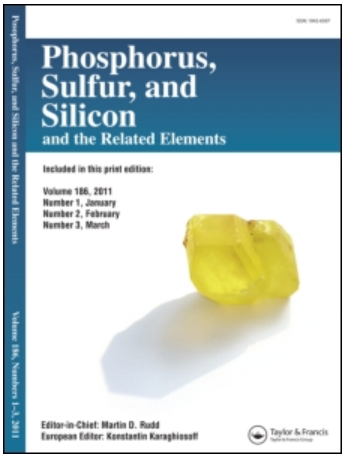

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SYNTHESIS OF RIBONUCLEOSIDES OF 2-THIOXOPYRIDO [2,3-*d*]PYRIMIDINES BY PHASE TRANSFER CATALYSIS AND THEIR ANTIMICROBIAL ACTIVITY

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SYNTHESIS OF RIBONUCLEOSIDES OF 2-THIOXOPYRIDO [2,3-*d*]PYRIMIDINES BY PHASE TRANSFER CATALYSIS AND THEIR ANTIMICROBIAL ACTIVITY

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The ribonucleosides viz; 2-thioxo-3,5,7-trisubstituted–1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine-4 (1*H*)-ones have been synthesized *via* phase transfer ribosylation of 2-thioxo- 3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-4(1*H*)-ones with 2,3,5-tri-O-benzoyl-β-D- ribofuranosyl bromide in biphasic solvent such as CH_2Cl_2-50% aqueous NaOH using tetrabutylammonium bromide as phase transfer catalysis (PTC). The synthesized compounds have been characterized by elemental analyses, spectral data and screened for their antimicrobial activity.

Keywords: Thioxopyridopyrimidine; Ribonucleoside; Phase transfer catalysis; spectral studies and antimicrobial-activity

INTRODUCTION

A perusal of the literature revealed that the nucleosides of pyrido[2,3-*d*]pyrimidines are of great medicinal value e.g. anticancer[1], antitumor[2], antihypertensive[3], antimalarial[4], antifungal[5], anti AIDS[6] and antibacterial drugs[7,8]. Seela and co-workers[9–11] have reported a considerable amount of work employing liquid -liquid/solid-liquid phase transfer catalysis (PTC) for a series of glycosylation of pyrazolo[3,4-*d*]pyrimidines,4-methoxy-1*H*-pyrazolo[2,3-*d*]pyrimidines with 2-deoxy-3,5-di-O- (p-tolyl)-α-δ-erythropentofuranosyl chloride.

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Our work explores a convenient, yield efficient novel procedure for the synthesis of newer ribonucleosides of 2-thioxopyrido[2,3-*d*]pyrimidines using PTC. The synthesized nucleosides have been screened for antimicrobial activity.

RESULTS AND DISCUSSION

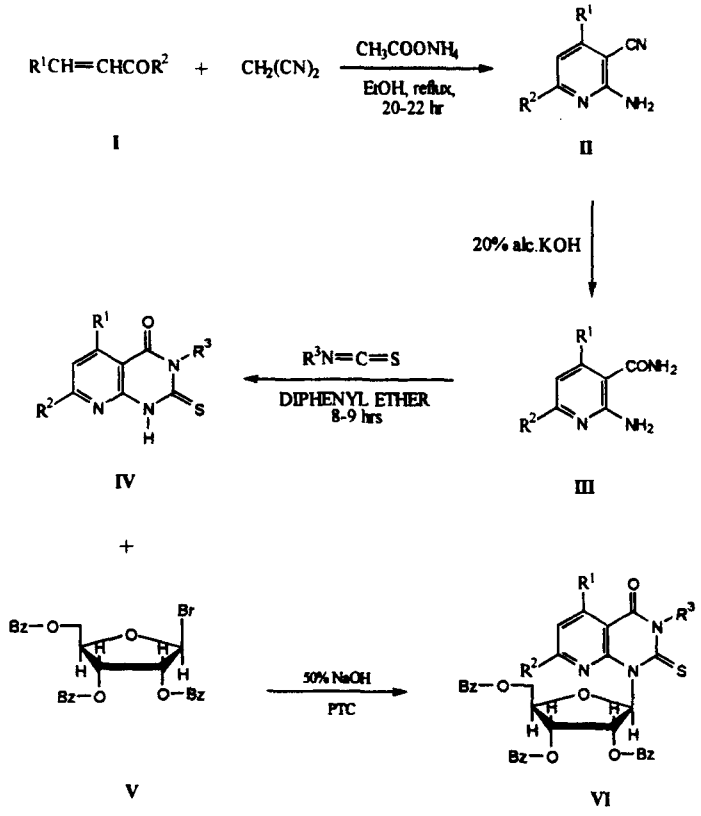
Chalcones **I** and malononitrile in presence of ammonium acetate and ethanol on condensation gave 2-amino-3- cyano-4,6- disubstituted pyridines **II** a through Michael type reaction. Compound **II** when refluxed with 20% alc. KOH was converted to 2-amino-3-carboxamido-4,6 -disubstituted pyridines **III** and refluxing with arylisothiocyanates in diphenyl ether at 150°C afforded **IV.** The compound 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide **V** was synthesized by the reaction of 2,3,5-tri-O-benzoyl-1-acetate-β-D-ribofuranose with hydrogen bromide in acetic acid in dry dichloromethane. Compounds **IV** were treated with **V** in a biphasic mixture of methylene chloride-50% aqueous NaOH in presence of tetrabutylammonium bromide (TBAB) as PTC to give 2-thioxo-3,5,7-trisubstituted-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine-4(1*H*)-ones **VI** (Scheme).

SPECTRAL STUDIES

The spectroscopic studies and elemental analyses (Table I) of the synthesized compounds are consistent with the proposed structures.

IR Spectra

The IR spectra of compounds **II,** showed a sharp band in the region 2230–2130 cm^{-1} indicating the presence of -C≡N group. Compounds **III** gave a band at 1690–1665 cm^{-1} due to >C=O in the -$CONH_2$ group with the complete disappearance of the -C≡N absorption band. In compounds **II** and **III** the stretching and bending vibrations of the - NH_2 group appeared in the region of 3450–3315 and 1525–1510 cm^{-1} respectively. Compounds **IV** gave a band at 1730–1690 for > C=O, at 1210–1165 cm^{-1} for >C=S and three bands in the region 1575–1410 cm^{-1} due to -NHCS moiety. An absorption band in the region of 3410–3385 cm^{-1} is found due to >NH



SCHEME

group in **IV** which disappeared in compounds **VI,** confirming the ribosylation at this position.

^{1}H NMR Spectra

The ^{1}H NMR spectra of compounds **II** showed a broad peak of-NH_2 protons in the region δ 5.30–5.61 ppm and a multiplet of aromatic protons in the region of δ 6.81–7.89 ppm. Compounds **IV,** gave a complex multiplet of aromatic protons at δ 6.82–8.00 ppm and a singlet due to >NH proton appeared at δ 8.1–8.9 ppm. Methoxy protons showed their presence by singlet at δ 3.96-4.20 ppm in compounds **IV.**

TABLE I Characterization data of compounds IVa-h & VIa-h

Compd. No.	R^1	R^2	R^3	*Molecular formula*	*Yield %*	*M.P. °C*	*Elemental analysis % found (calculated)*			
							C	*H*	*N*	*S*
IVa	$-C_4H_3O$	4-Cl-C_6H_4	2-OCH_3-C_6H_4	$C_{24}H_{16}N_3O_3SCl$	80	210–212	62.43(62.41)	3.49(3.46)	9.02(9.10)	6.90(6.93)
IVb	$-C_4H_3O$	4-Cl-C_6H_4	4-$OCH_3C_6H_4$	$C_{24}H_{16}N_3O_3SCl$	81	250–252	62.44(62.41)	3.48(3.46)	9.08(9.10)	6.91(6.93)
IVc	$-C_4H_3O$	C_6H_5	2-$OCH_3C_6H_4$	$C_{24}H_{17}N_3O_3S$	69	200–202	67.45(67.44)	3.99(3.98)	9.80(9.83)	7.42(7.49)
IVd	$-C_4H_3O$	C_6H_5	4-$OCH_3C_6H_4$	$C_{24}H_{17}N_3O_3S$	72	171–173	67.47(67.44)	4.01(3.98)	9.81(9.83)	7.48(7.49)
IVe	$-C_6H_5$	4-Cl-C_6H_4	2-$OCH_3C_6H_4$	$C_{26}H_{18}N_3O_2SCl$	68	251–253	66.21(66.17)	3.87(3.81)	8.89(8.90)	6.73(6.79)
IVf	$-C_6H_5$	4-Cl-C_6H_4	4-$OCH_3C_6H_4$	$C_{26}H_{18}N_3O_2SCl$	67	245–247	66.20(66.17)	3.84(3.81)	8.85(8.90)	6.75(6.79)
IVg	4-F-C_6H_4	4-Cl-C_6H_4	2-$OCH_3C_6H_4$	$C_{26}H_{17}N_3O_2SCl\,F$	72	198–200	63.76(63.73)	3.51(3.47)	8.52(8.58)	6.53(6.54)
IVh	4-F-C_6H_4	4-Cl-C_6H_4	4-$OCH_3C_6H_4$	$C_{26}H_{17}N_3O_2SClF$	70	219–221	63.79(63.73)	3.50(3.47)	8.54(8.58)	6.50(6.54)
VIa	$-C_4H_3O$	4-Cl-C_6H_4	2-$OCH_3C_6H_4$	$C_{50}H_{36}N_3O_{10}SCl$	67	150–152	66.30(66.26)	3.98(3.97)	4.62(4.63)	3.51(3.53)
VIb	$-C_4H_3O$	4-Cl-C_6H_4	4-$OCH_3C_6H_4$	$C_{50}H_{36}N_3O_{10}SCl$	68	149–151	66.28(66.26)	3.99(3.97)	4.60(4.63)	3.50(3.53)
VIc	$-C_4H_3O$	C_6H_5	2-$OCH_3C_6H_4$	$C_{50}H_{37}N_3O_{10}S$	73	138–140	68.89(68.88)	4.28(4.24)	4.78(4.82)	3.62(3.65)
VId	$-C_4H_3O$	C_6H_5	4-$OCH_3C_6H_4$	$C_{50}H_{37}N_3O_{10}S$	71	141–143	68.90(68.88)	4.26(4.24)	4.80(4.82)	3.64(3.65)
VIe	$-C_6H_5$	4-Cl-C_6H_4	2-$OCH_3C_6H_4$	$C_{52}H_{38}N_3O_9SCl$	70	165–167	68.16(68.15)	4.16(4.15)	4.51(4.58)	3.48(3.50)
VIf	$-C_6H_5$	4-Cl-C_6H_4	4-$OCH_3C_6H_4$	$C_{52}H_{38}N_3O_9SCl$	68	162–163	68.10(68.15)	4.18(4.15)	4.54(4.58)	3.45(3.50)
VIg	4-F-C_6H_4	4-Cl-C_6H_4	2-$OCH_3C_6H_4$	$C_{52}H_{37}N_3O_9SClF$	75	152–150	66.85(66.84)	3.99(3.96)	4.48(4.49)	3.41(3.43)
VIh	4-F-C_6H_4	4-Cl-C_6H_4	4-$OCH_3C_6H_4$	$C_{52}H_{37}N_3O_9SClF$	77	155–157	66.87(66.84)	3.98(3.96)	4.46(4.49)	3.39(3.43)

TABLE II Antimicrobial activity of compounds IVa-h & VIa-h Zone of growth inhibition (mm) (activity index)*

Compd. No.	*Escherichia coli (gram − ve)*	*Staphylococcus aureus (gram +ve)*	*Aspergillus niger*	*Aspergillus flavus*	*Curvularia lunata*	*Fusarium oxysporium*
IVa	8.0(0.80)	9.0(1.00)	8.0(0.66)	8.1(0.81)	8.3(0.92)	7.6(0.95)
IVb	7.5(0.75)	8.0(0.88)	8.8(0.73)	7.9(0.79)	8.5(0.94)	8.3(1.03)
IVc	8.0(0.80)	8.8(0.97)	8.9(0.74)	8.2(0.82)	7.9(0.87)	7.4(0.92)
IVd	9.5(0.95)	10.0(1.11)	8.5(0.70)	8.4(0.84)	7.7(0.85)	7.6(0.95)
IVe	9.0(0.90)	9.8(1.08)	8.9(0.74)	9.2(0.92)	7.6(0.86)	8.1(1.01)
IVf	9.7(0.97)	9.1(1.01)	9.3(0.77)	9.0(0.90)	7.9(0.87)	7.5(0.93)
IVg	9.2(0.92)	8.1(0.90)	9.8(0.81)	9.3(0.93)	7.2(0.80)	8.5(1.06)
IVh	8.9(0.89)	7.9(0.87)	9.6(0.80)	8.4(0.84)	7.5(0.83)	7.9(0.98)
VIa	9.5(0.95)	9.5(1.05)	10.2(1.27)	9.2(1.12)	8.4(0.93)	10.1(1.01)
VIb	11.2(1.12)	11.5(1.27)	9.2(1.15)	7.8(0.95)	8.9(0.98)	10.8(1.08)
VIc	10.4(1.04)	10.1(1.12)	10.1(1.26)	8.8(1.07)	9.9(1.10)	11.2(1.12)
VId	11.8(1.18)	10.7(1.18)	7.8(0.97)	7.7(0.93)	10.2(1.13)	11.5(1.15)
VIe	9.8(0.98)	9.0(1.09)	7.4(0.92)	7.9(0.96)	9.8(1.08)	9.8(0.98)
VIf	10.2(1.02)	9.4(1.04)	8.1(1.01)	9.3(1.13)	8.2(0.91)	10.0(1.00)
VIg	10.7(1.07)	10.2(1.13)	8.4(1.05)	8.6(1.04)	9.0(10.0)	11.3(1.13)
VIh	11.0(1.10)	8.9(0.98)	9.5(1.18)	8.9(1.08)	9.2(10.02)	11.4(1.14)

*Activty index = Inhibition area of the sample/linhibition area of the standard.

The disappearance of >NH signal in compounds **VI,** revealed that N-1 substituted nucleosides are produced. The nucleosides **VI,** showed aromatic protons as a multiplet in the region δ 6.6–7.8 ppm, which is slightly downfield as compared to the multiplet of aromatic protons of **IV.** The protons of the sugar in **VI** were observed slightly downfield, as compared to the protons of the bromosugar.

ANTIMICROBIAL ACTIVITY

All the synthesized 2-thioxo-pyrido[2,3-d]pyrimidines and their ribonucleosides were screened for their antimicrobial activity against *E. coli, S. aureus* (bacteria) and *A. niger, A. flavus, C. lunata* and *F. oxysporium* (fungi) at the conc. of 100 μg/disc in agar media following the paper disc method of Gould et al[12]. Streptomycin and Mycostatin were used as the reference compounds in antibacterial and antifungal activities, respectively. The results have been tabulated in the form of inhibition zones (mm) and activity indices (inhibition area of sample/inhibition area of the standard). Comparison of activity indices shows that the ribonucleosides of 2-thioxo pyrido[2,3-*d*]pyrimidines possess better activities than correspoding 2-thioxo pyrido[2,3-*d*]pyrimidines (Table II).

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a NICOLET MEGNA FT-IR 550 spectrometer and ^{1}H NMR spectra in $CDCl_3$/DMSO-d_6 on FX 90Q JEOL spectrometer (90 MHz), using TMS as an internal reference. The purity of the synthesized compounds were checked by TLC, using silica gel "G" as adsorbent and visualization was accomplished by U.V. light and iodine. Chalcones **I** were synthesized by reported method.

Synthesis of 2-amino-3-cyano-4, 6-disubstituted pyridine II

A mixture of appropriate chalcone **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 hr., cooled and poured into crushed ice with constant stirring. A solid mass, thus obtained was washed with water and ethanol. The dried crude product was recrystallized from ethanol.

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

A mixture of **II** (0.04 mole), KOH (0.7 mole) and ethanol (150 ml) was refluxed on a water bath for 20–22 hr. After cooling, the contents were poured on crushed ice with constant stirring to obtain a yellow solid mass. The solid, thus obtained was washed with water and ethanol. The dried crude product was recrystallized from ethanol.

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

A mixture of **III** (0.01 mole), appropriate arylisothiocyanate (0.01 mole) and diphenyl ether (10 ml) was refluxed for 8–9 hr. The reaction mixture after cooling was added to ethanol and separated solid was filtered, washed with water and recrystallized from DMF -EtOH mixture (1:2).

Synthesis of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide V

To a solution of 5 g (0.01 mole) of 2,3,5-tri-O-benzoyl-1-acetate-β-D-ribofuranose in 1 ml of dry dichloromethane, 300 ml of 30% hydrogen bromide in acetic acid was added and then reaction mixture was stirred for 3 hr. Hydrogen bromide was removed by evaporation under diminished pressure (bath temperature below 30°C) followed by addition and evaporation of five, 1 ml portion of dry toluene. The reddish oil consisting of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide was obtained.

Synthesis of 2-thioxo-3,5, 7-trisubstituted-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-4(1H)-ones VI

A mixture of **IV** (0.002 mole) and tetrabutylammonium bromide (0.0002 mole) in dichloromethane (5 ml) was stirred at room temperature. 50% aqueous NaOH (10 ml) was added dropwise in this mixture and stirred for 30 min. To it a solution of **V** (0.002 mole) in a small volume of dichlo-

romethane was gradually poured in three-four instalments. The reaction mixture was again stirred for 3 hr.

After completion of the reaction, dichloromethane (50 ml) and water (50 ml) was added and shaked in a separatory funnel. The layers were separated and the organic layer was washed twice with water (25 ml). The organic layer was dried over anhydrous sodium sulphate and the solvent was removed by distillation. The residue was chromatographed on a silica gel column with solvent (CH_2Cl_2 : EtOAC, 95:5). Distillation of the solvent from main zone yielded a solid which crystallized from methanol gave crystals.

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References

[1] H. Motoo, P. Yoshio, I. Tsuneo, R.J.M. Ohanj, I.Ichiro, M.Yoshihisa, K. Tokyo and O.Haruo, Jpn. Kokai Tokkyo Koho **Jp** 01, 143, 895, [89, 143, 895](Cl.CO7H 19/ 23), 06 Jun. 1989, Appl.87/299,679,30 Nov(1987)6PP; *Chem. Abstr.,* **112**, 7859 (1990).
[2] E.M.Griusky, S. Lee, C.W. Sigel, D.S. Duch and C.A.Nichol, *J.Med. Chem.,* **23,** 327 (1980).
[3] T.H. Athius, P.F. Moore and H.J.Hess, *J. Med. Chem.,* **22,** 44 (1979).
[4] J.Heider, Ger. Offen. DE 3, 320,898 (1983), *Chem. Abstr.,* **100,** 103384 (1984).
[5] M. Mohesen Ismail, *J. Serb. Chem.Soc.* **56(7),** 383 (1991).
[6] F. Seela, and K. Kaiser, *chem, pharm. Bull.,* **36 (10)** 4153 (1988).
[7] I.D. Bystryakova, I.A. Brova, G.M. Chelysheva, S.V. Zhilinkova, N.H. Smirnova, T.S. Safonova, *Khim,-Farm Zh.,* **25,** 31 (1991) : *Chem. Abstr.,* **116,** 106231 (1992).
[8] Shaihla, S.S. Verma. S. Malik, R.L. Mital, L. Prakash, *J. Indian Chem. Soc.* ***67,*** 687 (1990).
[9] F. Seela, B. Westermann and U. Binding, *J. Chem. Soc. Perkin* **1,** 697 (1988).
[10] F. Seela and K. Kaiser, *Halv Chemica Acta;* **71,** 1813 (1988).
[11] F. Seela and H. Stekar, *J. Chem. Soc. perkin* **1,** 2573 (1985).
[12] J.C.Gould and J.H. Bowir, *Edin. Med J.,* **59** 178 (1950).