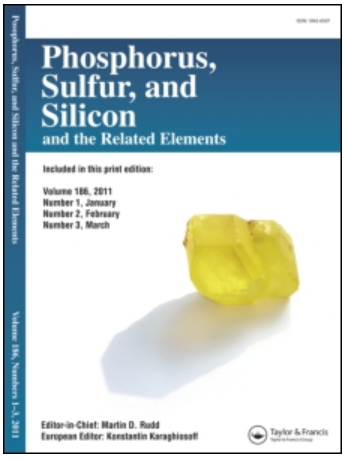

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REACTIONS WITH CYANOTHIOACETAMIDE AND ITS DERIVATIVES: SYNTHESIS AND REACTIONS OF SEVERAL NEW THIENO- AND AZOLOPYRIDINE DERIVATIVES

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REACTIONS WITH CYANOTHIOACETAMIDE AND ITS DERIVATIVES: SYNTHESIS AND REACTIONS OF SEVERAL NEW THIENO- AND AZOLOPYRIDINE DERIVATIVES

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Several new thieno- and azolopyridine derivatives were synthesized via a new route by reaction of some new di- and tetrahydropyridine thiones with different halogeno-ketones and halogeno-esters. Structures were elucidated by elemental analysis and spectral data.

Keywords: Pyridines; cyanothioacetamide; thiocarboxamidoacrylonitriles; thienopyridines; azolopyridines

INTRODUCTION

In the last decade, our group has been interested in the chemistry of cyanothioacetamide (1) and its ylidene derivatives (3) and several publications had appeared concerning this field of research from this laboratory[1–10]. Most of these publications dealt with the synthesis of new heterocyclic derivatives with expected biological activity.

As pyridine and its annelated derivatives constitute a very important source for compounds of biological activity[11–15], it was of value to utilize cyanothio-

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acetamide (1) or its derivatives (3) for the synthesis of some pyridines and annelated pyridines.

RESULTS AND DISCUSSION

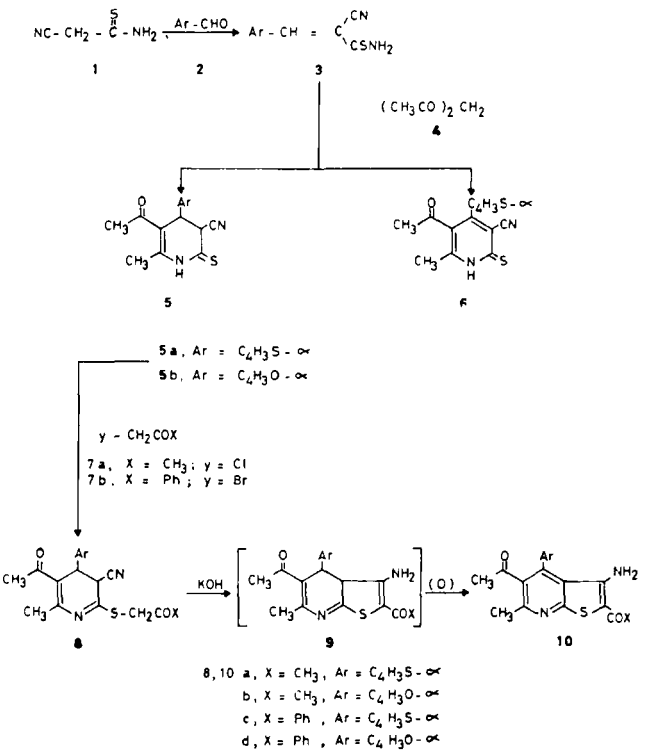
In a previous paper[16], the synthesis of two new tetrahydropyridines 5a,b and dihydropyridine 6 has been reported. The compounds are used for the synthesis of new heterocyclic derivatives.

In this work more light is shed on the synthetic potential of the three active starting materials in the field of heterocyclic synthesis. It has been found that 5a reacted with chloroacetone (7a) yielded a product of molecular formula $C_{16}H_{16}N_2S_2O_2$ corresponding to the simple addition of equimolar amounts of the reactants followed by elimination of HCl. *The IR spectrum of this reaction product showed bands attributed to CN and two CO groups while its ^{1}H-NMR spectrum showed the presence of signals of pyridine H-3 and H-4 in their proper positions (cf. Experimental Part). Based on the above data, the reaction product was formulated as the 2-S-acetonyldihydropyridine derivtive 8a.

Similarly, 5b reacted with 7a under the same experimental conditions to give the corresponding 2-S-acetonyldihydropyridine derivative 8b whose structure was established from elemental and spectral data (cf. Experimental Part). A further proof for the structure of both 8a, and 8b was achieved via their cyclization by the action of ethanolic KOH into the corresponding 3-acetylthieno[2,3-b]pyridine derivatives 10a,b, most likely formed via the intermediacy of the corresponding thienodihydropyridines 9a,b. The absorption bands of the nitrile functions were entirely absent from the IR spectra of 10a,b and the broad signal of the newly formed NH_2 group was detected in the ^{1}H-NMR spectrum of both.

In addition 5a,b were each reacted with phenacylbromide (7b) to yield products corresponding to the addition of 7b with the loss of HBr. IR and ^{1}H-NMR spectral data of the reaction products agreed with the assignment of the 2-S-benzoyldihydropyridine structures 8c,d respectively to the reaction products (cf. Experimental Part). Compounds 8c,d could also be cyclized by the action of ethanolic KOH to yield the corresponding 2-benzoylthieno[2,3-b]pyridine derivatives 10c,d, respectively, most likely formed via the intermediacy of the corresponding 9c,d (cf. Chart 1).

Work was also extended to the investigation of the behavior of 5a,b towards some halo-ketones. It has been found that 5a,b each reacted with ethyl-α-chloroacetoacetate (11a) to yield condensation products which could be formulated as the 2-S-alkyldihydropyridines 12a,b based on spectral studies. 12a,b



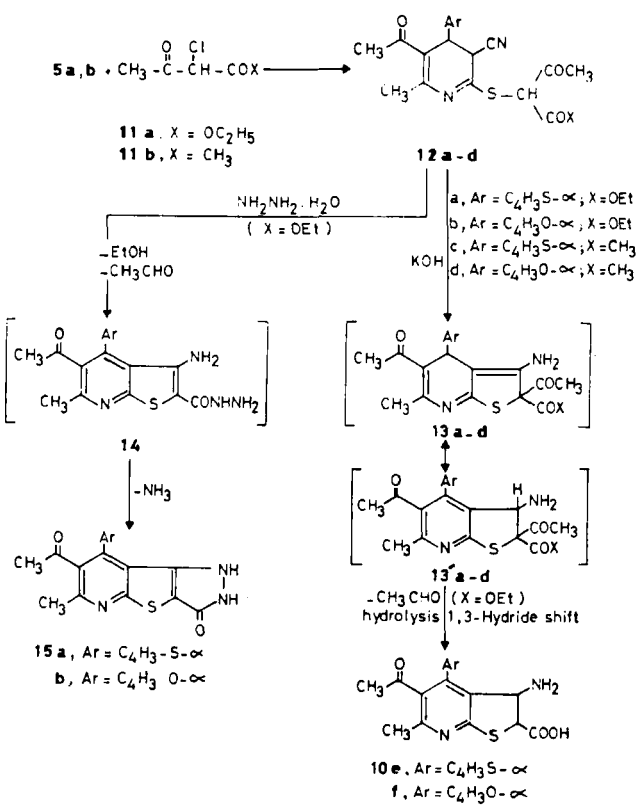
were cyclized into the corresponding thieno[2,3-b]-pyridines 10e,f[16] by the action of ethanolic KOH. The cyclized product 13a–d was be converted into 13″a–d which is responsible for 1,3-hydride shift and this followed by the loss of acetaldehyde to yield 10e,f[16].

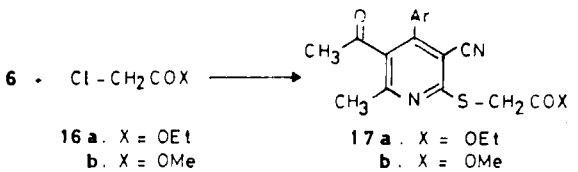
Similar to the behavior towards 11a, compounds 5a,b reacted with α-chloroacetylacetone (11b) to give the condensation products 12c,d respectively whose structures were also established using elemental analysis and spectral data (cf. Experimental Part and Table II). In addition, compounds 12c,d could also be cyclized by the action of ethanolic KOH into the corresponding thieno[2,3-b]pyridine derivatives 10a,b respectively through a 1,3-hydride shift followed by the loss of one molecule of acetaldehyde from the intermediate 13 a–d in each case (cf. Chart 2).

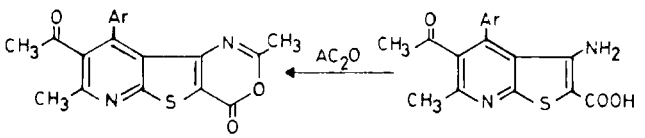
12a,b reacted with hydrazine hydrate to give products resulting from the addition of one molecule of each of 12a,b to one molecule of hydrazine hydrate and the loss of one molecule of ethanol, one molecule of ammonia and one molecule acetaldhyde in each case. The IR spectra of these reaction products showed the absence of NH_2 and CN groups while their ^{1}H-NMR spectra re-

vealed the absence of signals from C_2H_5 and $COCH_3$ groups. Based on the above data, the reaction products were formulated as the thieno[3,2-c]pyrazolo[2,3-b]pyridine derivatives 15a,b, most likely formed via the intermediate of the corresponding 14 (cf. Chart 2). Several reactions of the dihydropyridine thione derivative 6 were also undertaken. Thus, 6 reacted with the chloroesters 16a,b to give the the corresponding 2-S-alkylpyridines 17a,b.

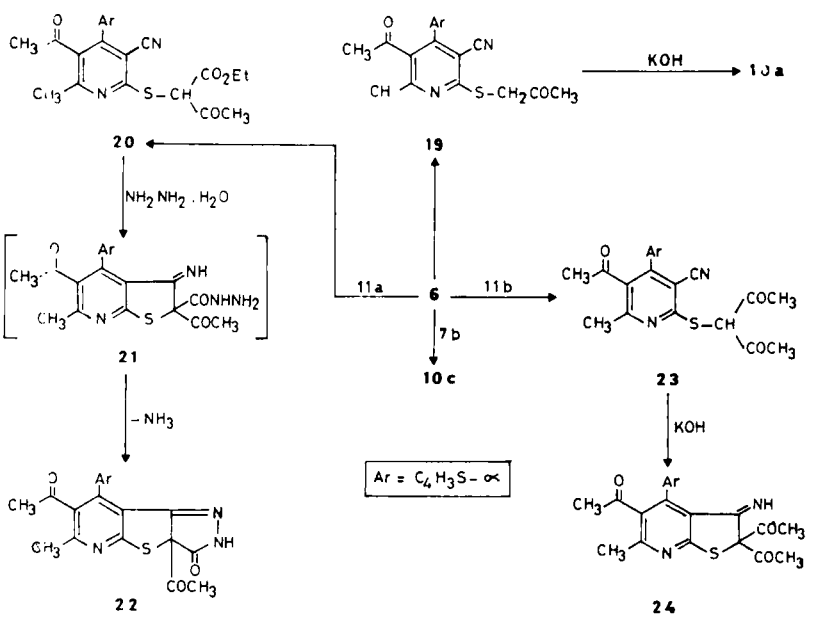
Compounds 17a,b were then cyclized by the action of ethanolic KOH into the 2-carboxy-thieno[2,3-b]pyridine derivative 10e[16] previously prepared in this laboratory. The formation of 10e involves de-esterification of the reaction products. Compound 10e could also be reacted with acetic anhydride to give the thieno[3,2-d]isoxazino[2,3-b]pyridine derivative 18 recently synthesized in this laboratory[16] (cf. Chart 3). 6 reacted with 7a to yield the 2-S-acetonylpyridine derivative 19 which could be cyclized, in turn, by the action of KOH into the corresponding thieno[2,3-b]pyridine derivative 10a previously obtained as described above (cf. Charts 1 and 4).







Ar = C_4H_3S-∝



In contrast to its behavior towards 7a, compound 6 reacted with phenacyl bromide (7b) to directly yield the thieno[2,3-b]pyridine derivative 10c previously obtained as described above (cf. Charts 1 and 4).

In addition, 6 reacted with ethyl-α-chloroacetoacetate (11a) to give a semi-solid reaction product which could be formulated as the 2-S-alkylpyridine derivative 20. The reaction of 20 with hydrazine hydrate afforded the thieno[3,2-c]pyrazolo[2,3-b]pyridine derivative 22 via 21 (cf. Chart 4). No nitrile absorption band was detected in the IR spectrum of 22. Analogously, 6 reacted with α-chloroacetylacetone (11b) to afford the 2-S-alkylpyridine derivative 23 which could be cyclized by reaction with KOH into the corresponding thieno[2,3-b]pyridine derivative 24 whose IR spectrum was entirely free from nitrile absorption bands.

EXPERIMENTAL

All melting points are uncorrected. IR spectra in KBr discs were recorded on a 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 CDCl3 and DMSO-d6 as solvents and TMS as an internal standard. Chemical shifts are expressed as δppm units.

Microanalyses were performed at the Microanalytical Center of Cairo University using Perkin-Elmar 2400 CHN Elemental Analyzer. Compounds 1[17], 3[17], 5[16] and 6[16] were prepared according to literature procedures.

Reactions of 5a,b and 6 with each of 7a,b, 11a,b and 16a,b

General Procedure

A solution of each of 5a,b or 6 (0.01 mole) in sodium methoxide (0.01 mole, prepared from the equivalent amounts of sodium metal and methanol) and each of 7a,b, 11a,b or 16a,b (0.01 mol) was heated under reflux for 4–5 h (TLC Monitoring). The solid products obtained were poured hot or after cooling onto cooled water, acidified with conc. HCl and filtered off then washed with water. Crystallization from ethanol gave 8a–d, 10c, 12a–d, 17a,b, 19, 20, and 23 respectively (cf. Tables I and II).

TABLE I Characterization data of the newly synthesized compounds

Comp.	*Mol. Formula*	*Yield %*	*Colour*	*M.P. (°C)*	*% Analysis, Calcd./found* C	H	N	S
8a	$C_{16}H_{16}N_2S_2O_2$	78	yellow	103	57.83	4.81	8.43	19.27
					57.9	4.8	8.5	19.3
8b	$C_{16}H_{16}N_2SO_3$	80	yellow	96	60.75	5.06	8.86	10.12
					60.8	4.9	8.9	10.1
8c	$C_{21}H_{18}N_2S_2O_2$	71	yellow	154	63.95	4.56	7.10	16.24
					63.9	4.6	7.0	16.3
8d	$C_{21}H_{18}N_2SO_3$	75	yellow	154–6	66.66	4.76	7.40	8.46
					66.7	4.8	7.3	8.5
10a	$C_{16}H_{14}N_2S_2O_2$	70	yellow	152–4	58.18	4.14	8.48	19.39
					58.2	4.2	8.5	19.4
10b	$C_{16}H_{14}N_2SO_3$	75	yellow	122	61.14	4.45	8.91	10.15
					61.2	4.5	9.0	10.2
10c	$C_{21}H_{16}N_2S_2O_2$	73	orange	108	64.28	4.08	7.14	16.32
					64.3	4.1	7.2	16.3
10d	$C_{21}H_{16}N_2SO_3$	78	yellow	140	67.02	4.25	7.44	8.51
					67.7	4.3	7.5	8.5
12a	$C_{19}H_{20}N_2S_2O_4$	75	yellow	semi-solid	56.43	4.95	6.93	15.84
					56.5	5.0	6.8	15.9
12b	$C_{19}H_{20}N_2SO_5$	80	yellow	94	58.76	5.15	7.21	8.24
					58.8	5.2	7.2	8.3
12c	$C_{18}H_{18}N_2S_2O_3$	80	yellow	130	57.75	4.81	7.48	17.11
					57.8	4.9	7.5	17.1
12d	$C_{18}H_{18}N_2SO_4$	64	yellow	110	60.33	5.02	7.82	8.93
					60.4	5.1	7.9	8.9
15a	$C_{15}H_{11}N_3S_2O_2$	70	orange	200–2	54.71	3.34	12.76	19.45
					54.8	3.4	12.8	19.5
15b	$C_{15}H_{11}N_3SO_3$	73	brown	236–8	57.50	3.51	13.41	10.22
					57.5	3.5	13.4	10.3
17a	$C_{17}H_{16}N_2S_2O_3$	65	yellow	118	56.66	4.44	7.77	17.77
					56.7	4.5	7.8	17.8
17b	$C_{16}H_{14}N_2S_2O_3$	70	yellow	170	55.46	4.04	8.09	18.45
					55.5	4.1	7.9	18.5
19	$C_{16}H_{14}N_2S_2O_2$	75	yellow	130	58.18	4.24	8.48	14.39
					58.2	4.3	8.5	14.4
20	$C_{20}H_{17}N_2S_2O_4$	78	yellow	semi-solid	58.11	4.11	6.77	15.49
					58.1	4.1	6.8	15.5
22	$C_{17}H_{13}N_3S_2O_3$	80	orange	212–4	50.36	3.20	10.37	15.80
					50.4	3.1	10.4	15.8
23	$C_{18}H_{16}N_2S_2O_3$	81	yellow	154	58.06	4.30	7.52	17.20
					57.9	4.3	7.6	17.2
24	$C_{18}H_{16}N_2S_2O_3$	82	yellow	180–2	58.06	4.30	7.52	17.20
					58.1	4.2	7.6	17.1

*Solvent of crystallization is ethanol.

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

Comp.	*IR (KBr, cm^{-1})*	*^{1}H-NMR (DMSO$_6$, CDCl$_3$ δ ppm)*
8a	3070 (CH aromatic); 2995 (CH, sat.); 2215 (CN); 1725 (CO acetonyl); 1720 (CO); 1699 (CO); 1620 (C=N); and 1600 (C=C)	1.2 (s, 3H, CH_3); 2.2 (s, 3H, CH_3-CO); 2.3 (s, 3H, CH_3-CO-CH_2-S); 3.1 (s, 2H, S-CH_2-CO-); 4.1 (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-3); and 6.5–6.8 (m, 3H, thienyl).
8c	3120 (Ch aromatic); 2980 (CH sat.); 2220 (CO acetyl); 1680 (CObenzoyl); 1620 (C=N); and 1600 (C=C).	1.2 (s, 3H, CH_3); 2.2 (s, 3H, CH_3-CO); 3.1 (s, 2H, S-CH_2-CO); 4.1, 1H, pyridine H-4); 4.4(d, 1H, pyridine H-3); 6.6–6.8 (m, 3H, thienyl); and 7.3–7.8 (m, 5H, phenyl protons).
10b	3457, 3307 (NH_2); 3079 (CH aromatic); 2975 (CH sat.); 1700 (CO acetyl); and 1650 (CO acetyl at thiophene hydrogen bonding).	1.2 (s, 3H, CH_3 at pyridine); 2.2(s, 3H, CH_3-CO); 2.3 (s, 3H, CH_3-CO at thiophene); 5.1 (s, 2H, NH_2); and 6.6–6.8 (m, 3H, furyl).
10d	3463, 3248 (NH_2); 3090 (CH aromatic); 2980 (CH sat.); 1698 (COacetyl); and 1945 (CO acetyl thiophene).	1.2 (s, 3H, CH_3 at pyridine); 2.2 (s, 3H, CH_3-CO at thiophene); 5.1 (s, 2H, NH_2); 6.6–6.8 (m, 3H, furyl) and 7.3–7.8 (m, 5H, phenyl protons).
12a	3090 (CH aromatic); 2985 CH, sat.); 2220 (CN); 1735 (CO estter); 1725 (CO acetyl at pyridine); 1620 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3-at pyridine); 1.5 (t, 3H, CH_2-CH_3); 2.1 (s, 3H, CH_3-CO at pyridine); 2.3 (s, 3H, CH_3-CO at S-alkyl); 2.3 (s, 1H, pyridine H-4); 4.4 (d, 1H, pyridine h-3 and 6.6–6.8 (m, 3H, thienyl).
12c	3080 (CH aromatic); 2985 (CH, sat.); 2220 (CN); 1735 (CO ester); 1725 (CO acetyl at S-alkyl); 1699 (CO acetyl at pyridine); 1620 (C=N) and 1600 (C=C)	1.1 (s, 3H, CH_3 at pyridine); 2.1 (s, 3H, CH_3-CO at pyridine); 2.4 (s, 6H, CH-(CO-CH_3)$_2$); 3.1 (s, 1H, CH-(CO-CH_3)$_2$), 4.1 (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-3) and 6.6–6.8 (m, 3H, thienyl).
15a	3300, 3250, (twoNH); 3100 (CH aromatic); 2950 (CH sat.); 1730 (COat pyrazole); 1695(CO acetyl at pyridine); 1620 (C=N) and 1600 (C=C)	1.2 (s, 3H, CH_3 at pyridine); 2.2(s, 3H, CH_3-CO at pyridine); 5.1(br. 2H, twoNH) and 6.6–6.9 (m, 3H, thienyl)

Cyclization of 8a–d, 12a–d, 17a,b, 19 and 23:

General Procedure

A solution of each of 8a–d, 12a–d, 17a,b, 19 and 23 (0.01 mole) in ethanol (30 ml) was treated with KOH (0.01 mole) and heated under reflux for 5h. The reaction mixture was poured onto cold water, acidified with conc. HCl and the solid obtained filtered off and washed with water. Crystallization from ethanol gave 10a–d, 10e,f[16], 10e[16], 10a and 24 respectively (cf Table I and 2).

Action of Hydrazine Hydrate on 12a,b and 20:

General Procedure

A solution of each of 12a,b or 20 (0,01 mole) and excess of hydrazine hydrate (2 ml) was heated under reflux for 4–5 h. The solid reaction products obtained after

TABLE II (cont'd)

Comp.	*IR (KBr, cm^{-1})*	*^{1}H-NMR ($DMSO_6$, $CDCl_3$ δ ppm)*
17b	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, CH_3-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).
19	3070 (CH aromatic); 2955 (CH, sat.); 2215 (CN); 1725 (CO acetonyl); 1720 (CO acetonyl); 1699 (CO); 1620 (C=N); and 1600 (C=C).	1.2 (s, 3H, CH_3); 2.2 (s, 3H, CH_3-CO); 2.3 (s, 3H, CH_3-CO-CH_2-S); 3.1 (s, 2H, S-CH_2-CO-); 4.1 (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-4); and 6.5–6.8 (m, 3H, thienyl).
20	3090 (CH aromatic); 2985 (CH, sat.); 2220 (CN); 1735 (CO ester); 1725 (CO acetyl at S-alkyl); 1699 (CO acetyl at pyridine); 1620 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3 at pyridine); 1.5 (t, 3H, CH_2-CH_3); 2.1 (s, 3H, CH_3-CO at pyridine); 2.3 (s, 3H, CH_3-CO at S-alkyl); 2.3 (s, 1H, at S-alkyl); 4.1 (d, 1H, pyridine H-4); 4.4 (d, 1H, pyridine H-3 and 6.6–6.8 (m, 3H, thienyl).
22	3400,3239 (two NH); 3090 (CH aromatic); 2960 (CH sat.); 1730 (CO at pyazole); 1694 (co acetyl at pyridine); 1620 (C=N) and 1600 (C=C).	1.2 (s, 3H, CH_3 at pyridine); 2.1 (s, 3H, CH_3-CO at pyridine); 2.5(s, 3H, CH_3-CO at thiophene); 5.1–5.4 (br, 2H, two NH) and 6.6–6.8 (m, 3H, thienyl).
23	3080 (CH aromatic); 2985 (CH, sat.); 2220 (CN); 1735 (CO ester); 1725 (CO acetyl at S-alkyl); 1699 (CO acetyl at pyridine); 1620 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3 at pyridine); 2.1(s, 3H, CH_3-CO at pyridine); 2.4 (s, 6H, CH-$(CO-CH_3)_2$); 3.1 (s, 1H, CH-$(CO-CH_3)_2$), 4.1 (d, 1H, pyridine H-3) and 6.6–6.8 (m, 3H, thienyl).
24	3300 (NH); 3090 (CH aromatic); 2980 (CH sat.) 1725 (two CO acetyl at thiophene); 1699 (CO acetyl at pyridine); 1620 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3 at pyridine); 2.3 (s, 3H, CH_3-CO at pyridine); 2.5 (s, 6H, two CH_3-CO at thiophene); 4.8 (s, 1H, NH imino) and 6.6–6.8 (m, 3H, thienyl).

cooling were filtered off and crystallized from ethanol to give 15a,b and 22 respectively (cf Tables I and II).

Reaction of 10e with Acetic Anhydride: A solution of 10e (0.01 mole) in an excess of acetic anhydride (20 ml) was heated under reflux for 5 h. The solid product obtained after cooling was filtered off and crystallized from ethanol to give 18[16].

References

[1] A.O. Abdelhamid and S.E. Abdou, *Sulfur Lett.*, **6**, 41, (1987).
[2] B.Y. Riad, S.E. Abdou, F.A. Attaby and S.A. Mansour, *Sulfur Lett.*, **6**, 105, (1987).
[3] B.Y. Riad, A.M. Negm, S.E. Abdou and H.A. Daboun, *Heterocycles*, **26**, 205, (1987).
[4] N.A. Ismail, S.M. Eldin, F.A. Attaby and M.B.A. Abou-Abdou, Pakistan. *J. Sci. Ind. Res.*, **35**, 165, (1992).
[5] H.A. Daboun and S.E. Abdou, *Heterocycless*, **20**, 1615, (1983).
[6] N.A. Ismail, S.M. Eldin, F.A. Attaby and M.B.A. Abou-Abdou, Egypt, J. Pharm. Sci., **33**, 983, (1992).
[7] F.A. Attaby, L.I. Ibrahim, S.M. Eldin and A.K.K. El-Louh, *Phosphorus, Sulfur and Silicon*, **73**, 127, (1992).

[8] B.Y. Riad and M.A. Abdel-Aziz, *Sulfur Lett.*, **9**, 175, (1989).
[9] B.Y. Riad and S.M. Hassan, *Sulfur Lett.*, **10**, 1, (1989).
[10] S.M. Eldin, N.G. Miccheal and F.A. Attaby, Egypt, *J. Pharm Sci.*, **34**, 805, (1993).
[11] G. Lohaus and W. Dittmar, S. Afric. Patent, 6 906 036 (1968); C.A., **73**, 120308 (1988).
[12] G.A. Youngdale, U.S. Patent, 4 288 440, (1980); C.A., **96**, 6596c, (1982).
[13] A.H. Todd, Br. Patent, 1 203 149, (1970); C.A., **73**, 120508b, (1970).
[14] J. Gante and S. Lust, Ger. Offen., 1908, 947, (1970); C.A., **73**, 1205010, (1970).
[15] H. Meyer, R. Sitt, G. Thomas and H. P. Krause, Ger. Offen., 3015, 219, (1980); C.A., **96**, 6604d, (1980).
[16] F.A. Attaby, S.M. Eldin, W.M. Bassouni and M.A.A. Elneary, *Phosphorus, Sulfur and Silicon*, **106**, 21, (1995).
[17] J.S.A. Brunskill, A.De and D.F. Ewing, *J. Chem. Soc. Perkin Trans.* I, 629, (1978).