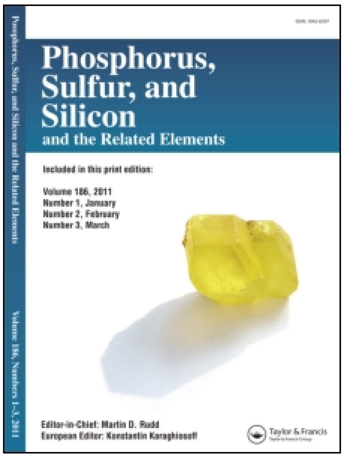

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SYNTHESIS OF SOME 2-THIOXOPYRIDO[2,3-*d*]PYRIMIDINE RIBOFURANOSIDES AND THEIR ANTIMICROBIAL ACTIVITY

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2-Thioxo-3,5,7-trisubstituted-1-[2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl]pyrido [2,3-*d*]pyrimidin-4(1*H*)-ones have been prepared by the condensation of trimethylsilyl derivative of 2-thioxo-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin-4(1*H*)-ones with β-D-ribofuranose 1-acetate-2,3,5-tribenzoate in 65%-78% yield. The structure of the synthesized ribofuranosides and their precursors have been established by IR, ^{1}H NMR and elemental analysis. These derivatives have been screened for their antimicrobial activity.

Keywords: Thioxopyridopyrimidines; ribofuranosides; antimicrobial activity

INTRODUCTION

Synthesis of pyrido[2,3-*d*]pyrimidines and their nucleosides have attracted tremendous interest evidenced by large number of publications[1–8] and patents[9–10] registered worldwide. These compounds are of immense importance and are extensively employed as antibacterial[1], antifungal[2], antiinflammatory[3], antitumor[4] and anticancer[5] agents etc. Some of the recent publications in this area has also demonstrated their significance, as antiviral[6], antifungal[7], antibacterial[8], antihypertensive[9] and antiAIDS[11]. Motoo *et al*[12] have shown that pyrido[2,3-*d*]pyrimidine nucleosides possess anticancer activity. The diverse importance of these derivatives and our interest in this area[13], to devise some novel derivatives of pyrido [2,3-*d*] pyrimidines and their ribofuranosides prompted us to undertake the synthesis of 2-thioxo-3,5,7-trisubstituted pyridopyrimidines and their ribo-

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furanosides. The synthesized heterocyclic bases and their ribofuranosides have been screened for antimicrobial activity.

RESULTS AND DISCUSSION

Chalcones **I** and malononitrile on refluxing with ethanol in presence of ammonium acetate afforded 2-amino-3-cyano-4,6-disubstituted pyridines **II** through Michael type condensation. Compounds **II**, when refluxed 20% alc. KOH solution, gave 2-amino-3-carboxamido-4,6-disubstituted pyridines **III**, which on refluxing with arylisothiocyanate in diphenylether produced **IV**. Compounds **IV** were treated with hexamethyldisilazane to give the corresponding trimethylsilyl derivatives, which on stirring with β-D-ribofuranose 1-acetate-2,3,5-tribenzoate **V**, in *vacuo*, at 150–55°C for 10 hrs gave respective ribofuranosides *viz.*, 2-thioxo-3,5,7-trisubstituted-1-[2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl]pyrido[2,3-*d*]pyrimidin-4(1H)-ones **VII**. Compounds **VII** assigned anomeric configuration as β on the basis small coupling constant between C_1' & C_2' protons (δ 6.40–6.53 ppm, *J*=2.5 Hz). This is in consonance of the earlier report[14]. The proposed structure of the synthesized compounds are well supported by elemental analysis and spectroscopic data.

IR Spectra

The characteristic IR bands of compounds **IVa-g** and **VIIa-g** are presented in table-I. Compounds **II**, showed a sharp band in the region 2210–2200 cm^{-1} attributed due to the presence of the -C≡N group. In compounds **II** & **III** the stretching vibrations of the-NH_2 group appeared, as a weak band, in the region 3450–3310 cm^{-1} and bending vibrations at 1520–1500 cm^{-1} respectively. Compounds **III** gave a band between 1685–1665 cm^{-1} due to >C=O of -$CONH_2$ group and complete disappearance of -C≡N absorption band, indicating its conversion to -$CONH_2$ group. Compounds **IV a-g** and **VII** a-g showed an intensive band in the region 1720–1690 cm^{-1} assigned to >C=O group. A weak band in the region 1200–1180 cm^{-1} and three characteristic bands in the region 1530–1390 cm^{-1} were assigned to >C=S and -NHCS moieties, respectively. Band due to >NH, in compounds **IVa-g** was appeared at 3450–3300 cm^{-1}, which was found absent, in compounds **VIIa-g** indicating site of ribosylation. Further, in compounds **VIIa-g**, bands due to C-O-C linkage of the sugar appeared in the region 1165–1040 cm^{-1}.

TABLE I The IR and ^{1}H NMR spectral data of synthesized compounds

Compd[a] No.	^{1}H NMR (δ ppm from TMS)						IR (KBr: ν_{max} cm^{-1})				
	>NH	Ar-H (multiplet)	-OCH_3	-OH	-CH_3	C_1'-H (doublet)	>NH	>C=O	>C=S	-NHCS	C-O-C
IVa	8.15	6.74–7.82	3.85	9.98	–	–	3320	1695	1180	1400, 1425, 1460	–
IVb	8.11	6.82–7.73	3.83	–	2.26	–	3350	1700	1185	1390, 1450, 1520	–
IVc	8.00	6.87–7.95	3.85	–	–	–	3440	1710	1200	1395, 1440, 1490	–
IVd	8.15	6.83–7.85	3.90	–	–	–	3450	1715	1195	1390, 1445, 1500	–
IVe	8.13	6.95–8.07	3.87	–	–	–	3445	1700	1190	1410, 1465, 1530	–
IVf	8.00	6.90–7.85	4.16	9.92	–	–	3385	1690	1185	1400, 1435, 1510	–
IVg	8.23	6.87–7.97	4.10	–	–	–	3300	1690	1180	1420, 1465,1530	–
VIIa	–	6.79–8.05	3.88	10.09	–	6.46	–	1700	1190	–	1140–1050
VIIb	–	6.87–8.08	3.93	–	2.35	6.48	–	1710	1185	–	1130–1045
VIIc	–	6.84–8.03	3.82	–	–	6.53	–	1720	1190	–	1165–1065
VIId	–	6.92–8.11	3.91	–	–	6.46	–	1715	1195	–	1125–1040
VIIe	–	7.10–8.09	3.93	–	–	6.50	–	1720	1190	–	1130–1055
VIIf	–	6.98–8.13	4.13	10.05	–	6.51	–	1710	1185	–	1135–1060
VIIg	–	6.91–8.08	3.97	–	–	6.40	–	1700	1180	–	1120–1040

a. The elemental analysis (C,H and N) of these compounds were obtained in reasonable agreement with the calculated value.

^{1}H NMR Spectra

The ^{1}H NMR data of compounds **IVa-g** and **VIIa-g** are presented in table-I. Compounds **IVa-g** showed multiplet due to aromatic protons, which appeared in the region δ 6.74–8.13 ppm. The >NH proton appeared as a singlet between δ 8.0–8.23 ppm.

The ^{1}H NMR spectra of ribofuranosides **VIIa-g** have not shown any peak due to >NH, indicating, the formation of ribofuranosides. The β-configuration of ribofuranosides were established by a doublet at δ 6.40–6.53 ppm (J=2.5 Hz). The -OCH_3 protons of compounds **IVa-g** & **VIIa-g** caused a singlet in the region δ 3.83–4.16 ppm & 3.82–4.13 ppm, respectively. A sharp singlet due to aromatic -CH_3 protons in compounds **IVb** and **VIIb** appeared at δ 2.26 and δ 2.35 ppm, while singlet due to aromatic -OH proton in compounds **IVa, IVf, VIIa** and **VIIf** appeared at δ 9.98,9.92,10.09 and 10.05 ppm, respectively.

ANTIMICROBIAL ACTIVITY

All the synthesized compounds **IVa-g** and their ribofuranosides **VIIa-g** were screened for their antibacterial and antifungal activity at the conc. of 100 μg per disc, using Streptomycin and Mycostatin respectively, as the reference compounds. The test organism used included *E. coli, S. aureus* (bacteria) and *A. niger, A. flavus* and *F. oxysporium* (fungi). These studies have been accomplished by a method due to Varma *et al*[15]. These results have presented in table-II, in the form of inhibition zones and activity indices. Although, all the compounds show moderate to fairly good activities, a close look on the activity indices reveals that the ribofuranosides are better antimicrobial agents than their respective bases.

EXPERIMENTAL

All the melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on NICOLET-MEGNA FT-IR 550 spectrometer and the ^{1}H NMR spectra on FX 90Q JEOL spectrometer (90 Mz) in $CDCl_3$/DMSO-d_6, using TMS, as an internal standard (Chemical shifts are measured in δ ppm). The purity of the compounds were checked by TLC using silica gel "G" as adsorbent, visualizating these by UV light or Iodine chamber.

TABLE II Antimicrobial activity of compounds VIa-g and VIIa-g, Zone of growth inhibition (mm) (activity index)

Compd. No.	*Escherichi coli (gram-ve)*	*Staphylococcus aureus (gram + ve)*	*Aspergillus niger*	*Aspergillus flavous*	*Fusarium oxyporium*
IVa	8.4 (1.01)	9.3 (1.06)	8.9 (0.94)	9.1 (0.98)	11.5 (1.13)
IVb	8.7 (1.05)	7.6 (0.86)	9.1 (0.96)	10.6 (1.14)	10.5 (1.03)
IVc	7.5 (0.90)	5.7 (0.65)	8.8 (0.93)	8.9 (0.96)	10.6 (1.04)
IVd	7.3 (0.88)	9.2 (1.04)	9.8 (1.03)	11.2(1.20)	7.8(0.76)
IVe	9.1 (1.10)	9.2 (1.04)	9.2 (0.97)	8.9 (0.96)	8.8 (0.86)
IVf	8.9(1.07)	9.7(1.10)	9.6(1.01)	8.6(0.92)	11.9(1.17)
IVg	8.3 (1.00)	8.0 (0.91)	9.8(1.03)	9.0(0.97)	9.6(0.94)
VIIa	9.3 (1.12)	9.4 (1.07)	9.7 (1.02)	10.3(1.11)	12.0(1.18)
VIIb	9.0(1.08)	8.8 (1.00)	9.5(1.00)	11.5(1.24)	13.1(1.28)
VIIc	8.9 (1.07)	8.9 (1.01)	10.1 (1.06)	9.3 (1.00)	11.3 (1.11)
VIId	10.0 (1.20)	9.4 (1.07)	10.5 (1.11)	12.1 (1.30)	9.8(0.96)
VIIe	9.7(1.17)	9.6(1.10)	10.1 (1.06)	9.7 (1.04)	12.1 (1.19)
VIIf	9.1 (1.10)	10.0 (1.14)	9.9 (1.04)	8.7 (0.94)	12.3 (1.21)
VIIg	8.6(1.04)	9.8(1.11)	10.0 (1.05)	9.5(1.02)	12.3(1.21)

Activity index = Inhibition area of sample/Inhibition area of the standard

Synthesis of 2-amino-3-cyono-4,6-disubstituted pyridines II

A mixture of appropriate chalcones **I** (0.05 mole), malononitrile (0.05 mole) and ammonium acetate (0.4 mole) in ethanol (50 ml) was refluxed on a water bath for 20–22 hrs, cooled and poured onto crushed ice with constant stirring to obtain a yellow solid mass. This mass was washed with water followed by ethanol and the products were recrystallized from ethanol.

Synthesis of 2-amino-3-carboxamido-4,6-disubstituted pyridines III

A mixture of **II** (0.04 mole), KOH (0.7 mole) in ethanol (150 ml) was refluxed on water bath for 8–9 hrs. After completing the reaction, the contents were cooled to room temperature and were poured onto crushed ice with constant stirring to obtain a yellow solid mass. The solid, thus obtained, was washed with water, dried and recrystallized from ethanol.

Synthesis of 2-thioxo-3,5,7-trisubstituted pyrido[2,3-d]pyrimidin-4 (1H)-ones IV

A mixture of **III** (0.01 mole) and appropriate arylisothiocyanate (0.01 mole) was refluxed in diphenylether (15 ml) for 8–9 hrs. The reaction mixture, after cooling, was added to cold ethanol and the separated solid was filtered, washed with ethanol and recrystallized from DMF-ethanol mixture.

Yield and m.p. of compounds. IVa-g

Compd. IVa : $R^1=C_4H_3O$, $R^2=2\text{-}OH\text{-}C_6H_4$, $R^3=2\text{-}OCH_3\text{-}C_6H_4$, yield 73%, m.p. 310°C.

Compd. IVb : $R^1=C_4H_3O$, $R^2=4\text{-}CH_3\text{-}C_6H_4$, $R^3=2\text{-}OCH_3\text{-}C_6H_4$; yield 67%; m.p.>340°C.

Compd. IVc : $R^1=C_4H_3O$, $R^2=2\text{-}F\text{-}C_6H_4$, $R^3=2\text{-}OCH_3\text{-}C_6H_4$; yield 77%; m.p. >340°C.

Compd. IVd : $R^1=C_4H_3O$, $R^2=4\text{-}Br\text{-}C_6H_4$, $R^3=2\text{-}OCH_3\text{-}C_6H_4$; yield 68%; m.p. >340°C.

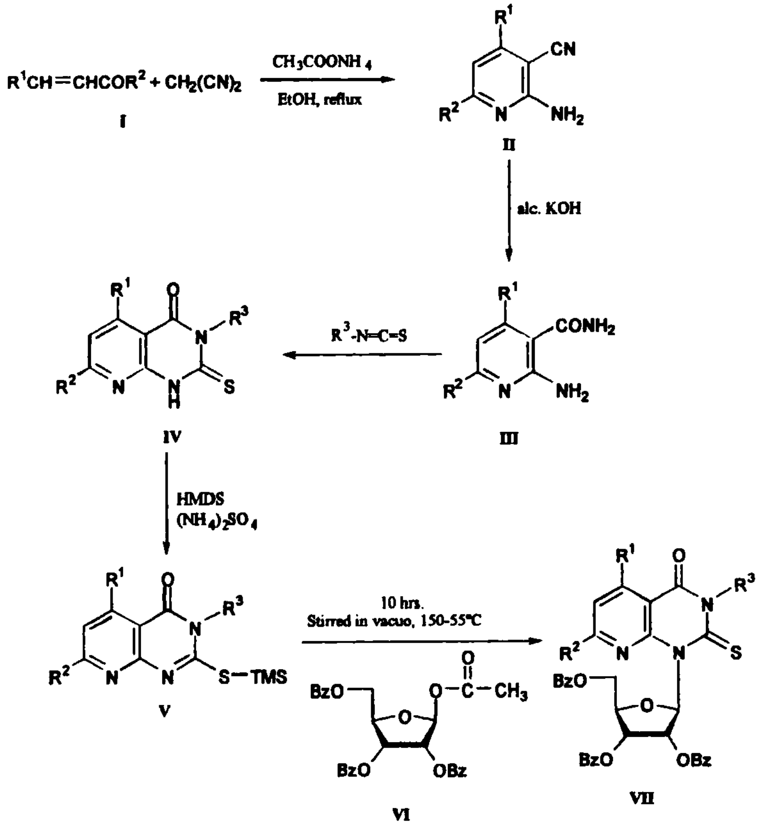
Compd. IVe : $R^1= 2\text{-}OCH_3\text{-}C_6H_4$, $R^2=4\text{-}Br\text{-}C_6H_4$, $R^3=2\text{-}OCH_3\text{-}C_6H_4$; yield 70%; m.p. 235°C.

Compd. IVf : $R^1=2\text{-}OCH_3\text{-}C_6H_4$, $R^2=2\text{-}OH\text{-}C_6H_4$, $R^3=4\text{-}OCH_3\text{-}C_6H_4$; yield 78%; m.p. 290°C.

Compd. IVg : $R^1=4\text{-}Cl\text{-}C_6H_4$, $R^2=4\text{-}Br\text{-}C_6H_4$, $R^3=4\text{-}OCH_3\text{-}C_6H_4$; yield 73%; m.p. >340°C.

Synthesis of 2-thioxo-3,5,7-trisubstituted-1-[2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl]pyrido[2,3-d]pyrimidin-4(1 H)-Oncs VII

Compounds **IVa-g** (0.002 mole) in toluene (30 ml), were mixed with hexamethyldisilazane (HMDS) (0.012 mole) and few crystals of ammonium



SCHEME

sulphate were added. The contents were refluxed for 4 hrs. The clear solution, thus obtained, was filtered and the solvent was removed in *vacuo* at 100°C. The sugar viz. β-D-ribofuranose 1-acetate-2,3,5-tribenzoate (0.002 mole) was added to the above pasty mixture and the contents were stirred at 150–55°C under *vacuum* for 15 min., in the absence of moisture. The reaction mixture was stirred for 10 hrs. During the reaction period, the *vacuum* was regularly applied for five minutes at the end of every one hour. The melt was boiled in methanol for 10 min, cooled and filtered. The viscous mass of the ribofuranoside thus obtained, was crystallised form diethyl ether.

Yield and m.p. of ribofuranusides. VIIa-g

VIIa- : R^1=C_4H_3O, R^2=2-OH-C_6H_4, R^3=2-OCH_3-C_6H_4; yield 73%; m.p. 202°C.

VIIb : R^1=C_4H_3O, R^2=4-CH_3-C_6H_4, R^3=2-OCH_3-C_6H_4; yield 69%; m p. 215°C.

VIIc : R^1=C_4H_3O, R^2=2-F-C_6H_4, R^3=2-OCH_3-C_6H_4; yield 78%; m.p. 208°C.

VIId : R^1=C_4H_3O, R^2=4-Br-C_6H_4, R^3=2-OCH_3-C_6H_4; yield 71%; m.p. 266°C.

VIIe : R^1=2-OCH_3-C_6H_4, R^2=4-Br-C_6H_4, R^3=2-OCH_3-C_6H_4; yield 65%; m.p. 193°C.

VIIf : R^1=2-OCH_3-C_6H_4, R^2=2-OH-C_6H_4, R^3=4-OCH_3-C_6H_4; yield 67%; m.p. 207°C.

VIIg : R^1=4-Cl-C_6H_4, R^2=4-Br-C_6H_4, R^3=4-OCH_3-C_6H_4; yield 77%; m.p. 273°C.

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