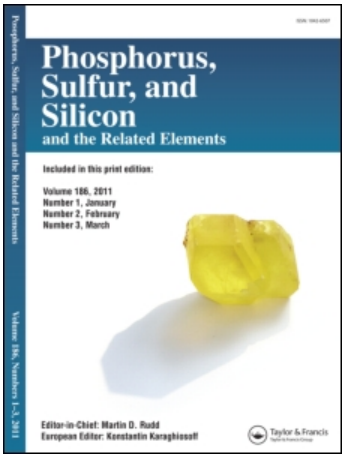

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NOVEL SYNTHESIS OF CONDENSED PYRIDINETHIONE NUCLEOSIDES AND CONDENSED THIENO[2,3-b]PYRIDINES

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Condensation of cyanothioacetamide with sodium salt of 2-(hydroxymethylene)-1-tetralone afforded the corresponding pyridine-2(1H)-thione **3**. Compound **3** served as a key intermediate for the synthesis of condensed thieno[2,3-b]pyridines and condensed pyridinethione glycosides.

Key words: Nucleosides, pyridines, IR spectra, NMR spectra.

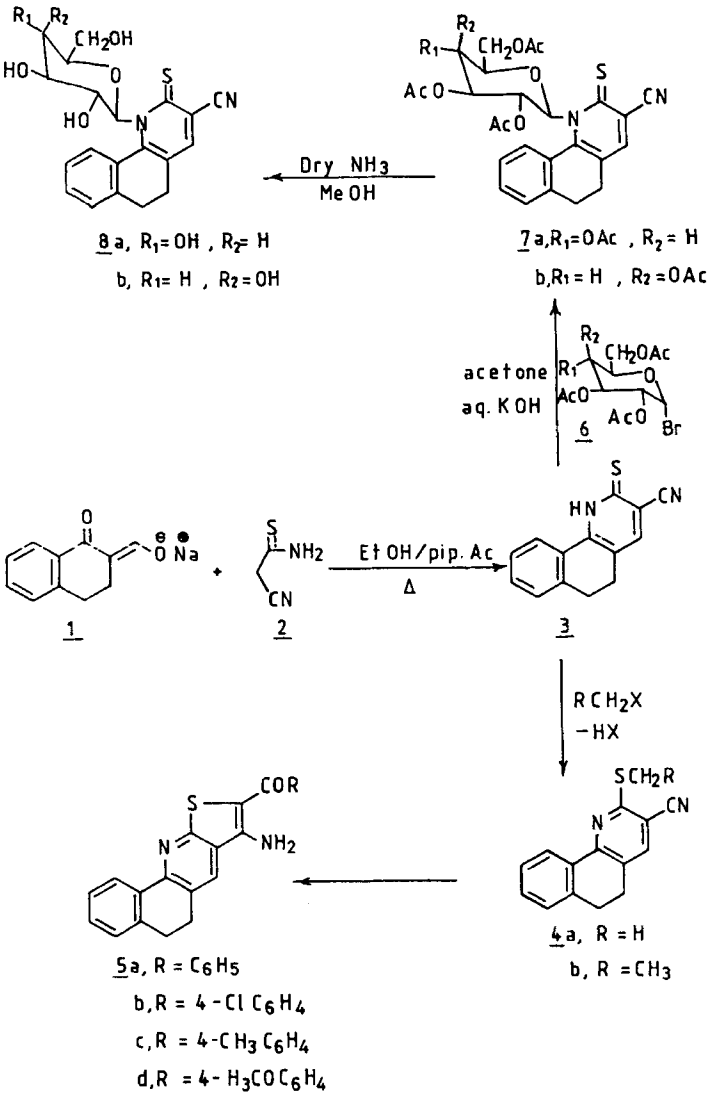
Over the past five years, pyridine-2(1H)thiones have gained considerable interest due to their importance as intermediates for the synthesis of the biologically active deazafolic acid and deazaaminopterine ring system.[1,2]

As a part of our program directed at the development of new, simple and efficient procedures for the synthesis of antimetabolites,[3,4] we have recently reported different successful approaches for the synthesis of purine and pyrimidine analogues.[5,6] Derivatives of these ring systems are interesting because they have useful properties as antimetabolites in biochemical reactions.

The present paper deals with a novel synthesis of condensed pyridine-2(1H)thione, condensed thieno[2,3-b]pyridines and condensed pyridinethione glycosides. Moreover, the results of our work aimed to define the scope and limitation of our procedures for the synthesis of pyridines and their important condensed derivatives are also reported.

Thus it has been found that cyanothioacetamide **2** reacted with the sodium salt of 2-(hydroxymethylene)-1-tetralone **1** to give the condensed 3-cyanopyridine-2(1H)thione **3**. The structure of **3** was established on the basis of its elemental analysis and spectral data. The structure of **3** is supported by its mass spectrum which showed a molecular formula $C_{14}H_{10}N_2S$ (M^+ 238).

The UV spectrum contains an absorption maximum at 335 nm indicating the presence of HNC=S fragment.[7] ^1H NMR spectroscopy was used to confirm this structure for the product. Thus ^1H NMR revealed a singlet at δ 8.27 assigned to the pyridine 4-H proton and a broad band at 14.02 ppm assigned to the NH proton. Compound **3** bearing a latent functional substituent was found useful for the synthesis of fused pyridines. Thus, compound **3** reacted with methyl and ethyl iodide in dry dimethylformamide-anhydrous potassium carbonate to afford the corresponding S-alkyl derivatives **4a,b**. The ^1H NMR spectrum of **4b** showed a triplet at δ 1.39 and a quartet at δ 3.34 assigned to the SCH_2CH_3 group. The mass spectrum indicated a molecular formula of $C_{16}H_{14}N_2S$ (M^+ 266). When compound **3** was subjected to the reaction of substituted phenacyl bromides as alkylating agents,



the S-alkylated derivatives could not be isolated, but it cyclized to the condensed thieno[2,3-b]pyridine derivatives **5a–d**.

The structure of compounds **5** was established on the basis of elemental analysis and spectral data. Thus, the IR spectrum of **5a** revealed the absence of a CN band, the mass was compatible with the molecular formula $C_{22}H_{16}N_2OS$ (M^+ 356) and the ^1H NMR contained a broad band at δ 8.4 assignable to an amino function.

We have investigated the utility of the reaction of condensed pyridine-2(1H)thione **3** with α-halogenosugars for the synthesis of 3-deazapyridine glycosides. Thus, it was found that compound **3** reacted with 2,3,4,6-tetra-O-acetyl-α-D-gluco- and galacto-pyranosyl bromide **6a,b** in the presence of aqueous potassium hydroxide through a Walden inversion to afford the corresponding N-glucoside **7a** and N-

galactoside **7b**. The structure of the reaction products **7** were established and confirmed on the basis of their elemental analysis and spectral data (MS, IR, UV and ^{1}H NMR). Thus the analytical data for **7b** revealed a molecular formula $C_{24}H_{28}N_2O_9S$ (M^+ 520). The ^{1}H NMR spectrum showed a doublet at δ 5.61 assigned to the anomeric proton of the galactose moiety with a spin-spin coupling constant equal to 10.00 Hz which corresponding to a diaxial orientation for the 1- and 2-H protons, i.e., the β-configuration. Another doublet appearing at δ 3.81 was assigned to the CH_2 protons of the sugar. The protons of the galactopyranosyl ring resonated as a multiplet at δ 4.55–5.38. The remaining four acetyl groups appeared as four singlets at δ 3.43–3.64. The UV spectrum of **7a** proved that the reaction had led selectively to the formation of N-glucosyl derivative and excluded substitution of the sulfur atom. Thus whereas the S-Ethyl derivative of **7a** showed two UV maxima at 275 and 356 nm, its N-glucosyl derivative exhibited three maxima at 270, 323 and 345 nm.

Moreover, hydrolysis of **7b** with 9% HCl afforded the corresponding pyridine-2(1H)thione **3** as the sole product (i.e. 2-oxopyridine was not formed) proving the existence of N-glycosides.

When compounds **7** were treated with methanolic ammonia at 0°C, the free glycoside derivatives **8** were obtained. The structure of which were established on the basis of elemental analysis and spectral data. Thus, the IR spectrum of **8a** showed a characteristic band at 3650–3250 cm^{-1} due to the hydroxy groups of the glucose moiety. The ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ 5.65 ($J_{1,2}$ 10.00 Hz) indicating the presence of only the β-configuration. The other six glucose protons appeared as a multiplet at δ 2.98–3.01 while the four hydroxy groups of the glucose moiety resonated at δ 4.1–5.5 exchangeable (by D_2O).

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40°C. Melting points are uncorrected. TLC aluminium sheets silica gel 60 F_{245} (MERCK) was used for thin layer chromatography. Detection was effected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disc) on a Pye-Unicam Spectra-1000. ^{1}H NMR spectra were measured on a Wilmad 270 MHz or on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Department at National Research Centre.

Condensed pyridine-2-(1H)-thione **3**

A mixture of Sodium Salt of 2-(hydroxymethylene)-1-tetralone **1** (0.13 mole), cyanothioacetamide **2** (0.13 mole) and piperidine acetate (9.7 ml) in water (50 ml) was heated under reflux for 15 min. Acetic acid (15 ml) was then added portion wise followed by heating for another 15 min. The resulting precipitate was filtered off and recrystallized from dioxane (cf. Tables I and II).

Condensed S-alkyl derivatives **4a,b** *and thieno[2,3-b]pyridines* **5a–d**

To a mixture of **3** (0.01 mol) in dry dimethylformamide (20 ml) and (0.02 mol) potassium carbonate was added the alkylating agent (0.01 mol). The mixture was stirred at room temperature for 1 h, and then diluted with water. The resulting solid was collected by filtration and recrystallized from the appropriate solvent (cf. Tables I and II).

TABLE I

Physical and analysis data for compounds

Compound Color	Recystn. Solvent	M.P θm/°C	Yield %	Mol. Formula	Found/calcd(%) C	H	N	M^+, m/z
3	Dioxane	229	85	$C_{14}H_{10}N_2S$	70.45	4.18	11.73	238
Yellow				(238.3)	70.56	4.23	11.76	
4a	MeOH	155-56	92	$C_{15}H_{12}N_2S$	71.36	4.78	11.10	252
Yellow				(252.3)	71.39	4.80	11.09	
4b	EtOH	157	90	$C_{16}H_{14}N_2S$	72.18	5.25	10.49	266
Brown				(266.3)	72.14	5.29	10.52	
5a	MeOH	192	65	$C_{22}H_{16}N_2OS$	74.16	4.48	7.79	356
Yellow				(356.4)	74.12	4.52	7.86	
5b	Benzene	197	60	$C_{22}H_{15}ClN_2OS$	67.62	3.84	7.09	390
Yellow				(390.8)	67.59	3.87	7.16	
5c	Benzene	221	83	$C_{23}H_{18}N_2OS$	74.39	4.93	7.48	370
Yellow				(370.4)	74.57	4.89	7.56	
5d	Dioxane	299	88	$C_{23}H_{18}N_2O_2S$	71.31	4.81	7.08	386
Yellow				(386.4)	71.48	4.69	7.25	
7a	EtOH	185	65	$C_{24}H_{28}N_2O_9S$	55.41	5.48	5.39	520
Yellow				(520.5)	55.37	5.42	5.38	
7b	EtOH	176	68	$C_{24}H_{28}N_2O_9S$	55.50	5.61	5.42	520
Yellow				(520.5)	55.37	5.42	5.38	
8a	EtOH	199	82	$C_{20}H_{20}N_2O_5S$	59.79	5.21	6.68	400
Brown				(400.4)	59.98	5.03	6.99	
8b	MeOH	214	80	$C_{20}H_{20}N_2O_5S$	59.69	5.12	6.71	400
Brown				(400.4)	59.98	5.03	6.99	

TABLE II

Spectral data for selected compounds

Compound	IR max/cm^{-1} selected bands	^{1}H NMR, δ
3	2220 (CN)	2.89 (s, 4H, 2CH_2); 7.23-7.95 (m, 4H, aromatic protons);
	3480,3320	8.27 (s, 1H ,pyridie 4-H); 14.02 (s, br, 1H, NH proton).
	(NH)	
4a	2220 (CN)	2.71 (s, 3H, SCH_3); 2.9(s, 4H, 2CH_2); 7.32-7.44 (m, 3H,
		aromatic protons); 8.1 (s, 1H, pyridine 4-H);
		8.28 (m, 1H, aromatic proton).
4b	2220 (CN)	1.39 (t, 3H, CH_3); 2.90 (s, 4H, 2CH_2); 3.34 (q, 2H, CH_2);
		7.34-7.44 (m 3H aromatic protons) 8.09 (s, 1H, pyridine 4-H);
		8.22 (t, 1H, aromatic proton).
5a	3500,	2.99 (m, 4H, 2CH_2); 7.36-8.26 (m, 9H, aromatic protons); 8.4 (s,
	3430 (NH_2)	br, 2H, NH_2); 8.53 (s, 1H, pyridine 4-H).
	1690(CO)	
5b	3480, 3400	2.97 (m, 4H, 2CH_2); 7.32-8.25 (m, 8H, aromatic protons);
	(NH_2)	8.43 (s, br, 2H, NH_2); 8.52 (s 1H, pyridine 4-H).
	1685 (CO)	
5c	3500, 3380	2.49 (s,, 3H, CH_3); 2.99 (m, 4H, 2CH_2);
	(NH_2)	7.33-7.74 (m, 8H,aromatic protons); 8.36 (s, br, 1H, NH_2);
	1690 (CO)	8.52 (s, 1H, pyridine 4-H).
5d	3480, 3400	2.99 (m, 4H, 2CH_2); 3.96 (s 3H, OCH_3);
	(NH_2)	7.25-8.25 (m, 8H, aromatic protons);
	1680 (CO)	8.38 (s, br, 1H, NH_2); 8.53 (s, 1H, pyridine 4-H).
7b	2220(CN)	2.91 (m, 4H, 2CH_2); 3.43-3.64 (4s, 12H, 4OAC);
		3.81 (d, 2H, 6`-$H_2$); 4.55 (d, 1H, 5`-H); 4.61 (t, 1H, 4`-H);
		5.00 (d, 1H, 3`-H); 5.38 (d, 1H, 2`-H); 5.61 (d, J 1`-2`=10.0Hz,1H, 1`-H
		7.32-7.43 (m, 3H, aromatic proton);
		8.11 (s, 1H, pyridine H-4); 8.28 (m, 1H, aromatic protons).
8a	2220 (CN)	2.91 (m, 4H, 2CH_2); 2.98-3.01 (m, 6H, 6`-$H_2$, 5`-, 4`-, 3`- and
	3650-3250	2`-H); 4.10 (s, 1H, 2`-OH); 4.50 (s, 1H, 3`-OH);
	(OH)	5.10(d,1H,4`-OH); 5.50 (d,1H,6`-OH); 5.65 (d,J 1`-2`=10.0Hz,1H,1`-H);
		7-8.28 (m, 4H, aromatic protons); 8.34 (s, 1H, pyridine H-4).

Condensed 3-Cyano-1-(2',3',4',6',-tetra-O-acetyl-β-D-gluco- and galactopyranosyl)pyridine-2(1H)thiones **7a,b**

To a solution of 3-Cyanopyridine **3** (0.01 mol) in aqueous potassium hydroxide [0.56 g (0.01 mol) in 6 ml of distilled water], a solution of 2,3,4,6-tetra-O-acetyl-α-D-gluco or galactopyranosyl bromide **6** (4.521 g, 0.011 mol) in acetone (30 ml) was added. The reaction mixture was stirred at room temperature until judged complete by TLC (30 min to 20 h), then evaporated under reduced pressure at 40°C and the residue washed with distilled water to remove the formed potassium bromide. The product was dried and crystallized from ethanol to afford yellow crystals (cf. Tables I and II).

Condensed 3-Cyano-1-(β-D-gluco- and galactopyranosyl)pyridine-2(1H)-thiones **8a,b**

Dry gaseous ammonia was passed through a solution of protected nucleosides **7** (0.5 g) in dry methanol (25 ml) at 0°C for about 0.5 hour, then the reaction mixture was stirred until judged complete by TLC (4–18 h). The resulting reaction mixture was evaporated under pressure at 40°C giving a solid residue which was crystallized from ethanol or methanol to afford a brown solid (cf. Tables I and II).

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