^{1}H-NMR spectrum revealed signals of two CH_3, CH_2, pyridine H-3 and H-4 in addition to thienyl and OH protons in the expected position (cf. Experimental Part). The reaction product was assigned the 2-carboxymethylthiodihydropyridine structure 15a.

Analogously, ethyl chloroacetate (14b), methyl chloroacetate (14c) and chloroacetamide (14d) reacted with 5a to afford the corresponding 2-S-alkyl-thiopyridine derivatives 15b–d respectively. Structures assigned for each of 15b–d was based on correct elemental analysis and spectral data as for 15b previously described (cf. Experimental Part). Further proof for the structure of each of 15a–d came from their cyclization by the action of boiling ethanolic KOH to yield *the same product* in each case which was formulated as the thieno[2,3-b]pyridine derivative 17a. The formation of 17a in this reaction is assumed to proceed via the initial formation of the non-isolable thieno[2,3-b]dihydropyridine derivative 16a which underwent autooxidation into 17a under the applied reaction conditions (cf. Chart 3).

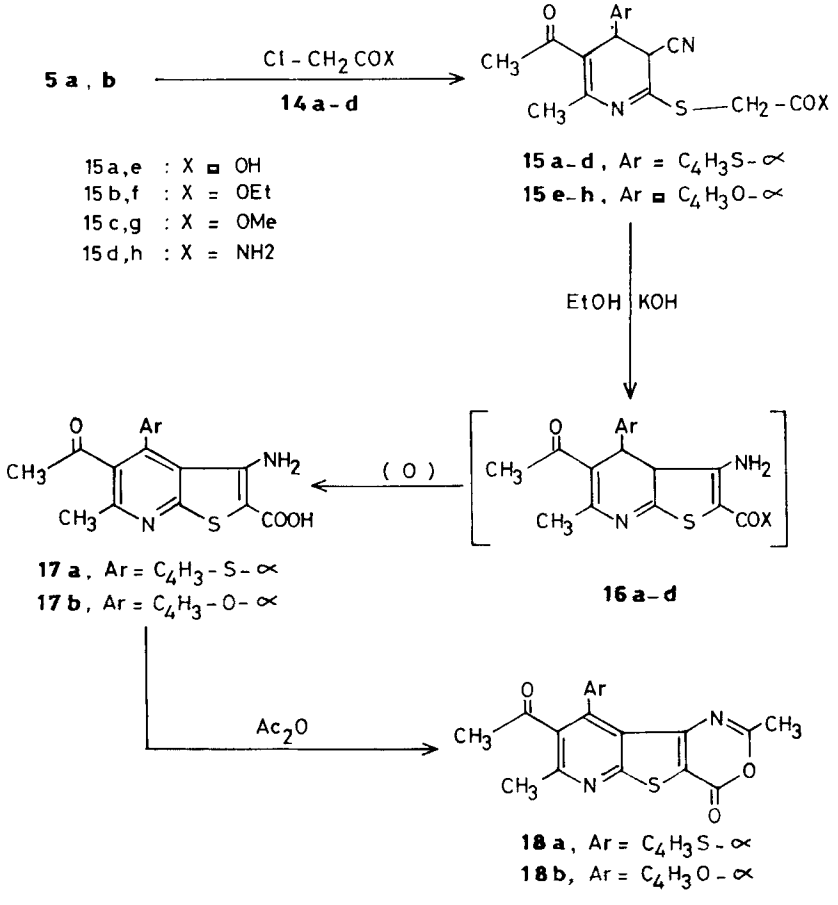

CHART 3

In support of this idea, the ^{1}H-NMR spectrum of 17a was found to be free from pyridine signals. Furthermore, 17a reacted with acetic anhydride to yield the thieno[3,2-d]-isoxazino[2′,3′-b′]pyridine derivative 18a whose IR and 1H-NMR data were in good agreement with the assigned structure (cf. Experimental Part). In the same manner, 5b reacted with each of 14a–d to give the corresponding to 2-S-alkylpyridines 15e–f respectively. Structure of 15e–f was also based on both elemental analysis and spectra previously reported for 15a–d (cf. Experimental Part).

Compounds 15e–h could also be cyclized into *the same reaction product* in each case which was formulated as the thieno[2,3-b]pyridine derivatives 17b most likely via the intermediate 16b. The structure of 17b was further established by the reaction with acetic anhydride to yield the corresponding thieno[3,2-d]isoxazino[2′,3′-b′]pyridine derivative 18b which gave correct elemental analysis and expected value in its IR and ^{1}H-NMR spectra (cf. Experimental Part). Work is now in progress to investigate the behavior of 5a,b and 6a towards the action of some halogeno ketones, esters and active methylene reagents.

EXPERIMENTAL

All melting points are uncorrected. IR spectra in KBr discs were recorded on Perkin-Elmer FT-IR type 4 and Pye-Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were recorded on Varian EM 390-90 MHz, Gemnaii 200 MHz and Brucker WP-80 spectrometers using $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ 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 the Microanalytical Center of Cairo University using Perkin-Elmer 2400 CHN Elemental Analyzer. Compounds 3a,b[16] and 7a,b[15] were prepared following literature procedure.

Synthesis of 5a,b *and* 6a: (*General Procedures*)

A) A solution of acetylacetone (4, 0.01 mole) and each of 3a,b (0.01 mole) in ethanol (30 ml) containing TEA (0.05 ml) was heated under reflux for 3 h. The product obtained after cooling was filtered off and crystallized from ethanol to give 5a,b respectively (cf. Tables I and II).

B) Performing the reaction between 4 (0.01 mole) and each of 3a,b (0.01 mole) for 5 h and isolation of the products as in (A) gave 6a and 5b respectively (cf. Tables I and II).

C) Compound 6a was also obtained by heating under reflux a solution of 5a in ethanol for 2 h in the presence of TEA.

D) A solution of 1 (0.01 mole) in absolute ethanol (20 ml) containing TEA (0.5 ml) was treated with each of 7a,b (0.01 mole) and heated under reflux for 5 h. The solid product obtained after cooling was crystallized from ethanol to give 5a,b respectively (cf. Tables I and II).

Reactions of Ethyl Iodide with 5a,b *and* 6a: (*General Procedure*)

A solution of each of 5a,b or 6a (0.01 mole) in ethanolic sodium ethoxide (0.01 mole) in ethanolic sodium ethoxide (0.01 mole), prepared from the equivalent amounts of sodium metal and ethanol, was treated with ethyl iodide (0.01 mole) and heated under reflux for 5 h. The solid product obtained on pouring onto cold water was filtered off, washed with water then crystallized from ethanol to give 12a,b and 13a respectively (cf. Tables I and II).

Reactions of Hydrazine Hydrate on Each of 5a,b, 6a, 12a,b *and* 13a (*General Procedure*)

A mixture of 5a,b, 6a, 12a,b or 13a (0.01 mole) was treated with an excess of hydrazine hydrate (2–3 ml) and heated under reflux until the odor of H_2S or C_2H_5SH ceased (4–5 h). The solid product obtained after cooling was filtered off and crystallized from ethanol to yield 10a,b and 11a respectively (cf. Tables I and II).

Reactions of 5a,b *with Each of* 14a–d: (*General Procedure*)

A solution of 5a,b (0.01 mole) in sodium ethoxide (0.01 mole, prepared from the equivalent amounts of sodium metal and methanol) and of 14a–d (0.01 mole) was heated under reflux for 4–5 h (TLC mon-

TABLE I

Characterization data of the newly synthesized compounds

Comp.	*Mol. Formula*	*Yield %*	*Colour*	*M.P. (° C)*	*% Analysis, Calc/found*			
					C	*H*	*N*	*S*
5a	$C_{13}H_{12}N_2S_2O$	70	red	188-9	56.52 56.5	4.34 4.4	10.14 10.2	23.18 23.2
5b	$C_{13}H_{12}N_2SO_2$	68	yellow	260-1	60.00 59.9	4.61 4.7	10.76 10.9	12.3 12.2
6a	$C_{13}H_{10}N_2S_2O$	65	yellow	266-8	56.93 56.8	3.64 3.7	10.21 10.1	23.35 23.4
10a	$C_{13}H_{14}N_4SO$	70	orange	240-2	56.93 56.9	5.10 5.2	20.43 20.5	11.67 11.6
10b	$C_{13}H_{14}N_4SO_2$	70	orange	234-6	53.79 53.8	4.82 4.9	19.30 19.3	11.03 11.1
11a	$C_{13}H_{13}N_4SO$	68	yellow	248-9	57.14 56.8	4.76 4.4	20.51 20.2	11.72 11.6
12a	$C_{15}H_{16}N_2S_2O$	60	yellow	206-8	59.20 58.9	5.26 5.1	9.21 9.2	21.05 21.1
12b	$C_{15}H_{16}N_2SO_2$	65	yellow	70-2	62.49 62.5	5.55 5.6	9.72 9.8	11.1 11.1
13a	$C_{15}H_{14}N_2S_2O$	68	yellow	90-2	59.60 59.3	4.30 4.3	9.27 9.0	21.19 21.2
15a	$C_{15}H_{14}N_2S_2O_3$	70	yellow	167-9	53.89 53.9	4.19 4.2	8.38 8.4	19.16 19.1
15b	$C_{17}H_{18}N_2S_2O_3$	72	yellow	136-8	56.35 56.4	4.97 5.0	7.73 7.8	17.67 17.7
15c	$C_{16}H_{16}N_2S_2O_3$	73	yellow	150-2	55.17 55.2	4.59 4.7	8.04 8.0	18.39 18.4
15d	$C_{15}H_{15}N_3S_2O_2$	75	yellow	130-2	54.05 54.0	4.50 4.5	12.61 12.7	19.21 19.3
15e	$C_{16}H_{14}N_2SO_4$	78	yellow	103-5	58.18 58.1	4.24 4.2	8.48 8.5	9.69 9.7
15f	$C_{17}H_{18}N_2SO_4$	72	yellow	145	58.95 58.9	5.20 5.1	8.09 8.0	9.24 9.3
15g	$C_{16}H_{16}N_2SO_4$	75	yellow	160-2	57.48 57.5	4.79 4.8	8.38 8.4	9.58 9.6
15h	$C_{15}H_{15}N_3SO_3$	74	pale yellow	200-1	56.78 56.8	4.73 4.8	13.24 13.3	10.09 10.1
17a	$C_{15}H_{12}N_2S_2O_3$	80	yellow	172	54.21 54.1	3.61 3.7	8.43 8.5	12.27 12.3
17b	$C_{15}H_{12}N_2SO_4$	72	yellow	176	56.96 56.9	3.79 3.8	8.86 8.9	10.12 10.2
18a	$C_{17}H_{12}N_2S_2O_3$	68	yellow	194-5	57.30 57.4	3.37 3.4	7.86 7.9	17.97 18.0
18b	$C_{17}H_{12}N_2SO_4$	70	pale yellow	180-2	59.99 60.0	3.52 3.6	8.23 8.1	9.41 9.4

* - Solvent of Crystallization is Ethanol

itered). The reaction products obtained after cooling were poured onto ice-cold water then acidified with conc. HCL (5 ml). The solid products obtained were filtered off, washed with water then crystallized from ethanol to give 15a–d and 15e–h respectively (cf. Tables I and II).

Cyclization of 15a–d *and* 15e–h: (*General Procedure*)

A solution of each of 15a–d or 15e–h (0.01 mole) in ethanol (30 ml) was treated with KOH (0.01 mole) and the reaction mixture was heated under reflux for 5 h then poured and rendered acidic using conc. HCl. The solid obtained was filtered off, washed with water then crystallized from ethanol to give 17a and 17b respectively (cf. Tables I and II).

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

Comp.	*IR (KBr,cm^{-1})*	*^{1}H-NMR (DMSO$_6$,CDCl$_3$ δ ppm)*
5a	3250 (NH); 3090 (CH aromatic); 2980 (CH sat.); 2210 (CN); 1700 (CO acetyl); 1625 (C=N); 1600 (C=C); and 1540 (C=S).	1.25 (s, 3H, CH_3); 2.5(s, 3H, CH_3-CO); 4.8 (s, 1H, NH); 4.1 (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-3); and 6.5-6.7 (m, 3H, thienyl).
6a	3281 (NH); 3065 (CH aromatic); 2951 (CH sat.); 2222 (CN); 1699 (CO acetyl); 1625 (C=N); 1600 (C=C); and 1545 (C=S).	1.3 (s, 3H, CH_3); 2.5(s, 3H, CH_3-CO); 4.9 (s, 1H, NH) and 6.4-6.8 (m, 3H, thienyl).
10a	3400, 3330, 3280 (NH_2 and NH), 3100 (CH) aromatic); 2985 (CH sat.); 1699 (CO acetyl); 1620 (C=N) and 1600 (C=C).	1.2 (s, 3H, CH_3); 2.4(s, 3H, CH_3-CO); 4.9 (br, 3H, NH_2 and NH); 4.2 (d, 1H, pyridine H-4); 4.4 (1H, pyridine H-3); and 6.3-6.6 (m, 3H, thienyl).
11a	3400, 3330, 3280 (NH_2 and NH); (CH aromatic); 2970 (CH, sat.); 1699 (CO acetyl); 1620(C=N); 1600 (C=C) and 1540 (C=S).	1.4 (s, 3H, CH_3); 2.5 (s, 3H, CH_3-CO); 4.8 (br, 3H, NH_2 and NH) and 6.5-6.8 (m, 3H, thienyl).
12b	3070 (CH, aromatic); 2975 (CH, sat.); 2210 (CN); 1699 (CO-acetyl); 1625 (C=n); 1600 (C=C); and 1540 (C=S).	1.2 (s, 3H, CH_3), 2.5 (s, 3H, CH_3-CO); 1.5 (t, CH_2-CH_3); 2.2 (q, 2H, CH_2-CH_3); 4.2 (d, 1H, pyridine H-3); 4.5 (d, 1H, pyridine H-4); 6.6-6.9 (m, 3H, furyl).
13a	3080 (CH aromatic); 2985 (CH, sat.); 2220 (CN), 1698 (CO-acetyl); 1625 (C=N), 1600 and (C=C).	1.2 (s, 3H, CH_3); 2.5 (s, 3H, CH_3-CO); 1.5 (t, CH_2-CH_3); 2.5 (2H, CH_2-CH_3) and 6.5-6.7 (m, 3H, thienyl).

Reaction of Acetic Anhydride with 17a,b: *(General Procedure)*

A mixture of each of 17a,b (0.01 mole) and acetic anhydride (20 ml) was heated under reflux for 5 h. The product obtained after cooling was filtered off and crystallized from ethanol to give 18a,b respectively (cf. Tables I and II).

TABLE II (*Continued*)

Comp.	*IR (KBr,cm^{-1})*	*^{1}H-NMR (DMSO$_6$,CDCl$_3$ δ ppm)*
15a	3400-2400 (OH acid);3090 (CH aromatic); 2980 (CH, sat.); 2210 (CN); 1730 (CO-acid); 1696 (CO acetyl); 1620 (C=N); and 1600 (C=C).	1.1 (s, 3H, CH_3); 2.5 (s, 3H, CH_3-CO); (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-3); 6.4-6.7 (m, 3H, thienyl) and 10.7 (s, 1H, acid).
15c	3070 (CH aromatic); 2950 (CH, sat.); 2222 (CN), 1728 (CO,ester); 1699 (CO acetyl); 1625 (C=N); and 1600 (C=C).	1.2 (s, 3H, CH_3); 2.1 (s, 3H, CH_3-CO); 3.1 (s, 3H, CH3- O-CO); 3.3 (s, 2H, S- CH_2-CO);4.1 (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-3) and 6.6-6.8 (m, 3H, thienyl).
15f	3080 (CH aromatic); 2975 (CH, sat.); 2210 (CN); 1730 (CO,ester); 1700 (CO acetyl); 1620 (C=N); and 1600 (C=C).	1.1 (s, 3H, CH_3); 2.5 (s, 3H, CH_3-CO);1.5(t,CH_2-CH_3); 2.5-(q,2H CH_2-CH_3); 4.1 (d, 1H, pyridine H-3); 6.6-6.8 (m, 3H, furyl) .
17a	3496-3369(NH_2) 3300-2400 (OH acid);3090 (CH aromatic); 2975 (CH,sat.);1697(COacetyl) ;1647 (CO-acid hydrogen bonding); 1620 (C=N); and 1600 (C=C).	1.2 (s, 3H, CH_3at pyridine); 2.2 (s, 3H, CH_3- CO); 5.1 (s, 2H, NH_2); 6.6-6.8 (m, 3H, thienyl) and 10.6 (s, 1H, acid).
18b	3100 (CH aromatic); 2980(CH sat.);1757 (CO oxazinone);1697(CO acetyl);1620(C=N) and (C=C)	1.1(s,3H,CH_3 at pyridine); 1.5 (s, 3H, CH_3 oxazinone); 2.2(s,3H,CH_3-CO) and 6.5-6.8(m,3H,furyl).

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